CLINICAL STUDY PROTOCOL

A phase II study of brentuximab vedotin in patients with relapsed or refractory EBV- and CD30-positive lymphomas

Indication: **EBV and CD30-positive lymphomas**
Phase: **II**

Protocol History

Original; 15-DEC-2013 (version 1.0)

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Investigator & Study Center

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This is an investigator-initiated study. The principal investigator < (Tae Min Kim)>, (who may also be referred to as the sponsor-investigator), is the person conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

Study Title: A phase II study of brentuximab vedotin in patients with relapsed or refractory EBV- and CD30-positive lymphomas

Phase: II

Number of Patients: 25

Study Objectives

Primary

- Objective: To evaluate the overall response rate (ORR) of brentuximab vedotin in EBV- and CD30-positive lymphomas

Secondary

- Objective 1: To evaluate the safety profile of brentuximab vedotin using CTCAE version 4.03
- Objective 2: To calculate progression-free survival (PFS) time
- Objective 3: To calculate the duration of response
- Objective 4: To calculate overall survival (OS) time

Exploratory

- Objective 1: To determine the CD30-positive rate of EBV-positive lymphomas
- Objective 2: To compare ORR according to the CD30 expression level
- Objective 3: To compare ORR according to the soluble CD30 level
- Objective 4: To compare ORR according to the EBV copy number

Overview of Study Design:

This is an open-label, non-randomized, multi-center, phase II trial of brentuximab vedotin to evaluate ORR primarily in patients with EBV- and CD30-positive lymphomas. The ORR will be evaluated based on the revised Cheson's criteria[1] or modified SWAT criteria[2] in case of cutaneous EBV- and CD30-positive lymphomas. Based on the optimal Simon's two-stage design, at least 3 responders among stage 1 patients (N=10) are required to enter into a stage 2. The stage 2 will be delayed until the completion of ≥4 cycles of study medication in the last patient in stage 1, so-called interim analysis of stage 1. Although an independent data monitoring committee (IDMC) is unplanned, central study coordinators will monitor the study and safety.

Study Population:

Inclusion criteria

1. Patients with relapsed or refractory EBV- and CD30-positive lymphomas
    i. EBV-positivity determined by EBV *in situ* hydridization at participating centers
        a. Extranodal NK/T-cell lymphoma, nasal type

b. EBV-positive peripheral T-cell lymphoma, not otherwise specified

c. EBV-positive diffuse large B-cell lymphoma of the elderly

d. Plasmablastic lymphoma

e. Lymphomatoid granulomatosis

f. Hydroa vacciniform-like T-cell lymphoma

g. Other EBV-positive lymphoproliferative disorders

ii. CD30-positivity determined by a specialized hemato-pathologist

iii. Relapsed or refractory disease that fails to at least one and maximum four regimens including anthracycline-based chemotherapy; if anthracycline-based regimen is not standard treatment of certain subtypes (e.g. hydroa vacciniforme-like T-cell lymphoma or EBV-positive lymphoproliferative disorder, etc), a prior chemotherapy is acceptable.

2. Age ≥ 18 years

3. ECOG performance status 0-2

4. At least one measurable lesion based on revised Cheson's or modified SWAT criteria

5. Provision archival tumor tissues (4 μm thickness x 5 unstained slides) and blood samples

6. Voluntary written informed 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.

7. Female patient is either post-menopausal for at least 1 year before the screening visit **or** surgically sterile **or** if of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, **or** agrees to completely abstain from heterosexual intercourse.

8. Male patients, even if surgically sterilized, (i.e., status post vasectomy) agree to practice effective barrier contraception during the entire study period and through 6 months after the last dose of study drug, **or** agrees to completely abstain from heterosexual intercourse.

9. Adequate hematologic function: absolute neutrophil count (ANC) ≥1,500/μL, platelet count ≥ 75,000/μL, and hemoglobin ≥8.0 g/dL unless there is known hematologic tumor marrow involvement (ANC ≥ 1,000/μL and platelet count ≥ 50,000/μL if there is known bone marrow involvement)

10. Adequate liver function: total bilirubin < 1.5 x the upper limit of the normal (ULN) unless the elevation is known to be due to Gilbert syndrome and ALT or AST < 3 x ULN (AST and AST < 5 x ULN if their elevation can be reasonably ascribed to the presence of hematologic tumor in liver)

11. Adequate renal function: serum creatinine < 2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance > 40 mL/minute.

