Title: A Phase 4, Open–label, Single-Arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

NCT Number: NCT01909934

Protocol Approve Date: 27 August 2021

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

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CLINICAL STUDY PROTOCOL C25006 AMENDMENT 2

Brentuximab vedotin

A Phase 4, Open–label, Single-Arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

Protocol Number:	C25006
Indication:	Relapsed or refractory systemic anaplastic large cell lymphoma
Phase:	4
Sponsor:	Takeda Development Center (TDC) Americas, Inc. 95 Hayden Avenue, Lexington, Massachusetts 02421 USA TDC Americas, Inc. may be referred to in this protocol as "sponsor" or "Takeda".
EudraCT Number:	2012-004128-39
Therapeutic Area:	Oncology

Protocol History

Amendment 2	27 August 2021
Amendment 1	15 March 2013
Original	29 November 2012

Approved by:

Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

PPD

Signature *Date*
DD Month YYYY

Signature *Date*
DD Month YYYY

Rationale for Amendment 2

The protocol is being amended to update the sponsor's name and legal entity responsible for the study.

Purposes for Amendment 2

The purpose of this amendment is to:

- Update the sponsor's name and legal entity responsible for the study.
- Update the protocol signatories.

For specific examples of changes in text and where the changes are located, see Section 15.5.

PROTOCOL SUMMARY

Study Title: A Phase 4, Open-label, Single-Arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

Name of Principal Investigator: PPD

Number of Patients: At least 45 patients with histologically confirmed relapsed or refractory systemic anaplastic large-cell lymphoma (sALCL) will be enrolled in the study.

Study Objectives

Primary

- To assess the antitumor efficacy of single-agent brentuximab vedotin (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall objective response rate (ORR) in patients with relapsed or refractory sALCL following at least 1 multiagent chemotherapy regimen (CHOP or equivalent multiagent chemotherapy regimens with curative intent)

Secondary

- To determine duration of tumor control, including duration of response, progression-free survival (PFS), and complete remission (CR) rate with brentuximab vedotin
- To determine the proportion of patients receiving hematopoietic stem cell transplant (either autologous or allogeneic) after brentuximab vedotin therapy
- To determine overall survival (OS) with brentuximab vedotin
- To assess the safety and tolerability of brentuximab vedotin
- To assess the pharmacokinetics of brentuximab vedotin
- To determine the immunogenicity of brentuximab vedotin

CCI

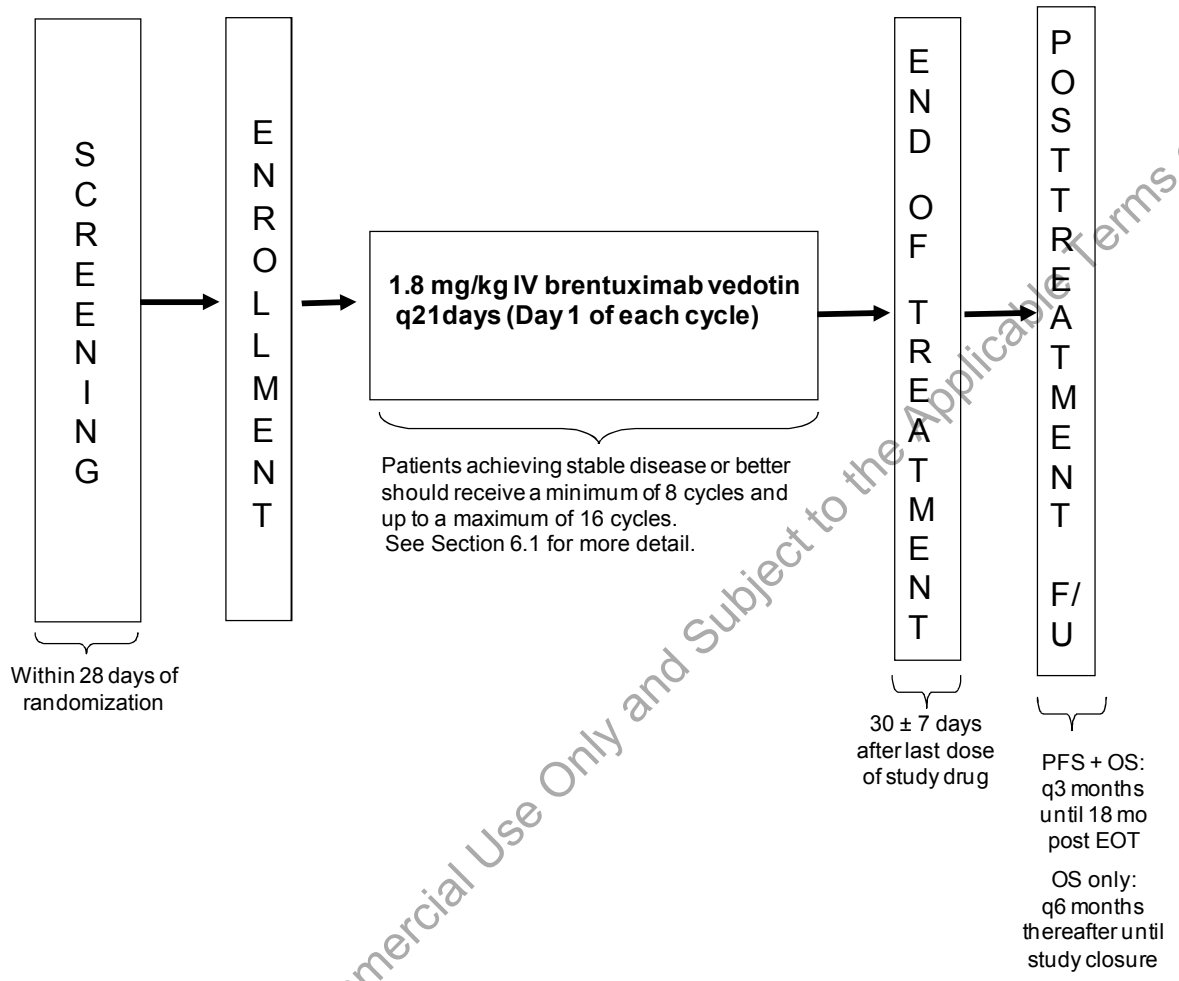
[redacted]

Overview of Study Design: This single-arm, open-label multicenter phase 4 clinical study seeks to evaluate the efficacy and safety of brentuximab vedotin as a single agent in patients with relapsed or refractory sALCL. Its primary objective is to determine the antitumor efficacy of single-agent brentuximab vedotin as measured by ORR in patients with relapsed or refractory sALCL following at least 1 multiagent chemotherapy regimen.

Brentuximab vedotin will be administered as a single intravenous (IV) infusion over 30 minutes on Day 1 of each 3-week cycle for up to a maximum of 16 cycles and should be administered for a minimum of 8 cycles for patients who achieve stable disease or better. Overall response will be

assessed by independent review facility (IRF) according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma (Cheson 2007).[1] Patients who experience disease progression at any time will be withdrawn from study drug treatment. Computed tomography (CT) scans (chest, neck, abdomen, and pelvis) will be performed at baseline and Cycles 2, 4, 7, 10, 13, and 16, and positron emission tomography (PET) scans will be done at baseline, Cycles 4 and 7, and, for patients who discontinue study treatment without a post-baseline PET assessment, at End of Treatment (EOT). Patients will have an EOT assessment 30 ± 7 days after receiving their final dose of study drug. Survival and disease status will be assessed every 3 months from EOT for 18 months, and then only OS will be assessed every 6 months thereafter until the sooner of death or study closure.
Study Population: Male or female patients aged 18 years or older, with histologically confirmed relapsed or refractory sALCL who have previously received at least 1 multiagent chemotherapy regimen (CHOP or equivalent multiagent chemotherapy regimens with curative intent) will be enrolled. Fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) and measurable disease of at least 1.5 cm by computed tomography ([CT] spiral preferred), as assessed by the site radiologist, are required.
Duration of Study: Patients will complete a Screening period of up to 28 days and receive treatment with study drug for a minimum of 8 cycles and up to a maximum of 16 cycles. Disease status (PFS and response) will be assessed every 3 months from EOT until the sooner of disease progression, death, or study closure. OS will be assessed every 3 months from EOT for 18 months, then every 6 months thereafter until the sooner of death or study closure. The study will be closed when 50% of patients have had an OS event or 5◦years after enrollment of the last patient, whichever occurs first. The total study duration is approximately 6 to 7 years.

STUDY OVERVIEW DIAGRAM



SCHEDULE OF EVENTS

		Screening	Enrollment (date of first dose)	Each 3 Week Cycle			Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 only	EOT[a]	PFSFUP/ OSFUP[b]
	Day (D)		Within 24 hours of first dose	D1	D2	D15	D15-21 of Cycle	30 ± 7 Days Post Last Dose	
	Visit Window	-28 to D1			+ 1D	± 5D			± 2 weeks
Screening/ Baseline	Informed consent	X	Enrollment						
	Inclusion/exclusion criteria	X							
	Tumor specimen	X[c]							
	Medical history	X							
	Demographics	X							
Safety Assessments	Height	X							
	Weight	X		X				X	
	Pregnancy test[d]	X		X[d]					
	Vital signs	X		X				X	
	Physical examination with focused lymphoma assessment[e]	X		X				X	X[f]
	ECOG performance status	X		X				X	
	Hematology and serum chemistry	X		X[g]				X	
	12-lead ECG	X						X	

		Screening	**Enrollment (date of first dose)**	**Each 3 Week Cycle**			**Additional Assessments at Cycles 2, 4, 7, 10, 13, and 16 only**	**EOT[a]**	**PFSFUP/ OSFUP[b]**
	Day (D)		**Within 24 hours of first dose**	**D1**	**D2**	**D15**	**D15-21 of Cycle**	**30 ± 7 Days Post Last Dose**	
	Visit Window	**-28 to D1**			**+ 1D**	**± 5D**			**± 2 weeks**
	Monitoring of concomitant medications and procedures	Recorded from signing informed consent form through 30 days after the last dose of study drug							
	Adverse event reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug						
	Serious adverse events	Serious adverse events[h] will be collected from signing informed consent form through 30 days after the last dose of study drug							
Disease Assessments	Dedicated CT (spiral preferred) of chest, neck, abdomen, pelvis[i]	X					X	X[j]	X[b]
	PET	X					X[k]	X[k]	
	B symptom assessment			X[l]				X[j]	
	Bone marrow biopsy	X[m]					X[n]		
	Survival/disease status and anticancer treatments for sALCL								X[o]
	CCI [redacted]								
	CCI [redacted]								
Treatment	Brentuximab vedotin administration			X					

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

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; BM = bone marrow; CR = complete response CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; CCI [redacted] ICF = informed consent form; OSFUP = overall survival follow-up; PET = positron emission tomography; PFSFUP = progression-free survival follow-up; PK = pharmacokinetics; SD = stable disease.

