Protocol Number:	SGN35-028
Version:	Amendment 3; 28-Apr-2020
Protocol Title:	A phase 2, multicenter, single-arm study of retreatment with brentuximab vedotin in subjects with relapsed or refractory classic Hodgkin lymphoma (cHL) or CD30-expressing peripheral T cell lymphoma (PTCL)
Investigational Product:	Brentuximab vedotin
Brief Title:	A phase 2 study of retreatment with brentuximab vedotin in subjects with classic Hodgkin lymphoma or CD30-expressing peripheral T cell lymphoma
Phase:	Phase 2
IND Number:	071634
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EudraCT Number:	2019-003983-28
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
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SAE Email or Fax:	See email or fax number specified on the SAE report form

PROTOCOL SYNOPSIS

Protocol Number SGN35-028 **Version** Amendment 3; 28-Apr-2020 **Phase** 2	**Product Name** Brentuximab vedotin **Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A phase 2, multicenter, single-arm study of retreatment with brentuximab vedotin in subjects with relapsed or refractory classic Hodgkin lymphoma (cHL) or CD30-expressing peripheral T cell lymphoma (PTCL)

Study Objectives

To assess the following with brentuximab vedotin retreatment in subjects with cHL, systemic anaplastic large cell lymphoma (sALCL), or other CD30-expressing peripheral T cell lymphoma (PTCL).

Primary

- Objective response rate (ORR) per blinded independent central review (BICR) (modified Lugano)
- Safety and tolerability

Secondary

- Duration of tumor control, including duration of response (DOR) per BICR (modified Lugano)
- Progression-free survival (PFS) per BICR (modified Lugano)
- Complete response (CR) rate per BICR (modified Lugano)
- Overall survival (OS)
- ORR per investigator (modified Lugano)
- DOR rate per investigator (modified Lugano)
- PFS per investigator (modified Lugano)
- CR rate per investigator (modified Lugano)
- ORR per BICR (Lugano)

Additional

- To assess the pharmacokinetic (PK) and immunogenicity with brentuximab vedotin retreatment
- To assess ORR per BICR (RECIL)

Study Population

Key eligibility criteria include subjects with relapsed or refractory cHL and sALCL or other CD30-expressing PTCL (age ≥18 years) who were previously treated with a brentuximab vedotin-containing regimen, had evidence of objective response, and subsequently had disease progression or relapse after discontinuing treatment.

Number of Planned Subjects

Approximately 80 subjects are planned for this study: approximately 40 subjects with cHL and approximately 40 subjects with CD30-expressing PTCL. In the PTCL cohort, sALCL will have an estimated enrollment cap of approximately 50%, and other CD30-expressing PTCL will have an estimated enrollment cap of approximately 50%.

Study Design

This is a phase 2, multicenter, single-arm study to determine the safety and efficacy of brentuximab vedotin in subjects with cHL and sALCL or other CD30-expressing PTCL who experienced CR or partial response (PR) with a brentuximab vedotin-containing regimen and subsequently experienced disease progression or relapse. It

is anticipated that approximately 80 subjects will enroll in this study. Subjects will be administered 1.8 mg/kg brentuximab vedotin intravenously (IV), up to a maximum of 180 mg, over 30 minutes once per 21-day cycle. Subjects who previously required a dose reduction due to adverse events (AE) will be administered brentuximab vedotin at 1.2 mg/kg and will not escalate to 1.8 mg/kg. Safety will be monitored throughout the trial via laboratory values and AE collection.

Investigational Product, Dose, and Mode of Administration

Brentuximab vedotin 1.8 or 1.2 mg/kg up to a maximum of 180 mg, administered IV over 30 minutes every 3 weeks.

Control Product, Dose, and Mode of Administration

Not applicable

Duration of Treatment

Subjects may continue on treatment until disease progression, unacceptable toxicity, or study closure occurs.

Efficacy Assessments

For subjects with cHL and sALCL or CD30-expressing PTCL, treatment response will be assessed by BICR and the investigator and based on objective response according to the modified Lugano Response Assessment Criteria for Malignant Lymphoma (Cheson 2014).

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments

Samples for serum antibody-drug conjugate (ADC) and plasma monomethyl auristatin E (MMAE) concentration will be analyzed using a validated enzyme-linked immunosorbent assay (ELISA), and a validated LC-MS/MS assay. A validated electrochemiluminescence (ECL) assay will be used to detect binding and neutralizing antibodies.

Safety Assessments

Safety assessments will include the surveillance and recording of AEs, physical examination findings, and laboratory tests.

Statistical Methods

Summaries of subject disposition, demographics, disease characteristics, and dosing of study drug will be provided.

The objective response rates and their two-sided 95% exact confidence intervals (CI) will be calculated (Clopper 1934). The CR rates will be analyzed using the same methodology. Time-to-event endpoints, such as DOR, PFS, and OS, will be estimated using Kaplan-Meier methodology. The median durations of response, PFS, OS, and their two-sided 95% CI will be calculated.

Approximately 40 cHL and 40 CD30-expressing PTCL subjects will be enrolled in this study. This sample size was chosen to allow adequate precision of estimates of response rates.

For the cHL cohort, if 24 responses are observed, the estimated ORR would be 60%, and the associated 2-sided 95% CI using the Clopper-Pearson method would be (43.3%, 75.1%).

For the CD30-expressing PTCL cohort, if 20 responses are observed, the estimated ORR would be 50%, and the associated 2-sided 95% CI using the Clopper-Pearson method would be (33.8%, 66.2%). The 50% ORR for the PTCL cohort was calculated based on a weighted average of subjects with sALCL and other CD30-expressing PTCL, where sALCL subjects have an ORR of 60% and an estimated enrollment cap of approximately 50%, and the other CD30-expressing PTCL subjects have an ORR of 40% and an estimated enrollment cap of approximately 50%.

Descriptive statistics will be provided for the safety data based on all subjects in the full analysis set.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADC	antibody-drug conjugate
AE	adverse event
ALK	Anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
ATLL	adult T cell leukemia/lymphoma
auto-HSCT	autologous hematopoietic stem cell transplantation
BICR	blinded independent central review
C_{eoi}	concentration at the end of infusion
C_{trough}	trough concentration
CBC	complete blood count
cHL	classic Hodgkin lymphoma
CI	confidence interval
CR	complete response
CT	computed tomography
CRF	case report form
CMV	cytomegalovirus
DILI	drug-induced liver injury
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GFR	glomerular filtration rate
GvHD	graft-versus-host disease
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HTLV-1	human T cell leukemia virus-1
ICH	International Council for Harmonisation
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
IV	intravenous
JCV	John Cunningham virus
MDRD	Modification of Diet in Renal Disease [study]
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin Lymphoma
OS	overall survival

ORR	objective response rate
PCR	polymerase chain reaction
PD	progressive disease
PET	Positron emission tomography
PFS	progression-free survival
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PR	partial response
PTCL	peripheral T cell lymphoma
RECIL	Response Evaluation Criteria in Lymphoma
SAE	serious adverse event
sALCL	Systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
Scr	serum creatinine
SD	stable disease
SLD	sum of the longest diameters
SPD	sum of the products of the longest perpendicular diameters
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
USAN	United States adopted name
USP	United States Pharmacopeia
USPI	United States Prescribing Information

1 INTRODUCTION

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30; 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. Targeted delivery of MMAE to CD30-expressing tumor cells is the primary mechanism of action of brentuximab vedotin (Sutherland 2006). Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell. Other nonclinical studies suggest additional contributory mechanisms of action, including antibody-dependent cellular phagocytosis (ADCP); bystander effects on nearby cells in the tumor microenvironment due to released MMAE; and immunogenic cell death due to endoplasmic reticulum stress which drives exposure of immune activating molecules that can promote a T cell response (Cao 2016; Gardai 2016; Kim 2015; Li 2014; Muller 2014; Oflazoglu 2007). A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the Investigator's Brochure.

1.1 Clinical Experience with brentuximab vedotin

The safety and efficacy of brentuximab vedotin has been evaluated in more than 2700 subjects in company-sponsored clinical trials, and approved by the Food and Drug Administration (FDA) for 6 indications:

- Classic Hodgkin lymphoma (cHL) after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least 2 prior multi-agent chemotherapy regimens in subjects who are not auto-HSCT candidates.
- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least 1 prior multi-agent chemotherapy regimen.
- cHL at high risk of relapse or progression as post auto-HSCT consolidation.
- Previously untreated Stage III or IV classic cHL, in combination with doxorubicin, vinblastine, and dacarbazine.
- Previously untreated sALCL or other CD30-expressing peripheral T cell lymphomas (PTCL), including angioimmunoblastic T cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.
- Primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy.

