Title: A Phase 1/2 Study of brentuximab vedotin (SGN-35) in Pediatric Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma

NCT Number: NCT01492088

Protocol Approve Date: 12 June 2014

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CLINICAL STUDY PROTOCOL C25002 AMENDMENT 4

Brentuximab vedotin (SGN-35)

A Phase 1/2 Study of brentuximab vedotin (SGN-35) in Pediatric Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma

Protocol Number:	C25002
Indication:	Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma
Phase:	1/2
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2011-001240-29
Therapeutic Area:	Oncology

Protocol History

Original	01 June 2011
Amendment 1	11 July 2011
Amendment 2 (France specific)	31 October 2011
Amendment 3	06 February 2012
Amendment 4	12 June 2014

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PPD

Signature *Date DD Month YYYY*

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Rationale for Amendment 4

The length of the follow-up period has been changed to align with the content of the pediatric investigation plan (PIP). The PIP states that patients will be followed for safety and survival for 2 years after enrollment. References to follow-up in Amendment 4 have been revised to state that patients will be followed for progression-free survival and overall survival (OS) every 12 weeks for 12 months after the End of Treatment (EOT) visit. Thereafter, assessment for OS will continue every 6 months until the sooner of death or study closure or a maximum of 2 years after enrollment of the last patient.

Protocol C25002 Amendment 4 describes the study procedures for patients who continue to receive brentuximab vedotin after Cycle 16 and further clarifies several other study procedures associated with study conduct.

The amended protocol clarifies the primary endpoint for the phase 2 portion of the study as best overall response rate (ORR) (which was previously written as ORR).

The following changes have been made to the inclusion/exclusion criteria: The inclusion criterion for total bilirubin has been revised to include patients with total serum bilirubin ≤ 3 times the upper limit of the normal range (ULN) if the abnormal value is due to indirect hyperbilirubinemia due to Gilbert's disease. Patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values 5 times the ULN may be enrolled if the elevation can be reasonably ascribed to the presence of metastatic disease in the liver. The exclusions of previous allogeneic stem cell transplant or autologous stem cell infusion have been changed from within 6 months and 6 weeks before the first dose of study drug, respectively, to within 3 months and 4 weeks before the first dose of study drug, respectively. These changes make it possible for patients to receive treatment sooner but with a sufficient amount of time for posttransplant recovery. This amendment also includes a change to the exclusion criterion for cytochrome P450 (CYP) 3A4 inhibitors to exclude both strong and listed moderate inhibitors of CYP3A4 within 2 weeks before the first dose of study drug, and a change to the timing for the exclusion of corticosteroids.

The following potential risks have been added to the Risks in Children section to align with updates to the safety profile of brentuximab vedotin: Stevens-Johnson syndrome (SJS), pancreatitis, hepatotoxicity (elevated AST and ALT).

The amendment also updates the protocol to align with the current Millennium protocol standards, and clarifies the collection and reporting requirements for serious adverse events (SAEs) that are considered to be drug related to align with the current guidelines of the Millennium Department of Pharmacovigilance.

Purposes for Amendment 4

The purposes of this amendment are to:

<u>Major Content Changes</u>

- Revise the length of the follow-up period to align with the PIP
- Clarify that the primary endpoint of the phase 2 study is best ORR

- Add safety language regarding the potential risk of SJS
- Add safety language regarding the potential risk of pancreatitis
- Add safety language regarding the potential risk of hepatotoxicity
- Revise the total bilirubin inclusion criterion to include patients with abnormal values due to indirect hyperbilirubinemia due to Gilbert's disease
- Revise study eligibility criterion regarding elevated ALT and AST values due to the presence of metastatic disease in the liver
- Revise the washout period for systemic corticosteroid treatment in the exclusion criteria
- Revise the required minimum time between previous allogeneic or autologous stem cell transplantation and the first dose of study drug
- Add to the exclusion criteria any history of progressive multifocal leukoencephalopathy
- Revise the CYP3A4 exclusion criterion to exclude listed moderate inhibitors of CYP3A4

Minor Content Changes

- Modify the contraception language regarding abstinence to align with company standards
- Revise language regarding dose adjustments for a ≥ 10% weight change; add language for patients weighing more than 100 kg
- Correct the units of measurement for platelet count, absolute neutrophil count, and white blood cell count
- Remove the restriction on the use of polyethylene infusion bags for dilution of brentuximab vedotin, as previously described in Administrative Letter 2
- Update packaging and labeling instructions for brentuximab vedotin
- Revise the timing for the development assessment and Tanner Scale
- Permit occasional changes in the timing of tests and procedures without permission from the project clinician
- Revise language regarding premedication for infusion-related reactions to allow the use of corticosteroids
- Add an assessment for immune reconstitution at the EOT visit, as previously described in Administrative Letter 1, and add a window to perform immune reconstitution
- Revise the section on Immune Reconstitution; revise the section heading and add separate sections for Immunogenicity Assessment and Tumor Specimen Measurements
- Add language regarding reporting requirements for SAEs
- Delete redundant SAE reporting language, update the period for reporting SAEs to Millennium from 1 calendar day to 24 hours, and update SAE reporting contact information
- Add language regarding the collection of events of peripheral neuropathy

- Redefine the population for analysis of the phase 2 exploratory endpoint as the [redacted]
- Update adverse event (AE) evaluation and analysis language
- Remove text regarding the start of antineoplastic or anticancer therapy as it relates to follow-up of AEs
- Update contact information for reporting product complaints and medication errors

Text Clarifications

- Clarify the sample size for the phase 1 and phase 2 portions of the study
- Revise language in the Study Design section of the Protocol Summary to align with previous updates made to the protocol body text
- Clarify the planned study procedures for patients who remain on treatment after Cycle 16, as previously outlined in Administrative Letter #3
- Specify that serum or urine pregnancy tests are acceptable at screening and before dosing on Day 1, and add a statement regarding the scheduling of pregnancy tests
- Clarify that the timeframe for collecting clinical laboratory values at screening is within 4 days before the first dose of the study drug
- Clarify that patients should be observed for anaphylaxis after each infusion of brentuximab vedotin
- Clarify that Grade 4 neutropenia lasting more than 7 days is considered a dose-limiting toxicity
- Clarify that unacceptable study drug-related toxicity or disease progression will result in mandatory, permanent discontinuation of the study drug
- Clarify that initiation of hematopoietic stem cell transplantation is a reason for study drug discontinuation
- Clarify that development assessments include weight-for-age and stature-for-age percentiles
- Clarify procedures for clinical laboratory evaluations
- Clarify the timing for collection of blood samples for pharmacokinetic assessments and remove reference to total blood volumes to be collected for these assessments
- Clarify the descriptions of Completion of Treatment and Completion of Study, and clarify language for posttreatment assessments
- Clarify efficacy analysis language to specify that the Kaplan-Meier method will be used to analyze efficacy parameters and specify the percentiles to be provided
- Clarify that assessments to be performed at the EOT visit are listed in the Schedule of Events
- Clarify that the frequency of radiological evaluations for patients who receive treatment past Cycle 16 is outlined in the Schedule of Events
- Clarify reasons for study withdrawal.

Adminstrative and Editorial Changes

- Remove Section 14.4, Strong Cytochrome P450 3A4 (CYP3A4) Inhibitors (the list of prohibited CYP3A4 inhibitors is located in the Study Manual)
- Replace references to PPDI with Millennium Department of Pharmacovigilance or designee
- Add abbreviations to table footnotes in the Schedule of Events
- Add bone marrow (BM) and United States Pharmacopeia (USP) to the List of Abbreviations and Glossary of Terms
- Update the name of the Group Head on the title page
- Replace references to medical monitor or study monitor with project clinician
- Correct typographical errors, punctuation, grammar, and formatting

For specific examples of changes in text and where the changes are located, see Section 14.7.

PROTOCOL SUMMARY

Study Title: A Phase 1/2 Study of brentuximab vedotin (SGN-35) in Pediatric Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma

Number of Patients: Approximately 42 evaluable patients as follows:

- Phase 1 dose escalation: at least 12 patients with any relapsed or refractory CD30-positive (CD30+) hematologic malignancy
- Phase 2 relapsed or refractory systemic anaplastic large-cell lymphoma (sALCL): at least 15 evaluable patients (including patients treated at the recommended phase 2 dose [RP2D] during phase 1) of whom at least 10 patients are in first relapse
- Phase 2 relapsed or refractory Hodgkin lymphoma (HL): at least 15 evaluable patients (including patients treated at the RP2D during phase 1).

Phase 1 Study Objectives

Phase 1 Primary

- To assess the safety profile and determine the pediatric maximum tolerated dose (MTD) and/or recommended phase 2 dose of brentuximab vedotin
- To assess the pharmacokinetics (PK) of brentuximab vedotin

Phase 1 Secondary

- To determine the immunogenicity of brentuximab vedotin
- To determine the best overall response rate (complete remission, partial remission) with brentuximab vedotin
- To determine the time to progression, time to response, duration of response, and event-free, progression-free, and overall survival with brentuximab vedotin

Phase 1 Exploratory

CCI [redacted]

Phase 2 Study Objectives

Phase 2 Primary

- To determine the best overall response rate (complete remission, partial remission) with brentuximab vedotin at the recommended phase 2 dose

Phase 2 Secondary

- To determine the time to progression, time to response, duration of response, and event-free, progression-free, and overall survival with brentuximab vedotin
- To assess the PK and safety profile of brentuximab vedotin
- To determine the immunogenicity of brentuximab vedotin

Phase 2 Exploratory

- CCI [redacted]

Overview of Study Design: This is a phase 1/2, open-label, single-agent, multicenter, dose-escalation study of brentuximab vedotin in pediatric patients with relapsed or refractory sALCL or HL for which standard, curative, life-prolonging, or palliative treatment does not exist or is no longer effective. Patients with primary mediastinal B cell lymphoma will be eligible during phase 1. The primary objectives of the study are to assess the safety and pharmacokinetics, and determine the pediatric MTD and/or RP2D of brentuximab vedotin in pediatric patients. In addition, the immunogenicity and antitumor activity of brentuximab vedotin will be evaluated in eligible patients.

Overall response will be evaluated beginning after 2 cycles of therapy. Objective response over the course of the study will be assessed by an independent review facility (IRF) according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma.[1] Patients, including those who achieve a CR, PR, or stable disease may receive brentuximab vedotin for up to 16 cycles. Treatment with brentuximab vedotin beyond 16 cycles may be permitted at the joint discretion of the sponsor and the investigator for those patients experiencing continued clinical benefit. Following administration of the final dose of brentuximab vedotin, patients will be monitored for adverse events for a minimum of 30 days. Patients will be followed for progression-free survival (PFS) and overall survival (OS) every 12 weeks for 12 months after the end of treatment (EOT) visit. Thereafter, assessment for OS will continue every 6 months until the sooner of death or study closure or a maximum of 2 years after enrollment of the last patient. Patients who remain on treatment after Cycle 16 will be followed according to the above schedule or until study closure.

Sample Size Determination: Approximately 42 evaluable patients will be enrolled in this study. In the phase 1 portion of the study, at least 12 patients with relapsed or refractory CD30+ malignancies will be enrolled in 2 planned dose cohorts (3-6 patients per cohort), according to the standard 3 + 3 dose escalation scheme.

Once the pediatric MTD and/or RP2D have been reached, patients will be enrolled by diagnosis into two phase 2 study arms: relapsed or refractory sALCL or relapsed or refractory HL. A sufficient number of patients will be enrolled in the phase 2 portion of the study to have at least 15 evaluable patients with sALCL (including patients treated at the RP2D during phase 1), of whom at least 10 patients are in first relapse, and at least 15 evaluable patients with HL (including patients treated at RP2D during phase 1).

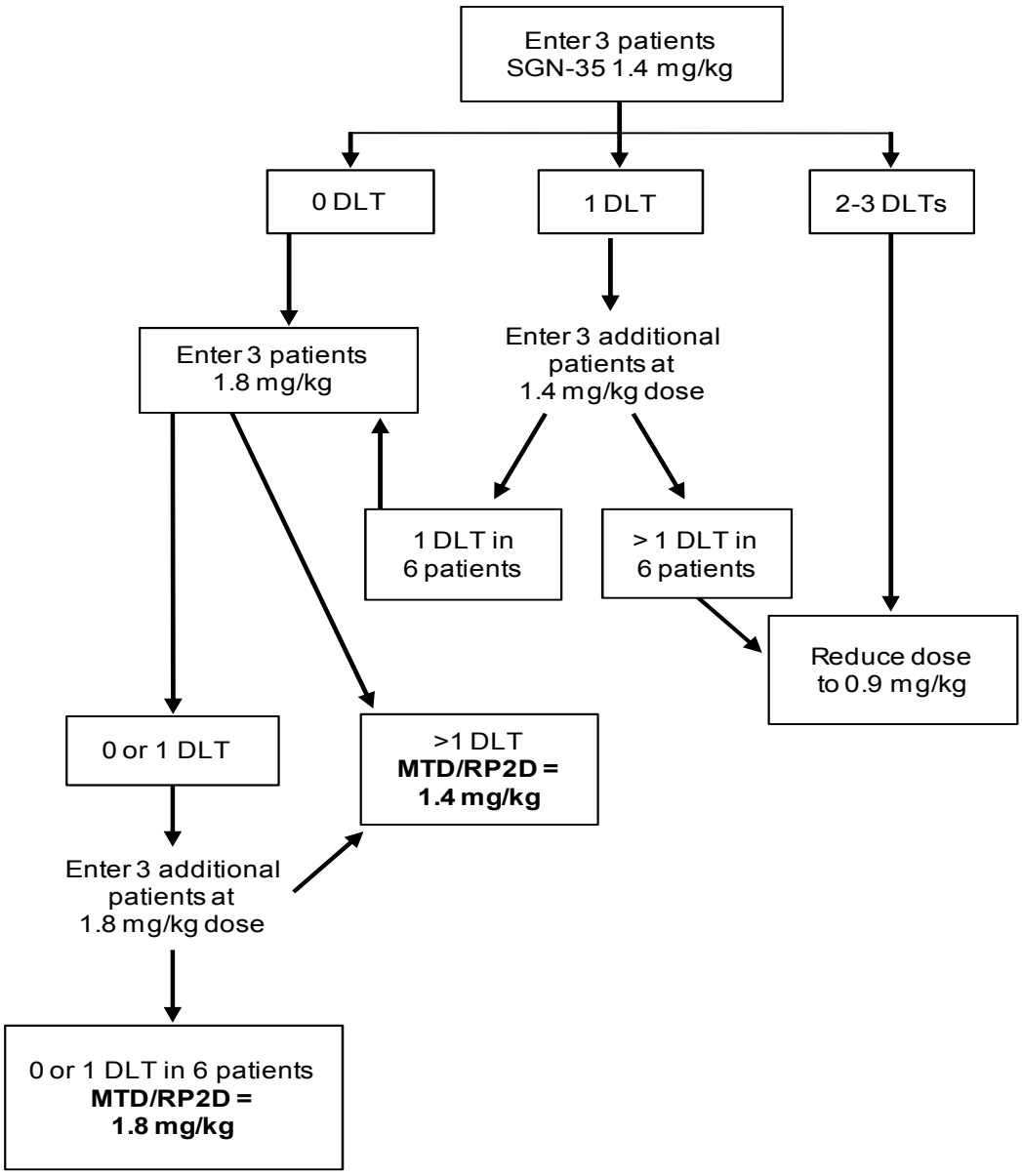
The sample size is not based on statistical consideration. Based on the exact binomial confidence interval (CI) calculation, 10 responses observed from 15 evaluable patients (overall response rate of 66.7%) will provide 95% CI (38%, 88%)**.**

Study Population: The study will enroll male or female patients aged 2 to <18 years, with relapsed or refractory sALCL or HL (5 to <18 years for HL), and radiographically or clinically evaluable tumor per the IWG revised response criteria (patients diagnosed with any relapsed or refractory CD30+ hematological malignancy may be included in phase 1 of the study). Anaplastic lymphoma kinase (ALK) status must be documented for patients with sALCL. Patients with HL must have failed systemic chemotherapy, either as induction therapy for advanced-stage disease or salvage therapy after initial radiotherapy for early stage disease, and be ineligible for, refused, or previously received a stem cell transplant. Patients with sALCL must be beyond first remission or refractory to front-line chemotherapy.

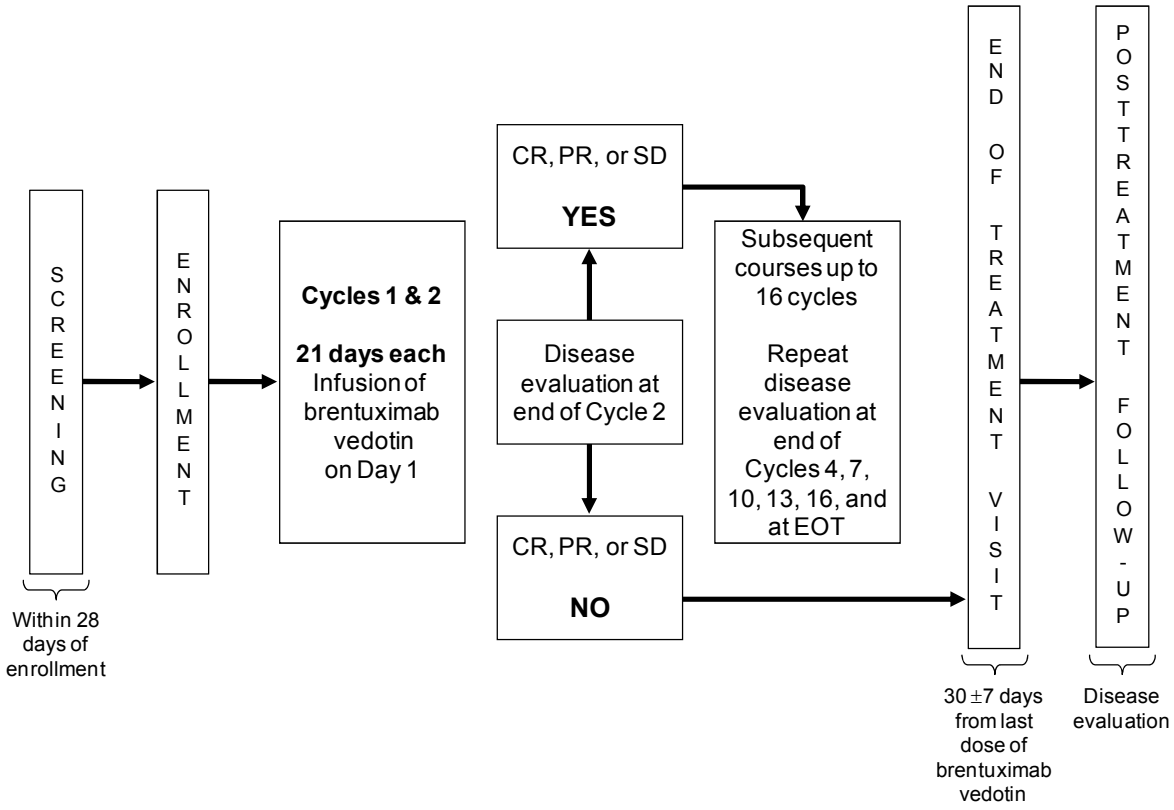
Patients with a current diagnosis of primary cutaneous ALCL, or who received any of the following: allogeneic stem cell transplant <3 months before the first dose of study medication, systemic therapy for chronic graft versus host disease, immunosuppressive therapy, any anti-CD30 antibody, therapeutic monoclonal antibodies (mAbs) within the longer of 6 weeks or 5 plasma half-lives, local palliative radiation therapy within 14 days, or radiation therapy to more than 25% of bone

marrow-containing spaces within 84 days prior to first dose, or prior autologous hematopoietic stem cell infusion <4 weeks prior to first study dose will be excluded from the study. Patients with symptomatic cardiac disease, history of another primary malignancy not in remission for at least 3 years (excluding nonmelanoma skin cancer and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear), or known cerebral/meningeal disease, including signs or symptoms or any history of PML, will be excluded.
Duration of Study: Following a screening period to determine eligibility, patients may receive up to 16 cycles (21 days per cycle) of treatment with brentuximab vedotin. Patients will be followed for at least 2 years from enrollment, until the sooner of death or study closure. Extended brentuximab vedotin therapy, beyond 16 cycles, may be permitted at the joint discretion of the sponsor and investigator for those patients experiencing continued clinical benefit. The overall expected study duration is approximately 5 years.

