Title: A Single-arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma Who Are Not Suitable for Stem Cell Transplantation or Multiagent Chemotherapy

NCT Number: NCT01990534

Protocol Approve Date: 11 July 2013

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CLINICAL STUDY PROTOCOL C25007

Brentuximab vedotin

A Single-arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma Who Are Not Suitable for Stem Cell Transplantation or Multiagent Chemotherapy

Protocol Number:	C25007
Indication:	Hodgkin lymphoma
Phase:	4
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2013-00232-10
Therapeutic Area:	Oncology

Protocol History
Original 11 July 2013

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PROTOCOL SUMMARY

Study Title: A Single-arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma Who Are Not Suitable for Stem Cell Transplantation or Multiagent Chemotherapy

Name of Principal Investigator: PPD

Number of Patients: At least 60 patients with relapsed or refractory classical Hodgkin lymphoma (HL) who are considered to be not suitable for stem cell transplantation (SCT) or multiagent chemotherapy will be enrolled in this study at approximately 20 investigative sites in Europe and potentially other regions of the world.

Study Objectives

Primary

- To assess the antitumor efficacy, as determined by the objective response rate (ORR) of single-agent brentuximab vedotin 1.8 mg/kg administered intravenously (IV) every 3 weeks, in patients with relapsed or refractory classical HL who are considered to be not suitable for SCT or multiagent chemotherapy

Secondary

- To determine the duration of tumor control, including the duration of response (DOR), progression-free survival (PFS), and complete remission (CR) rate by independent review facility (IRF) assessment after treatment with brentuximab vedotin
- To determine the proportion of patients who receive hematopoietic SCT, either autologous stem cell transplantation (ASCT) or allogeneic stem cell transplantation (alloSCT) after treatment with brentuximab vedotin
- To determine overall survival (OS) after treatment with brentuximab vedotin
- To assess the safety and tolerability of brentuximab vedotin in this patient population
- To assess the pharmacokinetics (PK) of brentuximab vedotin
- To determine the immunogenicity of brentuximab vedotin

Tertiary/Exploratory

CCI

Overview of Study Design: This phase 4, single-arm, multicenter study will evaluate the efficacy

and safety of brentuximab vedotin in adult patients 18 years or older with histologically confirmed CD30-positive (CD30+) relapsed or refractory classical HL who have not received a prior ASCT and are considered to be not suitable for SCT or multiagent chemotherapy at the time of study entry. Patients who are considered to be not suitable for SCT or multiagent chemotherapy include those who experience disease progression within 90 days of the earliest date of complete remission (CR) or complete remission unconfirmed (CRu) after the end of treatment with multiagent chemotherapeutic regimens and/or radiotherapy, or experience disease progression during frontline multiagent chemotherapy or alternatively, experience disease relapse after treatment with at least 2 chemotherapeutic regimens, including any salvage treatments.

Brentuximab vedotin will be administered as a single, outpatient, 1.8-mg/kg IV infusion on Day 1 of each 3-week cycle. Patients with a CR, a partial remission (PR), or stable disease should receive a minimum of 8 cycles, and all patients will be given the opportunity to complete a maximum of 16 cycles (see Section 15.1). Dedicated computed tomography (CT) scans (spiral preferred) of chest, neck, abdomen, and pelvis will be performed at baseline and at Cycles 2, 4, 7, 10, 13, and 16; and fluorodeoxyglucose (FDG) positron-emission tomography (PET) scans will be done at baseline (screening) and at Cycles 4 and 7. No additional PET scans are required during the treatment period after Cycle 7 unless they are clinically indicated. A PET scan should be done at the end of treatment only for those patients who discontinue study treatment without a postbaseline PET assessment.

Measures of anticancer activity will be assessed by an IRF according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma.[1] Patients who experience disease progression at any time will discontinue receiving the study drug. These patients will continue to be followed for overall survival (OS). Patients with an objective response, either a CR or a PR, and who are eligible for an SCT may discontinue receiving brentuximab vedotin and proceed to an SCT. These patients should receive at least 4 cycles of brentuximab vedotin before proceeding to SCT.

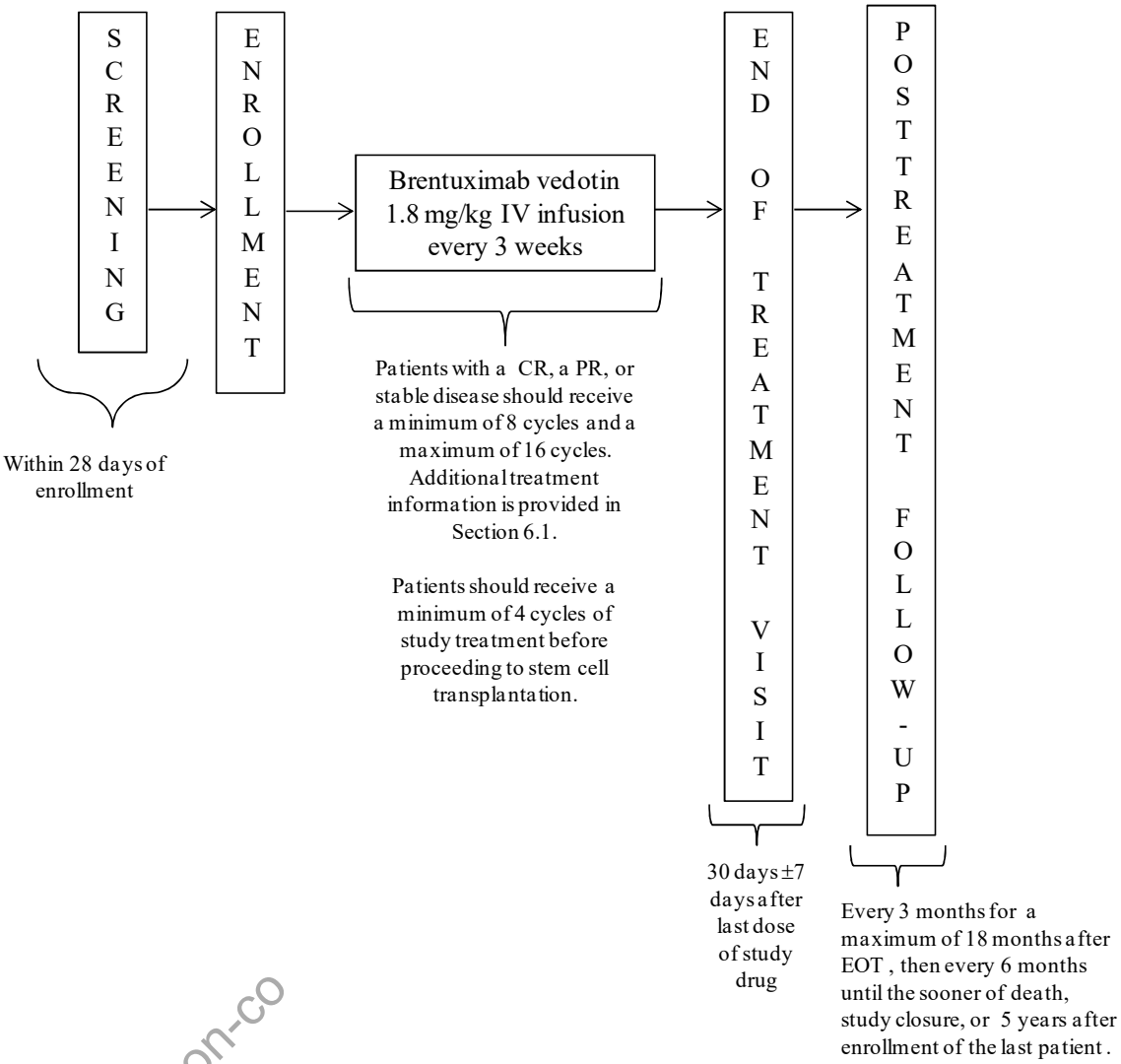
Safety assessments will include the incidence and severity of AEs and changes in clinical laboratory values, vital signs measurements, and physical examination findings. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, effective 14 June 2010.

Patients may continue to receive the study treatment for a maximum of 16 cycles or until disease progression or unacceptable toxicity. Patients will have an end-of-treatment (EOT) visit 30 days (± 7 days) after receiving their last dose of study drug. Patients who discontinue the study treatment with a CR, a PR, or stable disease will have CT scans performed for assessment of PFS every 3 months for 18 months after EOT or until the sooner of disease progression, death, or study closure. For patients who complete the 18-month PFS follow-up assessment period with a CR, a PR, or stable disease, a CT scan will be performed during the OS follow-up period at the time of disease progression, and the results will be sent to the IRF. Posttreatment follow-up assessments for OS will be performed every 3 months for 18 months after the EOT; thereafter, assessment for OS will continue every 6 months until the sooner of death, study closure, or 5 years after enrollment of the last patient.

Study Population: Male or female patients aged 18 years or older, with a histologically confirmed diagnosis of relapsed or refractory classical HL, a history of at least 1 prior systemic chemotherapeutic regimen, and considered to be not suitable for SCT or multiagent chemotherapy, according to 1 of the following criteria: disease progression within 90 days of the earliest date of CR or CRu after the end of treatment with multiagent chemotherapeutic regimens and/or radiotherapy, progressive disease during frontline multiagent chemotherapy, or disease relapse after treatment with at least 2 chemotherapeutic regimens, including any salvage treatments. Patients must have bidimensional measurable disease, of at least 1.5 cm, as documented by radiographic technique

(spiral CT scan preferred), per IWG Revised Response Criteria for Malignant Lymphoma.[1]
Duration of Study: Study enrollment is expected to take approximately 15 months. Patients will complete a Screening period of up to 28 days and may receive a maximum of 16 cycles of brentuximab vedotin. Patients will be followed for 30 days (+ 7 days) after administration of the last dose of brentuximab vedotin to permit the detection of any delayed treatment-related AEs. For patients who discontinue the study treatment with a CR, a PR, or stable disease, posttreatment follow-up assessments for PFS will be performed every 3 months for 18 months after the EOT or until the sooner of disease progression, death, or study closure. For patients who complete the 18-month PFS follow-up assessment period with a CR, a PR, or stable disease, a CT scan will be performed during the OS follow-up period at the time of disease progression, and the results will be sent to the IRF. Posttreatment follow-up assessments for OS will be performed every 3 months for 18 months after the EOT; thereafter, assessment for OS will continue every 6 months until the sooner of death, study closure, or 5 years after enrollment of the last patient. The total study duration is anticipated to be approximately 6 to 7 years.