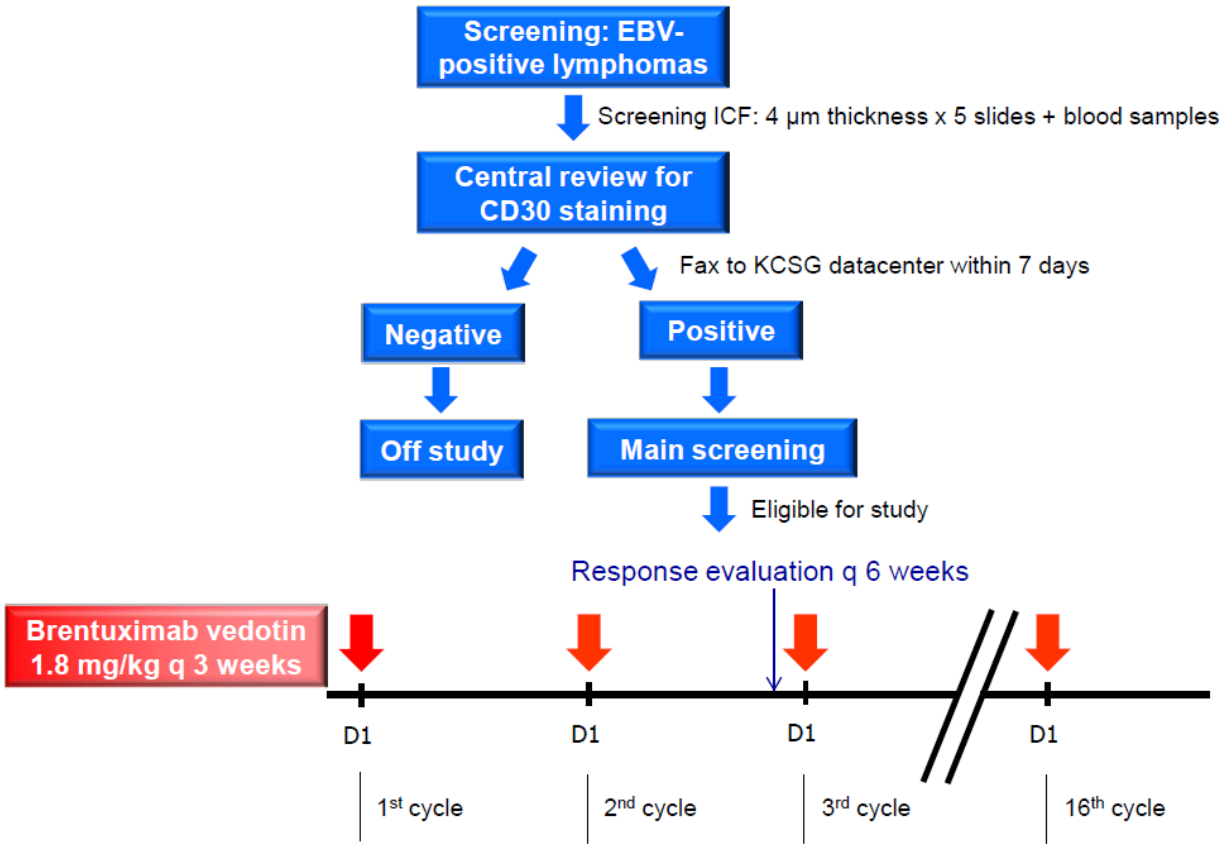
12. Expected survival > 3 months

Exclusion criteria

1. Female patient who are both lactating and breast-feeding or have a positive serum pregnancy test
2. Any serious medical or psychiatric illness
3. Known cerebral or meningeal involvement (EBV- and CD30-positive lymphoma or any other etiology), including signs or symptoms of PML
4. Symptomatic neurologic disease compromising normal activities or requiring medication
5. Any sensory or motor peripheral neuropathy greater than or equal to Grade 2
6. Known history of myocardial infarction within 1 year, NYHA class III/IV heart failure, or uncontrolled cardiovascular conditions including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Recent evidence (within 6 months before first dose of study drug) of a left-ventricular ejection fraction <50%.
7. Any active systemic viral, bacterial, or fungal infection within 2 weeks prior to first study drug dose
8. Any prior chemotherapy and/or other investigational agents within at least 5 half-lives of last dose
9. Prior stem cell transplantation within 100 days or radioimmunotherapy within 8 weeks
10. Prior exposure to CD30-targeted agents
11. Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin
12. Known human immunodeficiency virus (HIV) positive
13. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection
14. Another malignancy within 3 years before the first dose or previously diagnosed with another malignancy and have evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

Duration of Study: This study will last approximately 30 months to reach the final analyses of the ORR and PFS (24 months of enrollment plus 6 months of additional follow-up after the last patient-in).

STUDY OVERVIEW DIAGRAM



SCHEDULE OF EVENTS

Timetables: screening ~ end of treatment

	Screening	Cycle 1	Cycle 2	Cycles 3~15	Cycle 16	EOT/EOS	FU[a]
	-28 to D1	D1	D1	D1	D1	30 ± 7 after last IP dose	q 3 mo till study closure
Visit window, days		± 3	± 3	± 3	± 3		
Informed consent	X						
Inclusion/exclusion	X						
Demographics	X						
Medical history	X						
Tumor specimen and biomarker sample	X[b]						
Height	X						
Weight	X	X	X	X	X		
Physical exam	X	X[c]	X	X	X	X	X
Serum β-hCG	X[d]						
Urine pregnancy test		X					
Vital signs	X	X[e]	X	X	X	X	X
ECOG performance status	X		X	X	X	X	
B symptoms	X	X	X	X	X	X	X
Hematology and chemistry[f]	X	X	X	X	X	X	X
12-lead ECG	X						
Concomitant medication	Concomitant medications and procedures will be recorded from signing the main ICF through 30 days after the last dose of brentuximab vedotin.						
AE reporting		Recorded from first dose of study drugs through 30 days after the last dose of brentuximab vedotin.					
SAEs	SAEs will be collected from signing of the main ICF through 30 days after the last dose of brentuximab vedotin.						
CTs of the neck, abdomen, and pelvis[g]	X		X	X		X	
Skin evaluation[h]	X		X	X		X	
PET/CT[i]	X		X				
Survival and disease status							X[j]

a. All treated patients will be followed for PFS and OS status every 12 weeks (± 1 week) until the study closure. For patients who have progressive disease, survival/disease status and information regarding the initiation of an alternative lymphoma treatment may be obtained by phone call.
b. Tumor tissue at any time will be collected (five unstained slides at 4µm thickness or a paraffin-embedded block) after the patient has signed the screening ICF. This will be used to assess CD30 status using Ber-H2 antibody (DAKO, Glostrup, Denmark) and biomarkers associated with sensitivity or resistance to brentuximab vedotin (eg, beta3- tubulin etc). Biomarker samples will be collected (EDTA 5mL x1 plus SST 3mL x1) to assess lymphocyte subsets and soluble CD30 quantification.
c. The Cycle 1 Day 1 physical exam is not required if the screening physical examination was conducted within 7 days before administration of the first dose of brentuximab vedotin. A limited physical exam may be administered at the treating physician's discretion.
d. A serum β-hCG pregnancy test will be performed for women of childbearing potential during screening. A negative urine pregnancy test is required if the serum pregnancy test was not done within 7 days of the first dose of study drug.
e. Vital signs should be measured at screening and within 1 hour prior to infusion of brentuximab at day 1 of each cycle and EOT.
f. A blood sample for hematology and serum chemistry including LDH will be obtained at screening and pre-dose at day 1 of each cycle and EOT. Hematology and chemistry blood samples for cycle 1, day 1 may be collected within 7 days prior to dosing to ensure patient eligibility on study day 1.
g. Response to treatment and disease status assessments will be evaluated according to the Revised Response Criteria for Malignant Lymphomas[1] and the modified SWAT criteria.[2] MRI scans may be substituted for CT scans only if a patient 1) has a glomerular filtration rate of less than 60 mL/min such that IV contrast presents a risk of renal failure, 2) develops anaphylaxis to IV contrast, or 3) becomes pregnant during long-term follow-up. If use of MRI is required, a consistent scanning modality must be maintained.

During the treatment phase CT scans will be performed at:

1) Screening
2) CT scans of involved sites after cycle 2 of brentuximab every 6 weeks (window, ± 7 days) until progressive disease or 16th cycle of brentuximab vedotin. After last dose of cycle 16: between 4 and 8 weeks following last dose of brentuximab. During the follow-up period: every 3 months until the study closure.

h. In case of cutaneous lymphomas, total body skin scoring is calculated based on modified Severity Weighted Assessment Tool (mSWAT). This involves the direct assessment of the BSA of each type of skin lesions (palm plus fingers of the patient = approximately 1% BSA) in each of 12 areas of the body, multiplying the sum of the BSA of each lesion by a weighting factor (patch=1, plaque =2, and tumor = 3 or 4) and generating a sum of the subtotals of each lesions.
i. This is mandatory at sites where a PET scanner is available. For all patients, if the screening FDG-PET scan is non-avid, the second interim FDG-PET scan will not be performed.
j. Subjects will be followed for survival disease status every 3 months till the study closure.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Definition
A+AVD	brentuximab vedotin (ADCETRIS™) plus doxorubicin (Adriamycin), vinblastine, dacarbazine
ABVD	doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine
ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATA	antitherapeutic antibody
AUC	area under the plasma concentration versus time curve
AVD	doxorubicin (Adriamycin), vinblastine, and dacarbazine
BEACOPP	bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine, procarbazine, and prednisone
β–hCG	beta-human chorionic gonadotropin
BPT	bleomycin pulmonary toxicity
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CHOP	cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin®), prednisone
CI	confidence interval
CL	clearance, IV dosing
C_{max}	single-dose maximum (peak) concentration
CO_2	carbon dioxide
COPD	chronic Obstructive Pulmonary Disease
CR	complete remission
CR(u)	unconfirmed complete response
CSF	cerebral spinal fluid

CT	computed tomography
CTACK	cutaneous T-cell-attracting chemokine
CTCL	cutaneous T-cell lymphoma
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOCR	duration of complete remission
DOR	duration of response
DTIC	dacarbazine
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study (visit)
EOT	End of Treatment (visit)
ESMO	European Society for Medical Oncology
EU	European Union
FDA	United States Food and Drug Administration
FDG	Fluorodeoxyglucose
FLAIR	fluid-attenuated inversion recovery
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GHSG	German Hodgkin Study Group
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HNSTD	highest nonseverely toxic dose