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

a EOT evaluations should be obtained before initiation of nonprotocol therapy.

b Patients who discontinue study treatment with SD or better will have CT scans done every 3 months from EOT for 18 months or until the sooner of disease progression, death, or study closure. Overall survival data will be collected every 3 months from EOT for 18 months, then every 6 months thereafter until the sooner of death or study closure.

c Tumor tissue from the most recent post-diagnosis biopsy is preferred. Unstained slides or a paraffin-embedded block will be obtained after the patient has signed the ICF. Patients without at least 10 histological slides from their most recent post-diagnosis biopsy will undergo a new tumor biopsy during screening. This sample will be used to confirm sALCL diagnosis and ALK status.

d A serum or urine pregnancy test will be performed for women of childbearing potential during screening. If the screening test was performed more than 4 days before the first dose of study drug, a serum or urine pregnancy test should be repeated. The results must be negative within 4 days before the first dose of brentuximab vedotin is administered. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of the IEC/IRB, or if required by local regulations.

e The focused lymphoma assessment will include a skin lesion assessment.

f Once disease progression is documented, the physical exam and lymphoma assessment are not required.

g Cycle 1, Day 1 samples may be collected within 4 days before dosing to ensure patient eligibility on study Day 1. In this situation it need not be repeated on Cycle 1, Day 1. Samples will be taken before dosing on Day 1 of each subsequent cycle.

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

h Includes serious pretreatment events. Serious pretreatment events will be reported to Takeda Pharmacovigilance or designee from the time of signing the ICF to first dose of study drug, but will not be recorded in the eCRF. See Section 10.3 of the study protocol for further SAE reporting details.

i Response to treatment and disease status assessments will be evaluated according to the Revised Response Criteria for Malignant Lymphomas (Cheson 2007) [(1)] and confirmed by an independent review facility.

j Assessment should be repeated if not done within the previous 6 weeks.

k PET scan done at Cycles 4 and 7. No additional PET scans are required during the treatment period beyond Cycle 7, unless clinically indicated. A PET scan should be done at EOT only for those patients who discontinue study treatment without a post-baseline PET assessment.

l B symptoms will be assessed before dosing on Cycle 1, Day 1 and on Day 1 of each subsequent cycle.

m May be obtained within 60 days of first dose of brentuximab vedotin. If a positive BM biopsy was taken more than 60 days before the first dose and the patient has not received treatment in the interim, this does not need to be repeated. When required, the BM biopsy will be obtained after the last dose of prior treatment and before the first dose of brentuximab vedotin.

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

o Patients who discontinue study treatment with SD or better will have disease status followup every 3 months from EOT for 18 months or until the sooner of disease progression, death, or study closure. Overall survival data will be collected every 3 months from EOT until 18 months, then every 6 months phone for patients with progressive disease during OSFUP.

p CCI [redacted]

q CCI [redacted]

r Pharmacokinetics, serum biomarkers, and immunogenicity will be assessed as indicated in the following table below.

Pharmacokinetic, CCI and Immunogenicity Sampling Time Points

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

Abbreviations: Ab = antibody; EOT = end of treatment; h = hours; min = minutes; PK = pharmacokinetics.

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LIST OF TABLES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATA	anti-therapeutic antibodies
BM	bone marrow
BMA	bone marrow aspirate
BUN	blood urea nitrogen
CBC	complete blood count
CHF	congestive heart failure
CR	complete remission
CT	computed tomography
CYP	cytochrome P_{450}
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment (visit)
EU	European Union
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GM-CSF	granulocyte macrophage-colony stimulating factor
HIV	human immunodeficiency virus
CCI	[redacted]
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee

Abbreviation	Term
IRB	institutional review board
IRF	independent review facility
IRR	infusion-related reactions
ITT	intent-to-treat
IV	intravenous; intravenously
IXRS	interactive voice and/or Web response system
JCV	John-Cunningham virus
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NYHA	New York Heart Association
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PR	partial response
CCI	[redacted]
QOL	quality of life
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SCT	stem cell transplant
SD	stable disease
TDC Americas	Takeda Development Services, Americas
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

CD30 is a cell surface antigen expressed on several malignancies including Hodgkin lymphoma (HL), anaplastic large cell lymphoma (ALCL), Kaposi's sarcoma (KS), cutaneous T cell lymphomas (CTCL), a fraction of diffuse large B-cell lymphomas (DLBCL), some follicular lymphomas, and other lymphoproliferative diseases.[2, 3, 4, 5, 6] Brentuximab vedotin is an antibody drug conjugate (ADC) directed against the CD30 antigen and is being developed to treat patients with CD30+ hematologic malignancies. Hodgkin lymphoma and ALCL are among the most common CD30+ malignancies.

Brentuximab vedotin received a conditional marketing authorization as ADCETRIS® in the European Union (EU) for the treatment of adult patients with relapsed or refractory sALCL; and for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least 2 prior therapies when ASCT or multiagent chemotherapy is not a treatment option. Brentuximab vedotin received an FDA approval in the United States (US) as ADCETRIS® for the treatment of patients with sALCL after failure of at least 1 prior multiagent chemotherapy regimen, for the treatment of patients with HL after failure of ASCT, and for the treatment of patients with HL who are not ASCT candidates after failure of at least 2 multiagent chemotherapy regimens.

1.1.1 Systemic Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) is a very rare disease that accounts for approximately 3% of the cases of adult non-Hodgkin lymphoma (NHL). In 5 of the more populated European Union (EU) countries (United Kingdom [UK], France, Germany, Italy, and Spain), estimated overall incidence ranges from 180 (Spain) to 420 (Italy) new cases per year.[7, 8] There are 2 major, distinct presentations of ALCL: a systemic disease (sALCL) involving lymph nodes and/or extranodal sites (gastrointestinal tract, soft tissues, lung, liver, bone) and a primary cutaneous form.[9, 10, 11]

Systemic ALCL is a subtype of mature T- and NK-cell lymphomas characterized by the uniform expression of the cell surface antigen CD30.[12, 13, 14] In addition to CD30 expression, sALCL has a number of histological and clinical similarities with HL. Systemic ALCL tumors present with large blastic cells with horseshoe-kidney-shaped nuclei. These so-called hallmark cells are present in all sALCL variants. However, sALCL may also

present with binucleated or multinucleated, pleiomorphic cells with prominent, often elongated nucleoli and abundant cytoplasm, similar to the Hodgkin and Reed-Sternberg cells of HL.[13, 14] Of interest, the histopathology of both diseases is characterized by a variable amount of tumor tissue fibrosis/sclerosis, foci of necrosis, and a variable mixture of histiocytes, epithelioid cells, neutrophils, eosinophils, lymphocytes, and plasma cells.[15] A differential diagnosis between both diseases is required in approximately 3% of cases (Hodgkin-like pattern sALCL) but this proportion can be higher for cases with a single mediastinal mass that mimics the presentation of the nodular sclerosis subtype of classical HL.[13, 16] Furthermore, both diseases have similar expression of T-cell, B-cell, and activation antigens and cytokines that translates to a similar array of B symptoms.[17, 18] Such similarities prompted the hypothesis of potential common steps in the tumorigenesis of both malignancies.[15]

There are also important differentiation features between both diseases. In approximately 50% to 80% of sALCL cases, the t(2;5)(p23;q35) chromosome translocation prompting the anaplastic lymphoma kinase (ALK) gene on chromosome 2 to fuse with the NPM (nucleophosmin) gene on chromosome 5 (ALK-positive) is detected. In general, ALK-positive disease occurs in younger patients and has a superior overall survival and failure-free survival (FFS) rate compared to ALK-negative disease; in addition, ALK-positive patients are generally more responsive to frontline chemotherapy regimens.[10, 19] The majority of sALCL cases (70%) present clinically, independent of ALK status, with advanced stage disease (stage III-IV) characterized by peripheral and/or abdominal lymphadenopathy, often associated with extranodal infiltrates and bone marrow involvement. Patients often have B symptoms (75%), especially high fever.[13]

The International Peripheral T-cell Lymphoma Project reported the clinical and immunophenotypic characteristics of adult sALCL.[19] As stated, the majority of newly diagnosed patients present with advanced stage disease and disease-related symptoms or B symptoms (fever, weight loss, night sweats). While 75% to 85% of patients achieve an objective response (either CR or PR) with frontline anthracycline-based therapy, the long-term prognosis for these patients is poor, particularly for the ALK-negative and high-risk ALK-positive population. The 5-year OS and failure-free survival rates reported were 49% and 36% in the ALK-negative group, and 70% and 60% in the ALK-positive group, respectively. Notably, the majority of treatment failures occurred in the first 1 to 2 years post diagnosis.