The pivotal clinical trials leading to these approvals included a phase 2 study of brentuximab vedotin monotherapy in relapsed or refractory HL after autologous stem cell transplant (SG035-0003), a phase 2 study of brentuximab vedotin monotherapy in relapsed or refractory sALCL (SG035-0004), a phase 3 study of brentuximab vedotin plus best supportive care versus placebo plus best supportive care in the treatment of subjects at high risk of residual HL following autologous stem cell transplant (SGN35-005), a phase 3 study of brentuximab

vedotin + doxorubicin, vinblastine, and dacarbazine (A+AVD) vs. doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as frontline therapy for newly diagnosed Stage III or IV cHL subjects (C25003), a phase 3 study of brentuximab vedotin + cyclophosphamide, doxorubicin, and prednisone (A+CHP) vs cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as frontline therapy for newly diagnosed CD30-expressing PTCL (SGN35-014), and a phase 3 study of brentuximab vedotin versus methotrexate or bexarotene in CD30-positive cutaneous T-cell lymphoma (C25001).

1.2 CD30 Expression in cHL and PTCL

CD30 is uniformly expressed and is pathognomonic in cHL and sALCL. Among non-sALCL PTCL subtypes, CD30 expression is more variable (Bossard 2014; Federico 2015; Sabattini 2013).

1.3 Study Rationale

There is precedent for effective retreatment with an antibody-based therapy in lymphoma. Rituximab (Rituxan®; Genentech and Biogen Idec) is a genetically engineered chimeric mouse/human monoclonal antibody directed against the antigen CD20 and approved for the treatment of non-Hodgkin lymphoma (NHL). As a retreatment therapy, rituximab has been evaluated in subjects with relapsed/refractory low-grade or follicular B-cell NHL who achieved objective clinical response to initial rituximab therapy (Davis 2000; Kahl 2014).

Study SGN35-006 demonstrated effective retreatment with brentuximab vedotin monotherapy in subjects who had previously achieved an objective response with brentuximab vedotin monotherapy as a treatment for relapsed or refractory cHL or sALCL. In that study the objective response rate (ORR) for retreatment of cHL was 60% (12 of 20 evaluable subjects) with a complete response (CR) rate of 30% (6 of 20 evaluable subjects). For retreated sALCL, the ORR was 88% (7 of 8 subjects) with a CR rate of 63% (5 of 8 subjects). The estimated median duration of response (DOR) for subjects with an objective response was 9.5 months and for subjects with a CR the estimated median DOR was 12.3 months (Bartlett 2014). However, this prior study did not enroll any subjects who received brentuximab vedotin as part of frontline treatment or in subjects with non-sALCL PTCL. The ECHELON-2 study compared brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (A+CHP) to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in previously untreated CD30-expressing PTCL. Of the 23 A+CHP patients who progressed and received treatment with a subsequent brentuximab vedotin containing therapy, 13 (57%) demonstrated an objective response, including patients with non-sALCL PTCL (reference is the SGN35-14 CSR).

2 OBJECTIVES

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of retreatment with brentuximab vedotin in subjects with cHL, sALCL, and CD30-expressing PTCL. Specific objectives and corresponding endpoints for the study are summarized below (Table 1).

Table 1: Objectives and corresponding endpoints

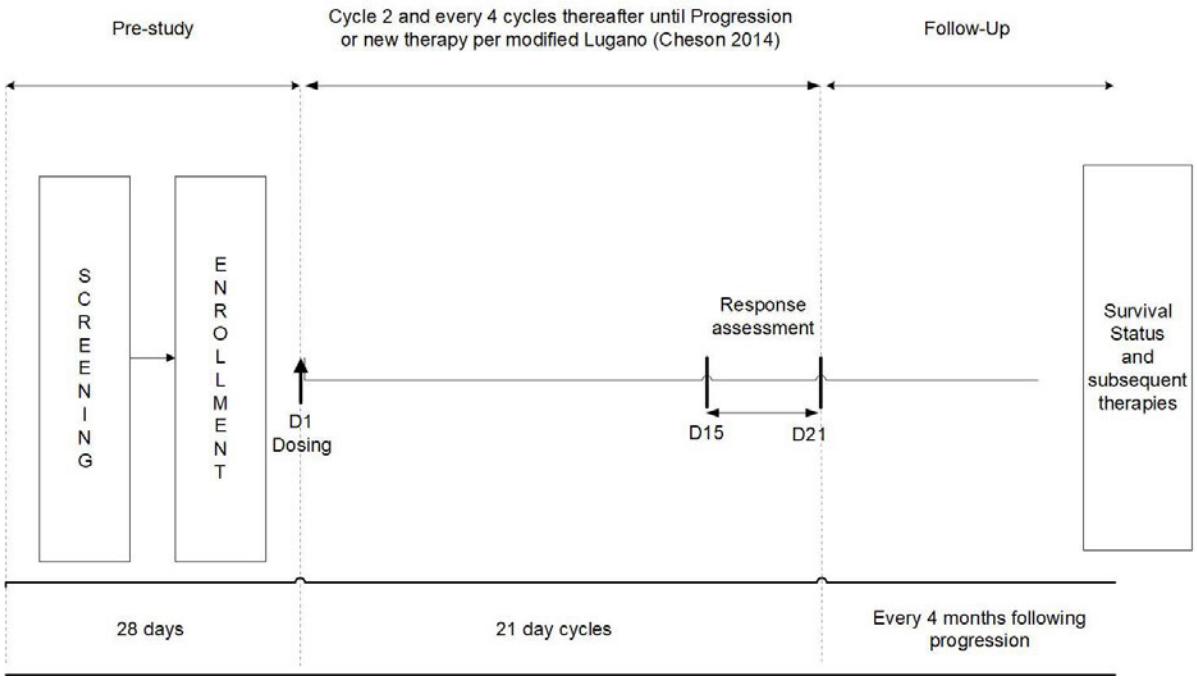
Primary Objective	Corresponding Primary Endpoint
• To assess the antitumor response by blinded independent central review (BICR) of brentuximab vedotin retreatment	• BICR reporting of objective response rate (ORR) per modified Lugano response criteria (Cheson 2014)
• To assess the safety of retreatment with brentuximab vedotin	• Type, incident, severity, seriousness, and relatedness of adverse events (AEs) • Type, incidence, and severity of laboratory abnormalities
Secondary Objectives	**Corresponding Secondary Endpoints**
• To assess duration of tumor control, including duration of response (DOR) as determined by BICR	• BICR reporting of DOR per modified Lugano response criteria (Cheson 2014)
• To assess progression-free survival (PFS) of retreatment with brentuximab vedotin as determined by BICR	• BICR reporting of PFS per modified Lugano response criteria (Cheson 2014)
• To assess overall survival (OS)	• OS
• To assess complete response (CR) rate per BICR	• Rate of CR per BICR per modified Lugano response criteria (Cheson 2014)
• To assess the antitumor response per investigator of brentuximab vedotin retreatment	• Investigator reporting of ORR per modified Lugano response criteria (Cheson 2014)
• To assess DOR rate per investigator assessment	• Investigator reporting of DOR per modified Lugano response criteria (Cheson 2014)
• To assess PFS per investigator assessment	• Investigator reporting of PFS per modified Lugano response criteria (Cheson 2014)
• To assess CR rate per investigator assessment	• Rate of CR per investigator per modified Lugano response criteria (Cheson 2014)
• To assess ORR as determined by BICR	• BICR reporting of ORR per Lugano response criteria (Cheson 2014)
Additional Objectives	**Corresponding Additional Endpoints**
• To assess the PK and immunogenicity of brentuximab vedotin	• Brentuximab vedotin PK concentrations and incidence of ATA to brentuximab vedotin
• To assess ORR as determined by BICR	• BICR reporting of ORR per RECIL (Younes 2017)

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a phase 2, multicenter, single-arm study to determine the safety and efficacy of brentuximab vedotin in subjects with cHL, sALCL, or other CD30-expressing PTCL who demonstrated an objective response to a prior brentuximab vedotin-containing treatment regimen and subsequently experienced disease progression or relapse. It is anticipated that approximately 80 subjects will enroll in this study: approximately 40 subjects with cHL and approximately 40 subjects with CD30-expressing PTCL. In the PTCL cohort, subjects with systemic anaplastic large cell lymphoma (sALCL) will have an estimated enrollment cap of approximately 50%, and subjects with other CD30-expressing PTCL will have an estimated enrollment cap of approximately 50%. Subjects will be administered 1.8 mg/kg brentuximab vedotin intravenously (IV), up to a maximum of 180 mg, over 30 minutes once per 21-day cycle. Subjects who previously required a dose reduction due to adverse events (AE) will start brentuximab vedotin at a dose of 1.2 mg/kg and will not escalate to 1.8 mg/kg. Safety of treatment will be monitored throughout the trial via laboratory values and AE collection.

Figure 1: Study design



3.2 Discussion and Rationale for Study Design

The endpoints of the study are appropriate for evaluating the safety and efficacy of SGN-35 in the retreatment setting. The primary efficacy endpoint of this study, ORR, is a direct measure of antitumor activity and is one of the surrogate endpoints recommended by FDA for approval of anti-cancer drugs (FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics"). To further assess the significance of ORR in this study, durability, CR rate, overall survival (OS), and progression-free survival (PFS) will be evaluated as secondary endpoints.