HR	heart rate
HRQoL	health-related quality of life
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
IL-6	interleukin-6
INN	International Nonproprietary Name
IPS	(Hasenclever) International Prognostic Score
IRB	institutional review board
IRF	independent review facility
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
JCV	John Cunningham virus
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MMAE	monomethyl auristatin E
mPFS	modified progression-free survival
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
NYHA	New York Heart Association
ORR	objective response rate

OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PN	peripheral neuropathy
PR	partial response
PRO	patient-reported outcome
q3wk	every 3 weeks
QALY	quality-adjusted life year
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SCT	stem cell transplant
SD	stable disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SPD	sum of the product of the (tumor) diameters
$t_{1/2}$	terminal disposition half-life
Tab	total antibody
TARC	thymus- and activation-regulated chemokine
TGD	tumor growth delay
TGI	tumor growth inhibition
TK	toxicokinetics
TLS	tumor lysis syndrome
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
TNF-R	tumor necrosis factor-receptor
UK	United Kingdom
ULN	upper limit of the normal range

URTI	upper respiratory tract infection
US	United States
USAN	United States Adopted Name
USP	United States Pharmacopeia
Vss	steady state volume of distribution
WBC	white blood cell
WFI	water for injection
WHO	World Health Organization

1 BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Epstein-Barr virus (EBV), a member of the herpes virus family has been implicated in the development of B-cell or T/NK cell lymphoproliferative disorders.[3] EBV-associated lymphomas expressed various latent genes including EBNA-1, EBERs, LMP-1, and LMP-2 (latency I, II, and III).[4] According to the International T-Cell Lymphoma Project, virus-associated lymphomas generally pursue a grave prognosis: 5-year overall survival (OS), 14% and 42% for adult T-cell leukemia/lymphoma and extranodal NK/T-cell lymphoma, nasal type (NTCL), respectively.[5] Especially, EBV has been detected virtually in all NTCL cases and patients with NTCL showed clinical heterogeneity and poor survival outcomes (5-year OS 38%) in a national survey of the Korean Cancer Study Group.[6] In general, EBV-associated lymphomas showed poorer outcomes compared with EBV-negative ones in Hodgkin lymphoma,[7] peripheral T-cell lymphoma,[8] and diffuse large B-cell lymphoma.[9]

1.1.2 Study Drug

Brentuximab vedotin is an antibody-drug conjugate (ADC) composed of the anti-CD30 chimeric immunoglobulin G1 (IgG1) monoclonal antibody cAC10 and the potent antimicrotubule drug monomethyl auristatin E 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 some tumor cells.

ADCETRIS was granted accelerated approval by the U.S. Food and Drug Administration (FDA) in August 2011 for two indications: (1) the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and (2) the treatment of patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen.

ADCETRIS was granted conditional marketing authorization by the European Commission in October 2012 for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): (1) following autologous stem cell transplant (ASCT), or (2) following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

ADCETRIS has also been approved or submitted for approval in multiple other countries.

Brentuximab vedotin is contraindicated for hypersensitivity to the active substance or to any of the excipients. Combined use of bleomycin and brentuximab vedotin causes pulmonary toxicity.

1.2 Preclinical Experience

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

1.3 Pharmacology and Drug Metabolism in Humans

Further detailed information regarding the pharmacology and drug metabolism may be found in the European Summary of Product Characteristics (SmPC) and Investigators Brochure (IB).

Pharmacokinetic properties

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 studies and in a population pharmacokinetic analysis of data from 314 patients. In all clinical trials, brentuximab vedotin was administered as an intravenous infusion. Further detailed information regarding the pharmacokinetic properties of brentuximab vedotin may be found in the European Summary of Product Characteristics (SmPC) and Investigators Brochure (IB).

Distribution, Metabolism, and Elimination

In vitro, the binding of MMAE to human serum plasma proteins ranged from 68-82%. MMAE is not likely to displace or to be displaced by highly protein-bound medicines. The ADC is expected to be catabolized as a protein with component amino acids recycled or eliminated. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes. The ADC is eliminated by catabolism with a typical estimated CL and half life of 1.457 l/day and 4-6 days respectively. The elimination of MMAE was limited by its rate of release from ADC, typical apparent CL and half life of MMAE was 19.99 l/day and 3-4 days respectively.

Detailed information regarding distribution, metabolism and elimination may be found in the European Summary of Product Characteristics (SmPC) and Investigators Brochure (IB).

Pharmacokinetics in Special Populations

Detailed information regarding hepatic impairment, renal impairment, elderly patients and pediatric population may be found in the European Summary of Product Characteristics (SmPC).

Drug-Drug Interaction, Cardiac electrophysiology, Immunogenicity

Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73% and

did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin; however, it reduced exposure to MMAE by approximately 31%. Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam.

Forty-six (46) patients with CD30-expressing hematologic malignancies were evaluable of the 52 patients who received 1.8 mg/kg of brentuximab vedotin every 3 weeks as part of a phase 1, single-arm, open-label, multicenter cardiac safety study. The upper 90% confidence interval (CI) around the mean effect on QTc was <10 msec at each of the Cycle 1 and Cycle 3 post-baseline time points. These data indicate the absence of clinically relevant QT prolongation due to brentuximab vedotin administered at a dose of 1.8 mg/kg every 3 weeks in patients with CD30-expressing malignancies.

Patients with relapsed or refractory HL or sALCL in two phase 2 studies were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Approximately 35% of patients in these studies developed antibodies to brentuximab vedotin. The presence of antibodies to brentuximab vedotin did not correlate with a clinically meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin.

Detailed information regarding drug-drug interaction, cardiac electrophysiology and immunogenicity may be found in the European Summary of Product Characteristics (SmPC) and Investigators Brochure (IB).

1.4 Clinical Experience

In Study SG035-0001, a total of 45 patients with CD30+ hematologic malignancies (42 with HL, 2 with sALCL, 1 with angioimmunoblastic T-cell lymphoma) were treated with brentuximab vedotin at dose levels of 0.1 to 3.6 mg/kg administered intravenously (IV) every 3 weeks (Younes *et. al.* N Engl J Med. 2010 Nov 4; 363(19):1812-21). In Study SG035-0002, a total of 44 patients with CD30-positive hematologic malignancies (including 38 with HL) were treated with brentuximab vedotin at dose levels of 0.4 to 1.4 mg/kg administered IV weekly for 3 of 4 weeks (Fanale *et. al.* Clin Cancer Res. 2012 Jan 1;18(1):248-55).

Following Phase I experience, SG035-0003, a phase 2, single-arm, open-label study in patients with relapsed or refractory HL after ASCT, and SG035-0004, a phase 2 trial conducted in

patients with relapsed or refractory sALCL, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks. One hundred two patients with relapsed and refractory HL and 58 patients with relapsed and refractory sALCL were exposed for a median duration of approximately 27 weeks (9 cycles) and 20 weeks (6 cycles), respectively. Most patients (89%) in the 2 phase 2 studies were between the ages of 18 and 65 years. The primary endpoint of both studies was overall response rate (ORR) as assessed by an independent review facility (IRF). Key secondary endpoints included duration of response, CR rate per IRF, OS, and progression free survival (PFS). The key efficacy results in HL (SG035-0003) include ORR per IRF (75% [95% confidence interval (CI): 64.9-82.6%]), CR rate per IRF (33% (34 of 102 patients in ITT set), B symptom resolution rate (77%), and duration of response (DOR; 6.7 months). After approximately 3 years of follow-up (median observation time from first dose = 32.7 months, range, 1.8 to 48.3 months), the median PFS was 5.6 months (95% CI: 5.0, 9.0 months [range, 1.2 to 44.4+ months]) and the median OS was 40.5 months (95% CI: 28.7, – months [range, 1.8 to 48.3+ mos]). The estimated 36-month survival rate was 54% (95% CI: 44%, 64%). Key efficacy endpoints in sALCL (SG035-0004) include ORR per IRF (88% [95% CI: 74.6-93.9%]), CR rate per IRF (59% (34 of 58 patients in ITT set), and B symptom resolution rate (82%). Patients have been followed for approximately 3 years (median observation time from first dose = 33.4 months, range, 0.8 to 45.6 months). The estimated 36-month survival rate was 63% (95% CI: 51%, 76%) and the median PFS was 14.6 months (95% CI: 6.9, 20.6 months [range, 0.8 to 40.4+ months]). The median OS has not yet been reached (95% CI: 21.3, – months [range, 0.8 to 45.6+ months]).

