Title: A Phase 2, Single-Arm, Open-label Study of Brentuximab Vedotin in Chinese Patients With Relapsed/Refractory CD30-Positive Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL)

NCT Number: NCT02939014

Protocol Approve Date: 20 April 2016

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:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

A Phase 2, Single-Arm, Open-label Study of Brentuximab Vedotin in Chinese Patients With Relapsed/Refractory CD30-Positive Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL)

Brentuximab Vedotin in Chinese Patients With Relapsed/Refractory CD30-Positive HL or sALCL

Sponsor:	Takeda Development Center Asia, Pte. Limited 21 Biopolis Road, Nucleos North Tower, Level 4, Singapore 138567		
Study Number:	C25010		
IND Number:	Not applicable	**EudraCT Number:**	Not applicable
Compound:	Brentuximab vedotin		
Date:	20 April 2016		Original

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 11.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	See Section 11.0.
Medical Monitor (medical advice on protocol and compound)	PPD
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic signatures may be found on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 11.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B–Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Asia, Pte. Limited	**Compound:** Brentuximab vedotin	
Title of Protocol: A Phase 2, Single-Arm, Open-label Study of Brentuximab Vedotin in Chinese Patients With Relapsed/Refractory CD30-Positive Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL)	**IND No.:** Not applicable	**EudraCT No.:** Not applicable
Study Number: C25010	**Phase:** 2	

Study Design:

This is a single-arm, open-label, multicenter, phase 2 study designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of brentuximab vedotin as a single agent in Chinese patients with relapsed/refractory CD30+ HL or sALCL. Brentuximab vedotin will be administered as a single, 1.8 mg/kg intravenous (IV) infusion on Day 1 of each 3-week cycle. Patients will receive a maximum of 16 cycles if they do not meet the criteria for removal from the study. Patients will be assessed for overall response using the Revised Response Criteria for Malignant Lymphoma [1]. Dedicated computed tomography (CT) scans (neck, chest, abdomen, and pelvis) will be performed at Baseline and at Cycles 2, 4, 7, 10, 13, and 16, and positron emission tomography (PET) scans will be performed at Baseline and at Cycles 4 and 7. No additional PET scanning is required beyond Cycle 7 unless clinically indicated. B symptoms will be assessed at Baseline and on Day 1 of each cycle. Patients may continue on study treatment until the sooner of disease progression, unacceptable toxicity, or completion of 16 cycles. Patients, including those who discontinue study treatment for any reason other than withdrawal of consent, will have safety follow-up assessments through 30 days after the last dose of study drug (end of treatment [EOT]). Patients who discontinue study treatment with stable disease or better will be followed for progression-free survival (PFS) until disease progression, death, withdrawal of consent, or initiation of a new treatment, whichever occurs first. A CT scan will be performed every 12 weeks for the first 12 months and at 18 months after the last dose (EOT). Patients will be followed for overall survival (OS) every 12 weeks until death, withdrawal of consent, or study closure, whichever occurs first. All patients will have the opportunity to be followed for 18 months after EOT. The study will be closed when all patients enrolled have completed the required follow-up. Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective 14 June 2010 [2]. Laboratory values, vital signs, and electrocardiograms will be obtained to evaluate the safety and tolerability of brentuximab vedotin. Serial blood samples for determination of the serum/plasma concentration and immunogenicity of brentuximab vedotin will be obtained at prespecified time points as described in Table B in Appendix A.

Primary Objectives:

To evaluate the efficacy and the safety of brentuximab vedotin in Chinese patients with relapsed/refractory CD30+ HL or sALCL.

Secondary Objectives:

To evaluate the PK and immunogenicity of brentuximab vedotin in Chinese patients with relapsed/refractory CD30+ HL or sALCL.

Subject Population: Chinese patients aged 18 years or older with relapsed/refractory CD30+ HL or sALCL.

Number of Subjects:	**Number of Sites:**
Approximately 30 subjects (HL, approximately 22 subjects; sALCL, approximately 8 subjects).	Approximately 7 sites.
Dose Level(s):	**Route of Administration:**
Brentuximab vedotin, 1.8 mg/kg, administered on Day 1 of each 21-day cycle.	IV
Duration of Treatment:	**Period of Evaluation:**
A maximum of 16 cycles (Approximately 12 months).	Approximately 30 months, including 18 months of long-term follow-up.

Main Criteria for Inclusion:

1. Male or female Chinese patients aged 18 years or older at the time of informed consent.
2. Patients must have histologically confirmed CD30+ HL or sALCL. Immunohistochemistry or flow cytometry may be performed on either original diagnostic biopsy material or biopsy of relapsed disease, and pathology reports of CD30+ or their copies should be retained at the site.
3. Patients with CD30+ HL or sALCL who have relapsed from or are refractory to previous treatments.
4. Fluorodeoxyglucose-PET positive and measurable disease of at least 1.5 cm in the longest diameter by CT, as assessed by the site.
5. Patients must have an Eastern Cooperative Oncology Group performance status of 0 or 1.
6. 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.
7. 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 6 months after the last dose of study drug.

   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.
8. Suitable venous access for the study-required blood sampling, including PK sampling.
9. Patients must have the following required screening laboratory data. Patients must not have received recombinant granulocyte-colony stimulating factor or platelet transfusion within 1 week before the screening hematology assessment.
   - Absolute neutrophil count $\geq$1500/μL.
   - Platelet count $\geq$75,000/μL.
   - Serum bilirubin level $\leq$1.5 times the upper limit of the normal range (ULN).
   - Serum creatinine level $\leq$1.5 times the ULN.
   - Alanine aminotransferase and aspartate aminotransferase $\leq$2.5 times the ULN.
10. Survival for 3 or more months must be expected.

Main Criteria for Exclusion:

1. Patients with current diagnosis of primary cutaneous ALCL (patients with other organ involvement who have transformed to sALCL are eligible).
2. Female patients who are lactating and breast-feeding or have a positive serum pregnancy test during the screening period.
3. Patients with any active viral, bacterial, or fungal infection within 2 weeks before the first dose of brentuximab vedotin.
4. Patients with cardiac failure categorized as Class III or IV according to the New York Heart Association criteria, uncontrolled coronary artery disease or uncontrolled arrhythmia despite of appropriate medical therapy, or a history of myocardial infarction within 6 months before the first dose of brentuximab vedotin.
5. Patients with uncontrolled diabetes mellitus.
6. Peripheral neuropathy ≥Grade 2 (NCI CTCAE version 4.03) [2].
7. Patients with a history of another malignancy that has not been in remission for at least 3 years. The following are exempt from the 3-year limit:
   - Nonmelanoma skin cancer.
   - Curatively treated localized prostate cancer.
   - Cervical carcinoma in situ.
8. Patients with known cerebral/meningeal disease (HL or any other etiology), including signs or symptoms of progressive multifocal leukoencephalopathy (see Section 9.6.5).
9. Patients with a positive result in the screening test for human immunodeficiency virus antibody.
10. Known hepatitis B virus (HBV) surface antigen seropositive or positive hepatitis C virus antibody. Note: patients who have positive HBV core antibody can be enrolled but must have an undetectable HBV viral load.
11. Patients with a history of liver fibrosis or cirrhosis and clinical signs and symptoms indicating liver fibrosis or cirrhosis.
12. Patients who have received autologous stem cell transplantation within 12 weeks before the first dose of brentuximab vedotin.
13. Patients with a history of allogeneic stem cell transplantation.
14. Patients who have received treatment for malignancies (including radiation, chemotherapy, and hormone therapy) within 4 weeks before the first dose of brentuximab vedotin and patients who have received treatment for malignancies with biologics (including molecular target drug) or radioisotopic therapy within 12 weeks before the first dose of brentuximab vedotin.
15. Patients who have unresolved toxicity higher than Grade 1 (NCI CTCAE version 4.03) [2] attributed to any prior therapy/procedure (excluding alopecia or non-clinically significant and asymptomatic laboratory abnormalities).
16. Patients who have received systemic corticosteroids at doses greater than the equivalent of 20 mg/day of prednisone within 1 week before the first dose of brentuximab vedotin.
17. Patients who have received other investigational products within 4 weeks before the first dose of brentuximab vedotin.
18. Patients who have received treatment with investigational medical devices within 4 weeks before the first dose of brentuximab vedotin.
19. Patients who have received previous treatment with brentuximab vedotin.
20. Patients with a known hypersensitivity to any excipient contained in the drug formulation.
21. Patients who have any kind of disorder that compromises the ability of the patient to give written informed consent and/or to comply with study procedures.
22. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would

make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of the safety and toxicity of the prescribed regimens.

Main Criteria for Evaluation and Analyses:

The endpoints for this study are as follows.

- Primary:
  - Overall response rate (ORR).
  - Safety: adverse events (AEs), assessments of clinical laboratory values, vital sign measurements.
- Secondary:
  - Complete remission (CR) rate.
  - Duration of response (DOR).
  - PFS.
  - OS.
  - B symptom resolution rate.
  - Maximum observed plasma concentration (C_{max}).
  - Time to reach Cmax (t_{max}).
  - Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$).
  - Presence of antitherapeutic antibodies (ATA) and neutralizing antitherapeutic antibodies (nATA) to brentuximab vedotin.

Statistical Considerations:

The following analyses will be conducted separately for patients with HL and patients with sALCL unless otherwise stated.

Efficacy Analysis

Analyses of efficacy measures will be descriptive. The ORR, along with CR, and partial remission (PR) rates will be analyzed based on the assessment by the investigators per International Working Group criteria. Other efficacy endpoints, including PFS, OS, and DOR, will also be analyzed.

PK Analysis

Descriptive statistics (number of patients, arithmetic mean, geometric mean, standard deviation, median, percentage of coefficient of variation, minimum, and maximum) will be used to summarize PK parameters of antibody-drug conjugate (ADC) and total antibody (TAb) in serum, and monomethylauristatin E (MMAE) in plasma. Arithmetic mean of the plasma or serum concentration of MMAE, ADC, and TAb will be plotted over time.

Immunogenicity Analysis

Immunogenicity parameters (ATA titer and nATA titer in serum) will be summarized using descriptive statistics. CC [redacted]

Safety Analysis

Safety will be evaluated by the incidence, severity, and type of AEs (eg, treatment-emergent AEs [TEAEs], drug-related TEAEs, Grade 3 or higher TEAEs, serious AEs) according to the Medical Dictionary for Regulatory Activities, and also by changes from Baseline in vital signs and clinical laboratory results using the safety population. Exposure to study drug, including the number of treated cycles, total amount of doses taken, and dose intensity, will be summarized.

Sample Size Justification:

The study will have approximately 30 evaluable patients including approximately 22 patients with HL and approximately 8 patients with sALCL. Based on the exact binomial CI calculations, a minimum of 9 responses observed from 22 evaluable patients with HL (ORR of 40.9%) will provide a 95% CI (20.7%, 63.6%); 5 responses observed from 8 evaluable patients with sALCL (ORR of 62.5%) will yield a 95% CI (24.5%, 91.5%). In both cases, the lower limits of the 95% CI for the ORR are greater than the threshold response rate of 20% obtained from the results of alternative therapies for the same indications.

HL (n=22)				sALCL (n=8)			
Responses	**ORR (%)**	**95% Exact CI**		**Responses**	**ORR (%)**	**95% Exact CI**	
8	36.4	(17.2	59.3)	4	50.0	(15.7	84.3)
9	**40.9**	**(20.7**	**63.6)**	**5**	**62.5**	**(24.5**	**91.5)**
10	45.5	(24.4	67.8)	6	75.0	(34.9	96.8)
11	50.0	(28.2	71.8)	7	87.5	(47.3	99.7)
12	54.5	(32.2	75.6)	8	100	(63.1	100.0)
13	59.1	(36.4	79.3)				

For information purposes, response rates achieved in previous studies in relapsed/refractory HL and sALCL are referenced below.