STUDY OVERVIEW DIAGRAM



SCHEDULE OF EVENTS

		Screening	Enrollment (date of first dose)	Each 3-Week Cycle			Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 Only	EOT[a]	PFSFUP/ OSFUP[b]
	Day (D)		**Within 24 Hours of First Dose**	**D1**	**D2**	**D15**	**D15-21 of Cycle**	**30 ± 7 Days After Last Dose**	
	Visit Window	**D -28 to D1**			**+ 1D**	**± 5D**			**± 2 weeks**
Screening/ Baseline	Informed consent	X	Enrollment						
	Inclusion/exclusion criteria	X							
	Tumor specimen	X[c]							
	Medical history	X							
	Demographics	X							
Safety Assessments	Height	X							
	Weight	X		X				X	
	Pregnancy test[d]	X		X[d]					
	Vital signs	X		X				X	
	Physical examination with focused lymphoma assessment	X		X				X	X[e]
	ECOG performance status	X		X				X	
	Hematology and serum chemistry	X		X[f]				X	
	12-lead ECG	X							
	Monitoring of concomitant medications and procedures	Recorded from signing the ICF through 30 days after the last dose of study drug							

		Screening	**Enrollment (date of first dose)**	**Each 3-Week Cycle**			**Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 Only**	**EOT[a]**	**PFSFUP/ OSFUP[b]**
	Day (D)		**Within 24 Hours of First Dose**	**D1**	**D2**	**D15**	**D15-21 of Cycle**	**30 ± 7 Days After Last Dose**	
	Visit Window	**D -28 to D1**			**+ 1D**	**± 5D**			**± 2 weeks**
	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	SAEs[g] will be collected from signing informed consent through 30 days after the last dose of study drug							
Disease Assessments	Dedicated CT (spiral preferred) of chest, neck, abdomen, pelvis[h]	X					X	X[i]	X[b]
	FDG PET scan	X[j]					X[j]	X[j]	
	CCI								
	Bone marrow biopsy	X[l]					X[m]		
	Survival/disease status and anticancer treatments for r/r HL								X[n]
Treatment	Brentuximab vedotin administration			X					
PK/ Serum biomarkers	PK sample			X	X[p]	X[p]		X	
	CCI								

		Screening	**Enrollment (date of first dose)**	**Each 3-Week Cycle**			**Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 Only**	**EOT[a]**	**PFSFUP/ OSFUP[b]**
	Day (D)		**Within 24 Hours of First Dose**	**D1**	**D2**	**D15**	**D15-21 of Cycle**	**30 ± 7 Days After Last Dose**	
	Visit Window	**D -28 to D1**			**+ 1D**	**± 5D**			**± 2 weeks**
	Immunogenicity			X				X	

Abbreviations: AE = adverse event; BM = bone marrow; CR = complete remission; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; FDG = fluorodeoxyglucose; HL = Hodgkin lymphoma; ICF = informed consent form; IEC = Independent Ethics Committee; CCI IRB = Independent Review Board; IRF = independent review facility; OS = overall survival; OSFUP = Overall survival follow-up; PET = positron emission tomography; PFSFUP = Progression-free survival follow-up; PK = pharmacokinetic(s); PN = peripheral neuropathy; r/r = relapsed or refractory; CCI

Tests and procedures should be performed on schedule, but occasional changes are allowable (± 3 days) for administrative reasons unless indicated otherwise.

a EOT evaluations should be obtained before initiation of nonprotocol therapy. If EOT evaluations are completed before 30 days±7 days after the last treatment, the site will conduct a phone screen 30 to 37 days after the patient's last treatment to ensure that no changes in the AE profile have occurred.

b Patients who discontinue study treatment with a CR, a PR, or stable disease will have CT scans done every 3 months for 18 months after EOT or until the sooner of disease progression, death, or study closure. For patients who complete the PFSUP period with a CR, a PR, or stable disease, a CT scan will be performed during OSFUP at the time of progressive disease, and the results will be sent to the IRF. Assessment for OS will be performed every 3 months for 18 months after the EOT; thereafter, assessment for OS will continue every 6 months until the sooner of death, study closure, or 5 years after enrollment of the last patient.

c Tumor tissue from the most recent biopsy is preferred. Unstained slides or a paraffin-embedded block will be obtained after the patient has signed the ICF. Patients who cannot provide at least 10 histological slides from their most recent biopsy will undergo a new tumor biopsy during screening. This sample will be used to confirm HL and CD30+ status by central laboratory review.

d A serum or urine pregnancy test will be performed for women of childbearing potential during screening. If the screening test was performed more than 4 days before the first dose of study drug, a serum or urine pregnancy test should be repeated. The results must be negative within 4 days before the first dose of brentuximab vedotin is administered. 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.

e Once disease progression is documented, the physical examination is not required.

f Cycle 1, Day 1 samples may be collected within 4 days before dose administration to ensure patient eligibility on study Day 1. In this situation, it need not be repeated on Cycle 1, Day 1. Samples will be taken before dose administration on Day 1 of each 3-week cycle at Cycles 2 through 16.

g Includes SAEs reported before treatment with the study drug. SAEs pretreatment will be reported to Millennium Pharmacovigilance or designee from the time of signing the ICF to time of administration of the first dose of study drug, but will not be recorded on the eCRF. After the 30-day posttreatment

		Screening	**Enrollment (date of first dose)**	**Each 3-Week Cycle**			**Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 Only**	**EOT[a]**	**PFSFUP/ OSFUP[b]**
	Day (D)		**Within 24 Hours of First Dose**	**D1**	**D2**	**D15**	**D15-21 of Cycle**	**30 ± 7 Days After Last Dose**	
	Visit Window	**D -28 to D1**			**+ 1D**	**± 5D**			**± 2 weeks**

period, SAEs that are considered to be related to the study drug must continue to be reported to the Millennium Department of Pharmacovigilance or designee for the duration of the study. See Section 10.3 of the study protocol for further SAE reporting details.

h Response to treatment and disease status assessments will be evaluated according to the Revised Response Criteria for Malignant Lymphomas[(1)] and confirmed by an IRF.

i Assessment should be repeated if the procedure was not done within the previous 6 weeks.

j PET scan done at baseline (screening) and at Cycles 4 and 7. No additional PET scans are required during the treatment period after Cycle 7, unless clinically indicated. A PET scan should be done at EOT only for those patients who discontinue study treatment without a postbaseline PET assessment.

k CCI [redacted]

l May be obtained within 60 days of administration of the first dose of brentuximab vedotin. If a positive BM biopsy was taken more than 60 days before the first dose and the patient has not received treatment in the interim, this procedure does not need to be repeated. A BM biopsy is required only for patients with previous known BM involvement or suspected infiltration suspicious of bone marrow involvement. When required, the BM biopsy will be obtained after the last dose of prior treatment and before the first dose of brentuximab vedotin.

m BM biopsy required to confirm a CR if the patient is BM positive at baseline. BM biopsy should be obtained within 2 weeks after documentation of a CR. BM biopsy does not need to be repeated once bone marrow is found to be negative.

n Patients will be followed for PFS every 3 months for a maximum of 18 months after the EOT. Assessment for OS will be done every 3 months for a maximum of 18 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 5 years after enrollment of the last patient. See Section 7.10 for posttreatment follow-up assessments. Information may be collected by telephone for patients with progressive disease during PFSFUP/OSFUP.

o [redacted]

p CCI [redacted]

Pharmacokinetic, Serum Biomarkers, and Immunogenicity Sampling Time Points

Cycle	Study Day	Time	Window	Relative Time	PK	CCI	Immunogenicity
Cycle 1	Day 1	Predose	within 2 h	START of infusion	X	[redacted]	X
		10 min	± 5 min	END of infusion	X		
	Day 2	24 h	+ 1 day	START of infusion	X		
	Day 15	336 h	± 5 days	START of infusion	X		
Cycle 2	Day 1	Predose	within 2 h	START of infusion	X		X
		10 min	± 5 min	END of infusion	X		
Cycle 3	Day 1	Predose	within 2 h	START of infusion	X		X
		10 min	± 5 min	END of infusion	X		
	Day 2	24 h	+ 1 day	START of infusion	X		
	Day 15	336 h	± 5 days	START of infusion	X		
Cycle 4 through 16	Day 1	Predose	within 2 h	START of infusion	X		X
		10 min	± 5 min	END of infusion	X		
EOT					X		X

Abbreviations: EOT = end of treatment; h = hours; CCI [redacted]; min = minutes; PK = pharmacokinetics; CCI [redacted]; CCI [redacted].

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
ABVD	doxorubicin, bleomycin, vinblastine, dacarbazine
ADC	antibody drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
alloSCT	allogeneic stem cell transplantation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
BM	bone marrow
BUN	blood urea nitrogen
CBC	complete blood count
CD30+	CD30-positive
C_{eoi}	concentration at the end of the infusion
CHF	congestive heart failure
CHL	classical Hodgkin lymphoma
CI	confidence interval
C_{max}	single-dose maximum (peak) concentration
CO_2	carbon dioxide
CR	complete remission or complete response
CRO	contract research organization
CRu	complete response unconfirmed
CSF	colony-stimulating factor
CT	computed tomography
CTCL	cutaneous T-cell lymphoma
CYP	cytochrome P_{450}
DLBCL	difuse large B-cell lymphoma
DNA	deoxyribonucleic acid

Abbreviation	Term
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOT	end of treatment
EU	European Union
EVA	ethyl vinyl acetate
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GM-CSF	granulocyte macrophage-colony stimulating factor
HED	human equivalent dose(s)
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HRS	Hodgkin-Reed-Sternberg
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IgG1	immunoglobulin G1
CCI	[redacted]
IND	Investigational New Drug
IRB	institutional review board
IRF	independent review facility
IRR	infusion-related reaction
IST	investigator sponsored trial
ITT	intent-to-treat
IV	intravenous; intravenously

Abbreviation	Term
IWG	International Working Group
IXRS® (IVRS/IWRS)	interactive voice response system and/or interactive web response system
JCV	John Cunningham virus
KS	Kaposi sarcoma
LDH	lactate dehydrogenase
LPHL	lymphocyte-predominant Hodgkin lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTCL	mature T cell lymphoma
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observable adverse effect level
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PE	polyethylene
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PR	partial remission or partial response
PT	preferred term
PVC	polyvinylchloride
sALCL	systemic anaplastic large cell lymphoma
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplantation
SPD	sum of the products of the largest diameters
SJS	Stevens-Johnson syndrome

Abbreviation	Term
SOC	system organ class
CCI	[redacted]
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
CCI	[redacted]
ULN	upper limit of the normal range
USA	United States of America
USP	United States Pharmacopeia
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

CD30 is a cell surface antigen expressed on several malignancies including Hodgkin lymphoma (HL), some mature T cell lymphoma (MTCL) subtypes, including anaplastic large cell lymphoma (ALCL), Kaposi sarcoma (KS), cutaneous T cell lymphomas (CTCL), a fraction of diffuse large B-cell lymphomas (DLBCL), some follicular lymphomas, and other lymphoproliferative diseases.[2, 3, 4, 5, 6] Brentuximab vedotin is an antibody drug conjugate (ADC) directed against the CD30 antigen and is being developed to treat patients with CD30-positive (CD30+) hematologic malignancies. HL is among the most common of these CD30+ malignancies.

1.1.1 Relapsed or Refractory Hodgkin Lymphoma

Hodgkin lymphoma is a malignancy involving the lymph nodes and lymphatic system. The World Health Organization (WHO) divides HL into 2 main types: classical HL (CHL), which accounts for 95% of reported cases and lymphocyte-predominant HL (LPHL), which accounts for 5% of reported cases. CHL is histopathologically defined by the presence of malignant Hodgkin-Reed-Sternberg (HRS) cells in a background of inflammatory cells. CD30 is the characteristic surface antigen expressed on HRS cells.