Summary of the safety profile

Brentuximab vedotin was studied as monotherapy in 160 patients in two pivotal phase 2 studies (SG035-0003 and SG035-0004) (see section 5.1 of SmPC). Serious infections and opportunistic infections have been reported in patients treated with this medicine (see section 4.4 of SmPC). In the phase 2 population, 16% of patients experienced treatment-related infections. Serious adverse drug reactions were: neutropenia, thrombocytopenia, constipation, diarrhea, vomiting, pyrexia, peripheral motor neuropathy and peripheral sensory neuropathy, hyperglycemia, demyelinating polyneuropathy, tumor lysis syndrome and Stevens-Johnson syndrome.

The most frequently observed adverse reactions in patients receiving this treatment were: peripheral sensory neuropathy, fatigue, nausea, diarrhea, neutropenia, vomiting, pyrexia, and upper respiratory tract infection. Overall, 20% of HL patients and 28% of systemic ALCL patients in the pivotal studies (Studies SG035-0003 and SG035-0004) discontinued treatment

because of AEs. AEs that led to the treatment discontinuation of ≥2 HL or sALCL patients were peripheral sensory neuropathy and peripheral motor neuropathy.

The safety data reported from the phase 1 dose escalation and clinical pharmacology studies (n=15 patients) and from the Named Patient Program (NPP; n= 26 patients), in patients with relapsed or refractory HL who had not received an autologous stem cell transplant (see section 5.1 of SmPC), and were treated with the recommended dose of 1.8 mg/kg every three weeks, were consistent with the safety profile of the pivotal clinical studies.

Description of selected adverse reactions

Doses were reduced in patients for peripheral sensory neuropathy, which was the only AE that led to the dose reduction of more than 1 patient in either of the phase 2 studies. Adverse events that led to dose delays in the most patients were neutropenia, peripheral sensory neuropathy, and thrombocytopenia; the total percentage of doses delayed in HL patients was 8% (80 of 985 doses) and the total percentage of doses delayed in sALCL patients was 10% (47 of 476 doses). A total of 13 patients had an interruption or early stoppage to the infusion due to an AE.

Thirty-four patients (21%) in SG035-0003 and SG035-0004 had a treatment-emergent AE of neutropenia; for 20% of patients, neutropenia was ≥Grade 3 (13% at Grade 3 and 7% at Grade 4). The first onset of neutropenia (any grade) occurred within the first 4 cycles of treatment for most patients (82%), suggesting that neutropenia is not cumulative. Neutropenia ≥Grade 3 tended to develop after a median of 2 doses and last a median of approximately 1 week. Of the 7% of patients with Grade 4 neutropenia, 3 had neutropenia that lasted ≥7 days. No treatment-emergent AEs of febrile neutropenia were reported in the pivotal studies and no patient discontinued treatment because of neutropenia. In the pivotal studies (Studies SG035-0003 and SG035-0004), 89 patients (56%) had at least 1 treatment-emergent AE within the PN SMQ (56 patients [55%] in SG035-0003 and 33 patients [57%] in SG035-0004). The peripheral neuropathy symptoms that occurred in ≥5% of HL or ALCL patients were peripheral sensory neuropathy (47% HL, 41% ALCL), peripheral motor neuropathy (12% HL, 5% ALCL), paraesthesia (9% ALCL), and neuralgia (5% ALCL).

The median time to onset of any grade PN SMQ event was approximately 12.4 (HL) to 15.0 (ALCL) weeks. Peripheral neuropathy tended to worsen with longer treatment exposure. Median time to onset of Grade 2 neuropathy was 27.3 weeks for HL patients and 17.0 weeks for ALCL patients. Median time to onset of Grade 3 neuropathy was 38.0 weeks for HL patients and 36.1 weeks for ALCL patients.

PML has been reported in patients treated with brentuximab vedotin and has been fatal in

some cases. (see section 4.4 of SmPC). Acute pancreatitis has been reported in patients treated with brentuximab vedotin and has contributed to fatal outcomes in some cases. Onset typically occurred after 1 to 2 doses of brentuximab vedotin. Early symptoms included severe abdominal pain, nausea, and vomiting. The estimated incidence of acute pancreatitis in patients treated with brentuximab vedotin is≤0.5%. Approximately 1% of patients treated with brentuximab vedotin in the commercial or investigational setting have had an AE that was suggestive of a hepatobiliary disorder. The majority of events occurred after 1 to 2 treatment cycles and were characterized by asymptomatic mild to moderate transient elevation in aspartate aminotransferase and alanine aminotransferase. Elevated liver enzymes were observed upon rechallenge for some patients. Serious hepatobiliary disorders have been reported, but were confounded by comorbidities and/or concomitant medications with known hepatotoxic potential. Anaphylaxis has been reported outside of the pivotal phase 2 clinical trials discussed in this section. Symptoms of anaphylaxis may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm. Febrile neutropenia has been reported outside of the pivotal phase 2 clinical trials described in this section (see section 4.2). A patient enrolled in a phase 1 dose escalation trial experienced Grade 5 febrile neutropenia after receiving a single dose of 3.6 mg/kg of brentuximab vedotin.

Further details on these and other ongoing studies are provided in the Investigators Brochure (IB) and SmPC.

1.5 Study Rationale and Selection of Study Drug Doses

Although anthracycline-based regimen such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) has been the standard treatment of aggressive non-Hodgkin's lymphomas,[10] patients with EBV-positive lymphomas might relapse more frequently than those with EBV-negative lymphomas. Because CD30 is frequently expressed in EBV-infected lymphoid cells,[11] it is a druggable target at EBV- and CD30-positive lymphomas. In addition, CD30 is overexpressed in EBV-positive lymphomas: extranodal NK/T-cell lymphoma, nasal type, 72%[12]; EBV-positive peripheral T-cell lymphoma, 43%[13]; and EBV-positive diffuse large B-cell lymphoma (DLBCL) of the elderly, 70%.[14]

The high CR rate and ORR obtained with brentuximab vedotin in 2 single-arm phase 2 studies in relapsed or refractory HL (SG035-0003) and relapsed or refractory sALCL(SG035-0004) suggest that single-agent brentuximab vedotin may be active against CD30-positive lymphomas other than HL and sALCL. Single-agent brentuximab vedotin showed antitumor activity against refractory B-cell lymphomas with variable CD30 expression (0-100%): ORR 40% (CR 16%) and median duration of response 36 weeks (range, 0.1-62.3 weeks) for DLBCL; and ORR 22% and

median duration of response 21.7 weeks (range, 6.1-37.1 weeks) for other B-cell lymphomas.[15] Similarly, brentuximab vedotin is active against CD30-positive cutaneous T-cell lymphomas and lymphoproliferative disorders: ORRs 50% and 100% for Mycosis Fungoides and primary cutaneous ALCL/lymphomatoid papulosis, respectively.[16] However, it is unknown whether single-agent brentuximab vedotin is active against EBV- and CD30-positive lymphomas. Brentuximab vedotin monotherapy has previously been shown to be reasonably well tolerated in a phase 1 study and a phase 2 pivotal trial at 1.8 mg/kg in every 3 week dosing. Therefore, brentuximab vedotin at 1.8 mg/kg in every 3 week will be delivered in this study.