Phase 1 Study Schema – Dose Escalation



Phase 2 Study Overview Diagram



Schedule of Events

				Cycles 1–16						Cycle 17 and Beyond (for patients who continue beyond 16 cycles)			
		Screening	Enrollment (date of first dose)	Each 21-Day Cycle					Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 only			EOT[a]	PFSFUP/ OSFUP[b]
	Day (D)			D1[c]	D2	D3	D5	D14	D15-21 of Cycle	D1[c]	D15-21 of Cycle	30 days post last dose	q 12 wks for 12 months/ q 6 months thereafter
	Visit Window	**-28 to D1**										**±7 days**	**±7 days**
Screening/ Baseline	Informed consent	X	Enrollment										
	Inclusion/exclusion	X											
	Tumor specimen CD30 expression[d]	X											
	Demographics	X											
	Medical history	X											
Safety Assessments	Height	X[e]		X[e]									
	Weight	X[e]		X[e]						X			
	Pregnancy test[f]	X		X								X	
	Vital signs	X		X[g]									
	Physical exam including focused lymphoma assessment	X		X[h]								X	
	Lansky/Karnofsky Scale[i]	X		X								X	
	Hematology/serum chemistry[j]	X		X[j]								X	
	12-lead ECG[k]	X		X								X	

		Screening	Enrollment (date of first dose)	Cycles 1–16						Cycle 17 and Beyond (for patients who continue beyond 16 cycles)		EOT[a]	PFSFUP/ OSFUP[b]
				Each 21-Day Cycle					Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 only				
	Day (D)			**D1[c]**	**D2**	**D3**	**D5**	**D14**	**D15-21 of Cycle**	**D1[c]**	**D15-21 of Cycle**	**30 days post last dose**	**q 12 wks for 12 months/ q 6 months thereafter**
	Visit Window	**-28 to D1**										**±7 days**	**±7 days**
Disease Assessment	Development assessment and Tanner Scale[l]	X		X[l]								X	
	Dedicated CT of chest	X							X		X[m]	X[n]	X[o]
	MRI of neck, abdomen, pelvis	X							X		X[m]	X[n]	X[o]
	B symptom assessment	X		X								X	
	PET	X							X[p]				
	Bone marrow aspirate and biopsy	X[q]							X[r]		X[r]		
	Disease progression status and subsequent anticancer treatment												X

		Screening	Enrollment (date of first dose)	Cycles 1–16						Cycle 17 and Beyond (for patients who continue beyond 16 cycles)		EOT[a]	PFSFUP/ OSFUP[b]
				Each 21-Day Cycle					Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 only				
	Day (D)			**D1[c]**	**D2**	**D3**	**D5**	**D14**	**D15-21 of Cycle**	**D1[c]**	**D15-21 of Cycle**	**30 days post last dose**	**q 12 wks for 12 months/ q 6 months thereafter**
	Visit Window	**-28 to D1**										**±7 days**	**±7 days**
Treatment	SGN-35 administration[s]			X						X			
	Monitoring of concomitant medications and procedures	Recorded from signing informed consent form through 30 days after the last dose of study drug											
	Adverse event reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug. All events related to PN, regardless of seriousness, will be followed for all changes in severity until resolution to baseline or study closure, whichever occurs first, and recorded in the eCRF.										
	Serious adverse events	Serious adverse events[t] will be collected from signing of the informed consent through 30 days after the last dose of study drug											
Samples	PK Sample			X[u]	X[u]	X[u]	X[u]	X[u]					
	Immunogenicity	X		X[v]								X	
	CCI												

Abbreviations: AE = adverse event; BM = bone marrow; BMA = bone marrow aspirate; CT = computed tomography; D = day; ECG = electrocardiogram; EOT = end of treatment; MRI = magnetic resonance imaging; OSFUP = Overall survival Follow-up; PET = positron emission tomography; PFSFUP = Progression-free survival Follow-up; PK = pharmacokinetics; PD = pharmacodynamics; q = every.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) for holidays, vacations, and other administrative reasons, unless otherwise indicated. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the project clinician or designee.**

a EOT evaluation should be obtained before initiation of nonprotocol therapy. If EOT evaluations are completed before 30 days after the last treatment, the site will conduct a phone screen 30-37 days following the patient's last treatment to ensure that no changes in adverse event profile have occurred.

b Patients will be followed for PFS and OS every 12 weeks for 12 months after the EOT visit. Thereafter, assessment for OS will continue every 6 months until the sooner of death or study closure or a maximum of 2 years after enrollment of the last patient. Patients who remain on treatment after Cycle 16 will be followed

				Cycles 1–16						Cycle 17 and Beyond (for patients who continue beyond 16 cycles)			
				Each 21-Day Cycle					Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 only			EOT[a]	PFSFUP/ OSFUP[b]
	Day (D)	Screening	Enrollment (date of first dose)	D1[c]	D2	D3	D5	D14	D15-21 of Cycle	D1[c]	D15-21 of Cycle	30 days post last dose	q 12 wks for 12 months/ q 6 months thereafter
	Visit Window	-28 to D1										±7 days	±7 days

according to the above schedule or until study closure.

c All procedures performed on Day 1 of each cycle should be performed prior to dosing unless otherwise specified.

d Tumor tissue collected at the time of original diagnosis or subsequent procedures (unstained) will be sent to central lab or affiliate for testing.

e Screening assessment must be performed within 14 days prior to the first dose of study drug. If screening assessment is performed within 4 days of Cycle 1, Day 1 dosing, it need not be repeated.

f A serum or urine pregnancy test will be performed for female patients of childbearing potential during screening, prior to dosing on Day 1 during Cycles 1–16, and at EOT. If the screening test was performed within 4 days before the Cycle 1, Day 1 dose, it need not be repeated on Cycle 1, Day 1. The results must be negative before brentuximab vedotin is administered. During Cycle 17 and beyond, a pregnancy test should be performed per institutional guidelines; any samples collected during Cycle 17 and beyond should not be sent to the central laboratory and data should not be captured in the eCRF. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of the IEC/IRB, or if required by local regulations.

g On Cycle 1, Day 1 only, also perform vital signs measurements at 1 hour (±10 minutes) postdose.

h The Cycle 1, Day 1 physical examination (including height and weight) is not required on Day 1 of Cycle 1 if the screening physical examination was conducted within 4 days before administration of the first (Cycle 1, Day 1) dose of study drug.

i The Lansky Scale will be used for patients ≤16 years of age; the Karnofsky Scale will be used for patients >16 years of age. See Section 14.1 for Lansky Play-Performance Scale information; see Section 14.2 for Karnofsky Performance Scale information.

j A blood sample for hematology and serum chemistry will be obtained at screening, prior to dosing on Day 1 during Cycles 1–16, and at EOT. The hematology and chemistry blood samples for Cycle 1, Day 1 must be collected within 4 days prior to dosing to ensure patient eligibility on Cycle 1 Day 1. If screening clinical laboratory testing was performed within 4 days before the Cycle 1, Day 1 dose, it need not be repeated on Cycle 1, Day 1. See Section 7.4.12 for a listing of the required hematology and serum chemistry parameters. During Cycle 17 and beyond, hematology and serum chemistry tests should be performed per institutional guidelines at the local laboratory; samples should not be sent to the central laboratory and data should not be captured in the eCRF, unless the laboratory result is assessed to contribute to an AE.

k A 12-lead ECG will be obtained at screening, Cycle 1, Day 1; and end of treatment only, unless clinically indicated. If the screening ECG is obtained within 4 days of study drug administration on Cycle 1, Day 1, the ECG assessment need not be repeated. ECG assessments are to be performed with the patient supine and rested for 5 minutes and before any closely timed PK blood collection.

				Cycles 1–16						Cycle 17 and Beyond (for patients who continue beyond 16 cycles)			
				Each 21-Day Cycle					Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 only			EOT[a]	PFSFUP/ OSFUP[b]
	Day (D)	Screening	Enrollment (date of first dose)	D1[c]	D2	D3	D5	D14	D15-21 of Cycle	D1[c]	D15-21 of Cycle	30 days post last dose	q 12 wks for 12 months/ q 6 months thereafter
	Visit Window	-28 to D1										±7 days	±7 days

l Development assessment and Tanner Scale to be performed on Day 1 of Cycles 2, 4, 7, 10, 13, and 16 only. Development assessment to include weight-for-age and stature-for-age percentiles; see Section 14.3 for Tanner Scale information.

m Disease assessment, according to IWG Revised Response Criteria for Malignant Lymphoma, should be performed on Day 15-21 of Cycles 20, 24, 28, and every 4 cycles thereafter.

n Disease assessment should be repeated if not done within the previous 6 weeks.

o Patients who discontinue study treatment with stable disease or better will have CT scans and MRI done every 12 weeks for 12 months.

p PET scans performed at Cycles 2 and 7. No additional PET scans are required beyond Cycle 7 unless clinically indicated.

q May be obtained within 60 days of first dose of brentuximab vedotin. If a positive bone marrow aspirate (BMA) and biopsy was taken more than 60 days before the first dose and the patient has not received treatment in the interim, these do not need to be repeated.

r BMA and biopsy required to confirm response if BM positive at baseline. BMA/biopsy should be obtained within 2 weeks after documentation of response. Does not need to be repeated once bone marrow is found to be negative.

s Patients will be weighed at each dosing visit. The brentuximab vedotin dose must be adjusted if patient weight has increased or decreased by at least 10% from the most recent dose calculation; otherwise, institutional practice should be followed.

t Including serious pretreatment events; see Section 9.3 of the study protocol.

u PK blood samples will be obtained at the following times:

- All Cycles: Day 1: within 4 hours before the start of the brentuximab vedotin infusion and 5 minutes (±1 minute) after the end of the brentuximab vedotin infusion.
- Cycles 1 and 8:
  - Day 2: 24 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion.
  - Day 3: 48 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion.
  - Day 5: 96 hours (±24 hours) from the start of the Day 1 brentuximab vedotin infusion.
  - Day 14: 312 hours (±48 hours) from the start of the Day 1 brentuximab vedotin infusion.

				Cycles 1–16						Cycle 17 and Beyond (for patients who continue beyond 16 cycles)			
				Each 21-Day Cycle					Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 only			EOT[a]	PFSFUP/ OSFUP[b]
	Day (D)	**Screening**	**Enrollment (date of first dose)**	**D1[c]**	**D2**	**D3**	**D5**	**D14**	**D15-21 of Cycle**	**D1[c]**	**D15-21 of Cycle**	**30 days post last dose**	**q 12 wks for 12 months/ q 6 months thereafter**
	Visit Window	**-28 to D1**										**±7 days**	**±7 days**

- Cycle 2:
  - Day 2 (phase 1 only): 24 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion.
  - Day 3: 48 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion.
  - Day 5: 96 hours (±24 hours) from the start of the Day 1 brentuximab vedotin infusion.

v Immunogenicity testing will be performed at screening, predose on Day 1 at Cycle 2 and Cycle 4, and at EOT.

w CCI [redacted]

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
ADC	antibody drug conjugate
AE	adverse event
ALCL	anaplastic large-cell lymphoma
alloSCT	allogeneic stem cell transplant
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
BFM	Berlin-Frankfurt-Munster
BM	bone marrow
BMA	bone marrow aspirate
BMT	bone marrow transplantation
CBC	complete blood count
CDC	Centers for Disease Control

Abbreviation	Term
CI	confidence interval
CMV	cytomegalovirus
CR	complete remission
CSF	colony-stimulating factor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P_{450} 3A4
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
EOT	end of treatment (visit)
EU	European Union
FAB	French-American-British
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HL	Hodgkin lymphoma
H/RS	Hodgkin-Reed-Sternberg
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFRT	involved field radiotherapy
IRB	institutional review board
IRF	independent review facility
IV	intravenous; intravenously
IWG	International Working Group
JCV	John Cunningham virus
K_D	dissociation constant
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NPM	nucleophosmin
ORR	overall response rate
OS	overall survival

Abbreviation	Term
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMBCL	primary mediastinal B-cell lymphoma
PML	progressive multifocal leukoencephalopathy
PN	peripheral neuropathy
PR	partial remission
RP2D	recommended phase 2 dose
SAE	serious adverse event
sALCL	systemic anaplastic large-cell lymphoma
SCT	stem cell transplant
SD	stable disease
SMQ	standardised MedDRA query
SOE	schedule of events
TNF	tumor necrosis factor
TTP	time to progression
ULN	upper limit of the normal range
USP	United States Pharmacopeia
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

1.1.1.1 Hodgkin Lymphoma in Pediatric Population

Classical Hodgkin lymphoma (HL) is defined histopathologically by the presence of malignant Hodgkin-Reed-Sternberg (H/RS) cells in a background of inflammatory cells. H/RS cells are characterized by the expression of CD30, a surface tumor marker and cell membrane protein belonging to the tumor necrosis factor (TNF) receptor superfamily. HL occurs in patients in all age groups and presents a bimodal distribution with peaks at 15 to 35 years of age and over the age of 60.[2] The median age at diagnosis is 38 years in adults and 13.5 years in the pediatric population. The disease is very uncommon in children under 4 years of age and almost nonexistent in those under 2 years of age.[3, 4]

Painless cervical lymphadenopathy is the most common presenting sign (>70%) in children with HL, often with a fluctuating course leading to a delay in diagnosis.[5] Mediastinal masses are frequent (about 60% of pediatric patients) and sometimes discovered after routine chest X-rays. Patients with mediastinal adenopathy may present with respiratory symptoms such as shortness of breath, chest pain, or cough. Fewer than 5% present with disease limited to the upper cervical lymph nodes, above the level of the hyoid bone. Disseminated lymphadenopathy is rare in patients with HL, as is involvement of Waldeyer's ring and occipital, epitrochlear, posterior mediastinal, and mesenteric sites.[5, 6] Approximately 25% of patients will have systemic B symptoms at presentation (as defined by the Ann Arbor system), typically fatigue, fever, weight loss, and night sweats. Pruritus and intermittent fever usually associated with night sweats are classic symptoms of HL. The frequency of these symptoms increases with advanced stage of the disease.[5, 6]

Accurate disease staging and classification of the histological subtype determine the most favorable treatment options and prognosis.[7, 8, 9] The stage of the disease is assigned according to the Ann Arbor staging system with Cotswold modifications for HL. All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms at presentation.[8, 10] Pediatric patients are more likely than adults to present with stage I/II disease and less likely to present with stage IV disease. Adolescents are more likely to have B symptoms than pediatric patients younger than 10 years and have a much higher relapse rate.[11]

Standard treatment of pediatric patients with HL requires a risk-based approach. This ensures that those with good prognosis, low-risk disease can be managed with regimens associated with minimal toxicity, while those at high risk of treatment failure can be treated more aggressively. Low-risk disease presents favorably and is usually defined as localized disease (stage I and II), no bulky disease and absence of B symptoms. Intermediate-risk disease has been defined as all stage I and II patients not classified as early stage and stage IIIA. High-risk disease generally means patients with stage IIIB and IV disease at presentation. Those with favorable risk disease typically receive 2 to 4 cycles of combination chemotherapy with low-dose involved field radiotherapy (IFRT), whereas those with higher-risk disease receive more intensive chemotherapy before IFRT. In contrast to the treatment of adult patients with HL, IFRT remains an important component of the treatment of advanced-stage HL in pediatric patients.[12, 13, 14]

HL is the childhood cancer with the highest cure rates with current OS more than 90% in low-stage disease and up to 70% for disseminated disease.[13, 15, 16, 17] Five-year event-free survival in pediatric HL is approximately 80 to 85%.[18] Pediatric patients less than 10 years of age had a significantly improved freedom from relapse and survival in comparison with adolescents and a highly significant improved outcome compared with adults. Although pediatric patients present high cure rates, multi-agent regimens confer a significant morbidity, including secondary malignancies, cardiovascular disease, male infertility, pulmonary diseases, and infections.[19, 20, 21, 22] Some of the serious sequelae of radiation and alkylating chemotherapy are most pronounced in younger patients, in whom growth and development are particularly active when therapy is administered. In addition, cardiac toxicity appears to be age related, with younger patients at the highest risk. Secondary malignancies represent the leading cause of mortality in survivor patients with HL.[8, 23]

Approximately 10 to 20% of patients presenting with HL will become refractory to initial therapy or will relapse. Given the high rate of success of initial treatment for pediatric HL, little has been published on the optimal management for relapsed or refractory patients. Historical data reveal that children managed initially with radiation alone and who then relapse can achieve cure (as high as 85%), whereas those who were initially treated with multi-agent chemotherapy or combined modality therapy have an unfavorable prognosis and are much more likely to subsequently experience treatment failure.[14] For patients with favorable disease at diagnosis, eg, with relapse confined to an area of initial involvement after chemotherapy and no radiation, salvage therapy consists of further chemotherapy and low-dose IFRT. Patients with an early relapse (between 3-12 months from the end of therapy) had a 10-year event-free survival (EFS) of 55% and a 5-year OS of 78%; those with

a late relapse (more than 12 months from the end of therapy) had a 10-year EFS and OS of 86% and 90%, respectively.[24, 25, 26] For these patients, there is little or no possibility that standard-dose chemotherapy will prove to be effective. High-dose chemotherapy plus allogeneic stem cell transplant (alloSCT) is the only curative option in both pediatric and adult patients.[27]

Transplantation-related mortality rates of more than 20% and even higher relapse rates in pediatric and adult series compromise the survival benefit. Patients who experience relapse or progressive HL post-alloSCT fare dismally and represent a clear unmet need.[28] A pooled analysis from 5 international transplant centers of 756 patients who experienced relapsed HL after autologous stem cell transplant (ASCT) revealed a median survival of 2.4 years, with fewer than 10% of patients alive at 5 years. When the collected data were analyzed by decade in which treatment was received, no difference in treatment outcome was apparent, suggesting that introduction of novel treatment approaches and allogeneic transplantation has not meaningfully improved OS.

Current therapies for pediatric HL have changed dramatically to reduce these toxicities—high-dose radiation therapy is no longer utilized, chemotherapy regimens utilize lower doses of alkylating agents, hybrid regimens allow for lower doses of anthracycline and bleomycin—minimizing the current late effects in patients receiving modern therapy. However, there is still a need to investigate the efficacy and safety of these regimens versus chemotherapy alone in children and adolescents. Because late effects may take 10 to 30 years or more to become clinically apparent, it is too early to conclude on the long-term safety of these treatments. The proposed pediatric study has been designed to study brentuximab vedotin in patients with relapsed or refractory HL, where adult data in this disease setting are presently available and where an unmet medical need for new treatments currently exists.

1.1.1.2 Anaplastic Large-Cell Lymphoma

Anaplastic large-cell lymphoma (ALCL) accounts for approximately 10% of all childhood non-Hodgkin's lymphomas. ALCL can occur at any age, even in infants, and incidence increases steadily with age. The incidence of non-Hodgkin lymphoma (NHL) in the pediatric population is much lower than in adults. The overall rate in pediatric patients is approximately 0.7 per 100,000.[29] The number of cases with NHL in patients 0 to 4 years of age across European regions was very low and cases in pediatric patients less than 2 to 3 years of age are extremely rare. Patients may present with isolated lymphadenopathy or

varied sites of extranodal disease such as the gastrointestinal tract, soft tissues, lung, liver, and/or bone. Systemic ALCL (sALCL) behaves similarly to other diffuse large-cell lymphomas and is aggressive but potentially curable with systemic combination chemotherapy.[30, 31]

Approximately 50% to 80% of pediatric ALCL cases are associated with a t(2;5)(p23;q35) chromosome translocation prompting the anaplastic lymphoma kinase (ALK) gene on chromosome 2 to fuse with the nucleophosmin (NPM) gene on chromosome 5 (ALK positivity). NPM/ALK fusion protein acts as a constitutively activated tyrosine kinase.[32, 33] Inappropriate expression and activation of the fusion kinase in the lymphoid compartment causes the pathogenesis of some forms of ALCL,[34, 35, 36, 37] however, some lymphomas positive for ALK lack this translocation. In these lymphomas, other chromosomal rearrangements, such as inv 2 (p23;q35) and t(1;2)(q25;p23), result in ALK expression.[32, 33] In general, ALK-positive sALCL has a superior OS and failure-free survival rate compared with ALK-negative sALCL.[38] ALK positivity is the most important prognostic indicator in adult ALCL but is less helpful in childhood sALCL where 80% to 95% of sALCL is ALK positive, which precludes comparison of treatment results between pediatric and adult studies.

