Protocol Number:	SGN35-032
Version:	Amendment 3; 10 March 2021
Protocol Title:	A dual-cohort, open-label, phase 2 study of brentuximab vedotin and CHP (A+CHP) in the frontline treatment of subjects with peripheral T-cell lymphoma (PTCL) with less than 10% CD30 expression
Investigational Drug:	Brentuximab vedotin
Indication:	Peripheral T-cell lymphoma
Phase:	2
IND Number:	71634
EudraCT Number:	2020-002336-74
Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Medical Monitor:	PPD , MD, PhD Seagen Inc. Tel: PPD E-mail: PPD
SAE Fax:	425.527.4308 (or fax number specified on sponsor's SAE report form)

PROTOCOL SYNOPSIS

Protocol Number SGN35-032 **Version** Amendment 3 **Phase** 2	**Product Name** Brentuximab vedotin **Sponsor** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A dual-cohort, open-label, phase 2 study of brentuximab vedotin and CHP (A+CHP) in the frontline treatment of subjects with peripheral T-cell lymphoma (PTCL) with less than 10% CD30 expression

Study Objectives

Primary:

- To evaluate the objective response rate (ORR) per blinded independent central review (BICR) using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007)

Secondary:

- To evaluate the complete response (CR) following completion of study treatment (Cheson 2007)
- To evaluate progression-free survival (PFS) (Cheson 2007)
- To evaluate overall survival (OS)
- To evaluate duration of response (DOR) (Cheson 2007)
- To evaluate ORR per BICR using modified Lugano criteria (Cheson 2014)
- To evaluate safety and tolerability

Study Population

Key inclusion criteria include subjects aged 18 years and older with newly diagnosed PTCL, excluding systemic anaplastic large cell lymphoma (sALCL), per the Revised European-American Lymphoma World Health Organization (WHO) 2016 classification; PTCL histology; CD30 expression <10% by local assessment; and fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by CT, as assessed by the site radiologist.

Number of Planned Subjects

Up to approximately 80 subjects will be enrolled in this study. Approximately 40 subjects with positive CD30 expression (≥1% to <10%) and up to approximately 40 subjects with negative CD30 expression (<1%) by local assessment (central confirmation) will be enrolled.

Study Design

This is a dual-cohort, open-label, multicenter, phase 2 clinical trial designed to evaluate the efficacy and safety of A+CHP in subjects with non-sALCL PTCL and tumor CD30 expression <10%. Enrollment will be based on CD30 expression per local lab assessment. An archived tumor biopsy specimen will be submitted to a central pathology lab for confirmation of CD30 expression. Only subjects with CD30 expression <10% per central confirmation will be analyzed for the primary and secondary endpoints. Subjects will receive 21-day cycles of A+CHP for a target of 6-8 cycles.

Test Product, Dose, and Mode of Administration

Subjects will receive 6-8 cycles of A+CHP in 21-day cycles as follows: brentuximab vedotin 1.8 mg/kg, cyclophosphamide 750 mg/m^2, and doxorubicin 50 mg/m^2, administered IV on Day 1 of each cycle, and prednisone 100 mg daily administered orally on Days 1–5 (±1 day window) of each cycle.

Duration of Treatment

Study treatment consists of 6-8 cycles of A+CHP. The maximum total duration of therapy is 8 cycles, or approximately 6 months.

Efficacy Assessments

Lymphoma response and progression will be assessed by BICR using Revised Response Criteria for Malignant Lymphoma and modified Lugano criteria. Radiographic disease evaluations, including CT scans of neck, chest, abdomen and pelvis, will be assessed at baseline, after Cycle 4 of treatment, after the completion of study treatment, at 9, 12, 15, 18, 21 and 24 months after initiation of study treatment, and every 6 months thereafter until disease progression, subject death, or analysis of the primary endpoint, whichever comes first. A CT scan will also be performed at the time of suspected clinical progression. A PET scan is required at baseline, after Cycle 4, and after the completion of study treatment. Subsequent restage assessments (CT scans only) will be performed according to the calendar, relative to the first dose of study treatment, to ensure that tumor progression is uniformly assessed between the treatment arms.

Safety Assessments

Safety assessments will consist of the surveillance and recording of adverse events (AEs) including serious adverse events (SAEs), recording of concomitant medication, and measurements of physical examination findings and laboratory tests.

Statistical Methods

Efficacy and safety endpoints will be summarized with descriptive statistics by cohort, with the CD30 negative cohort and the CD30 positive cohort consisting of subjects with CD30 expression level <1% and ≥1% to <10% per central testing, respectively. The summary of overall (CD30 negative and positive cohort combined) may be presented as appropriate. Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be used to describe continuous variables. Frequencies and percentages will be used when presenting categorical variables (eg, ORR). Time-to-event endpoints, such as PFS, will be estimated using Kaplan-Meier methodology and Kaplan-Meier plots will be presented. Medians for time-to-event analyses (eg, median PFS), will be presented and two-sided 95% confidence intervals (CIs) will be calculated using the log-log transformation method.

Sample size determination

Clinical data from this study will be presented in a descriptive manner to demonstrate consistency with non-anaplastic large cell lymphoma (ALCL) subjects receiving A+CHP enrolled in ECHELON-2 study. The study is designed to estimate the ORR at a reasonable level of precision. Up to approximately 80 non-sALCL PTCL will be enrolled in this study, with up to approximately 40 subjects in the CD30 negative (<1%) cohort and approximately 40 subjects in the CD30 positive (1% to <10%) cohort. In the CD30 positive (1% to <10%) cohort with 40 subjects, if 28 responses are observed, the estimated ORR would be 70%, and the associated 2-sided 95% CI using the Clopper-Pearson method would be (53.5%, 83.4%).

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

A+CHP	brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone
ADC	antibody drug conjugate
AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
ATLL	adult T-cell leukemia/lymphoma
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotrophin
BICR	blinded independent central review
BSA	body surface area
CBC	complete blood count
C_{eoi}	concentration at the end of infusion
CFR	Code of Federal Regulations
CHOEP	etoposide to CHOP
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHOP-21	cyclophosphamide, doxorubicin, vincristine, and prednisone administered every 21 days
CHP	cyclophosphamide, doxorubicin, and prednisone
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
C_{trough}	trough concentration
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FSH	follicle stimulating hormone

GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
HIV	human immunodeficiency virus
HR	hazard ratio
HTLV-1	human T-cell leukemia virus-1
IV	Intravenous
IDMC	Independent Data Monitoring Committee
IPI	International Prognostic Index
IEC	Independent Ethics Committee
IND	investigational new drug
IRB	Institutional Review Board
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MF	mycosis fungoides
MMAE	monomethyl auristatin E
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PR	partial response
PTCL	peripheral T-cell lymphoma
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
SCT	stem cell transplant
T_{max}	time at which the maximum concentration occurs
ULN	upper limit of normal
USP	United States Pharmacopeia
WHO	World Health Organization

1 INTRODUCTION

Brentuximab vedotin is a CD30-directed 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; bystander effects on nearby cells in the tumor microenvironment due to released MMAE; and immunogenic cell death (ICD) due to endoplasmic reticulum stress which drives exposure of immune activating molecules that can promote a T-cell response (Oflazoglu 2007; Li F 2014; Muller 2014; Kim 2015; Cao A 2016; Gardai 2016).

The phase 3 ECHELON-2 trial (NCT01777152) demonstrated that the combination of brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone (A+CHP) was superior to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for the frontline treatment of subjects with systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphoma (PTCL) (Horwitz 2019) and supported the 2018 FDA approval for this use. This study is being conducted as part of a post-marketing commitment to FDA to assess the efficacy and safety of A+CHP as frontline treatment of subjects with non-sALCL PTCL and CD30 expression less than 10%, which was the cutoff used to define CD30 positivity in the ECHELON-2 trial.

1.1 CD30-Positive Peripheral T-Cell Lymphomas

PTCL is a heterogeneous group of rare lymphoproliferative disorders that originate from clonal proliferation of mature, post-thymic T lymphocytes (T cells) (Winberg 1993). The 2008 World Health Organization (WHO) classification recognized 14 distinct subtypes of PTCL, with differentiation based on histology and sites of involvement (Bellei 2012; Zinzani 2016). Overall, PTCL represents approximately 10% to 15% of non-Hodgkin lymphoma (NHL) cases worldwide, with the greatest prevalence in Asian populations due to subtypes associated with viral infection (Anderson 1998; Vose 2008; Bellei 2012). Based on SEER data, approximately 4,000 new cases of PTCL were diagnosed in the United States in 2016 (Teras 2016).

PTCL generally occurs in older individuals, with a median age at diagnosis in the sixth or seventh decade. Published clinical studies and retrospective reviews show a higher incidence of PTCL in males than females and in African American versus Caucasian racial groups (Vose 2008; Ellin 2014; Teras 2016).

Historically, CHOP given for 6 to 8 cycles was considered to be the standard of care for the majority of PTCL subtypes (Vose 2008; Ellin 2014; Armitage 2017; NCCN 2018). Comparison of non-randomized clinical trials does not support a difference in activity between 6 or 8 cycles of CHOP and both approaches were commonly used in clinical

practice (Coiffier 2002; Schmitz 2010). Guidelines recommend administration of 6 cycles of CHOP for subjects with Stage I-II disease and International Prognostic Index (IPI) score of 0-2, 6 to 8 cycles of CHOP for subjects with Stage I-II disease and an IPI score of 3-5, and 6 to 8 cycles for all subjects with Stage III-IV disease (Schmitz 2010; NCCN 2018). Real world data from the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study and the Swedish Lymphoma Registry indicate that more than 85% of PTCL subjects were treated with an anthracycline-based multi-agent chemotherapy regimen, of which CHOP was the most commonly used (Vose 2008; Ellin 2014).