Systemic ALCL is an extremely rare disease and relapsed or refractory sALCL is even less common; approximately half of sALCL patients develop recurrent disease following frontline therapy.[19] There is consequently a paucity of comprehensive data describing the outcomes of these patients. However, it is generally accepted that when sALCL recurs it behaves aggressively and requires intensive treatment. Due to its rarity, recurrent sALCL has often been included as a subset of aggressive lymphomas in large prospective studies of salvage therapy. As a result, limited data are available to estimate the benefit of salvage therapy in sALCL. Multiple chemotherapy agents and combination regimens are used as second-line treatment for relapsed or refractory sALCL; however, a second complete remission with standard salvage chemotherapy such as ICE (ifosfamide, carboplatin, etoposide), which is also commonly used in relapsed and refractory HL, is achieved in less than 30% of patients.[20, 21, 22, 23, 24] Some patients may benefit from high-dose therapy with autologous stem cell transplant (ASCT); however, clinical benefit may be limited to only those with chemotherapy-sensitive disease,[25, 26, 27] and use of ASCT is not a standard practice in relapsed or refractory sALCL. Acknowledging the limited therapeutic options for these patients, the National Comprehensive Cancer Network (NCCN) 2012 guidelines currently support enrollment on a clinical trial or the use of a second-line therapy regimen. From a short list, single-agent brentuximab vedotin is a second-line therapy recommended for patients with relapsed or refractory sALCL.[28] Of 58 patients with relapsed or refractory sALCL, in the phase 2 study (SG035-0004) which supported the United States (US) approval and the European conditional marketing authorization of brentuximab vedotin, an ORR of 86% was observed with 53% of patients achieving a CR. Pralatrexate, a folate analog, was approved in the US for the treatment of patients with peripheral T-cell lymphoma (PTCL), which includes sALCL. In the phase 2 study that supported approval for pralatrexate, 109 patients were evaluable of which 17 sALCL patients were enrolled. An ORR of 35% was observed in the 17 sALCL patients.[29, 30] Similarly, the efficacy of romidepsin (which has also been approved in the US) was evaluated in 130 relapsed or refractory PTCL patients in a pivotal phase 2 study that resulted in an ORR of 25%.[31]

The European Society for Medical Oncology (ESMO) has no current guidelines available for the treatment of relapsed or refractory sALCL. However, brentuximab vedotin has conditional marketing authorization in the EU as ADCETRIS® for adult patients with relapsed or refractory sALCL.

In summary, sALCL is a very rare, aggressive lymphoma that is potentially curable with frontline multiagent chemotherapy; however, approximately half of sALCL patients develop recurrent disease for which many current multiagent or single-agent salvage therapies offer

little benefit. Brentuximab vedotin is a single-agent therapy approved in the US and has a conditional marketing authorization in the EU and addresses this unmet medical need.

1.1.2 Study Drug

Brentuximab vedotin (ADCETRIS®), 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 ALCL cells, the Hodgkin Reed-Sternberg (HRS) cells of HL, and on tumor cells of other varied lymphoproliferative disorders.

The European Medicines Agency (EMA) granted brentuximab vedotin a conditional marketing authorization as ADCETRIS® on 25 October 2012 for the treatment of adult patients with relapsed or refractory sALCL and for the treatment of adult patients with relapsed or refractory CD30+ HL after ASCT or after at least 2 previous treatments when ASCT or multiagent chemotherapy is not an option for treatment. On 19 August 2011 the United States Food and Drug Administration (FDA) granted accelerated approval to brentuximab vedotin as ADCETRIS® for the treatment of patients with sALCL after failure of at least 1 prior multiagent chemotherapy regimen and for the treatment of patients with HL after failure of ASCT or after failure of at least 2 prior multiagent chemotherapy regimens in patients who are not ASCT candidates.

1.2 Nonclinical Experience

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

The toxicity of multiple doses of brentuximab vedotin has been assessed in rats and monkeys. In both species, the primary test article-related toxicity was hypocellularity of the bone marrow and lymphoid depletion of the thymus. Microscopic lesions were also observed in the spleen in monkeys and rats, and in the lung, intestines, liver, and testes in rats. In addition, decreases in peripheral blood counts were observed in both species, and elevations in liver enzymes were seen in rats only. The most clinically significant toxicity in

monkeys was neutropenia, which resulted in secondary bacterial infections leading to early deaths after a single 6-mg/kg dose. Toxicity was dose-dependent, with a no-observable-adverse-effect level (NOAEL) of brentuximab vedotin of 0.5 mg/kg in rats and 1 mg/kg in monkeys. Human equivalent doses (HED) are 0.32 and 0.08 mg/kg respectively.

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

1.3 Clinical Experience

To date, the safety and efficacy of brentuximab vedotin have been evaluated in 738 patients with sALCL, HL, and other CD30+ hematologic malignancies in completed company-sponsored studies. Clinical data have been collected from 2 completed phase 1 dose escalation studies (SG035-0001 and SG035-0002), a pivotal phase 2 study in relapsed or refractory HL after ASCT (SG035-0003), and a pivotal phase 2 study in relapsed or refractory sALCL (SG035-0004), as further described in the following. A phase 1 thorough QTc study (SGN35-007) and a phase 1 drug-drug interaction study (SG035-008A) have also been completed. Clinical trial data to date indicate that brentuximab vedotin has a tolerable and manageable safety profile in patients with CD30-positive hematologic malignancies.

Phase 1, Dose-Escalating Studies

In Study SG035-0001, a total of 45 patients with CD30-positive hematologic malignancies were treated with brentuximab vedotin at dose levels of 0.1 to 3.6 mg/kg administered intravenously every 3 weeks. The most common adverse events (AEs) were fatigue (36%), pyrexia (33%), diarrhea, nausea, peripheral neuropathy, and neutropenia (22% each). Notable serious adverse events assessed by the investigator to be at least possibly related to treatment included anaphylaxis, myocardial infarction, and peripheral neuropathy. Of interest, 2 of 2 sALCL patients achieved a complete response. The maximum tolerated dose (MTD) was determined to be 1.8 mg/kg administered intravenously (IV) over 30 minutes every 3 weeks.

In Study SG035-0002, 44 patients with CD30-positive hematologic malignancies, 5 of whom had sALCL were treated with brentuximab vedotin at dose levels of 0.4 to 1.4 mg/kg administered intravenously weekly for 3 of 4 weeks. This weekly regimen was designed to enable combination use with gemcitabine, efficacy with brentuximab vedotin monotherapy was deemed sufficient and the planned brentuximab vedotin/gemcitabine combination arm of the study was not pursued. In relapsed or refractory HL patients receiving brentuximab

vedotin 1.2 mg/kg weekly for 3 of 4 weeks, the ORR and CR rates were 58% (95% CI: 27.7%-84.8%) and 25% (95% CI: 5.5%-57.2%), respectively. For all patients, the most common adverse events were peripheral sensory neuropathy (66%), fatigue (52%), nausea (50%), diarrhea (32%), arthralgia (27%), pyrexia (25%), and decreased appetite, myalgia, and upper respiratory tract infection (23% each). The most frequent AE that led to dose modification or delay was peripheral sensory neuropathy. Acute infusion reaction AEs occurred in a total of 6 patients. Overall, 2 patients (14%) who had an acute infusion reaction also had antitherapeutic antibodies at any postbaseline visit. Brentuximab vedotin was generally safe and well-tolerated up to the maximum tolerated dose of 1.2 mg/kg administered weekly for 3 out of 4 weeks.

Phase 2 Studies

In SG035-0003, a pivotal phase 2, single-arm, open-label study in patients with relapsed or refractory HL post ASCT, and SG035-0004, a pivotal phase 2, single-arm, open-label study conducted in patients with relapsed or refractory sALCL, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks. One-hundred two patients with relapsed and refractory HL and 58 patients with relapsed and refractory sALCL were exposed for a median duration of approximately 27weeks (9 cycles) and 20 weeks (6 cycles), respectively. Most patients (89%) in the two phase 2 studies were between the ages of 18 and 65 years. The primary endpoint of both studies was overall response rate (ORR) as assessed by an independent radiographic facility. Key secondary endpoints included duration of response, OS, and PFS. The key efficacy results in HL (SG035-0003) include ORR per IRF (75% [95% CI: 64.9%-82.6%]), CR rate (34% [95% CI: 25.2%-44.6%]), B symptom resolution rate (77%), and duration of response (DOR, 6.7 months). Of interest, for those patients achieving a CR, the median DOR was 20.5 months. Key efficacy points in sALCL (SG035-0004) include ORR (86% [95% CI: 74.6%-93.9%]), CR rate (53% [95% CI: 39.6%-66.7%]), and B symptom resolution rate (82%).

Treatment-emergent AEs occurring in ≥ 20% of patients in the phase 2 studies (SG035-0004 and SG035-0003) were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily mild to moderate in severity and reversible. Approximately half of patients had treatment-emergent peripheral neuropathy, predominantly sensory neuropathy, with an onset and severity pattern consistent with a cumulative effect. Dose delay and subsequent reduction to 1.2 mg/kg was generally effective in managing peripheral neuropathy. Grades 3 and 4 neutropenia occurred in 13%

and 7% of patients, respectively; these events were typically of short duration and well managed by brief dose delays with growth factor support in some cases.

Infusion-related reactions (IRRs) were reported for 17 patients (11%) in the phase 2 population (Studies SG035-0003 and SG035-0004), and were reported in similar proportions of HL and ALCL patients. The preferred terms reported most frequently were chills in 6 (4%) patients, nausea in 5 (3%) patients, dyspnoea and pruritus in 4 patients each (3%), and cough in 3 (2%) patients. All IRRs in the phase 2 population (Studies SG035-0003 and SG035-0004) were Grade 1 or 2 in severity. No serious IRRs, nor any events of anaphylaxis, were reported in the phase 2 population. All but 1 patient had their first IRR within the first 3 cycles (9 patients in Cycle 1; 6 patients in Cycle 2; and 1 patient in Cycle 3); 1 patient had a first IRR in Cycle 15. Of the 17 patients with IRRs reported by the investigator, 7 patients received no IRR prophylaxis and had no further IRRs reported, while 10 received IRR prophylaxis. Of the 10 patients who received IRR prophylaxis, no additional IRRs were reported for 8 of these patients. Incidences of IRRs were also observed in the phase 1 studies. Most IRRs occurred within the first 2 cycles. Most IRRs in the phase 1 studies were Grade 1 or 2. Grade 3 IRRs occurred in 2 patients (both in phase 1 dose-escalation safety studies). Two SAEs of anaphylaxis occurred, both in phase 1 safety (SG035-0001) and clinical pharmacology (SGN35-007) studies. One of these 2 cases of anaphylaxis resulted in treatment discontinuation. The other patient continued treatment with IRR prophylaxis and a longer infusion time.