An estimated 11,777 new cases of HL were diagnosed in 2008 in the European Union (EU) and approximately 2631 deaths were reported as a result of the disease.[7]

Advances in the use of combined chemotherapy and radiotherapy over the past half century have dramatically improved outcomes for patients with HL. Common combination frontline therapies such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), result in complete remission for more than 80% to 90% of treated patients.[8, 9] However, after frontline treatment with multimodality therapy, including combination chemotherapy and radiation, relapse can be observed in up to 35% of patients with advanced-stage disease. An additional 5% to 20% of patients are refractory to treatment in the frontline setting.[10, 11, 12]

Therapeutic options for patients with refractory or relapsed disease are very limited, offer only modest clinical benefit, and carry a high morbidity rate.[13, 14] For patients whose disease is either refractory to, or relapses shortly after frontline therapy, the chance of a

complete response (CR) with second-line therapy has historically been approximately 20%.[15]

Multiagent chemotherapy followed by autologous stem cell transplantation (ASCT) remains a widely advocated salvage therapy for patients after failure of frontline therapy. However, more than half of these patients will eventually have disease relapse again or die of their disease, and others will be ineligible for transplantation because their disease does not respond to pre-ASCT salvage regimens.[8, 13, 14, 16, 17] Furthermore, while ASCT results in improved disease-free survival in clinical studies, an improvement in overall survival (OS) has not yet been shown from this treatment modality.[15, 18] ASCT is also known to be associated with significant morbidity and mortality.[19] Importantly, experiencing a CR with systemic therapy before stem cell transplantation (SCT) is the most critical clinical factor for long-term survival after SCT.[20]

1.1.2 Brentuximab Vedotin

Brentuximab vedotin (ADCETRIS®) is an ADC directed against the CD30 antigen. It is composed of the anti-CD30 chimeric immunoglobulin G1 (IgG1) monoclonal antibody cAC10 and the potent antimicrotubule drug monomethyl auristatin E (MMAE) connected by a protease-cleavable linker. cAC10 binds to the CD30 antigen, which has a very low expression on normal cells but is found on the HRS cells of HL, ALCL cells, and tumor cells of other lymphoproliferative disorders.

Brentuximab vedotin received accelerated approval from the United States (US) Food and Drug Administration (FDA) as ADCETRIS® on 19 August 2011 for the treatment of patients with HL after failure of ASCT and for the treatment of patients with HL who are not ASCT candidates after failure of at least 2 multiagent chemotherapy regimens, and for the treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least 1 prior multiagent chemotherapy regimen. Brentuximab vedotin also received conditional marketing authorization as ADCETRIS® in the EU by the European Medicines Agency (EMA) on 25 October 2012 for the treatment of adult patients with relapsed or refractory CD30+ HL following ASCT or following at least 2 prior therapies when ASCT or multiagent chemotherapy is not a treatment option, and for the treatment of adult patients with relapsed or refractory sALCL.

1.2 Preclinical Experience

Brentuximab vedotin has the potential to target and selectively deliver the microtubule-disrupting agent MMAE to CD30-expressing tumor cells. In vitro, cytotoxicity studies showed that it selectively killed human CD30+ HL and ALCL cells with nanomolar concentrations producing 50% inhibition (IC_{50} values). Antitumor activity has been demonstrated in xenograft models derived from human CD30+ HL and ALCL tumor cell lines.

The toxicity of multiple doses of brentuximab vedotin has been assessed in rats and monkeys. In both species, the primary test article-related toxicity was hypocellularity of the bone marrow and lymphoid depletion of the thymus. Microscopic lesions were also observed in the spleen in monkeys and rats, and in the lung, intestines, liver, and testes in rats. In addition, decreases in peripheral blood counts were observed in both species, and elevations in liver enzymes were seen in rats only. Neutropenia was the most clinically significant toxicity in monkeys, which resulted in secondary bacterial infections leading to early deaths after a single 6-mg/kg dose. Toxicity was dose dependent, with a no observable adverse effect level (NOAEL) of brentuximab vedotin 0.5 mg/kg in rats and 1 mg/kg in monkeys. Human equivalent doses (HED) are 0.32 and 0.08 mg/kg respectively.

Detailed information regarding the nonclinical pharmacology and toxicology of brentuximab vedotin may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

The accelerated approval of brentuximab vedotin in the USA and conditional approval in the EU was obtained on the basis of results from 6 completed phase 1 and phase 2 clinical studies, conducted in patients with CD30+ hematologic malignancies. A total of 357 patients received at least 1 dose of brentuximab vedotin in these 6 clinical studies, including 160 patients in the two pivotal phase 2 studies who received brentuximab vedotin 1.8 mg/kg intravenously (IV) every 3 weeks. The clinical data to date from sponsor-initiated studies support a favorable benefit-risk ratio for brentuximab vedotin in patients with relapsed or refractory classical HL.

Fourteen clinical studies with brentuximab vedotin were ongoing as of January 2013, sponsored either by Millennium Pharmaceuticals Inc. (Millennium: The Takeda Oncology Company) or Seattle Genetics Inc. In addition, brentuximab vedotin has been administered to patients with HL in a completed single-patient Investigational New Drug (IND) program

in the USA, a Canadian Special Access Program, and a Named Patient Program in countries worldwide other than the USA and Canada. Several investigator-sponsored trials (ISTs) are also in progress worldwide.

Phase 1, Dose-Escalation Studies

In the first-in-humans study, Study SG035-0001, a total of 45 patients with CD30+ hematologic malignancies received brentuximab vedotin at doses of 0.1 to 3.6 mg/kg IV every 3 weeks. The most commonly reported treatment-emergent adverse events (TEAEs) were fatigue (36% of patients), pyrexia (33%), and diarrhea, nausea, peripheral neuropathy, and neutropenia (22% each). Notable serious adverse events (SAEs) assessed by the investigator to be at least possibly related to study treatment included anaphylaxis, myocardial infarction, and peripheral neuropathy. The maximum tolerated dose (MTD) was determined to be 1.8 mg/kg administered IV every 3 weeks. Forty-two of the 45 patients in the study had a primary diagnosis of HL. The objective response rate (ORR) was 40%; 17 of 42 evaluable patients had an objective response, which included a CR for 9 patients and a partial remission (PR) for 6 patients with HL, according to the investigator assessment. Similar results were obtained by independent review facility (IRF) assessment.

In the second phase 1, dose-escalation study, Study SG035-0002, 44 patients with CD30+ hematologic malignancies received brentuximab vedotin at doses of 0.4 to 1.4 mg/kg IV weekly for 3 weeks of a 4-week cycle. This weekly regimen was designed to enable combination use with gemcitabine. However, efficacy with brentuximab vedotin monotherapy was considered to be sufficient, and no patient was enrolled in the planned brentuximab vedotin/gemcitabine combination treatment arm of the study. In patients with relapsed or refractory HL who received brentuximab vedotin 1.2 mg/kg weekly for 3 weeks of a 4-week cycle, the ORR (CR + PR) was 58% (95% confidence interval [CI], 27.7%; 84.8%) and the CR rate was 25% (95% CI, 5.5%; 57.2%). The most commonly reported TEAEs were peripheral sensory neuropathy (66% of patients), fatigue (52%), nausea (50%), diarrhea (32%), arthralgia (27%), pyrexia (25%), and decreased appetite, myalgia, and upper respiratory tract infection (23% each). Acute infusion-related reactions (IRRs) were reported for 6 patients and 2 patients (14%) who had an acute infusion reaction also had antitherapeutic antibodies (ATAs) at a postbaseline visit. Brentuximab vedotin was generally safe and well tolerated up to the MTD of 1.2 mg/kg.

Phase 2 Studies

In Study SG035-0003, a pivotal phase 2, single-arm, open-label study in patients with relapsed or refractory classical HL post-ASCT, brentuximab vedotin was administered IV at a dose of 1.8 mg/kg every 3 weeks. The median age of enrolled patients was 31 years (range, 15 to 77 years). The median duration of treatment with brentuximab vedotin was 27 weeks (range, 3 to 56 weeks), and the patients received a median of 9 cycles (range, 1 to 16 cycles) of therapy. Patients who had an objective response by IRF assessment received a median of 10 cycles of therapy per patient. The primary endpoint of the study was ORR (CR + PR), by an IRF assessment. Key secondary endpoints included duration of response, OS, and progression-free survival (PFS). The ORR, by IRF assessment was 75% (95% CI, 64.9%; 82.6%); the CR rate was 34% (95% CI, 25.2%; 44.4%); CCI [redacted]; and the median duration of response was 29.0 weeks (95% CI, 15.9, 52.1 weeks).

Similarly, brentuximab vedotin administered IV at the dose of 1.8 mg/kg every 3 weeks in Study SG035-0004, a pivotal phase 2, single-arm, open-label study conducted in patients with relapsed or refractory sALCL induced clinically meaningful and durable objective responses (CR + PR) and a high rate of CRs, and had a manageable safety profile in patients with relapsed or refractory sALCL.

1.3.1 Patients With Relapsed or Refractory HL and No Prior Autologous Stem Cell Transplantation

Limited data are available on the efficacy and safety of brentuximab vedotin in transplant-naïve patients with relapsed or refractory classical HL. However, a retrospective analysis was performed on data from 41 patients with relapsed or refractory HL who had not received a prior ASCT and received brentuximab vedotin 1.8 mg/kg every 3 weeks. Fifteen of these patients were enrolled in phase 1, dose-escalation or clinical pharmacology studies. The analysis also included data from patients who participated in a Named Patient Program.[21, 22]

These patients had received a median of 3 prior chemotherapeutic regimens (range, 1 to 7 regimens); 59% had Stage III or Stage IV disease at the time of study entry; and 25% of patients had an Eastern Cooperative Oncology Group (ECOG) performance score of ≥ 2. The results showed that these patients had clinically meaningful responses with an ORR of 54% and a CR rate of 22%, according to the investigator assessment, after a median of 5 cycles of brentuximab vedotin. In addition, the safety profile of brentuximab vedotin

appeared to be similar for patients who had received a prior ASCT and those who had not received an ASCT.[23]

1.4 Study Rationale

Brentuximab vedotin has demonstrated a compelling level of antitumor activity in terms of ORR (CR + PR) and CR rates in several studies conducted in patients with relapsed or refractory HL. Meta analyses based on CR rate, an endpoint associated with long-term clinical benefit in patients with HL, suggest that brentuximab vedotin may be superior to other third-line options in patients with relapsed or refractory HL post-ASCT and is comparable with salvage regimens used in the pretransplantation setting.[24] The robust antitumor efficacy of brentuximab vedotin may translate into substantive rates of durable remissions that do not appear to be observed with current therapies, without the severe or life-threatening toxicities that patients experience with those regimens.

For the subset of patients with relapsed disease who may be sensitive to salvage chemotherapy, current second-line regimens followed by ASCT may represent a curative approach. However, data are limited on therapy outcomes for patients with primary refractory disease, those who fail to experience a CR with second-line treatments, or those who are otherwise either not suitable for or do not have access to an ASCT.