	ORR (CR+PR) by Independent Review Facility (95% CI)
Global Study SGN035-0003 (HL: n=102)	74.5 (64.9, 82.6)
Global Study SGN035-0004 (sALCL: n=58)	86.2 (74.6, 93.9)
Japan Study TB-BC010088 (HL: n=9)	66.7 (29.9, 92.5)
Japan Study TB-BC010088 (sALCL: n=5)	100 (54.9, 100)

Assuming similar ORR results to those in Study TB-BC010088 will be obtained, the expected response rates are 65% for HL and 80% for sALCL. With 22 patients with HL and 8 patients with sALCL, the study will have >99% and >94% probability, respectively, to detect an ORR greater than the 20% threshold (ie, ≥9 responses for HL and ≥5 responses for sALCL).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

Abbreviation	Term
ABVD	doxorubicin+bleomycin+vinblastine+dacarbazine
ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
allo-SCT	allogeneic stem cell transplantation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
AUC	area under the concentration-time curve
auto-SCT	autologous stem cell transplantation
cAC10	anti-CD30 monoclonal antibody
CHL	classical Hodgkin lymphoma
CHOP	cyclophosphamide+doxorubicin+vincristine+prednisone
C_{max}	maximum observed concentration
CR	complete remission
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HRS	Hodgkin Reed-Sternberg
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee

Abbreviation	Term
IRB	institutional review board
IRF	independent review facility
IV	intravenous(ly)
IWRS	interactive web response system
JCV	John Cunningham virus
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMAE	monomethylauristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
nATA	neutralizing antitherapeutic antibodies
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NLPHL	nodular lymphocyte-predominant Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PR	partial remission
PTE	pretreatment event
Q3W	every 3 weeks
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
SD	stable disease
SJS	Stevens-Johnson syndrome
TAb	total antibody
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of the normal range
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

4.1.1 Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma

Lymphoma is the most common blood cancer. The 2 main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphomas (NHL). The World Health Organization (WHO) classification divides HL into 2 main subtypes: classical HL (CHL) and nodular lymphocyte-predominant HL (NLPHL). CHL is characterized by the presence of malignant Hodgkin Reed-Sternberg (HRS) cells in an inflammatory background, whereas NLPHL lacks HRS cells but is characterized by the presence of lymphocyte-predominant cells.

In 2015, it was estimated that 9050 new cases of HL were diagnosed in the United States and 1150 patients died from the disease [3].

NHL is the major population of malignant lymphoma and is heterogeneous in nature originating in B lymphocytes, T lymphocytes, or natural killer cells. Anaplastic large cell lymphoma (ALCL) is a rare type of NHL (5% of all cases of NHLs) [4] but one of the more common subtypes of T-cell lymphoma. There are 3 distinctly recognized subtypes of ALCL: systemic anaplastic lymphoma kinase (ALK)-positive ALCL, systemic ALK-negative ALCL, and primary cutaneous ALCL. ALK-positive ALCL is most common in children and young adults. It is characterized by the overexpression of ALK protein, which is the result of chromosomal translocation [t(2;5)].

4.1.1.1 HL in China

In China, the 2008 annualized incidence of HL was 0.4/100,000, with a slight male predominance (0.5 men vs 0.3 women per 100,000 [5]. The incidence peak occurs in adults aged around 40 years.

HL is classified into Stage I to IV according to Ann-Arbor staging. In general, the treatment for HL in China follows the comprehensive clinical practice guidelines for the management of HL issued by the National Comprehensive Cancer Network (NCCN), except brentuximab vedotin, which has not been approved in China. HL is typically treated with chemotherapy as frontline therapy, and the doxorubicin+bleomycin+vinblastine+dacarbazine (ABVD) regimen has been adopted nationally and globally as a standard of care; vincristine instead of vinblastine is common in China. For early-stage HL (mainly Stage I or II), 4 to 6 cycles of the ABVD regimen are used in combination with radiotherapy to disease areas. For advanced HL (Stage III or IV), the bleomycin+etoposide+doxorubicin+cyclophosphamide+vincristine+procarbazine+prednisone (BEACOPP) regimens might be a treatment option.

Approximately 30% to 40% of patients with advanced-stage HL will be refractory to initial therapy or will relapse. HL that has relapsed or is refractory to therapy is associated with significant patient morbidity and mortality [6,7]. Patients with HL experiencing relapse after achieving response to frontline therapy and those showing disease progression during frontline therapy or failing to achieve complete remission (CR) are unlikely to experience long-term, disease-free survival even after standard-dose chemotherapy as second-line therapy; observed

overall response rates (ORRs) are from 22% to 48% with the single use of gemcitabine or in combination use with rituximab for the treatment of patients with relapsed or refractory HL, both before and after autologous stem cell transplantation (auto-SCT) [8-11]. The survival rates are as low as 10% to 30% [12-14].

Therefore, patients with relapsed/refractory HL are treated with high-dose chemotherapy (radiotherapy). For patients who are not candidates for auto-SCT or do not have access to auto-SCT, or whose disease relapses following auto-SCT, no therapies have consistently resulted in substantive rates of durable remission or extension of overall survival (OS), which are currently 10.7 months and 26.9 months, respectively [8,10]. Although other salvage chemotherapy and allogeneic stem cell transplantation (allo-SCT) have been attempted, no standard therapy is available yet for relapsed patients. Novel agents are therefore needed at an early date.

4.1.1.2 ALCL in China

In China, the 2008 annualized incidence of NHL was 2.1/100,000 with a slight male predominance (2.5 vs 1.7 per 100,000) [5], for an approximate annualized incidence of ALCL in China of 0.042 to 0.11 per 100,000. ALCL is an aggressive disease that is potentially curable with frontline multiagent chemotherapy; however, 40% to 65% of patients will develop recurrent disease for which multi- or single-agent salvage therapy offers little benefit. OS is poor, with contemporary registry data showing a median OS of 3.3 months.

ALCL has a bimodal distribution in age of onset, with a first peak in the younger than 30 years of age group, with men accounting for a higher percentage than women, and a second peak in the older than 60 years of age group.

The cyclophosphamide+doxorubicin+vincristine+prednisone (CHOP) regimen or a CHOP-like regimen has been used as the standard frontline therapy for ALCL in China and other countries [4]. Second-line therapies for ALCL include single- or multi-agent salvage regimens, though the benefit is limited. Auto-SCT and allo-SCT have been used, but standard therapy has not yet been established for relapsed/refractory ALCL in any countries. Novel agents are therefore needed at an early date.

4.1.2 Brentuximab Vedotin

4.1.2.1 CD30 Antigen

CD30 is a transmembrane glycoprotein receptor, originally identified on HRS cells, belonging to a superfamily of tumor necrosis factor receptors. CD30 antigen is expressed on the surface of HRS cells, cells in ALCL, and in other T-cell lymphoproliferative disease. It is also slightly expressed on normal cells, such as activated T cells and various hematopoietic cells. The function of CD30 has not been defined, but it is thought to be involved in both cellular death and proliferation [15]. The attention drawn to the usefulness of CD30 as a diagnostic marker for HL and ALCL and its apoptosis-induction activity have led to the investigation of CD30 as a new therapeutic target.

In Western countries, CHL accounts for 90% to 95% and NLPHL accounts for 5% to 10% of all HL [16]. Therefore, 90% to 95% of HL is CD30 antigen positive. Almost 100% of ALCL is positive for CD30.

4.1.2.2 Antibody-Drug Conjugate Therapy and Brentuximab Vedotin

Brentuximab vedotin is an antibody drug conjugate (ADC) that targets CD30 and consists of the following: 1) anti-CD30 monoclonal antibody (cAC10), 2) a potent microtubule inhibitor monomethylauristatin E (MMAE), and 3) a linker cleavable by protease, through which cAC10 is conjugated to MMAE. The biological activity of brentuximab vedotin consists of several steps. First, after binding to CD30 on the surface of tumor cells, brentuximab vedotin is uptaken to the cells as ADC-CD30 complex and transported to lysosomes. Then, MMAE is released within the cells by a proteolytic reaction. Binding of MMAE to tubulin disrupts the microtubule network, leading to cell cycle arrest and apoptosis of CD30-expressing tumor cells.

As of February 2016, brentuximab vedotin has been approved for patients with relapsed/refractory, CD30-positive HL or systemic anaplastic large cell lymphoma (sALCL) in 62 countries, including the United States, European Union, and Asian countries such as Korea, Japan, Taiwan, and Hong Kong.

Refer to the brentuximab vedotin Investigator's Brochure (IB) for details.

4.1.3 Nonclinical Studies

Bone marrow cytopenia, depletion of lymphatic tissue, and associated decrease in blood cells in the peripheral blood were observed in rats and monkeys following repeated doses of brentuximab vedotin. These were consistent with inhibitory effects of MMAE on microtubules. Similar effects were seen following repeated doses of MMAE, while no related adverse effects were noted following repeat doses of cAC10. The no observable adverse effect level of brentuximab vedotin following repeated doses in rats and monkeys was estimated to be 0.5 mg/kg and 1 mg/kg, respectively. The highest nonseverely toxic dose of brentuximab vedotin following repeated doses in rats and monkeys was considered to be 5 mg/kg and 3 mg/kg, respectively. In a repeat-dose toxicity study in which rats were given the highest dose of 15 mg/kg of brentuximab vedotin for up to 1 month, changes were observed in bone marrow (cytopenia), thymus (depletion of lymphatic tissue), spleen (depletion of lymphatic tissue), liver (focal coagulation necrosis), intestine (single cell necrosis), testes (seminiferous tubule degeneration), and lung (alveolar histiocytosis). At the end of a recovery period of 4 weeks, the toxicity to all target organs were reversed except for testicular toxicity. The testicular toxicity in rats was partially reversed following a recovery period of 16 weeks.

Refer to the brentuximab vedotin IB for details.

4.1.4 Clinical Studies

Table 4.a and Table 4.b summarize completed and ongoing clinical studies of brentuximab vedotin.

Table 4.a List of Completed Clinical Studies With Brentuximab Vedotin (as of February 2016)

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration (a)	Primary Endpoint	Planned/ Treated/ Analyzed (b)	M:F Median Age (Range)	Study Dates (c)	Sites/ Regions
Clinical Pharmacology Studies									
SGN35-007 Phase 1	Open-label, single-arm	Clinical pharmacology	CD30+ hematologic malignancies	1.8 mg/kg IV q3wk 16 cycles	Duration of ventricular repolarization	48/52/46	48%:52% 34.5 (19–76)	Feb 10-Aug 11	9/US, W Europe
SGN35-008A Phase 1	Open-label, nonrandomized, 3-arm, drug-drug interaction, excretion	Clinical pharmacology	CD30+ hematologic malignancies	1.2 or 1.8 mg/kg IV q3wk 2 cycles	PK parameters	36/56/45	59%:41% 33.5 (16–71)	Dec 09–Jun 10	7/US
SGN35-008B Phase 1	Open-label, nonrandomized, hepatic or renal impairment	Clinical pharmacology	CD30+ hematologic malignancies	1.2 mg/kg IV q3wk 2 cycles	PK parameters	12/17/17	Hepatic 57%:43% 55.0 (22-72) Renal 50%:50% 56.5 (29-78)	Jan 10-May 12	6/US
C25005 Phase 1	Open-label, 1:1 randomized, single agent or with rifampicin	Metabolite quantification	Relapsed/ refractory classical HL or sALCL	1.8 mg/kg IV q3wk 16 cycles	PK parameters	20/20	≥18 and ≤75	Nov 13–Jun 15	Europe

Footnotes are on last table page.