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 aspartate aminotransferase (AST).

In the phase 2 studies (SG035-0003 and SG035-0004), 31% of patients had a serious adverse event (SAE), 28% had an SAE of Grade 3 or higher, and 15% had an SAE that was determined by the investigator to be related to brentuximab vedotin. The most common SAEs, reported in ≥ 2% of patients, were abdominal pain, disease progression (recurrent sALCL), pulmonary embolism, and septic shock. A higher proportion of sALCL patients experienced SAEs, including deaths within 30 days of last dose, relative to HL patients, likely due to the older age and more aggressive nature of the malignancy in this patient population.

A total of 9 deaths were reported within the safety evaluation period (within 30 days of the last dose of brentuximab vedotin) in 357 patients across the 6 phase 1 and phase 2 studies for which data are available. Two patient deaths (0.6%) were considered related to study treatment. One patient in study SG035-0001 who received 3.6 mg/kg in phase 1 died due to febrile neutropenia and presumed septic shock. A second treatment-related death in study SG035-008A was attributed to pancytopenia, cytomegalovirus (CMV) infection, and intracranial hemorrhage. This patient received 1.8-mg/kg brentuximab vedotin. The remaining on study deaths were primarily related to disease progression in sALCL (SG035-0004) patients.

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

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

1.4 Study Rationale

As described in Section 1.3, Study SG035-0004, a prior multicenter, open-label, phase 2 study of 58 patients with relapsed or refractory sALCL was conducted at sites in North American and Western Europe. In this study, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks for up to 16 cycles. The primary endpoint was objective response rate (ORR) as assessed by an independent radiographic facility. Key secondary endpoints included duration of response (DOR), overall survival (OS), progression-free survival (PFS), and B symptom resolution rate. The ORR observed in this study was 86% (95% CI: 74.6%-93.9%), with a median DOR of 13.2 months (95% CI: 0.1-21.7). The median PFS was 14.3 months (95% CI: 0.8%-23.6%), and 82% of patients experiencing B symptom at baseline experienced B symptom resolution. This 58-patient study formed the basis for the US accelerated and EU conditional approvals of brentuximab vedotin as ADCETRIS® for the treatment of relapsed or refractory sALCL. Confirmatory Study C25006 seeks to further evaluate the safety and efficacy of 1.8 mg/kg of brentuximab vedotin q3wk for up to 16 cycles in this patient population in countries outside North

America and is a Specific Obligation for conversion to full approval in the EU. This study will investigate a similar population of adult patients with relapsed or refractory sALCL that has failed at least 1 multiagent chemotherapy regimen and uses the same ORR primary endpoint as Study SG035-0004 (EudraCT No. 2008-006035-12).

1.5 Potential Risks and Benefits

As detailed in Section 1.3 and Section 1.4, brentuximab vedotin monotherapy has demonstrated therapeutic activity in CD30+ hematological malignancies including HL and relapsed or refractory sALCL for which brentuximab vedotin was granted conditional marketing authorization in the EU by the EMA and accelerated approval in the US by the FDA.

Brentuximab vedotin treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. Brentuximab vedotin-induced peripheral neuropathy is typically cumulative and generally reversible. In the SG035-0003 and SG035-0004 clinical trials, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time the data cutoff date for clinical study reporting. Monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, 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.

Infusion-related reactions, including anaphylaxis, have occurred with brentuximab vedotin.[32] 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 have been reported as adverse events per the phase 2 study protocols (SG035-0003 and SG035-0004). Central laboratory data were collected only predose for each treatment cycle. Few patients overall had postbaseline worsening to Grade 3 or higher in clinical laboratory values. 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 infections; patients are to be monitored for these events during the treatment period and up to and including 30 days after the last dose.

Complete blood counts (CBCs) should be monitored before 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.

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 has been reported with brentuximab vedotin. If Stevens-Johnson syndrome occurs, 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). 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, as described in Section 6.6.

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

Monomethyl auristatin E (MMAE) is primarily metabolized by CYP3A. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions.

The effects of brentuximab vedotin on embryogenesis, reproduction, and spermatogenesis in humans are unknown. In addition, data about the effects of brentuximab vedotin in pregnant women are unavailable. Please see Section 6.5 for appropriate precautions following the administration of study medication.

Overall, considering the potential for therapeutic benefit of brentuximab vedotin in sALCL and the frequently limited treatment options available to these patients with this life threatening disease, as well as the manageable safety profile of brentuximab vedotin, the benefit-risk assessment is favorable.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the antitumor efficacy of single-agent brentuximab vedotin (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall objective response rate (ORR) in patients with relapsed or refractory sALCL following at least 1 multiagent chemotherapy regimen (CHOP or equivalent multiagent chemotherapy regimens with curative intent).

2.2 Secondary Objectives

The secondary objectives include:

- To determine duration of tumor control, including duration of response, progression-free survival (PFS), and complete remission rate (CR) with brentuximab vedotin
- To determine the proportion of patients receiving hematopoietic stem cell transplant (SCT, either autologous or allogeneic) after brentuximab vedotin therapy
- To determine overall survival (OS) with brentuximab vedotin
- To assess the safety and tolerability of brentuximab vedotin
- To assess the pharmacokinetics of brentuximab vedotin

- To determine immunogenicity of brentuximab vedotin

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[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is ORR per independent review facility (IRF)

3.2 Secondary Endpoints

The secondary endpoints include:

- Duration of response per IRF
- PFS per IRF
- CR rate per IRF
- Proportion of patients receiving hematopoietic stem cell transplant (SCT) following treatment with brentuximab vedotin
- OS

- Type, incidence, severity, seriousness, and relatedness of adverse events, and laboratory abnormalities
- Selected pharmacokinetic parameters
- The presence of anti-therapeutic antibodies (ATA) to brentuximab vedotin

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4. STUDY DESIGN

4.1 Overview of Study Design

This single-arm, open-label, multicenter phase 4 clinical study seeks to evaluate the efficacy and safety of brentuximab vedotin as a single agent in adult patients with relapsed or refractory sALCL who have previously received at least 1 multiagent chemotherapy regimen. Its primary objective is to determine the antitumor efficacy of single-agent brentuximab vedotin as measured by ORR in patients with relapsed or refractory sALCL following at least 1 multiagent chemotherapy regimen. A minimum of 45 patients will be treated in this study.

Brentuximab vedotin will be administered as a single outpatient 1.8-mg/kg IV infusion on Day 1 of each 3-week cycle. Patients who achieve SD or better should receive a minimum

of 8 cycles and all patients will be given the opportunity to complete a maximum of 16 cycles. Dedicated CT scans (spiral preferred) of chest, neck, abdomen, and pelvis will be performed at baseline and Cycles 2, 4, 7, 10, 13, and 16, and PET scans will be done at baseline, Cycles 4 and 7, and, for patients who discontinue study treatment without a post-baseline PET assessment, at EOT. Measures of anticancer activity will be assessed by an independent review facility (IRF) according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma (Cheson 2007).[(1)] Patients who experience disease progression at any time will be withdrawn from study drug treatment. Clinical laboratory samples will be taken before dosing on Day 1 of each 3-week cycle. Cycle 1, Day 1 clinical laboratory samples may be collected within 4 days before dosing to ensure patient eligibility on study Day 1. Physical examination, including vital signs, weight, ECOG performance status, CCI [redacted]; brentuximab vedotin PK; immunogenicity; CCI [redacted] will be performed on Day 1 of each cycle. In addition, a bone marrow biopsy is required to confirm responses in patients who have bone marrow involvement at baseline. The follow-up bone marrow biopsy must be done within 2 weeks of documentation of response. Once bone marrow is negative no further bone marrow evaluations are required.

Patients may continue on study treatment until disease progression or unacceptable toxicity. Patients who discontinue study treatment with SD or better will have CT scans done every 3 months for 18 months from EOT or until the sooner of disease progression, death, or study closure. Overall survival data will be collected every 3 months from EOT for 18 months, then every 6 months thereafter until the sooner of death or study closure. The study will be closed when 50% of the patients have had an OS event or 5 years after enrollment of the last patient, whichever occurs first.

Additional efficacy endpoints will be evaluated CCI [redacted]

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

CCI [redacted]

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010.[33]

Safety assessments will include the incidence and severity of adverse events and changes in clinical laboratory values, vital signs, and physical examination findings.

4.2 Number of Patients

At least 45 patients with sALCL will be enrolled in this study from approximately 20 study centers. The study will be conducted mainly in Europe, including Eastern Europe, and could include study centers in Latin America and possibly other regions.

Enrolled patients who do not receive study drug for any reason will not be replaced; however, additional patients may be enrolled to ensure a minimum of 45 patients with confirmed sALCL histology per central review.

4.3 Duration of Study

Patients will complete a Screening period of up to 28 days and should receive treatment with study drug for a minimum of 8 cycles and up to a maximum of 16 cycles. The final analysis of the primary endpoint will be conducted when all patients have had the opportunity to complete 16 cycles of brentuximab vedotin and have had their EOT visit. Study closure will occur when 50% of patients have had an OS event or 5 years after enrollment of the last patient, whichever occurs first. The total study duration is anticipated to be approximately 6 to 7 years.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. Patients with relapsed or refractory sALCL who have previously received at least 1 multiagent chemotherapy regimen (CHOP or equivalent multiagent chemotherapy regimen with curative intent).

2. Histologically-confirmed sALCL based on local pathology report. Refer to Section 7.4.10 for details.

3. Age greater than or equal to 18 years.

4. Patients must have bidimensional measurable disease of ≥ 1.5 cm as documented by radiographic technique (spiral CT preferred) per the International Working Group Revised Criteria for Response Assessment for Malignant Lymphoma.[(1)]

5. At least ONE of the following as evidence of relapsed or refractory sALCL:

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

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

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

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

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

6. Received any previous ASCT at least 12 weeks (3 months) before the first study dose prior to study entry.

7. Completed any previous treatment with radiotherapy, immunotherapy, chemotherapy, and/or other investigational agents at least 2 weeks prior to the first dose of brentuximab.