The observed efficacy results for transplant-naïve patients with relapsed or refractory HL represent meaningful activity of brentuximab vedotin in this patient population and provide the opportunity for a higher proportion of this subset of patients to receive potentially curative SCT. While brentuximab vedotin has been approved for patients in this setting, the results from this study will further support the usefulness of this treatment option in this setting.

1.5 Potential Risks and Benefits

Brentuximab vedotin monotherapy was granted accelerated approval in the USA and conditional marketing authorization in the EU on the basis of results from 6 completed clinical studies, including two pivotal phase 2 studies, which showed a high rate of durable responses for patients with CD30+ hematological malignancies including HL. In the pivotal phase 2 study conducted in patients with HL, the ORR (CR + PR), by IRF assessment was 75% (95% CI, 64.9%; 82.6%) post-ASCT with a median duration of response of 29.0 weeks (95% CI, 15.9, 52.1 weeks).

Brentuximab vedotin is associated with peripheral neuropathy that is predominantly sensory. Peripheral motor neuropathy has also been reported. The data suggest that the risk of peripheral neuropathy and, in particular, Grade 3 peripheral neuropathy is related to cumulative exposure to brentuximab vedotin and the first onset of peripheral neuropathy tended to be reported at later cycles of brentuximab vedotin administration. Most reports of peripheral neuropathy were Grade 1 or Grade 2. Neuropathy was generally reversible with a median of approximately 16 weeks from onset to resolution or improvement of peripheral neuropathy symptoms. Neuropathy associated with brentuximab vedotin was managed by dose delay and/or dose reduction to 1.2 mg/kg, which seemed to mitigate worsening of neuropathy. No Grade 4 peripheral neuropathy was reported in the 6 completed studies that supported the marketing authorization applications. However, the administration of brentuximab vedotin should be discontinued for any patient who develops Grade 4 peripheral neuropathy. It is required that patients be monitored for symptoms of neuropathy, including hypoesthesia, hyperesthesia, paresthesia, a burning sensation, neuropathic pain, and weakness.

IRRs, including anaphylaxis, have been reported with brentuximab vedotin.[25] Without routine prophylaxis, approximately 11% of patients in the 2 pivotal phase 2 studies conducted with brentuximab vedotin, Studies SG035-0003 and SG035-0004, experienced IRRs. A similar incidence was reported for patients in the phase 1 studies. Most IRRs were Grade 1 or Grade 2 and were reported within the first 2 cycles of therapy. It is required that patients who are receiving brentuximab vedotin be monitored for IRRs. The experience with IRRs related to the administration of brentuximab vedotin supports administration by appropriately trained personnel and without routine prophylaxis. If an IRR occurs, the infusion should be interrupted, and the patient should receive appropriate medical management. Infusion interruption for IRR treatment generally resulted in completion of the dose. The brentuximab vedotin infusion may be continued after interruption at a lower rate of administration. Patients who experience a prior IRR should be premedicated according to institutional guidelines before the administration of subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid. If anaphylaxis occurs, the administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy administered.

Clinically significant clinical laboratory abnormalities were reported as adverse events (AEs) in the 2 pivotal phase 2 studies, Studies SG035-0003 and SG035-0004, conducted in patients with relapsed or refractory HL and sALCL, respectively. Central laboratory data were collected before dose administration only in each treatment cycle. Few patients in

these 2 studies had postbaseline worsening to Grade 3 or higher in clinical laboratory values. The most commonly reported clinical laboratory data for which new or worsening shifts to Grade 3 or higher were reported were low neutrophil and low lymphocyte counts (11% each of patients), low platelet counts and high glucose levels (6% each), and low leukocyte counts (5%). Only 1 patient in the pivotal phase 2 studies had Grade 3 increased alanine aminotransferase (ALT) and Grade 3 increased aspartate aminotransferase (AST) levels.

Complete blood counts (CBCs) are measured before each dose of brentuximab vedotin, and more frequent monitoring of the CBC should be considered for patients with Grade 3 or Grade 4 neutropenia. Severe, prolonged neutropenia of ≥ 1 week duration has been reported. If Grade 3 or Grade 4 neutropenia develops, the clinical management of the patient can include dose delays, dose reductions, or the permanent discontinuation of study treatment.

Any treatment that can decrease immune function may increase the risk of infections. Patients should therefore be monitored for the development of infection during the treatment period and up through 30 days after the last dose of brentuximab vedotin is administered.

Tumor lysis syndrome (TLS) has been reported in patients who received brentuximab vedotin. The reported cases of TLS were not considered to be life threatening, and affected patients continued to receive brentuximab vedotin after TLS was resolved. Patients with rapidly proliferating tumor and high tumor burden are at risk of TLS and should be closely monitored. If TLS is diagnosed, medically appropriate measures should be taken.

Stevens-Johnson syndrome (SJS) 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. If SJS occurs, the administration of brentuximab vedotin must be discontinued and the appropriate medical therapy administered.

Progressive multifocal leukoencephalopathy (PML), including fatal PML, has been reported in patients who received brentuximab vedotin. PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). PML is typically reported in immunocompromised patients and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, higher cortical dysfunction such as dysphasia or agnosia, and seizures. The onset of neurological deficits may occur over weeks to months. 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. Peripheral neuropathy, which has been reported with brentuximab vedotin, is not commonly reported with PML. If PML is suspected, a diagnostic evaluation should be performed (Section 6.6).

Preliminary population PK analyses of the effects of renal impairment on brentuximab vedotin metabolism suggest that no dose adjustments are necessary for patients with moderate renal impairment.

MMAE is primarily metabolized by cytochrome P450 (CYP)3A. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for AEs.

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. Please see Section 6.5 for appropriate precautions after administration of brentuximab vedotin.

Overall, considering the potential for therapeutic benefit of brentuximab vedotin in patients with relapsed or refractory classical HL and the frequently limited treatment options available to these patients with this life threatening disease, and the manageable safety profile of brentuximab vedotin, the benefit-risk assessment is considered to be favorable.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the antitumor efficacy, as determined by the ORR of single-agent brentuximab vedotin 1.8 mg/kg administered intravenously (IV) every 3 weeks, in patients with relapsed or refractory classical HL who are considered to be not suitable for SCT or multiagent chemotherapy.

2.2 Secondary Objectives

The secondary objectives are:

- To determine the duration of tumor control, including the duration of response (DOR), PFS, and CR rate, by IRF assessment after treatment with brentuximab vedotin

- To determine the proportion of patients who receive hematopoietic SCT, either ASCT or allogeneic stem cell transplantation (alloSCT) after treatment with brentuximab vedotin
- To determine OS after treatment with brentuximab vedotin
- To assess the safety and tolerability of brentuximab vedotin in this patient population
- To assess the pharmacokinetics (PK) of brentuximab vedotin
- To determine the immunogenicity of brentuximab vedotin

2.3 Tertiary/Exploratory Objectives

CCI

[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of the study is ORR (CR + PR), by IRF assessment.[1]

3.2 Secondary Endpoints

The secondary endpoints are:

- Duration of response, PFS, CR rate, and duration of CR, by IRF assessment

- Proportion of patients who receive SCT after treatment with brentuximab vedotin
- OS
- Incidence, severity, and relatedness of AEs; SAEs; and clinical laboratory abnormalities
- PK for brentuximab vedotin, MMAE, and total antibody
- The presence of ATAs to brentuximab vedotin

3.3 Tertiary/Exploratory Endpoints

CCI

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This phase 4, single-arm, multicenter study is designed to evaluate the efficacy and safety of brentuximab vedotin in adult patients 18 years or older with histologically confirmed CD30+ relapsed or refractory classical HL who have not received a prior ASCT and are considered to be not suitable for SCT or multiagent chemotherapy at the time of study entry. Patients who are considered to be not suitable for SCT or multiagent chemotherapy include those who experience disease progression within 90 days of the earliest date of complete remission (CR) or complete remission unconfirmed (CRu) after the end of treatment with multiagent chemotherapeutic regimens and/or radiotherapy, or experience disease progression during frontline multiagent chemotherapy or alternatively, experience disease relapse after treatment with at least 2 chemotherapeutic regimens, including any salvage treatments.

Brentuximab vedotin will be administered as a single, outpatient, 1.8-mg/kg IV infusion on Day 1 of each 3-week cycle. Patients with a CR, a PR, or stable disease should receive a minimum of 8 cycles, and all patients will be given the opportunity to complete a maximum of 16 cycles (see Section 15.1). Dedicated computed tomography (CT) scans (spiral preferred) of chest, neck, abdomen, and pelvis will be performed at baseline (screening) and Cycles 2, 4, 7, 10, 13, and 16; and fluorodeoxyglucose (FDG) positron-emission tomography (PET) scans will be done at baseline and at Cycles 4 and 7. No additional PET scans are required during the treatment period after Cycle 7 unless they are clinically indicated. A PET scan should be done at the end of treatment only for those patients who discontinue study treatment without a postbaseline PET assessment.

Measures of anticancer activity will be assessed by an IRF according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma.[1] Patients who experience disease progression at any time will discontinue the study drug. These patients will continue to be followed for OS. Patients with an objective response, either a CR or a PR, and are eligible for an SCT may discontinue receiving brentuximab vedotin and proceed to an SCT. These patients should receive at least 4 cycles of brentuximab vedotin before proceeding to SCT.

Safety assessments will include the incidence and severity of AEs and changes in clinical laboratory values, vital signs measurements, and physical examination findings. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, effective 14 June 2010.[26]

Clinical laboratory samples will be obtained before dose administration on Study Day 1 of each 3-week cycle at Cycle 2 through Cycle 16. Cycle 1, Day 1 samples may be collected within 4 days before dose administration to ensure patient eligibility on Day 1. Physical examination, including vital signs measurements, weight, ECOG performance status score, and CCI [redacted] will be performed on Day 1 of each treatment cycle. In addition, samples for PK, immunogenicity, [redacted] will be collected on Day 1 of each treatment cycle. [redacted]

A bone marrow biopsy is required only for those patients with previous known bone marrow involvement or suspected infiltration suspicious of bone marrow involvement. In addition, a bone marrow biopsy is required to confirm a CR in patients who have bone marrow

involvement or suspected infiltration suspicious of bone marrow involvement at baseline. The follow-up bone marrow biopsy specimen must be obtained within 2 weeks of documentation of a CR. Once the bone marrow specimen is negative, no further bone marrow evaluations are required.

Serum concentrations of brentuximab vedotin, ATA, and free drug (MMAE) will be measured. CCI [redacted]. A possible dose response for any such effects and the presence of ATAs may be subsequently examined. [redacted].

Patients may continue to receive the study treatment for a maximum of 16 cycles or until disease progression or unacceptable toxicity. Patients will have an end-of-treatment (EOT) visit 30 days (± 7 days) after receiving their last dose of study drug.