CHOP has remained the most commonly used frontline regimen for previously-untreated subjects with PTCL for decades (Savage 2008a; Vose 2008; Ellin 2014; Federico 2015b), and efforts to improve upon it have been disappointing. Although few randomized trials have been conducted in subjects with PTCL, results from 2 small prospective studies showed that more aggressive chemotherapy regimens consisting of VIP+ABVD (etoposide, ifosfamide, and cisplatin + doxorubicin, bleomycin, vinblastine, and dacarbazine) or GEM-P (gemcitabine, methylprednisolone, and cisplatin) offered no meaningful advantage over CHOP (Simon 2010; Gleeson 2018). Though a post-hoc analysis of pooled data from PTCL subjects treated on multiple phase 2 and 3 studies suggested that the addition of etoposide to CHOP (CHOEP) resulted in improved 3-year EFS (time to standard progression-free survival [PFS] or unplanned therapy) in younger (age $\leq$ 60 years) subjects, this more aggressive regimen produced added toxicity without an improvement in OS (Schmitz 2010). Further intensification of the CHOEP regimen (Mega-CHOEP) in younger subjects actually resulted in worse outcomes (Schmitz 2010). Similarly, retrospective analysis of PTCL subjects treated with intensive chemotherapy regimens (such as hyper-CHOP and hyper-CVAD) also suggested that these subjects experienced worse outcomes than those treated with CHOP (Escalon 2005).

Non-sALCL PTCLs are aggressive neoplasms with poor prognosis despite treatment with conventional chemotherapy. Complete response (CR) rates with CHOP in these aggressive lymphomas range from approximately 40% to 60% with objective response rates (ORRs) of approximately 75% (Mercadal 2008; Simon 2010; Dearden 2011; Gleeson 2018). Estimates of long-term outcome in the PTCL population include a median PFS of 12 to 18 months and a median OS of less than 4 years (Savage 2008b; Vose 2008; Ellin 2014). The low rate of CR and 5-year OS rates of <50% underscore the high unmet need in this subject population.

The high rate of subsequent disease progression among subjects responding to frontline therapy has led to the use of consolidative treatment with autologous stem cell transplant (ASCT) as a means of improving long-term outcomes. While some single-arm studies have shown promising results with the use of consolidative ASCT, no randomized studies have been conducted (Reimer 2009; d'Amore 2012). Post-treatment consolidation with ASCT has nevertheless become part of the standard treatment plan at many centers, particularly for subjects with PTCL subtypes other than anaplastic lymphoma kinase + sALCL (Moskowitz 2014; Armitage 2017). Guidelines support observation, a clinical trial, or the use

of ASCT as acceptable options for subjects who achieve a CR following frontline therapy (Dearden 2011; NCCN 2018).

Evaluation of CD30 expression in the initial diagnostic workup for PTCL is recommended: CD30 is universally expressed and is pathognomonic in sALCL. Among non-sALCL subtypes, CD30 expression is more variable (Sabattini 2013; Bossard 2014; Federico 2015a; Hsi 2017). Enrollment criteria for ECHELON-2 required CD30 expression of ≥10% as determined by standard immunohistochemistry (IHC). The PTCL subtypes enrolled in ECHELON-2 were considered to have a meaningful prevalence of CD30 expression and were generally treated with CHOP as frontline therapy.

1.2 Clinical Experience with Brentuximab Vedotin

In ECHELON-2, treatment with A+CHP resulted in statistically significant and clinically meaningful improvements in the primary endpoint of PFS per blinded independent central review (BICR), with a 29% reduction in the risk of a PFS event versus CHOP (stratified HR=0.71 [95% CI: 0.54, 0.93], P=0.011); the median PFS with A+CHP was 48.2 months versus 20.8 months with CHOP. The A+CHP arm also demonstrated a statistically significant survival benefit (HR=0.66 [95% CI 0.46, 0.95], P=0.0244). With a median follow-up of 42 months, the median OS was not reached for either arm. The 75th percentile of OS was not reached with A+CHP compared to 17.5 months with CHOP. The A+CHP regimen was well-tolerated and had a manageable safety profile that was comparable with that of CHOP (Horwitz 2019). The FDA approved A+CHP for previously untreated sALCL or other CD30-expressing PTCLs in November 2018 based on this study.

A complete summary of the clinical and nonclinical data relevant to brentuximab vedotin and its study in human subjects is provided in the Investigator's Brochure.

1.3 Overall Risk and Benefit Assessment

Brentuximab vedotin is approved in six indications as monotherapy or in combination with chemotherapy. Data from prior studies support the combination of brentuximab vedotin with chemotherapy regimens in both classic Hodgkin lymphoma and NHL. In ECHELON-2, in the setting of previously untreated PTCL expressing CD30 on >10% of cells, the combination of A+CHP was superior to CHOP as frontline therapy and led to the approval of this regimen by the FDA (for CD30 expressing PTCL) and the European Commission (for sALCL).

There are multiple reasons to expect that A+CHP will have efficacy in PTCL with <10% CD30 expression. In ECHELON-2, CD30 levels were not predictive of the likelihood or duration of response (DOR) to A+CHP in patients with non-ALCL PTCL down to the 10% cutoff enrolled in the trial (Advani 2019). Brentuximab vedotin monotherapy has also been shown to have activity in PTCL and other lymphomas with low (<10%) or negative CD30 expression (Jagadeesh 2019). The lack of correlation between CD30 expression and response to brentuximab vedotin is likely multifactorial, with tumor heterogeneity and biopsy sampling error playing a significant role. In addition, CD30 expression may be dynamic with

intratumoral levels varying over time. Brentuximab vedotin is also highly potent and may have a significant treatment effect at CD30 expression levels below the cutoff detectable by IHC. Furthermore, the activity of cyclophosphamide, doxorubicin, and prednisone (CHP) chemotherapy in PTCL is not dependent on CD30 expression. It is therefore reasonable to expect that A+CHP will demonstrate efficacy in subjects with PTCL and CD30 expression <10%. Since CD30 is universally highly expressed in sALCL and sALCL was over-represented in ECHELON-2, this study will be limited to PTCL subtypes other than sALCL.

In this SGN35-032 study of subjects with PTCL with low levels of CD30 expression, it is not anticipated that the safety profile of the A+CHP regimen will differ from that seen in ECHELON-2. In patients with PTCL with lower levels of CD30 expression in the tumor, it is not expected that A+CHP will result in new or more severe safety findings. The CHP chemotherapy components do not target CD30, and thus the side effect profiles of these agents should not be affected by the amount of CD30 expression in the tumor biopsy. Furthermore, there are no data that suggest the safety profile of brentuximab vedotin is related to the amount of CD30 expression.

Based on the totality of the observed safety and activity data in ongoing clinical studies of brentuximab vedotin, the benefits appear to outweigh the risks for the patient populations under study.

1.4 Rationale for Current Trial

In ECHELON-2, A+CHP showed efficacy across a range of CD30 expression levels, even at the lowest allowed level of 10% per local assessment. In order to support the indication of CD30-expressing PTCL, the sponsor submitted data from an additional 344 subjects with CD30-expressing PTCL and other large-cell lymphomas who had been treated in studies with brentuximab vedotin as a single agent or in combination with chemotherapy, in both frontline and relapsed/refractory settings. Among these 344 subjects, 184 had tumors with CD30 expression <10%, including 83/184 with undetectable CD30 by IHC (CD30=0). Activity with brentuximab vedotin was observed at all levels of CD30 expression, including in tumors with undetectable CD30 levels (Advani 2019; Horwitz 2019).

Because brentuximab vedotin has activity in lymphomas with low CD30 expression, and because the activity of CHP chemotherapy in PTCL is not dependent on CD30 expression, it is reasonable to expect that A+CHP will demonstrate efficacy in subjects with PTCL and CD30 expression <10%. Since CD30 is universally expressed and is pathognomonic in sALCL, this study will be limited to PTCL subtypes other than sALCL.

2 OBJECTIVES

2.1 Primary Objective

- To evaluate the ORR per blinded independent central review (BICR) using Revised Response Criteria for Malignant Lymphoma criteria (Cheson 2007)

2.2 Secondary Objectives

- To evaluate the complete response (CR) rate following completion of study treatment (Cheson 2007)
- To evaluate the progression-free survival PFS (Cheson 2007)
- To evaluate overall survival (OS)
- To evaluate DOR (Cheson 2007)
- To evaluate ORR per BICR, using modified Lugano criteria (Cheson 2014)
- To evaluate the safety and tolerability

2.3 Endpoints

2.3.1 Primary Endpoint

- ORR per BICR following the completion of study treatment using Revised Response Criteria for Malignant Lymphoma criteria (Cheson 2007)

2.3.2 Secondary Endpoints

- Complete response rate per BICR (Cheson 2007)
- PFS per BICR (Cheson 2007)
- OS
- DOR per BICR (Cheson 2007)
- ORR per BICR, using modified Lugano criteria (Cheson 2014)
- Type, incidence, severity, seriousness, and relatedness of adverse events
- Laboratory abnormalities

2.3.3 Additional Endpoints

- ORR, CR rate, DOR, and PFS as assessed by the Investigator using Cheson 2007 criteria