Prognostic factors are crucial for selecting an appropriate treatment strategy. Prognosis in children and adults is determined by staging. Younger age, absence of B symptoms, absence of extranodal disease, and good performance status predict a better prognosis. Three main clinical factors are associated with an increased risk of failure in childhood sALCL: mediastinal involvement, visceral involvement, and skin lesions.[39, 40, 41, 42, 43] The presence of 1 or more of these has been associated with a poor prognosis: 5-year progression-free survival (PFS) ranging from 90 to 61%. Recent studies have associated poor prognosis with the presence of minimal disseminated residual disease and a low titer of antibodies to the anaplastic lymphoma kinase (ALK) at diagnosis. Patients lacking the t(2;5) translocation in their tumor cells (ALK-negative ALCL) typically have advanced stage disease and a 5-year survival of approximately 40%, whereas ALK-positive disease has a more favorable prognosis with 5-year survival as high as 80 to 90%.[39, 40, 41, 42, 43]

In pediatric frontline sALCL, current therapeutic approaches employ combination chemotherapy. Significant hematological toxicity has been observed. Improvements in first-line therapies have increased survival such that today, pediatric patients presenting with sALCL have an excellent prognosis. Event-free-survival (EFS) in pediatric patients suffering from sALCL is up to 100% for early stage and 70% in advanced stage. OS has

been reported to be up to 90% for early stage, and 80% for advanced stage. Recent trials from the Pediatric Oncology Group, the Children's Cancer Group, and European cooperative groups have shown disease-free survival for advanced-stage disease in the range of 50% to 80% using chemotherapeutic regimens varying in duration and intensity.[39, 41, 44, 45]

Nonetheless, 25% to 35% of patients develop recurrent disease.[41] For recurrent or refractory sALCL, 40% to 60% of patients can achieve long-term survival. There is no standard treatment approach; chemotherapy, ASCT, and alloSCT have all been employed in this setting. Several studies suggest that alloSCT may result in better outcomes for refractory/relapsed sALCL. The treatment of relapsed sALCL is still a matter of debate. Induction therapy followed by high-dose chemotherapy and autologous allogeneic hematopoietic stem cell transplant after a second complete remission (CR) is the standard treatment for relapsed lymphoma in children and is currently used by most groups as first-line treatment for relapsed sALCL. Vinblastine is active as a single agent in recurrent/refractory sALCL, in 1 study inducing CR in 25 of 30 evaluable patients (83%) with acceptable toxicity. Nine of the 25 patients experiencing a CR with vinblastine monotherapy remained in CR with median follow-up of 7 years since the end of treatment.[42]

The choice of salvage therapy for sALCL patients in first relapse is largely driven by assessment of prognostic factors at diagnosis and by response to front-line therapy. AlloSCT is effective and has acceptable toxicity as rescue therapy for high-risk sALCL relapse. It even offers a cure for patients who are refractory to chemotherapy, suggesting a graft-versus-ALCL effect. The Berlin-Frankfurt-Münster group reported outcomes for 20 children and adolescents with high-risk relapsed or refractory sALCL who underwent alloSCT. Nine patients received alloSCT after their first relapse and 11 patients were transplanted after multiple relapses. Event-free survival at 3 years after allogeneic transplant was 75% ±10%. There was no influence of donor type or conditioning regimen on outcome. Two of 6 patients with progressive disease during frontline therapy survived, compared with 13 of 14 patients with a first relapse after frontline therapy.[46] Patients allografted in complete remission showed a better PFS and OS.[47]

In our proposed study, patients with very high risk disease, particularly those who progress while receiving standard therapy and are eligible for bone marrow transplantation (BMT), may use brentuximab vedotin to bridge to alloSCT. This population constitutes ~50 to 60% of the high-risk relapsed patients. Patients who respond to 2 cycles or more of brentuximab

vedotin therapy would be eligible to continue therapy with SCT or BMT. These patients will be transitioned to BMT and may no longer receive brentuximab vedotin.

1.1.1.3 Primary Mediastinal B-Cell Lymphoma

In addition to sALCL, primary mediastinal B-cell lymphoma (PMBCL) is a CD30-positive (CD30+) expressing malignancy. PMBCL is a pathological and clinical subtype of NHL derived from mature thymic B cells. In children, PBMCL comprises 1.8% and 3.8% of patients registered on the Berlin–Frankfurt–Munster (BFM) and the French-American-British (FAB) LMB96 B-cell NHL studies, respectively. PMBCL has the poorest survivals in the pediatric age range, but one of the best among adults with large B-cell lymphomas. PMBCL are consistently positive for CD19, CD20, and CD45 and often for CD79a, CD11c, and CD23. CD30 is usually positive while CD10 and CD21 are negative.[48, 49, 50, 51, 52] The BFM group reported 30 PMBCL cases out of 1,650 B-NHL pediatric patients, 28 of whom were treated on BFM B-NHL therapy.[53] From 1984 to 2003, 116 pediatric patients represented <2% of NHL. The OS rate was 79% and EFS was 67%, which were significantly lower than that in other pediatric B-cell lymphomas, such as diffuse large B-cell lymphoma or Burkitt's lymphoma, and inferior to the results obtained in adult patients with PMLBL who have up to 100% progression-free survival using dose-adjusted EPOCH with rituximab.[54]

Table 1-1 Summary of Results of Chemotherapy Treatment in Pediatric PMBCL Studies

Study	Number of patients	Event-Free Survival	Overall Survival
NHL–BFM 86-90-95[51]	28	5 year 75%	N/A
FAB/LMB 96[52]	43	3 year 66%	3 year 73%
FAB/LMB 96 NHL–BFM 86-90-95 AIEOP LNH 92[53]	116	3 year 67.4%	3 year 78.6%

High-dose therapy followed by ASCT has historically been and remains the standard approach for pediatric patients with chemosensitive relapse or primary refractory NHL. Won, et al, reported an estimated 2-year OS of 62.8±9.1% and EFS of 59.1±9.3% in 33 pediatric patients with relapsed (n=16) or refractory (n=17) NHL following high-dose therapy and ASCT compared to an EFS of 16.3±4.6% in those who received conventional chemotherapy. The European Group for Blood and Marrow Transplantation reported on one of the largest series of 89 pediatric patients with poor risk B-cell lymphoma who underwent

high-dose chemotherapy followed by ASCT. The major factor determining survival in this study was the remission status of patients before ASCT. They report a 5-year EFS of 48.7% for patients with chemosensitive relapse but a dismal outcome for patients with primary refractory disease, all of whom died within 1 year posttransplant, with a 5-year EFS of only 8%.[55]

1.1.2 Study Drug

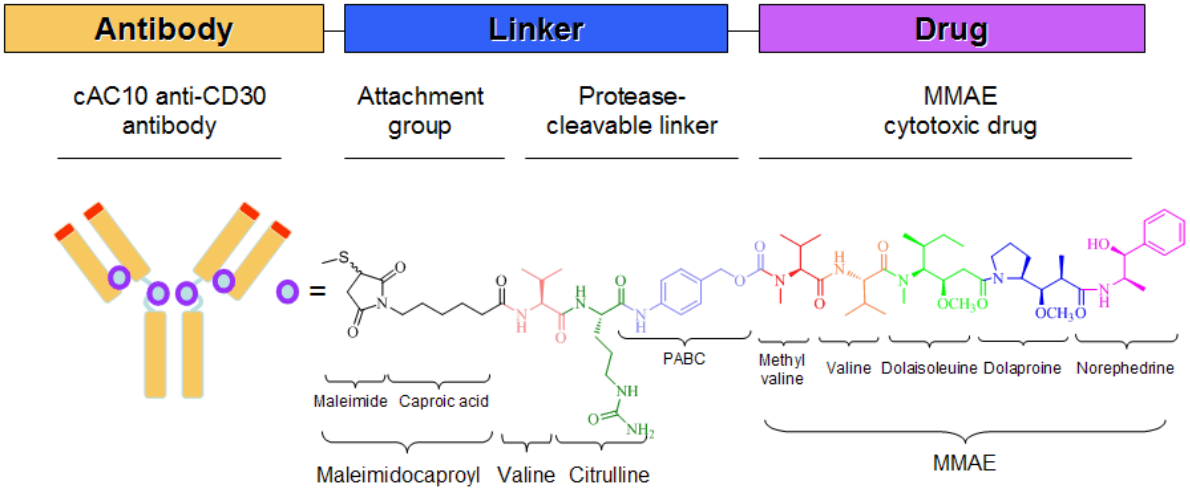
Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the antibody cAC10, specific for human CD30, 2) the highly potent antimicrotubule agent monomethyl auristatin E (MMAE), and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The biological activity of brentuximab vedotin results from a multistep 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 M-phase cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

1.2 Preclinical Experience

1.2.1 In Vitro Activity of Brentuximab vedotin

The chimeric antibody (cAC10) has a typical structure of the human IgG1 subclass (Figure 1-1) and is designed to deliver the cytotoxic agent specifically to tumor cells. Brentuximab vedotin binds to the cell surface protein CD30, which is expressed at high concentrations on tumor cells in HL and sALCL. Target antigen specificity allows preferential delivery of the drug to tumor cells when drug is conjugated to the antibody as an ADC.

Figure 1-1 Schematic Diagram of Brentuximab vedotin



Brentuximab vedotin binds to CD30+ cells (ALCL cell line Karpas 299) at a dissociation constant (K_D) of approximately 2 nM, similar to that of the unconjugated cAC10 anti-CD30 antibody. Cell surface and intracellular localization of brentuximab vedotin was demonstrated by fluorescence microscopy after binding to CD30+ cells (HL cell line L540cy). Within 16 hours of incubation at 37°C, brentuximab vedotin was detected inside cells and co-localized with intracellular lysosomes indicating internalization and trafficking to lysosomes. Monomethyl auristatin E (MMAE) was released from brentuximab vedotin intracellularly by CD30+ human HL (L540cy and L428) and ALCL (Karpas 299) cell lines as determined by liquid chromatography with tandem mass spectrometry analysis of cell culture medium. In addition, studies demonstrating release of MMAE from brentuximab vedotin by purified cathepsin B and lysosome-enriched tumor cell extracts were performed supporting the concept of release of MMAE via the conditionally labile linker (Figure 1-1). Free MMAE inhibited microtubule polymerization in vitro and tumor cells (CD30+ embryonal carcinoma Tera-2 cells) treated with MMAE or brentuximab vedotin displayed a rounded morphology and disrupted micotubule network.

The primary pharmacodynamic effect of brentuximab vedotin was to induce cell cycle arrest in the G2/M phase of the cell cycle. An increase in the percent of cells in G2/M phase was observed over time in cultures of CD30+ cells (HL cell line L540cy and ALCL cell line Karpas 299) treated with brentuximab vedotin. Brentuximab vedotin selectively killed CD30+ HL and ALCL cell lines (IC_{50} of 0.089 and 0.031 nM, respectively), but not CD30-negative cells (WSU-NHL) at concentrations of approximately 100-fold higher.

Similarly, MMAE killed the CD30+ cells at low nM concentrations (1.2 and 0.5 nM, respectively).

Brentuximab vedotin demonstrated antitumor activity in xenograft models derived from human HL and ALCL tumor cell lines. Additional details may be found in the brentuximab vedotin Investigator Brochure (IB).

1.2.2 Pharmacokinetics and Product Metabolism in Humans

Pharmacokinetic parameters for individual patients were determined in Study SG035-0001 using concentrations of serum brentuximab vedotin ADC, plasma MMAE, and serum total antibody. Brentuximab vedotin ADC pharmacokinetics demonstrated that increases in exposure were approximately dose proportional. The geometric mean terminal half-life was approximately 4 to 6 days for the 1.8-mg/kg dose level. The first time to maximum concentration typically occurred immediately after the end of infusion. Steady-state was achieved by Cycle 2, consistent with the half-life estimate. Accumulation was slight.

MMAE pharmacokinetics demonstrated that increases in exposure were approximately dose proportional. The apparent terminal half-life was approximately 3 days for the 1.8-mg/kg dose level.

Although the relative expression of CD30 in pediatric patients with sALCL and HL compared to adult patients with sALCL and HL has not been quantified, in vitro cytotoxicity experiments suggest that brentuximab vedotin will have activity across a large range of CD30 expression. Therefore, it is anticipated that brentuximab vedotin would successfully target CD30 similarly in pediatric HL, sALCL, and other rare lymphoma expressing CD30 as observed in adults and based upon the clinical data in adult sALCL.

From a pharmacokinetic perspective, age-related changes in the disposition of monoclonal antibodies are not often observed.[56, 57] The toxin portion of brentuximab vedotin, MMAE, is metabolized to several inactive metabolites via CYP3A4. Expression of this isoform is approximately 50% of adult levels in pediatric patients between 6 and 12 months of age[58] and is similar in pediatric patients ≥1 year old and adult patients.[59] CCI [redacted]

1.2.3 Preclinical Toxicology

Several toxicity studies have been conducted with brentuximab vedotin in vitro and in vivo (monkeys and rats). Overall brentuximab vedotin demonstrated an acceptable safety profile in nonclinical studies. Hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed in both rats and monkeys. In addition, lesions were seen in the kidneys, liver, and spleen in monkeys and in the liver and testes in rats. Reversibility of toxicity was demonstrated for all of the findings with the exception of the testicular changes in rats. At the recovery sacrifice 4 weeks following the last dose of brentuximab vedotin (10 mg/kg), testicular changes (diffuse seminiferous tubule degeneration) were still evident. Further details are provided in the brentuximab vedotin IB.

1.2.4 Immune Function

Detailed information regarding the nonclinical pharmacology and toxicology of brentuximab vedotin may be found in the brentuximab vedotin IB.

1.3 Clinical Experience

The safety and efficacy of brentuximab vedotin has been evaluated in more than 300 patients with HL, sALCL, and other CD30+ hematologic malignancies in 11 clinical studies. Clinical data have been collected from 2 completed phase 1 dose escalation studies (SG035-0001 and SG035-0002), a pivotal phase 2 study in relapsed or refractory HL after ASCT (SG035-0003), a pivotal phase 2 study in relapsed or refractory sALCL (SG035-0004), and a phase 1, drug-drug interaction study (SG035-008A). Preliminary and final analyses of safety data indicate that brentuximab vedotin has a tolerable and manageable safety profile in the studied populations.

In Study SG035-0001, a total of 45 patients with CD30+ hematologic malignancies (42 with HL, 2 with sALCL, 1 with angioimmunoblastic T-cell lymphoma) were treated with brentuximab vedotin at dose levels of 0.1 to 3.6 mg/kg administered intravenously (IV) every 3 weeks. The primary objectives of the study were to establish a maximum tolerated dose (MTD) of brentuximab vedotin and to assess the associated toxicity profile. The most common adverse events were fatigue (36%), pyrexia (33%), and diarrhea, nausea, peripheral neuropathy, and neutropenia (22% each). Notable serious adverse events considered at least possibly related to treatment included anaphylaxis, myocardial infarction, and peripheral neuropathy.

In Study SG035-0002, 44 patients with CD30+ hematologic malignancies (38 with HL, 5 with sALCL, and 1 with peripheral T-cell lymphoma) were treated with brentuximab vedotin at dose levels of 0.4 to 1.4 mg/kg administered IV weekly for 3 of 4 weeks. The primary objectives explored in this study were to establish the safety profile and MTD of weekly brentuximab vedotin monotherapy in patients with relapsed or refractory CD30+ hematologic malignancies. Although this weekly regimen was designed to enable combination use with gemcitabine, efficacy with brentuximab vedotin monotherapy was deemed sufficient and the planned brentuximab vedotin/gemcitabine combination was not pursued. The most common adverse events were peripheral sensory neuropathy (66%); fatigue (52%); nausea (50%); diarrhea (32%); arthralgia (27%); pyrexia (25%); and decreased appetite, myalgia, and upper respiratory tract infection (23% each). Treatment discontinuations due to adverse events were observed in 30% of patients. The most frequent AE that led to dose modification or delay was peripheral sensory neuropathy. Acute infusion reaction AEs occurred in a total of 6 patients. Overall, these acute infusion reaction AEs were reported as less than Grade 2 in severity and resolved. Overall, 2 patients (14%) who had an acute infusion reaction also had antitherapeutic antibodies at any postbaseline visit.

In SG035-0003, a phase 2, single-arm, open-label study in patients with relapsed or refractory HL postASCT, and SG035-0004, a phase 2 study conducted in patients with relapsed or refractory sALCL, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks. One hundred two patients with relapsed and refractory HL and 58 patients with relapsed and refractory sALCL were exposed for a median duration of approximately 27 weeks (9 cycles) and 20 weeks (6 cycles), respectively. Most patients (89%) in the two phase 2 studies were between the ages of 18 and 65 years. The primary endpoint of both studies was overall response rate (ORR) as assessed by an independent radiographic facility. Key secondary endpoints included duration of response, OS, and PFS. The key efficacy results in HL (SG035-0003) include ORR per IRF (75% [95% CI: 64.9-82.6%]), CR rate (34% [95% CI: 25.2-44.6%]), B symptom resolution rate (77%), and duration of response (DOR, 29 weeks). Key efficacy points in sALCL (SG035-0004) include ORR (86% [95% CI: 74.6-93.9%]), CR rate (53% [95% CI: 39.6-66.7%]), and B symptom resolution rate (82%).

Treatment-emergent AEs occurring in ≥20% of patients in phase 2 were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily mild to moderate in severity and reversible. Approximately half of patients

had treatment-emergent peripheral neuropathy, predominantly sensory neuropathy, with an onset and severity pattern consistent with a cumulative effect. Dose delay and subsequent reduction to 1.2 mg/kg was generally effective in managing peripheral neuropathy. Grade 3 and Grade 4 neutropenia occurred in 13% and 7% of patients, respectively; these events were typically of short duration and well managed by brief dose delays with growth factor support in some cases. Infusion-related reactions occurred in approximately 10% of patients and were typically managed by dose delay or reduction. Infusion-related reaction prophylaxis in subsequent treatment cycles was instituted at the discretion of the investigator. The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%). Only 1 patient in the phase 2 studies had Grade 3 increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

In the phase 2 studies, 31% of patients had a serious adverse event, 28% had an SAE of Grade 3 or higher, and 15% had an SAE that was determined by the investigator to be related to brentuximab vedotin. The most common SAE preferred terms (2%) were abdominal pain, disease progression (recurrent sALCL), pulmonary embolism, and septic shock. A higher proportion of sALCL patients experienced SAEs, including deaths within 30 days of last dose, relative to patients with HL, likely due to the older age and more aggressive nature of the malignancy in this patient population.

A total of 9 deaths were reported within the safety evaluation period (within 30 days of the last dose of brentuximab vedotin) in 357 patients across the 6 phase 1 and phase 2 studies for which data are available. Two patient deaths (0.6%) were considered related to study treatment. One patient in Study SG035-0001 who received 3.6 mg/kg in phase 1 died due to febrile neutropenia and presumed septic shock. A second treatment-related death in Study SG035-008A was attributed to pancytopenia, cytomegalovirus (CMV) infection, and intracranial hemorrhage. The remaining on-study deaths were primarily related to disease progression in patients with sALCL.

Four pediatric patients (aged 14-17 years) were included in Study SG035-0004 in sALCL, and 1 pediatric patient (aged 15 years) was included in Study SG035-0003 in HL. All of these patients experienced at least 1 adverse event, and the event types observed were similar to those reported in the adult study population. Most of the AEs were mild to moderate, resolved without action, and were unrelated to brentuximab vedotin. Three of the 5 pediatric patients experienced at least 1 event of peripheral neuropathy, ranging from Grade 1 to Grade 3, and 2 patients reported events of neutropenia. One patient experienced

treatment-related Grade 3 neutropenia, and 1 patient experienced Grade 3 and Grade 4 neutropenia and Grade 3 and Grade 4 thrombocytopenia that were assessed as not related to brentuximab vedotin. This same patient experienced an SAE of Grade 2 viral gastroenteritis, which was unrelated to study drug. The patient with HL in Study SG035-003 achieved a CR and completed treatment. The patient's DOR was 50.4 weeks. Three of the 4 pediatric patients with sALCL in Study SG035-004 achieved CR and 1 achieved partial remission (PR); 1 patient was transitioned to ASCT.

Brentuximab vedotin has been shown to induce durable remissions in patients with HL both pre- and post-ASCT, and in patients with relapsed or refractory sALCL. Progression-free survival results comparing PFS with brentuximab vedotin to PFS from prior systemic therapy indicate that PFS is significantly prolonged with brentuximab vedotin for both HL and sALCL. A substantial number of patients with HL and sALCL and B symptoms at baseline saw these symptoms resolve during treatment with brentuximab vedotin. In addition, the large majority of patients with sALCL presenting with cutaneous lesions at baseline experienced resolution of these symptoms after receiving brentuximab vedotin.

Further details on clinical studies with brentuximab vedotin are provided in the brentuximab vedotin IB.

1.3.1 Study Rationale

Most patients diagnosed with HL or sALCL respond to initial chemotherapy. However, 20% to 40% of these patients will eventually relapse, and approximately 10% of patients will have refractory disease. Salvage chemotherapeutic regimens and ASCT are secondary options for these patients, but both are associated with a significant morbidity rate. Immunotherapy with an ADC represents an additional therapeutic modality with the potential to maintain or improve efficacy without concomitant increase in toxicity.

Brentuximab vedotin is a novel ADC directed against the CD30 surface antigen expressed on hematologic malignancies including HL and sALCL tumor cells. Preclinical studies of brentuximab vedotin demonstrated antitumor activity in both in vitro and in vivo models. This study is the first clinical use of brentuximab vedotin exclusively in pediatric patients with relapsed or refractory CD30+ malignancies, the majority of which are expected to be HL and sALCL. The safety, pharmacokinetics (PK), immunogenicity, and antitumor activity of brentuximab vedotin will be evaluated in eligible patients.

As the goal of phase 1 of this study is to establish safety and define the MTD and/or recommended phase 2 dose of brentuximab vedotin in pediatric hematological malignancies with high expression of CD30, patients with relapsed or refractory CD30+ malignancies (including HL and sALCL) are planned for inclusion in the phase 1 study population.

The phase 2 portion of the study will enroll patients into 2 separate arms based on diagnosis of relapsed or refractory sALCL, or relapsed or refractory HL; patients will receive brentuximab vedotin at the MTD and/or recommended phase 2 dose (RP2D) determined in the phase 1 portion of the study. Best overall response rate (CR+PR) and DOR will be evaluated.