This study will enroll subjects with relapsed or refractory cHL, sALCL, or CD30 expressing PTCL who have previously had an objective response to a regimen containing brentuximab vedotin, but have experienced subsequent disease progression or relapse at least 6 months or longer from their last dose. Given that these subjects are not refractory to brentuximab vedotin, it is clinically reasonable to evaluate retreatment in this setting.

3.2.1 Method of Assigning Subjects to Treatment Groups

This is single-arm study.

3.2.2 Rationale for Selection of Doses

The recommended dose for brentuximab vedotin per its prescribing information is 1.8 mg/kg via IV infusion administered every 3 weeks. This dose and schedule were evaluated in two pivotal phase 2 studies (SG035-0003 and SG035-0004) in subjects with CD30-positive hematologic malignancies.

3.2.3 Blinding and Unblinding

This study will not be blinded.

3.3 End of Study

The study will be closed 2 years after the last subject receives their last dose or when the last subject completes the last visit, last contact, discontinues from the study, or when no subjects remain in follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.3.2).

4 STUDY POPULATION

All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. Eligibility criteria may not be waived by the investigator and are subject to review in the event of Good Clinical Practice (GCP) or Health Regulatory Authority (HRA) inspection. Any questions regarding a subject's eligibility should be discussed with the Sponsor's study management group prior to enrollment.

In order to be enrolled in this study, subjects must meet all the inclusion and exclusion criteria outlined below. Following informed consent and satisfaction of eligibility criteria,

enrollment in the study will be documented in the case report form (CRF). Subjects who undergo screening and are found to be ineligible will not be enrolled.

4.1 Inclusion Criteria

1. Histologically confirmed cHL, sALCL, or other CD30-expressing PTCL. CD30-expressing PTCL is defined as a tumor having a CD30 expression level ≥1% by local testing.
2. Previously treated with brentuximab vedotin containing regimen, with evidence of objective response, and subsequent disease progression or relapse after discontinuing treatment.
3. Documentation of disease relapse or progression ≥6 months after the last dose of brentuximab vedotin based on the Lugano Response Assessment Criteria for Malignant Lymphoma (Cheson 2014).
4. Fluorodeoxyglucose positron emission tomography- (FDG-PET) avid and bidimensional measurable disease of at least 1.5 cm in longest axis as documented by radiographic technique (spiral computed tomography [CT] preferred)
5. An Eastern Cooperative Oncology Group (ECOG) performance status ≤2
6. The following required baseline laboratory data:
   - absolute neutrophil count (ANC) ≥750 cells/µL (unless documented bone marrow involvement with lymphoma)
   - platelets ≥50,000/µL (unless documented bone marrow involvement with lymphoma)
   - serum bilirubin ≤1.5 x upper limit of normal (ULN) or ≤3 x ULN for subjects with Gilbert's disease
   - serum creatinine (Scr) ≤1.5 x ULN
   - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN for subjects with documented hepatic involvement with lymphoma
   - estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) study equation as applicable
7. Subjects of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 7 days prior to the first dose of brentuximab vedotin. Subjects with false positive results and documented verification that the subject is not pregnant are eligible for participation.
8. Subjects of non-childbearing potential are those who are postmenopausal >1 year or who have had a bilateral oophorectomy or hysterectomy.
9. If sexually active in a way that could result in pregnancy, subjects of childbearing potential and subjects who can father children and have partners of childbearing potential must agree to use 2 effective contraception methods during the study and for 6 months following the last dose of study drug.

10. The following requirements for subjects who are human immunodeficiency virus (HIV)-positive:
    - CD4+ T cell counts ≥350 cell/μL
    - No AIDS-defining opportunistic infection within the past 12 months
    - On established highly active antiretroviral therapy (HAART) for at least 4 weeks with an HIV viral load less than 400 copies/mL
11. Age 18 or older.
12. The subject or subject's legally acceptable representative must provide written informed consent.

4.2 Exclusion Criteria

1. Subjects who previously discontinued brentuximab vedotin due to any Grade 3 or higher toxicity.
2. Subjects with existing Grade 2 or higher peripheral neuropathy.
3. Subjects who were previously refractory to treatment with brentuximab vedotin.
4. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III to IV (see Appendix C) within 6 months prior to their first dose of brentuximab vedotin.
5. History of another malignancy within 3 years before the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year (OS) ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
6. Subjects with acute or chronic graft-versus-host-disease (GvHD) or receiving immunosuppressive therapy as treatment for or prophylaxis agent against GvHD.
7. Active cerebral/meningeal disease, including history of progressive multifocal leukoencephalopathy (PML). Subjects with a history of cerebral/meningeal disease related to the underlying malignancy are allowed if prior CNS disease has been treated.
8. History of PML.
9. Any active uncontrolled Grade 3 or higher (per the National Cancer Institute's Common Terminology Criteria for AEs, NCI CTCAE Version 5.0) viral, bacterial, or fungal infection requiring treatment with antimicrobial therapy within 2 weeks prior to the first dose of brentuximab vedotin in this study. Routine antimicrobial prophylaxis is acceptable.

10. Chemotherapy, radiotherapy, biologics, and/or other antitumor treatment with immunotherapy that is not completed 4 weeks prior to first dose of study drug, unless underlying disease has progressed on treatment.
11. Subjects who are pregnant or breastfeeding.
12. Subjects with known hypersensitivity to any excipient contained in the drug formulation.
13. Subjects <100 days from allogeneic transplant.
14. Post-allogeneic transplant subjects with any detectable level of cytomegalovirus (CMV) by polymerase chain reaction (PCR). Prior PCR positivity that was successfully treated is acceptable provided the baseline PCR result is negative prior to first dose of study drug.
15. Prior donor lymphocyte infusion <8 weeks prior to first dose of study drug.
16. Other serious underlying medical condition that, in the opinion of the investigator, would impair the subject's ability to receive or tolerate the planned treatment and follow-up.
17. Subjects enrolled and treated in this study cannot enroll in this study again.

4.3 Removal of Subjects from Therapy or Assessment

Seattle Genetics or their designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and CRF.

4.3.1 Discontinuation of Study Treatment

Subjects may continue on treatment for unlimited cycles until any of the following occur:

- Progressive disease (PD)
- AE with unacceptable toxicity
- Pregnancy
- Investigator decision
- Subject decision, non-AE
- Study termination by sponsor
- Other, non-AE

Subjects who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

4.3.2 Subject Withdrawal from Study

Any subject may be discontinued from the study for any of the following reasons:

- Subject withdrawal of consent
- Study termination by sponsor
- Lost to follow-up

- Death
- Other

5 TREATMENTS

5.1 Treatments Administered

Brentuximab vedotin, the investigational agent under study in this protocol, is an ADC consisting of the antibody cAC10, specific for human CD30; the microtubule-disrupting agent MMAE; and a protease-cleavable linker that covalently attaches MMAE to cAC10.

5.2 Investigational Product

Detailed information describing the preparation, administration, and storage of brentuximab vedotin is located in the Pharmacy Instructions.

5.2.1 Description

Brentuximab vedotin is a sterile, preservative free, white to off-white lyophilized cake or powder supplied by Seattle Genetics in single-use vials for reconstitution for IV administration. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. See the Pharmacy Instructions for further information.

5.2.2 Dose and Administration

Brentuximab vedotin will be administered by IV infusion given over approximately 30 minutes. The starting dose of brentuximab vedotin will be 1.8 mg/kg every 21 days. Subjects who had required a previous dose reduction due to AEs will start at 1.2 mg/kg and will not escalate to 1.8 mg/kg. In the absence of infusion-related reactions, the infusion rate for all subjects should be calculated in order to achieve a 30-minute infusion period. Brentuximab vedotin must not be administered as an IV push or bolus. Brentuximab vedotin should not be mixed with other medications.

Weight-based dosing is based on subject actual body weight. Doses must be adjusted for subjects who experience a ≥10% change in weight from baseline. Subject weight must be measured during all relevant assessment windows as described in the schedule of events. Other dose adjustments for changes in body weight are permitted per institutional standard. Rounding is permissible within 5% of the nominal dose. **An exception to weight-based dosing is made for subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose calculated per cycle in this study is 180 mg for subjects receiving the 1.8 mg/kg dose level, and 120 mg for subjects receiving 1.2 mg/kg dose level.**

5.2.3 Dose Modifications

For post-allogeneic transplant subjects, any post baseline instances of detectable levels of CMV must be discussed with the Medical Monitor prior to continued dosing of brentuximab vedotin. Table 2 describes the recommended dose modifications for study treatment-associated toxicity.

Doses reduced for treatment-related toxicity should not be re-escalated without discussion with the sponsor.