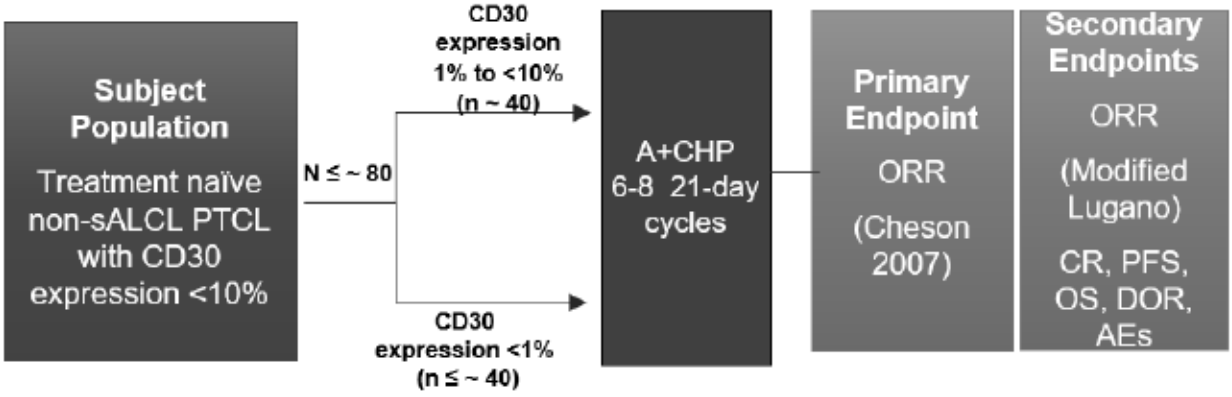
3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a dual-cohort, open-label, multicenter, phase 2 clinical trial designed to evaluate the efficacy and safety of A+CHP in subjects with non-sALCL PTCL and CD30 expression <10%. An archived tumor biopsy specimen will be submitted to a central pathology lab for confirmation of CD30 expression. Enrollment will be based on CD30 expression per local lab assessment. Only subjects with CD30 expression <10% per central confirmation will be analyzed for the primary and secondary endpoints. Subjects will receive 21-day cycles of A+CHP for a target of 6-8 cycles. A target of 6-8 cycles of study treatment will be administered, per investigator decision, based on subject-specific characteristics, including stage of disease and IPI risk score.

Up to approximately 80 subjects will be enrolled in this study; approximately 40 subjects will be enrolled into the CD30 positive cohort and up to approximately 40 subjects will be enrolled into the CD30 negative cohort. A study schema is provided in Figure 1. See Appendix A for a schedule of evaluations.

Figure 1: Study design



3.2 Discussion and Rationale for Study Design

The ECHELON-2 trial demonstrated a statistically significant difference in ORR between the 2 arms (83% in the A-CHP arm vs. 72% in the CHOP arm; p-value=0.003). This significant improvement in ORR is consistent with the statistically significant and clinically meaningful improvement in both PFS (HR= 0.71, p-value= 0.011) and OS (HR= 0.66, p-value = 0.003).

Based on the ECHELON-2 results, Seagen believes that ORR is a suitable primary endpoint to demonstrate clinical benefit in this dual-cohort, single-arm trial. This is consistent with the recommendation outlined in FDA (FDA 2018) and EMA guidance (EMA 2017) for single-arm trials. Progression-free survival will be analyzed as a secondary endpoint for supportive evidence.

Clinical data from this study will be presented in a descriptive manner to demonstrate consistency with non-anaplastic large cell lymphoma (ALCL) subjects receiving A-CHP enrolled in ECHELON-2 study. The sample size of 40 subjects in the ≥1% to < 10% cohort was chosen to allow adequate precision of estimates of response rates. Based on the ECHELON-2 study, if 28 responses are observed, the estimated ORR would be 70%, and the associated 2-sided 95% CI using the Clopper-Pearson method would be (53.5%, 83.4%).

Lymphoma response and progression will be defined using the same criteria that was used in the ECHELON-2 study (Cheson 2007). Modified Lugano criteria will be applied in evaluating ORR as a secondary endpoint.

3.2.1 Method of Assigning Subjects to Treatment Groups

This is a single arm study. Subjects will be assigned to 1 of 2 cohorts based on CD30 expression; up to approximately 40 subjects will be enrolled in the negative CD30 expression (<1%) cohort and approximately 40 subjects will be enrolled in the positive CD30 expression (≥1% to <10%) cohort.

3.2.2 Rationale for Selection of Doses

In a phase 1 dose-escalation study of brentuximab vedotin (Study SGN035-001), the MTD was defined as 1.8 mg/kg IV administered every 3 weeks. This dose and schedule was further evaluated in two pivotal phase 2 studies (Studies SG035-0003 and SG035-0004) in subjects with CD30-positive hematologic malignancies.

In the phase 1 (Study SGN35-011) study of brentuximab vedotin in combination with CHP, the MTD was defined as 1.8 mg/kg IV administered concomitantly with CHP every 3 weeks. The phase 3 study (ECHELON-2; SGN35-014) confirmed that this dose was well tolerated in combination with CHP.

3.2.3 Blinding

This is an open-label study.

4 STUDY POPULATION

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.

Subjects must meet **ALL** of the following inclusion criteria to be eligible for this study:

4.1 Inclusion Criteria

1. Age 18 years or older.
2. Newly diagnosed PTCL, excluding sALCL, per the Revised European-American Lymphoma World Health Organization (WHO) 2016 classification.

3. The following non-sALCL PTCL subtypes are eligible:

   a. PTCL – not otherwise specified (PTCL-NOS)
   b. Angioimmunoblastic T-cell lymphoma (AITL)
   c. Adult T-cell leukemia/lymphoma (ATLL; acute and lymphoma types only, must be positive for human T cell leukemia virus 1)
   d. Enteropathy-associated T-cell lymphoma (EATL)
   e. Hepatosplenic T-cell lymphoma
   f. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITCL)
   g. Indolent T-cell lymphoproliferative disorder (T-LPD) of the gastrointestinal (GI) tract
   h. Follicular T-cell lymphoma
   i. Nodal PTCL with T-follicular helper (TFH) phenotype

4. CD30 expression <10% by local assessment in tumor containing lymph node or other extranodal soft tissue biopsy (See Section 7.1.1)

5. Fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm by CT, as assessed by the site radiologist.

6. An Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2 (see Appendix B).

7. The following required baseline laboratory data:

   - bilirubin ≤1.5X upper limit of normal (ULN) or ≤3X ULN for subjects with Gilbert's disease or documented hepatic involvement with lymphoma
   - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3X ULN or ≤5X ULN for subjects with document hepatic involvement with lymphoma
   - serum creatinine ≤2X ULN
   - estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation provided below.
     eGFR (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)

     Conversion to creatinine clearance (CrCl) (mL/min) from eGFR using the Mosteller body surface area (BSA) equation and dividing by 1.73 to determine dosing holds.
     BSA (m^2) = (Height [cm] x Weight [kg] / 3600)$^{1/2}$
     CrCl (mL/min) = (eGFR [mL/min/1.73 m^2] x BSA [m^2])/1.73
   - absolute neutrophil count (ANC) ≥1000/µL (unless documented bone marrow involvement with lymphoma)
   - platelet count ≥50,000/µL (unless documented bone marrow involvement with lymphoma)

8. The following requirements for subjects who are human immunodeficiency virus (HIV)-positive:

   - CD4+ T-cell counts ≥350 cell/µL within 28 days of Day 1

- No acquired immune deficiency syndrome-defining opportunistic infection within the past 12 months
- On established highly active antiretroviral therapy for at least 4 weeks with an HIV viral load less than 400 copies/mL within 28 days of Day 1

9. Females of childbearing potential must have a negative serum beta human chorionic gonadotrophin (β-hCG) pregnancy test result within 7 days prior to the first dose of study treatment and must agree to use an effective contraception method during the study and for at least 12 months after the last dose of cyclophosphamide or 6 months after the last dose of other study treatment, whichever is later (see Appendix C). Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.

10. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 12 months after the last dose of cyclophosphamide or 6 months after the last dose of other study treatment, whichever is later (see Appendix C).

11. Subjects or their legally authorized representative must provide written informed consent. If informed consent is obtained from a legally authorized representative for a subject who is unable to provide informed consent at study entry, but the subject is later able to provide informed consent, the investigator must obtain written informed consent from the subject.

4.2 Exclusion Criteria

1. Current diagnosis of any of the following:
   a. sALCL
   b. Primary cutaneous T-cell lymphoproliferative disorders and lymphomas
   c. Mycosis fungoides (MF), including transformed MF
2. History of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS ≥90%), such as carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
3. History of progressive multifocal leukoencephalopathy (PML).
4. Cerebral/meningeal disease related to the underlying malignancy.
5. Prior treatment with brentuximab vedotin or doxorubicin.
6. Baseline peripheral neuropathy Grade ≥ 2 (per the NCI CTCAE, Version 4.03) or subjects with the demyelinating form of Charcot-Marie-Tooth syndrome.

7. Left ventricular ejection fraction less than 45% or symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), or myocardial infarction within the past 6 months, or previous treatment with complete cumulative dose of >300 mg/m^2 of doxorubicin.
8. Any uncontrolled Grade 3 or higher (per the National Cancer Institute's Common Terminology Criteria for Adverse Events, NCI CTCAE Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study drug. Routine antimicrobial prophylaxis is permitted.
9. Current therapy with other systemic anti-neoplastic or investigational agents. Participation in other clinical trials for any condition is not allowed. Participation in observational studies is permitted.
10. Females who are pregnant or breastfeeding.
11. Subjects with a known hypersensitivity to any excipient contained in any of the drug formulations of study treatments.
12. Subjects with known urinary outflow obstruction.
13. Any other condition that in the opinion of the investigator would impact patient safety or ability to participate in the trial.
14. Contraindications to any of the study drugs.
15. Has received a live vaccine within 30 days prior to the first dose of study drug and must not receive a live vaccine within 90 days after the last dose of study drug (see Section 5.5.3). Vaccines other than live vaccines are permitted.