Conducting the phase 2 part of the study as a nonrandomized study is consistent with many phase 2 pediatric oncology studies. Based on interactions with various agencies and extensive consultation with HL experts, a comparative trial was determined to be not feasible because it is anticipated that most patients randomized to the control arm would leave the trial to obtain treatment with other investigational products.

1.4 Potential Risks and Benefits

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

1.4.1 Benefit Analysis in Hodgkin Lymphoma

Study SG035-0003, a phase 2 study of brentuximab vedotin evaluated 1.8 mg/kg administered IV every 3 weeks in a relatively homogeneous population of 102 adult patients with HL whose lymphoma had relapsed or was refractory to multiple-agent, high-dose chemotherapy and autologous SCT.

A 75% ORR (representing the predefined primary endpoint of the trial) with a durability of 6.7 months was observed. A substantial proportion (34%) of all treated patients obtained a complete remission as manifested by no evidence of lymphoma by clinical, laboratory, or radiographic measures. Observed CRs were durable, with the median duration not reached and a lower 95% confidence interval bound of 8.8 months. Achievement of CR in lymphoma is highly correlated with prolonged survival after a subsequent alloSCT, and this potentially curative treatment option was enabled in a meaningful fraction of patients with HL treated in the study.

In a preplanned analysis of PFS per investigator assessment in which each patient served as his or her own control, PFS with brentuximab vedotin was nearly twice that of the most recently delivered treatment. Analysis of transplant-ineligible patients in phase 1 studies demonstrated clinical benefit in the pretransplant setting.

1.4.2 Benefit Analysis in Systemic Anaplastic Large Cell Lymphoma

Study SG035-0004, a phase 2 study of brentuximab vedotin 1.8 mg/kg administered IV every 3 weeks in 58 patients 12 years of age or older with sALCL, an ORR of 86% was observed and 53% of patients obtained a CR as manifested by no evidence of lymphoma by clinical, laboratory, or radiographic measures. The ability to attain a second CR or achieve a first CR after the failure of frontline therapy enables an improved opportunity for SCT, an exploratory yet potentially curative treatment.

As for HL, an intrapatient comparison of PFS per investigator assessment obtained with brentuximab vedotin versus the most recent prior therapy was conducted. In 90% of cases, the most recent prior therapy was multiagent chemotherapy, delivered with or without ASCT. The median PFS duration achieved with brentuximab vedotin was approximately 8 months longer than that achieved with the most recent prior therapy.

1.4.3 Potential Risks in Children

The recommended dose of brentuximab vedotin in adult patients is 1.8 mg/kg administered IV every 3 weeks as long as the patient continues to benefit from and tolerates therapy. At this dose and schedule, the most common adverse events were peripheral sensory neuropathy, fatigue, nausea, diarrhea, pyrexia, upper respiratory tract infection, neutropenia, and vomiting. These events have been primarily mild or moderate in severity.

The most notable adverse event associated with brentuximab vedotin is peripheral neuropathy that tends to increase in severity with longer duration of therapy, consistent with that observed with other antimicrotubule agents such as vinca alkyloids or taxanes. Sensory events were more common than motor events, and the peripheral neuropathy (PN) events typically followed a distal to proximal pattern of development, also similar to the PN seen with other tubulin disruptors. Approximately half of patients in the phase 2 studies experienced treatment-emergent PN, which was primarily mild to moderate (Grade 1 or Grade 2). The most frequently occurring events were peripheral sensory neuropathy (44%), peripheral motor neuropathy (9%), and paresthesia (4%). Grade 3 peripheral neuropathy events occurred in 18 (11%) patients. No Grade 4 PN events were reported.

For those patients in the phase 2 study with at least 1 PN Standardised MedDRA Query (SMQ) event, the median time to onset of any PN SMQ event was 12.4 weeks. For ≥Grade 3 events, there was a clear trend toward first onset in later cycles, with the majority of events having first onset between Cycles 9 and 16. Overall, 15% of patients had dose modifications for PN SMQ events. Dose delays for PN SMQ events occurred in 20 patients (13%) and dose reductions occurred in 12 patients (8%). Treatment discontinuations for PN SMQ events occurred in 14 patients (9%). Neuropathy was generally reversible, with a median time from onset to resolution or improvement of 6.6 weeks (range, 0.3 to 54.4 weeks).

The majority of peripheral neuropathy events were Grade 1 or Grade 2 and were manageable by dose delay and reduction. For new or worsening events of Grade 2 or Grade 3 neuropathy, dosing should be held until neuropathy improves to ≤Grade 1 and then restarted at the 1.2 mg/kg dose level. For Grade 4 (life-threatening) peripheral neuropathy, brentuximab vedotin should be discontinued.

Infusion-related reactions (IRRs) are possible with brentuximab vedotin, especially related to the development of clinically significant titers of antitherapeutic antibodies (ATAs). Patients must be monitored for the possibility of an acute reaction during brentuximab vedotin administration. If IRR symptoms develop, the infusion should be interrupted and appropriate medical management instituted. Further information on the management of IRRs is provided in Section 6.1.

Progressive multifocal leukoencephalopathy (PML) has been reported with brentuximab vedotin use. PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%). The onset of neurological deficits may occur over weeks to months.[60] Cognitive decline without accompanying deficits in motor or sensory function is uncommon. Optic nerve involvement, fever, and spinal cord disease are not typically associated with PML. In addition, peripheral neuropathy, which has been reported with brentuximab vedotin treatment, is not commonly reported with PML. If PML is suspected, a diagnostic work-up should be performed, as described in Section 6.8.2.

Stevens-Johnson syndrome (SJS), including toxic epidermal necrolysis, has been reported in patients who received brentuximab vedotin. Patients were concurrently receiving other medications (naproxen and tramadol, respectively) that are known to cause SJS and may have contributed to the development of SJS. Stevens-Johnson syndrome is considered to be an unacceptable study drug-related toxicity. If SJS occurs, the administration of brentuximab vedotin must be discontinued and the appropriate medical therapy administered.

Acute pancreatitis has been reported in patients treated with brentuximab vedotin and has contributed to fatal outcomes in some cases. Onset typically occurred after 1 to 2 doses of brentuximab vedotin. Early symptoms included severe abdominal pain, nausea, and vomiting. Some of the pancreatitis cases were complicated by other possible contributory factors, including cholelithiasis and alternate etiologies (eg, pancreatic lymphoma progression, displacement of bile duct stent).

Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial that studied brentuximab vedotin with bleomycin as part of a combination regimen, the rate of noninfectious pulmonary toxicity was higher than the historical incidence reported with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids.

Hepatotoxicity, predominately in the form of asymptomatic mild to moderate transient elevations in AST and/or ALT, has been reported in patients treated with brentuximab vedotin. Patients should be monitored for elevated liver enzymes.

Preliminary population PK analyses of the effects of brentuximab vedotin on renal and hepatic function suggest that no dose adjustments are necessary for patients with renal or hepatic impairment. Additional analysis is planned to more fully characterize the pharmacokinetics in this patient population.

The effects of brentuximab vedotin on embryogenesis, reproduction, and spermatogenesis in humans are unknown. In addition, data about the effects of brentuximab vedotin in pregnant women are unavailable. Patients of childbearing potential are advised to use adequate and effective contraception during brentuximab vedotin treatment and for a 6-month period thereafter.

Brentuximab vedotin recognizes the CD30 antigen on tumor cells and normal activated T cells. In nonclinical toxicology studies, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed in rats and monkeys. It is possible that binding of brentuximab vedotin to normal CD30+ T cells could render these cells ineffective, thus leading to alterations in immune function. To date, the effect of brentuximab vedotin on the immune system of pediatric patients and the extent or duration of immune dysfunction following the completion of brentuximab vedotin is unknown. A pediatric population has a rapidly developing immune system characterized by continual exposure to neoantigens and a large thymus where T cell selection is actively engaged. CD30 is expressed on medulary cells of the thymus however, the role of CD30 in T-cell selection is controversial.[61, 62] Preclinical data suggest a potential impact of brentuximab vedotin on thymic cell populations. Additionally, younger patients are more likely to have immune suppression after completion of chemotherapy, including the loss of protective serum antibody concentrations against vaccines. There is a reduction in vaccine-antigen specific antibody concentrations after completion of chemotherapy.[63]

The extent and duration of immune dysfunction following the completion of standard-dose chemotherapy will depend on the antineoplastic agent used and its dose intensity, and can therefore vary widely. This may influence immunity to vaccine antigens and responses to vaccination. Total B- and T-lymphocytes usually recover fully, quantitatively and functionally, 6 months after completion of chemotherapy; although in some cases, recovery may take up to 1 year. There is a reduction of immunoglobulin levels after completion of chemotherapy, particularly of IgG2 levels. Normalization of immunoglobulin levels can take up to 1 year after completion of treatment. A recent study looking at immunity to vaccines at a median time of 7 months after completion of treatment for acute leukemia in British children demonstrated protective antibody concentrations for all patients to tetanus, 87% to Hib, 71% to measles, 12% to *Neisseria meningitidis* group C (meningococcus C), and 11% to all 3 poliovirus-serotypes. Therefore, in order to assess the effect of brentuximab vedotin on pediatric immune function, the duration of any changes to the levels of CCI [redacted] will be examined at baseline and 6 and 12 months (± 1 month) after treatment is completed.

To address safety concerns regarding growth and development in children treated with brentuximab vedotin, Centers for Disease Control (CDC) recommended 2006 World Health

Organization (WHO) international growth charts for children aged <24 months (available at cdc.gov/growthcharts) and CDC growth charts in persons aged 2 to 19 years will be used. Clinical charts are available for boys and for girls at cdc.gov/growthcharts/clinical_charts.htm. A sexual maturity scale such as the one developed by Tanner is used to assess the physical developmental stage of a patient. This scale assigns a Tanner stage of 1 (prepubertal) to 5 (adult) to girls based on breasts and pubic hair and to boys based on genitalia and pubic hair.

The multiagent chemotherapy regimens often employed as salvage therapy in patients with relapsed or refractory HL or sALCL carry significant toxicities. Given the benefit observed with brentuximab vedotin monotherapy in this population with aggressive disease, the manageable adverse event profile is notable.

2. STUDY OBJECTIVES

2.1 Phase 1 Primary Objectives

The primary objectives in phase 1 are:

- To assess the safety profile and determine the pediatric maximum tolerated dose and/or recommended phase 2 dose of brentuximab vedotin
- To assess the pharmacokinetics of brentuximab vedotin

2.2 Phase 1 Secondary Objectives

The secondary objectives in phase 1 are:

- To determine the immunogenicity of brentuximab vedotin
- To determine best overall response rate (complete remission, partial remission) with brentuximab vedotin
- To determine the time to progression, time to response, duration of response, and event-free, progression-free, and overall survival with brentuximab vedotin

2.3 Phase 1 Exploratory Objectives

The exploratory objective in phase 1 is:

CCI [redacted]

2.4 Phase 2 Primary Objectives

The primary objective in phase 2 is:

CCI [redacted]

2.5 Phase 2 Secondary Objectives

The secondary objectives in phase 2 are:

- To determine the time to progression, time to response, duration of response, and event-free, progression-free, and overall survival with brentuximab vedotin
- To assess the pharmacokinetics and safety profile of brentuximab vedotin
- To determine the immunogenicity of brentuximab vedotin

2.6 Phase 2 Exploratory Objectives

The exploratory objective in phase 2 is:

CCI [redacted]

3. STUDY ENDPOINTS

3.1 Phase 1 Primary Endpoints

The primary endpoints in phase 1 are:

- Adverse events (AEs), serious adverse events (SAEs), assessments of clinical laboratory values, and vital signs measurements
- Plasma concentrations of brentuximab vedotin, total therapeutic antibody, and MMAE

3.2 Phase 1 Secondary Endpoints

The secondary endpoints in phase 1 are:

- Antitherapeutic antibody (ATA) titer and neutralizing ATA titer
- Best overall response rate (CR, PR) as determined by an independent review facility (IRF) using positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), and clinical assessment, according to International Working Group (IWG) revised response criteria
- Time to progression
- Time to response
- Duration of response
- Event-free survival
- Progression-free survival
- Overall survival

3.3 Phase 1 Exploratory Endpoints

The exploratory endpoints in phase 1 are:

CCI

3.4 Phase 2 Primary Endpoints

The primary endpoint in phase 2 is:

- Best overall response rate (CR, PR) as determined by an IRF using PET, CT, MRI, and clinical assessment according to IWG revised response criteria

3.5 Phase 2 Secondary Endpoints

The secondary endpoints in phase 2 are:

- Time to progression
- Time to response
- Duration of response
- Event-free survival
- Progression-free survival
- Overall survival
- Adverse events, serious adverse events, assessments of clinical laboratory values, and vital signs measurements
- Plasma concentrations of brentuximab vedotin, total therapeutic antibody, and MMAE
- Antitherapeutic antibody (ATA) titer and neutralizing ATA titer

3.6 Phase 2 Exploratory Endpoints

The exploratory endpoint in phase 2 is:

CCI

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This is a phase 1/2, open-label, single-agent, multicenter, dose-escalation study of brentuximab vedotin in pediatric patients with relapsed or refractory sALCL or HL for which standard, curative, life-prolonging, or palliative treatment does not exist or is no

longer effective. The primary objectives of the study are to assess the safety and pharmacokinetics, determine the pediatric MTD and/or RP2D of brentuximab vedotin in pediatric patients, and evaluate the antitumor activity of brentuximab vedotin in eligible patients.

Approximately 42 evaluable patients will be enrolled in this study. In the phase 1 portion of the study, at least 12 patients with relapsed or refractory CD30+ malignancies (including HL and sALCL) will be enrolled in 2 planned dose cohorts (3 to 6 patients per cohort) according to the standard 3 + 3 dose escalation scheme.

Once the MTD and/or RP2D have been reached, patients will be enrolled by diagnosis into two phase 2 study arms: relapsed or refractory sALCL, or relapsed or refractory HL. A sufficient number of patients will be enrolled in the phase 2 portion of the study to have at least 15 evaluable patients with sALCL (including patients treated at the RP2D during phase 1), of whom at least 10 patients are in first relapse, and at least 15 evaluable patients with HL (including patients treated at RP2D during phase 1).

Brentuximab vedotin will be administered by IV infusion once every 21 days. Each 21-day treatment cycle is composed of 1 day of study drug treatment, followed by a monitoring period of 20 days. The starting dose in phase 1 will be 1.4 mg/kg, and escalation will proceed using a traditional 3 + 3 design to a maximum dose of 1.8 mg/kg.

Overall response will be evaluated beginning after 2 cycles of therapy. Objective response over the course of the study will be assessed by an IRF according to the IWG Revised Response Criteria for Malignant Lymphoma.[(1)] Patients, including those who achieve a CR, a PR, or stable disease (SD), may receive brentuximab vedotin for up to 16 cycles. Treatment with brentuximab vedotin beyond 16 cycles may be permitted at the joint discretion of the sponsor and the investigator for those patients experiencing continued clinical benefit. Following administration of the final dose of brentuximab vedotin, patients will be monitored for adverse events for a minimum of 30 days. Patients will be followed for PFS and OS every 12 weeks for 12 months after the EOT visit. Thereafter, assessment for OS will continue every 6 months until the sooner of death or study closure or a maximum of 2 years after enrollment of the last patient. Patients who remain on treatment after Cycle 16 will be followed according to the above schedule or until study closure.

Study drug will be discontinued due to occurrence of unacceptable AE, progressive disease, patient withdrawal, or study termination. Patients may discontinue therapy at any time. Additionally, those patients who experience a CR and are candidates for hematopoietic stem

cell transplantation must discontinue brentuximab vedotin prior to chemotherapy and transplant; these patients will be followed for survival analyses until study closure.

AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of brentuximab vedotin.

Serial blood samples for determination of the plasma concentration of brentuximab vedotin, total therapeutic antibody, and MMAE will be obtained during Cycle 1 and subsequent cycles at prespecified time points as described in the Schedule of Events (SOE) and in Section 7.4.14.

Radiological evaluations, (CT scan or magnetic resonance imaging [MRI], and PET as clinically indicated), will be employed to assess the status of the patient's underlying disease. An evaluation of disease response will be assessed by an IRF according to the IWG Revised Response Criteria for Malignant Lymphoma[1] evaluated at Cycles 2, 4, 7, 10, 13, and 16 and then at the end of treatment. The scan frequency for patients who receive treatment past Cycle 16 is outlined in the Schedule of Events. Additional evaluations may be necessary when clinically indicated.

4.2 Number of Patients

Approximately 42 evaluable patients will be enrolled in this study from approximately 25 study centers globally. At least 12 evaluable patients are planned for the phase 1 portion of the study, and a sufficient number of patients will be enrolled in phase 2 to have at least 30 evaluable patients (15 with sALCL and 15 with HL) at RP2D, including the patients from the phase 1 portion of the study who receive the RP2D. A patient is considered enrolled in the study at the time of first dose of study drug.

Patients who are withdrawn from treatment during Cycle 1 for reasons other than dose limiting toxicities (DLTs) will be replaced; additional patients may be enrolled to ensure up to 12 evaluable patients in phase 1.

4.3 Duration of Study

Patients who achieve a CR, a PR, or SD may receive brentuximab vedotin for up to 16 cycles, until they experience disease progression. Extended brentuximab vedotin therapy, beyond 16 cycles, may be permitted at the joint discretion of the sponsor and investigator for those patients experiencing continued clinical benefit.

Patients will be followed for safety for a minimum of 30 days after the last dose of brentuximab vedotin, to permit the detection of any delayed treatment-related AEs. Patients will be followed for PFS and OS every 12 weeks for 12 months after the EOT visit. Thereafter, assessment for OS will continue every 6 months until the sooner of death or study closure or a maximum of 2 years after enrollment of the last patient.

The final analyses for the clinical study report will be conducted after all patients enrolled in the study have had the opportunity to complete 16 cycles of treatment with brentuximab vedotin.

It is anticipated that this study will last for approximately 5 years.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria for study enrollment:

1. Male or female patients aged 2 to <18 years (5 to <18 years for patients with HL).

2. Have a diagnosis of systemic anaplastic large-cell lymphoma, or Hodgkin lymphoma for which standard, curative, life-prolonging, or palliative treatment does not exist or is no longer effective. (Patients diagnosed with any relapsed or refractory CD30+ hematological malignancy [eg, primary mediastinal B-cell lymphoma] may be included in phase 1 of the study.)

3. Patients with sALCL must have documented anaplastic lymphoma kinase (ALK) status.

4. Patients with HL must be in their second or later relapse or have failed systemic chemotherapy either as induction therapy for advanced stage disease or salvage therapy, and be ineligible for, refused, or previously received a stem cell transplant.

5. Patients with relapsed or refractory sALCL must be beyond first remission or refractory to front-line chemotherapy.

6. Performance score ≥60 from Lansky Play Performance Scale if ≤16 years

7. Female patients who:

   - Are surgically sterile, OR

   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, or

   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

8. Male patients, even if surgically sterilized (ie, status postvasectomy), who:

   - Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or

   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

9. Voluntary written consent (and institution-specific assent as appropriate based upon patient comprehension) must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent/assent may be withdrawn by the patient or patient guardian at any time without prejudice to future medical care.

10. Suitable venous access for the study-required procedures.

11. Clinical laboratory values as specified below within 4 days before the first dose of study drug:

    - Absolute neutrophil count greater than or equal to 1,500/μL.

    - Platelet count greater than or equal to 75,000/μL.

- Serum bilirubin level less than or equal to 1.5 × upper limits of normal (ULN) or less than or equal to 3 × ULN for patients with an indirect hyperbilirubinemia due to Gilbert's disease.

- Serum creatinine less than or equal to 1.5 × ULN.

- Alanine aminotransferase (ALT or SGPT) and aspartate aminotransferase (AST or SGOT) less than or equal to 2.5 × ULN. AST and ALT levels may be elevated up to 5 × ULN if their elevation can be reasonably ascribed to the presence of metastatic disease in the liver.

12. Patients must have a radiographically or clinically evaluable tumor per the IWG criteria.[1]

5.2 Exclusion Criteria

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study. Patients meeting any of the following exclusion criteria are not to be enrolled in the study. If a patient is positive for ANY of the exclusion criteria, the patient will not be eligible for the study.

1. Current diagnosis of primary cutaneous ALCL (those with sALCL are eligible).

2. Received an allogeneic stem cell transplant <3 months prior to first dose of study medication, or presence of polymerase chain reaction (PCR)-detectable CMV in any post-allogeneic transplant patient. (Prior PCR positivity that was successfully treated is acceptable provided the baseline PCR result is negative prior to first dose of study drug.)

3. Receiving immunosuppressive therapy.

4. Receiving systemic therapy for chronic graft-versus-host disease (topical therapy is allowed).

5. Previous treatment with any anti-CD30 antibody.

6. Therapeutic monoclonal antibody use within the longer of 6 weeks or 5 plasma half-lives.

7. Symptomatic cardiac disease including ventricular dysfunction, coronary artery disease, or arrhythmias, if this would, in the opinion of the investigator or project clinician, interfere with assessment of efficacy or safety of the drug.

8. History of another primary malignancy not in remission for at least 3 years. (The following are exempt from the 3-year limit: nonmelanoma skin cancer and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear.)