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

9. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Refer to Section 15.1).

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

11. Female patients who:

    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, or
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

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

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

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

13. Clinical laboratory values as specified below within 4 days before the first dose of study drug unless due to the presence of underlying lymphoma involvement, then patient must have recovered to less than or equal to Grade 2 toxicity:

    - Absolute neutrophil count ≥ 1,000/μL without growth factor support

- Platelet count ≥ 50,000/μL without transfusion support unless thrombocytopenia is due to documented bone marrow involvement with lymphoma
- Serum bilirubin level ≤ 1.5 × the upper limit of normal (ULN) or ≤ 3 × ULN for patients with an indirect hyperbilirubinemia due to Gilbert's disease or documented hepatic involvement with lymphoma
- Serum creatinine ≤ 1.5 × ULN
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than or equal to 2.5 × ULN

5.2 Exclusion Criteria

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

1. Previous treatment with brentuximab vedotin.
2. Previously received an allogeneic transplant.
3. Patients with current diagnosis of primary cutaneous ALCL (patients whose ALCL has transformed to sALCL are eligible).
4. Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug:
   - Myocardial infarction within 6 months before the first dose of study drug
   - New York Heart Association (NYHA) Class III or IV heart failure (Refer to Section 15.2).
   - 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
5. History of another primary malignancy that has not been in remission for at least 3 years. The following are exempt from the 3-year limits: nonmelanoma skin cancer, curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear.

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

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

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

9. Current therapy with other systemic anti-neoplastic or investigational agents.

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

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

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

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

14. Known human immunodeficiency virus (HIV) positive.

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

6. STUDY DRUG

6.1 Study Drug Administration

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

Brentuximab vedotin will be administered on Day 1 of each 3-week cycle. The dose of brentuximab vedotin is 1.8 mg/kg and is administered by outpatient IV infusion given over approximately 30 minutes. Patients with stable disease or better should receive a minimum

of 8 cycles and, all patients will be given the opportunity to complete a maximum of up to 16 cycles of brentuximab vedotin. In the absence of infusion toxicities, the infusion rate for all patients must be calculated to achieve a 30-minute infusion period. Brentuximab vedotin must not be administered as an IV push or bolus. Brentuximab vedotin should be administered through a dedicated IV line and cannot be mixed with other medications.

Dosing is based on patients' weight; 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. Brentuximab vedotin dose should be rounded to the nearest whole number of milligrams.

Further brentuximab vedotin administration information can be found in the Pharmacy Manual.

6.2 Dose-Modification Guidelines

6.2.1 Recommended Brentuximab Vedotin Dose Modifications for Treatment-associated Toxicity

Table 6-1 details 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

	Nonhematologic (Excluding Neuropathy)	Hematologic	Peripheral Neuropathy
Grade 1	Continue at same dose level	Continue at same dose level	Continue at same dose level
Grade 2	Continue at same dose level	Continue at same dose level	For Grade 2 neuropathy, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks.
Grade 3	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level[a].	Withhold dose until toxicity is ≤ Grade 2, or has returned to baseline, then resume treatment at the same dose level.[b] Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles.	Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks.

Table 6-1 Recommended Brentuximab Vedotin Dose Modifications for Treatment-Associated Toxicity

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

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

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

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

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

6.2.2 Criteria for Dose Interruption During a Cycle

Please refer to Table 6-1 for further information.

6.2.3 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with brentuximab vedotin will use a cycle length of 3 weeks. For a new cycle of treatment to begin, all drug-related toxicity must have resolved per the guidelines provided in Table 6-1.

If the patient fails to meet the criteria for retreatment cited previously, initiation of the next cycle of treatment should be delayed up to 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. The start of the next cycle may be delayed for up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle. Delays of greater than 3 weeks for study-drug-related toxicities require

discontinuation from study treatment, unless the sponsor agrees the benefit:risk assessment supports continued treatment.

6.2.4 Criteria for Dose Reduction

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

Doses reduced for drug-related toxicity should generally not be re-escalated. However, intrapatient re-escalation to the previous dose level may be permitted at the discretion of the investigator after discussion with the sponsor.

6.2.5 Criteria for Discontinuation of Brentuximab Vedotin

At the time of study drug discontinuation, all study procedures outlined for the EOT visit will be completed. The primary reason for study drug discontinuation will be recorded on the electronic case report form (eCRF). Criteria for discontinuation of study are provided in Section 7.7. Please refer to Table 6-1 for further information regarding dosing requirements for patients who discontinue study drug due to toxicity.

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

6.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Chemotherapy
- Immunotherapy
- No other investigational drug may be used during treatment on this study
- Concurrent participation in another clinical trial of medical intervention is not allowed

6.4 Permitted Concomitant Medications and Procedures

The following medications and procedures are allowed during the study:

- The use of topical steroids, inhalational steroids, and ophthalmic steroids is permitted. Corticosteroids are permitted as part of a premedication regimen per institutional standards or to manage potential hypersensitivity.
- Patients may receive concomitant hormonal therapy provided they have been on a stable dosage for at least 1 month prior to enrollment. No restrictions are placed upon the use of hormonal contraceptives.
- 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.
- Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids should be available for immediate use.
- Palliative radiation or surgery is permitted if other sites of measurable disease remain.

6.5 Precautions and Restrictions

CYP3A/4 Inhibitor Use

Monomethyl auristatin E (MMAE) is primarily metabolized by CYP3A. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions. Please refer to the Study Manual for a list of examples of strong CYP3A4 inhibitors.

Infusion-Related Reactions

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 each infusion of brentuximab vedotin. During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive

measures consistent with optimal patient care will be given throughout the study according to institutional standards. Medications for infusion-related reactions, such as epinephrine and antihistamines should be available for immediate use. However, routine premedication should not be administered prior to the first dose of brentuximab vedotin.

Patients who experience a Grade 1 or 2 infusion-related reaction may receive subsequent brentuximab vedotin 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.

Patients who experience a Grade 3 or 4 infusion-related reaction may potentially receive additional treatment with brentuximab vedotin at the discretion of the investigator after discussion with the sponsor.

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

Pregnancy

It is not known what effects brentuximab vedotin has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age 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 at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal,

post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

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

6.6 Management of Clinical Events

Nausea and/or Vomiting

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

Diarrhea

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

Peripheral Neuropathy

AEs of peripheral neuropathy will be monitored closely throughout the study. Events that are greater than Grade 1 in severity will result in brentuximab vedotin dose modification.

Suspected Progressive Multifocal Leukoencephalopathy (PML)

Signs and symptoms of PML may include altered mental status; motor deficits, such as hemiparesis or ataxia; visual disturbances; or higher cortical dysfunction, such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%). The onset of neurological deficits may occur over weeks to months. See the IB for further details.

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

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

If PML is confirmed, permanently discontinue treatment with brentuximab vedotin.

6.7 Blinding and Unblinding

This is an open-label, single arm study.

6.8 Description of Investigational Agents

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

6.9 Preparation, Reconstitution, and Dispensation

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

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

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

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

The required volume of 5 mg/mL reconstituted brentuximab vedotin solution needed must be calculated and withdrawn from the vial(s). The reconstituted solution should be added immediately to an infusion bag containing a minimum volume of 100 mL. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

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

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

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

6.10 Packaging and Labeling

Vials of study treatment will be packaged in cardboard kits. Each kit will contain 1 vial of investigational product. Vials and kits will be labeled to meet country-specific regulatory requirements.

6.11 Storage, Handling, and Accountability

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

Study treatment does not contain preservatives; therefore, opened and reconstituted vials of study treatment must be used within 24 hours when stored under refrigeration at 2°C to 8°C. Reconstituted study treatment should not be stored at room temperature. It is recommended

that study treatment vials and solutions be protected from direct sunlight until the time of use. **Reconstituted vials must not be shaken**.

Drug accountability instructions are provided in the Pharmacy Manual.

7. STUDY CONDUCT

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

7.1 Study Personnel and Organizations

The contact information for the Takeda project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, the independent radiologic review facility, interactive voice and/or Web response system (IXRS) provider, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

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

7.3 Treatment Group Assignments

This is an open label, nonrandomized study with no reference therapy. Treatment group assignments are not applicable to this study.

7.4 Study Procedures

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

7.4.1 Informed Consent

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

7.4.2 Patient Demographics

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

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 7.4.12.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events.

Physical examination will include a focused lymphoma assessment and an evaluation of skin, head, eyes, ears, nose, throat, nodes, heart, lungs, abdomen, back, extremities, and neurology.

7.4.5 Patient Height

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

7.4.6 Patient Weight

Weight will be measured at times specified in the Schedule of Events. Dosing with brentuximab vedotin is based on patients' weight; however, doses will be adjusted for patients who experience a ≥ 10% change in weight from baseline (Section 6.1).

7.4.7 Vital Signs

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

7.4.8 Pregnancy Test

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

7.4.9 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed at times specified in the Schedule of Events. See Section 15.1 for ECOG grade classifications.

7.4.10 Tumor Specimen

Tumor tissue from the most recent post-diagnosis biopsy is preferred. Unstained slides or a paraffin-embedded block will be obtained after the patient has signed the ICF. Patients without at least 10 histological slides from their most recent post-diagnosis biopsy will undergo a new tumor biopsy during screening. This sample will be used to confirm sALCL diagnosis and ALK status. Central laboratory results for sALCL diagnosis are not required prior to the first dose of study drug. Refer to the Schedule of Events for details regarding tumor tissue collection.

7.4.11 Electrocardiogram

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

7.4.12 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF as specified in the Schedule of Events. Refer to Section 6.3 and Section 6.4 for a list of medications and therapies that are prohibited and/or allowed during the study.

7.4.13 Adverse Events

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

7.4.14 Enrollment

A patient is considered to be enrolled in the study when enrolled in the IXRS.

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

7.4.15 Clinical Laboratory Evaluations

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

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

Clinical laboratory evaluations will be performed as outlined in the following.