4.3 Removal of Subjects From Therapy or Assessment

Seagen 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 case report form (CRF). If a subject discontinues study treatment, every attempt should be made to follow the subject until progression, death, or administrative study closure. Final assessments will be performed before any other therapeutic intervention if possible. Additionally, any subsequent treatments should be documented on the subject's medical records and CRF.

4.3.1 Discontinuation of Study Treatment

The study treatment will be discontinued in case of pregnancy.

A subject's treatment with study drug may be discontinued for any of the following reasons:

- Completed treatment
- Progressive disease
- Adverse event

- 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 until withdrawal from the study (reasons for study discontinuation listed in Section 4.3.2).

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

In case of pregnancy, study treatment must be terminated, and the subject must be withdrawn from the clinical trial.

5 TREATMENTS

5.1 Treatments Administered

The study treatments to be administered are described in Table 1.

Table 1: Study treatment

Study Treatment in Each 21-Day Cycle
Brentuximab vedotin 1.8 mg/kg IV on Day 1[a]
Cyclophosphamide 750 mg/m^2 IV on Day 1
Doxorubicin 50 mg/m^2 IV on Day 1
Prednisone 100 mg po daily on Days 1-5 (±1 day window)

a Administered over approximately 30 minutes within 1 hour of completing treatment with other agents administered via IV

5.2 Investigational Study Drug

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. All subjects in the study will be administered brentuximab vedotin.

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 Seagen 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 Method of Procurement

Brentuximab vedotin will be provided by the sponsor.

5.2.3 Dose and Administration

Brentuximab vedotin will be administered on Day 1 of every 21-day cycle by IV infusion given over approximately 30 minutes (see Table 1) and within 1 hour of completing treatment with other agents administered via IV. 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.

Dosing is based on subject weight according to the institutional standard; however, doses will be adjusted for subjects who experience a ≥10% change in weight from baseline. 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. Rounding is permissible within 5% of the nominal dose.

Dose modifications of the brentuximab vedotin are described in Section 5.4.

5.2.4 Required Premedication and Postmedication

Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of study treatment. However, subjects who experience an infusion-related reaction may receive subsequent infusions of study treatment with premedication as described in Section 5.2.5. Subjects who experience a Grade 3 or Grade 4 infusion-related reaction may potentially continue to 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.

5.2.5 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 will be monitored for a period of 2 hours post-infusion of brentuximab vedotin. Subjects who have experienced an infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 30–60 minutes prior to each infusion or according to institutional standards.

If anaphylaxis occurs, study treatment administration should be immediately and permanently discontinued.

5.2.6 Management of Suspected PML

Signs and symptoms of progressive multifocal leukoencephalopathy (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 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, brentuximab vedotin should be permanently discontinued.

5.2.7 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.

5.2.8 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.

5.2.9 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 standard (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 Cyclophosphamide, Doxorubicin, and Prednisone

5.3.1 Description

All subjects in the study will be administered the CHP components of the CHOP regimen.

Cyclophosphamide is a nitrogen mustard alkylating agent. Doxorubicin is a cytotoxic anthracycline antibiotic. Prednisone is a corticosteroid. Refer to the Summary of Product Characteristics of CHP for further details on each study drug and associated safety risks.

5.3.2 Method of Procurement

CHP are commercially available and approved by the United States FDA and other regulatory agencies for use in treating subjects with multiple types of cancer.

In the United States, CHP will be supplied by the study site and will be billed to subjects and/or their third-party payer (insurance, a healthcare provider, or applicable government program).

In regions outside of the United States, CHP will be supplied to study sites by the sponsor.

5.3.3 Dose and Administration

Refer to Table 1 for specific doses. Administration of study treatment should be according to the institutional standard. Dosing should be based on the subject's baseline (predose, Cycle 1 Day 1) height and weight or per institutional standards at the site.

Dose modification guidelines for cyclophosphamide, doxorubicin, or prednisone are described in Section 5.4.

5.3.4 Required Premedication and Postmedication

There are no protocol-required pre- or postmedications for CHP. Routine anti-emetic prophylaxis should be administered per institutional standards.

5.3.5 Packaging and Labeling

In the United States, supplies of CHP are commercially available. Outside of the United States, supplies will be labeled to meet country-specific regulatory requirements.

5.3.6 Preparation

CHP should be prepared per institutional guidelines.

5.3.7 Storage and Handling

CHP should be stored and handled per institutional guidelines.

5.4 Dose Modifications

Table 2 describes the recommended dose modifications for brentuximab vedotin treatment-associated neuropathy.

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

Table 2: Recommended dose modifications for treatment-associated neuropathy

Grade of Treatment-Associated Neuropathy	Recommended Dose Modification	
	Sensory Neuropathy	Motor Neuropathy
1	Continue study treatment at same dose level.	Continue study treatment at same dose level.
2	Continue study treatment at the same dose level.	Reduce dose levels of brentuximab vedotin to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks.
3	Reduce dose levels of brentuximab vedotin to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks	Discontinue treatment with brentuximab vedotin.
4	Discontinue treatment with brentuximab vedotin.	Discontinue treatment with brentuximab vedotin.

Table 3 describes the recommended dose modifications for brentuximab vedotin for subjects with renal impairment.

Table 3: Recommended dose modifications for subjects with renal impairment

Impairment	Degree of Impairment	Recommended Dose Modification
Renal	Normal (CrCl ≥80 mL/min)[a] Mild (CrCl >50-80 mL/min)[a] Moderate (CrCl >30-50 mL/min)[a]	No dosage adjustment is required for normal, mild, or moderate renal impairment.
	Severe (CrCl <30 mL/min)[a]	Avoid the use of brentuximab vedotin in subjects with severe renal impairment.

a. eGFR >45 mL/min/1.73 m^2 using the MDRD study equation provided below.
eGFR (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)
Conversion to CrCl (mL/min) from eGFR using the Mosteller BSA equation and dividing by 1.73 to determine dosing holds.
BSA (m^2) = (Height [cm] x Weight [kg] / 3600)$^{1/2}$
CrCl (mL/min) = (eGFR [mL/min/1.73 m^2] x BSA [m^2])/1.73

Dose modifications for brentuximab vedotin other than neuropathy and renal impairment should be at the discretion of the investigator; dose reductions of brentuximab vedotin below 1.2 mg/kg are not permitted. Prolonged dose holds of brentuximab vedotin (greater than 21 days) should be discussed with the Medical Monitor.

Dose modifications of cyclophosphamide, doxorubicin, or prednisone are allowed per institutional standard of care or per the package insert at the discretion of the investigator. Permitted dose modifications include discontinuation of a treatment component.

5.5 Concomitant Therapy

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

5.5.1 Required Concomitant Therapy for HIV-Positive Subjects

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

5.5.1.1 Highly Active Antiretroviral Therapy

Highly Active Antiretroviral Therapy (HAART) is a requirement for the duration of the study. Participants must be on stable HAART therapy for at least 7 days before Cycle 1 Day 1. 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 at least 7 days prior to therapy initiation (see Section 5.5.3). Changes to HAART therapy may be made if medically necessary while on study treatment (toxicity, failure of regimen, etc.).

5.5.1.2 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 should be continued once therapy has been discontinued.

5.5.1.3 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, and 19 of each cycle.

5.5.1.4 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.

5.5.2 Allowed Concomitant Therapy

Routine premedication for infusion-related reactions should not be administered prior to the first dose of brentuximab vedotin. However, subjects who experience an infusion-related reaction may receive subsequent treatment with premedication as described in Section 5.2.5.

Routine infectious prophylaxis for Pneumocystis jiroveci pneumonia (PCP) should be considered for all subjects.

The use of transfusions, platelet and/or colony-stimulating factors per institutional practice is permitted. Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the investigator.

The use of colony-stimulating factors and/or chemotherapy for stem-cell collection to enable a future autologous SCT is permitted per institutional standards. Chemomobilization of stem cells is only permitted after end of treatment (EOT) procedures are completed.

Consolidative SCT or radiotherapy may be given at the investigator's discretion after EOT procedures are completed. At least 6 cycles of study treatment should be given prior to initiating post treatment consolidative SCT or radiotherapy.

5.5.3 Prohibited Concomitant Therapy

Subjects must not receive a live vaccine within 30 days prior to the first dose of study drug and must not receive a live vaccine within 90 days after the last dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines

and are not allowed. Vaccines other than live vaccines are permitted. Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy from Day 1 through EOT. In addition, other prohibited concomitant therapies should be excluded in accordance with the approved prescribing information for each agent. Exceptions are noted in Section 5.5.2.