1.6 Potential Risks of brentuximab vedotin

As detailed in the Clinical Experience Section 1.4, brentuximab vedotin monotherapy has demonstrated therapeutic activity in CD30+ hematological malignancies.

Brentuximab vedotin treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. Monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness is required. Patients experiencing new or worsening peripheral neuropathy may require brentuximab vedotin dose modifications, including a dose delay (see Section 5.2 Dose Modification Guidelines).

Infusion-related reactions, including anaphylaxis, have occurred with brentuximab vedotin.[17] Monitoring of patients during infusion is required. If anaphylaxis occurs, the administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy administered. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related reaction should be premedicated according to institutional guidelines for subsequent infusions. Premedication may include acetaminophen, an antihistamine and a corticosteroid.

Clinically significant laboratory abnormalities were to be reported as adverse events per the phase 2 study protocols. The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥ Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%). Only 1 patient in the phase 2 studies had Grade 3 ALT and AST.

Any treatment that can decrease immune function may contribute to malignancy and infections; patients are to be monitored for these events during the treatment period and up to and including 30 days after the last dose of frontline therapy.

Complete blood counts should be monitored prior to each dose of brentuximab vedotin and more frequent monitoring should be considered for patients with Grade 3 or 4 neutropenia. Prolonged (≥ 1 week) severe neutropenia can occur. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions, or discontinuations (see Section 5.2 Dose Modification Guidelines).

Tumor lysis syndrome may occur. Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome and should be closely monitored. If tumor lysis syndrome occurs, take medically appropriate measures.

Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with brentuximab vedotin. Fatal outcomes have been reported. If Stevens-Johnson syndrome or toxic epidermal necrolysis occur, brentuximab vedotin must be discontinued and the appropriate medical therapy administered.

Progressive multifocal leukoencephalopathy (PML) has been reported with brentuximab vedotin use. PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). If PML is suspected, a diagnostic work-up should be performed, as described in Section 5.6 Management of Clinical Events.

Acute pancreatitis has been observed in patients treated with brentuximab vedotin. Fatal outcomes have been reported. Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis.

Cases of pulmonary toxicity have been reported in patients receiving brentuximab vedotin. Although a causal association with brentuximab vedotin has not been established, the risk of pulmonary toxicity cannot be ruled out.

Hepatotoxicity, predominantly in the form of asymptomatic, mild to moderate transient elevations in ALT/AST, has been observed during use of brentuximab vedotin.

Monomethyl auristatin E (MMAE) is primarily metabolized by CYP3A. Co-administration of brentuximab vedotin with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions. Co-administration of brentuximab vedotin with rifampicin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

Further detailed information regarding the potential risks and benefits of brentuximab vedotin may be found in the European Summary of Product Characteristics (SmPC) and Investigators Brochure (IB).

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 5.5 Precautions and Restrictions for appropriate precautions triggered by the administration of study medication.

Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial that studied brentuximab vedotin with bleomycin as part of a combination regimen (ABVD), the rate of noninfectious pulmonary toxicity was higher than the historical incidence reported with ABVD. Two events of pulmonary toxicity led to death. Monotherapy with brentuximab vedotin has not been associated with a clinically meaningful risk of pulmonary toxicity.

2 STUDY OBJECTIVES

2.1 Primary Objectives

To evaluate the overall response rate (ORR) of brentuximab vedotin in relapsed or refractory EBV- and CD30-positive lymphomas

2.2 Secondary Objectives

The key secondary objective is

To evaluate the safety profile of brentuximab vedotin using CTCAE version 4.03

Other secondary objectives include:

- To calculate progression-free survival (PFS) time
- To calculate the duration of response
- To calculate overall survival (OS) time

2.3 Exploratory Objectives

The exploratory objectives include:

- To determine the CD30-positive rate of EBV-positive lymphomas
- To compare ORR according to the CD30 expression level
- To compare ORR according to the soluble CD30 level
- To compare ORR according to the EBV copy number

3 STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoint is

ORR using the revised response criteria for malignant lymphoma or modified SWAT criteria

3.2 Secondary Endpoints

The key secondary endpoint is

AEs, SAEs, and assessments of clinical laboratory values

Other secondary endpoints include:

- PFS
- Duration of response
- CR rate
- The rate of interim PET-negativity
- OS

3.3 Exploratory Endpoints

Exploratory endpoints include:

- CD30-positivity
- Qualitative and semi-quantitative measures of CD30 expression
- Serum concentrations of soluble CD30 receptor
- Serum concentrations of EBV titer

4 STUDY DESIGN

4.1 Overview of Study Design

This is an open-label, non-randomized, multi-center, phase II trial of brentuximab vedotin to evaluate ORR primarily in patients with EBV- and CD30-positive lymphomas. The ORR will be evaluated based on the revised Cheson's criteria[1] or modified SWAT criteria[2] in case of cutaneous EBV- and CD30-positive lymphomas. Patients may receive up to 16 cycles of brentuximab vedotin.

Tumor measurements will be assessed (CT and PET scans) at screening, after completion of cycle 2 (Cycle 2 Day 21 ± 7 day), and at 4 to 8 weeks after the last dose of brentuximab vedotin. CT scans only will be used for the disease assessment follow-up every 3 months until the study closure.

Safety will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, as well as by measuring changes from baseline in the patient's vital signs, ECOG performance status, electrocardiogram (ECG), and clinical laboratory results.

Patients may discontinue therapy at any time. Patients will attend the EOT visit 30 (±7) days after completion of their last dose of brentuximab vedotin.

4.2 Number of Patients

Based on the optimal Simon's two-stage design, at least 3 responders among stage 1 patients (N=10) are required to enter into a stage 2. The stage 2 will be delayed until the completion of ≥4 cycles of study medication in the last patient in stage 1, so-called interim analysis of stage 1. A total of 25 patients with EBV- and CD30-positive lymphomas will be enrolled.

4.3 Duration of Study

This study will last approximately 30 months to reach the final analyses of the ORR and PFS (24 months of enrollment plus 6 months of additional follow-up after the last patient-in).

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. Patients with relapsed or refractory EBV- and CD30-positive lymphomas

a. EBV-positivity determined by EBV *in situ* hydridization at participating centers
   i. Extranodal NK/T-cell lymphoma, nasal type
   ii. EBV-positive peripheral T-cell lymphoma, not otherwise specified
   iii. EBV-positive diffuse large B-cell lymphoma of the elderly
   iv. Plasmablastic lymphoma
   v. Lymphomatoid granulomatosis
   vi. Hydroa vacciniform-like T-cell lymphoma
   vii. Other EBV-positive lymphoproliferative disorders

b. CD30-positivity determined by a specialized hemato-pathologist. CD30 positivity defined as 10% or greater tumor cells expressing CD30 at any intensity greater than or equal to 1+ with any cellular distribution pattern.

c. Relapsed or refractory disease that fails to at least one and maximum four regimens including anthracycline-based chemotherapy; if anthracycline-based regimen is not standard treatment of certain subtypes (e.g. hydroa vacciniforme-like T-cell lymphoma or EBV-positive lymphoproliferative disorder, etc), a prior chemotherapy is acceptable.