Table 4.a List of Completed Clinical Studies With Brentuximab Vedotin (as of February 2016) (continued)

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration (a)	Primary Endpoint	Planned/ Treated/ Analyzed (b)	M:F Median Age (Range)	Study Dates (c)	Sites/ Regions
Efficacy and Safety Studies									
SG035-0001 Phase 1	Open-label, single-arm, dose-escalation	Safety	CD30+ hematologic malignancies	0.1–3.6 mg/kg IV q3wk NA	AEs; laboratory abnormalities	51/45/45	62%:38% 36 (20–87)	Nov 06–Jul 09	4/US
SG035-0002 Phase 1	Open-label, single-arm, dose-escalation	Safety	CD30+ hematologic malignancies	0.4–1.4 mg/kg IV q1wk 12 cycles	AEs, laboratory abnormalities	72/44/44	70%:30% 33 (12–82)	Mar 08-Feb 10	5/US
SG035-0003 Phase 2	Open-label, single-arm	Efficacy and safety	HL	1.8 mg/kg IV q3wk 16 cycles	ORR	100/102/102	47%:53% 31 (15–77)	Feb 09-Aug 10 (d)	25/US, Canada, W Europe
SG035-0004 Phase 2	Open-label, single-arm	Efficacy and safety	sALCL	1.8 mg/kg IV q3wk 16 cycles	ORR	55/58/58	57%:43% 52 (14–76)	Jun 09–Jun 11 (d)	22/US, Canada, W Europe
SGN35-005 Phase 3	Randomized, double-blind, 2-arm, placebo-controlled	Efficacy and safety	HL (high risk post-auto-SCT)	1.8 mg/kg or placebo IV q3wk 16 cycles	Progression-free survival	322/327/329	53%:47% 32 (18-76)	Apr 10-Aug 14 (d)	78/US, EU, Russia, Serbia

Footnotes are on last table page.

Table 4.a List of Completed Clinical Studies With Brentuximab Vedotin (as of February 2016) (continued)

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration (a)	Primary Endpoint	Planned/ Treated/ Analyzed (b)	M:F Median Age (Range)	Study Dates (c)	Sites/ Regions
SGN35-006 Phase 2	Open-label, nonrandomized, 2-arm	Efficacy and safety	CD30+ hematologic malignancies	1.2 or 1.8 mg/kg IV q3wk NA	Retreatment arm (Report A): AEs, laboratory abnormalities, ORR	125(e)/32/34 (f)	47%:53% 37 (16–72)	Jul 09–Mar 13	11/ 10 US, 1 France
					Extension arm (Report B): AEs, laboratory abnormalities	125(e)/78/78	55%:45% 32 (15–78)	Jul 09–Mar 13	14/US
SGN35-009 Phase 1	Open-label, 2-arm, dose-escalation with ABVD/AVD	Safety	HL (treatment naïve)	0.6, 0.9, or 1.2 mg/kg IV q2wk 6 cycles	AEs, laboratory abnormalities	50-70/51/51	73%:27% 33 (18-59)	Jan 10–Sep 12	4/US, Canada
TB-BC010088 Phase 1/2	Open-label, nonrandomized, single-arm, 2 part	Efficacy and safety in Japanese patients	CD30+ relapsed/ refractory HL or sALCL	1.2 or 1.8 mg/kg IV q3wk 16 cycles	Phase 1: DLT, AEs, weight, vital signs, ECGs, lab parameters	17–23/20/20	55%:45% 41 (22-88)	Oct 11-Oct 13	5/Japan
					Phase 2: AEs, weight, vital signs, ECGs, lab parameters, and ORR				

Table 4.a List of Completed Clinical Studies With Brentuximab Vedotin (as of February 2016) (continued)

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration (a)	Primary Endpoint	Planned/ Treated/ Analyzed (b)	M:F Median Age (Range)	Study Dates (c)	Sites/ Regions
Compassionate Use Programs									
Single-patient IND use	NA	NA	HL ALCL	1.8 mg/kg IV q3wk 16 cycles	NA	NA/36/NA	NA	Aug 10–Jul 11	NA/US
Canadian Special Access Program	NA	NA	HL ALCL	1.8 mg/kg IV q3wk 16 cycles	NA	NA/52/NA	NA	Oct 11–Jan 13	Canada

AE=adverse event; AVD=doxorubicin+ vinblastine+dacarbazine; b-v=brentuximab vedotin; DLT=dose-limiting toxicity; ECG=electrocardiogram; EU=European Union; IND=Investigational New Drug (application); IV=intravenous(ly); NA=not applicable; PK=pharmacokinetic(s); qXwk=every X week(s); US=United States; W=Western.
(a) Maximum treatment duration represented as treatment cycles (1 cycle=q3wk, 1 dose/21-day cycle; q2wk, 2 doses/28-day cycle; or q1wk, 3 doses/28-day cycle).
(b) Contributed to evaluation of the primary endpoint.
(c) First patient visit (or first patient randomized) to last patient visit (as reported in the clinical study report).
(d) Long-term follow-up ongoing.
(e) Per the study design, this number represents the planned patients for the retreatment and extension arms combined.
(f) Includes 3 patients who were re-treated twice in this study.

Table 4.b List of Ongoing Clinical Studies With Brentuximab Vedotin (as of February 2016)

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration (a)	Primary Endpoint	Planned/ Enrolled (b)	Age	Study Dates (c)	Regions
Efficacy and Safety Studies									
SGN35-011 Phase 1	Open-label, nonrandomized, 3-arm, with CHOP/CHP	Safety	CD30+ mature T-cell and Natural killer-cell neoplasms (treatment naive)	1.2 or 1.8 mg/kg IV q3wk 16 cycles	AEs, laboratory abnormalities	52/39 (d)	≥18	Feb 11– ongoing	US, W Europe
SGN35-012 Phase 2	Open-label, nonrandomized, 3-part, single-agent or with rituximab	Efficacy and safety	NHL including DLBCL	1.8 mg/kg IV q3wk NA	Parts A and C: ORR Part B: AEs, laboratory abnormalities	160/176 (d)	≥6	Aug 11– ongoing	US, Canada
SGN35-013 Phase 2	Open-label, nonrandomized	Efficacy and safety	CD30+ non-lymphomatous malignancies	1.8 or 2.4 mg/kg IVq3wk or 1.2 mg/kg IV q1wk NA	ORR	80/83 (d)	≥6	Oct 11– ongoing	US
SGN35-014 Phase 3	Randomized, double-blind, 2-arm, A+CHP vs CHOP	Efficacy and safety	CD30+ mature T-cell lymphomas (treatment naïve)	1.8 mg/kg IV q3wk 6-8 cycles	Progression-free survival	450/363	≥18	Jan 13– ongoing	US, Asia, Canada, Europe, Israel
SGN35-015 Phase 2	Open-label, nonrandomized, 3-part, single agent or with dacarbazine or bendamustine	Efficacy and safety	HL (treatment naïve)	1.8 mg/kg IV q3wk 16 cycles	ORR	80/72	≥60	Oct 12– ongoing	US

Footnotes are on last table page.

Table 4.b List of Ongoing Clinical Studies With Brentuximab Vedotin (as of February 2016) (continued)

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration (a)	Primary Endpoint	Planned/ Enrolled (b)	Age	Study Dates (c)	Regions
SGN35-016 Phase 1/2	Open-label, single-arm, with bendamustine	Efficacy and safety	HL (post-frontline)	1.8 mg/kg IV q3wk 16 cycles	CR rate	50/55 (d)	≥18	Jun 13– ongoing	US
SGN35-017 Phase 2	Open-label, randomized, 3-part, with RCHOP/RCHP	Efficacy and safety	DLBCL (treatment naïve)	1.2 mg/kg or 1.8 mg/kg IV q3wk Up to 6 cycles	CR rate, AEs, laboratory abnormalities	75/68	≥18	Aug 13– ongoing	US
SGN35-022	Randomized, double-blind, dose-escalation	Efficacy and safety	SLE	0.3–1.8 mg/kg IV q3wk 4 cycles	SRI response, AEs, laboratory abnormalities	40/10	≥18		US
SGN35-025	Open-label, single-arm with nivolumab	Efficacy and safety	HL (post-frontline)	1.2 mg/kg or 1.8 mg/kg IV q3wk 4 cycles	CR rate, AEs, laboratory abnormalities	56–60/6	≥18	Oct 15– ongoing	US
C25001 Phase 3	Open-label, randomized, 2-arm, single-agent vs physician's choice of methotrexate or bexarotene	Efficacy, quality of life, and safety	CD30+ mycosis fungoides or primary cutaneous ALCL	1.8 mg/kg IV q3wk 16 cycles	ORR lasting ≥4 months	124/132 (d)	≥18	Aug 12– ongoing	US

Footnotes are on last table page.

Table 4.b List of Ongoing Clinical Studies With Brentuximab Vedotin (as of February 2016) (continued)

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration (a)	Primary Endpoint	Planned/ Enrolled (b)	Age	Study Dates (c)	Regions
C25002 Phase 1/2	Open-label, dose escalation in pediatric patients	Phase 1: pediatric MTD and PK Phase 2: ORR	Phase 1: CD30+ malignancies Phase 2: r/r HL or sALCL	1.4 or 1.8 mg/kg IV q3wk 16 cycles	AEs, laboratory abnormalities, PK, ORR	42/33	≥2,<18 ALCL ≥5,<18 HL	Apr 12–ongoing	US, W Europe
C25003 Phase 3	Open-label, randomized, 2-arm, A+AVD vs ABVD	Efficacy, quality of life, and safety	Advanced classical HL (treatment naïve)	1.2 mg/kg IV q2wk 6 cycles	Modified progression-free survival per IRF	1240/1334 (d)	≥18	Nov 12–ongoing	US, Canada, Europe, Asia
C25006 Phase 4	Open-label, single-arm	Efficacy and safety	sALCL	1.8 mg/kg IV q3wk 16 cycles	ORR per IRF	45/21	≥18	Feb 14–ongoing	Europe, Latin America
C25007 Phase 4	Open-label, single-arm	Efficacy and safety	r/r HL not suitable for SCT or multiagent chemotherapy	1.8 mg/kg IV q3wk 16 cycles	ORR per IRF	60/60 (d)	≥18	Mar 14–ongoing	Europe
Compassionate Use Programs and Other Studies									
SGN35-010 Expanded Access Program	Open-label, treatment option	Safety and expanded access	HL, ALCL, CD30+ CTCL	1.8 mg/kg IV q3wk NA	AEs	410/361	≥6	Sep 10–ongoing	US, Europe

Footnotes are on last table page.

Table 4.b List of Ongoing Clinical Studies With Brentuximab Vedotin (as of February 2016) (continued)

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration (a)	Primary Endpoint	Planned/ Enrolled (b)	Age	Study Dates (c)	Regions
Named Patient Program	NA	NA	HL, ALCL	1.8 mg/kg IV q3wk 16 cycles	NA	NA/2561	NA	Nov 10–ongoing	Global (ex-North America)
MA25101 Post-authorization	Prospective observational cohort	Safety	CD30+ r/r HL or sALCL	Per label and routine practice	SAEs, AEs of special interest, and risk factors	500/174	>18	Jun 13–ongoing	Europe
CCI									
Special Drug Use Survey (All-Patients Surveillance)	Prospective observational cohort	Efficacy and safety	CD30+r/r HL or ALCL	1.8 mg/kg IV q3wk 16 cycles	AEs	140/293 (d)	NA	Apr 14–ongoing	Japan

A+AVD=brentuximab vedotin+ doxorubicin+ vinblastine+dacarbazine; AE=adverse event; b-v=brentuximab vedotin; CHP=cyclophosphamide+doxorubicin+prednisone; CTCL=cutaneous T-cell lymphoma; DLBCL=diffuse large B-cell lymphoma; IRF=independent review facility; IV=intravenous(ly); MTD=maximum tolerated dose; NA=not applicable; PK=pharmacokinetic(s); PN=peripheral neuropathy; qXwk=every X week(s); r/r=relapsed/refractory; RCHOP= rituximab +cyclophosphamide+doxorubicin+vincristine+prednisone; RCHP= rituximab + cyclophosphamide+doxorubicin+prednisone; SAE=serious adverse event; SCT=stem cell transplant; SLE= systemic lupus erythematosus; SRI= SLE Responder Index; US=United States; W=Western.

(a) Maximum treatment duration represented as treatment cycles (1 cycle=q3wk, 1 dose/21-day cycle; or q2wk, 2 doses/28-day cycle; or q1wk, 3 doses/28-day cycle).

(b) Approximate number of patients enrolled as of 31 October 2015.

(c) First patient visit to last patient visit.

(d) Enrollment completed.

The results of the relevant clinical studies are summarized below. Refer to the brentuximab vedotin IB for details.