Patients who discontinue study treatment with a CR, a PR, or stable disease will have CT scans performed for assessment of PFS every 3 months for 18 months after EOT or until the sooner of disease progression, death, or study closure. For patients who complete the 18-month PFS follow-up assessment period with a CR, a PR, or stable disease, a CT scan will be performed during the OS follow-up period at the time of disease progression, and the results will be sent to the IRF. Posttreatment follow-up assessments for OS will be performed every 3 months for 18 months after the EOT; thereafter, assessment for OS will continue every 6 months until the sooner of death, study closure, or 5 years after enrollment of the last patient.

4.2 Number of Patients

At least 60 patients with relapsed or refractory classical HL who are considered to be not suitable for SCT or multiagent chemotherapy will be enrolled in this study at approximately 20 investigative sites in Europe and potentially other regions of the world. Patients who are enrolled in the interactive voice response system (IVRS) or interactive web response system (IWRS) (known as IXRS®) will be considered to be enrolled in the study. Enrolled patients who do not receive the study drug for any reason will not be replaced.

4.3 Duration of Study

Study enrollment is expected to take approximately 15 months. Patients will complete a Screening period of up to 28 days and may receive a maximum of 16 cycles of brentuximab vedotin. Patients will be followed for 30 days (+ 7 days) after administration of the last dose of brentuximab vedotin to permit the detection of any delayed treatment-related AEs. For

patients who discontinue the study treatment with a CR, a PR, or stable disease, posttreatment follow-up assessments for PFS will be performed every 3 months for 18 months after the EOT or until the sooner of disease progression, death, or study closure. For patients who complete the 18-month PFS follow-up assessment period with a CR, a PR, or stable disease, a CT scan will be performed during the OS follow-up period at the time of disease progression, and the results will be sent to the IRF. Posttreatment follow-up assessments for OS will be performed every 3 months for 18 months after the EOT; thereafter, assessment for OS will continue every 6 months until the sooner of death, study closure, or 5 years after enrollment of the last patient. The total study duration is anticipated to be approximately 6 to 7 years.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.
2. A diagnosis of relapsed or refractory classical HL, confirmed by biopsy if clinically feasible on the basis of local pathology review.
3. A history of at least 1 prior systemic chemotherapeutic regimen.
4. Not suitable for SCT or multiagent chemotherapy, according to 1 of the following criteria:
    - Disease progression within 90 days of the earliest date of complete remission (CR) or complete remission unconfirmed (CRu) after the end of treatment with multiagent chemotherapeutic regimens and/or radiotherapy
    - Progressive disease during frontline multiagent chemotherapy
    - Disease relapse after treatment with at least 2 chemotherapeutic regimens, including any salvage treatments

5. Bidimensional measurable disease, of at least 1.5 cm, as documented by radiographic technique (spiral CT scan preferred), per IWG Revised Response Criteria for Malignant Lymphoma.[1]

6. At least 1 of the following as evidence of relapsed or refractory classical HL:

    - Histologically documented CD30+ CHL from a biopsy obtained at least 4 weeks subsequent to the most recently delivered prior treatment with radiation, chemotherapy, biologics, immunotherapy, and/or other investigational agents

    - Interval tumor growth documented between 2 successive CT evaluations with the second evaluation occurring at least 4 weeks after delivery of any radiation, chemotherapy, biologics, immunotherapy, and/or other investigational agents

    - FDG-avidity by PET in a new tumor mass on CT that is unlikely to have an alternative explanation

    - Recurrent FDG-avidity by PET in a previously identified FDG-avid tumor mass on CT that had become negative

    - FDG-avid tumor mass by PET in conjunction with HL- related symptoms such as pruritus and B symptoms such as fever, night sweats, or > 10% weight loss, after infectious causes have been excluded.

7. Patients must have completed any prior immunotherapy (eg, rituximab) or radioisotopic therapy at least 12 weeks before the first dose of brentuximab vedotin in the absence of clear disease progression.

8. Patient has recovered to Grade 1 or lower toxicity related to radiotherapy, immunotherapy, and chemotherapy unless evidence of toxicity is due to underlying HL. If toxicity is related to underlying HL, Grade 2 or lower toxicity is acceptable.

9. ECOG performance status score of 0 or 1 (refer to Section 15.2).

10. Female patients who:

    - Are postmenopausal for at least 1 year before the screening visit, OR
    - 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 30 days 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.)

11. 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.)

12. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

13. Suitable venous access for the study-required blood sampling, including PK and serum biomarker sampling.

14. Clinical laboratory values as specified within 4 days before the first dose of study drug, unless due to the presence of underlying disease involvement, then recovery to less than or equal to Grade 2 toxicity:

    - Absolute neutrophil count ≥ 1000/μL, without growth factor support.

- Platelet count ≥ 50,000/μL, without transfusion support unless thrombocytopenia is due to documented bone marrow involvement with lymphoma.

- Total serum bilirubin must be < 1.5 × the upper limit of normal range (ULN) or ≤ 3 × ULN for patients with an indirect hyperbilirubinemia due to Gilbert's disease or documented hepatic involvement with lymphoma.

- ALT or AST must be ≤ 2.5 × ULN. AST and ALT may be elevated up to 5 times the ULN if their elevation can be reasonably ascribed to the presence of metastatic disease in the liver.

- Serum creatinine must be ≤ 1.5 × ULN.

5.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria are not to be enrolled in the study:

1. Previous treatment with brentuximab vedotin.

2. Previously received an ASCT or alloSCT.

3. Female patients who are 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 first dose of study drug.

4. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

5. Treatment with any investigational products within 4 weeks before the first dose of study drug.

6. Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug:

    - New York Heart Association Class III or IV heart failure (refer to Section 15.3)

    - Myocardial infarction within 6 months before the first dose of study drug

- Evidence of current uncontrolled cardiovascular conditions, including clinically relevant cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities

7. History of another primary malignancy that has not been in remission for at least 3 years. (The following are exempt from the 3-year limit: nonmelanoma skin cancer, curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear.)

8. Any active uncontrolled systemic viral, bacterial, or fungal infection.

9. Any antimicrobial, antiviral, or antifungal therapy within 1 week prior to the first dose of brentuximab vedotin (routine prophylaxis is acceptable).

10. Known cerebral/meningeal disease, including signs or symptoms suggestive of PML, or any history of PML.

11. Known human immunodeficiency virus (HIV).

12. Known hepatitis B surface antigen positive, or known or suspected active hepatitis C infection.

13. Grade 2 or higher peripheral neuropathy.

14. Current therapy with other systemic antineoplastic or investigational agents.

15. Therapy with corticosteroids at higher than or equal to 20 mg/day of prednisone equivalent within 1 week before administration of the first dose of brentuximab vedotin.

16. Patients with a known hypersensitivity to recombinant proteins, murine proteins, or any excipient contained in the drug formulation.

17. Patients with dementia or an altered mental state that would preclude the understanding and rendering of informed consent.

6. STUDY DRUG

6.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Brentuximab vedotin will be administered on Day 1 of each 3-week cycle. The dose of brentuximab vedotin is 1.8 mg/kg and is administered by outpatient IV infusion over approximately 30 minutes. Patients who have a CR, a PR, or stable disease should receive a minimum of 8 cycles and all patients will be given the opportunity to complete a maximum of up to 16 cycles of brentuximab vedotin. In the absence of infusion toxicities, the infusion rate for all patients must be calculated to achieve an approximate 30-minute infusion period. Brentuximab vedotin must not be administered as an IV push or bolus. Brentuximab vedotin should be administered through a dedicated IV line and cannot be mixed with other medications.

Dose administration is determined on the basis of the patient's weight, according to institutional guidelines; however, doses will be adjusted for patients who experience a ≥ 10% change in weight from baseline. The patient's actual body weight will be used except for those patients who weigh more than 100 kg. For patients who weigh more than 100 kg, the dose will be calculated on the basis of 100 kg. Brentuximab vedotin dose should be rounded to the nearest whole number of milligrams.

Additional information on the administration of brentuximab vedotin can be found in the Pharmacy Manual.

6.2 Dose-Modification Guidelines

6.2.1 Recommended Brentuximab Vedotin Dose Modifications for Treatment-associated Toxicity

Table 6-1 describes the recommended dose modifications for brentuximab vedotin for treatment-associated toxicity.

Table 6-1 Dose Modification Guidelines for Brentuximab Vedotin for Treatment-Associated Toxicity

	Nonhematologic (Excluding Neuropathy)	Hematologic	Peripheral Neuropathy
Grade 1	Continue at same dose.	Continue at same dose.	Continue at same dose.
Grade 2	Continue at same dose.	Continue at same dose.	For Grade 2 neuropathy, withhold dose until toxicity is ≤ Grade 1 or baseline, then resume treatment at the reduced dose of 1.2 mg/kg every 3 weeks.
Grade 3	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose.[a]	Withhold dose until toxicity is ≤ Grade 2, or has returned to baseline, then resume treatment at the same dose level.[b] Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles.	Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks.
Grade 4	Withhold dose until toxicity is ≤Grade 1 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the investigator after discussion with the sponsor.[a]	Withhold dose until toxicity is ≤ Grade 2, then resume treatment at the same dose. Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles. For the second occurrence of Grade 4 toxicity (if neutropenia, while receiving growth factor support), withhold dose until toxicity is ≤ Grade 2, then reduce the dose to 1.2 mg/kg and resume treatment after discussion with the sponsor.[b]	Discontinue brentuximab vedotin.

Abbreviations: G-CSF = granulocyte-colony stimulating factor; GM-CFS = granulocyte macrophage-colony stimulating factor.

Toxicity grading based on NCICTCAE version 4.03.

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

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

6.2.2 Criteria for Dose Interruption During a Cycle

Please refer to Table 6-1 for instructions on the criteria to determine the requirement for a dose interruption.

6.2.3 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

The cycle length for treatment with brentuximab vedotin will be 3 weeks. For a new cycle of treatment to begin, all drug-related toxicity must have resolved, according to the guidelines presented in Table 6-1.

If the patient fails to meet the criteria for treatment at the scheduled time for the next cycle of treatment, initiation of the next cycle should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for treatment have been met. 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 drug-associated toxicity experienced during the current cycle. Delays of longer than 3 weeks for drug-related toxicities require discontinuation of study treatment, unless the sponsor agrees that the benefit-risk assessment supports continued treatment with the study drug.

6.2.4 Criteria for Dose Reduction

Intrapatient dose reduction to 1.2 mg/kg may be allowed depending on the type and severity of toxicity (as previously described in Table 6-1) and after the sponsor and investigator review the available data for that patient.

After a dose has been reduced for a patient because of drug-related toxicity, the dose should generally not be increased for that patient to the previous dose at which the toxicity occurred. However, an intrapatient re-escalation to the previous dose may be permitted at the discretion of the investigator and only after discussion with the sponsor.

6.2.5 Criteria for Discontinuation of Brentuximab Vedotin

Criteria for discontinuation of the study drug are provided in Section 7.7. Please refer to Table 6-1 for further information regarding dose requirements for patients who discontinue the study drug due to toxicity.

Patients will attend the EOT visit 30 days (± 7 days) after receiving their last dose of the study drug. At the time of discontinuation of the study drug, all study procedures outlined for the EOT visit will be completed. The primary reason for study drug discontinuation will be recorded on the electronic case report form (eCRF).