9. Known active cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML) or any history of PML.

10. History of cirrhosis.

11. Active systemic viral, bacterial, or fungal infection requiring antimicrobial, antiviral therapy or antifungal therapy within 2 weeks prior to first dose of study drug (routine antimicrobial prophylaxis is acceptable).

12. Concurrent therapy with other anti-neoplastic or experimental agents.

13. Systemic corticosteroid therapy <7 days prior to first dose of study medication.

14. Any serious underlying medical condition that, in the opinion of the investigator or project clinician, would impair the patient's ability to receive or tolerate the planned treatment.

15. Known hypersensitivity to recombinant proteins, murine proteins, or any excipient contained in the drug formulation.

16. Received nitrogen mustard agents, melphalan, or BCNU therapy within 6 weeks prior to first study dose.

17. Prior autologous hematopoietic stem cell infusion <4 weeks prior to first study dose.

18. Grade 2 or greater unresolved toxicity from prior antineoplastic therapy.

19. Received any strong or listed moderate inhibitor of CYP3A4 <2 weeks prior to first study dose. (Please refer to the Study Manual for an example list of prohibited CYP3A4 inhibitors.)

20. Grade 2 or greater peripheral neuropathy.

21. Female patients who are both lactating and breastfeeding, or have a positive serum or urine pregnancy test during the screening period or a positive serum or urine pregnancy test on Day 1 before the first dose of study drug.

22. Received local palliative radiation therapy <14 days prior to the first dose of study medication.

23. Received radiation therapy to more than 25% of the bone marrow-containing spaces <84 days prior to first dose of study medication.

6. STUDY DRUG

6.1 Study Drug Administration

Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Infusion-related reactions may occur during the infusion of brentuximab vedotin. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for 60 minutes after each infusion of brentuximab vedotin.

During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institutional standards. Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use.

Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent brentuximab infusions with premedication consisting of acetaminophen (650 mg orally) and diphenhydramine (25–50 mg orally or 10–25 mg IV) or according to institutional standards, administered 30 to 60 minutes prior to each 30-minute brentuximab vedotin infusion. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

If a Grade 3 or greater infusion-related reaction consistent with anaphylaxis occurs, immediately and permanently discontinue administration of brentuximab vedotin and administer appropriate medical therapy per institutional guidelines.

Brentuximab vedotin must not be administered as an IV push or bolus. Study treatment will be administered by outpatient IV infusion given over approximately 30 minutes on Day 1 of each 21-day cycle. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute infusion period. Study treatment will be administered through a dedicated IV line and cannot be mixed with other medications.

In the phase 1 portion of the study, the starting dose will be 1.4 mg/kg and escalation will proceed using a traditional 3 + 3 design to a maximum dose of 1.8 mg/kg. Dosing is based on patients' weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥ 10% change in weight from the most recent dose calculation. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

The dose for the phase 2 portion of the study will be the MTD and/or RP2D, as determined during phase 1. Each 21-day treatment cycle is composed of 1 day of study drug treatment, followed by a monitoring period of 20 days.

Patients who achieve a CR, a PR, or SD, may receive study drug for up to 16 cycles, until they experience disease progression or have unacceptable toxicity. Additional treatment cycles, beyond 16 cycles, may be permitted at the joint discretion of the sponsor and investigator for those patients experiencing continued clinical benefit. Patients eligible for alloSCT must discontinue brentuximab vedotin prior to initiating a conditioning regimen; these patients will be followed for survival analyses until study closure. Following administration of the final dose of brentuximab vedotin, patients will be followed for safety for a minimum of 30 days.

6.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, effective 14 June 2010.[64] These criteria are provided in the Study Manual. DLT will be defined as discussed in Sections 6.2.2 and 6.2.3.

6.2.1 Toxicity

The investigators and project clinician will discuss and document the overall toxicity profile in detail before deciding whether to initiate cohort expansion, dose escalation, dose modification, and/or future prophylaxis with colony-stimulating factors (CSFs).

6.2.2 Nonhematologic Toxicity

For nonhematologic toxicities, DLT will be defined as any CTCAE v. 4.03 Grade 3 or greater toxicity except for:

- Grade 3 fatigue
- Grade 3 or 4 nausea and vomiting lasting less than 24 hours
- Grade 3 nonhematologic laboratory abnormalities that resolve to Grade 1 or baseline (if the patient entered the study with existing toxicity) within 14 days

6.2.3 Hematologic Toxicity

DLT for hematologic toxicity will be defined as:

- Grade 4 neutropenia lasting longer than 7 days
- Grade 3 febrile neutropenia requiring antibiotics
- Grade 4 febrile neutropenia
- Grade 4 platelet count (<25,000/μL) at any time

6.2.4 Phase 1: Dose Modification for an Individual Patient Who Experiences DLT

Any patient experiencing DLT lasting 14 days or longer will be discontinued from the study. Dose modification for further treatments with brentuximab vedotin will only occur for individual patients who experience a protocol defined DLT of less than 14 days' duration, yet whom the site investigator and project clinician believe can safely receive additional treatment. Subsequent doses should be decreased to the previous dose level or to 0.9 mg/kg for patients in the 1.4-mg/kg cohort.

The DLT experienced by the patient must return to less than or equal to Grade 1 or baseline at the time of the next scheduled dose. If toxicity does not return to less than or equal to Grade 1 or baseline within 14 days, the patient should be taken off study; every effort should be made to ensure that early termination procedures are followed.

6.2.5 Phase 1: Dose Elimination/Holding/Reduction for Patients Who Have Not Experienced a DLT

A scheduled dose of brentuximab vedotin may be held up to 14 days in patients who have not experienced DLT, but have not yet recovered from an adverse event (AE) before the next scheduled dose administration. For patients with AEs that have returned to baseline or Grade 1 values, a held dose may be administered up to 14 days after the scheduled time of the dose. In view of the potential for myelosuppression with brentuximab vedotin, it is particularly important that patients are not dosed until any neutrophil toxicity has resolved to at least Grade 1. If the dose is eliminated, and/or the toxicities have not resolved within 14 days, the patient should be taken off study; every effort should be made to ensure that early termination procedures are followed.

6.2.6 Maximum Tolerated Dose or Recommended Phase 2 Dose

The pediatric MTD and/or RP2D will be the highest dose at which no more than 1 in 6 of the patients in the cohort experiences 1 or more DLTs in the first treatment cycle. The MTD and/or RP2D will be established without the use of colony stimulating factors (CSFs) in Cycle 1.

6.3 Dose Escalation Rules

The dose intervals will follow the 3 + 3 traditional escalation rules, starting with the treatment of 3 patients at the 1.4-mg/kg dose:

- If 0 of 3 patients experiences DLT, dose escalation will proceed to the 1.8-mg/kg dose at which 3 patients will be enrolled.
- If 1 of 3 patients experiences DLT, 3 additional patients will be enrolled at the 1.4-mg/kg dose level.
- If no more than 1 of 6 patients experiences DLT, escalation will continue to the 1.8-mg/kg dose level.
- If 0 or 1 patient experiences DLT, 3 additional patients will be enrolled at the 1.8 mg/kg dose level.
- If 2 or more patients in either dose level experience DLT, dosing will stop, and the previous dose level will be considered the MTD.

- If 2 or more DLTs are experienced at the 1.4-mg/kg dose, the dose will be reduced to 0.9 mg/kg.

- If 2 or more DLTs are experienced at the 1.8-mg/kg dose, the previous dose level (1.4 mg) is considered the MTD and RP2D.

Figure 6-1 is a diagrammatical representation of these rules.

Figure 6-1 Dose Escalation Algorithm

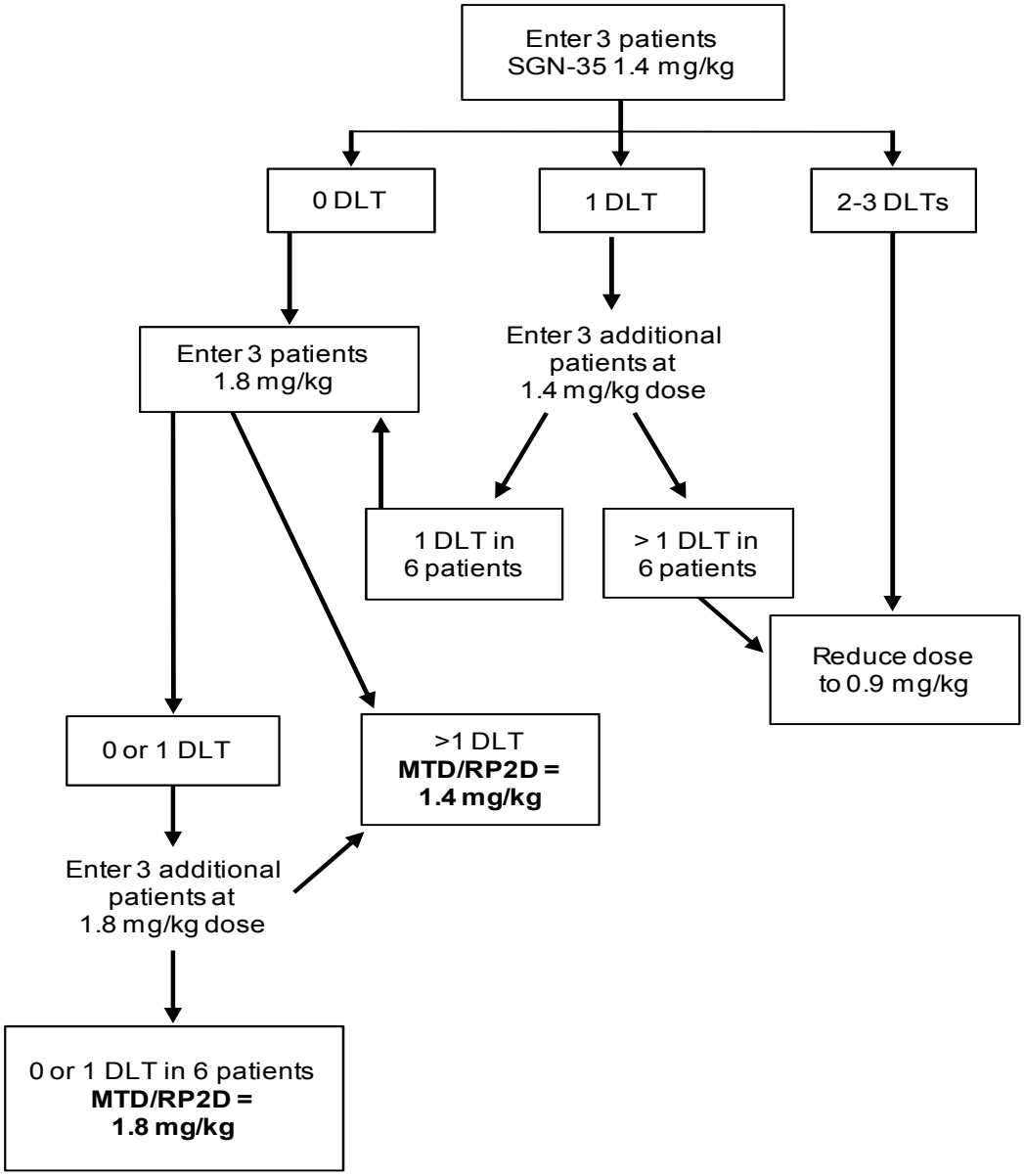


Table 6-1 Planned Dose Levels

Dose Level	Dose (mg/kg)
1	1.4
2	1.8

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of brentuximab vedotin.

The starting dose of brentuximab vedotin will be approximately 80% of the adult MTD, equal to 1.4 mg/kg, given on Day 1 of a 21-day cycle. Patients not receiving all doses of brentuximab vedotin in Cycle 1 for reasons other than DLTs, will be replaced within the cohort; additional patients may be enrolled to ensure up to 12 evaluable patients in phase 1.

6.4 Phase 2 Dose-Modification Guidelines

6.4.1 Criteria for Dose Modification*

The start of the next cycle may be delayed for up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle. The brentuximab vedotin dose should be reduced by at least 1 dose level (or to 0.9 mg/kg if the patient is receiving the 1.4-mg/kg dose) if the patient has any of the following:

- Brentuximab vedotin-related toxicity that results in a delay of more than 14 days in the start of a subsequent cycle of treatment because of lack of recovery to the specified re-treatment criteria
- Grade 4 thrombocytopenia (platelet count <25,000/µL) lasting more than 7 consecutive days.
- Grade 3 or greater nonhematologic toxicity attributed to brentuximab vedotin except for the following, which do not require dose reduction:
    - Grade 3 or greater nausea and/or emesis in the absence of optimal anti-emetic prophylaxis (Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs both a 5-HT_3 antagonist and a corticosteroid given in standard doses and according to standard schedules.)

- Grade 3 or greater diarrhea that occurs in the absence of optimal supportive therapy
- Grade 3 fatigue

Brentuximab vedotin-related neuropathy should be managed with a combination of dose delay and reduction to 1.2 mg/kg (or to 0.9 mg/kg if the patient is receiving the 1.4-mg/kg dose). For new or worsening Grade 2 or 3 neuropathy, dosing should be held for up to 21 days until neuropathy improves to ≤Grade 1 and then restarted at 1.2 mg/kg (or to 0.9 mg/kg if the patient is receiving the 1.4-mg/kg dose). For Grade 4 peripheral neuropathy, brentuximab vedotin should be discontinued.

When a dose reduction of brentuximab vedotin is required, no re-escalation of dose will be permitted.*

6.4.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with brentuximab vedotin will use a cycle length of 21 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥1,000/μL
- Platelet count must be ≥75,000/μL
- For therapy to resume, toxicity considered to be related to treatment with brentuximab vedotin must have resolved to ≤Grade 1, to the patient's baseline values, or to a level considered acceptable by the physician (eg, hypophosphatemia that can be managed by oral replacement).

For the phase 1 portion of the study, if the patient fails to meet the previously cited criteria for retreatment, initiation of the next cycle of treatment may be delayed for 14 days. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. Should the start of the next cycle during phase 1 need to be delayed for more than 14 days because of incomplete recovery from treatment-related toxicity, this will be considered a DLT and the patient should be discontinued from study. If a patient recovered from a DLT in less than 14 days, the patient may receive additional

* The phase 2 dose modification guidelines included in Section 6.4 will be applicable to patients who have received the RP2D in phase 1 of the study.

treatment with brentuximab vedotin; the dose will be reduced by at least 1 dose level (or to 0.9 mg/kg for patients receiving the 1.4-mg/kg dose) when treatment resumes.

6.4.3 Criteria for Discontinuation of Brentuximab vedotin

Study drug must be discontinued if a patient experiences progressive disease or an unacceptable study drug-related toxicity. Patients may discontinue therapy at any time. Additionally, those patients who experience a CR and are candidates for allogeneic stem cell transplantation must discontinue brentuximab vedotin prior to chemotherapy and transplant; these patients will be followed for overall survival until study closure.

Grade 4 nonhematologic toxicities will in general require that treatment with brentuximab vedotin be permanently discontinued. If, in the opinion of the investigator and the project clinician, it is in the patient's best interest to continue treatment with brentuximab vedotin, then the dose of brentuximab vedotin should be reduced by at least 1 dose level (or to 0.9 mg/kg if the patient is receiving the 1.4-mg/kg dose) after recovery of the toxicity or toxicities in question to Grade 1 or to baseline values.

A patient's treatment with study drug may also be discontinued for any of the following reasons:

- Patient withdrawal.
- Stable disease or better and completed 16 treatment cycles (brentuximab vedotin).
- The investigator or patient deems it in the patient's best interest to discontinue, including patients who experience a CR and are candidates for hematopoietic stem cell transplantation. The reason justifying study treatment withdrawal must be documented in the CRF.

Patients will attend the end-of treatment-visit 30 days (±7 days) after receiving their last dose of study drug.

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

- Death
- Patient withdraws consent for further follow-up

- Lost to follow-up

- Study termination by Millennium (If the sponsor and/or the investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted.)

Patients who discontinue from study treatment will remain on study and followed for a minimum of 30 days for safety unless they withdraw consent. All patients who receive at least 1 dose of study drug will be followed PFS and OS every 12 weeks for 12 months after the EOT visit. Thereafter, assessment for OS will continue every 6 months until the sooner of death or study closure. Patients who remain on treatment after Cycle 16 will be followed according to the above schedule or until study closure.

6.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Radiation therapy for disease under study

- Any investigational agent other than brentuximab vedotin, including agents that are commercially available for indications other than sALCL or HL that are under investigation for the treatment of sALCL or HL

- Any anticancer treatment with activity against sALCL and HL other than brentuximab vedotin

- Myeloid growth factors (eg, G-CSF, GM-CSF) (Cycle 1 only)

- Any strong and listed moderate CYP3A4 inhibitors (prohibited CYP3A4 inhibitors are listed in the Study Manual).

In addition, the concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity.

6.6 Permitted Concomitant Medications and Procedures

The use of intermittent corticosteroid treatment to manage hypersensitivity reactions is allowed. The use of platelets and/or red blood cell supportive growth factors or transfusions when applicable is allowed. Colony-stimulating factors may not be used for any patient in a prophylactic setting during the first treatment cycle but can be administered thereafter as per

ASCO guidelines or local institutional practice if the patient has experienced complicated and/or prolonged neutropenia. However, any patient who experiences a hematological DLT may not continue brentuximab vedotin treatment with concomitant CSFs, and CSFs may not be used to meet eligibility criteria.

6.7 Precautions and Restrictions

It is not known what effects brentuximab vedotin has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified.

Female patients of reproductive age must meet 1 of the following:

- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the ICF through 6 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterile, must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.).

6.8 Management of Clinical Events

6.8.1 Management of Peripheral Neuropathy

Adverse events of peripheral neuropathy will be monitored closely throughout the study. These events may include, but are not limited to, peripheral sensory neuropathy, peripheral motor neuropathy, pareaesthesia, hypoaesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy. Such events, regardless of seriousness, will be followed for all changes in severity until resolution to baseline or study closure, whichever occurs first, and recorded in the eCRF. Events that are greater than Grade 1 in severity will result in dose delay, reduction, or discontinuation. Guidelines for brentuximab vedotin dose modification in the event of peripheral neuropathy are shown in Section 6.4.

6.8.2 Management of Progressive Multifocal Leukoencenphalopathy

Signs and symptoms of progressive multifocal leukoencephalopathy (PML) may include altered mental status; motor deficits, such as hemiparesis or ataxia; visual disturbances; or higher cortical dysfunction, such as dysphasia or agnosia. See the IB for further details.

If PML is suspected, hold further brentuximab vedotin dosing and undertake a diagnostic work-up that may include (but is not limited to):

- Neurologic examinations, as warranted
- Brain MRI: features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically nonenhancing and do not have mass effect
- Polymerase chain reaction analysis: John Cunningham virus (JCV) DNA detectable in cerebrospinal fluid or there is evidence of JCV in a brain biopsy
- Neurology consultation

If PML is confirmed, treatment with brentuximab vedotin should be discontinued permanently.

6.8.3 Nausea and/or Vomiting

Although this study will not initially employ prophylactic anti-emetics, there is no prohibition against their use in the management of a patient who develops nausea and/or vomiting. As in the prophylactic setting, 5-HT_3 receptor antagonists should be tried first.

6.8.4 Diarrhea

Prophylactic antidiarrheals (eg, loperamide) will not be used in this protocol; however, patients will be instructed to take antidiarrheal medications at physician's discretion until they are diarrhea-free for at least 12 hours. Fluid intake should be maintained to avoid dehydration.

6.9 Blinding and Unblinding

This is an open-label study.

6.10 Description of Investigational Agents

Brentuximab vedotin for Injection is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. Brentuximab vedotin for Injection is supplied in single-use, Type 1 borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. The lyophilized product, after reconstitution with 10.5 mL sterile Water for Injection, United States Pharmacopeia (USP), yields 11 mL of brentuximab vedotin solution (5 mg/mL).

6.11 Preparation, Reconstitution, and Dispensation

Brentuximab vedotin is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling brentuximab vedotin. Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

Study treatment vials are single-use containers. Any partially used vials or diluted dosing solutions are to be discarded using appropriate institutional drug disposal procedures.

Study treatment must be reconstituted with the appropriate amount of Sterile Water for Injection, USP (see Pharmacy Manual for details). GENTLY swirl the vial until the contents are completely dissolved. **The vial must not be shaken or vigorously swirled**; excess agitation may cause aggregate formation. Visually inspect the reconstituted drug product for any particulate matter and discoloration.

The appropriate amount of reconstituted study treatment will be withdrawn from the vial(s) and diluted in a 50- to 100-mL infusion bag containing 0.9% Sodium Chloride Injection, USP.

There are no known incompatibilities between study treatment and polyvinyl chloride bags. The bag should be gently inverted to mix the solution. **The bag must not be shaken**; excess agitation may cause aggregate formation. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

The formulation contains no preservative and is intended for single use only; infusion solutions should be prepared and transferred using aseptic technique in a biosafety hood.

Refer to the Directions for Use/ Pharmacy Manual for more specific instructions on reconstitution and use.

6.12 Packaging and Labeling

Brentuximab vedotin vials will be packaged as single-use cartons. Each carton will contain 1 vial of the investigational product, and the vial and carton will be labeled to meet country-specific regulatory requirements.