3. ECOG Performance status 0-2
4. At least one measurable lesion based on revised Cheson's or modified SWAT criteria
5. Provision archival tumor tissues (4 μm thickness x 5 unstained slides) and blood samples
6. Adequate hematologic function: absolute neutrophil count (ANC) ≥1,500/μL, platelet count ≥ 75,000/μL, and hemoglobin ≥8.0 g/dL unless there is known hematologic tumor marrow involvement (ANC ≥ 1,000/μL and platelet count ≥ 50,000/μL if there is known bone marrow involvement)
7. Adequate liver function: total bilirubin < 1.5 x the upper limit of the normal (ULN) unless the elevation is known to be due to Gilbert syndrome and ALT or AST < 3 x ULN (AST and AST < 5 x ULN if their elevation can be reasonably ascribed to the presence of hematologic tumor in liver)
8. Adequate renal function: serum creatinine < 2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance > 40 mL/minute.
9. Expected survival > 3 months
10. Voluntary written informed 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.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Female patient who are both lactating and breast-feeding or have a positive serum pregnancy test during the screening period or a positive pregnancy test on Day 1 before first dose of study drug
2. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to the protocol.
3. Known cerebral or meningeal disease (EBV- and CD30-positive lymphoma or any other etiology), including signs or symptoms of PML
4. Symptomatic neurologic disease compromising normal activities of daily living or requiring medications
5. Any sensory or motor peripheral neuropathy greater than or equal to Grade 2
6. Known history of any of the following cardiovascular conditions
    a. Myocardial infarction within 1 year of study enrollment
    b. New York Heart Association (NYHA) Class III or IV heart failure (see Appendix 12.2)
    c. Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities
    d. Recent evidence (within 6 months before first dose of study drug) of a left-ventricular ejection fraction <50%
7. Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to first study drug dose
8. Patients that have not completed any prior treatment chemotherapy and/or other investigational agents within at least 5 half-lives of last dose of that prior treatment
9. Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin.
10. Known human immunodeficiency virus (HIV) positive
11. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection
12. Diagnosed or treated for another malignancy within 3 years before the first dose or previously diagnosed with another malignancy and have evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

6 STUDY DRUG

6.1 Brentuximab Vedotin Administration

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

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

The dose of brentuximab vedotin is 1.8 mg/kg. Dosing is based on patients' weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥ 10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

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

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

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

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

6.2 Dose Modification Guidelines

Brentuximab vedotin dose modifications may change depending on the disease and combination with other drug(s).

Table 6-1 and Table 6-2 detail the recommended brentuximab vedotin dose modifications to be enacted in the event of treatment-associated toxicity.

Table 6-1 Recommended brentuximab vedotin Dose Modifications for Treatment-Associated Toxicity Excluding Neuropathy

Toxicity	≤Grade 2	Grade 3	Grade 4
Non-hematologic (excluding neuropathy)	Continue at same dose level.	Withhold dose until toxicity is ≤ Grade 1 or baseline, then resume treatment at the same dose and schedule [a].	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.[a]
Hematologic	Continue at same dose level.	Withhold dose until toxicity is ≤ Grade 2, or baseline, then resume treatment at the same dose level[b]. Consider growth factor support (G-CSF or GM-CSF) in subsequent cycles. [b]	Withhold dose until toxicity is ≤ Grade 2 or baseline, then resume treatment at the same dose and schedule. Consider growth factor support (G-CSF or GM-CSF) in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia .[b]

NOTE: Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03

a Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption. Brentuximab vedotin will be held for clinically meaningful Grade 3 or 4 electrolyte abnormalities.

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

Table 6-2 Dosing Recommendations for Treatment-Emergent or Worsening Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Sensory or Motor Neuropathy (Signs and Symptoms [abbreviated description of CTCAE])	Modification of Dose and Schedule
Grade 1(Asymptomatic; clinical or diagnostic observations only; intervention not indicated; paresthesia and/or loss of deep tendon reflexes)	Continue with the same dose and schedule
Grade 2 (Moderate symptoms; limiting instrumental activities of daily living)	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 3 (Severe symptoms; limiting self care activities of daily living)	
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue treatment
Grade 5 (Death)	

NOTE: Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03; see neuropathy; peripheral motor neuropathy; peripheral sensory neuropathy.

6.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Bleomycin: The concomitant use of brentuximab vedotin and bleomycin has resulted in increased pulmonary toxicity versus bleomycin alone. Co-administration of brentuximab vedotin and bleomycin is a contraindication.

Use of the following medications and procedures should be considered with caution:

Interaction with medicinal products metabolized through CYP3A4 route:

CYP3A4 Inhibitors: Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4/P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73%, and did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, refer to Table 6-1 Recommended brentuximab vedotin Dose Modifications for Treatment Associated Toxicity Excluding Neuropathy

CYP3A4 Inducers: Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4/P-gp inhibitor inducer, did not alter the plasma exposure to brentuximab vedotin; however it reduced exposure to MMAE by approximately 31

CYP3A4 Substrates: Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam; therefore brentuximab vedotin is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes.

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 chemotherapy premedication regimen or for the treatment of study disease per institutional standards.
- The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed.
- The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy.

6.5 Precautions and Restrictions

Infusion-Related Reactions

All infusions should be administered at a site properly equipped and staffed for anaphylaxis should it occur. Medications for treatment of hypersensitivity reactions, such as epinephrine, antihistamines and steroids, should be available for immediate use in the event of a reaction during administration and also during the observation period following the first brentuximab vedotin infusion.

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. Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below:

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 the informed consent form through 6 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse.

Male patients, even if surgically sterilized (i.e., status post-vasectomy) must agree to one 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 completely abstain from heterosexual intercourse.

6.6 Management of Clinical Events

Peripheral Neuropathy

Collectively, the data support that peripheral neuropathy is an effect of cumulative exposure to brentuximab vedotin. The first onset of any grade peripheral neuropathy increased incrementally with increasing numbers of cycles, and a trend toward increased incidence of first onset of Grade 3 peripheral neuropathy and peripheral motor neuropathy in later cycles was apparent. In line with these observations, the incidences of peripheral neuropathy (any SMQ event, Grade 3 event, and/or motor event) were highest in later cycles.

Neuropathy associated with brentuximab vedotin was managed using a combination of dose delay and reduction to 1.2 mg/kg. Dose delay and reduction appeared to mitigate worsening of neuropathy. For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at the 1.2 mg/kg dose level (or as specified in individual protocols). For Grade 4 peripheral neuropathy, brentuximab vedotin should be discontinued.

Hematological Toxicities

The hematological AEs of thrombocytopenia, anemia, and neutropenia were reported in the pivotal studies. Neutropenia was the most common hematological AE (21%) and was not unexpected based on the toxicology results from the sponsor's nonclinical program and phase 1 safety and clinical pharmacology studies. Although neutropenia was a common treatment-emergent AE in the pivotal studies, it appeared to be well managed with the protocol-specified recommendations for hematologic toxicity (i.e., dose delay, growth factor support). The median duration of Grade 3 or Grade 4 neutropenia was limited (1 week); 3 patients had Grade 4 neutropenia that lasted ≥7 days. Less than half of the patients with Grade 3 or 4 neutropenia had temporally associated infections, and the majority of temporally associated infections were Grade 1 or 2. Although not reported in the pivotal studies, febrile neutropenia has been reported in additional completed studies with brentuximab vedotin. Patients should be monitored for cytopenias.