If the sponsor and/or the investigator should discover conditions arising during the study that indicate that the study should be stopped, an appropriate schedule for termination will be instituted.

6.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Chemotherapy.
- Immunotherapy.
- No other investigational drug may be used during the treatment period of this study.
- Concurrent participation in another clinical study with medical intervention.

6.4 Permitted Concomitant Medications and Procedures

The following medications and procedures are allowed during the study:

- The use of topical, inhalational, and ophthalmic steroids is permitted. Corticosteroids are permitted as part of a premedication regimen or for the treatment of HL-related symptoms, according to institutional standards or to manage potential hypersensitivity.
- The use of hormonal therapy, provided that a stable dose was being administered for at least 1 month before study enrollment. No restrictions are placed on the use of hormonal contraceptives.
- The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable.
- The use of colony-stimulating factors (CSFs) for the treatment of neutropenia, according to institutional practice.
- Medications for IRRs, such as epinephrine, antihistamines, and corticosteroids; these medications should be available for immediate use.
- Palliative radiation or surgery if other sites of measurable disease remain.

6.5 Precautions and Restrictions

Use of CYP3A Inhibitors

MMAE is primarily metabolized by CYP3A. Patients who are receiving strong CYP3A inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse

reactions. Please refer to the Study Manual for a list of examples of strong CYP3A inhibitors.

Infusion-related Reactions

An IRR 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 for the IV administration of drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institutional standards. Medications for IRRs, such as epinephrine and antihistamines, should be available for immediate use. However, premedication should not be routinely administered before administration of the first dose of brentuximab vedotin.

Patients who experience a Grade 1 or Grade 2 IRR may receive subsequent brentuximab vedotin infusions with premedication consisting of acetaminophen, 650 mg orally, and diphenhydramine, 25 to 50 mg orally or 10 to 25 mg IV or according to institutional standards, administered 30 to 60 minutes before each 30-minute brentuximab vedotin infusion.

Patients who experience a Grade 3 or Grade 4 IRR may potentially receive additional treatment with brentuximab vedotin at the discretion of the investigator only after discussion with the sponsor. If anaphylaxis occurs, the administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered to the affected patient.

Pregnancy

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 must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or

- Surgically sterile, or

- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent through 30 days 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.)

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

6.6 Management of Clinical Events

Nausea and/or Vomiting

Although this study will not initially employ prophylactic antiemetics, their use is not prohibited in the management of a patient who develops nausea and/or vomiting. As in the prophylactic setting, 5-hydroxytryptamine 3 ($5\text{-}HT_3$) serotonin receptor antagonists and corticosteroids should be used for treatment first in the management of patients with these side effects.

Diarrhea

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

Peripheral Neuropathy

Patients will be monitored closely for peripheral neuropathy throughout the study. Grade 2 or higher peripheral neuropathy may result in a dose modification for brentuximab vedotin, according to the guidelines previously described (Table 6-1).

Suspected Progressive Multifocal Leukoencephalopathy

Signs and symptoms of PML 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 approximately 20% of patients with PML. The onset of neurological deficits may occur over weeks to months. Refer to the IB for further details.

If PML is suspected, stop administration of brentuximab vedotin and undertake a diagnostic workup that may include (but is not limited to):

- Neurologic examinations, as warranted.
- Brain magnetic resonance imaging (MRI): Features suggestive of PML include presence of a focal lesion or multifocal lesions, mainly of the white matter, which are typically nonenhancing and do not have mass effect.
- Polymerase chain reaction (PCR) analysis: JCV deoxyribonucleic acid (DNA) detectable in cerebrospinal fluid or there is evidence of JCV in a brain biopsy.
- Neurology consultation.

Treatment with brentuximab vedotin must be permanently discontinued for patients with a confirmed diagnosis of PML.

Anaphylaxis

If anaphylaxis occurs, the administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered to the affected patient.

6.7 Blinding and Unblinding

Blinding is not applicable in this single-arm study.

6.8 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) or an equivalent standard, yields 11 mL of brentuximab vedotin solution (5 mg/mL).

6.9 Preparation, Reconstitution, and Dispensation of Brentuximab Vedotin

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 dose solutions are to be discarded using appropriate institutional drug disposal procedures according to the guidelines in the Study Manual.

Study treatment must be reconstituted with the appropriate amount of sterile water for injection (see the 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 an infusion bag containing a minimum volume of 100 mL.

No incompatibilities are known between brentuximab vedotin and polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), polyolefin, or polyethylene (PE) bags. The bag should be gently inverted to mix the solution. **The bag must not be shaken**; excess agitation may cause aggregate formation. The reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration before it is administered to the patient.

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.

6.10 Packaging and Labeling

Brentuximab 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.

6.11 Storage, Handling, and Accountability

Brentuximab vedotin must be refrigerated at 2°C to 8°C in a secure location (eg, locked room) that is accessible to the pharmacist, the investigator, or a duly designated person only.

Brentuximab vedotin does not contain preservatives; therefore, opened and reconstituted vials of brentuximab vedotin must be used within 24 hours of reconstitution when they are stored under refrigeration at 2°C to 8°C. Reconstituted brentuximab vedotin should not be stored at room temperature. It is recommended that brentuximab vedotin 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 study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

7.1 Study Personnel and Organizations

The contact information for the Millennium project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, the IRF, the IXRS (IVRS/IWRS) provider, and the contract research organization (CRO) 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

This is a single-arm study with no reference therapy. Treatment group assignments are not applicable. An IXRS (IVRS/IWRS) system will be used to enroll patients in this study.

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 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, according to country and local regulations.

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 7.4.12.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events. Physical examination will include a focused lymphoma assessment and an evaluation of skin, head, eyes, ears, nose, throat, nodes, heart, lungs, abdomen, back, extremities, and neurology.

7.4.5 Patient Height

Height will be measured only during screening (within 28 days before the first dose of brentuximab vedotin).

7.4.6 Patient Weight

Weight will be measured at times specified in the Schedule of Events. The actual dose of brentuximab vedotin is determined on the basis of the patients' weight, according to institutional guidelines; however, doses will be adjusted for patients who experience a 10% change from baseline in body weight (Section 6.1).

7.4.7 Vital Signs

Vital signs measurements will be assessed at times specified in the Schedule of Events and include seated (after 3 to 5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral temperature.

7.4.8 Pregnancy Test

A serum or urine pregnancy test will be performed for female patients of childbearing potential at times specified in the Schedule of Events.

7.4.9 Eastern Cooperative Oncology Group Performance Status

ECOG performance status score will be assessed at times specified in the Schedule of Events. See Section 15.2 for a description of the ECOG scale for performance status.

7.4.10 Tumor Specimen Measurements

If available, tumor tissue collected from the time of the most recent diagnostic biopsy of the original diagnosis or subsequent procedures for relapsed or refractory disease (unstained slides or a paraffin embedded block) will be obtained after the patient has signed the informed consent form (ICF). Patients who have an archived tumor specimen or at least 10 histological slides will not need to undergo a biopsy procedure at the time of screening. Patients who cannot provide archived tissue or at least 10 histological slides from their most recent biopsy will undergo a new tumor biopsy during screening. This sample will be used to confirm the diagnosis of classical HL and CD30 expression by central laboratory review. Central laboratory results for classical HL diagnosis are not required before administration of the first dose of study drug. Refer to the Schedule of Events for details regarding tumor tissue collection.

7.4.11 Electrocardiograms

A 12-lead electrocardiogram (ECG) will be administered at the time of screening, as specified in the Schedule of Events.

7.4.12 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures that the patient completes will be recorded in the eCRF as specified in the Schedule of Events. Refer to Section 6.3 for a list of excluded concomitant medications procedures and Section 6.4 for a list of permitted concomitant medications and procedures during the study.

7.4.13 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.14 Enrollment

A patient is considered to be enrolled in the study when he or she is enrolled in the IXRS (IVRS/IWRS). Procedures for completion of the enrollment information are described in the Study Manual.

7.4.15 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed centrally. Decisions regarding eligibility and administration of the study drug may be made by using local laboratory results. If local clinical laboratory values are used for either eligibility or study dose administration decisions, samples for central laboratory confirmation must be collected as specified in the Schedule of Events. 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 and urine samples for urinalysis will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (absolute neutrophil count [ANC])

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Gamma glutamyl transferase (GGT)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium

7.4.16 Disease Assessment

Response to treatment and disease status assessments will be evaluated according to the IWG criteria for patients with lymphoma.[1] Disease assessments will be performed as specified in the Schedule of Events. Records of disease assessments will be provided to the IRF for central review.

A CT scan, spiral preferred (chest, neck, abdomen, and pelvis), with contrast as appropriate, and PET scans will be performed at time points described in the Schedule of Events. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation by 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.

MRI scans may be substituted for CT scans for patients who have a glomerular filtration rate of < 60 mL/min and the IV contrast, therefore, presents a risk of renal failure; patients who develop anaphylaxis to IV contrast; or patients who become pregnant during posttreatment follow-up. If use of MRI is required, a consistent scanning modality must be maintained. Further details may be found in the Imaging Manual.

CCI [redacted] will be performed at the time points indicated in the Schedule of Events. A bone marrow biopsy may also be obtained for bone marrow assessment as specified in the Schedule of Events. A

bone marrow biopsy is required only for those patients with previous known bone marrow involvement or suspected infiltration suspicious of bone marrow involvement.

7.4.17 Pharmacokinetic Measurements

PK measurements will be taken for MMAE, ADC, and total antibody. PK values to be estimated may include the maximum plasma concentration (C_{max}) for MMAE, and concentration at the end of infusion (C_{eoi}) for brentuximab vedotin. Population PK methodologies may be used to determine PK parameters and covariates in this population.

All sampling times are relative to the end of the brentuximab vedotin infusion. For sample collection time points refer to the Schedule of Events. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

7.4.18 Serum Biomarkers

CCI

[redacted]

7.4.19 Immunogenicity

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

[redacted]

[redacted]

7.4.21 Cost Assessment

The cost of treatment will be assessed through the collection of health care utilization data. Valuation of the costs will be undertaken separately.

7.5 Completion of Treatment

Patients will be considered to have completed study treatment if they complete 16 cycles of 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 the EOT visit.

Regardless of the duration of treatment, all patients will remain on study for follow-up after receiving the last dose of study treatment until they withdraw consent for further follow-up, are lost to follow-up, or the study closes. Study closure will occur when 50% of patients have had an OS event or 5 years after the last patient is enrolled in the study, whichever occurs first. The total study duration is anticipated to be approximately 6 to 7 years. Refer to Section 7.10 for a posttreatment follow-up schedule.

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 the maximum number of cycles of brentuximab vedotin, as described in the protocol
- Progressive disease
- Initiation of hematopoietic stem cell transplantation
- Withdrawal of informed consent by the subject.

The reason for withdrawal from the study should be documented in the eCRF. Patients who discontinue the study treatment will remain on study for follow-up unless they withdraw consent for the follow-up phase of the study.

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

- Adverse event
- Protocol violation
- Symptomatic deterioration
- Study terminated by sponsor
- Withdrawal by patient
- 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. Some patients may discontinue the study drug for reasons other than progressive disease before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the Schedule of Events. Patients who experience disease progression will continue to be followed for OS.