6.13 Storage, Handling, and Accountability

Vials of brentuximab vedotin for Injection are to be stored at 2ºC to 8ºC in a secure location (eg, locked room) accessible only to the pharmacist, the investigator, or a duly designated person.

Study treatment does not contain preservatives; therefore, opened and reconstituted vials of study treatment must be used on the same day when stored under refrigeration at 2 ^{o}C to 8^{o}C. Reconstituted study treatment should not be stored at room temperature. It is recommended that study treatment vials and solutions be protected from direct sunlight until the time of use. **Reconstituted vials must not be shaken**.

Drug accountability instructions are provided in the Pharmacy Manual.

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

7.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, and the ICON contract research organization study team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

Patients will be enrolled according to the standard 3 + 3 dose escalation scheme in the phase 1 portion of the study. Two ascending dose cohorts are planned (3 to 6 patients per cohort).

Once the MTD and/or RP2D has been reached, patients will be enrolled by diagnosis into two phase 2 study arms by diagnosis: relapsed or refractory sALCL or relapsed or refractory HL.

7.4 Study Procedures

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 Informed Consent

Each patient (or patient's legal guardian) must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 7.4.8.

7.4.4 Physical Examination

A complete physical examination—including assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system—will be completed at the times specified in the Schedule of Events.

7.4.5 Patient Height and Weight

Height and weight will be obtained during screening (within 14 days before the first dose of brentuximab vedotin) and on Day 1 of each 21-day cycle.

7.4.6 Vital Signs

Vital signs measurements include supine (after 3-5 minutes in this position) and standing (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral temperature.

7.4.7 Pregnancy Test

Patients of childbearing potential will complete a serum or urine pregnancy test during screening, prior to dosing on Day 1 during Cycles 1 through 16, and at EOT. If the screening test was performed within 4 days before the Cycle 1, Day 1 dose, it need not be repeated on Cycle 1, Day 1. A serum or urine pregnancy test will be performed prior to dosing on Day 1 of each subsequent cycle. The results must be negative before brentuximab vedotin is administered. During Cycle 17 and beyond, a pregnancy test should be performed per institutional guidelines; any samples collected during Cycle 17 and beyond should not be sent to the central laboratory, and data should not be captured in the eCRF. Additional pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

7.4.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the electronic case report form (eCRF) from signing of informed consent form through 30 days after the last dose of brentuximab vedotin. See Sections 6.5 and 6.6 for a list of medications and therapies that are prohibited or allowed during the study.

7.4.9 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 9 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs. Changes in the severity of events relating to peripheral neuropathy will be recorded as described in Section 9.3.

7.4.10 Enrollment

A patient is considered to be enrolled in the study at the time of first dose of study drug.

Procedures for completion of the enrollment information are described in the Study Manual.

7.4.11 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be obtained at screening and at Cycle 1, Day 1 (baseline), and at EOT. If the screening ECG was obtained within the 4 days prior to the Cycle 1, Day 1 dose of study drug, a repeat ECG at Cycle 1, Day 1 is not necessary. Additional ECGs may be obtained if clinically indicated. ECG assessments are to be performed with patient supine and rested for 5 minutes and before any closely timed PK blood collection.

7.4.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed centrally. Decisions regarding eligibility and study drug dosing may be made by using local laboratory results. If local clinical laboratory values are used for either eligibility or study dosing decisions, the local laboratory results do not replace central laboratory testing, and samples for central laboratory confirmation must be collected as specified in the Schedule of Events.

During Cycle 17 and beyond, hematology and serum chemistry tests should be performed per institutional guidelines at the local laboratory; samples should not be sent to the central

laboratory, and data should not be captured in the eCRF, unless the laboratory result is assessed to contribute to an AE.

Handling and shipment of clinical laboratory samples will be outlined in the Study Manual.

Clinical laboratory evaluations will be performed as outlined:

Clinical Chemistry and Hematology

Blood samples for analysis of the following clinical chemistry and hematological parameters will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Total WBC count
- Differential WBC count

Machine counts are acceptable.

Serum Chemistry

- Blood urea nitrogen
- Creatinine
- Urate
- Bilirubin (total, direct, indirect)
- Lactate dehydrogenase
- Gamma glutamyl transferase
- Phosphorus
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Fasting glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide
- Magnesium

7.4.13 Disease Assessment

7.4.13.1 Development Assessment and Tanner Scale

Development assessment and Tanner Scale are to be performed as specified in the Schedule of Events. The development assessment will include weight-for-age and stature-for-age percentiles; see Section 14.3 for Tanner Scale information.

7.4.13.2 Imaging

Patients will undergo CT with contrast as appropriate, MRI, and PET to monitor and assess disease progression. CT scans will be used to evaluate the chest only; MRI will be used to evaluate the neck, abdomen, and pelvis. PET, CT, and MRI scans will be performed as specified in the Schedule of Events. Objective response over the course of the study will be assessed by an IRF according to the IWG Revised Response Criteria for Malignant Lymphoma.[1] Contrast CT scans of the chest will be obtained at screening. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation using an imaging modality consistent with that used at screening. Objective assessments will be performed at each time point as described in the Schedule of Events. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents.

7.4.13.3 B Symptom Assessments

B symptom assessments, including fever, night sweats, and weight loss, will be evaluated at the time points indicated in the Schedule of Events.

7.4.14 Pharmacokinetic Measurements

Blood samples for the determination of serum brentuximab vedotin concentrations will be collected at the following time points:

- **All Cycles:** Day 1: within 4 hours before the start of the brentuximab vedotin infusion and 5 minutes (±1 minute) after the end of the brentuximab vedotin infusion
- **Cycles 1 and 8:**
    - Day 2: 24 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion
    - Day 3: 48 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion
    - Day 5: 96 hours (±24 hours) from the start of the Day 1 brentuximab vedotin infusion
    - Day 14: 312 hours (±48 hours) from the start of the Day 1 brentuximab vedotin infusion

- **Cycle 2:**
    - Day 2 (phase 1 only): 24 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion
    - Day 3: 48 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion
    - Day 5: 96 hours (±24 hours) from the start of the Day 1 brentuximab vedotin infusion.

Serum concentrations of brentuximab vedotin, total therapeutic antibody, and MMAE will be determined using validated assays.

Details regarding the handling, processing, and shipping of PK samples can be found in the Study Manual.

7.4.15 Pharmacodynamic Measurements

7.4.15.1 CCI

CCI

7.4.16 Immunogenicity

Blood samples will be collected as specified in the Schedule of Events to evaluate serum ATAs and neutralizing ATAs. On the days of dose administration, the blood samples for ATA and neutralizing ATA assessment must be collected before the brentuximab vedotin

dose is administered. Neutralizing ATA assessment will be performed for ATA-positive samples only. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

7.4.17 Tumor Specimen Measurements

This sample will be used to confirm CD30 expression by central laboratory review. Refer to the Schedule of Events for details regarding tumor specimen collection.

7.5 Completion of Treatment

Patients will be considered to have completed study treatment if they complete 16 cycles of treatment with brentuximab vedotin.

7.6 Completion of Study

Patients will be considered to have completed the study if they complete 16 cycles of treatment with brentuximab vedotin and complete 30 days of safety follow-up.

7.7 Discontinuation of Treatment With Study Drug, and Patient Replacement

Study drug must be permanently discontinued for patients meeting any of the following criteria:

- Completed 16 cycles of brentuximab vedotin therapy (unless extended treatment is warranted due to clinical benefit).
- The investigator or patient, or patient's legal guardian deems it is in the patient's best interest to discontinue. (The reason justifying study treatment withdrawal must be documented in the eCRF.)
- Progressive disease.

Treatment with study drug may also be discontinued for any of the following reasons:

- Adverse event
- Protocol violation
- Initiation of hematopoietic stem cell or bone marrow transplant
- Study terminated by sponsor

- Withdrawal of consent by patient or patient's guardian
- Lost to follow-up
- Other.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced; additional patients may be enrolled to ensure at least 12 evaluable patients in phase 1.

7.8 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal of consent by patient or patient guardian
- Death
- Other

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

7.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

7.10 Posttreatment Follow-up Assessments

Patients who stop treatment for any reason other than progressive disease (PD) or the start of subsequent anticancer therapy will continue to have follow-up visits to determine time to

progression, duration of response, event-free survival, progression-free survival, and overall survival. The follow-up visits for PFS assessment should be conducted at the site every 12 weeks for 12 months from the EOT visit until the occurrence of PD, the patient withdraws consent for further follow-up, or the start of subsequent anticancer therapy.

After the occurrence of PD or the start of subsequent anticancer therapy, patients will continue to have OS follow-up visits every 6 months until the sooner of death or study closure or a maximum of 2 years after enrollment of the last patient. Patients who remain on treatment after Cycle 16 will be followed according to the above schedule or until study closure.

Survivor information may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieved from online or other databases (eg, social security indexes). In addition, information pertaining to the start of another anticancer therapy will be collected.

See the Schedule of Events for appropriate assessments during follow-up.

NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 9 for details regarding definitions, documentation, and reporting of SAEs.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed. A formal statistical analysis plan will be developed and finalized before database lock.

8.1.1 Determination of Sample Size

Approximately 42 evaluable patients will be enrolled in this study. In the phase 1 portion of the study, at least 12 patients with relapsed or refractory CD30+ malignancies will be enrolled in 2 planned dose cohorts (3-6 patients per cohort), according to the standard 3 + 3 dose escalation scheme.

Once the MTD and/or RP2D have been reached, patients will be enrolled by diagnosis into two phase 2 study arms: relapsed or refractory sALCL or relapsed or refractory HL. A sufficient number of patients will be enrolled in the phase 2 portion of the study to have at least 15 evaluable patients with sALCL (including patients treated at the RP2D during phase 1), of whom at least 10 patients are in first relapse, and at least 15 evaluable patients with HL (including patients treated at the RP2D during phase 1).

The sample size is not based on statistical consideration. Based on the exact binomial confidence interval calculation, 10 responses observed out of the 15 evaluable patients (overall response rate of 66.7%) will provide 95% confidence interval (38%, 88%).

8.1.2 Randomization and Stratification

In phase 1, patients will be enrolled in successive dose cohorts. No randomization is planned for either phase 1 or phase 2 of this study.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: Patients who receive at least 1 dose of study drug will be used for all safety analyses, as well as efficacy analyses.
- PK population: Patients with sufficient dosing and PK data to reliably estimate PK parameters will be used for PK analyses.
- Immune reconstitution population: Patients with sufficient dosing and sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation will be included in the immune reconstitution population.
- Response-evaluable population: Patients who receive at least 1 dose of study drug, have measurable disease at baseline, and 1 postbaseline disease assessment will be used for analyses of disease response and duration of response.
- The DLT-evaluable population: Patients who either experience DLT during phase 1 or receive all scheduled doses and complete all study procedures in phase 1 without DLT.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed. The relevance of missing sample data will be assessed.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized, including sex, age, race, weight, height, body surface area, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

The best overall response rate, CR rate, PR rate, time to progression, time to response, and duration of response will be analyzed. The 2-sided 95% exact binomial confidence interval on the percentage of patients falling into each response category will be established. Duration of response (DOR), time to response, time to progression (TTP), EFS, PFS, and OS will be analyzed using the Kaplan-Meier method. The 25th, 50th (median), and 75th percentiles (if estimable) with associated 2-sided 95% confidence interval will be provided.

8.1.7 Pharmacokinetics/Pharmacodynamics

8.1.7.1 Pharmacokinetic and Immunogenicity Analysis

Descriptive statistics (eg, number of patients, arithmetic mean, geometric mean, standard deviation, median, percentage of coefficient of variation, minimum, and maximum) will be used to summarize PK parameters of brentuximab vedotin, total therapeutic antibody, and MMAE for each cohort. Immunogenicity parameters (ATA titer and neutralizing ATA titer) will be summarized using descriptive statistics. Individual and mean plasma concentration data will be plotted over time. Descriptive statistics will be presented for serum PK parameters.

8.1.7.2 CCI

CCI

CCI

[redacted]

8.1.8 Safety Analysis

A listing of DLTs for each dose level will be provided. Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, neurotoxicity assessment, ECGs, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated. AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs
- Study drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher study drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (ie, those events reported for ≥10% of all patients)
- SAEs

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided. The individual patient's information on the DLTs will also be presented in a listing.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the brentuximab vedotin safety profile.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of brentuximab vedotin.

8.1.9 Electrocardiogram Analysis

ECG intervals (QT and corrected QT intervals [QTcF], PR, QRS, and ventricular rate) will be summarized at each scheduled time point, along with mean change from baseline to posttreatment time point.

8.1.10 Interim Analysis

No interim analysis is planned for this study.

8.2 Pharmacokinetic Modeling

Pharmacokinetic modeling will be performed to obtain pharmacokinetic parameters and intrinsic covariates of the pharmacokinetics of brentuximab vedotin and MMAE.

9. ADVERSE EVENTS

9.1 Definitions

9.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

9.1.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

9.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the following paragraph on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive

treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE version 4.03, effective 14 June 2010.[64] Clarification should be made between an SAE and an AE that is considered to be severe (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described previously, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/µL to less than 2000/µL is considered Grade 3 (severe) but may not be considered to be an SAE. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

9.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 9.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 9.1) must be reported (see Section 9.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE version 4.03, effective 14 June 2010.[64] The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

9.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs. All events relating to peripheral neuropathy regardless of seriousness will be followed for all changes in severity until resolution to baseline or study closure, whichever occurs first, and recorded in the eCRF.

- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the ICF up to first dose of study drug, but will not be recorded in the eCRF.

- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a patient becomes pregnant or suspects that she is pregnant while participating in this study, the investigator must be informed immediately and the patient must permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 9.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 9.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10. ADMINISTRATIVE REQUIREMENTS

10.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the Investigator Brochure.

10.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study

patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

The study monitor will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

10.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) or other electronic media will be placed in the investigator's study file.

10.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent

regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

10.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

10.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

10.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

10.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

10.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

10.11 Product Complaints and Medication Errors

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact PPD PPD (see the next paragraph) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact PPD (see below) and report the event.

For Product Complaints or Medication Errors,
call PPD [redacted]

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to the Millennium Department of Pharmacovigilance or designee (refer to Section 9.2).

10.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the

event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

10.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

11. USE OF INFORMATION

All information regarding brentuximab vedotin supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of brentuximab vedotin and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

12. INVESTIGATOR AGREEMENT

I have read Protocol C25002 Amendment 4: A Phase 1/2 Study of brentuximab vedotin (SGN-35) in Pediatric Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

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14. APPENDICES

14.1 Lansky Play-Performance Scale

The Play-Performance Scale for children is designed to provide a standardized measure of the performance status of the child with cancer. Appropriate for use with children aged 1 to 16. Have parent select description which best describes child's play during the past week, averaging out good days and bad days.

100 - Fully active, normal.

90 - Minor restrictions in physically strenuous activity.

80 - Active, but tires more quickly.

70 - Both greater restriction of and less time spent in play activity.

60 - Up and around, but minimal active play; keeps busy with quieter activities.

50 - Gets dressed but lies around much of the day; no active play; able to participate in all quiet play and activities.

40 - Mostly in bed; participates in quiet activities.

30 - In bed; needs assistance even for quiet play.

20 - Often sleeping; play entirely limited to very passive activities.

10 - No play; does not get out of bed.

0 - Unresponsive.

14.2 Karnofsky Performance Scale

Karnofsky Performance Scale

100 - Normal; no complaints; no evidence of disease.

90 - Able to carry on normal activity; minor signs or symptoms of disease.

80 - Normal activity with effort; some signs or symptoms of disease.

70 - Cares for self; unable to carry on normal activity or to do active work.

60 - Requires occasional assistance, but is able to care for most of own needs.

50 - Requires considerable assistance and frequent medical care.

40 - Disabled; requires special care and assistance.

30 - Severely disabled; hospitalization is indicated although death is not imminent.

20 - Hospitalization necessary; very sick; active supportive treatment necessary.

10 - Moribund; fatal processes progressing rapidly.

0 - Dead.

14.3 Tanner Scale

Table 14-1 Criteria for Distinguishing Tanner Stages 1 to 5 During Pubertal Maturation

Stage	Breast	Pubic Hair
1 (prepubertal)	No palpable glandular tissue or pigmentation of areola; elevation of areola only	No pubic hair; short, fine vellus hair only
2	Glandular tissue palpable with elevation of breast and areola together as a small mound; areolar diameter increased	Sparse, long, pigmented terminal hair chiefly along the labia majora
3	Further enlargement without separation of breast and areola; although more darkly pigmented, areola still pale and immature; nipple generally at or above midplane of breast tissue when individual is seated upright	Dark, coarse, curly hair, extending sparsely over mons
4	Secondary mound of areola and papilla above breast	Adult-type hair, abundant but limited to mons and labia
5 (adult)	Recession of areola to contour of breast; development of Montgomery's glands and ducts on areola; further pigmentation of areola; nipple generally below midplane of breast tissue when individual is seated upright; maturation independent of breast size	Adult-type hair in quantity and distribution; spread to inner aspects of the thighs in most racial groups

Data from Ross GT: Disorders of the ovary and female reproductive tract. In Wilson JD, Foster DW (eds): Textbook of Endocrinology, 7th ed. Philadelphia, WB Saunders, 1985, p 206.

Table 14-2 Pubertal Stages in Boys

Stage	Pubic Hair	Genital
1	Absence of pubic hair	Childlike penis, testes, and scrotum (testes 2 mL)
2	Sparse, lightly pigmented hair mainly at the base of the penis	Scrotum enlarged with early rugation and pigmentation; testes begin to enlarge (3–5 mL)
3	Hair becomes coarse, darker, and more curled and more extensive	Penis has grown in length and diameter; testes now 8–10 mL; scrotum more rugated
4	Hair adult in quality, but distribution does not include medial aspect of thighs	Penis further enlarged with development of the glans; scrotum and testes (10–13 mL) further enlarged
5	Hair is adult and extends to thighs	Penis and scrotum fully adult; testes 15 mL and greater

Modified from Marshall WA, Tanner JM: Variation in pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–23.

14.4 Amendment 1 Rationale and Purposes

Rationale for Amendment 1

This amendment seeks to promote patient safety by reducing the opportunity for potential drug-drug interactions, using an objective definition of dose-limiting toxicity (DLT), and specifying administration equipment that ensures drug compatibility.

Purposes for Amendment 1

- Exclude those patients receiving strong inhibitors of CYP3A4 and institute a 2-week washout period prior to first brentuximab vedotin dose for those patients who have received strong inhibitors of CYP3A4
- Prohibit concomitant administration of strong inhibitors of CYP3A4 during the brentuximab vedotin treatment period
- Remove investigator attributions from the definitions of dose-limiting toxicities (DLTs)
- Prohibit the use of polyethylene IV bags for the administration of brentuximab vedotin in this trial
- Correct typographical errors, punctuation, grammar, and formatting

14.5 Amendment 2 Rationale and Purposes (France-Specific Amendment)

Rationale for Amendment 2

One case of progressive multifocal leukoencephalopathy (PML) was reported in a 48-year-old male patient with Hodgkin lymphoma (HL) who developed progressive disease after undergoing an autologous bone marrow transplant. He subsequently received both local radiation therapy and 2 cycles of combination chemotherapy before receiving the first of 3 doses of brentuximab vedotin. Two months after his initial dose, he presented with focal neurologic symptoms and was later diagnosed with PML. As HL and immunosuppressive therapies are known risk factors for PML, it is unclear what role brentuximab vedotin played in the development of PML, although a contributory role cannot be excluded. Therefore, the protocol now excludes patients with signs or symptoms of PML and contains instructions for the suggested management of suspected PML that include immediate brentuximab vedotin discontinuation.

Purposes for Amendment 2

- Revise exclusion criteria to exclude patients with signs or symptoms of PML
- Add instructions for the management of suspected PML
- Add PML and John Cunningham virus (JCV) to the List of Abbreviations

14.6 Amendment 3 Rationale and Purposes

Rationale for Amendment 3

Events of progressive multifocal leukoencephalopathy (PML) have been reported in patients who received brentuximab vedotin. The protocol now excludes patients with signs or symptoms of PML and contains instructions for the suggested management of suspected PML that include brentuximab vedotin discontinuation.

Infusion-related reactions (IRRs) have been reported in previous studies with brentuximab vedotin. Information has been added on the management of infusion-related reactions, including instructions to immediately and permanently discontinue administration of brentuximab vedotin for Grade 3 or higher infusion-related reactions consistent with anaphylaxis.

Events of pulmonary toxicity were reported in a study with brentuximab vedotin given with bleomycin as part of a combination regimen. The protocol now includes information on the occurrence of pulmonary toxicity and specifies that the concomitant use of bleomycin with brentuximab vedotin is contraindicated.

Peripheral neuropathy has been a frequently reported adverse event in previous studies with brentuximab vedotin. Cumulative dosing with brentuximab vedotin has been associated with an increased incidence of peripheral neuropathy. The original protocol states that the brentuximab vedotin dose should be held in the case of new or worsening events of Grade 2 or 3 neuropathy. To ensure patient safety and conform to dosing guidelines, an exclusion criterion has been added for patients with Grade 2 or higher peripheral neuropathy at the time of screening.