- Phase 1 study (United States): Study SG035-0001

  Study SG035-0001 was a phase 1 dose-escalation study in patients with CD30-positive relapsed/refractory hematopoietic neoplasms (0.1-3.6 mg/kg every 3 weeks [Q3W]). A total of 45 patients were enrolled in each dose cohort and the maximum tolerated dose (MTD) was defined as 1.8 mg/kg. Dose-limiting toxicity (DLT) was observed in 1 of 12 patients in the 1.8 mg/kg cohort (thrombocytopenia [Grade 4]), 3 of 12 patients in the 2.7 mg/kg cohort (acute renal failure [Grade 3], prostatitis [Grade 3], febrile neutropenia [Grade 3], and hyperglycemia [Grade 3]), and 1 of 1 patient in the 3.6 mg/kg cohort (febrile neutropenia and septic shock [Grade 5]). The most common treatment-emergent adverse events (TEAEs) (≥20%) were fatigue (36%), fever (33%), diarrhea, nausea, peripheral neuropathy, and neutropenia (22% each), and headache and vomiting (20% each). A number of patients achieved response, with an ORR of 40% (17/42) and a CR rate of 26%.

- Phase 1/2 study (Japan): Study TB-BC010088

  Study TB-BC010088 was a phase 1/2 study that evaluated single-agent brentuximab vedotin in Japanese patients with relapsed/refractory CD30-positive HL or sALCL (1.2 or 1.8 mg/kg Q3W). The phase 1 part of the study was a dose-escalation study that enrolled 6 patients sequentially into cohort 1 (3 patients; 2 patients with HL and 1 patient with sALCL) at 1.2 mg/kg or into cohort 2 at 1.8 mg/kg (3 patients with HL). In this part, no DLT was observed in the 1.2 or 1.8 mg/kg dose cohorts, and the treatment was well tolerated. In the phase 2 part, 14 patients (9 patients with HL and 5 patients with sALCL) received 1.8 mg/kg of brentuximab vedotin. The phase 2 part resulted in a high objective response rate in Japanese patients (67% for patients with HL and 100% for patients with sALCL), including CR for 56% of patients with HL and 80% of patients with sALCL with a manageable toxicity profile.

- Pivotal phase 2 studies (United States, Canada, and Western Europa):
  - Study SG035-0003 was a phase 2, single-arm, open-label study in patients with relapsed/refractory HL after auto-SCT.
  - Study SG035-0004 was a phase 2 study conducted in patients with relapsed/refractory sALCL.

  Brentuximab vedotin was administered at a dose of 1.8 mg/kg Q3W. One hundred two patients with relapsed/refractory HL and 58 patients with relapsed/refractory sALCL were enrolled in Study SG035-0003 and Study SG035-0004, respectively.

  The key efficacy results in HL (SG035-0003) include ORR per an independent review facility (IRF) (75% [95% CI; 64.9, 82.6]), CR rate per IRF (34% [95% CI; 25.2, 44.6]), B symptom resolution rate (77%), and duration of response (DOR; 6.7 months). Key efficacy endpoints in sALCL (SG035-0004) include ORR per IRF (88% [95% CI, 74.6; 93.9]), CR rate per IRF (53% [95% CI, 39.6; 66.7]), and B symptom resolution rate (82%). Brentuximab vedotin has

been shown to induce durable remissions in patients with HL both before and after auto-SCT, and in patients with relapsed/refractory sALCL. Progression-free survival (PFS) results comparing PFS after brentuximab vedotin with PFS from prior systemic therapy indicate that PFS is significantly prolonged with brentuximab vedotin in both HL and sALCL. A substantial number of patients with HL and sALCL and B symptoms at Baseline saw these symptoms resolve during treatment with brentuximab vedotin. In addition, the large majority of patients with sALCL presenting with cutaneous lesions at Baseline experienced resolution of these symptoms after receiving brentuximab vedotin.

TEAEs occurring in ≥20% of patients in the phase 2 studies 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. In the phase 2 studies, 31% of patients had a serious adverse event (SAE), 28% had a Grade 3 or higher SAE, and 15% had an SAE that was determined by the investigator to be related to brentuximab vedotin. The most common SAE preferred terms (2%) were abdominal pain, disease progression (recurrent sALCL), pulmonary embolism, and septic shock. A higher proportion of patients with sALCL experienced SAEs, including deaths within 30 days of the last dose, relative to patients with HL, likely due to the older age and more aggressive nature of the malignancy in this patient population. No deaths considered related to study treatment have been reported within the safety evaluation period (within 30 days after the last dose of brentuximab vedotin) in these 2 phase 2 studies.

4.1.5 Known or Potential Risks of Brentuximab Vedotin

- Brentuximab vedotin treatment causes peripheral neuropathy, both sensory and motor. Brentuximab vedotin-induced peripheral neuropathy is typically cumulative and generally reversible. Monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, and neuropathic pain or weakness, is required. Patients experiencing new or worsening peripheral neuropathy may require brentuximab vedotin dose modifications, including a dose delay (see Table 9.a).
- Complete blood counts 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 with dose delays, reductions, or discontinuations (see Table 9.a).
- Infusion-related reactions, including anaphylaxis, have occurred with brentuximab vedotin. 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. 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.

- Any treatment that can decrease immune function may contribute to malignancy and infections; patients are to be monitored for these events during the treatment period and up to and including 30 days after the last dose.
- Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) have been reported with brentuximab vedotin. If SJS/TEN occurs, brentuximab vedotin must be discontinued and the appropriate medical therapy administered.
- Tumor lysis syndrome may occur. Patients with rapidly proliferating tumors 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.
- Progressive multifocal leukoencephalopathy (PML) has been reported with brentuximab vedotin use. If PML is suspected, a diagnostic work-up should be performed as described in Section 9.6.5.
- Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity. In a clinical study that studied brentuximab vedotin with bleomycin as part of a combination regimen (ABVD), the rate of noninfectious pulmonary toxicity was higher than the historical incidence reported with ABVD.

  Pulmonary toxicity, including events of pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, has been reported in patients receiving brentuximab vedotin monotherapy. Based on a cumulative review of all nonstudy derived events of acute pulmonary toxicity associated with brentuximab vedotin monotherapy and safety results in patients with HL after auto-SCT in Study SGN35-005, pulmonary toxicity associated with brentuximab vedotin treatment cannot be ruled out although clear evidence of a causal relationship was not found. Patients being treated with brentuximab vedotin should be closely and continuously monitored. If pulmonary toxicity is suspected, a prompt diagnostic evaluation should be performed, and patients should be treated appropriately. Consider holding brentuximab vedotin during evaluation and until symptomatic improvement.
- Acute pancreatitis has been reported in patients treated with brentuximab vedotin and has contributed to fatal outcomes in some cases. Onset typically occurred after 1 to 2 doses of brentuximab vedotin. Early symptoms included severe abdominal pain, nausea, and vomiting. The majority of pancreatitis cases were complicated by other possible contributory factors, including cholelithiasis and alternate etiologies (eg, pancreatic lymphoma progression and displacement of bile duct stent).
- Approximately 10% of patients treated with brentuximab vedotin within the defined overall clinical study population have had an adverse event (AE) that was suggestive of a hepatobiliary disorder; <1% have experienced an SAE. Fatal outcomes have occurred; these cases were confounded by pre-existing liver disease, comorbidities, and concomitant medications with known hepatotoxic potential. The majority of hepatic AEs have been reported as Grade 1 to 2 in intensity. Increased liver enzymes have constituted the majority of hepatic AEs.

- Gastrointestinal complications, including events of intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation, and hemorrhage, some with fatal outcomes, have been reported in patients treated with brentuximab vedotin. Some cases of gastrointestinal perforations were reported in patients with gastrointestinal involvement of underlying lymphoma. In the event of new or worsening gastrointestinal symptoms, perform a prompt diagnostic evaluation and treat appropriately.
- The pharmacokinetic (PK) of brentuximab vedotin was studied in patients with hepatic or renal impairment. Patients with hepatic impairment (Child-Pugh class A to C) and patients with severe renal impairment (creatinine clearance lower than 30 mL/min) exhibited a trend toward moderate decreases in ADC exposure and increases in MMAE exposure. Therefore, patients with hepatic impairment and/or severe renal impairment at Baseline will not be enrolled in this study. Patients with hepatic or renal impairment during study treatment should be closely monitored for AEs and will be treated based on the local standard of care.
- Co-administration of brentuximab vedotin with ketoconazole, a strong cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp) inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73% and did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, refer to Table 9.a.
- Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin; however, it reduced exposure to MMAE by approximately 31%.
- Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam; therefore, brentuximab vedotin is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes.
- 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 9.5 for appropriate precautions triggered by the administration of study medication.

Refer to the brentuximab vedotin IB for details.

4.2 Rationale for the Proposed Study

4.2.1 Rationale for Evaluation of HL and sALCL in One Study

The mechanism and site of action of brentuximab vedotin are the same for both HL and sALCL because brentuximab vedotin exhibits antitumor effects by binding to CD30 on the surface of tumor cells. Additionally, the same tumor response criteria are used for both diseases. The therapeutic strategy is similar for relapsed/refractory HL and sALCL. The phase 2 studies showed that brentuximab vedotin has comparable antitumor effects in patients with relapsed/refractory HL

and sALCL, and there is no marked difference in safety profile. It is therefore appropriate to evaluate brentuximab vedotin in patients with relapsed/refractory HL and sALCL in one study.

4.2.2 Rationale for Dose

In Study SG035-0001 (first-in-human study), brentuximab vedotin doses from 0.1 to 3.6 mg/kg Q3W were evaluated. No DLT was observed in the cohorts up to 1.2 mg/kg Q3W. DLTs observed in 3 of 12 patients treated at the 2.7 mg/kg dose level included Grade 4 neutropenic fever, Grade 3 prostatitis, Grade 3 hyperglycemia, and 1 case of unrelated acute renal failure. One occurrence of Grade 4 thrombocytopenia qualified as a DLT at the 1.8 mg/kg dose level. The MTD was defined as 1.8 mg/kg administered intravenously (IV) Q3W.

Tumor response (CR+partial remission [PR]) was observed at doses above 1.2 mg/kg Q3W. The subsequent clinical studies have used a dose of 1.8 mg/kg Q3W as the optimal dose.

In the phase 1 part of Study TB-BC010088 (Japan phase 1/2 study), brentuximab vedotin was evaluated at dose levels of 1.2 and 1.8 mg/kg administered Q3W to determine the phase 2 dose. No DLT was observed in the phase 1 part of this study, and the 1.8 mg/kg dose level was selected for the phase 2 part. The resulting tumor response at 1.8 mg/kg by the IRF was 67% (95% CI; 29.9, 92.5) for relapsed/refractory HL and 100% (95% CI; 54.9, 100.0) for relapsed/refractory sALCL. Tumor sizes were reduced in all subjects in the phase 2 part for whom measurements were available, and the safety profile was manageable.

The same brentuximab vedotin dosing schedule of 1.8 mg/kg Q3W was used in the Study SGN35-005 (global phase 3 study). The safety findings from this study were similar to those from pivotal phase 2 studies SG035-0003 and SG035-0004. At the time of the interim OS analysis, data are immature and limited by the small number of events observed within a relatively short follow-up period; however, the difference in median PFS in this study per IRF between the brentuximab vedotin arm and placebo arm was statistically significant by the stratified log rank test (p=0.001).

Based on these data, it is appropriate to use 1.8 mg/kg Q3W as the brentuximab vedotin dose in Chinese patients. This dose has been approved in 62 countries for patients with relapsed or refractory CD30-positive HL and sALCL.

5.0 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective is to evaluate the efficacy and the safety of brentuximab vedotin in Chinese patients with relapsed/refractory CD30+ HL or sALCL.

5.2 Secondary Objective

The secondary objective is to evaluate the PK and immunogenicity of brentuximab vedotin in Chinese patients with relapsed/refractory CD30+ HL or sALCL.

6.0 STUDY ENDPOINTS

6.1 Primary Endpoints

The primary endpoints are:

- ORR.
- Safety: AEs, assessments of clinical laboratory values, and vital sign measurements.