For new or worsening Grade 3 or 4 neutropenia, dosing should be held until neutropenia improves to ≤ Grade 2 or baseline and then restarted at the same dose level (or as specified in individual protocols). Growth factor support (G-CSF or GM-CSF) should be considered for subsequent cycles (refer to Dose Modification Section 6.2).

Infusion-Related Reactions

Brentuximab vedotin is administered via IV infusion. Infusion of proteins can result in hypersensitivity reactions that may be fatal if not rapidly and appropriately managed. Infusion

interruption for IRR treatment generally led to the successful completion of the dose and continued treatment with brentuximab vedotin with or without IRR prophylaxis, according to the clinical judgment of the investigator.

Although the experience with IRRs related to brentuximab vedotin is limited, in part due to the low incidence observed to date, data support brentuximab vedotin administration by appropriately trained personnel without the need for routine prophylaxis. If IRR symptoms develop, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Premedication should be administered for subsequent infusions in patients who have experienced a prior IRR. If anaphylaxis occurs, brentuximab vedotin should be immediately and permanently discontinued and appropriate medical management instituted.

Infections

Serious and opportunistic infections have been reported for patients treated with brentuximab vedotin. Monitor patients for the emergence of possible bacterial, fungal, or viral infections.

Although infections were observed in 61% of patients in the completed phase 2 studies (Studies SG035-0003 and SG035-0004), the majority of infections were Grade 1 to 2 and occurred with an incidence comparable to that reported in similar populations. While serious infections were reported in 10% of patients, the majority of infections were not considered by the investigator to be related to brentuximab vedotin. Infection led to dose delay in 14% of HL patients and 7% of ALCL patients. No patient discontinued treatment because of infection. The infection with the highest incidence was Grade 1 or 2 URTI, which occurred in more HL than ALCL patients. Grade 3 or 4 infections occurred in 7% of HL patients and 12% of ALCL patients. No Grade 5 infections were reported. HL patients had a higher incidence of infections, largely reflective of the higher incidence of Grade 1 to 2 URTI (37%). Several factors may have contributed to this higher incidence, including the high frequency of respiratory tract infections in HL patients post-transplant, the lower median age of the HL patients compared with systemic ALCL patients, and differences in exposure to respiratory viruses. These URTIs, while frequent, led to dose delay in only 3 patients. Importantly, the rate of pneumonia was low, which is indicative of a low rate of progression from URTI to pneumonia, and the incidence was lower than that reported in the literature for comparable populations.

Stevens-Johnson Syndrome

Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with brentuximab vedotin. Fatal outcomes have been reported. If Stevens-Johnson syndrome or toxic epidermal necrolysis occur, brentuximab vedotin must be discontinued and the appropriate medical therapy administered.

Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) is typically reported in patients with acute leukemias and high-grade non-Hodgkin lymphomas after the initiation of cytotoxic therapy.

TLS has been reported with brentuximab vedotin. Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome. These patients
Should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.

Progressive Multifocal Leukoencephalopathy
PML can occur in patients receiving brentuximab vedotin. PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%). The onset of neurological deficits may occur over weeks to months.

Cognitive decline without accompanying deficits in motor or sensory function is uncommon. Optic nerve involvement, fever, and spinal cord disease are not typically associated with PML. In addition, peripheral neuropathy, which has been reported with brentuximab vedotin treatment, is not commonly reported with PML.

If PML is suspected, a diagnostic work-up should be performed. The work-up may include, but is not limited to:

- Neurologic examinations, as warranted
- Brain MRI: features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically non-enhancing and do not have mass effect.
- PCR analysis: JCV DNA detectable in CSF or there is evidence of JCV in a brain biopsy
- Neurology consultation

Brentuximab vedotin dosing should be held if PML is suspected. If PML is confirmed, brentuximab vedotin should be permanently discontinued.

Pulmonary Toxicity in Combination with Bleomycin
Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial that studied brentuximab vedotin with bleomycin as part of a combination regimen (ABVD), the rate of noninfectious pulmonary toxicity was higher than the

historical incidence reported with ABVD. Monotherapy with brentuximab vedotin has not been associated with a clinically meaningful risk of pulmonary toxicity. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately.

Acute Pancreatitis

Acute pancreatitis has been reported for patients treated with brentuximab vedotin. Patients should be monitored for signs of new or worsening acute abdominal pain and, if observed, a diagnostic workup for pancreatitis should be considered. A diagnostic workup may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. Brentuximab vedotin should be held for any suspected case of acute pancreatitis. Brentuximab vedotin should be discontinued if a diagnosis of acute pancreatitis is confirmed.

Hepatotoxicity

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

Embryogenesis, Reproduction, and Spermatogenesis

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. Therefore, women of childbearing potential and fertile men should be advised to use adequate and effective contraception during and after treatment with brentuximab vedotin.

6.7 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 50 mg of useable brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. The lyophilized product, after reconstitution with 10.5 mL sterile Water for Injection, USP, yields 11 mL of brentuximab vedotin solution (5 mg/mL concentration after reconstitution).

6.8 Preparation, Reconstitution and Dispensing

Brentuximab vedotin is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling brentuximab vedotin.

Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

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

Study treatment must be reconstituted with the appropriate amount of sterile water for injection. GENTLY swirl the vial until the contents are completely dissolved. **The vial must not be shaken or vigorously swirled**; excess agitation may cause aggregate formation. Visually inspect the reconstituted drug product for any particulate matter and discoloration.

The appropriate amount of reconstituted study treatment will be withdrawn from the vial(s) and diluted in a 150 to 250 mL infusion bag containing 0.9% Sodium Chloride Injection, USP.

There are no known incompatibilities between study treatment and polypropylene (PP), 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. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

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

6.9 Packaging and Labeling

Vials of study treatment will be packaged as one single-use vial per carton (kit). Vials and kits will be labeled to meet country-specific regulatory requirements.

6.10 Storage, Handling and Accountability

Vials containing brentuximab vedotin must be refrigerated at 2°C to 8°C in a secure location (e.g., locked room) accessible only to the pharmacist, the investigator, or a duly designated person.

Brentuximab vedotin does not contain preservatives; therefore, opened and reconstituted vials of study treatment must be used within 24 hours when 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**.

A study drug accountability log must be completed for all brentuximab vedotin dispensed and administered to study patients.

6.11 Study Compliance

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

6.12 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Lost to follow-up
- Progressive disease
- Study terminated
- Other

Patients who are withdrawn from the study will not be replaced.
At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents and CRF.

7 STATISTICAL AND QUANTITATIVE ANALYSES

7.1 Statistical Methods

In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. Kaplan-Meier survival curves will be provided along with their 2-sided 95% CIs for time-to-event data.

7.1.1 Determination of Sample Size

Optimal Simon's two-stage design

- α=0.05, β=0.20
- P_0=0.20, P_1=0.45
- Stage 1: 2/10 ($\geq$3 responders are required to move to stage 2)
- Stage 2: 7/22 (8 or more responses are required to reject the null hypothesis)
- Total patients: 22 + 3 (10% drop-out rate) = 25 patients

7.1.2 Randomization and Stratification

Not applicable

7.1.3 Populations for Analyses

The populations used for analysis will include the following:

Safety population: patients who receive at least 1 dose of study drug will be used for all safety analyses. All patients in the safety population will be analyzed according to the actual treatment received.

Intent-to-Treat (ITT) population: all patients randomized to treatment. All patients in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

Per-Protocol (PP) population: a subset of ITT patients who do not have a major protocol violation as determined by the project clinician. All decisions to exclude patients from the PP population will be made prior to database lock.