Patients who are pregnant or both lactating and breastfeeding are not eligible for the study. This exclusion criterion was inadvertently omitted from the original protocol and has been added to this amendment.

A washout period of at least 14 days is required for patients who received local palliative radiation therapy; a washout period of at least 84 days is required for patients who receive radiation therapy to more than 25% of bone marrow-containing spaces. Exclusion criteria have been added to specify these restrictions on receiving radiation therapy prior to the first dose of study drug.

Planned imaging assessments have been revised in order to minimize radiation exposure in this pediatric population. Magnetic resonance imaging (MRI) will be performed for neck, abdomen, and pelvis evaluations; computed tomography (CT) scans will be used for chest evaluations only.

Patient enrollment was defined as at the time of informed consent in the original version of the protocol. To conform to Millennium protocol standards, the definition of enrollment has been changed to at the time of first dose of study drug.

The contact information for serious adverse events (SAEs) and events of pregnancy has been revised. Section 14.5 has been added and contains phone, fax, and e-mail contact information by country for reporting SAEs and events of pregnancy.

Purposes for Amendment 3

The purposes of this amendment are to:

- Add information on the occurrence and management of progressive multifocal leukoencephalopathy (PML).
- Add information on the occurrence and management of infusion-related reactions.
- Add information on the risk of pulmonary toxicity with brentuximab vedotin when given in combination with bleomycin.
- Add exclusion criterion for patients with signs or symptoms of PML.
- Add exclusion criterion for patients with Grade 2 or higher peripheral neuropathy.
- Add exclusion criterion for patients who are pregnant or both lactating and breastfeeding.
- Add exclusion criterion for patients who received local palliative radiation therapy within 14 days prior to first dose of study drug.
- Add exclusion criterion for patients who received radiation therapy to more than 25% of bone marrow-containing spaces within 84 days prior to first dose of study drug.
- Revise planned imaging assessments to include MRI.
- Change the definition of enrollment to at the time of first dose of study drug.
- Add section in the appendix containing updated SAE and pregnancy reporting contact information.
- Add development assessment and Tanner Scale and B symptom assessments to study procedures section.
- Revise inclusion criterion for pregnancy.
- Revise dose modification section for clarity.
- Revise time frame for reporting SAEs to the sponsor.
- Revise time frames for prior alloSCT and autologous hematopoietic stem cell transplantation for study eligibility.
- Revise exclusion criteria for corticosteroid therapy.
- Revise assessment times for pregnancy tests.
- Specify that patients must have recovered from any toxic effects of prior radiotherapy, chemotherapy, or immunotherapy prior to enrollment.
- Specify that direct and indirect bilirubin assessments will be performed.
- Specify that weight and height screening assessments must be performed within 14 days prior to the first dose of study drug.
- Clarify that an independent review facility (IRF) will assess objective response over the course of the study, per International Working Group (IWG) criteria.
- Clarify that concomitant medications will be monitored starting at the time of signed informed consent form.
- Clarify that a 10% or greater change in patient weight (increase or decrease) will require brentuximab vedotin dose adjustment.

- Clarify that patients who are withdrawn from treatment during Cycle 1 for reasons other than dose-limiting toxicities (DLTs) will be replaced.
- Clarify the use of concomitant colony-stimulating factors (CSFs).
- Clarify that the central laboratory will be used for clinical chemistry, hematology, and immune reconstitution evaluations, and that local labs may be used for dosing decisions only.
- Clarify that medical history is not obtained on Day 1, Cycle 1.
- Clarify timing of hematology and serum chemistry samples.
- Clarify that patients who respond may receive up to 16 cycles of brentuximab until disease progression.
- Remove Eastern Cooperative Oncology Group (ECOG) Performance Status from appendices.
- Rename the Pharmacodynamics/Biomarkers Analysis section to Immune Reconstitution Analysis.
- Correct typographical errors, punctuation, grammar, and formatting.

For specific examples of changes in text and where the changes are located, see Section 14.7.

14.7 Amendment 4 Detailed Summary of Changes

THE PRIMARY SECTIONS OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 4 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Revise the length of the follow-up period to align with the PIP

The primary change occurs in Section 4.1, Overview of Study Design:

Formerly read:	Patients will be followed for 12 months ~~following the last dose of brentuximab vedotin to assess overall survival~~.
Now reads:	Patients will be followed for **PFS and OS every 12 weeks for** 12 months **after the EOT visit**. **Thereafter, assessment for OS will continue every 6 months until the sooner of death or study closure or a maximum of 2 years after enrollment of the last patient. Patients who remain on treatment after Cycle 16 will be followed according to the above schedule or until study closure.**

Sections that also contain this change are:

- PROTOCOL SUMMARY
- Schedule of Events
- Section 4.3, Duration of Study
- Section 6.4.3, Criteria for Discontinuation of Brentuximab vedotin
- Section 7.10, Posttreatment Follow-up Assessments

Purpose: Clarify that the primary endpoint of the phase 2 study is best ORR

The primary change occurs in Section 2.4, Phase 2 Primary Objectives:

Formerly read:	The primary objectives in phase 2 ~~include~~: • To determine the overall response rate (complete remission, partial remission) with brentuximab vedotin at the recommended phase 2 dose
Now reads:	The primary objective in phase 2 **is**: • To determine the **best** overall response rate (complete remission, partial remission) with brentuximab vedotin at the recommended phase 2 dose

Sections that also contain this change are:

- PROTOCOL SUMMARY
- Section 1.3.1, Study Rationale
- Section 2.2, Phase 1 Secondary Objectives

- Section 3.2, Phase 1 Secondary Endpoints
- Section 3.4, Phase 2 Primary Endpoints
- Section 8.1.6, Efficacy Analysis

Purpose: Add safety language regarding the potential risk of SJS

The primary change occurs in Section 1.4.3, Potential Risks in Children:

Added text: **Stevens-Johnson syndrome (SJS), including toxic epidermal necrolysis, has been reported in patients who received brentuximab vedotin. Patients were concurrently receiving other medications (naproxen and tramadol, respectively) that are known to cause SJS and may have contributed to the development of SJS. Stevens-Johnson syndrome is considered to be an unacceptable study drug-related toxicity. If SJS occurs, the administration of brentuximab vedotin must be discontinued and the appropriate medical therapy administered.**

Purpose: Add safety language regarding the potential risk of pancreatitis

The primary change occurs in Section 1.4.3, Potential Risks in Children:

Added text: **Acute pancreatitis has been reported in patients treated with brentuximab vedotin and has contributed to fatal outcomes in some cases. Onset typically occurred after 1 to 2 doses of brentuximab vedotin. Early symptoms included severe abdominal pain, nausea, and vomiting. Some of the pancreatitis cases were complicated by other possible contributory factors, including cholelithiasis and alternate etiologies (eg, pancreatic lymphoma progression, displacement of bile duct stent).**

Purpose: Add safety language regarding the potential risk of hepatotoxicity

The primary change occurs in Section 1.4.3, Potential Risks in Children:

Added text: **Hepatotoxicity, predominately in the form of asymptomatic mild to moderate transient elevations in AST and/or ALT, has been reported in patients treated with brentuximab vedotin. Patients should be monitored for elevated liver enzymes.**

Purpose: Revise the total bilirubin inclusion criterion to include patients with abnormal values due to indirect hyperbilirubinemia due to Gilbert's disease

The primary change occurs in Section 5.1, Inclusion Criteria, criterion 11:

Formerly read:

- Serum bilirubin level less than or equal to 1.5 × upper limits of normal (ULN).

Now reads:	• Serum bilirubin level less than or equal to 1.5 × upper limits of normal (ULN) **or less than or equal to 3 × ULN for patients with an indirect hyperbilirubinemia due to Gilbert's disease**.

Purpose: Revise study eligibility criterion regarding elevated ALT and AST values due to the presence of metastatic disease in the liver

The primary change occurs in Section 5.1, Inclusion Criteria, criterion 11:

Formerly read:	• Alanine aminotransferase (ALT or SGPT) and aspartate aminotransferase (AST or SGOT) less than or equal to 2.5 × ULN.
Now reads:	• Alanine aminotransferase (ALT or SGPT) and aspartate aminotransferase (AST or SGOT) less than or equal to 2.5 × ULN. **AST and ALT levels may be elevated up to 5 × ULN if their elevation can be reasonably ascribed to the presence of metastatic disease in the liver.**

Purpose: Revise the washout period for systemic corticosteroid treatment in the exclusion criteria

The primary change occurs in Section 5.2, Exclusion Criteria, criterion 13:

Formerly read:	13. Systemic corticosteroid therapy <~~14~~ days prior to first dose of study medication.
Now reads:	13. Systemic corticosteroid therapy <**7** days prior to first dose of study medication.

Purpose: Revise the required minimum time between previous allogeneic or autologous stem cell transplantation and the first dose of study drug

The primary changes occur in Section 5.2, Exclusion Criteria, criteria 2 and 17:

Formerly read:	2. Received allogeneic stem cell transplant <~~6~~ months prior to first dose of study medication, or presence of polymerase chain reaction (PCR)-detectable CMV in any post-allogeneic transplantation patient. (Prior PCR positivity that was successfully treated is acceptable provided the baseline PCR result is negative prior to first dose of study drug.) … 17. Prior autologous hematopoietic stem cell infusion <~~6~~ weeks before first study dose.

Now reads:

2. Received allogeneic stem cell transplant <**3** months prior to first dose of study medication, or presence of polymerase chain reaction (PCR)-detectable CMV in any post-allogeneic transplantation patient. (Prior PCR positivity that was successfully treated is acceptable provided the baseline PCR result is negative prior to first dose of study drug.)

…

17. Prior autologous hematopoietic stem cell infusion <**4** weeks before first dose of the study drug.

The PROTOCOL SUMMARY also contains this change.

Purpose: Add to the exclusion criteria any history of PML

The primary change in Section 5.2, Exclusion Criteria, criterion 9:

Formerly read:

9. Known active cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML).

Now reads:

9. Known active cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML) **or any history of PML**.

The PROTOCOL SUMMARY also contains this change.

Purpose: Revise the CYP3A4 exclusion criterion to exclude listed moderate inhibitors of CYP3A4

The primary change occurs in Section 5.2, Exclusion Criteria, criterion 19:

Formerly read:

19. Received ~~a~~ strong inhibitor of CYP3A4 <2 weeks prior to first study dose. (~~Strong inhibitors of~~ CYP3A4 ~~are listed in Appendix~~.)

Now reads:

19. Received **any** strong **or listed moderate** inhibitor of CYP3A4 <2 weeks prior to first study dose. (**Please refer to the Study Manual for an example list of prohibited** CYP3A4 **inhibitors**.)

Section 6.5, Excluded Concomitant Medications and Procedures, also contains this change.

Purpose: Modify the contraception language regarding abstinence to align with company standards

The primary change occurs in Section 5.1, Inclusion Criteria, criterion 7:

Formerly read:

7. Female patients who are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form (ICF) through 6 months after the last dose of study drug, or agree to ~~completely abstain from heterosexual intercourse~~.
8. Male patients, even if surgically ~~sterile~~, who agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or agree to ~~completely abstain from heterosexual intercourse~~.

Now reads:

7. Female patients who:
   - **Are surgically sterile, OR**
   - **If they** are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, or
   - Agree to **practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)**
8. Male patients, even if surgically **sterilized** (**ie, status postvasectomy**), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or
   - Agree to practice **true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)**

Section 6.7, Precautions and Restrictions, also contains this change.

Purpose: Revise language regarding dose adjustments for a ≥ 10% weight change; add language for patients weighing more than 100 kg

The primary change occurs in Section 6.1, Study Drug Administration:

Added text:	**Dosing is based on patients' weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥ 10% change in weight from the most recent dose calculation. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams**.

The Schedule of Events, footnote s, also contains this change.

Purpose: Correct the units of measurement for platelet count, absolute neutrophil count, and white blood cell count

The primary change occurs in Section 6.4.2, Criteria for Beginning or Delaying a Subsequent Treatment Cycle:

Formerly read:	• ANC must be ≥1,000/~~mm~~^{3} • Platelet count must be ≥75,000/~~mm~~^{3}
Now reads:	• ANC must be ≥1,000/**µL** • Platelet count must be ≥75,000/**µL**

The sections that also contain this change are:

- Section 6.2.3, Hematologic Toxicity
- Section 6.4.1, Criteria for Dose Modification*
- Section 9.1.3, Serious Adverse Event Definition

Purpose: Remove the restriction on the use of polyethylene infusion bags for dilution of brentuximab vedotin, as previously described in Administrative Letter 2

The primary change occurs in Section 6.11, Preparation, Reconstitution, and Dispensation:

Deleted text:	The appropriate amount of reconstituted study treatment will be withdrawn from the vial(s) and diluted in a 50- to 100-mL infusion bag containing 0.9% Sodium Chloride Injection, USP. ~~Do not use polyethylene infusion bags.~~

Purpose: Update packaging and labeling instructions for brentuximab vedotin

The primary change occurs in Section 6.12, Packaging and Labeling:

Formerly read:	Brentuximab vedotin ~~for Injection is supplied in 5 mL (10 mg) single use, Type 1 borosilicate glass vials~~.
Now reads:	Brentuximab vedotin **vials will be packaged as single-use cartons**. **Each carton will contain 1 vial of the investigational product, and the vial and carton will be labeled to meet country-specific regulatory requirements**.

Purpose: Revise the timing for the development assessment and Tanner Scale

The primary change occurs in the Schedule of Events:

Removed the X in the Development assessment and Tanner Scale row under the D15-21 of Cycle column.

Added an X in the Development assessment and Tanner Scale row in the Each 21-Day Cycle: D1 column.

Purpose: Permit occasional changes in the timing of tests and procedures without permission from the project clinician

The primary change occurs in the Schedule of Events footnotes:

Formerly read:	Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) ~~with permission of the medical monitor~~ for holidays, vacations, and other administrative reasons.
Now reads:	Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) for holidays, vacations, and other administrative reasons**, unless otherwise indicated**.

Purpose: Revise language regarding premedication for infusion-related reactions to allow the use of corticosteroids

The primary change occurs in Section 6.1, Study Drug Administration:

Formerly read:	Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent brentuximab infusions with premedication consisting of acetaminophen (650 mg orally) and diphenhydramine (25–50 mg orally or 10–25 mg IV) or according to institutional standards, administered 30 to 60 minutes prior to each 30-minute brentuximab vedotin infusion. ~~The routine use of steroids as premedication is discouraged.~~
Now reads:	Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent brentuximab infusions with premedication consisting of

acetaminophen (650 mg orally) and diphenhydramine (25–50 mg orally or 10–25 mg IV) or according to institutional standards, administered 30 to 60 minutes prior to each 30-minute brentuximab vedotin infusion.
Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

Purpose: Add an assessment for immune reconstitution at the EOT visit, as previously described in Administrative Letter 1, and add a window to perform immune reconstitution

The primary change occurs in the Schedule of Events:

Added an X in the Immune reconstitution row in the EOT/ET: 30 days post last dose ±7 days column.

The primary change also occurs in Section 3.3, Phase 1 Exploratory Endpoints:

Added text: CCI [redacted]

Sections that also include this change include:

- The Schedule of Events, footnote w
- Section 1.4.3, Potential Risks in Children
- Section 3.6, Phase 2 Exploratory Endpoints

Purpose: Revise the section on Immune Reconstitution; revise the section heading and add separate sections for Immunogenicity Assessment and Tumor Specimen Measurements

The primary changes occur in new Section 7.4.15.1, Immune Reconstitution, new Section 7.4.16, Immunogenicity, and new Section 7.4.17, Tumor Specimen Measurements:

Formerly read: 7.4.15 Pharmacodynamic Measurements

The effects of brentuximab vedotin on the pediatric peripheral immune system will be examined by measuring peripheral blood cell populations and the circulating Ig subclasses. Peripheral cell populations will be examined ~~by drawing 5 mL of peripheral blood into a heparinized tube~~ at the designated time points in the Schedule of Events. Cellular populations, including T cells subsets (T helper, cytotoxic, and memory cells), B cells, NK cells, and granulocytes will be measured using flow cytometry. Immunoglobulin subclasses will be examined ~~by taking approximately 2.5 mL of serum and examining~~ using standard clinical laboratory procedures.

Now reads:

7.4.15.1 Immune Reconstitution

The effects of brentuximab vedotin on the pediatric peripheral immune system will be examined by measuring peripheral blood cell populations and the circulating Ig subclasses **as outlined**:

Immune Reconstitution

- **IgG**
- **IgM**
- **IgA**
- **Tetanus antibodies**
- **HiB**
- **Polioserotypes**
- **Total immunoglobulin**
- **Lymphocyte count**
- **Lymphocyte subsets**

Peripheral cell populations will be examined **using serum from the heparinized blood specimens** obtained at the designated time points, **as specified** in the Schedule of Events. Cellular populations including T cell subsets (T helper, cytotoxic, and memory cells), B cells, NK cells, and granulocytes will be measured by using flow cytometry. Immunoglobulin subclasses will be examined using standard clinical laboratory procedures.

Added text:

7.4.16 Immunogenicity

Blood samples will be collected as specified in the Schedule of Events to evaluate ATAs and neutralizing ATAs. On the days of dose administration, the blood samples for ATA and neutralizing ATA assessment must be collected before the brentuximab vedotin dose is administered. Neutralizing ATA assessment will be performed for ATA-positive samples only. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

Added text:

7.4.17 Tumor Specimen Measurements

This sample will be used to confirm CD30 expression by central laboratory review. Refer to the Schedule of Events for details regarding tumor specimen collection.

Purpose: Add language regarding reporting requirements for SAEs

The primary change occurs in Section 7.10, Posttreatment Follow-up Assessments:

Added text:

NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 9 for details regarding definitions, documentation, and reporting of SAEs.

Purpose: Delete redundant SAE reporting language, update the period for reporting SAEs to Millennium from 1 calendar day to 24 hours, and update SAE reporting contact information

The primary change occurs in Section 9.2, Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Formerly read:

~~All~~ SAEs and serious pretreatment events (as defined in Section 9.1) must be reported (see Section 9.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee by faxing the SAE Form within ~~1 calendar day~~ after becoming aware of the event. ~~All SAEs and serious pretreatment events (which include all deaths) must be reported whether or not considered causally related to the study drug or study procedures.~~ The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

~~For~~ SAE ~~and Pregnancy~~ Reporting Contact Information~~,~~
~~please refer to Appendix 14.5~~

Now reads:

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 9.1) must be reported (see Section 9.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee **(contact information provided below). This should be done** by faxing the SAE Form within **24 hours** after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

PPD

PPD

This change also resulted in the removal of Section 14.5, SAE and Pregnancy Reporting Contact Information.

Purpose: Add language regarding the collection of events of peripheral neuropathy

The primary change occurs in Section 6.8.1, Management of Peripheral Neuropathy:

Added text: **These events may include, but are not limited to, peripheral sensory neuropathy, peripheral motor neuropathy, pareaesthesia, hypoaesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy. Such events, regardless of seriousness, will be followed for all changes in severity until resolution to baseline or study closure, whichever occurs first, and recorded in the eCRF.**

The Schedule of Events also contains this change.

Purpose: Redefine the population for analysis of the phase 2 exploratory endpoint as the CCI [redacted]

The primary change occurs in Section 8.1.3, Populations for Analysis:

Formerly read: CCI [redacted]

Now reads: CCI [redacted]

Purpose: Update AE evaluation and analysis language

The primary change occurs in Section 8.1.8, Safety Analysis:

Formerly read: A listing of DLTs for each dose level will be provided. Safety will be evaluated by the incidence of ~~treatment-emergent~~ AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, neurotoxicity assessment, ECGs, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) ~~by system organ class, high level terms, and preferred terms~~ and will include the following categories:

- Treatment-emergent AEs
- ~~D~~rug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- ~~Treatment-emergent AEs resulting in study drug discontinuation~~
- SAEs

~~The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients) will be tabulated by high level term and preferred term.~~

Now reads:

A listing of DLTs for each dose level will be provided. Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, neurotoxicity assessment, ECGs, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated. AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs
- **Study d**rug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher **study** drug-related treatment-emergent AEs
- **The most commonly reported treatment-emergent AEs (ie, those events reported for ≥10% of all patients)**
- SAEs

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

Purpose: Remove text regarding the start of antineoplastic or anticancer therapy as it relates to follow-up of AEs

The primary change occurs in Section 9.3, Monitoring of Adverse Events and Period of Observation:

Formerly read:

AEs, both nonserious and serious ~~(which include all deaths)~~, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug ~~or the start of subsequent anticancer therapy,~~ whichever occurs first, and recorded in the eCRFs. ~~That is, if a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.~~

…

- SAEs will be reported to Millennium Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. ~~All~~ SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). ~~Any~~

~~SAE that occurs at any time after completion of the study and the designated follow-up period that the investigator considers to be related to study drug must be reported to the Millennium Department of Pharmacovigilance.~~

Now reads:

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs. **All events relating to peripheral neuropathy regardless of seriousness will be followed for all changes in severity until resolution to baseline or study closure**, whichever occurs first, and recorded in the eCRF.