6.2 Secondary Endpoints

The secondary endpoints are:

- CR rate.
- DOR.
- PFS.
- OS.
- B symptom resolution rate.
- Maximum observed plasma concentration (C_{max}).
- Time to reach Cmax (t_{max}).
- Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$).
- Presence of antitherapeutic antibodies (ATA) and neutralizing antitherapeutic antibodies (nATA) to brentuximab vedotin.

7.0 STUDY DESIGN

7.1 Overview of Study Design

This is a single-arm, open-label, multicenter, phase 2 study designed to evaluate the efficacy, safety, and PK of brentuximab vedotin as a single agent in Chinese patients with relapsed/refractory CD30+ HL or sALCL. Brentuximab vedotin will be administered as a single, 1.8 mg/kg IV infusion on Day 1 of each 3-week cycle.

Patients will receive a maximum of 16 cycles if they do not meet the criteria for removal from the study. Patients will be assessed for overall response using the Revised Response Criteria for Malignant Lymphoma [1]. Dedicated computed tomography (CT) scans (neck, chest, abdomen, and pelvis) will be performed at Baseline and at Cycles 2, 4, 7, 10, 13, and 16, and positron emission tomography (PET) scans will be performed at Baseline and at Cycles 4 and 7. No additional PET scanning is required beyond Cycle 7 unless clinically indicated. B symptoms will be assessed at Baseline and on Day 1 of each cycle.

Patients may continue on study treatment until the sooner of disease progression, unacceptable toxicity, or completion of 16 cycles. Patients, including those who discontinue study treatment for any reason other than withdrawal of consent, will have safety follow-up assessments through 30 days after the last dose of study drug (end of treatment [EOT]). Patients who discontinue study treatment with stable disease (SD) or better will be followed for PFS until disease progression, death, withdrawal of consent, or initiation of a new treatment, whichever occurs first. A CT scan will be performed every 12 weeks for the first 12 months and at 18 months after EOT. Patients will be followed for OS every 12 weeks until death, withdrawal of consent, or study closure, whichever occurs first. All patients will have the opportunity to be followed for 18 months after EOT. The study will be closed when all patients enrolled have completed the required follow-up.

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective 14 June 2010 [2]. Laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of brentuximab vedotin. Serial blood samples for determination of the serum/plasma concentration and immunogenicity of brentuximab vedotin will be obtained at prespecified time points as described in Table B in Appendix A.

7.2 Number of Patients

It is expected that approximately 30 evaluable subjects (approximately 22 subjects with HL and approximately 8 subjects with sALCL) will be enrolled in this study. The justification for the sample size is described in Section 14.3.

7.3 Duration of Study

The screening period will be up to 4 weeks, and the treatment period will be up to 16 cycles (approximately 12 months). Patients will have safety follow-up assessments through 30 days after the last dose of brentuximab vedotin. All patients who discontinue brentuximab vedotin for any

reason other than withdrawal of full consent will undergo a long-term follow-up every 12 weeks after the safety follow-up assessments. Patients will be followed until all patients have had the opportunity to be followed for 18 months after EOT. The study will be closed when all patients enrolled have completed the required follow-up. It is expected that the study will last approximately 3.5 years.

8.0 STUDY POPULATION

8.1 Inclusion Criteria

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

1. Male or female Chinese patients aged 18 years or older at the time of informed consent.
2. Patients must have histologically confirmed CD30+ HL or sALCL. Immunohistochemistry or flow cytometry may be performed on either original diagnostic biopsy material or biopsy of relapsed disease, and pathology reports of CD30+ or their copies should be retained at the site.
3. Patients with CD30+ HL or sALCL who have relapsed from or are refractory to previous treatments.
4. Fluorodeoxyglucose (FDG)-PET positive and measurable disease of at least 1.5 cm in the longest diameter by CT, as assessed by the site.
5. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. 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.
7. 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 6 months after the last dose of study drug.

   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.
8. Suitable venous access for the study-required blood sampling, including PK sampling.
9. Patients must have the following required screening laboratory data. Patients must not have received recombinant granulocyte-colony stimulating factor (G-CSF) or platelet transfusion within 1 week before the screening hematology assessment.
   - Absolute neutrophil count ≥1500/μL.
   - Platelet count ≥75,000/μL.
   - Serum bilirubin level ≤1.5 times the upper limit of the normal range (ULN).
   - Serum creatinine level ≤1.5 times the ULN.

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the ULN.

10. Survival for 3 or more months must be expected.

8.2 Exclusion Criteria

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

1. Patients with current diagnosis of primary cutaneous ALCL (patients with other organ involvement who have transformed to sALCL are eligible).
2. Female patients who are lactating and breast-feeding or have a positive serum pregnancy test during the screening period.
3. Patients with any active viral, bacterial, or fungal infection within 2 weeks before the first dose of brentuximab vedotin.
4. Patients with cardiac failure categorized as Class III or IV according to the New York Heart Association criteria, uncontrolled coronary artery disease or uncontrolled arrhythmia despite of appropriate medical therapy, or a history of myocardial infarction within 6 months before the first dose of brentuximab vedotin.
5. Patients with uncontrolled diabetes mellitus.
6. Peripheral neuropathy ≥Grade 2 (NCI CTCAE version 4.03) [2].
7. Patients with a history of another malignancy that has not been in remission for at least 3 years. The following are exempt from the 3-year limit:
   - Nonmelanoma skin cancer.
   - Curatively treated localized prostate cancer.
   - Cervical carcinoma in situ.
8. Patients with known cerebral/meningeal disease (HL or any other etiology), including signs or symptoms of PML (see Section 9.6.5).
9. Patients with a positive result in the screening test for human immunodeficiency virus (HIV) antibody.
10. Known hepatitis B virus (HBV) surface antigen seropositive or positive hepatitis C virus (HCV) antibody. Note: patients who have positive HBV core antibody can be enrolled but must have an undetectable HBV viral load.
11. Patients with a history of liver fibrosis or cirrhosis and clinical signs and symptoms indicating liver fibrosis or cirrhosis.
12. Patients who have received auto-SCT within 12 weeks before the first dose of brentuximab vedotin.
13. Patients with history of allo-SCT.

14. Patients who have received treatment for malignancies (including radiation, chemotherapy, and hormone therapy) within 4 weeks before the first dose of brentuximab vedotin and patients who have received treatment for malignancies with biologics (including molecular target drug) or radioisotopic therapy within 12 weeks before the first dose of brentuximab vedotin.
15. Patients who have unresolved toxicity higher than Grade 1 (NCI CTCAE version 4.03) [2] attributed to any prior therapy/procedure (excluding alopecia or non-clinically significant and asymptomatic laboratory abnormalities).
16. Patients who have received systemic corticosteroids at doses greater than the equivalent of 20 mg/day of prednisone within 1 week before the first dose of brentuximab vedotin.
17. Patients who have received other investigational products within 4 weeks before the first dose of brentuximab vedotin.
18. Patients who have received treatment with investigational medical devices within 4 weeks before the first dose of brentuximab vedotin.
19. Patients who have received previous treatment with brentuximab vedotin.
20. Patients with a known hypersensitivity to any excipient contained in the drug formulation.
21. Patients who have any kind of disorder that compromises the ability of the patient to give written informed consent and/or to comply with study procedures.
22. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of the safety and toxicity of the prescribed regimens.

9.0 STUDY DRUG

9.1 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.

Brentuximab vedotin will be administered as an IV infusion over approximately 30 minutes on Day 1 of each 21-day cycle at a dose of 1.8 mg/kg. After Cycle 2, except when it takes longer for the subject to recover from toxicity that is possibly related to brentuximab vedotin after the most recent cycle (refer to Section 9.2), an administration window of -1 to +3 days is allowed. Patients with a tumor response (CR or PR) or SD for whom there are no safety concerns may receive up to 16 cycles of brentuximab vedotin.

Brentuximab vedotin should not be given as a rapid IV dose or bolus injection. Brentuximab vedotin should be given through a dedicated infusion line and should not be mixed with other drug products.

The infusion line should be flushed with saline solution before and after brentuximab vedotin administration to avoid mixing with other drug products.

The dose of brentuximab vedotin will be calculated based on the subject's actual body weight at Baseline, and the calculated brentuximab vedotin dose will be rounded to the nearest whole number. If the subject experiences a ≥10% change in body weight during the study, the dose should be adjusted. Note that if a patient weighs more than 100 kg, the dose for the patient will be calculated assuming the body weight to be 100 kg.

Patients will be monitored at bedside from the start of dosing for the first and second doses of brentuximab vedotin. Premedication to prevent infusion-related reactions may be used before dosing of brentuximab vedotin according to investigator discretion and institutional guidelines. Premedication use is further described in Section 9.6.3. If an infusion-related reaction occurs, continuation of brentuximab vedotin dosing will be based on the severity of the event and at the discretion of the investigator following discussion with the sponsor.

9.2 Dose Modification Guidelines

If treatment-related toxicity occurs, intrapatient dose reduction will be allowed to 1.2 mg/kg for each subject depending on the type and severity of the toxicity. If a patient requires further dose reductions, brentuximab vedotin will be permanently discontinued. Table 9.a provides the criteria for dose adjustments and delays for treatment-related toxicity. Toxicity will be evaluated according to the NCI CTCAE, version 4.03 [2].

If a patient fails to meet the criteria for re-treatment cited in Table 9.a, 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 re-treatment have been met. The start of the next cycle may be delayed for up to 3 weeks (6 weeks after the most recent dose) if additional time is

required for the patient to recover from treatment-related toxicity experienced during the current cycle. Delays of longer than 3 weeks (after Day 22) are prohibited without approval from the sponsor.

Doses reduced for treatment-related toxicity should generally not be re-escalated; however, intrapatient re-escalation to 1.8 mg/kg may be permitted at the discretion of the investigator after a discussion with the sponsor.

Table 9.a Criteria for Dose Adjustments and Delays

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level (1.8 mg/kg).	Continue at the same dose level (1.8 mg/kg), except in the event of Grade 2 neuropathy. For Grade 2 neuropathy, withhold dose until toxicity is ≤Grade 1 or has returned to baseline, then resume treatment at the same dose level (1.8 mg/kg). 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.	The investigator/subinvestigator will make decisions on the appropriateness of brentuximab vedotin treatment in subsequent cycles after discussion with the sponsor. For subjects who are determined to be able to continue treatment with brentuximab vedotin, continue treatment at the same dose level (1.8 mg/kg) or by reducing the dose to 1.2 mg/kg. Confirm that toxicity is ≤Grade 1 or has returned to baseline before continuing treatment (a). For Grade 3 or higher neuropathy, consider discontinuing treatment after discussion with the sponsor.	The investigator/subinvestigator will make decisions on the appropriateness of brentuximab vedotin treatment in subsequent cycles after discussion with the sponsor. For subjects who are determined to be able to continue treatment with brentuximab vedotin, confirm that toxicity is ≤Grade 1 or has returned to baseline, then continue treatment by reducing the dose to 1.2 mg/kg (a).
Hematologic	Continue at the same dose level (1.8 mg/kg).	Continue at the same dose level (1.8 mg/kg).	The investigator/subinvestigator will make decisions on the appropriateness of brentuximab vedotin treatment in subsequent cycles after discussion with the sponsor. For subjects who are determined to be able to continue treatment with brentuximab vedotin, continue treatment at the same dose level (1.8 mg/kg) or by reducing the dose to 1.2 mg/kg. Confirm that toxicity is ≤Grade 2 or has returned to baseline before continuing treatment (b). Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles.	The investigator/subinvestigator will make decisions on the appropriateness of brentuximab vedotin treatment in subsequent cycles after discussion with the sponsor. For subjects who are determined to be able to continue treatment with brentuximab vedotin, continue treatment at the same dose level (1.8 mg/kg) or by reducing the dose to 1.2 mg/kg. Confirm that toxicity is ≤Grade 2 before continuing treatment (b). 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), the investigator/subinvestigator will make decisions on the appropriateness of brentuximab vedotin treatment in subsequent cycles after discussion with the sponsor. For subjects who are determined to be able to continue treatment with brentuximab vedotin, confirm that toxicity is ≤Grade 2, then continue treatment by reducing the dose to 1.2 mg/kg (b).