Clinical Chemistry and Hematology

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

Hematology

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

Serum Chemistry

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

7.4.16 Disease Assessment

Response to treatment and disease status assessments will be evaluated according to the Revised Response Criteria for Malignant Lymphomas.[1] Disease assessments will be

performed as specified in the Schedule of Events. Records of disease assessments will be provided to the IRF for central review.

Computed tomography (CT), spiral preferred, with contrast as appropriate (chest, neck, abdomen, and pelvis), and positron emission tomography (PET) scans will be performed at time points described in the Schedule of Events. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation using an imaging modality consistent with that used at screening. Objective assessments will be performed at each time point as described in the Schedule of Events. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents.

MRI scans may be substituted for CT scans 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. Further detail may be found in the Imaging Manual.

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

A bone marrow (BM) biopsy will be obtained for BM assessment as specified in the Schedule of Events.

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7.4.19 Cost Assessment

The cost of treatment will be assessed through the collection CCI [redacted]. Valuation of the costs will be undertaken separately.

7.4.20 Pharmacokinetic Measurements

Pharmacokinetic measurements will be assessed for MMAE, ADC, and free antibody (cAC10). Pharmacokinetic parameters to be estimated may include the maximum concentration for MMAE (C_{max}), and concentration at the end of infusion for brentuximab vedotin (C_{eoi}). Population Pharmacokinetics methodologies may be used to determine PK parameters and covariates in this population.

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

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7.4.22 Immunogenicity Measurements

Blood for serum samples will be collected as specified in the Schedule of Events to evaluate ATA and neutralizing ATA as a safety assessment. On dosing days, the blood samples for ATA and neutralizing ATA assessment must be collected before dosing. Neutralizing ATA assessment will be performed only for ATA-positive samples. Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

7.5 Completion of Treatment

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

7.6 Completion of Study

Study closure will occur when enrollment is complete and 50% of patients have experienced OS events or 5 years after enrollment of the last patient, whichever occurs sooner.

Regardless of the duration of treatment, all patients will remain on study for follow-up after receiving the last dose of study treatment until they withdraw consent for further follow-up, are lost to follow-up, or until study closure. The study is expected to close approximately 6 to 7 years after the first patient starts study treatment.

Refer to Section 7.10 for posttreatment follow-up schedule.

7.7 Discontinuation of Treatment With Study Drug, and Patient Replacement

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

- Completed maximum number of cycles per protocol
- Progressive disease

- Initiation of hematopoietic stem cell transplant
- Withdrawal by subject

The reason justifying the study treatment withdrawal should be documented in the eCRF.

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent for the follow-up phase of the study.

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

- Adverse event
- Symptomatic deterioration
- Unsatisfactory therapeutic response
- Protocol violation
- Study terminated by sponsor
- Lost to follow-up
- Other

Once study drug has been discontinued, all study procedures outlined for the End of Treatment visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF. Some patients may discontinue study drug for reasons other than progressive disease before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the Schedule of Events.

Enrolled patients who do not receive study drug for any reason will not be replaced; however, additional patients may be enrolled to ensure an adequate number of patients with histologically confirmed sALCL in the study.

All subsequent anticancer therapies will be recorded, regardless if they are initiated before or after progressive disease.

7.8 Withdrawal of Patients From Study

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

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal by subject
- Death
- Other

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

The reason(s) for withdrawal must be documented in the patient's medical records. The investigators will make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. Final treatment assessments will be performed before any other therapeutic intervention if possible. Patients who withdraw from study treatment with SD or better will continue to be followed for PFS and will have CT scans done every 3 months for 18 months from EOT or until the sooner of disease progression, death, or study closure. Overall survival data will be collected every 3 months from EOT for 18 months, then every 6 months thereafter until the sooner of death or study closure. Additionally, any planned alternative treatments should be documented on the patient's medical records and CRF.

7.9 Study Compliance

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

7.10 Posttreatment Follow-up Assessments

Posttreatment follow-up for all patients consists of a physical exam, QOL assessments, CT scan, and collection of survival/disease status and anticancer treatment for sALCL as specified in the Schedule of Events.

Patients who discontinue study treatment with SD or better will have CT scans done every 3 months from EOT for 18 months or until the sooner of disease progression, death, or study closure. Overall survival data will be collected every 3 months from EOT for 18 months, then every 6 months thereafter until the sooner of death or study closure. The study will be closed when 50% of the patients have had an OS event or 5 years after enrollment of the last patient, whichever occurs first.

NOTE: Related SAEs must be reported to the Takeda Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 10 for details regarding definitions, documentation, and reporting of SAEs.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

Statistical analyses will be primarily descriptive and graphical in nature. For continuous variables, descriptive statistics will be used including n, mean, median, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be used for the analyses. The Kaplan-Meier survival curves will be provided along with their two-sided 95% CIs for time-to-event data.

No formal statistical hypothesis testing will be performed.

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

8.1.1 Determination of Sample Size

A minimum of 45 patients with relapsed or refractory sALCL will be enrolled in the study. Based on previous study results, with a sample size of 45, observing 31 (69%) objective responses (complete or partial remission) would provide a 95% confidence (two-sided) that the true ORR is greater than 53%.

8.1.2 Randomization and Stratification

This is an open-label, single-arm study. Randomization and stratification are not applicable to this study.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

Intent-to-Treat

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

Per-Protocol

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

Safety

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

Pharmacokinetic

Patients with sufficient dosing and pharmacokinetic concentration-time data to reliably estimate pharmacokinetic parameters will be included in the Pharmacokinetic analysis population.

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8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. The relevance of missing sample data will be assessed. Details on any sensitivity analyses and data handling details regarding issues such as missing data will be discussed in the SAP.

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

8.1.5 Demographic and Baseline Characteristics

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

8.1.6 Efficacy Analysis

The primary and secondary efficacy endpoints will be summarized. The corresponding two-sided 95% confidence intervals will be presented for selected efficacy endpoints. The standard survival analysis techniques of Kaplan-Meier method will be utilized for time-to-event including during of response, duration of response in the subset of patients achieving CR, PFS per IRF, time to response, time to CR, time to progression, and OS.

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

To investigate the impact of informative events, sensitivity analyses are planned for selected efficacy endpoints such as ORR, duration of response, PFS, and OS by switch of therapy and withdrawal/discontinuation of informed consent.

Detailed methodology will be provided in the SAP.

8.1.6.1 Primary Efficacy Analyses

The primary efficacy endpoint is the overall ORR per IRF in patients with relapsed or refractory sALCL following frontline treatments.

The ORR per IRF and its two-sided 95% exact confidence interval will be calculated using the F distribution method.[34] This endpoint may also be tabulated by covariates such as sex, age, race, categorized weight (≤ 100 kg and > 100 kg), prior treatment, and ECOG performance status, etc. The maximum percent reduction in the sum of the products of the

largest diameters (SPD) of the nodes or nodal masses being followed for response assessment will be graphically displayed.

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

The ORR per investigator and its two-sided 95% exact confidence interval will also be calculated. The difference of objective responses between assessments by IRF and investigator will be tabulated.

8.1.6.2 Secondary Efficacy Analyses

The complete remission rate per IRF will be derived and its two-sided 95% exact confidence interval will be calculated using the F distribution method.[34]

Duration of response per IRF, duration of response per IRF in the subset of patients achieving complete remission, progression free survival per IRF, and overall survival will be estimated using Kaplan Meier methodology and Kaplan-Meier plots will be provided. The median duration of response per IRF, duration of response per IRF in the subset of patients achieving CR, PFS per IRF, OS and their two-sided 95% CI by Brookmeyer and Crowley[35] will be calculated. These endpoints may also be summarized by covariates such as sex, age, race, ALK status, categorized weight, prior treatment, and ECOG performance status, etc.

Descriptive statistics will be used to present percent of patients receiving stem cell transplantation (SCT) following treatment with brentuximab vedotin.

These efficacy endpoints per investigator will be similarly analyzed.

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8.1.8 Pharmacokinetics/Biomarkers

Pharmacokinetic Analysis

Pharmacokinetics of antibody drug-conjugate (brentuximab vedotin), total antibody, and unconjugated drug (MMAE) will be derived from serum or plasma concentrations versus time data for all subjects who met study inclusion criteria, received study drug, and had evaluable and adequate PK data. The reporting of pharmacokinetic parameters will be determined based on the final parameter analysis on the available data.

Immunogenicity

All patients who were administered at least 1 dose of brentuximab vedotin will be evaluated for antitherapeutic antibody (ATA) development. A list/table of ATA status will be provided. Antibody neutralizing status (neutralizing or not neutralizing) will also be listed for patients who have positive antibody status.

Immunogenicity information, including ATA and neutralizing ATA, will be summarized in descriptive statistics as applicable.

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8.1.9 Safety Analysis

8.1.9.1 Safety Analysis

The safety population will be used for all safety analyses.

8.1.9.2 Adverse Events

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

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

AEs will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) by primary system organ class (SOC), high-level term, preferred term (PT), severity, and relationship to study medication. The relationship to study medication will be classified as "related" or "unrelated". All AEs will be listed with the pertinent patient information.

AEs will include the following categories

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

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

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

ECOG performance status information will be summarized.

All medications taken by subjects during the course of the study will be recorded. Concomitant medications will be summarized by the World Health Organization (WHO) Drug Dictionary substance name. A listing of all concomitant medications taken by subjects will be provided.

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

Electrocardiogram Analysis

A listing of ECG results will be provided for each patient by visit.

8.1.10 Interim Analysis

No formal interim analysis is planned for this study.

9. STUDY COMMITTEES

9.1 Data Safety Monitoring Board

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

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 Adverse Event Definition

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

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

10.1.3 Serious Adverse Event Definition

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

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

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

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[33] 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/mm^3 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.

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

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE and Pregnancy Reporting Contact Information, please refer to Section 15.3

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

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

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[33] The criteria are provided in the Study Manual.