…

- **Related and unrelated** SAEs will be reported to **the** Millennium **Department of** Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. **After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee**. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Sections that also contain this change are:

- Section 4.1, Overview of Study Design
- Section 4.3, Duration of Study
- Section 6.1, Study Drug Administration
- Section 7.10, Posttreatment Follow-up Assessments

Purpose: Update contact information for reporting product complaints and medication errors

The primary change occurs in Section 10.11, Product Complaints and Medication Errors:

Formerly read:	For Product Complaints or Medication Errors, PPD
Now reads:	For Product Complaints or Medication Errors, PPD

Purpose: Clarify the sample size for the phase 1 and phase 2 portions of the study

The primary change occurs in Section 4.1, Overview of Study Design:

Formerly read:

Approximately 42 evaluable patients will be enrolled in this study. In the phase 1 portion of the study, ~~up to~~ 12 patients with relapsed or refractory CD30+ malignancies (including HL and sALCL) will be enrolled in 2 planned dose cohorts (3 to 6 patients per cohort) according to the standard 3 + 3 dose escalation scheme.

Once the MTD and/or RP2D have been reached, patients will be enrolled by diagnosis into two phase 2 study arms: relapsed or refractory sALCL, or relapsed or refractory HL. The phase 2 portion of the study study ~~plans to enroll~~ 15 evaluable patients with sALCL (including patients treated at the RP2D during phase 1), of whom at least 10 patients are in first relapse, and 15 evaluable ~~HL~~ patients (including patients treated at RP2D during phase 1).

Now reads:

Approximately 42 evaluable patients will be enrolled in this study. In the phase 1 portion of the study, **at least** 12 patients with relapsed or refractory CD30+ malignancies (including HL and sALCL) will be enrolled in 2 planned dose cohorts (3 to 6 patients per cohort) according to the standard 3 + 3 dose escalation scheme.

Once the MTD and/or RP2D have been reached, patients will be enrolled by diagnosis into two phase 2 study arms: relapsed or refractory sALCL, or relapsed or refractory HL. **A sufficient number of patients will be enrolled in** the phase 2 portion of the study to **have at least** 15 evaluable patients with sALCL (including patients treated at the RP2D during phase 1), of whom at least 10 patients are in first relapse, and **at least** 15 evaluable patients **with HL** (including patients treated at RP2D during phase 1).

Sections that also contain this change are:

- PROTOCOL SUMMARY
- Section 4.2, Number of Patients
- Section 6.3 Dose Escalation Rules
- Section 7.7, Discontinuation of Treatment With Study Drug, and Patient Replacement
- Section 8.1.1, Determination of Sample Size.

Purpose: Revise language in the Study Design section of the Protocol Summary to align with previous updates made in the protocol body text

The primary change occurs in the PROTOCOL SUMMARY:

Formerly read	This is a phase 1/2, open-label, single-agent, multicenter, dose-escalation study of brentuximab vedotin in pediatric patients with relapsed or refractory sALCL or HL. Patients with primary mediastinal B cell lymphoma will be eligible during phase 1. The primary objectives of the study are to assess the safety and pharmacokinetics, and determine the pediatric maximum tolerated dose (MTD) and/or RP2D of brentuximab vedotin in pediatric patients. In addition, the immunogenicity and antitumor activity of brentuximab vedotin will be evaluated in eligible patients. Overall response will be evaluated beginning after 2 cycles of therapy. Objective response over the course of the study will be assessed by an independent review facility (IRF) according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma.(1) Patients ~~who respond~~ or ~~experience~~ stable disease may receive up to 16 cycles ~~of brentuximab vedotin~~.
Now reads:	Overview of Study Design: This is a phase 1/2, open-label, single-agent, multicenter, dose escalation study of brentuximab vedotin in pediatric patients with relapsed or refractory sALCL or HL **for which standard, curative, life-prolonging, or palliative treatment does not exist or is no longer effective**. Patients with primary mediastinal B cell lymphoma will be eligible during phase 1. The primary objectives of the study are to assess the safety and pharmacokinetics, and determine the pediatric MTD and/or RP2D of brentuximab vedotin in pediatric patients. In addition, the immunogenicity and antitumor activity of brentuximab vedotin will be evaluated in eligible patients. Overall response will be evaluated beginning after 2 cycles of therapy. Objective response over the course of the study will be assessed by an independent review facility (IRF) according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma.(1) Patients, **including those** who **achieve a CR, PR,** or stable disease may receive brentuximab vedotin **for up to 16 cycles**. **Treatment with brentuximab vedotin beyond 16 cycles may be permitted at the joint discretion of the sponsor and the investigator for those patients experiencing continued clinical benefit.**

Purpose: Clarify the planned study procedures for patients who remain on treatment after Cycle 16, as previously outlined in Administrative Letter #3

The primary change occurs in the Schedule of Events:

A column has been added in the Schedule of Events under the column header Cycle 17 and Beyond (for patients who continue beyond 16 cycles) that indicates which procedures are to be performed after Cycle 16. Footnote m has also been added to the Schedule of Events.

Purpose: Specify that serum or urine pregnancy tests are acceptable at screening and before dosing on Day 1, and add a statement regarding the scheduling of pregnancy tests

The primary change occurs in Section 7.4.7, Pregnancy Test:

Formerly read:	Patients of childbearing potential will complete a serum pregnancy test during screening ~~and at Cycle 1 Day 1; this test must be confirmed negative prior to receipt of the first dose of brentuximab vedotin~~. A urine pregnancy test will be performed prior to dosing on Day 1 of each subsequent cycle.
Now reads:	Patients of childbearing potential will complete a serum **or urine** pregnancy test during screening, **prior to dosing on Day 1 during Cycles 1 through 16, and at EOT. If the screening test was performed within 4 days before the Cycle 1, Day 1 dose, it need not be repeated on Cycle 1, Day 1**. A **serum or** urine pregnancy test will be performed prior to dosing on Day 1 of each subsequent cycle. **The results must be negative before brentuximab vedotin is administered. During Cycle 17 and beyond, a pregnancy test should be performed per institutional guidelines; any samples collected during Cycle 17 and beyond should not be sent to the central laboratory, and data should not be captured in the eCRF. Additional pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.**

The sections that also contain this change are:

- Schedule of Events, footnote f
- Section 5.2, Exclusion Criteria, criterion 21

Purpose: Clarify that the timeframe for collecting clinical laboratory values at screening is within 4 days before the first dose of the study drug

The primary change occurs in Section 5.1, Inclusion Criteria, criterion 11:

Formerly read:	11. Clinical laboratory values as specified within ~~14~~ days before the first dose of study drug:
Now reads:	11. Clinical laboratory values as specified within **4** days before the first dose of study drug:

Purpose: Clarify that patients should be observed for anaphylaxis after each infusion of brentuximab vedotin

The primary change occurs in Section 6.1, Study Drug Administration:

Formerly read:	The patient should be observed for 60 minutes ~~following the first~~ infusion of brentuximab vedotin.
Now reads:	The patient should be observed for 60 minutes **after each** infusion of brentuximab vedotin.

Purpose: Clarify that Grade 4 neutropenia lasting more than 7 days is considered a DLT

The primary change occurs in Section 6.2.3, Hematologic Toxicity:

Formerly read:	DLT for hematologic toxicity will be defined as: • Grade 4 neutropenia lasting ~~greater~~ than 7 days
Now reads:	DLT for hematologic toxicity will be defined as: • Grade 4 neutropenia lasting **longer** than 7 days

Purpose: Clarify that unacceptable study drug-related toxicity or disease progression will result in mandatory, permanent discontinuation of the study drug

The primary change occurs in Section 6.4.3, Criteria for Discontinuation of Brentuximab vedotin:

Formerly read:	Study drug ~~will~~ be discontinued ~~early~~ if a patient experiences unacceptable study drug-related ~~toxicities~~. … A patient's treatment with study drug may also be discontinued for any of the following reasons: • ~~Unacceptable AE.~~ • ~~Disease progression.~~ • Patient withdrawal. • Stable disease or better and completed 16 treatment cycles (brentuximab vedotin). • The investigator or patient deems it in the patient's best interest to discontinue, including patients who experience a CR and are candidates for hematopoetic stem cell transplantation. The reason justifying study treatment withdrawal must be documented in the CRF.

Now reads:

Study drug **must** be discontinued if a patient experiences **progressive disease or an** unacceptable study drug-related **toxicity**.

…

A patient's treatment with study drug may also be discontinued for any of the following reasons:

- Patient withdrawal.
- Stable disease or better and completed 16 treatment cycles (brentuximab vedotin).
- The investigator or patient deems it in the patient's best interest to discontinue, including patients who experience a CR and are candidates for hematopoetic stem cell transplantation. The reason justifying study treatment withdrawal must be documented in the CRF.

Sections that also contain this change are:

- Section 4.3, Duration of Study
- Section 7.7, Discontinuation of Treatment With Study Drug, and Patient Replacement.

Purpose: Clarify that initiation of hematopoietic stem cell transplantation is a reason for study drug discontinuation

The primary change occurs in Section 7.7, Discontinuation of Treatment With Study Drug, and Patient Replacement:

Added text:

Treatment with study drug may also be discontinued for any of the following reasons:

…

- Initiation of **hematopoietic** stem cell or bone marrow transplant

Section 6.4.3, Criteria for Discontinuation of Brentuximab vedotin, also contains this change.

Purpose: Clarify that development assessments include weight-for-age and stature-for-age percentiles

The primary change occurs in Section7.4.13.1, Development Assessment and Tanner Scale:

Formerly read:

Development assessment and Tanner Scale to be performed ~~according to the timelines~~ in the Schedule of Events. The development assessment will include ~~height and~~ weight; see Section 14.3 for Tanner Scale information.

Now reads: Development assessment and Tanner Scale **are** to be performed **as specified** in the Schedule of Events. The development assessment will include weight-**for-age and stature-for-age percentiles**; see Section 14.3 for Tanner Scale information.

The Schedule of Events, footnote l, also contains this change.

Purpose: Clarify procedures for clinical laboratory evaluations

The primary change occurs in Section 7.4.12, Clinical Laboratory Evaluations:

Formerly read: Clinical [redacted] laboratory evaluations will be performed centrally [redacted] ~~the study. For treatment decisions, separate samples~~ [redacted] Handling and shipment of clinical laboratory samples will be outlined in the study manual [redacted]

Handling and shipment of clinical laboratory samples will be outlined in the Study Manual.

Clinical laboratory evaluations will be performed as outlined:

Clinical Chemistry~~,~~ Hematology~~, and~~ [redacted]

Blood samples for analysis of the following clinical chemistry and hematological parameters will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Total WBC count
- Differential WBC count

Serum Chemistry

- Blood urea nitrogen
- Creatinine
- Urate
- Bilirubin (total, direct, indirect)
- Lactate dehydrogenase
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- ~~G~~lucose
- Calcium
- Chloride
- Carbon dioxide
- Magnesium

- Gamma glutamyl transferase
- Phosphorus
- Sodium
- Potassium

CCI

[redacted]

Now reads:

Clinical laboratory evaluations will be performed centrally. **Decisions regarding eligibility and study drug dosing may be made by using local laboratory results. If local clinical laboratory values are used for either eligibility or study dosing decisions, the local laboratory results do not replace central laboratory testing, and samples for central laboratory confirmation must be collected as specified in the Schedule of Events.**

During Cycle 17 and beyond, hematology and serum chemistry tests should be performed per institutional guidelines at the local laboratory; samples should not be sent to the central laboratory, and data should not be captured in the eCRF, unless the laboratory result is assessed to contribute to an AE.

Handling and shipment of clinical laboratory samples will be outlined in the Study Manual.

Clinical laboratory evaluations will be performed as outlined:

Clinical Chemistry **and** Hematology

Blood samples for analysis of the following clinical chemistry and hematological parameters will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Total WBC count
- Differential WBC count

Machine counts are acceptable.

Serum Chemistry

- Blood urea nitrogen
- Albumin
- Alkaline phosphatase
- Calcium
- Chloride

- Creatinine
- Urate
- Bilirubin (total, direct, indirect)
- Lactate dehydrogenase
- Gamma glutamyl transferase
- Phosphorus
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- **Fasting g**lucose
- Sodium
- Potassium
- Carbon dioxide
- Magnesium

The Schedule of Events, footnote j, also contains this change.

Purpose: Clarify the timing for collection of blood samples for PK assessments and remove reference to total blood volumes to be collected for these assessments

The primary change occurs in Section 7.4.14, Pharmacokinetic Measurements:

Formerly read:

Blood samples for the determination of serum brentuximab vedotin concentrations will be collected at the following time points:

- All Cycles: Day 1 ~~immediately before and 5 minutes after the brentuximab vedotin infusion~~
- ~~Cycle 1: Days 2, 3, 5, 14~~
- ~~Cycle 2: Days 2 (phase 1 only), 3, 5~~
- ~~Cycle 8: Days 2, 3, 5, 14~~

~~Postdose PK samples on Day 1 should be obtained at 5 (±1) minutes after the end of the brentuximab vedotin infusion. The total amount of blood drawn for obtaining serum or plasma from each patient for PK measurements will be approximately 172 mL (43 specimens × 4 mL blood per specimen) over 16 cycles of treatment.~~

Now reads:

Blood samples for the determination of serum brentuximab vedotin concentrations will be collected at the following time points:

- All Cycles: Day 1: **within 4 hours before the start of the brentuximab vedotin infusion and 5 minutes (±1 minute) after the end of the brentuximab vedotin infusion**
- **Cycles 1 and 8:**
  - **Day 2: 24 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion**
  - **Day 3: 48 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion**
  - **Day 5: 96 hours (±24 hours) from the start of the Day 1 brentuximab vedotin infusion**

  - **Day 14: 312 hours (±48 hours) from the start of the Day 1 brentuximab vedotin infusion**

- **Cycle 2:**
  - **Day 2 (phase 1 only): 24 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion**
  - **Day 3: 48 hours (±4 hours) from the start of the Day 1 brentuximab vedotin infusion**
  - **Day 5: 96 hours (±24 hours) from the start of the Day 1 brentuximab vedotin infusion.**

The Schedule of Events, footnote u, also contains this change.

Purpose: Clarify the descriptions of Completion of Treatment and Completion of Study, and clarify language for posttreatment assessments

The primary changes occur in Section 7.5, Completion of Treatment and Section 7.6, Completion of Study:

Deleted text:

Section 7.5 Completion of Treatment

Patients will be considered to have completed study treatment if they complete ~~up to~~ 16 cycles of treatment with brentuximab vedotin ~~or experience progressive disease or unacceptable toxicity, and have 30 days of safety follow-up~~.

~~Regardless of the duration of treatment, all patients will remain on study for up to 12 months following the last dose of study treatment for posttreatment follow-up assessments, or until they withdraw consent for further follow-up, or are lost to follow-up. The study is expected to close approximately 5 years after the first patient starts study treatment.~~

~~Patients will be followed for overall survival and disease status every 12 weeks until 12 months after the end of treatment (EOT) visit. Information regarding the initiation of an alternative form of treatment for lymphoma will also be collected. For patients who have progressive disease, survival/disease status and information regarding the initiation of an alternative lymphoma treatment may be obtained by phone call.~~

Section 7.6 Completion of Study

Patients will be considered to have completed the study if they complete ~~up to~~ 16 cycles of treatment with brentuximab vedotin ~~or experience progressive disease or unacceptable toxicity,~~ and complete 30 days of safety follow-up.

Purpose: Clarify efficacy analysis language to specify that the Kaplan-Meier method will be used to analyze efficacy parameters and specify the percentiles to be provided

The primary change occurs in Section 8.1.6, Efficacy Analysis:

Formerly read:	Duration of response (DOR), time to response, time to progression (TTP), EFS, PFS, and OS will be analyzed using ~~standard survival analysis techniques based on~~ Kaplan-Meier ~~life test~~ method. ~~Time to event data will be summarized by~~ 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence interval~~, as well as the percentage of censored observations~~.
Now reads:	Duration of response (DOR), time to response, time to progression (TTP), EFS, PFS, and OS will be analyzed using **the** Kaplan-Meier method. **The** 25th, 50th (median), and 75th percentiles **(if estimable)** with associated 2-sided 95% confidence interval **will be provided**.

Purpose: Clarify that assessments to be performed for the EOT visit are listed in the Schedule of Events

The primary change occurs in Section 7.7, Discontinuation of Treatment With Study Drug, and Patient Replacement:

Formerly read:	~~At the time of~~ study drug ~~discontinuation~~, all study procedures outlined for the ~~end of treatment~~ visit will be completed.
Now reads:	**Once** study drug **has been discontinued**, all study procedures outlined for the **EOT** visit will be completed **as specified in the Schedule of Events**.

Purpose: Clarify that the frequency of radiological evaluations for patients who receive treatment past Cycle 16 is outlined in the Schedule of Events

The primary change occurs in Section 4.1, Overview of Study Design:

Added text:	An evaluation of disease response will be assessed by an IRF according to the IWG Revised Response Criteria for Malignant Lymphoma(1) evaluated at Cycles 2, 4, 7, 10, 13, and 16 and then at the end of treatment. **The scan frequency for patients who receive treatment past Cycle 16 is outlined in the Schedule of Events.** Additional evaluations may be necessary when clinically indicated..

Purpose: Clarify reasons for study withdrawal.

The primary change occurs in Section 7.8, Withdrawal of Patients From Study:

Formerly read:

A patient may be withdrawn from the study for any of the following reasons:

- ~~Completed study~~
- Lost to follow-up
- Study terminated by sponsor
- Withdrawal of consent by patient or patient guardian
- Death
- Other

Now reads:

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal of consent by patient or patient guardian
- Death
- Other

Purpose: Remove Section 14.4, Strong Cytochrome P450 3A4 (CYP3A4) Inhibitors (the list of prohibited CYP3A4 inhibitors is located in the Study Manual)

The primary change occurs in deleted Section 14.4, Strong Cytochrome P450 3A4 (CYP3A4) Inhibitors:

Deleted text:

~~**Section 14.4, Strong Cytochrome P450 3A (CYP3A) Inhibitors**~~

~~The following are considered to be strong inhibitors of CYP3A:~~

- ~~atazanavir~~
- ~~clarithromycin~~
- ~~indinavir~~
- ~~itraconazole~~
- ~~ketoconazole~~
- ~~nefazodone~~
- ~~nelfinavir~~
- ~~posaconazole~~
- ~~ritonavir~~
- ~~saquinavir~~
- ~~telithromycin~~
- ~~voriconazole~~.

Purpose: Replace references to PPDI with Millennium Department of Pharmacovigilance or designee

The primary change occurs in Section 10.11, Product Complaints and Medication Errors:

Formerly read:	Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to ~~PPDI~~ (refer to Section 9.2).
Now reads:	Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to **the Millennium Department of Pharmacovigilance or designee** (refer to Section 9.2).

Purpose: Add abbreviations to table footnotes in the Schedule of Events

The primary change occurs in the Schedule of Events:

Formerly read:	Abbreviations: AE=adverse event; CT=computed tomography; ECG=electrocardiogram; EOT=end of treatment; PET=positron emission tomography; PK=pharmacokinetics; PD=pharmacodynamics.
Now reads:	Abbreviations: AE = adverse event; **BM = bone marrow; BMA = bone marrow aspirate;** CT = computed tomography; **D = day;** ECG = electrocardiogram; EOT = end of treatment; **MRI = magnetic resonance imaging; OSFUP = Overall survival Follow up;** PET = positron emission tomography; **PFSFUP = Progression-free survival Follow up;** PK = pharmacokinetics; PD = pharmacodynamics**; q = every**.

Purpose: Add bone marrow (BM) and United States Pharmacopeia (USP) to the List of Abbreviations and Glossary of Terms

The primary change occurs in the LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS:

Added text:	**BM bone marrow** **USP United States Pharmacopeia**

Purpose: Update the name of the Group Head on the title page

The primary change occurs on the title page:

Formerly read:	PPD [redacted]

Now reads:

Purpose: Replace references to medical monitor or study monitor with project clinician

The primary change occurs in Section 6.2.1, Toxicity:

Formerly read: The investigators and ~~medical monitor~~ will discuss and document the overall toxicity profile in detail before deciding whether to initiate cohort expansion, dose escalation, dose modification, and/or future prophylaxis with colony-stimulating factors (CSFs).

Now reads: The investigators and **project clinician** will discuss and document the overall toxicity profile in detail before deciding whether to initiate cohort expansion, dose escalation, dose modification, and/or future prophylaxis with colony-stimulating factors (CSFs).

Sections that also contain this change are:

- Schedule of Events
- Section 5.2, Exclusion Criteria, criteria 7 and 14
- Section 6.2.4, Phase 1: Dose Modification for an Individual Patient Who Experiences DLT
- Section 6.4.3, Criteria for Discontinuation of Brentuximab vedotin
- Section 7.1, Study Personnel and Organizations

Purpose: Correct typographical errors, punctuation, grammar, and formatting

These changes are not listed individually.

A Phase 1/2 Study of brentuximab vedotin (SGN-35) in Pediatric Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Clinical Approval	12-Jun-2014 14:34
	Clinical Science Approval	13-Jun-2014 17:54