Enrolled patients who do not receive the study drug for any reason will not be replaced. Patient enrollment will continue until at least 60 patients with relapsed or refractory HL who are considered to be not suitable for SCT or multiagent chemotherapy are available for analysis of the primary study endpoint, ORR (CR + PR).

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 by subject
- 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.

The reason(s) for withdrawal must be documented in the patient's medical records. The investigators will make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. Final treatment assessments will be performed before any other therapeutic intervention if possible.

Patients who discontinue study treatment with a CR, a PR, or stable disease will continue to be followed for PFS and will have CT scans performed every 3 months for 18 months after the EOT or until the sooner of disease progression, death, or study closure. For patients who complete the 18-month PFS follow-up assessment period with a CR, a PR, or stable disease, a CT scan will be performed during the OS follow-up period at the time of disease progression, and the results will be sent to the IRF. Posttreatment follow-up assessments for OS will be performed every 3 months for 18 months after the EOT; thereafter, assessment for OS will continue every 6 months until the sooner of death, study closure, or 5 years after enrollment of the last patient. Additionally, any planned alternative treatments should be documented on the patient's medical records and CRF.

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 (Progression-Free Survival and Overall Survival)

Posttreatment follow-up for all patients consists of a physical examination, CT scan, collection of OS/PFS status, and anticancer treatment for HL as specified in the Schedule of Events.

Patients who discontinue study treatment with a CR, a PR, or stable disease will have CT scans done every 3 months for 18 months after the EOT or until the sooner of disease

progression, death, or study closure. For patients who complete the 18-month PFS follow-up assessment period with a CR, a PR, or stable disease, a CT scan will be performed during the OS follow-up period at the time of disease progression, and the results will be sent to the IRF. Posttreatment follow-up assessments for OS will be performed every 3 months for 18 months after the EOT; thereafter, assessment for OS will continue every 6 months until the sooner of death, study closure, or 5 years after enrollment of the last patient. 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 to be related to study drug that occur during the posttreatment follow-up period. Refer to Section 10 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. For continuous variables, descriptive statistics will be used including number (n), mean, median, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be used for the analyses. The Kaplan-Meier survival curves will be provided along with their two-sided 95% CIs for time-to-event data.

No formal statistical hypothesis testing will be performed.

The statistical methods are outlined in subsequent sections; analysis details will be provided in the statistical analysis plan (SAP). The formal SAP will be developed and finalized before database lock.

8.1.1 Determination of Sample Size

At least 60 patients with relapsed or refractory classical HL who are considered to be not suitable for SCT or multiagent chemotherapy will be enrolled in this study. With a sample size of 60 patients and different ORRs, the two-sided 95% CIs will vary. An example is shown (Table 8-1).

Table 8-1 Overall Objective Response Rates and 95% Confidence Intervals (N = 60)

Response Rate, %	Number of Responders (CR or PR)	95% CI, %
20	12	(11, 32)
30	18	(19, 43)
40	24	(27, 53)
50	30	(37, 63)
60	36	(47, 72)

Abbreviations: CI = confidence interval; CR = complete remission; PR = partial remission.

8.1.2 Randomization and Stratification

Randomization and stratification are not applicable to this single-arm study.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

Intent-to-Treat (ITT): The ITT analysis population includes all patients enrolled in the study. The ITT analysis population will be used for analysis of the primary efficacy endpoint. Secondary and additional efficacy endpoints will also be analyzed using this analysis set.

Per-Protocol: The per-protocol analysis population includes all patients who receive at least 1 dose of brentuximab vedotin and who have measurable disease at baseline, the correct histological cancer type per central pathology review, and no other major protocol deviations that could potentially affect tumor response. The per-protocol analysis population will be used for analysis of the primary efficacy endpoint.

Safety: The safety analysis population includes all patients who receive at least 1 dose of brentuximab vedotin. The safety analysis population will be used for all safety analyses, and for patient demographics and baseline disease characteristics.

Pharmacokinetic: Patients with sufficient dosing and PK concentration-time data to reliably estimate PK parameters will be used for the PK analysis.

Biomarker: Patients with sufficient dosing and sufficient blood samples for analysis of serum biomarkers will be included in the biomarker analysis population.

Additional details of analyses and analysis sets of patients may be defined in the SAP.

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. The relevance of missing sample data will be assessed. Details on any sensitivity analyses and data handling details regarding issues such as missing data will be discussed in the SAP.

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

8.1.5 Demographic and Baseline Characteristics

Demographics, baseline characteristics, and prior medications will be summarized. Selected listings will also be provided.

8.1.6 Efficacy Analysis

The primary and secondary efficacy endpoints will be summarized. The corresponding two-sided 95% CI will be presented for selected efficacy endpoints. The standard survival analysis techniques of the Kaplan-Meier method will be utilized for time-to-event endpoints including duration of response, duration of response in the subset of patients with a CR, PFS by IRF assessment, CCI [redacted]

The primary efficacy analysis will use the ITT population. Secondary and additional efficacy endpoints will also be analyzed using the ITT population.

Detailed methodology will be provided in the SAP.

8.1.6.1 Primary Efficacy Analysis

The primary efficacy endpoint is the overall ORR (CR + PR), by IRF assessment, in patients with relapsed or refractory classical HL who are considered to be not suitable for SCT or multiagent chemotherapy.

The ORR by IRF assessment, and its two-sided 95% exact CI will be calculated by using the F distribution method.[27] This endpoint may also be tabulated by covariates such as sex, age (≤ 60 years and > 60 years), race, categorized weight (≤ 100 kg and > 100 kg), prior treatment, and ECOG performance status score. The maximum percent reduction in the sum of the products of the largest diameters (SPD) of the nodes or nodal masses being followed for response assessment will be graphically displayed.

The primary efficacy endpoint will also be analyzed for the per-protocol population.

The ORR (CR + PR), according to the investigator assessment and its two-sided 95% exact CI, will also be calculated.

8.1.6.2 Secondary Efficacy Analyses

The CR rate by IRF assessment will be derived and its two-sided 95% exact CI will be calculated by using the F distribution method.[27]

Duration of response by IRF assessment, duration of response in the subset of patients with a CR, PFS by IRF assessment, and OS will be estimated by using the Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. The median duration of response by IRF assessment, duration of response by IRF assessment in the subset of patients with a CR, PFS by IRF assessment, and OS and their two-sided 95% CI by Brookmeyer and Crowley[28] will be calculated. These endpoints may also be summarized by covariates such as sex, age, race, categorized weight, prior treatment, and ECOG performance status score, etc.

Descriptive statistics will be used to present the percentage of patients receiving SCT after treatment with brentuximab vedotin.

These efficacy endpoints, according to the investigator assessment will be similarly analyzed.

8.1.6.3 Additional Efficacy Analyses

Analysis of Other Efficacy Endpoints

PFS from the most recent prior treatment versus PFS as determined by the investigator from the current study will be presented by a Kaplan-Meier plot. CCI will be analyzed in the same manner.

CCI [redacted]

8.1.8 Pharmacokinetics/Biomarkers

Pharmacokinetic Analysis

The PK of MMAE and total antibody (free antibody and ADC) will be derived from serum or plasma concentrations versus time data for all patients who met study inclusion criteria, received the study drug, and had evaluable and adequate PK data. The reporting of PK parameters will be determined on the basis of final parameter analysis on the available data.

Immunogenicity

All patients who receive at least 1 dose of brentuximab vedotin will be evaluated for ATA development. A list/table of ATA status will be provided. ATA status (neutralizing or not neutralizing) will also be listed for patients who have positive antibody status. Immunogenicity information, including ATA and neutralizing ATA, will be summarized in descriptive statistics as applicable.

CCI [redacted]

8.1.9 Safety Analysis

The safety population will be used for all safety analyses.

8.1.9.1 Adverse Events

Safety will be evaluated by the incidence of AEs, treatment-emergent AEs, severity and type of AEs, the summary of ECOG performance status score, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results. Exposure to study drug and reasons for discontinuation will be tabulated. Total dose and duration of treatment will be summarized and listed. Dose modifications will also be summarized and listed.

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 summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) by primary system organ class (SOC), high-level term, preferred term (PT),

severity, and relationship to study drug. The relationship to study drug will be classified as "related" or "unrelated". All AEs will be listed with the pertinent patient information.

AEs will include the following categories:

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

AEs leading to dose modification, study medication discontinuation, or patient withdrawal will be summarized and listed in the same manner.

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. ECOG performance status scores will be summarized.

All medications taken by patients during the study will be recorded. Concomitant medications will be summarized by the WHO Drug Dictionary substance name. A listing of all concomitant taken by patients will be provided.

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

Electrocardiogram Analysis

A listing of ECG results at screening will be provided for each patient.

8.1.10 Interim Analysis

No formal interim analysis is planned for this study.

9. STUDY COMMITTEES

9.1 Data Safety Monitoring Board

An independent data monitoring committee (IDMC) will not be required for this single-arm study.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 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.

10.1.2 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.

10.1.3 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 paragraph below 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.[26] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or Grade 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 above, 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 Grade 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 serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 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 10.3 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 10.1) must be reported (see Section 10.3 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 and Pregnancy Reporting Contact Information

please refer to Section 15.4

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered to be AEs unless the condition deteriorated in an unexpected manner during the study (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.[26] 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?

10.3 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 time of administration of the first dose of the 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 the resolution to baseline or study closure, whichever occurs first, and recorded in the eCRF.

- SAEs that occur pretreatment will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the ICF up to the time of administration of the 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 administration of 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).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and 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 10.2). 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 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 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 IB.

11.2 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.

Study monitors 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.

11.3 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.

11.4 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. **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.

11.6 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.

11.7 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.

11.8 Investigator Compliance

The investigator will conduct the clinical study 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.

11.9 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.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the study 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.

11.11 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 MedComm Solutions (see below) 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 MedComm Solutions (see below) and report the event.

For Product Complaints and Medication Errors,
call MedComm Solutions at
1-510-740-1273 (international number)
1-866-835-2233 (for US sites)

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 PPD (refer to Section 10.2).

11.12 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 study 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.

11.13 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.

12. 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 study results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group comprising Millennium employees and study investigators will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual investigators may publish results from the study in compliance with their agreements with Millennium.

A prepublication manuscript or abstract is to be provided to Millennium a minimum of 30 days before the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by Millennium of the notification, Millennium shall inform the study centers whether it has objections to the publication for reasons including, but not limited to, those defined as follows:

- If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from Millennium's receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.

- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at Millennium's request.

The overall principal investigator will be the last author on abstracts and publications of the data generated from this study. Other authors will be listed according to number of patients enrolled to the study. If the principal investigator has the highest enrollment, he/she may choose to be either first or last author. This policy may be changed with the agreement of both the investigators and Millennium.

13. INVESTIGATOR AGREEMENT

I have read Protocol C25007: A Single-arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma Who Are Not Suitable for Stem Cell Transplantation or Multiagent Chemotherapy.