Table 2: Recommended dose modifications for brentuximab vedotin-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral Neuropathy	Continue at same dose level	Withhold until toxicity resolves to Grade 1 or baseline, then resume treatment at 1.2 mg/kg[a]		Discontinue treatment
Non-hematologic (except peripheral neuropathy)	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then resume treatment at the same dose level[b].	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the investigator [a,b,c].
Hematologic[d]	Continue at same dose level	Continue at same dose level	Withhold until toxicity resolves to ≤ Grade 2 or baseline, then resume treatment at the same dose level[e]. For Grade 3 or 4 neutropenia, growth factor support (G-CSF or GM-CSF) should be considered for subsequent cycles. If Grade 4 neutropenia recurs despite growth factor support, consider discontinuation or dose reduction to 1.2 mg/kg.	

a Dose reductions below 1.2 mg/kg are not allowed, and toxicities should be managed with dose delays.
b Subjects who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.
c Treatment should be discontinued for subjects who experience Grade 4 infusion-related reactions.
d Support with blood product transfusions allowed per institutional standard of care.
e Subjects who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

5.2.4 Storage and Handling

Refrigeration should be set at 2 to 8°C for storage of vials and solutions containing brentuximab vedotin. The controlled location must be accessible only to the pharmacist, the investigator, or a duly designated person. Brentuximab vedotin does not contain preservatives; therefore, opened and reconstituted vials of brentuximab vedotin should be used as soon as possible. If not used immediately, the in-use storage should not be longer than 24 hours. It is recommended that brentuximab vedotin vials and solutions be protected from direct sunlight until the time of use. Reconstituted vials and solutions must not be shaken.

Drug accountability instructions are provided in the Pharmacy Binder.

5.2.5 Packaging and Labeling

Drug product vials may be labeled as brentuximab vedotin, the United States adopted name (USAN) and the International Nonproprietary Name (INN), or as SGN-35, the compound code; the 2 names can be used interchangeably.

5.2.6 Preparation

Brentuximab vedotin vials are provided via single-use containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate institutional drug disposal procedures.

Brentuximab vedotin should be reconstituted with the appropriate amount of Sterile Water for Injection, United States Pharmacopeia (USP) or equivalent (see Pharmacy Instructions for details). The vial should be gently swirled until the contents are completely dissolved. The vial must not be shaken. The reconstituted drug product should be inspected visually for any particulate matter and discoloration.

The required volume of reconstituted drug product should be diluted into an infusion bag. The bag should be gently inverted to mix the solution. The bag must not be shaken. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

Detailed drug preparation instructions are provided in the Pharmacy Instructions.

5.3 Required Premedication and Post medication

Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of brentuximab vedotin. However, subjects who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent brentuximab vedotin infusions with premedication as described in Section 5.5.1. Subjects who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with brentuximab vedotin at the discretion of the investigator after discussion with the sponsor.

Subjects should be individually evaluated to assess the need for tumor lysis prophylaxis prior to the first dose of brentuximab vedotin. Subjects should receive prophylaxis as appropriate per the institutional standards.

5.4 Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.4.1 Required Concomitant Therapy for HIV-Positive Subjects

HIV-positive subjects must be managed in conjunction with an HIV specialist. The following measures are recommended.

5.4.1.1 HAART

Highly Active Antiretroviral Therapy (HAART) is a requirement for the duration of the study. Participants must be on HAART therapy for at least 7 days before therapy. The specific agents are at the discretion of the Investigator and use of agents currently available on an expanded access basis is allowed. Use of experimental antiretroviral agents or those containing zidovudine (including Combivir® and Trizivir®), ritonavir (including Kaletra®), Cobicistat (Stribild®), or another potent CYP3 inhibitor are prohibited. Participants taking zidovudine- or ritonavir-based HAART must change to a different regimen 7 days prior to therapy initiation (see Section 5.4.3). Changes to HAART therapy may be made if medically necessary (toxicity, failure of regimen, etc.).

5.4.1.2 Pneumocystis Prophylaxis

Trimethoprim sulfamethoxazole (Bactrim) must be given at the onset of therapy for Pneumocystis and Toxoplasmosis prophylaxis, according to current NIH Guidelines for the Prevention of Opportunistic Infections in HIV-Infected Adults and Adolescents.

Alternatively, dapsone (50 mg PO twice daily), atovaquone, or aerosolized pentamidine may be substituted for Pneumocystis prophylaxis in participants allergic to sulfonamides. Pneumocystis prophylaxis will be continued once therapy has been discontinued.

5.4.1.3 Mycobacterium avium complex (MAC) Prophylaxis

Azithromycin 1,200 mg PO once weekly must be initiated for prophylaxis if the CD4 count falls below 50 cells/µL or is expected to drop below 50 cells/µL while on chemotherapy. Prophylaxis may be discontinued once the CD4 count is deemed reliably above 50 cells/µL by the treating investigator.

Due to the glycoprotein P inhibition properties of azithromycin, this may increase the drug exposure and contribute to increased toxicity. Careful monitoring for brentuximab vedotin-related toxicities should be instituted in subjects receiving Azithromycin.

Based on the PK of azithromycin and brentuximab vedotin, the study team recommends giving the azithromycin on Days 5, 12, 19, and 21 of each cycle.

5.4.1.4 Effect of Other Drugs on Brentuximab Vedotin

CYP3A4 Inhibitors/Inducers: MMAE is primarily metabolized by CYP3A4. Co-administration of brentuximab with strong CYP3A4 inhibitors may increase exposure to MMAE. Subjects who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions. Additionally, co-administration of brentuximab vedotin with potent CYP3A4 inducers may reduce exposure to MMAE.

P-glycoprotein (P-gp) Inhibitors: Co-administration of brentuximab vedotin with P-gp inhibitors may increase exposure to MMAE. Subjects who are receiving P-gp inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions.

5.4.2 Allowed Concomitant Therapy

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. Concomitant prednisone (or equivalent) may be used at a dose of ≤20 mg/day.

Routine premedication for infusion reactions should not be administered prior to the first dose of brentuximab vedotin. However, subjects who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent treatment with premedication as described in Section 5.5.1.

Subjects who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions.

Routine prophylaxis with vaccines is permitted; it is recommended that vaccines used do not contain live micro-organisms.

5.4.2.1 Post-Allogeneic Transplant Therapy Recommendations

For subjects who are post-allogeneic transplant, if a post baseline sample is positive for CMV by PCR, initiation of pre-emptive therapy with ganciclovir or valganciclovir per institutional guidelines is recommended until CMV PCR becomes negative (Tomblyn 2009). Granulocyte colony-stimulating factor support is recommended to maintain ANC ≥750 cells/μL.

5.4.3 Prohibited Concomitant Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy (except for palliative radiotherapy), or systemic anti-neoplastic therapy during the study. Use of experimental antiretroviral agents or those containing zidovudine (including Combivir® and Trizivir®), ritonavir (including Kaletra®), Cobicistat (Stribild®), or another potent CYP3 inhibitor are prohibited. In order to be eligible, participants taking zidovudine- or ritonavir-based HAART must change to a different regimen 7 days prior to therapy initiation.

5.5 Management of Adverse Reactions

5.5.1 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for infusion-related reactions.

Subjects who have experienced a Grade 1 or Grade 2 infusion-related reaction to brentuximab vedotin may be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 30 to 60 minutes prior to each brentuximab vedotin infusion or according to institutional standards. If

anaphylaxis occurs, administration of brentuximab vedotin should be immediately and permanently discontinued.

5.5.2 Management of 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 Investigator's Brochure for further details.

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

- Neurologic examinations, as warranted
- Brain radiologic features by magnetic resonance imaging (MRI)
- PCR analysis: John Cunningham virus (JCV) DNA detectable in cerebrospinal fluid

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

5.5.3 Management of Overdose

Weight-based dosing for brentuximab vedotin is based on subject actual body weight (see Section 5.2.2), with the exception of subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. **The maximum dose calculated per cycle in this study is 180 mg for subjects receiving the 1.8 mg/kg dose level, and 120 mg for subjects receiving 1.2 mg/kg dose level.**

In the event of an overdose of brentuximab vedotin ≥10%, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of brentuximab vedotin.
- Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of brentuximab vedotin administered, subject weight) and AEs, if any.

5.6 Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF.

6 STUDY ACTIVITIES

6.1 Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.6.1.3). Any study protocol-related AE, as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (serum chemistry panel, complete blood count [CBC] with differential [manual differential if clinically indicated], as well as physical exam, weight, and ECOG performance status) may be performed within 1 day prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

A schedule of events is provided in Appendix A. Study activities are listed by visit in this section and descriptions of study assessments are presented in Section 7.