Response-Evaluable population: all patients with diagnosis as confirmed by an independent pathology review facility, with measurable disease at baseline, who receive at least 1 dose of study drug, and have at least 1 postbaseline response assessment.

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

7.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized, including gender, age, weight, height, BSA, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

7.1.6 Efficacy Analysis

All efficacy evaluations will be conducted using the ITT population unless otherwise specified. ORR will be used for the primary efficacy analysis using revised response criteria for malignant lymphoma (Appendix 12.3) or modified SWAT (Appendix 12.4) criteria. Duration of response in subjects with confirmed response is the time between first documentation of response and disease progression.

PFS and OS will be analyzed based on the ITT population using a stratified log-rank test. PFS is defined as the time from the date of randomization to the date of the first of (1) documentation of PD; (2) death due to any cause; (3) for patients who are confirmed non-complete responders, receipt of anticancer chemotherapy or radiotherapy for EBV- and CD30-positive lymphoma after completion of brentuximab vedotin. OS is defined as the time from the date of study enrollment to the date of death. Patients without documented death at the time of analysis will be censored at the date last known to be alive. Stratified log-rank testing will be used to compare OS between the groups. The hazard ratios along with the 95% CIs will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of the OS endpoint. Median survival times (if estimable), along with the 2-sided 95% CIs will be presented. Analysis of OS will be performed based on the ITT population.

7.1.7 Biomarkers

Baseline value of circulating biomarkers will be summarized by time point using descriptive statistics, as applicable. Descriptive statistics (eg, number of patients, mean, standard deviation, median, minimum, maximum) will also be provided to summarize the levels of soluble CD30 receptor and qualitative and semiquantitative measures of CD30 expression.

7.1.8 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to frontline therapy and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of brentuximab vedotin will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities

(MedDRA) and will include the following categories:

- Treatment-emergent AEs
- 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 by 10% of all patients)
- SAEs

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

7.1.9 Interim Analysis

Not applicable

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Drug Reaction (ADR)

An adverse reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure*.

* This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.

8.1.2 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.

8.1.3 Serious Adverse Event Definition

Serious adverse event (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 ho**spitalization (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 one 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 (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), whether pathogenic or non-pathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described 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 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.2 Procedures for Reporting Serious Adverse Events

AEs may be 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. 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 one comprehensive event. AEs which are serious must be reported to Millennium/Takeda Pharmacovigilance (or designee) from the first dose of brentuximab vedotin up to and including 30 days after administration of the last dose of brentuximab vedotin. Any SAE that occurs at any time after completion of brentuximab vedotin treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium/Takeda Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, the principal investigator, Tae Min Kim, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB. Regardless of expectedness or causality, all SAEs must also be reported to Millennium/Takeda Pharmacovigilance (or designee) within 24 hours of the sponsor-investigator's observation or awareness of the event (contact information provided below).

The sponsor-investigator should fax the SAE Form within 24 hours after becoming aware of the event. A sample of an SAE Form will be provided. Follow-up information on the SAE may be requested by Millennium/Takeda. The SAE report must include event term(s), serious criteria, and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the causality of the event(s) in relationship to study drug administration. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium/Takeda Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium/Takeda Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the sponsor-investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Millennium/Takeda Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study or study drug(s), as soon as possible but no later than 4 calendar days of such communication.

Millennium/Takeda Pharmacovigilance

SAE and Pregnancy Reporting Contact Information
US and Canada
Toll-Free Fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

All other countries (Rest of World)
Fax #: 1 202 315-3560
E-mail: takedaoncocases@cognizant.com

8.3 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. All pregnancies and suspected pregnancies must be reported to Millennium/Takeda Pharmacovigilance (or designee) immediately (see Section 8.2 for contact information). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Millennium/Takeda Pharmacovigilance will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium/Takeda Pharmacovigilance or designee

immediately (see Section 8.2 for contact information). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

9 ADMINISTRATIVE REQUIREMENTS

9.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (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 Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

9.2 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 in order 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, Investigator's Brochure, informed consent form, 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. Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB/IEC submission.

9.3 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 requirement(s).

9.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. If requested, the investigator will grant monitor(s) and auditor(s) from Millennium or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.5 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the

approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.
Any departures from the protocol must be fully documented in the source documents.

9.6 On-site Audits

Regulatory authorities, the IEC/IRB and/or Millennium may request access to all source documents, data capture records, 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.

9.7 Investigator and site Responsibility for Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. 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 applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

9.8 Product Complaints

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/Takeda 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 or Medication Errors, call MedComm Solutions at (US and International) 877-674-3784

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 Millennium/Takeda (refer to **S**ection 8.2).

9.9 Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Millennium/Takeda, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium/Takeda 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 drug

Should the study be closed prematurely, all study materials must be returned to Millennium/Takeda.

9.10 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

10 USE OF INFORMATION

All information regarding brentuximab vedotin supplied by Millennium/Takeda 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/Takeda. It is understood that there is an obligation to provide Millennium/Takeda 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/Takeda, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

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12 APPENDICES

12.1 Common Terminology Criteria for Adverse Events Version 4.03[4]

http://ctep.cancer.gov/reporting/ctc.html

12.2 New York Heart Association Classification of Cardiac Disease[5]

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 54angina 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 54angina 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 angina 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 54angina 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.

12.3 Revised response criteria for malignant lymphoma

Complete Remission (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptom if present prior to therapy.
2. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear.
3. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have been cleared on repeat bone marrow biopsy and EBV should be negative by EBV in situ hybridization (ISH).
4. In patients for whom FDG by PET is avid, incorporation of interim PET imaging results as follows: All CR requirements as described above. However, if a patient's PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative

Partial Remission (PR)

1. ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses.
2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the EBV-positivity should be specified by EBV ISH. Patients who achieve a CR by the above criteria, but who have persistent morphologic or molecular bone marrow involvement will be considered partial responders.
6. No new sites of disease should be observed (e.g., nodes > 1.5 cm in any axis).
7. For patients with FDG-avidity, an interim assessment should be made. For patients whose PET scan was positive before therapy, the post-treatment PET scan should be positive in at

least one previously involved site.

Stable Disease (SD)

1. Failure to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease
2. PET imaging should be positive at prior sites of disease with no new areas of involvement on the post-treatment PET scan.

Relapsed Disease (RD; after CR) or Progressive Disease (PD; for Patients with PR or SD)

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 × 1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. If FDG-PET imaging has been obtained, PD should only be designated if the CT criteria for progression have been met and the lesions are PET positive for patients with PET-positive disease prior to therapy. FDG-PET is not mandatory for surveillance of progression.

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, IHC 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; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
RD 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 one 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

12.4 Modified SWAT criteria for skin lesions

Definitions of skin lesions

1. Patch: any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present.
2. Plaque: any size lesion that is elevated or indurated: crusting or poikiloderma may be present.
3. Tumor: any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Modified SWAT tool

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

NOTE. mSWAT score equals summation of each column line.
Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.
*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Response in skin

T1 Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T1a (patch only) *v* T1b (plaque ± patch)

T2 Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T2a (patch only) *v* T2b (plaque ± patch)

T3 One or more tumors (≥ 1 cm diameter)

T4 Confluence of erythema covering ≥ 80% body surface area

Response	Definition
Complete response	100% clearance of skin lesions*
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease†	≥ 25% increase in skin disease from baseline or New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

NOTE. Based on modified Severity Weighted Assessment Tool score.
*A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome (see histologic criteria for early mycosis fungoides[7]), the response should be considered a partial response only.
†Whichever criterion occurs first.