5.6 Treatment Compliance

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

6 STUDY ACTIVITIES

6.1 Schedule of Events

Adverse events and concomitant medications will be collected from Day 1 (predose) through the safety reporting period. Any study protocol-related adverse event should be recorded from the time of informed consent as well as any concomitant medications given for treatment of the adverse event. A schedule of events is provided in Appendix A. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

6.2 Screening Visit (Day -28 to Day 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- CD30/histological confirmation – submission of tumor containing lymph node or other extranodal soft tissue biopsy within 30 days of enrollment for central pathology confirmation of histology, CD30 expression (see Section 7.1.1)
- Human T-cell leukemia virus-1 (HTLV-1) status (see Section 7.1)
- CD4 count for HIV positive subjects only (see Sections 5.5.1 and 7.3.5) (submit results to central laboratory)
- HIV viral load for HIV positive subjects only (see Sections 5.5.1 and 7.3.5) (submit results to central laboratory)
- Hemoglobin (Hgb) A1c (see Section 7.3.3)
- CT of chest, neck, abdomen, pelvis (see Section 7.2)
- PET scan (see Section 7.2)
- Bone marrow biopsy (may be obtained within 60 days of the first dose of study treatment; see Section 7.2)
- Echocardiogram or multi-gated acquisition (MUGA) scan (may be obtained up to 1 month prior to the first dose of study treatment)

6.2.1 Baseline Visit (Day -7 to Day 1)

- Height and weight

- Electrocardiogram (ECG)
- Pregnancy test for females of childbearing potential (see Section 7.3.3)
- ECOG performance status (see Section 7.3.4)
- Serum chemistry panel (see Section 7.3.3)
- CBC with differential (see Section 7.3.3)
- eGFR using the MDRD equation (see Section 7.3.3)

6.3 Treatment Period (21-day cycles)

6.3.1 Every Cycle: Day 1

- Vital signs (see Section 7.3.2)
- Pregnancy test for females of childbearing potential (see Section 7.3.3)
- Lymphoma assessment (see Section 7.2; conducted within ≤48 hours prior to study treatment in Cycle 1)
- ECOG performance status (not required in Cycle 1)
- Serum chemistry
- CBC with differential
- Study treatment; administered after all assessments have been conducted
  - Subjects will be monitored for a period of 2 hours post-infusion of brentuximab vedotin.
- HIV positive subjects only: CD4 count and HIV viral load at Cycle 2 and every 4 cycles thereafter
- eGFR

6.3.2 Cycle 4 Only: Day 15-21

- CT of chest, neck, abdomen, pelvis
- PET scan
- Bone marrow biopsy to confirm response (if positive at baseline)

6.3.3 Last Planned Cycle of Treatment: Day 15-21

The following assessments must be obtained for subjects who complete the last planned cycle of treatment. Subjects who discontinue treatment prior to the planned last cycle of treatment should have an EOT visit, as described in Section 6.4.

- Lymphoma assessment
- CT of chest, neck, abdomen, pelvis
- PET scan
- Bone marrow biopsy to confirm response (if positive at baseline and not found to be negative at a prior restage, see Section 7.2)

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

If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted by phone 30-37 days following the last treatment to assess for adverse events.

EOT assessments will be performed before any other therapeutic intervention, if possible.

- Pregnancy test for females of childbearing potential
- ECOG performance status
- Serum chemistry
- CBC with differential
- HIV positive subjects only: CD4 count and HIV viral load
- eGFR

The following response assessments are required if they were not conducted at last cycle of treatment:

- Lymphoma assessment
- CT of chest, neck, abdomen, pelvis
- PET scan
- Bone marrow biopsy to confirm response (if positive at baseline and not found to be negative at a prior restage)

6.5 Follow-up

Subjects who have not yet experienced disease progression per investigator assessment (based on the Revised Response Criteria for Malignant Lymphoma) (Cheson 2007), the following assessments must be obtained at 9, 12, 15, 18, 21, and 24 months (±1 week) after the first dose of study treatment, and every 6 months thereafter (±1 week) until progression per investigator, death, or analysis of the primary endpoint, whichever comes first.

- CT of chest, neck, abdomen, pelvis
- Lymphoma assessment

The following assessments are required during follow up at the time points described. Months are relative to the first dose of study treatment. Assessments are to be conducted until death or study closure unless otherwise specified. Assessments occurring after 24 months from first dose may be conducted via a phone call.

- Survival status and subsequent anticancer therapies received – every 6 months (±1 week up to Month 30, ±1 month after Month 30) starting at Month 12 and after disease progression

6.6 End of Study/End of Follow-up

The study will be closed 2 years after enrollment of the last subject, or when no subjects remain in long-term follow-up, whichever occurs first. Additionally, the sponsor may terminate the study at any time.

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

7 STUDY ASSESSMENTS

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.

Cardiac function will be determined by performing either an echocardiogram or MUGA scan (may be obtained up to 1 month prior to the first dose of study treatment).

HTLV-1 status must be obtained by local laboratory assessment to inform the diagnosis.

7.1.1 Histologic Subtype and Characterization of Tumor Tissue

Histologic subtype must be determined by local pathology assessment to enable enrollment. Tissue samples will be sent to the central pathology laboratory within 30 days of enrollment for confirmation of CD30 expression. Tumor blocks are preferred if available. Subjects with negative CD30 expression (<1%) and positive CD30 expression (1% to <10%) by local testing are eligible for enrollment.

CD30 expression is to be assessed by immunohistochemistry using tissue from the diagnostic biopsy. The 3 following criteria must be met to declare CD30 positivity:

a. CD30 detected in ≥1% of neoplastic cells (in cases where enumeration of neoplastic cells is not possible, total lymphocytes may be used).
b. CD30 staining at any intensity.
c. Membranous, cytoplasmic, and/or golgi pattern of expression of the CD30 antigen.

Submission of the tumor tissue samples from a diagnostic biopsy within 30 days of enrollment is required for central confirmation of CD30 expression and disease subtype. The diagnostic specimen must be from a malignant lymph node or extranodal tissue obtained by core or excisional/incisional biopsy, and should be from the same specimen used for local CD30 expression testing. Cutaneous bone, bone marrow samples, fine needle aspirates, and cytology samples are unacceptable.

Additional biomarker assessments in tumor tissue may include, characterization of the tumor microenvironment, tumor subtyping, profiling of somatic mutations or alterations in genes or RNA commonly altered in cancer, and drug effects. Assays may include, but not limited to, immunohistochemistry and next generation sequencing of RNA and DNA.

Details and shipping instructions are provided in the Research Specimen Laboratory Manual.

7.2 Response/Efficacy Assessments by the Investigator

Lymphoma assessments are to be performed at the time points outlined in Section 6 and Appendix A. An adequate focused lymphoma assessment consists of:

- Subject medical history, including a thorough review of:
  - The subject's current signs and symptoms, including B symptoms (fever, night sweats, or weight loss >10%)
  - Concomitant medications
- Physical examination, including evaluation of skin, head, eyes, ears, nose, throat, lymph nodes, heart, lungs, abdomen, back, extremities, and neurology

Radiographic assessments (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 by the investigator will be made according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).Treatment decisions by the investigator will be based on these assessments. CT and PET scans are required per protocol as directed in Section 6 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.

A bone marrow biopsy is required at baseline. Information from an assessment performed within 60 days of the first dose of study treatment, as part of clinical care, may be used to satisfy the baseline bone marrow biopsy requirement. Postbaseline biopsies are required to confirm response if bone marrow is positive at baseline; this confirmation is to be obtained within 4 weeks of documentation of response by radiographic assessment. Repeat bone marrow biopsies are not required once bone marrow is found to be negative.

If cutaneous lesions are the sole site of progressive disease, a biopsy must be obtained to histologically confirm progression.

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. Refer to the Study Manual for details (instructions on collecting and submitting tumor imaging studies for third-party imaging core laboratory review).

The secondary determination of antitumor efficacy will be ORR according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014) modified to take into account CT response in the event of a PET PR (modified Lugano criteria).

7.2.1 Biospecimen Samples for Future Research

In the United States, remaining de-identified unused tissue will be retained by Seagen and used for future research for subjects who provide additional consent. The planned future research includes, but is not limited to, the evaluation of targets for novel ADCs, the biology of ADC sensitivity and resistance mechanisms, and to identify predictive pharmacodynamic biomarkers of ADCs. Tissue samples donated for future research will be retained for a period of 25 years.

For subjects treated outside of the United States, or if additional consent is not granted, any tissue samples remaining after all study testing is completed will be destroyed following study closure.

7.3 Safety Assessments

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

7.3.1 Adverse Events

7.3.1.1 Definitions

Adverse Event

According to the International Conference on Harmonization (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an adverse event 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 Adverse Events and Pre-existing Conditions case report form (CRF):

- From the time of informed consent through the day prior to study Day 1, only study protocol-related adverse events should be recorded.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All adverse events (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 7.3.1.3). Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and adverse events, 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 adverse event unless it is associated with clinical signs or symptoms, requires an intervention, results in a serious adverse event, or results in study termination or interruption/discontinuation of study treatment. When recording an adverse event resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An adverse event should be classified as a serious adverse event (SAE) if it meets one of the following criteria:

Fatal:	Adverse event resulted in death
Life threatening:	The adverse events placed the subject at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient 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 serious adverse events 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:	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 adverse event 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.

Adverse Event Severity

AE severity should be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. 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 Serious Adverse Events).

Relationship of the Adverse Event to Study Treatment

The relationship of each adverse event to each study treatment [brentuximab vedotin or any component of CHP] should be evaluated by the investigator using the following criteria:

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

7.3.1.2 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 Adverse Events and Pre-existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met serious 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 adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of the brentuximab vedotin. 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 adverse event. 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 primary event on both the CRF and an SAE form; events occurring secondary to the primary event should be described on the SAE form in the narrative description of the case.

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: Based on the estimated date of conception, complete a Pregnancy Report Form for all pregnancies that occur from the time of informed consent to the end of the protocol-defined contraception period, including any pregnancies that occur in the partner of a male study subject. Fax the form to the sponsor's Drug Safety Department within 24 hours of becoming aware of the pregnancy. All pregnancies that occur during this time period 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: Based on the estimated date of conception, all pregnancies that occur from time of informed consent to within 30 days of last study drug dose, including any pregnancies that occur in the partner of a male study subject, will also be recorded on the Adverse Events 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 7.3.1.1) should be reported as SAEs.

Potential Drug-Induced Liver Injury

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 drug-induced liver injury (DILI) 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 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 (ie, 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 serious adverse event (SAE) 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 >3xULN 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. During this investigation, consider withholding study drug.

7.3.1.3 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 (brentuximab vedotin or any component of CHP), whichever is later. However, all study protocol-related AEs are to be collected 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.

7.3.1.4 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 (or designee), 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 faxed to the sponsor's Drug Safety Department at **(425) 527-4308** within 24 hours.