6.2 Screening Visit (Day –28 to Day 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria (see Section 4)
- Medical history
- CD30-expression and histological confirmation of cHL and PTCL performed by the local laboratory
    - Confirmation of human T cell leukemia virus-1 (HTLV-1) positivity for adult T cell leukemia/lymphoma (ATLL) subjects
- Contrast enhanced CT of neck, chest, abdomen, pelvis
- PET scan
- Prior disease therapies
- A biopsy within 60 days prior to study start to confirm CD30 expression is required, but may be omitted if, in the opinion of the Investigator, obtaining the biopsy would place the subject at undue risk.
- Bone marrow biopsy for sALCL or other CD30-expressing PTCL subjects (Day –14 to Day 1)

6.2.1 Baseline Visit (Day –7 to Day 1)

- Height and weight
- Electrocardiogram (ECG)
- Urine and/or serum pregnancy test for subjects of childbearing potential
- Physical exam
- ECOG performance status
- Serum chemistry panel (fasting glucose required at baseline only) (submit results to central laboratory)

- CBC with differential (submit results to central laboratory)
- Hemoglobin (Hgb) A1c (submit results to central laboratory)
- CMV PCR (post-allogeneic stem cell transplant subjects only). Results must be ready prior to C1D1 (see Section 7.5.1) (submit results to central laboratory)
- CD4 count for HIV positive subjects only (see Sections 5.4.1 and 7.5.2) (submit results to central laboratory)

6.3 Treatment Period (Day 1 to Day 21)

6.3.1 All Cycles, Day 1

- Cycle 1 only, prior to dosing, confirm subject eligibility per inclusion/exclusion criteria
- If the following activities occur within 1 day prior to Cycle 1, Day 1 (or occur within 2 days prior to Day 1 of all other cycles), they do not need to be repeated on Day 1:
  - ECOG performance status
  - Serum chemistry panel (submit results to central laboratory)
  - CBC with differential (submit results to central laboratory)
- Results from clinical laboratory assessments must be reviewed and must confirm eligibility prior to study drug administration
- Physical examination, including weight
- B symptom assessment
- Blood samples for PK assessment (Cycles 1–4 only)
- Blood sample for antitherapeutic antibodies (ATA) assessment (Cycles 1–4 only)
- CMV PCR (post-allogeneic stem cell transplant subjects only) (not required at Cycle 1 if done at baseline) (submit results to central laboratory)
- CD4 count for HIV positive subjects only (not required at Cycle 1 if done at baseline. Required at Cycle 2 and every 4 cycles thereafter) (submit results to central laboratory)
- brentuximab vedotin administration

6.3.2 Cycle 2 and Every 4 Cycles Thereafter: Day 15-21 Until Progression or Initiation of Subsequent Therapy

- CT of neck, chest, abdomen, pelvis
- PET scan if not found to be negative at a prior restage
- Bone marrow biopsy to confirm CR for sALCL or other CD30-expressing PTCL subjects (if not found to be negative at screening and the post baseline PET/CT shows a CR; D15-D21 or D1-D2 of Cycle 3 and every 4 cycles thereafter)

6.4 End of Treatment Visit (30 to 37 days after last dose of study drug)

End of Treatment (EOT) visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted 30 to 37 days following the last treatment to assess for AEs.

- ECOG performance status (Appendix B)
- Physical examination
- B symptom assessment
- Serum chemistry panel (submit results to central laboratory)
- CBC with differential (submit results to central laboratory)
- Urine and/or serum pregnancy test for subjects of childbearing potential
- Blood sample for PK and ATA assessment
- CMV PCR (post-allogeneic stem cell transplant subjects only) (submit results to central laboratory)
- If not done in the previous 6 weeks and/or the subject came off treatment for reasons other than progression:
  - CT of neck, chest, abdomen, pelvis
  - PET scan if not found to be negative at a prior restage
  - Bone marrow biopsy to confirm CR for sALCL or other CD30-expressing PTCL subjects (if not found to be negative at screening and the post baseline PET/CT shows a CR)

6.5 Follow-up: Every 4 Months From the Last Scan Performed Until Date of Progression/Subsequent Therapy

For subjects who are off treatment but have not progressed and have not started a subsequent therapy:

- CT of neck, chest, abdomen, pelvis
- PET scan if not found to be negative at a prior restage
- Bone marrow biopsy to confirm CR for sALCL or other CD30-expressing PTCL subjects (if not found to be negative at a prior restage)
- After 24 months, scanning schedule may be determined by institutional standard of care

For subjects who have progressed and/or have started a subsequent therapy

- Survival status and subsequent anticancer therapies received – every 4 months (±1 week) after disease progression or new therapy

6.6 Subject End of Study/End of Follow-up

The date the subject met criteria for study discontinuation and the reason for study discontinuation will be recorded.

7 STUDY ASSESSMENTS

For blood sampling planning purposes, see Clinical Operations blood draw volumes reference spreadsheet.

7.1 Screening/Baseline Assessments

Only subjects who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

Subject medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications. HTLV-1 status must be obtained by local laboratory assessment to inform the diagnosis.

7.1.1 Histological Diagnosis

A histological diagnosis for cHL or CD30-expressing PTCL and PTCL subtype must be determined by local pathology assessment. Local pathology will also assess anaplastic lymphoma kinase (ALK) status for subjects with a diagnosis of sALCL. CD30 expression level ≥1% will be considered positive. Submission of the tumor block, or freshly cut, unstained slides (with medical monitor approval) from a diagnostic biopsy will be required for subsequent central confirmation of CD30 expression; central confirmation is not required prior to the first dose of the study drug. The diagnostic specimen must be from a malignant lymph node or extranodal tissue obtained by core or excisional/incisional biopsy. Cutaneous, bone, or bone marrow samples alone are unacceptable. Fine needle aspirate and cytology samples are also unacceptable. Details and shipping instructions are provided in the Laboratory Manual.

7.2 Response/Efficacy Assessments

Radiographic assessments (contrast enhanced CT of chest, neck, abdomen, and pelvis) will be performed at protocol-specified time points or if disease progression is suspected. Assessment of lymphoma progression will be made according to the modified Lugano Criteria for Response Assessment (Cheson 2014). Treatment decisions by the investigator will be based on these assessments. CT and PET scans are required per protocol as directed in Section 6.3.2 and Appendix A.

A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning when both are required per protocol, as long as the CT scan is of diagnostic quality. CT and/or PET scans may also be obtained throughout the study if clinically indicated; if scans are performed at non-protocol specified time points, results will be collected in the subject's CRF and images will be submitted for central review.

PET and CT scanning of diagnostic quality will be required until disease is PET negative; responses will then be assessed by CT scan of diagnostic quality only. A bone marrow biopsy is required at screening for sALCL and other CD30-expressing PTCL subjects. Post baseline biopsies are also required to confirm a complete radiographic response for sALCL and other

CD30-expressing PTCL subjects; this confirmation is to be obtained within 4 weeks of documentation of response by radiographic assessment. However, repeat bone marrow biopsies are not required if bone marrow is found to be negative at screening or post baseline. All subjects' clinical data and tumor images must be available for CRF source verification. Copies of all imaging studies must be made available for review by the Sponsor (or its designee) and the third-party imaging core laboratory.

7.2.1 Modified Lugano Criteria

The primary determination of antitumor efficacy will be ORR according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas modified to take into account CT response in the event of a PET partial response (PR) (modified Lugano criteria). Treatment decisions by the Investigator will be based on local disease assessments according to modified Lugano criteria. Disease response of PD, stable disease (SD), PR, CR, or not evaluable (NE) will be determined at each assessment by BICR and the Investigator. Selection of up to 6 of the largest dominant nodes or other tumor lesions to follow for response assessment must be PET FDG-avid at baseline. Investigator evaluation of baseline radiographic assessment will enable study enrollment per Inclusion Criterion 4. In addition, per Lugano criteria, these nodes or masses should be selected according to all of the following: they should be clearly measurable in at least two perpendicular dimensions; if possible, they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved. The nodes or masses should have bidimensional measurements with at least 1.5 cm in the longest axis. For PET scans, Deauville scores of 1, 2, and 3 will be regarded as "negative" while scores of 4 and 5 with uptake greater than background liver uptake will be regarded as positive.

As detailed in the Independent Review Charter, the integrated response at each disease assessment will be determined on the basis of PET and CT responses according to modified Lugano criteria, as summarized in Table 3.

For time points where both PET and CT disease assessments are available, the response assessment will in general default to the PET assessment; however, when a PR is determined by PET but the CT response in neither CR nor PR, the integrated response will be SD. Once a CR has been determined by PET assessment, the integrated response will continue to be CR until PD is detected by PET or CT, even if there are no further PET assessments. When the CT response is PD and PET was not evaluated the integrated response will be PD.

Table 3: Integrated PET and CT response according to modified Lugano criteria

PET Response	CT Response		Integrated Response
CR	Any		CR
PR	CR, PR		PR
	Non-CR, Non-PR		SD
SD	Any		SD
PD	Any		PD
	Prior PET response[a]	CT Response	
Not done or	CR	Non-PD	CR[b]
Not evaluable	non-CR	Non-PD	NE
	Any	PD	PD
No FDG-avid disease at baseline[c]	No disease present (NE)		NE
	PD		PD

NE=not evaluable.

a "Prior PET response" refers to the latest prior PET assessment that was evaluable. PET responses may be carried forward over multiple CT assessments.

b A CR according to PET will be carried forward irrespective of CT response, until CT shows PD or is assessed as NE.

c Per protocol all subjects must have FDG-avid disease at baseline.