G-CSF= granulocyte colony-stimulating factor, GM-CSF= granulocyte macrophage colony-stimulating factor.
(a) Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without dose delay.
(b) Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without dose delay.

9.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited from enrollment to completion of the safety follow-up assessments:

- Antineoplastic agents other than brentuximab vedotin.
- Any surgery requiring general anesthesia.
- Radiotherapy.
- Any other investigational drugs.
- Any other investigational device.
- Long-term treatment with corticosteroids at doses greater than the equivalent of 20 mg/day of prednisone.

9.4 Permitted Concomitant Medications and Procedures

- Patients are allowed to receive treatment with corticosteroids at doses less than or equal to the equivalent of 20 mg/day of prednisone for longer than 1 month before enrollment. Intermittent use of corticosteroids for treating hypersensitivity reactions is permitted.
- 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.

Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73% and did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, refer to Table 9.a.

Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin; however, it reduced exposure to MMAE by approximately 31%.

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

9.5 Precautions and Restrictions

It is not known what effects brentuximab vedotin has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female

patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form (ICF) through 6 months after the last dose of brentuximab vedotin.

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

- Practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of brentuximab vedotin.

Contraception methods meeting the criteria defined above are provided below. If male condoms are used as a barrier method by male subjects, his partner must use an intrauterine devices (Copper T, or Progesteron T) or hormonal contraceptive (combined pills) instead of spermicide.

Barrier Methods (Each Time the Subject Has Intercourse)	Intrauterine Devices	Hormonal Contraceptives
• Male condom PLUS spermicide. • Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide. • Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.	• Copper T PLUS condom or spermicide. • Progesterone T PLUS condom or spermicide.	• Implants. • Hormone injections. • Combined pills. • Minipills. • Patches. • Vaginal ring PLUS male condom and spermicide.

9.6 Management of Clinical Events

9.6.1 Nausea and/or Vomiting

Although this study will not require prophylactic antiemetics, there is no prohibition against their use.

9.6.2 Diarrhea

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

9.6.3 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 an infusion-related reaction, including anaphylaxis should it occur. The patient should be observed for approximately 60 minutes following the first infusion of brentuximab vedotin. During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institution standards. Medications for infusion-related reactions, such as epinephrine and antihistamines, should be available for immediate use.

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 before each 30-minute brentuximab vedotin infusion.

9.6.4 Peripheral Neuropathy

AEs of peripheral neuropathy will be monitored closely throughout the study. These events may include, but are not limited to, peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy. Such events, regardless of seriousness, will be followed for all changes in severity until the sooner of resolution to baseline or study closure and recorded in the electronic case report form (eCRF). Events that are higher than Grade 1 will result in brentuximab vedotin dose modification as shown in Table 9.a.

9.6.5 Suspected 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. See the IB for further details.

If PML is suspected, hold further dosing and undertake a diagnostic work-up including (but not limited to):

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

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

9.7 Blinding and Unblinding

This is an open-label study.

9.8 Description of Investigational Agents

Brentuximab vedotin is manufactured by BSP Pharmaceuticals S.p.A (formerly named BSP Pharmaceuticals S.r.l.) (Italy) under the manufacturing license issued by Takeda Pharma A/S (Denmark).

Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake or powder supplied in single-use vials. Each vial contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80.

For further details, see the IB.

9.9 Preparation, Reconstitution, and Dispensation

Brentuximab vedotin is supplied in single-use glass vials and will be reconstituted in the vial with 10.5 mL of sterile water for injection. The appropriate amount of reconstituted brentuximab vedotin should be withdrawn from the vial and diluted in an infusion bag containing saline solution to produce a final brentuximab vedotin concentration of 0.4 to 1.8 mg/mL. For further details, see the Pharmacy Manual.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever the solution and container permit.

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

9.10 Packaging and Labeling

The specifications and storage conditions of brentuximab vedotin are provided in Table 9.b.

Brentuximab vedotin vials will be packaged as single-use cartons. Each carton will contain 1 vial of the investigational product, and the vial and carton will be labeled to meet the requirements of the China Food and Drug Administration.

Table 9.b Investigational Product

Investigational product	Brentuximab vedotin
Content	50 mg/vial
Concentration	5 mg/mL (after reconstitution)
Container	Clear, colorless, glass vial
Packing unit	1 vial/carton
Property	Sterile white to off-white lyophilized cake or powder. Reconstituted products are clear or slightly opaque.
Protection from light	Reconstituted products should be protected from light until preparation.
Storage	Refrigeration (2°C-8°C)
Manufacturer and country	CCI [redacted]

9.11 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.

10.0 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.

10.1 Study Personnel and Organizations

The contact information for the clinical laboratories, the coordinating investigator, the interactive web response system (IWRS) provider, and the contract research organization (CRO) is presented in the attachment. A full list of investigators is available in the sponsor's investigator database.

10.2 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).

10.3 Study Procedures

Refer to the Schedule of Events (Appendix A) for the study procedures. Additional details are provided as necessary in the sections that follow.

10.3.1 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. All the results of examinations (eg, HIV, HBV, HCV), imaging studies (eg, CT or MRI), tumor histology (CD30+ HL or sALCL, and ALK status for patients with sALCL), and bone marrow examination that were performed as part of routine care before informed consent has been signed may be used as screening data if the informed consent is obtained from the patient and the tests are performed within 28 days (14 days for bone marrow examination) before the first dose.

10.3.2 Enrollment

The investigator or investigator's designee will access the IWRS at the screening visit to obtain a unique subject identification number. A subject is considered to be eligible to enter the enrollment visit when the eligibility criteria are met. The subject identification numbers will be used consistently throughout the entire study and must not be changed.

Subjects who do not meet eligibility criteria within the screening period will not be eligible for enrollment. However, subjects may be rescreened at the discretion of the investigator/ subinvestigator, provided that the subject has not been registered as a screen failure. If a subject is being rescreened, the investigator/subinvestigator must obtain additional written informed consent to reconfirm the subject's consent to participate in this study. Subjects may be rescreened only

once. Subjects who will not be rescreened or are determined not eligible after rescreening must be considered screen failures.

The first dose of brentuximab vedotin should be started within 7 days after enrollment. If the first dose cannot be started within 7 days, screening can be repeated after reconsenting.

10.3.3 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during the screening period (Days -28 to 0).

10.3.4 Medical History

During the screening period (Days -28 to 0), 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 and procedures will be recorded as specified in Section 10.3.12.

Medical history will be evaluated for the following categories of clinically significant diseases or procedures that have been resolved or completed by the day before the first dose of brentuximab vedotin:

1. Any diseases that meet the exclusion criteria (including all that were resolved before enrollment).
2. Any diseases or procedures within the past 3 months that do not fall within category 1, except transient diseases (eg, upper respiratory inflammation, common cold, headache, diarrhea).
3. Any other diseases that are considered to possibly affect the evaluation of drug efficacy.

Complications will also be evaluated for any symptoms or diseases that are present at the first dose of brentuximab vedotin. Complications include clinically relevant abnormalities in laboratory tests, 12-lead ECGs, or physical findings. Details of complications (diagnostic results, whenever possible) should be given.

10.3.5 ECOG Performance Status

ECOG performance status (see Appendix D) will be measured during the screening and treatment periods. The timing of assessments will be as follows:

- Screening period: Days -28 to 0.
- Cycles 1 and 2: Days 1, 8, and 15; to be performed before study treatment on Day 1.
- Cycle 3 and subsequent cycles: Days 1 and 15; to be performed before study treatment on Day 1.
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

10.3.6 Patient Height

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

10.3.7 Weight

Weight will be measured during the screening and treatment periods. The timing of assessments will be as follows:

- Screening period: Days -28 to 0.
- Cycle 1: Day 1 within 3 days before study treatment.
- Cycle 2 and subsequent cycles: Day 1 of each cycle within 1 day before study treatment.
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

10.3.8 Vital Signs

Vital sign measurements include blood pressure in the sitting position, pulse rate, and axillary temperature. The timing of assessments will be as follows:

- Screening period: Days -28 to 0.
- Cycles 1 and 2: Days 1, 8, and 15; to be measured on Day 1 of Cycles 1 and 2 at predose, 15 minutes (±5 minutes) and 30 minutes (±5 minutes) after the start of study drug infusion and at the end of dosing (±10 minutes).
- Cycle 3 and subsequent cycles: Days 1 and 15; to be measured on Day 1 of Cycle 3 and subsequent cycles at predose and at the end of dosing (-5 minutes to +10 minutes).
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

10.3.9 ECGs

A 12-lead ECG will be administered as follows:

- Screening period: Days -14 to 0; the screening ECG within 3 days of study dose on Day 1 of Cycle 1 may be substituted for the ECG on Day 1 of Cycle 1.
- Cycle 1: Day 1 within 3 days before study treatment and after completion of the infusion (+2 hour).
- Cycle 2 and subsequent cycles: Day 1 of each cycle within 1 day before study treatment.
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

10.3.10 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Clinical laboratory evaluations will be performed as outlined in this section.

10.3.10.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters and urine samples for analysis of the parameters shown in Table 10.a will be collected. The timing of the assessments will be as follows:

Hematology

- Screening period: Days -14 to 0; screening testing within 3 days of study dose on Day 1 of Cycle 1 may be substituted for testing on Day 1 of Cycle 1.
- Cycles 1 and 2: Days 1, 2, 4, 8, and 15; the testing on Day 1 of Cycle 1 is to be performed within 3 days before study treatment and the testing on Day 1 of Cycle 2 is to be performed within 1 day before study treatment.
- Cycle 3 and subsequent cycles: Days 1 and 15; the testing on Day 1 of each cycle is to be performed within 1 day before study treatment on Day 1.
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

Chemistry A

- Screening period: Days -14 to 0; screening testing within 3 days of study dose on Day 1 of Cycle 1 may be substituted for testing on Day 1 of Cycle 1.
- Cycles 1 and 2: Days 1, 8, and 15; the testing on Day 1 of each cycle is to be performed within 3 days before study treatment and the testing on Day 1 of Cycle 2 is to be performed within 1 day before study treatment.
- Cycle 3 and subsequent cycles: Days 1 and 15; the testing on Day 1 of each cycle is to be performed within 1 day before study treatment.
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

Samples of glucose must be taken under fasting conditions (at least 4 hours after a meal) at screening and on Day 1 of Cycle 1. At other time points, although fasting levels (at least 4 hours after a meal) should be measured as a rule, nonfasting levels are also permitted; if a nonfasting level is measured, meal times must be recorded on the source document.

Chemistry B

- Screening period: Days -14 to 0.
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

Samples of total cholesterol and triglycerides must be taken under fasting conditions (at least 4 hours after a meal) at screening. At other time points, although fasting levels (at least 4 hours after a meal) should be measured as a rule, nonfasting levels are also permitted; if a nonfasting level is measured, meal times must be recorded on the source document.

Coagulation

- Screening period: Days -14 to 0; screening testing within 3 days of study dose on Day 1 of Cycle 1 may be substituted for testing on Day 1 of Cycle 1.
- Cycle 1: Days 1 and 15; the testing on Day 1 to be performed within 3 days before study treatment.
- Cycle 2 and subsequent cycles: Day 1 of each cycle; to be performed within 1 day before study treatment.
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

Viral test

- Screening period: Day -28 to 0.

For patients who are HBV core antibody positive/HBV surface antigen negative/HBV surface antibody negative at screening, it is recommended to follow-up for HBV-DNA levels per local practice.