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

7.3.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 7.3.1.4). The sponsor will report all SAEs, including suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities as required per local legislation or regulatory reporting requirements.

7.3.2 Vital Signs

Vital signs measures are to include heart rate, blood pressure, and temperature. Vital signs will be measured and recorded prior to the start of study drug administration at each cycle as specified in Section 6 and Appendix A.

7.3.3 Clinical Laboratory Tests

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 the central lab:

- The serum chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, uric acid, and glucose.
- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell count, platelet count, and hemoglobin/hematocrit.
- Hgb A1c will be obtained at baseline.
- A serum or urine β-hCG pregnancy test for females of childbearing potential
- eGFR >45 mL/min/1.73 m^2 using the MDRD study equation provided below.
  eGFR (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)

  Conversion to CrCl (mL/min) from eGFR using the Mosteller BSA equation and dividing by 1.73 to determine dosing holds.
  BSA (m^2) = (Height [cm] x Weight [kg] / 3600)$^{1/2}$
  CrCl (mL/min) = (eGFR [mL/min/1.73 m^2] x BSA [m^2])/1.73

7.3.4 ECOG Performance Status

ECOG performance status (see Appendix B) will be evaluated at protocol-specified time points.

7.3.5 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 and HIV viral load will be done at screening, Cycle 2 and every 4 cycles thereafter, at EOT, and should be performed according to institutional standard of care. Carriers of chronic hepatitis C should be closely monitored for clinical and laboratory signs of active infection during study treatment.

7.4 Appropriateness of Measurements

Internationally accepted criteria for the evaluation of lymphoma will be employed to assess tumor lesion size and extent of disease in the determination of PFS and response rate in this study (Cheson 2007; Cheson 2014). The schedule for tumor imaging is consistent with general oncological practice and appropriately balances measurement of tumor control with the expense and subject inconvenience associated with CT and PET scanning.

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

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, Seagen 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
- GCP 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 Seagen representative will 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 Seagen or its designated monitors and by quality assurance auditors, FDA representatives, or representatives of other regulatory agencies.

8.2 Data Management Procedures

Seagen will provide CRF Completion Guidelines for 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 be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm information contained in the CRFs, such as past history, secondary diagnoses, disease assessment records, adverse events, and concomitant medications. 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 the FDA or other regulatory agencies.

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 by the designated monitor(s) during monitoring visits to the study centers. 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 Clinical Quality Assurance group of Seagen 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.

The investigator should retain records of the changes and corrections, written and/or electronic.

Data handling procedures for this trial have been designed to permit data changes so that they are documented by an audit trail. Data changes may only be made by those individuals so authorized.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records, copies of CRFs (or electronic files), and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and Institution in which the study will be conducted, or for the period specified by Seagen, whichever is longer. The investigator must contact Seagen 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 Seagen.

9 DATA ANALYSIS METHODS

9.1 Determination of Sample Size

Clinical data from this study will be presented in a descriptive manner to demonstrate consistency with non-ALCL subjects receiving A-CHP enrolled in ECHELON-2 study. The study is designed to estimate the ORR at a reasonable level of precision. Up to approximately 80 non-sALCL PTCL subjects will be enrolled in this study, with up to approximately 40 subjects in the CD30 negative (<1%) cohort and approximately 40 subjects in the CD30 positive (1% to <10%) cohort. In the CD30 positive (1% to <10%) cohort with 40 subjects, if 28 responses are observed, the estimated ORR would be 70%, and the associated 2-sided 95% CI using the Clopper-Pearson method would be (53.5%, 83.4%). Additional possible response rates and the associated 95% confidence intervals are shown in Table 4.

Table 4: Response rates and associated 95% confidence intervals

N	Observed Responses	Response Rate	2-sided 95% CI using the Clopper-Pearson method
40	30	75%	(58.8%, 87.3%)
40	28	70%	(53.5%, 83.4%)
40	24	60%	(43.3%, 75.1%)
40	20	50%	(33.8%, 66.2%)

9.2 Study Endpoint Definitions

9.2.1 Primary Endpoint: Objective Response Rate (Cheson 2007)

The primary endpoint of this study is ORR per BICR (Cheson 2007). ORR is defined as the proportion of subjects with CR or PR following the completion of study treatment (at EOT) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Subjects whose disease response cannot be assessed will be scored as non-responders for calculating the ORR.

9.2.2 Secondary Efficacy Endpoints

9.2.2.1 Objective Response Rate (modified Lugano criteria [Cheson 2014])

ORR is defined as the proportion of subjects with CR or PR following the completion of study treatment (at EOT) according to the modified Lugano criteria (Cheson 2014). Subjects whose disease response cannot be assessed will be scored as non-responders for calculating the ORR. ORR using modified Lugano criteria (Cheson 2014) will be assessed by BICR only.

9.2.2.2 Duration of Response

DOR is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression (per Cheson 2007) or death, whichever comes first. Subjects without progression or death will be censored; details will be provided in the statistical analysis plan (SAP). DOR will only be calculated for the subset of subjects achieving a CR or PR. DOR as a secondary endpoint will be assessed by BICR.

9.2.2.3 Complete Response Rate

Complete response (CR) rate is defined as the proportion of subjects with CR following the completion of study treatment (at EOT) using Revised Response Criteria for Malignant Lymphoma criteria (Cheson 2007). Subjects whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate. The CR rate as a secondary endpoint will be assessed by BICR.

9.2.2.4 PFS

PFS is defined as the time from start of study treatment to first documentation of objective tumor progression using Revised Response Criteria for Malignant Lymphoma criteria (Cheson 2007) 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. PFS as a secondary endpoint will be assessed by BICR.

9.2.2.5 Overall Survival

Overall survival (OS) is defined as the time from first dose to death due to any cause. Specifically,

$$OS = \text{Date of death} - \text{Date of first dose} + 1$$

For a subject who is not known to have died by the end of study follow-up, observation of OS is censored on the date the subject was last known to be alive (ie, date of last contact).

Subjects lacking data beyond the day of first dose will have their survival time censored on the date of first dose (ie, OS duration of 1 day).

9.2.3 Additional Endpoints

9.2.3.1 ORR, CR rate, DOR, and PFS per Investigator

ORR, CR rate, DOR and PFS per investigator (Cheson 2007) will be assessed as additional efficacy endpoints.

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 a principal feature of the protocol. The SAP will be finalized before the database lock for the study. 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

Unless otherwise specified, tabular summaries will be presented separately by cohort, CD30 negative (<1%) and CD30 positive (≥1% and <10%) per central confirmation, and may be presented for the total.

Similar summaries for selected endpoints will be provided based on CD30 expression by local evaluation. For subjects with central CD30 ≥10% and local CD30 <10%, if any, their data will be listed, but may not be summarized if the number of such subjects is not sufficiently large.

Descriptive comparison of results from the two cohorts (CD30 <1% and CD30 ≥1% to <10%) in this study with historical data in non-ALCL subjects in ECHELON-2 study will be performed separately to demonstrate consistency.

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be used to describe continuous variables. Frequencies and percentages will be used when presenting categorical variables (eg, ORR). Time-to-event endpoints, such as PFS, will be estimated using Kaplan-Meier methodology and Kaplan-Meier plots will be presented. Medians for time-to-event analyses (eg, median PFS), will be determined and two-sided 95% confidence intervals (CIs) will be calculated using the log-log transformation method.

9.3.1.1 Randomization and Blinding

This is an open-label, single arm trial. No randomization or blinding will be utilized.

9.3.1.2 Adjustments for Covariates

Adjustments for covariates are not planned.

9.3.1.3 Handling of Dropouts and Missing Data

With the exception of the scenarios covered in this section, missing data will not be imputed.

AE dates will be imputed for the purpose of calculating duration of events and treatment-emergent status.

Subjects with missing values of a variable other than response endpoints (eg, ORR and CR rate) and time-to-event endpoints (eg, OS and PFS) will be excluded from the analysis of that endpoint. Subjects whose disease response cannot be assessed will be scored as non-responders for calculating ORR and CR rate. Censoring rules will be applied to the estimation of the distribution of the time-to-event endpoints, details will be provided in the SAP.

9.3.1.4 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough subjects to warrant an analysis by center.

9.3.1.5 Multiple Comparisons and Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed.

9.3.1.6 Data Transformations and Derivations

The date of progression will be the earliest of all radiologic scan dates for the given disease assessment. No other data transformation is planned for the primary or secondary efficacy endpoints.

9.3.1.7 Analysis Sets

Full Analysis Set: The Full Analysis Set will include all subjects who receive any amount of brentuximab vedotin or any component of CHP.

Intent to treat (ITT) Set: The ITT set will include all enrolled subjects, regardless of whether subjects receive any amount of brentuximab vedotin or any component of CHP after the completion of enrollment.

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 database cutoff date for the primary analysis will be conducted when all treated patients in the CD30 positive (≥1% and <10%) cohort have been followed for at least 6 months, discontinued from study, or had 30 days safety follow-up after PD, whichever comes first.

9.3.2 Subject Disposition

An accounting of study subjects by disposition will be tabulated by cohort. Subjects who discontinue study treatment and subjects who withdraw from the study will be summarized by cohort and reason for discontinuation or withdrawal and listed.

9.3.3 Subject Characteristics

Demographics, other baseline characteristics, and concomitant medications will be summarized by cohort and listed.

9.3.4 Treatment Compliance

The dose 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

The Full Analysis Set will be used for all efficacy analyses. Sensitivity analysis using all enrolled subjects will be conducted if appropriate.

9.3.5.1 Primary Efficacy Analyses

The primary endpoint for the study is ORR per BICR (Cheson 2007), and it will be summarized by cohort. An exact two-sided 95% confidence interval using the Clopper-Pearson method (Clopper 1934) will be calculated. The primary analysis on the primary endpoint will be conducted based on the Full Analysis Set.