7.2.2 Lugano Criteria

Response will also be assessed, by the BICR, according to the unmodified Lugano criteria (Cheson 2014). Assessment of response will be undertaken in the same manner as for modified Lugano criteria (Section 7.2.1), with the exception that if the PET response is PR the integrated response will be PR, irrespective of CT response (Table 4).

Table 4: Integrated PET and CT response according to Lugano criteria per BICR

PET Response	CT Response		Integrated Response
CR	Any		CR
PR	Any		PR
SD	Any		SD
PD	Any		PD
	Prior PET response[a]	CT Response	
Not done or	CR	Non-PD	CR[b]
Not evaluable	non-CR	Non-PD	NE
	Any	PD	PD
No FDG-avid disease	No disease present (NE)		NE
at baseline[c]	PD		PD

NE=not evaluable.

a "Prior PET response" refers to the latest prior PET assessment that was evaluable. PET responses may be carried forward over multiple CT assessments.

b A CR according to PET will be carried forward irrespective of CT response, until CT shows PD or is assessed as NE.

c Per protocol all subjects must have FDG-avid disease at baseline.

7.2.3 International Working Group Consensus Response Evaluation Criteria in Lymphoma

ORR according to RECIL (Younes 2017) per BICR assessment will be evaluated as an additional efficacy endpoint.

7.3 Pharmacokinetic and Immunogenicity Assessments

Sensitive, qualified assays will be used to measure drug analytes including brentuximab vedotin ADC and MMAE concentrations in serum or plasma. These assays will include enzyme linked immunosorbent assays (ELISA) and liquid chromatography/tandem mass spectrometry (LC-MS/MS) assays, as well as other assays if further characterization is required.

Blood samples for PK testing will be collected at predose in Cycles 1 through 4, at end of infusion in Cycles 1 and 2 and at EOT (see Table 5). ATA to brentuximab vedotin will also be measured predose at Cycles 1 through 4 and at EOT using an appropriate qualified assay.

Selected PK parameters to be estimated include trough concentration (C_{trough}), and concentration at the end of infusion for brentuximab vedotin (C_{eoi}). The incidence of ATA to brentuximab vedotin will also be assessed.

Table 5: Pharmacokinetic, pharmacodynamic, and immunogenicity sampling time points

Cycle	Study Day	Time	Window	Relative Time[a]	PK	ATA
1 and 2	Day 1	Pre-dose	Within prior 24 hr	Start of infusion	X	X
		End of infusion (30 min)	Within 30 min post end of infusion	End of infusion	X	
3 and 4	Day 1	Pre-dose	Within prior 24 hr	Start of infusion	X	X
EOT					X	X

a Relative to infusion of brentuximab vedotin

7.4 Biospecimen Repository

In the US only, for subjects who provide additional consent, remaining de-identified unused blood may be retained by Seattle Genetics and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of pharmacodynamic biomarkers of ADCs. Blood samples donated for future research may be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.5 Other Study Assessments

7.5.1 Additional Monitoring for Post-Allogeneic Transplant Subjects

Subjects who have previously received an allogeneic transplant are at greater risk of developing opportunistic infections than subjects who have not received an allogeneic transplant. While risk of infection may be greatest in the first 100 days post-transplant, late infections (>100 days post-transplant) occur with some subjects remaining immunocompromised >2 years post-transplant (Tomblyn 2009). Consequently, post-allogeneic transplant subjects should be monitored by the investigator for signs or symptoms of potential opportunistic infections during the subject observation visits.

In addition, all post-allogeneic transplant subjects must participate in CMV surveillance during treatment with brentuximab vedotin. At the time of enrollment, the investigator needs to discuss the surveillance schedule with the medical monitor and have it approved before initiating treatment. For subjects who are <1-year post-transplant and considered at high risk for reactivation, blood samples for CMV surveillance should be drawn at least weekly while on therapy and at EOT. For subjects who are ≥1-year post-transplant, or <1-year post transplant and not considered at high risk for reactivation, blood samples for surveillance should be drawn at least Day 1 of every treatment cycle and at EOT. Local laboratory will assess levels of CMV DNA using PCR.

If at any time CMV level is detectable (defined as >0 copies/mL), initiation of pre-emptive therapy with ganciclovir or valganciclovir is recommended until CMV PCR becomes negative. Once CMV is no longer detectable by PCR, assessments will be conducted at least weekly during subsequent treatment on study.

Any post baseline instances of detectable levels of CMV must be discussed with the Medical Monitor prior to continued dosing of brentuximab vedotin.

7.5.2 Additional Monitoring for HIV-Positive and Hepatitis C-Positive Subjects

HIV-positive subjects must be co-managed with an HIV specialist; monitoring of CD4 counts will be done at baseline, Cycle 2 and every 4 cycles thereafter, at EOT, and should be performed according to institutional standard of care. Hepatitis C-positive subjects should be monitored for viral reactivation according to institutional standards.

7.6 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including serious adverse events (SAEs), recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests.

7.6.1 Adverse Events

7.6.1.1 Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a subject or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the AEs and Pre-existing Conditions CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.6.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in an SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing in subject hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.6.1.2 for the definition of potential DILI.)

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, Version 5.0. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (brentuximab vedotin) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.6.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the AEs and Pre-existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI CTCAE terms of 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction.' Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and the SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Cancer

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression," "Progression of Disease," or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

Pregnancy

Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of study drug(s), including any pregnancies that occur in the partner of a male study subject. Only report pregnancies that occur in a male subject's partner if the estimated date of conception is after the male subject's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of Data on the CRF

All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s), will also be recorded on the AEs and Pre-Existing Conditions CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.6.1.1) should be reported as SAEs.

Potential Drug-Induced Liver Injury

The observation of the critical importance of altered liver function has been referred to informally as Hy's Law (Reuben 2004). Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential hepatotoxicity in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe drug-induced liver injury (DILI).

Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 x ULN

   AND

2. Total bilirubin >2 x ULN, without initial findings of cholestasis (i.e., elevated serum alkaline phosphatase),

   AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Reporting Requirements

Any potential Hy's Law case should be handled as a suspected unexpected serious adverse reaction (SUSAR) associated with the use of the drug and reported promptly to the Sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3 x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. Consider withholding study drug during the investigation.

7.6.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment, whichever is later. However, all study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

7.6.1.4 Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Subject number
- Date of event onset
- Description of the event
- Study treatment, if known

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email address or fax number specified on the SAE report form)

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.6.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 7.6.1.4).

The sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity, as well as other SAEs that are not study endpoints but are known consequences of the underlying disease or condition that are anticipated to occur in the study population, should not be reported to the FDA as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Assessment for IND Safety Reporting Guidance for Industry (draft guidance December 2015).

In this study, progression of underlying malignancy is not reported as AEs or SAEs. No individual IND safety reports will be submitted for progression of underlying malignancy. Progression of underlying malignancy will be evaluated as an efficacy endpoint.

7.6.2 Clinical Laboratory Tests

Samples will be drawn for local labs. The following laboratory assessments will be performed by the local lab to evaluate safety at scheduled time points (see Appendix A) during the course of the study and the results (no blood) will be sent to central lab:

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, amylase, lipase, and uric acid.
- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit.
- The estimated GFR should be calculated using the MDRD equation as applicable, with Scr reported in mg/dL.
    - GFR (mL/min/1.73 m^2) =175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)
- A serum or urine β-hCG pregnancy test for subjects of childbearing potential at screening/baseline and EOT.

7.6.3 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Measurements of height obtained within the prior 12 months may be utilized.

7.7 Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Response will be assessed according to Lugano Criteria for Response Assessment (Cheson 2014) which are standardized criteria for evaluating response in cHL, PTCL, and sALCL. The intervals of evaluation in this protocol are considered appropriate for disease management.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to brentuximab vedotin. PK assessments are also common in clinical studies to help characterize dose-exposure-response relationships.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of subjects at the site, Seattle Genetics or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration, and withdrawal processes
- Current Investigator's Brochure/package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional review board/independent ethics committee (IRB/IEC) review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Subject coding and randomization (if applicable)
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seattle Genetics representative will typically review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study subjects, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is

suitable for inspection by Seattle Genetics or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for electronic CRF (eCRF) data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect subject confidentiality are to be employed during monitoring. The CRFs and related source documents will typically be reviewed by the monitor at each site visit to ensure data quality. Original source documents or certified copies are needed for review. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5 Quality Assurance Procedures

The Research and Development Quality group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Seattle Genetics as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, insubject or office subject records) for the maximum period required by the country and Institution in which the study will be conducted, or for the period specified by Seattle Genetics, whichever is longer. The investigator must contact Seattle Genetics prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seattle Genetics.

9 DATA ANALYSIS METHODS

9.1 Determination of Sample Size

It is anticipated that approximately 40 cHL and 40 CD30-expressing PTCL subjects will be enrolled in this study. This sample size was chosen to allow adequate precision of estimates of response rates.