Urinalysis

- Screening period: Day -14 to 0.
- Cycle 2 and subsequent cycles: Day 1 of each cycle; to be performed within 1 day before study treatment.
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

Table 10.a Clinical Laboratory Evaluations

Tests	Panels
Hematology	Red blood cells, hemoglobin content, hematocrit, white blood cells, platelets, differential white blood cells (neutrophils, eosinophils, basophils, lymphocytes, monocytes), reticulocyte
Chemistry A (a)	Sodium, potassium, chloride, albumin, calcium, phosphorus, glucose, BUN, uric acid, creatinine, total bilirubin, AST, ALT, ALP, LDH, GGT
Chemistry B (b)	HbA1c, total cholesterol, triglycerides, TSH, FT3, FT4
Coagulation test	INR, PT, APTT
Viral test	HIV antibody, HBV surface antigen, HBV surface antibody, HBV core antibody, HBV DNA if appropriate, HCV antibody
Urinalysis	pH, protein, glucose, ketones, blood, urobilinogen

ALP=alkaline phosphatase, ALT=alanine aminotransferase, APTT=activated partial thromboplastin time, AST= aspartate aminotransferase, BUN=blood urea nitrogen, FT3=free triiodothyronine, FT4=free thyroxine, GGT=gamma-glutamyl transpeptidase, HbA1c=hemoglobin A1c, HBV=hepatitis B virus, HCV= hepatitis C virus, HIV= human immunodeficiency virus, INR=international normalized ratio, LDH=lactate dehydrogenase, PT=prothrombin time, TSH= thyroid-stimulating hormone.
(a) Samples for glucose must be taken under fasting conditions (at least 4 hours after a meal) at screening and on Day 1 of Cycle 1. At other time points, although fasting levels (at least 4 hours after a meal) should be measured as a rule, nonfasting level are also permitted; if a nonfasting level is measured, meal times must be recorded on the source document.
(b) Samples for total cholesterol and triglycerides must be taken under fasting conditions (at least 4 hours after a meal) at screening. At other time points, although fasting levels (at least 4 hours after a meal) should be measured as a rule, nonfasting levels are also permitted; if a nonfasting level is measured, meal times must be recorded on the source document.

10.3.11 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening within 2 weeks before the first dose of brentuximab vedotin. The results from this test must be available and negative before the first dose of brentuximab vedotin is administered. Timing of assessments will be as follows:

- Screening period: Days -14 to 0.
- Safety follow-up period: on the 30th day (±7 days) after the last dose of brentuximab vedotin.

10.3.12 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the eCRF from the first dose of study medication through the safety follow-up visit. During outpatient treatment, the use of medications other than brentuximab vedotin and/or medical procedures will be elicited every visit. See Section 9.3 and Section 9.4 for a list of medications and therapies that are prohibited and/or allowed, respectively, during the study.

10.3.13 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study. Changes in severity of peripheral neuropathy should be monitored in detail.

Refer to Section 11.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

10.3.14 Disease Assessment

Tumor response will be evaluated according to the Revised Response Criteria for Malignant Lymphoma [1].

All imaging will be performed with contrast, except for subjects in whom contrast imaging is difficult because of hypersensitivity to contrast medium, bronchial asthma, renal impairment, or other conditions.

Measurable lesions are those that meet all the following criteria:

- Lymph nodes diagnosed as lymphoma lesions, or nodular masses involving extranodal organs on CT imaging.
- Lesions that can be accurately measured in 2 perpendicular directions on CT cross-sectional images.
- Lesions with longest diameter ≥1.5 cm on CT cross-sectional images.
- FDG-PET positive lesions.

As many as 6 target lesions will be selected among the measurable lesions, whether nodal or extranodal, in order of decreasing longest diameter on CT cross-sectional images.

B symptoms will be assessed at prespecified time points as described in the Schedule of Events (Appendix A).

Bone marrow aspirate or biopsy will be performed within 2 weeks before the first dose of brentuximab vedotin (it is not necessary to repeat these procedures in patients with a positive bone marrow aspirate or biopsy performed after the most recent antineoplastic therapy). For patients with bone marrow involvement at Baseline, bone marrow aspirate or biopsy is required to confirm the CR status. Bone marrow aspirate or biopsy samples will be collected within 2 weeks after CT scans. Further bone marrow assessments are not required after bone marrow aspirate or biopsy becomes negative.

Timing of CT scans will be as follows:

- Screening period: Days -28 to 0.
- Cycles 2, 4, 7, 10, 13, and 16: Days 15 through 21 (before study treatment in the next cycle).

Subjects who discontinue study treatment or assessments for the reasons stated in Section 10.6 other than progressive disease (PD) and have not undergone assessment within the past 6 weeks should have tumor response assessed during the safety follow-up whenever possible.

Subjects who discontinue study treatment for any reason other than PD will have CT scans every 12 weeks (±14 days) for the first 12 months and at 18 months after EOT until disease progression, death, withdrawal of consent, or initiation of a new treatment, whichever occurs first.

Subjects with symptoms suggestive of PD should be evaluated radiographically to assess disease status at the time the symptoms occur whenever possible.

PET scans will be performed at baseline and on Days 15 through 21 of Cycles 4 and 7 (before study treatment of next cycle). No additional PET scanning is required beyond Cycle 7 unless clinically indicated.

Refer to the study manual for the details of CT/PET scans for the assessment of antitumor effect.

10.3.15 PK Measurements

Blood samples for PK (ADC and total antibody [TAb] in serum, MMAE in plasma) will be taken at prespecified time points as described in Table B (Appendix A).

Refer to Sample Management Plan and Laboratory Manual for PK sample collection, processing, storage condition, and shipment.

10.3.16 Immunogenicity Measurements

Blood samples for immunogenicity (in serum) assessments will be taken at prespecified time points as described in Table B (Appendix A). On dosing days, the blood samples for immunogenicity assessments must be collected before dosing.

Detailed information about the immunogenicity blood volume, blood sample collection, processing, storage conditions, and shipment will be provided in the Sample Management Plan and Laboratory Manual.

Positive ATA screening samples will be further tested for true positivity. Confirmed true positive ATA samples will be further characterized for neutralizing activity.

10.4 Completion of Treatment

Patients will be considered to have completed study treatment if they complete 16 cycles of treatment with brentuximab vedotin or if they experience PD. Patients who discontinue study treatment for any reason other than withdrawal of consent will have safety follow-up assessments through 30 days (±7 days) after receiving their last dose of brentuximab vedotin.

10.5 Completion of Study

Patients will be considered to have completed the study if they complete 16 cycles of treatment with brentuximab vedotin and have completed the 18-month follow-up or have died.

10.6 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- AE.
- Protocol violation.
- PD.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Administrative decision by the investigator/subinvestigator or the sponsor.
- Pregnancy.
- Completed 16 cycles of treatment at response (CR or PR) or SD.
- Initiation of subsequent stem cell transplant
- Other.

Once study drug has been discontinued, all study procedures outlined for the safety follow-up visit will be completed as specified in the Schedule of Events (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

Reasons that may cause a subject to be replaced include but are not limited to:

- Patient does not meet Inclusion Criterion 2.
- Patient has not taken at least 1 dose of brentuximab vedotin.
- Patient is not response evaluable according to the Revised Response Criteria for Malignant Lymphoma [1].

10.7 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.
- 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 sponsor or 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. The investigators should make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. If a patient withdraws from study treatment, every attempt should be made to follow the patient until death or study closure. Final treatment assessments should be performed before any other therapeutic intervention when possible. Additionally, any planned alternative treatments should be documented in the patient's medical records and eCRF.

10.8 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.

10.9 Long-term Follow-up Assessments

Patients who discontinue study treatment with SD or better will be followed for PFS until disease progression, death, withdrawal of consent, or initiation of a new treatment, whichever occurs first. A CT scan will be performed every 12 weeks (±14 days) for the first 12 months and at 18 months after the EOT. Patients will be followed for OS every 12 weeks (±14 days) until death, withdrawal of consent, or study closure, whichever occurs first. Survival information may be collected by methods including, but not limited to, telephone, e-mail, or mail. Patients will be followed until all patients have had the opportunity to be followed for 18 months after EOT. The study will be closed when all patients enrolled have completed the required follow-up.

11.0 ADVERSE EVENTS

11.1 Definitions

11.1.1 PTE Definition

A PTE 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.

11.1.2 AE Definition

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.

11.1.3 SAE Definition

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 in Section 11.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home,

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

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective 14 June 2010 [2]. Clarification should be made between an 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.

11.2 Procedures for Recording and Reporting AEs and SAEs

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 11.3 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 PTEs (as defined in Section 11.1) must be reported (see Section 11.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department 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 PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

CCI [redacted]

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

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

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective 14 June 2010 [2]. 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?

11.3 Monitoring of AEs and Period of Observation

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

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to the first dose of study drug, but will not be recorded in the eCRF.
- Related and unrelated SAEs will be reported to the Takeda Global Pharmacovigilance department 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 Global Pharmacovigilance department 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).

11.4 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 Global Pharmacovigilance department or designee (see Section 11.2). 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 Global Pharmacovigilance department or designee (see Section 11.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.5 Procedures for Reporting 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 report this via the phone numbers or email addresses below:

Product	Call center	Phone number	E-mail	Fax
ADCETRIS	PPD			

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 CCI (refer to Section 11.2)

12.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

13.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

13.1 eCRFs

Completed eCRFs are required for each subject who is enrolled in the study.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

13.2 Record Retention

The investigator agrees to keep the records stipulated in Section 13.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain

essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

14.0 STATISTICAL METHODS

14.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The primary analysis for the clinical study report including the primary and the secondary endpoints will be conducted when all patients have had the opportunity to receive 16 cycles of treatment and have had EOT assessments. The final analysis will be conducted at the time of study closure.

14.1.1 Analysis Populations

Safety/Modified Intent-to-Treat Population

The safety/modified intent-to-treat (mITT) population consists of all subjects who have measurable lesions at Baseline and receive at least 1 dose of brentuximab vedotin. The safety/mITT population will be used for analyses of efficacy, safety, and patient demographic and baseline disease characteristics, unless otherwise stated.

Per-protocol Population

The per-protocol population consists of all subjects who have measurable lesions at Baseline and no protocol deviations determined by the project clinician. The per-protocol population will be used for secondary analyses of tumor response.

PK Population

The PK analysis population consists of patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by the clinical pharmacologist. The PK population will be used for all PK analyses.

14.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized, including sex, age, race, weight, height, medical history, prior medication, and other parameters as appropriate. No inferential statistics will be conducted.

14.1.3 Efficacy Analysis

Efficacy will be analyzed using the safety/mITT population for HL and sALCL patients separately.

Primary efficacy endpoint:

- The ORR, defined as the proportion of patients who have achieved CR or PR by EOT.

Secondary efficacy endpoints:

- The CR rate, defined as the proportion of patients who have achieved CR by EOT.

- DOR, defined as the time between the first documentation of objective tumor response (CR or PR) and the first subsequent documentation of objective tumor progression or death due to any cause, whichever occurs first.
- PFS, defined as the time from the start of study treatment to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first.
- OS.
- B symptom resolution rate.

Pertinent variables will be summarized descriptively. Continuous variables will be summarized, including the number of subjects, mean, standard deviation, median, minimum, and maximum values; for categorical variables, the frequency and percentage per category will be summarized. Two-sided exact 95% CIs will be computed using appropriate techniques for ORR and CR. Time-to-event variables will be summarized by the Kaplan-Meier method with the associated 95% CIs when estimable.

14.1.4 PK Analysis

Descriptive statistics (number of patients, arithmetic mean, geometric mean, standard deviation, median, percentage of coefficient of variation, minimum, and maximum) will be used to summarize ADC and TAb in serum, and MMAE in plasma.

The following PK parameters of ADC, MMAE, and TAb will be estimated where applicable:

- C_{max}: maximum observed concentration (measured value).
- t_{max}: time of first occurrence of C_{max}.
- $AUC_{0\text{-}21d}$: AUC for the 21-day dosing interval.
- $t_{1/2}$: terminal elimination half-life.
- $AUC_{0\text{-}inf}$: AUC from time 0 to infinity.
- CL: total clearance after intravenous administration, calculated using the observed value of the last quantifiable concentration.
- V_{ss}: volume of distribution at steady state after intravenous administration, calculated using the observed value of the last quantifiable concentration.

Arithmetic mean of the plasma or serum concentration of MMAE, ADC and TAb will be plotted over time.

14.1.5 Immunogenicity Analysis

Immunogenicity information, including ATA and nATA, will be summarized using descriptive statistics as applicable (based on the SAP). CCI [redacted]

14.1.6 ECG Analysis

A summary of ECG abnormalities will be presented by visit. ECG intervals (QT, corrected QT QTcB [Bazett] and QTcF [Frederica], PR, QRS, and RR) and ventricular rate will be summarized at each scheduled time point, along with change from Baseline.