In the event that there are subjects who are enrolled but not treated, a sensitivity analysis will be performed based on ITT set, where the subjects who are enrolled but not treated are counted "non-responders" in the ORR calculation.

9.3.5.2 Secondary Efficacy Analyses

ORR per BICR by modified Lugano criteria (Cheson 2014) and CR rate per BICR (Cheson 2007) will be summarized by cohort. Their exact two-sided 95% confidence intervals using the Clopper-Pearson method (Clopper 1934) will be calculated.

Time-to-event secondary endpoints including DOR, PFS per BICR (Cheson 2007) and OS will be estimated using Kaplan-Meier methodology and Kaplan-Meier plots will be presented. Medians for time-to-event analyses (median DOR, PFS and OS), will be presented and two-sided 95% confidence intervals (CIs) will be calculated using the log-log transformation method. Details on the censoring algorithm will be provided in the SAP.

9.3.5.3 Additional Efficacy Analyses

ORR, CR rate, DOR, and PFS per investigator (Cheson 2007) will be analyzed using the corresponding methods specified in Sections 9.3.5.1 and 9.3.5.2.

Details will be provided in the SAP.

9.3.6 Safety Analyses

The Full Analysis Set will be used for all safety analyses.

9.3.6.1 Extent of Exposure

Duration of treatment, number of cycles, total dose and dose intensity will be summarized by cohort. Dose modifications will also be summarized.

Details will be provided in the SAP.

9.3.6.2 Adverse Events

Adverse events will be defined as treatment emergent if they are newly occurring or worsen following treatment with brentuximab vedotin, cyclophosphamide, doxorubicin, or prednisone. The incidence of all AEs, treatment-emergent AEs, and treatment-related AEs will be tabulated by cohort. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be listed and summarized by 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 one subject, the AE will be counted once as the occurrence (if applicable, at the highest severity grade). The incidence of AEs will be tabulated by preferred term and cohort. AEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner. In addition, severity grade and resolution of each AE will be provided in data listing.

9.3.6.3 Deaths and Serious Adverse Events

Serious adverse events will be listed and summarized in the same manner as all AEs. Adverse events with a fatal outcome will be listed.

9.3.6.4 Clinical Laboratory Results

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by cohort and scheduled visit. Subjects with laboratory values outside of the normal reference range at any postbaseline assessment will be listed.

9.3.7 Interim Analysis

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 authorized representative, if applicable, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from a legally authorized representative for a subject who is unable to provide informed consent at study entry, 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 (eg, 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 federal, state, and local laws, rules, and regulations.

All data recorded in the CRF for subjects participating in this study will be transcribed from medical records or other source documents.

10.3.1 Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators 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. The clinical trial will not be terminated early due to evidence of efficacy.

10.4 Study Documentation, Privacy and Records Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator until notified by the sponsor in writing that retention is no longer necessary.

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 the requirements of the Health Information Portability and Accountability Act (HIPAA) Privacy Rule 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, case report forms 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.

11 REFERENCES

Advani RH, Horwitz SM, Iyer SP, et al. Response to A+CHP by CD30 expression in the ECHELON-2 trial. J Clin Oncol. 2019;37(Suppl 15):Abstract 7538.

Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. Ann Oncol. 1998;9(7):717-20.

Armitage JO. The aggressive peripheral T-cell lymphomas: 2017. Am J Hematol. 2017;92(7):706-15.

Bellei M, Chiattone CS, Luminari S, et al. T-cell lymphomas in South america and europe. Rev Bras Hematol Hemoter. 2012;34(1):42-7.

Bossard C, Dobay MP, Parrens M, et al. Immunohistochemistry as a valuable tool to assess CD30 expression in peripheral T-cell lymphomas: high correlation with mRNA levels. Blood. 2014;124(19):2983-6.

Cao A HR, Law C-L, Gardai SJ. Auristatin-based antibody drug conjugates activate multiple ER stress response pathways resulting in immunogenic cell death and amplified T-cell responses. Cancer Res. 2016;76(14 Supplement).

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235-42.

d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30(25):3093-9.

Dearden CE, Johnson R, Pettengell R, et al. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). Br J Haematol. 2011;153(4):451-85.

Ellin F, Landstrom J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014;124(10):1570-7.

Escalon MP, Liu NS, Yang Y, et al. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer. 2005;103(10):2091-8.

FDA. Clinical trial endpoints for the approval of cancer drugs and biologics. FDA Guidance for Industry. 2018:1-19.

Federico M, Bellei M, Luminari S, et al. CD30+ expression in peripheral T-cell lymphomas (PTCLs): a subset analysis from the international, prospective T-Cell Project. J Clin Oncol. 2015a;33(15 Suppl):Abstract 8552.

Federico M, Bellei M, Pesce EA, et al. T-cell project: an international, prospective, observational study of patients with aggressive peripheral NK/T-cell lymphoma. Lesson from the first 1308 patients. Hematol Oncol. 2015b;33(S1):136-7.

Gardai S, Heiser R, Cao A, et al. Additional, non-classical antibody-drug conjugate functions contribute to the antitumor activity of brentuximab vedotin. Proceedings of 2016 ASH Meeting on Lymphoma Biology. 2016:88-9.

Gleeson M, Peckitt C, Cunningham D, et al. Outcomes following front-line chemotherapy in peripheral T-cell lymphoma: 10-year experience at The Royal Marsden and The Christie Hospital. Leuk Lymphoma. 2018;59(7):1586-95.

Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229-40.

Hsi ED, Horwitz SM, Carson KR, et al. Analysis of peripheral T-cell lymphoma diagnostic workup in the United States. Clin Lymphoma Myeloma Leuk. 2017;17(4):193-200.

Jagadeesh D, Horwitz SM, Bartlett NL, et al. Response to brentuximab vedotin by CD30 expression: results from five trials in PTCL, CTCL, and B-cell lymphomas. J Clin Oncol. 2019;37(Suppl 15):Abstract 7543.

Kim YH, Tavallaee M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sezary syndrome with variable CD30 expression level: a multi-institution collaborative project. J Clin Oncol. 2015;33(32):3750-8.

Li F ZX, Emmerton K, Jonas M, Setter J, Arthur B, Okeley N, Lyon R, Benjamin D, Law C-L. Relationship between in vivo antitumor activity of ADC and payload release in preclinical models. Cancer Res. 2014;74(19 Supplement).

Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol. 2008;19(5):958-63.

Moskowitz AJ, Lunning MA, Horwitz SM. How I treat the peripheral T-cell lymphomas. Blood. 2014;123(17):2636-44.

Muller P, Martin K, Theurich S, et al. Microtubule-depolymerizing agents used in antibody-drug conjugates induce antitumor immunity by stimulation of dendritic cells. Cancer Immunol Res. 2014;2(8):741-55.

NCCN. *RETIRED* Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-Cell Lymphomas Version 4.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed July 18, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. 2018.

Oflazoglu E, Stone IJ, Gordon KA, et al. Macrophages contribute to the antitumor activity of the anti-CD30 antibody SGN-30. Blood. 2007;110(13):4370-2.

Reimer P, Rudiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol. 2009;27(1):106-13.

Sabattini E, Pizzi M, Tabanelli V, et al. CD30 expression in peripheral T-cell lymphomas. Haematologica. 2013;98(8):e81-2.

Savage KJ. Prognosis and primary therapy in peripheral T-cell lymphomas. Hematology Am Soc Hematol Educ Program. 2008a:280-8.

Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood. 2008b;111(12):5496-504.

Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010;116(18):3418-25.

Simon A, Peoch M, Casassus P, et al. Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol. 2010;151(2):159-66.

Sutherland MS, Sanderson RJ, Gordon KA, et al. Lysosomal trafficking and cysteine protease metabolism confer target-specific cytotoxicity by peptide-linked anti-CD30-auristatin conjugates. J Biol Chem. 2006;281(15):10540-7.

Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 2016;66(6):443-59.

Vose J, Armitage J, Weisenburger D, International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-30.

Winberg CD. Peripheral T-cell lymphoma. Morphologic and immunologic observations. Am J Clin Pathol. 1993;99(4):426-35.

Zinzani PL, Bonthapally V, Huebner D, et al. Panoptic clinical review of the current and future treatment of relapsed/refractory T-cell lymphomas: peripheral T-cell lymphomas. Crit Rev Oncol Hematol. 2016;99:214-27.