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)

14. REFERENCES

1. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. Journal of Clinical Oncology 2007;25(5):579-86.
2. Pizzolo G, Romagnani S. CD30 molecule (Ki-1 Ag): more than just a marker of CD30+ lymphoma. Haematologica 1995;80(4):357-66.
3. Horie R, Watanabe T. CD30: expression and function in health and disease. Seminars in Immunology 1998;10(6):457-70.
4. Chiarle R, Podda A, Prolla G, Gong J, Thorbecke GJ, Inghirami G. CD30 in normal and neoplastic cells. Clinical Immunology 1999;90(2):157-64.
5. Younes A, Carbone A. CD30/CD30 ligand and CD40/CD40 ligand in malignant lymphoid disorders. International Journal of Biological Markers 1999;14(3):135-43.
6. Gardner LJ, Polski JM, Evans HL, Perkins SL, Dunphy CH. CD30 expression in follicular lymphoma. Archives of Pathology & Laboratory Medicine 2001;125(8):1036-41.
7. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. In. Lyon, France: International Agency for Research on Cancer; 2010, accessed on 15 August, 2011.
8. Connors JM. State-of-the-art therapeutics: Hodgkin's lymphoma. Journal of Clinical Oncology 2005;23(26):6400-8.
9. Carde P, Johnson P. Principles of Chemotherapy in Hodgkin Lymphoma. In: Engert A, Horning S, editors. Hematologic Malignancies: Hodgkin Lymphoma. A Comprehensive Update on Diagnostics and Clinics. Berlin Heidelberg: Springer-Verlag; 2011. p. 141-161.
10. Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992;327(21):1478-84.
11. Kuppers R, Yahalom J, Josting A. Advances in biology, diagnostics, and treatment of Hodgkin's disease. Biol Blood Marrow Transplant 2006;12(1 Suppl 1):66-76.
12. Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Bezjak A, Wells WA, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. Journal of Clinical Oncology 2005;23(21):4634-42.

13. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. New England Journal of Medicine 1998;339(21):1506-14.

14. Baker KS, Gordon BG, Gross TG, Abromowitch MA, Lyden ER, Lynch JC, et al. Autologous hematopoietic stem-cell transplantation for relapsed or refractory Hodgkin's disease in children and adolescents. Journal of Clinical Oncology 1999;17(3):825-31.

15. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet 1993;341(8852):1051-4.

16. Horning SJ, Chao NJ, Negrin RS, Hoppe RT, Long GD, Hu WW, et al. High-dose therapy and autologous hematopoietic progenitor cell transplantation for recurrent or refractory Hodgkin's disease: analysis of the Stanford University results and prognostic indices. Blood 1997;89(3):801-13.

17. Kleiner S, Kirsch A, Schwaner I, Kingreen D, Schwella N, Huhn D, et al. High-dose chemotherapy with carboplatin, etoposide and ifosfamide followed by autologous stem cell rescue in patients with relapsed or refractory malignant lymphomas: a phase I/II study. Bone Marrow Transplantation 1997;20(11):953-9.

18. Holland DW, Engelhardt BG, Goodman SA, Greer JP, Morgan DS, Schuening FG, et al. High dose chemotherapy followed by autologous stem cell transplantation for relapsed or refractory Hodgkin's lymphoma. J Clin Oncol (Meeting Abstracts) 2006;24(18 suppl):abstr 7552.

19. Sureda A, Constans M, Iriondo A, Arranz R, Caballero MD, Vidal MJ, et al. Prognostic factors affecting long-term outcome after stem cell transplantation in Hodgkin's lymphoma autografted after a first relapse. Annals of Oncology 2005;16(4):625-33.

20. Horning S, Fanale M, deVos S, Borchmann P, Illidge T, Engert A, et al. Defining a population of Hodgkin lymphoma patients for novel therapeutics: an international effort. Annals of Oncology 2008;19(Suppl 4):iv121.

21. Rothe A, Sasse S, Goergen H, Eichenauer DA, Lohri A, Jager U, et al. Brentuximab Vedotin (SGN-35) in Patients with Relapsed/Refractory CD30-Positive Hematologic Malignancies without Prior High-Dose Chemotherapy and Stem Cell Transplantation. In: 54th ASH Annual Meeting and Exposition; 2012; Atlanta, GA; p. abstr 2743.

22. Gibb A, Jones C, Bloor A, Kulkarni S, Illidge T, Linton K, et al. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK Centre. Haematologica 2012.

23. ADCETRIS 50 mg powder for concentrate for solution for infusion [Summary of Product Characteristics]. London, United Kingdom: Takeda Global Research and Development Centre (Europe) Ltd; 2012. Report No.: EU/1/12/794/001.

24. Huebner D, Chi A, Liu Y. Activity of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large-cell lymphoma: Comparisons with meta-analyses of historical chemotherapy data. In: The 17th Congress of the European Hematology Association (EHA); 2012 14-7 June; Amsterdam, The Netherlands.

25. Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 2010;363(19):1812-21.

26. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

27. Collett D. Statistical inference for binary data. In: Modelling Binary Data. London, England: Chapman and Hall; 1991. p. 23-26.

28. Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

29. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

30. The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9 ed. Boston, MA: Little, Brown & Co; 1994.

15. APPENDICES

15.1 Response Definitions for Clinical Studies

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

Source: Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579-86.[1]

Abbreviations: CR = complete remission; CT = computed tomography; FDG = fluorodeoxyglucose; PD = progressive disease; PET = positron emission tomography; PR = partial remission; SPD = sum of the product of diameters; SD = stable disease.

15.2 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[29]

15.3 New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[30]

15.4 Serious Adverse Event and Pregnancy Reporting Contact Information

Please refer to Section 10 of the study protocol for complete details on AE/SAE definitions and reporting (including pregnancy and birth defects).

International (Countries Outside United States and Canada)
(24 hours/7 days a week)

Phone/ Helpline Instructions

To place a call using World Phone (WP)

1. Get a line with dial tone
2. Dial the Worldwide access number (international toll free number listed)
3. Listen for tone/chime and menu; enter five digit WP access code listed beside applicable Worldwide access number in the following table.

American Samoa	CCI [redacted]
Anguilla	
Antigua	
Argentina	
Aruba	
Austria	
Australia	
Bahamas	
Bahrain	
Bangladesh	
Barbados	
Belarus	
Belgium	
Belize	
Bermuda	
Bolivia	
Brazil	
British Virgin Islands	
Brunei	
Bulgaria	
Cayman Islands	
Chile	
China	
Colombia	
Cook Islands	
Costa Rica	

Croatia	CCI [redacted]
Cyprus	
Czech Republic	
Denmark	
Dominica	
Dominican Republic	
Ecuador	
Egypt	
El Salvador	
Estonia	
Fiji	
Finland	
France	
French Antillies	
French Guiana	
Gabon	
Georgia	
Germany	
Ghana	
Greece	
Grenada	
Guam	
Guatemala	
Guyana	
Haiti	
Honduras	
Hong Kong	
Hungary	
Iceland	
India	
Indonesia	
Iran	

CCI

Iraq	[redacted]
Ireland	
Israel	
Italy	
Ivory Coast	
Jamaica	
Japan	
Jordan	
Kazakhstan	
Kenya	
Latvia	
Lebanon	
Liechtenstein	
Lithuania	
Luxembourg	
Macau	
Macedonia	
Malaysia	
Malta	
Marshall Islands	
Mexico	
Micronesia	
Monaco	
Montserrat	
Morocco	
Netherlands	
Netherlands Antilles	
New Zealand	
Nicaragua	
Norway	
Pakistan	
Panama	
Paraguay	
Peru	

Philippines	CCI [redacted]
Poland	
Portugal	
Puerto Rico	
Romania	
Russia	
Rwanda	
Saipan	
Sakhalin Islands	
San Marino	
Saudi Arabia	
Senegal	
Singapore	
Slovak Republic	
South Africa	
South Korea	
Spain	
Sri Lanka	
St. Kitts/Nevis	
St. Lucia	
St. Pierre & Miquelon	
St. Vincent	
Sweden	
Switzerland	
Taiwan	
Thailand	
Tonga Islands	
Trinidad & Tobago	
Turkey	
Turks & Caicos	
Ukraine	
United Arab Emirates	
United Kingdom	

Uruguay	CCI [redacted]
U.S. Virgin Islands	
Uzbekistan	
Vatican City	
Venezuela	
Vietnam	
Zimbabwe	

International
(Countries Outside United States & Canada)

Reporting via Fax

All SAEs (regardless of their relationship to study drug), **must be reported within 24 hours of knowledge of the event** by FAX to the appropriate PPD PVG safety fax number:

To fax using World Phone (WP)

1. Get a line with a dial tone
2. Dial the Worldwide access number (international toll free number listed in table)
3. Listen for tone/chime and menu; enter five digit WP access code listed beside applicable worldwide access number provided in the table.
4. Note: Some fax machines may require pushing the “pause” or “add digit” or “star” button either 2 or 3

American Samoa	CCI [redacted]
Anguilla	
Antigua	
Argentina	
Aruba	
Austria	
Australia	
Bahamas	
Bahrain	
Bangladesh	
Barbados	
Belarus	
Belgium	
Brazil	
British Virgin Islands	

Brunei	CCI [redacted]
Bulgaria	
Cayman Islands	
Chile	
China	
Colombia	
Cook Islands	
Costa Rica	
Croatia	
Cyprus	
Czech Republic	
Denmark	
Dominica	
Dominican Republic	
Ecuador	
Egypt	
El Salvador	
Estonia	
Fiji	
Finland	
France	
French Antillies	
French Guiana	
Gabon	
Georgia	
Germany	
Ghana	
Greece	
Grenada	

CCI

Guam
Guatemala
Guyana
Haiti
Honduras
Hong Kong
Hungary
Iceland
India
Indonesia
Iran
Iraq
Ireland
Israel
Italy
Ivory Coast
Jamaica
Japan
Jordan
Kazakhstan
Kenya
Latvia
Lebanon
Liechtenstein
Lithuania
Luxembourg
Macau
Macedonia
Malaysia
Malta
Marshall Islands
Mexico
Micronesia
Monaco
Montserrat
Morocco

Netherlands	CCI
Netherlands Antilles	
New Zealand	
Nicaragua	
Norway	
Pakistan	
Panama	
Paraguay	
Peru	
Philippines	
Poland	
Portugal	
Puerto Rico	
Romania	
Russia	
Rwanda	
Saipan	
Sakhalin Islands	
San Marino	
Saudi Arabia	
Senegal	
Singapore	
Slovak Republic	
South Africa	
South Korea	
Spain	
Sri Lanka	
St. Kitts/Nevis	
St. Lucia	
St. Pierre & Miquelon	
St. Vincent	
Sweden	
Switzerland	

Taiwan	CCI
Thailand	
Tonga Islands	
Trinidad & Tobago	
Turkey	
Turks & Caicos	
Ukraine	
United Arab Emirates	
United Kingdom	
Uruguay	
U.S. Virgin Islands	
Uzbekistan	
Vatican City	
Venezuela	
Vietnam	
Zimbabwe	

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Clinical Approval	12-Jul-2013 14:17
	Clinical Approval	15-Jul-2013 21:06