14.1.7 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from Baseline in the patient's vital signs and clinical laboratory results using the safety population. Exposure to study drug, including the number of treated cycles, total amount of doses taken, and dose intensity will be summarized.

TEAEs 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. A listing of deaths and TEAEs resulting in study drug discontinuation will be provided.

AEs will be tabulated according to the MedDRA and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- SAEs.

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

Descriptive statistics for the actual values (and/or the changes from Baseline) of vital signs (eg, blood pressure, pulse rate, and axillary temperatures) and weight over time will be tabulated by scheduled time point. ECOG performance status scores over time will also be tabulated.

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

14.1.8 Other Analyses

Important protocol deviations and the number of subjects with important protocol deviations will be tabulated for enrolled subjects with HL, with sALCL, and for the combined populations.

14.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

14.3 Determination of Sample Size

The study will enroll approximately 30 evaluable patients, including approximately 22 patients with HL and approximately 8 patients with sALCL. For information purposes, response rates achieved in previous studies in relapsed/refractory HL and sALCL are referenced below.

	ORR (CR+PR) by IRF (95% CI)
Global Study SGN035-0003 (HL: n=102)	74.5 (64.9, 82.6)
Global Study SGN035-0004 (sALCL: n=58)	86.2 (74.6, 93.9)
Japan Study TB-BC010088 (HL: n=9)	66.7 (29.9, 92.5)
Japan Study TB-BC010088 (sALCL: n=5)	100 (54.9, 100)

The observed response rates and the 95% exact CIs for 22 patients with HL and 8 patients with sALCL are summarized as follows.

HL (n=22)				**sALCL (n=8)**			
Responses	**ORR (%)**	**95% Exact CI**		**Responses**	**ORR (%)**	**95% Exact CI**	
8	36.4	(17.2	59.3)	4	50.0	(15.7	84.3)
9	**40.9**	**(20.7**	**63.6)**	**5**	**62.5**	**(24.5**	**91.5)**
10	45.5	(24.4	67.8)	6	75.0	(34.9	96.8)
11	50.0	(28.2	71.8)	7	87.5	(47.3	99.7)
12	54.5	(32.2	75.6)	8	100	(63.1	100.0)
13	59.1	(36.4	79.3)				

Based on the exact binomial CI calculations, a minimum of 9 responses observed from 22 evaluable patients with HL (ORR of 40.9%) will provide a 95% CI (20.7%, 63.6%); 5 responses observed from 8 evaluable patients with sALCL (ORR of 62.5%) will yield a 95% CI (24.5%, 91.5%). In both cases, the lower limits of the 95% CIs are greater than the threshold response rate of 20% obtained from the results of alternative therapies for the same indications.

Assuming similar ORR results to those in Study TB-BC010088 will be obtained, the expected response rates are 65% for HL and 80% for sALCL. With 22 patients with HL and 8 patients with sALCL, the study will have >99% and >94% probability, respectively, to detect an ORR greater than the 20% threshold (ie, ≥9 responses for HL and ≥5 responses for sALCL).

15.0 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

15.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

15.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States Food and Drug Administration, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 15.1.

16.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

16.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

16.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the

revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

16.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, the United States Food and Drug Administration, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 16.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

16.4 Publication, Disclosure, and Clinical Trial Registration Policy

16.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

16.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city,-country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

16.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

16.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

17.0 REFERENCES

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Appendix A Schedule of Events

Table A Schedule of Events

	Screening Period										Treatment Period										Safety Follow-up	Long-term Follow-up
	Screening		Enroll-ment	Cycle 1							Cycle 2						Cycle 3 and Subsequent Cycles					
Basis Date: Number of Days Starting on Day 1 of Each Cycle	**-28 to 0**	**-14 to 0**	**-7 to 0**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**1**	**2**	**4**	**8**	**15**	**15 to 21[j]**	**1**	**15**	**15 to 21[j]**		**Day 30 after final dose[o]**	**Every 12 weeks**
Visit Window								**±1D**		**±1D**	**-1D to +3D**			**±3D**	**±3D**		**-1D to +3D**	**±3D**			**±7D**	**±14D**
Informed consent	x																					
Enrollment[a]			x																			
Demographics	x																					
Medical history	x																					
Brentuximab vedotin administration[b]				x							x[b]						x[b]					
ECOG performance status[c]	x			x				x		x	x			x	x		x	x		x		
Height	x																					
Weight	x			**X**							x[s]						x[s]			x		
Vital signs[d]	x			x				x		x	x			x	x		x	x		x		
12-lead ECG		x		**X[i]**							x[s]						x[s]			x		
Hematology		x		**X**	x		x	x		x	x[s]	x	x	x	x		x[s]	x		x		
Chemistry A[e]		x		**X**				x		x	x[s]			x	x		x[s]	x		x		
Chemistry B[f]		x																		x		
Coagulation		x		**X**						x	x[s]						x[s]			x		
Viral test	x																					
Urinalysis		x									x[s]						x[s]			x		
Pregnancy test		x																		x		
Concomitant medications/ procedures				←																→		
AEs	SAE			←																→		
CT scan	x															x			x[l]	x[p]	x[q]	
PET scan	x																		x[m]	(x[m])		
B symptom assessment	x			x							x						x			x[p]		

	Screening Period										Treatment Period									Safety Follow-up	Long-term Follow-up
	Screening		Enroll-ment	Cycle 1							Cycle 2						Cycle 3 and Subsequent Cycles				
Basis Date: Number of Days Starting on Day 1 of Each Cycle	**-28 to 0**	**-14 to 0**	**-7 to 0**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**1**	**2**	**4**	**8**	**15**	**15 to 21[j]**	**1**	**15**	**15 to 21[j]**	**Day 30 after final dose[o]**	**Every 12 weeks**
Visit Window								**±1D**		**±1D**	**-1D to +3D**			**±3D**	**±3D**		**-1D to +3D**	**±3D**		**±7D**	**±14D**
Bone marrow aspirate or biopsy		x[h]														x[n]			x[n]	(x[n])	
PK[g]				x	x	x	x	x	x	x	x	x	x	x	x		x[k]			x	
Immunogenicity[g]				x							x						x[k]			x	
Survival follow-up																					x[r]

CT= computed tomography, ECOG PS=Eastern Cooperative Oncology Group performance status, ECG=electrocardiogram, IWRS=interactive web response system, PET=positron emission tomography, PK=pharmacokinetics, SAE=serious adverse events.

Tests and procedures should be performed on schedule, but occasional changes may be allowed (± 3 days) for holidays, vacations, and other administrative reasons. If the study schedule is shifted, assessments must be shifted to ensure collection of assessments is completed prior to dosing.

X=Within 3 days before the first dose. Screening tests within 3 days before the study dose on Day 1 of Cycle 1 may be substituted for testing on Day 1 of Cycle 1.

(a) The investigator or investigator's designee will access the IWRS at the screening visit to obtain a unique subject identification number. A subject is considered to be eligible to enter the enrollment visit when eligibility criteria are met. The subject identification numbers will be used consistently throughout the entire study and must not be changed.

(b) The start of the next cycle may be delayed for up to 3 weeks (up to 6 weeks from the current administration of brentuximab vedotin) 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 (after Day 22) are prohibited without approval from the sponsor.

(c) Assessments on Day 1 of each cycle must be administered before dose of the study treatment.

(d) On Day 1 of Cycles 1 and 2, vital signs must be measured and recorded at the following times: predose; 15 (±5) minutes, and 30 (±5) minutes after the start of infusion; and upon completion of the infusion (±10 minutes). On Day 1 of Cycle 3 and subsequent cycles, vital signs must be measured and recorded at the following times: before the start of infusion and upon completion of the infusion (-5 to +10 minutes).

(e) Samples of glucose must be taken under fasting conditions (at least 4 hours after a meal) at screening and on Day 1 of Cycle 1. At other time points, although fasting levels (at least 4 hours after a meal) should be measured as a rule, nonfasting levels are also permitted; if a nonfasting level is measured, the meal times must be recorded on the source document.

(f) Samples of total cholesterol and triglycerides must be taken under fasting conditions (at least 4 hours after a meal) at screening. At other time points, although fasting levels (at least 4 hours after a meal) should be measured as a rule, nonfasting levels are also permitted; if a nonfasting level is measured, the meal times must be recorded on the source document.

(g) See Table B for details regarding PK and immunogenicity draws and windows. Immunogenicity samples must be taken before dosing.

(h) In patients with a positive bone marrow aspirate or biopsy following the most recent treatment of malignant tumor, bone marrow aspirate or biopsy do not need to be repeated.

(i) ECG on Day 1 of Cycle 1 within 3 days before study treatment and after completion of the infusion (+2 hours).

(j) On Days 15-21 after study drug dose of each cycle and before study drug dose of the next cycle.

(k) Sampling for PK and immunogenicity will be taken every 2 cycles after Cycle 3.

(l) CT scan will be performed every 3 cycles after Cycle 4 (Cycles 4, 7, 10, 13 and 16). It does not need to be performed at Cycle 3.

(m) PET scan will be performed at Cycles 4 and 7. No additional PET scanning is required beyond Cycle 7 unless clinically indicated.

(n) For patients with bone marrow involvement at Baseline, bone marrow aspirate or biopsy is required to confirm the CR status. Bone marrow aspirate or biopsy samples will be collected within 2 weeks after CT scans. Further bone marrow assessments are not required after bone marrow aspirate or biopsy becomes negative.

(o) Safety follow-up assessments should be performed before initiation of subsequent antineoplastic therapy.
(p) If possible, CT scans and B symptom assessments should be performed if not done within the previous 6 weeks.
(q) Patients who discontinue study treatment with SD or better will be followed for PFS until disease progression, death, withdrawal of consent, or initiation of a new treatment, whichever occurs first. A CT scan will be performed every 12 weeks (±14 days) for the first 12 months and at 18 months after EOT.
(r) Patients will be followed for OS every 12 weeks (±14 days) until death, withdrawal of consent, or study closure, whichever occurs first.
(s) The testing on Day 1 is to be performed within 1 day before study treatment.

Table B Serial Sample Breakdown

Cycle	Study Day	Time	Window	PK	Immunogenicity
Cycle 1	Day 1	Predose	Within 2 hr	x	x
		10 min after the end of brentuximab vedotin infusion	±5 min	x	
		4 hr after the end of brentuximab vedotin infusion	±30 min	x	
	Day 2	24 hr after the end of brentuximab vedotin infusion	±1 hr	x	
	Day 3	48 hr after the end of brentuximab vedotin infusion	±2 hr	x	
	Day 4	72 hr after the end of brentuximab vedotin infusion	±2 hr	x	
	Day 8	168 hr after the end of brentuximab vedotin infusion	±3 hr	x	
	Day 11	240 hr after the end of brentuximab vedotin infusion	±3 hr	x	
	Day 15	336 hr after the end of brentuximab vedotin infusion	±3 hr	x	
Cycle 2	Day 1	Predose	Within 2 hr	x	x
		10 min after the end of brentuximab vedotin infusion	±5 min	x	
		4 hr after the end of brentuximab vedotin infusion	±30 min	x	
	Day 2	24 hr after the end of brentuximab vedotin infusion	±1 hr	x	
	Day 4	72 hr after the end of brentuximab vedotin infusion	±2 hr	x	
	Day 8	168 hr after the end of brentuximab vedotin infusion	±3 hr	x	
	Day 15	336 hr after the end of brentuximab vedotin infusion	±3 hr	x	
Cycle 3 and subsequent cycles	Day 1	Predose	Within 2 hr	x[a]	x[a]
		10 min after the end of brentuximab vedotin infusion	±5 min	x[a]	
–	Safety follow-up			x	x

(a) To be performed every 2 cycles after Cycle 3 and subsequent cycles.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D 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. American Journal of Clinical Oncology 1982;5(6):649-55.

Appendix E New York Heart Association Functional Classification

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Clinical Approval	21-Apr-2016 08:22
	Clinical Approval	21-Apr-2016 10:48
	Clinical Pharmacology Approval	21-Apr-2016 12:33
	Biostatistics Approval	21-Apr-2016 15:21