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

10.3 Monitoring of Adverse Events and Period of Observation

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

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- Treatment-related AEs will be reported from first dose of study drug through 30 days after administration of the last dose of study drug and monitored for resolution through event resolution or study closure, and recorded in the eCRFs.
- Serious pretreatment events will be reported to the Takeda Department of Pharmacovigilance or designee from the time of the signing of the ICF up to first dose of study drug, but will not be recorded in the eCRF.

- Related and unrelated SAEs will be reported to the Takeda Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Any SAE that occurs between 30 days post last dose of study drug and study closure that the investigator considers to be related to study drug therapy must be reported to the Takeda Department of Pharmacovigilance & Risk Management or designee.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Department of Pharmacovigilance or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Department of Pharmacovigilance or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

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

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated,

web-based electronic data capture (EDC) application. Takeda will have access to all data upon entry in the EDC application.

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

11.3 Electronic Case Report Form Completion

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

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

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

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

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

11.4 Study Monitoring

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

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

11.5 Ethical Considerations

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

11.6 Patient Information and Informed Consent

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

11.7 Patient Confidentiality

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

11.8 Investigator Compliance

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

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Takeda, or a designee, if circumstances

permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

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

11.10 Investigator and Site Responsibility for Drug Accountability

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

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

11.11 Product Complaints

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 Takeda Quality representative.

For Product Complaints, call MedComm Solutions at 877-674-3784 (877 MPI DRUG) (US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 10.2).

11.12 Closure of the Study

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

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

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

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Takeda once the site's participation in the study has concluded.

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

11.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last

marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Takeda notified.

12. USE OF INFORMATION

All information regarding brentuximab vedotin supplied by 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 Takeda. It is understood that there is an obligation to provide 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 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.

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

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

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

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

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

13. INVESTIGATOR AGREEMENT

I have read Protocol C25006 Amendment 2: A Phase 4, Open-label, Single-Arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma.

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

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

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

14. REFERENCES

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15. APPENDICES

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

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[36]

15.2 New York Heart Association Classification of Cardiac Disease

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

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[37]

15.3 Serious Adverse Event and Pregnancy Reporting Contact Information

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

International (Countries Outside United States and Canada)

(24 hours/7 days a week)

Phone/ Helpline Instructions

To place a call using World Phone (WP)

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

American Samoa	PPD
Anguilla	
Antigua	
Argentina	
Aruba	
Austria	
Australia	
Bahamas	
Bahrain	
Bangladesh	
Barbados	
Belarus	
Belgium	
Belize	
Bermuda	
Bolivia	
Brazil	
British Virgin Islands	
Brunei	
Bulgaria	
Cayman Islands	
Chile	

China	PPD
Colombia	
Cook Islands	
Costa Rica	
Croatia	
Cyprus	
Czech Republic	
Denmark	
Dominica	
Dominican Republic	
Ecuador	
Egypt	
El Salvador	
Estonia	
Fiji	
Finland	
France	
French Antillies	
French Guiana	
Gabon	
Georgia	
Germany	
Ghana	
Greece	
Grenada	
Guam	
Guatemala	
Guyana	
Haiti	

Honduras	PPD
Hong Kong	
Hungary	
Iceland	
India	
Indonesia	
Iran	
Iraq	
Ireland	
Israel	
Italy	
Ivory Coast	
Jamaica	
Japan	
Jordan	
Kazakhstan	
Kenya	
Latvia	
Lebanon	
Liechtenstein	
Lithuania	
Luxembourg	
Macau	
Macedonia	
Malaysia	
Malta	
Marshall Islands	
Mexico	
Micronesia	
Monaco	
Montserrat	
Morocco	
Netherlands	
Netherlands Antilles	
New Zealand	

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

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

International
(Countries Outside United States & Canada)

Reporting via Fax

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

To fax using World Phone (WP)

1. Get a line with a dial tone
2. Dial the Worldwide access number (international toll free number listed below)
3. Listen for tone/chime and menu; enter five digit WP access code listed beside applicable worldwide access number below.
4. Note: Some fax machines may require pushing the “pause” or “add digit” or “star” button either 2 or 3 times before entering the 5 digit access code.

American Samoa	PPD
Anguilla	
Antigua	
Argentina	
Aruba	
Austria	
Australia	
Bahamas	
Bahrain	
Bangladesh	
Barbados	
Belarus	

Belgium	PPD
Brazil	
British Virgin Islands	
Brunei	
Bulgaria	
Cayman Islands	
Chile	
China	
Colombia	
Cook Islands	
Costa Rica	
Croatia	
Cyprus	
Czech Republic	
Denmark	
Dominica	
Dominican Republic	
Ecuador	
Egypt	
El Salvador	
Estonia	
Fiji	
Finland	
France	
French Antillies	
French Guiana	
Gabon	
Georgia	
Germany	

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

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

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

If there are difficulties using the international toll free access, please fax SAEs to the back-up RightFax number below. Note that this number is dialed direct and not toll free.

PPD

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

15.4 Amendment 1 Detailed Summary of Changes

THE PRIMARY SECTION(S) OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 1 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Specify that a minimum of 45 patients with histologically confirmed systemic anaplastic large cell lymphoma (sALCL) will be enrolled

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

Formerly read:	~~Approximately~~ 45 patients will be treated in this study.
Now reads:	**A minimum of** 45 patients will be treated in this study.

Sections that also contain this change are:

- Protocol Summary
- Section 4.2, Number of Patients
- Section 8.1.1, Determination of Sample Size

The primary change denoting histology occurs in Section 4.2, Number of Patients:

Formerly read:	Enrolled patients who do not receive study drug for any reason will not be replaced; however, additional patients may be enrolled to ensure ~~an adequate number~~ of ~~evaluable~~ patients with sALCL ~~in the study~~.
Now reads:	Enrolled patients who do not receive study drug for any reason will not be replaced; however, additional patients may be enrolled to ensure **a minimum** of **45** patients with **confirmed** sALCL **histology per central review**.

Sections that also contain this change are:

- Protocol Summary
- Section 7.7, Discontinuation of Treatment With Study Drug, and Patient Replacement

Purpose: Increase the duration of disease status follow-up (minimum not formerly stated but now 18 months after End of Treatment [EOT]) and overall survival (OS) follow-up (minimum not formerly stated but now until the sooner of 50% of patients having OS events or 5 years after enrollment of the last patient); these changes extend the predicted study duration approximately 4 years

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

Formerly read:	Patients who discontinue study treatment with SD or better will have CT scans done every 3 months for ~~2 years and then every 6~~ months ~~thereafter~~ until disease progression, death, or study closure. Overall survival will be ~~followed~~ until the sooner of death or study closure.
Now reads:	Patients who discontinue study treatment with SD or better will have CT scans done every 3 months for **18** months **from EOT or** until **the sooner of** disease progression, death, or study closure. Overall survival **data** will be **collected every 3 months from EOT for 18 months, then every 6 months thereafter** until the sooner of death or study closure. **The study will be closed when 50% of the patients have had an OS event or 5 years after enrollment of the last patient, whichever occurs first.**

Sections that also contain this change are:

- Protocol Summary
- Schedule of Events
- Section 7.8, Withdrawal of Patients From Study
- Section 7.10, Posttreatment Follow-up Assessments

Purpose: Note that sensitivity analyses of selected efficacy endpoints such as overall response rate, duration of response, progression-free survival, and OS are planned to investigate any impact of events such as switching therapy, study withdrawal, or withdrawal of informed consent

The change occurs in Section 8.1.6, Efficacy Analysis:

Added text:	The primary efficacy analysis will use the ITT population. Secondary and additional efficacy endpoints will be analyzed using ITT population as well. **To investigate the impact of informative events, sensitivity analyses are planned for selected efficacy endpoints such as ORR, duration of response, PFS, and OS by switch of therapy and withdrawal/discontinuation of informed consent.**

Purpose: Specify that positron emission tomography (PET) scan should be done at EOT only for those patients who discontinue study treatment without a post-baseline PET assessment

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

Formerly read:	Dedicated CT scans (spiral preferred) of chest, neck, abdomen, and pelvis will be performed at baseline and Cycles 2, 4, 7, 10, 13, and 16, and PET scans will be done at baseline ~~and~~ Cycles 4 and 7~~.~~
Now reads:	Dedicated CT scans (spiral preferred) of chest, neck, abdomen, and pelvis will be performed at baseline and Cycles 2, 4, 7, 10, 13, and 16, and PET scans will be done at baseline, Cycles 4 and 7, **and, for patients who discontinue study treatment without a post-baseline PET assessment, at EOT**.

Sections that also contain this change are:

- Protocol Summary
- Schedule of Events

Purpose: Clarify that patients should be observed for infusion-related reactions for 60 minutes following every brentuximab vedotin infusion

The change occurs in Section 6.5, Precautions and Restrictions, Infusion-Related Reactions:

Formerly read:	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.
Now reads:	The patient should be observed for 60 minutes following **each** infusion of brentuximab vedotin. During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary.

Purpose: Add the warning that brentuximab vedotin administration should immediately and permanently be discontinued in the event of anaphylaxis

The primary change occurs in Section 6.5, Precautions and Restrictions:

Added text:	Patients who experience a Grade 3 or 4 infusion-related reaction may potentially receive additional treatment with brentuximab vedotin at the discretion of the investigator after discussion with the sponsor. **If anaphylaxis occurs, the administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical**

therapy administered.

Section 1.5, Potential Risks and Benefits, also contains this change.

Purpose: Remove the assessment of B symptoms during screening and the progression-free survival follow-up period (PFSFUP)/overall survival follow-up period (OSFUP) and specify that B symptoms must be assessed before dosing on Cycle 1, Day 1 and on Day 1 of each subsequent cycle, remove the assessment of health care utilization during screening and PFSFUP/OSFUP, and remove the assessment of quality-of-life (QOL) measures during screening

The changes summarized below occur in the Schedule of Events:

Deleted text:
- Xs were removed from the *B symptoms* assessment row in the screening and PFSFUP/OSFUP columns
- The X was removed from the *health care utilization* row in the screening and PFSFUP/OSFUP columns
- The X was removed from the *quality of life assessments* row in the screening column.