APPENDIX A: STUDY SCHEDULE

		Screening/Baseline		Treatment Period				EOT visit	Long-term F/U						
									Months after first dose						
				Cycle 1	Cycles 2+	Cycle 4 only	Last planned cycle of treatment		9	12	15	18	21	24	>24
Visit Window		D-28 to 1	D-7 to 1	D1	D1±1	Day 15-21	Day 15-21	30-37 days post last dose[f]	±1 wk						Every 6 mos ±1 wk
Screening/Baseline Assessments	Informed consent	X													
	Inclusion/exclusion	X													
	Enrollment		X												
	Medical history	X													
	Vital signs			X	X										
	CD30/histology[a]	X													
	HTLV-1 status	X													
	Hgb A1c	X													
	Echocardiogram or MUGA scan	X[k]													
	Height & weight		X												
	Electrocardiogram		X												
	Pregnancy test		X	X[m]	X[m]			X							
Treatment	Study treatment administration			X	X										
Response Assessment	Lymphoma assessment[b]			X[i]	X		X	X[f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
	CT (chest, neck, abdomen, pelvis)	X				X	X	X[f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
	PET[c]	X				X	X	X[f]							
	Bone marrow biopsy	X[d]				X[e]	X[e]	X[e,f]							
	Survival status									X[h]		X[h]		X[h]	X[h]
Safety Assessments	ECOG performance status		X		X			X							
	CD4 count for HIV positive subjects[j]	X			X[j]			X							
	HIV viral load for HIV positive subjects[j]	X			X[j]			X							
	Serum chemistry[n]		X	X	X			X							
	CBC with differential		X	X	X			X							
	Estimated glomerular filtration rate[o]		X	X	X			X							
	Con meds & AEs	Collect any related to study protocol procedures		Collect from Day 1 (predose) through 30 days post last dose or through EOT visit, whichever is later											

a. Tumor specimen must be submitted for central pathology review within 30 days of enrollment to confirm histology and CD30 expression (see Section 7.1.1 for definition of CD30-positivity).
b. Consists of the following: physical examination, subject medical history, including a thorough review of the subject's current signs and symptoms, B symptoms, and concomitant medications. See Section 7.2.
c. 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.
d. Obtained within 60 days of first dose of study treatment.
e. Bone marrow biopsy is required to confirm response if bone marrow is positive at baseline and should be obtained within 4 weeks after documentation of response; does not need to be repeated once bone marrow is negative.
g. Obtain until subject experiences PD per investigator assessment, death, or analysis of the primary endpoint, whichever comes first. Visits occurring after 24 months from first dose may be conducted via a phone call; imaging and other lymphoma assessments are optional in this setting.
h. Survival status is required every 6 months until death or study closure, whichever comes first. After 30 months, the window for the assessment is ±1 month. Collect information regarding subsequent anticancer therapies.
i. Within ≤48 hours prior to study treatment.
j. Not required if subject has experienced PD per investigator assessment
k. May be obtained up to 1 month prior to the first dose of study treatment

f. Response assessments at EOT required if not performed at last cycle of treatment. 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.

l. Monitoring of CD4 counts and HIV viral load will be done at screening, Cycle 2 and every 4 cycles thereafter, at EOT, and should be performed according to institutional standard of care (see Section 7.3.5).

m. To be performed prior to study treatment

n. The serum chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, uric acid, and glucose.

o. eGFR (mL/min/1.73 m^2) by MDRD. Converting to CrCl (mL/min) using the Mosteller BSA equation and dividing by 1.73 to determine dosing holds.

APPENDIX B: ECOG PERFORMANCE STATUS

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

APPENDIX C: 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 (12 months after the last dose of cyclophosphamide or 6 months after the last dose of other study treatment, whichever is later); 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 and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods (please see acceptable combinations below):

- 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 (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)[b]
    - All male subjects should use a condom (with pregnant/breastfeeding and non-pregnant/non-breastfeeding partners) during treatment and until the end of relevant systemic exposure in the male subject (12 months after the last dose of cyclophosphamide or 6 months after the last dose of other study treatment, whichever is later), plus a further 90-day period

a A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (eg, 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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

b A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception).

Acceptable combinations of contraceptive methods:

- Hormonal method and vasectomy
- Hormonal method and barrier method
- Intrauterine device and vasectomy
- Intrauterine device and barrier method
- Tubal ligation and vasectomy
- Tubal ligation and barrier method

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
- Barrier methods alone, including double-barrier methods

APPENDIX D: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled "A dual-cohort, open-label, phase 2 study of brentuximab vedotin and CHP (A+CHP) in the frontline treatment of subjects with peripheral T-cell lymphoma (PTCL) with less than 10% CD30 expression".

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 E: DOCUMENT HISTORY

Version	Date
Original	29-May-2020
Amendment 1	13-Aug-2020
Amendment 2	27-Oct-2020

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
CCI		
4.2	Added "Participation in other clinical trials for any condition is not allowed, other than observational studies."	Clarification
6.2, 7.1.1,, Appendix A	Clarified that tumor specimens from biopsy should be submitted within 30 days of enrollment.	Clarification
CCI		
7.3.1.2	Updated the text for "Progression of the Underlying Cancer" to align with current company standards.	Clarification
CCI		
Appendix C	Updated contraceptive guidance.	Improve subject safety
Throughout	Minor corrections to formatting, grammar, and spelling.	Clarification

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Title page	Update medical monitor	Study update
4.1, 4.2	Moved inclusion criterion #12 to Section 4.2 as an exclusion criterion.	Correction
7.3.1.2	Added drug-induced liver injury definition, reporting, and follow-up instructions	Subject safety
7.3.1.5	Updated the "Sponsor Safety Reporting to Regulatory Authorities" instructions	To expand instructions from beyond US only

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Title page, throughout	Changed Sponsor name "Seattle Genetics, Inc." to "Seagen Inc." and changed "Seattle Genetics" to "Seagen"	Sponsor update
List of Abbreviations and Definitions of Terms	Added abbreviation and definition for "DOR" Added abbreviation and definition for "ALCL" Added abbreviation and definition for "GFR" and "eGFR" Added abbreviation and definition for "CrCl" Added abbreviation and definition for "BSA" Added abbreviation and definition for "MDRD" Removed abbreviation and definition for "LDH"	Correction
1	Removed abbreviation "antibody-dependent cellular phagocytosis ~~(ADCP)~~" Removed abbreviation "endoplasmic reticulum ~~(ER)~~"	Correction
CCI		
3.2	Updated: "Based on the ECHELON-2 results, Seagen believes that ORR is a suitable **primary endpoint to demonstrate**~~surrogate for~~ clinical benefit in this dual-cohort, **single-arm** trial. **This is consistent with the recommendation outlined in FDA (FDA 2018) and EMA guidance (EMA 2017) for single-arm trials.** Progression-free survival will be analyzed as a secondary endpoint for supportive evidence."	Clarification
3.2	Added definition to first use of abbreviation "ALCL"	Correction
CCI		
4.1, 7.3.3	Changed "estimated glomerular filtration rate (eGFR) ~~≥60~~**>45** mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation **provided below**."	Expand subject inclusion
4.1, 5.4, 7.3.3	Added conversion from eGFR (mL/min/1.73 m^2) to CrCl (mL/min)	Clarification
4.1	Changed inclusion criteria 9 and 10 from "6 months following the last dose of study drug" to "12 months after the last dose of cyclophosphamide or 6 months after the last dose of other study treatment, whichever is later"	Subject safety
4.1	Added to inclusion criterion #11: "If informed consent is obtained from a legally authorized representative for a subject who is unable to provide informed consent at study entry, but the subject is later able to provide informed consent,	Subject consent

	the investigator must obtain written informed consent from the subject."	
4.2	Added to exclusion criterion #5 "or doxorubicin".	Clarification
4.2	Added exclusion criterion excluding subjects with contraindications to any study drug.	Subject safety
4.2, 5.5.3	Added exclusion criterion of live vaccines 30 days prior to the first dose of study drug and 90 days after the last dose of study drug.	Subject safety
4.3.1	Added "The study treatment will be discontinued in case of pregnancy."	Subject safety
4.3.2	Added "In case of pregnancy, study treatment must be terminated, and the subject must be withdrawn from the clinical trial."	Subject safety
5.2.5, 6.3.1	Added "Subjects will be monitored for a period of 2 hours post-infusion of brentuximab vedotin."	Subject safety
5.3.1	Added "Refer to the Summary of Product Characteristics of cyclophosphamide, doxorubicin, and prednisone for further details on each study drug and associated safety risks."	Subject safety
CCI [redacted]		
6.2, Appendix A	MUGA scan to be allowed up to 1 month prior (changed from 6 months)	Subject safety
6.2.1, Appendix A	Added serum chemistry panel definition and footnote "n"	Clarification
6.2.1, Appendix A, 6.3.1, 6.4	Added eGFR to baseline visit, every cycle: Day 1, and end-of-treatment visit Added footnote "o": "eGFR (mL/min/1.73 m^2) by MDRD. Converting to CrCl (mL/min) using the Mosteller BSA equation and dividing by 1.73 to determine dosing holds."	Clarification
6.3.1, Appendix A	Added vital signs assessments and pregnancy test on Day 1 of every cycle before study drug administration	Subject safety
7.1.1	Modified "Cutaneous~~,~~ bone~~,~~ ~~or~~ bone marrow samples~~, alone are unacceptable. F~~fine needle aspirates, and cytology samples are ~~also~~ unacceptable.	Clarification
7.2	Removed abbreviation "~~HEENT (~~skin, head, eyes, ears, nose~~, and~~ throat~~)~~, lymph nodes, heart, lungs, abdomen, back, extremities, **and** neurology"	Correction

7.3.1.2	"Fax the form to the sponsor's Drug Safety Department within ~~48~~ **24** hours of becoming aware of the pregnancy."	Subject safety
7.3.1.4	Removed ", unless otherwise instructed on the sponsor's SAE form"	Clarification
7.3.2	Added section detailing vital sign assessments	Subject safety
CCI [redacted]		
9.3.6.2	Added "(if applicable, at the highest severity grade)" Added "In addition, severity grade and resolution of each AE will be provided in data listing."	Clarification
10.3.2	Added "The clinical trial will not be terminated early due to evidence of efficacy."	Clarification
Appendix A	Modified "Cycle 1~~ / Enrollment~~" Added enrollment row in Screening/Baseline Assessments	Clarification
Appendix C	Changed "at least 2 months after the final dose of study drug" to "12 months after the last dose of cyclophosphamide or 6 months after the last dose of other study treatment, whichever is later" Added "All male subjects should use a condom (with pregnant/breastfeeding and non-pregnant/non-breastfeeding partners) during treatment and until the end of relevant systemic exposure in the male subject (12 months after the last dose of cyclophosphamide or 6 months after the last dose of other study treatment, whichever is later), plus a further 90-day period" Added "A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient."	Subject safety
Throughout	Minor corrections to formatting, style, and grammar	Clarification