For the cHL cohort, if 24 responses are observed, the estimated ORR would be 60%, and the associated 2-sided 95% confidence interval (CI) using the Clopper-Pearson method would be (43.3%, 75.1%).

For the CD30-expressing PTCL cohort, if 20 responses are observed, the estimated ORR would be 50%, and the associated 2-sided 95% CI using the Clopper-Pearson method would be (33.8%, 66.2%). The 50% ORR for the PTCL cohort was calculated based on a weighted average of subjects with sALCL and other CD30-expressing PTCL, where subjects with sALCL have an ORR of 60% and an estimated enrollment cap of approximately 50%, and subjects with other CD30-expressing PTCL have an ORR of 40% and an estimated enrollment cap of approximately 50%.

9.2 Study Endpoint Definitions

9.2.1 Objective Response Rate

Objective Response Rate (ORR) is defined as the portion of subjects with CR or PR according to the modified Lugano Criteria for Response Assessment (Cheson 2014) based on BICR or investigator as specified in Section 2. The ORR according to Lugano Criteria for response Assessment (Cheson 2014) per BICR, and the ORR according to RECIL (Younes 2017) per BICR will be evaluated as a secondary endpoint and an additional endpoint, respectively.

9.2.2 Duration of Response

DOR is defined as the time from start of the first documentation of objective tumor response (CR or PR) based on BICR or investigator to the first documentation of objective tumor progression or to death due to any cause, whichever comes first. DOR data will be censored on the day following the date of the last radiological assessment of measured lesions documenting absence of PD for subjects who do not have objective tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment or stem cell transplant (includes donor lymphocyte infusion), or are removed from study prior to documentation of objective tumor progression. DOR will only be calculated for the subgroup of subjects with OR. Duration of CR will also be analyzed in the subset of subjects who achieve a CR.

9.2.3 Progression-Free Survival

PFS is defined as the time from start of study treatment to first documentation of objective tumor progression based on BICR or investigator or to death due to any cause, whichever comes first. PFS data will be censored on the date of the last radiological assessment of measured lesions documenting absence of PD for subjects who do not have objective tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment or stem cell transplant (includes donor lymphocyte infusion), or are removed from study prior to documentation of objective tumor progression. Subjects lacking an evaluation of tumor response after their first dose will have their event time censored at 1 day.

9.2.4 Overall Survival

OS is defined as the time from start of study treatment to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive. Subjects lacking data beyond the day of first dose will have their survival time censored at 1 day. The start of study treatment is defined as the first dose of brentuximab vedotin on the current study.

9.2.5 Complete Response Rate

CR rate is defined as the portion of subjects with CR according to the modified Lugano Criteria for Response Assessment (Cheson 2014) based on BICR or investigator.

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (e.g., adding baseline assessments to define a subgroup). The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1 General Considerations

9.3.1.1 Randomization and Blinding

Randomization and blinding will not be performed.

9.3.1.2 Adjustments for Covariates

Covariates are not considered for adjustment in the analyses.

9.3.1.3 Handling of Dropouts and Missing Data

With the exception of time-related endpoints, no imputation will be conducted for missing data unless otherwise specified in the SAP.

For time-related endpoints, e.g., DOR, OS, and PFS, etc., subjects who have no specified event will be censored at the time of the last valid assessment of the endpoint(s).

9.3.1.4 Multicenter Studies

Site-to-site variation will not be adjusted in the analyses.

9.3.1.5 Multiple Comparisons and Multiplicity

No multiple comparisons are planned, and no alpha adjustment is needed because no formal hypotheses are being tested.

9.3.1.6 Data Transformations and Derivations

Baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of brentuximab vedotin unless otherwise specified in the analysis plan.

9.3.1.7 Analysis Sets

Full Analysis Set

The full analysis set includes all subjects who receive at least 1 dose of brentuximab vedotin on this study. The full analysis set will be used for efficacy analyses and all safety analyses. Demographics and baseline disease characteristics will be summarized based on full analysis set.

Additional analysis sets of subjects may be defined in the SAP.

9.3.1.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.9 Timing of Analyses

The primary analysis will be conducted when all treated subjects have been followed for at least 6 months, discontinued from study, or had 30 days of safety follow-up after PD, whichever comes first.

9.3.2 Subject Disposition

An accounting of study subjects by disposition will be tabulated and the number of subjects will be summarized. All enrolled subjects who discontinue study treatment and subjects who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.3 Subject Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the SAP.

9.3.4 Treatment Compliance

The dose (mg/kg) administered at each cycle will be assessed and dose intensity will be summarized. Details will be provided in the SAP.

9.3.5 Efficacy Analyses

9.3.5.1 Primary Efficacy Analyses

The ORR by BICR and its two-sided 95% exact CI will be calculated using the Clopper-Pearson method (Clopper 1934). The maximum percent reduction in the sum of the products of the largest diameters (SPD) per the modified Lugano Response Assessment Criteria for Malignant Lymphoma (Cheson 2014) will be graphically displayed. Detailed methodology will be provided in the SAP.

9.3.5.2 Secondary Efficacy Analyses

The CR rate will be derived and its two sided 95% exact confidence interval will be calculated using the Clopper-Pearson method (Clopper 1934). DOR and PFS in the FAS will be estimated using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median DOR, PFS, and OS and their two sided 95% CI by Brookmeyer and Crowley (Brookmeyer 1982) will be calculated. The ORR by investigator per the modified Lugano Response Assessment Criteria for Malignant Lymphoma (Cheson 2014) and its two-sided 95% exact CI will be calculated using the Clopper-Pearson method (Clopper 1934). The ORR by BICR per the Response Assessment Criteria for Malignant Lymphoma (Cheson 2014) will be analyzed similarly. The maximum percent reduction in the sum of the products of the longest perpendicular diameters (SPD) per the modified Lugano Response Assessment

Criteria for Malignant Lymphoma (Cheson 2014) will be graphically displayed. Detailed methodology will be provided in the SAP.

9.3.5.3 Additional Efficacy Analyses

The ORR by BICR and its two-sided 95% exact CI will be calculated using the Clopper-Pearson method (Clopper 1934). The maximum percent reduction in the sum of the longest diameters (SLD) per the RECIL Criteria (Younes 2017) will be graphically displayed.

9.3.6 Pharmacokinetic and Immunogenicity Analyses

Antibody drug-conjugate (brentuximab vedotin) and unconjugated drug (MMAE) levels in serum or plasma will be summarized with descriptive statistics at each PK sampling time point. Any additional PK and PK/PD analyses may be described in a separate analysis plan and presented in a separate report.

9.3.7 Safety Analyses

9.3.7.1 Extent of Exposure

Total dose, duration of treatment, number of cycles and dose intensity will be summarized and listed. Dose modifications will also be summarized and listed. Details will be provided in the SAP.

9.3.7.2 Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will be defined as treatment emergent if they are newly occurring or worsen following study treatment.

AEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 subject, the AE will be counted once as the occurrence for that subject. The incidence of AEs will be tabulated by preferred term. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

9.3.7.3 Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.7.4 Clinical Laboratory Results

For laboratory results, summary statistics for actual values and for change from baseline may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE version 5.0 and flagged when values are outside the normal reference range.

9.3.8 Interim Analyses

No formal interim analyses are planned.

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 (R2); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1 Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring subjects are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each subject, or legally acceptable representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

For phase 1 studies, it is preferable for a subject to provide consent themselves. If informed consent is obtained from a legally acceptable representative for a subject who is unable to provide informed consent at study entry (if applicable), but the subject is later able to provide informed consent, the investigator must obtain written informed consent from the subject.

10.2 Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1 Investigator Information

The contact information and qualifications of the principal investigator and sub investigators and name and address of the research facilities are included in the investigator file.