Added text: Footnote "l": **B symptoms will be assessed before dosing on Cycle 1, Day 1 and on Day 1 of each subsequent cycle.**

Purpose: Remove the stipulation that serum pregnancy testing must be beta human chorionic gonadotropin (β-hCG) testing

The primary change occurs in Section 7.4.8,Pregnancy Test:

Deleted text: A serum ~~β-hCG~~ or urine pregnancy test will be performed for female patients of childbearing potential at times specified in the Schedule of Events.

Sections that also contain this change are:

- Schedule of Events
- LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Purpose: Specify that serious adverse events that occur between 30 days after the last dose of brentuximab vedotin and study closure that the investigator considers related to brentuximab vedotin will be reported to the Takeda Department of Pharmacovigilance & Risk Management or its designee

The change occurs in Section 10.3, Monitoring of Adverse Events and Period of Observation:

Formerly read: Any SAE that occurs ~~at any time after completion~~ of ~~the~~ study and ~~the designated follow-up period~~ that the investigator considers to be related to study drug therapy must be reported to the Takeda Department of

Pharmacovigilance & Risk Management or designee.

Now reads: Any SAE that occurs **between 30 days post last dose** of study **drug** and **study closure** that the investigator considers to be related to study drug therapy must be reported to the Takeda Department of Pharmacovigilance & Risk Management or designee.

Purpose: Specify that a tumor specimen from patients' most recent post-diagnosis biopsy is preferred

The primary change occurs in Section 7.4.10, Tumor Specimen:

Formerly read: ~~If available, tumor tissue collected at the time of original diagnosis or subsequent procedures (unstained slides or a paraffin-embedded block) will be obtained after the patient has signed the informed consent form (ICF). Patients who have an archived tumor specimen or histological slides will not need to undergo a biopsy at the time of screening. If archived tissue cannot be obtained, a biopsy should be performed at screening.~~ This sample will be used to confirm sALCL diagnosis and ALK status by central laboratory review.

Now reads: **Tumor tissue from the most recent post-diagnosis biopsy is preferred. Unstained slides or a paraffin-embedded block** will be obtained after the patient has signed the ICF. **Patients without at least 10 histological slides from their most recent post-diagnosis biopsy will undergo a new tumor biopsy during screening.** This sample will be used to confirm sALCL diagnosis and ALK status by central laboratory review.

The Schedule of Events footnote "c" also contains this change.

Purpose: Remove the nonspecific symptom "discomfort" from the list of neuropathy symptoms for which patients should be monitored

The change occurs in Section 1.5, Potential Risks and Benefits:

Deleted text: Of the patients who reported neuropathy, 51% had residual neuropathy at the time the data cutoff date for clinical study reporting. Monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, ~~discomfort,~~ a burning sensation, neuropathic pain, or weakness is required.

Purpose: Remove "malignancy" as a symptom for which patients should be specially observed during the treatment period and up to 30 days after the last brentuximab vedotin dose

The change occurs in Section 1.5, Potential Risks and Benefits:

Deleted Any treatment that can decrease immune function may contribute to ~~malignancy and~~ infections; patients are to be monitored for these events

text: during the treatment period and up to and including 30 days after the last dose.

Purpose: Clarify in the inclusion criteria that, for male patients, the described methods of periodic abstinence apply to the female partner

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

Added text: Male patients, even if surgically sterilized (ie, status postvasectomy), who:

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

Section 6.5, Precautions and Restrictions, **Pregnancy** also contains this change.

Purpose: Add a criterion excluding patients who have received any investigational products within 4 weeks before the first dose of brentuximab vedotin

The primary change occurs in Section 5.2, Exclusion Criteria, new criterion 8:

Added text: **8. Treatment with any investigational products within 4 weeks before the first dose of study drug**

The latter portion of the Exclusion Criteria was also reorganized to better accommodate this change.

Purpose: Align the recommended brentuximab vedotin dose modification to be enacted in the event of Grade 2 neuropathy with that in the European Union Summary of Product Characteristics (Specifically, brentuximab vedotin dosing should be restarted at a reduced dose level upon recovery to ≤ Grade 1 or baseline; restarting at the previous dose level upon recovery for the first occurrence of Grade 2 neuropathy is no longer permitted.)

The change occurs in Section 6.2.1, Recommended Brentuximab Vedotin Dose Modifications for Treatment-associated Toxicity, in Table 6-1 Recommended Brentuximab Vedotin Dose Modifications for Treatment-Associated Toxicity

Formerly read: For Grade 2 neuropathy, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then ~~resume~~ treatment at ~~the same~~ dose ~~level. For the second occurrence of Grade 2 neuropathy, withhold dose until toxicity is ≤ Grade 1, then reduce the dose to~~ 1.2 mg/~~kg and resume treatment after discussion with the sponsor~~.

Now reads: For Grade 2 neuropathy, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, **restart** treatment at **a reduced** dose of 1.2 mg/kg **every 3 weeks**.

Purpose: Specify that enrollment may occur either through an interactive voice response system or an interactive Web response system (IXRS)

The primary change occurs in Section 7.1, Study Personnel and Organizations:

Formerly read:	The contact information for the Takeda project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, the independent radiologic review facility, interactive voice response system (~~IVRS~~) provider, and the contract research organization (CRO) team may be found in the Study Manual.
Now reads:	The contact information for the Takeda project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, the independent radiologic review facility, interactive voice **and/or Web** response system (**IXRS**) provider, and the contract research organization (CRO) team may be found in the Study Manual.

Sections that also contain this change are:

- LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS
- Section 7.4.14, Enrollment

Purpose: Clarify the instructions for dispensation of reconstituted brentuximab vedotin

The change occurs in Section 6.9, Preparation, Reconstitution, and Dispensation:

Formerly read:	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~~.
Now reads:	The **required volume** of **5 mg/mL** reconstituted **brentuximab vedotin solution needed must** be **calculated and** withdrawn from the vial(s). **The reconstituted solution should be added immediately** to **an** infusion bag containing **a minimum volume of 100 mL. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.**

Purpose: Specify seated rather than supine measurements of vital signs

The change occurs in Section 7.4.7, Vital Signs:

Formerly read:	Vital sign measurements include ~~supine~~ (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral temperature.
Now reads:	Vital sign measurements include **seated** (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral

temperature.

Purpose: Add gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) to the serum chemistry panel

The change occurs in Section 7.4.15, Clinical Laboratory Evaluations, in the table of serum chemistry evaluations:

Added text:
- **Gamma glutamyl transferase (GGT)**
- **Alkaline phosphatase (ALP)**

Purpose: Move "unsatisfactory therapeutic response" from a mandatory to a voluntary reason for discontinuation of treatment with study drug and add the voluntary reason of "symptomatic deterioration"

The changes occur in Section 7.7, Discontinuation of Treatment With Study Drug, and Patient Replacement:

Formerly read:

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

- Completed maximum number of cycles per protocol
- Progressive disease
- Initiation of hematopoietic stem cell transplant
- Withdrawal by subject
- ~~Unsatisfactory therapeutic response~~

The reason justifying the study treatment withdrawal should be documented in the eCRF.

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent for the follow-up phase of the study.

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

- Adverse event
- Protocol violation
- Study terminated by sponsor
- Lost to follow-up
- Other

Now reads:

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

- Completed maximum number of cycles per protocol
- Progressive disease
- Initiation of hematopoietic stem cell transplant

- Withdrawal by subject

The reason justifying the study treatment withdrawal should be documented in the eCRF.

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent for the follow-up phase of the study.

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

- Adverse event
- **Symptomatic deterioration**
- **Unsatisfactory therapeutic response**
- Protocol violation
- Study terminated by sponsor
- Lost to follow-up
- Other

Purpose: Specify that all subsequent anticancer therapies will be recorded, regardless if they are initiated before or after the onset of progressive disease

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

Added Text: All subsequent anticancer therapies will be recorded, regardless if they are initiated before or after progressive disease.

Purpose: Delete "completed study" from the list of reasons a patient may be withdrawn from the study and remove the requirement that Takeda or their designee must be notified in writing if a patient is withdrawn from study treatment or the study itself

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

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

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal by subject
- ~~Completed study~~
- Death
- Other

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

~~Takeda or their designee must be notified in writing if a patient is withdrawn~~

~~from study treatment or from the study.~~ The reason(s) for withdrawal must be documented in the patient's medical records.

Purpose: Specify that serious adverse events in countries other than the United States and Canada must be reported within 24 hours (formerly "1 working day" in the SAE reporting appendix)

The change occurs in Appendix 15.3, Serious Adverse Event and Pregnancy Reporting Contact Information:

Formerly read:	All SAEs (regardless of their relationship to study drug), **must be reported within ~~1 working day~~ of knowledge of the event** by FAX to the appropriate PPD PVG safety fax number:
Now reads:	All SAEs (regardless of their relationship to study drug), **must be reported within *24 hours* of knowledge of the event** by FAX to the appropriate PPD PVG safety fax number:

Purpose: Remove the term "pharmacodynamic" throughout the protocol

The primary change occurs in Section 8.1.8, Pharmacokinetics/Biomarkers:

Formerly read:

CCI [redacted]

Now reads:

Sections that also contain this change are:

- Schedule of Events
- Section 4.2, Number of Patients
- Section 8.1.1, Determination of Sample Size
- Section 8.1.3, Populations for Analysis

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

These changes are not listed individually.

15.5 Amendment 2 Detailed Summary of Changes

THE PRIMARY SECTION OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 2 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Update the sponsor's name and legal entity responsible for the study.

The primary change occurs on the Title Page:

Formerly read:	Millennium Pharmaceuticals, Inc. 40 Landsdowne Street Cambridge, MA USA 02139 CCI [redacted]
Now reads:	Takeda Development Center (TDC) Americas, Inc. 95 Hayden Avenue, Lexington, Massachusetts 02421 USA TDC Americas, Inc. may be referred to in this protocol as "sponsor" or "Takeda".

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	29-Sep-2021 17:48 UTC
	Biostatistics Approval	29-Sep-2021 18:08 UTC