10.3.2 Protocol Amendments and Study Termination

Protocol amendments will be submitted to the IRB/IEC prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4 Study Documentation, Privacy and Records Retention

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of subject identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

10.5 Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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APPENDIX A: SCHEDULE OF EVENTS

		Screening/ Baseline		Enrollment	Every 21-day cycle	Cycle 2 and every 4 cycles thereafter	Cycle 2 and every 4 cycles thereafter	EOT	Long-term follow-up (Every 4 months since last scan)
	Day	D –28 to 1	D –7 to 1	Within 7D of 1st dose	D1	D1	D15-21 (or D1-2 of Cycle 3 and every 4 cycles thereafter)[N]	Within 30–37D of last dose[A]	Every 4 months
	Visit window				±2d	–2d			±2 wk
Screening/ Baseline Assessments	Informed consent	X		Submit eligibility confirmation to Sponsor prior to treatment					
	Inclusion/Exclusion, medical history	X			X[K]				
	Medical History	X							
	CD30/histology	X							
	HTLV-1 status for ATLL subjects/ALK status for sALCL subjects	X							
	Prior disease therapies	X							
	ECG		X						
	Pregnancy test – urine and/or serum (subjects of childbearing potential)		X					X	
	Height		X						
	Weight		X		X[B]				
	Biopsy to confirm CD30 expression[L]	X							
Safety Assessments	Physical exam		X		X[B]			X	X
	ECOG performance status		X		X[B]			X	
	CBC with differential		X		X[B]			X	
	Chemistry panel		X		X[B]			X	
	Hgb A1c		X						
	B symptom assessment				X			X	
	CMV PCR for post-allogeneic subjects		X	See Section 7.5.1				X	
	CD4 count for HIV positive subjects		X			X		X	
	Monitoring for Hep C positive subjects	Monitor for viral reactivation per institutional standards							
	Concomitant medications	Related to study procedures[E]			Collect from Day 1 predose through safety reporting period of study drug				
	Adverse event collection								
Treatment	Study drug administration				X				
PK/Immunogenicity	Blood sample collection	See Table 5 for sample collection details							
Response Assessment	CT of neck, chest, abdomen, pelvis	X					X[C]	X[D]	X[I]
	PET[F]	X					X[G]	X[D,G]	X[G, I]
	Bone marrow biopsy	X[M]					X[H]	X[D]	X[H]
	Survival Status								X[J]

A. EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.
B. Does not need to be repeated if done within 1 day prior to C1D1 or 2 days prior to any other cycle.
C. Window Day 15–21
D. Not required if conducted 6 weeks prior to EOT.
E. From time of informed consent.
F. A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as a diagnostic quality CT scan is obtained; PET scans may also be obtained any time during the study if clinically indicated.
G. Once disease is determined to be PET negative, only CT scans are required.
H. Bone marrow biopsy is required only to confirm complete response for sALCL and other CD30-expressing PTCL subjects and should be obtained within 4 weeks after documentation of response; does not need to be repeated once bone marrow is negative.
I. Required every 4 months for 24 months for subjects that came off treatment but have not progressed or initiated a new therapy. Obtain until subject experiences PD per investigator assessment, initiation of new therapy, death, or analysis of the primary endpoint, whichever comes first. After 24 months, scanning schedule may be per institutional standard of care.
J. Once a subject experiences PD per investigator assessment or initiates a new therapy, survival status is required every 4 months (±1 week) until death or study closure, whichever comes first. Collect information regarding subsequent anticancer therapies.
K. Cycle 1 only.
L. A biopsy within 60 days prior to study start to confirm CD30 expression is required, but may be omitted if, in the opinion of the Investigator, obtaining the biopsy would place the subject at undue risk.
M. Window Day -14 to Day 1; for sALCL and other CD30-expressing PTCL subjects only.
N. Study drug may only be administered after the response assessment is confirmed to show lack of PD.

APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		Lansky		ECOG	
Percent	Description	Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.		
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restriction of, and less time spent in, play activity.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.	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.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet active play and activities.		
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.		
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.		
0	Dead.	0	Dead.	5	Dead.

APPENDIX C: NEW YORK HEART ASSOCIATION CLASSIFICATION

A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Subjects

Class I:	subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	subjects with marked limitation of activity; they are comfortable only at rest.
Class IV:	subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Online source: http://www heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX D: GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 6 after the final dose of study drug; see Section 4.1).

Acceptable methods for highly effective birth control (preventing conception)

Subjects who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods:

- Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- Barrier method/s (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)

a A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

Acceptable methods for preventing secondary exposure to seminal fluid

Subjects born male and who are sexually active with a pregnant or breastfeeding person, must use the contraceptives in Option 1 or 2:

- Option 1: Male condom (with or without spermicide) and cervical cap
- Option 2: Male condom (with or without spermicide) and diaphragm

Unacceptable methods of contraception

- Periodic abstinence
- No method
- Withdrawal
- Rhythm
- Spermicide only
- Progestin-only pills
- Concomitant use of female and male condoms

APPENDIX E: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol titled "A phase 2, multicenter, single-arm study of treatment with brentuximab vedotin in subjects with relapsed or refractory classic Hodgkin lymphoma (cHL) or CD30-expressing peripheral T cell lymphoma (PTCL)."

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature	Date
Investigator Name, Printed	

APPENDIX F: DOCUMENT HISTORY

Version	Date
Original	16-Apr-2019
Amendment 1	26-Aug-2019
Amendment 2	20-Nov-2019
Amendment 3	28-Apr-2020

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Title page	Change of medical monitor to Julie Lisano	Change in medical monitor.
3.1, 5.2.2, and Synopsis	Clarified that subjects who start at a dose of 1.2 mg/kg because of prior dose reduction due to AEs will not escalate to 1.8 mg/kg.	Subjects who previously required a dose reduction due to AEs may potentially have a repeat of the AEs at the higher dose.
3.2	Modified inclusion criterion 3 by changing documentation of disease or relapse progression from 3 months to 6 months and removing language about brentuximab vedotin treatment in frontline and second line or beyond setting. Criterion now reads: <u>Documentation of disease relapse or progression ≥6 months after the last dose of brentuximab vedotin based on the Lugano Response Assessment Criteria for Malignant Lymphoma (Cheson 2014).</u>	Lengthened requirement for duration of brentuximab vedotin treatment from 3 months to 6 months.
4.1	Modified inclusion criterion 6: Bullet 1: Changed ANC count from ≥1000 cells/µL to ≥750 cells/µL and added "unless documented bone marrow involvement with lymphoma." Bullet 2: Added "unless documented bone marrow involvement with lymphoma" Bullet 5: Added "for subjects with documented hepatic involvement with lymphoma."	Clarification
4.2	Removal of the following exclusion criterion: "Subjects with dementia or altered mental state that would preclude the understanding and rendering of informed consent." Added: <u>Subjects who were previously refractory to treatment with brentuximab vedotin.</u>	Conflicted with inclusion criterion. Clarification.
5.4.1.4	Added new section to include the effects of other drugs (CYP3A4 and P-gp inhibitors/inducers) on brentuximab vedotin	Included to keep the protocol language consistent with the USPI label.
5.4.2.1	Changed ANC from ≥1000 cells/µL to ≥750 cells/µL	To harmonize with change made in Section 4.1
6.2 and Appendix A	Included biopsy requirement.	For confirmation for CD30 expression
7.1.1	Added language for CD30 expression and biopsy requirements.	Clarification
7.2	Added Table 3 (Integrated PET and CT Response) to expand on the response assessment.	Clarification
7.3	Clarified that blood samples for PK will be collected at predose Cycles 1 through 4. Deleted PK collection at 48 hours.	Clarification
7.6.2	Change made from central to local labs and clarified that only results will be sent to central lab.	Clarification

Section(s)	Change	Rationale
3.1, 9.1 and synopsis	Changed sample size and ORR rates for cHL and CD30-expressing PTCL	Changed from a previous heterogeneous population with a sample size of approximately 50 to two distinct samples sizes: approximately 40 subjects each for cHL and other CD30-expressing PTCL
Throughout	Minor administrative edits and corrections.	Corrections

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
2 (Table 1), 9 (Table 5) and Synopsis	Changed primary endpoint to ORR per modified Lugano criteria, added a secondary endpoint for ORR per unmodified Lugano criteria, and added an additional endpoint for ORR per Response Evaluation Criteria in Lymphoma (RECIL).	Regulatory feedback indicated that Lugano criteria should be modified in the trial.
7.2.1 and 7.2.2	Added new sections that include text and tables to specify how PET and CT response assessments are integrated for modified Lugano criteria and unmodified Lugano criteria.	Clarification
9.3.5.1	Added response criteria to “modified” Lugano.	Clarification
9.3.5.2	Added language to reflect addition of secondary objective of ORR by investigator.	Clarification
9.3.5.3	Added language to include ORR per RECIL as determined by BICR.	Clarification
Throughout protocol	Minor administrative changes, corrections, renumbering of sections, and rearrangement of text.	Clarity and consistency

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Title Page	Addition of NCT and EudraCT numbers and change in medical monitor.	Administrative update
3.3	New section to define end of study.	Updated to meet EU regulatory requirements
4.1 and 7.1.1	Added language to inclusion criterion 1 to include CD30 expression threshold for eligibility	Clarification to correct inconsistency
5.4.3	Added exception of palliative radiotherapy.	Clarification
6.2	Specified window for bone marrow biopsy.	To align with existing practice
6.3.2, 6.4, and 7.2	Added language to clarify requirement to confirm CR for sALCL or other CD30-expressing PTCL subjects	To align with existing practice
6.6	Modified section header to distinguish it from Section 3.3 header.	Clarification
7.2.1 and Table 4	Added language to clarify that disease response will be assessed by BICR and the Investigator.	Clarification
Table 6	Table removed	To streamline the protocol and avoid redundancy
Appendix A	Added bone marrow biopsy specific to PTCL subjects during screening. Added language and footnote to expand screening window.	To align with existing practice Expanded scanning window due to COVID-19 pandemic
Appendix D	Added appendix for Guidance on Contraception.	Guidance to the investigator that encompasses US and EU contraception requirements
Throughout protocol	Minor administrative changes, corrections, clarifications, and rearrangements of text.	Clarity and consistency