Revised Clinical Study Protocol

Protocol Title:	**A Multi-center, Randomized, Double-blinded, Placebo-controlled, Multiple-ascending-dose Study of Brentuximab Vedotin in Adults With Active Systemic Lupus Erythematosus**
Protocol Number:	**SGN35-022**
Date of Protocol:	**17 February 2015**
Date of Amendment 1:	**19 May 2015**
Date of Amendment 2:	**25 July 2016**
Product:	**Brentuximab Vedotin**
IND No.:	**124561**
Study Phase:	**Phase 2a**
Sponsor:	**Seattle Genetics, Inc.** **21823 30th Drive SE** **Bothell, WA 98021, United States**
Sponsor's Representative:	[redacted]

[redacted]

SYNOPSIS

Name of Sponsor/Company:	Seattle Genetics, Inc.	[redacted]
Name of Finished Product:	Brentuximab vedotin	
Name of Active Ingredient:	Brentuximab vedotin	
Title of Study:	A Multi-center, Randomized, Double-blinded, Placebo-controlled, Multiple-ascending-dose Study of Brentuximab Vedotin in Adults With Active Systemic Lupus Erythematosus	
Protocol No:	SGN35-022	
Investigators:	Multicenter	
Study center(s):	Approximately 20 sites in the United States	
Study duration: The duration of treatment for each subject is 12 weeks. The overall duration of the study for each subject is up to 22 weeks, including the screening and follow-up periods.		**Phase:** 2a

Objectives:

Primary: to evaluate the safety and tolerability of brentuximab vedotin in adults with active systemic lupus erythematosus (SLE).

Secondary: to explore the pharmacokinetics (PK) and pharmacodynamics (PD) of brentuximab vedotin and to explore the efficacy of brentuximab vedotin in adults with active SLE.

Methodology:

This is a multicenter, randomized, placebo-controlled, double-blind, multiple-ascending-dose study to evaluate the safety and tolerability of brentuximab vedotin in subjects with active SLE. Approximately 40 subjects in 4 dosing cohorts (10 subjects per cohort) are planned at approximately 20 study sites in the United States. Subjects will be randomly assigned in a 4:1 ratio within each dosing cohort to receive intravenous (IV) brentuximab vedotin or placebo every 3 weeks for a total of 4 doses. The doses planned for each ascending dose cohort include 0.3, 0.6, 1.2, and 1.8 mg/kg.

In each dose cohort, 8 subjects will be randomly assigned to each of the 4 brentuximab vedotin doses and 2 subjects to placebo (total of 8 placebo subjects overall). Initiation of enrollment at the next dose level will only commence after the final subject of each cohort has been evaluated at the Day 43 visit, and upon endorsement of the Safety Monitoring Committee (SMC) following review of the safety data. Depending on the findings, the SMC may recommend additional enrollment of subjects at specific dose levels to better characterize the safety of a particular dose, or may recommend different dose regimens based on the emerging safety data. When available from each full cohort, the SMC will review all Day 85 safety data and may recommend that an already enrolled succeeding dose cohort be discontinued, or its treatment regimen truncated. Doses are not to exceed 1.8 mg/kg IV every 3 weeks or equivalent.

Assessments for safety (including progressive multifocal leukoencephalopathy [PML] monitoring), efficacy, PK, and PD will be performed throughout the study. Following the last dose of study drug, there will be a 6-week observation period and a final follow-up visit 3 weeks later.

Number of Subjects:

40 (10 per dosing cohort); up to 20 additional subjects may be enrolled via additional SMC-recommended cohorts for a total of up to 60 subjects.

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Diagnosis and Main Criteria for Inclusion:

Subjects must have a documented diagnosis of SLE for at least 6 months prior to screening according to both of the following:

- fulfills at least 4 of 11 of the 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of SLE; and
- has a history of positive antinuclear antibody (≥ 1:80) or anti-double-stranded deoxyribonucleic acid (≥ 30 IU/mL) test prior to screening.

Subjects must demonstrate active SLE as indicated by SLE Disease Activity Index (SLEDAI) score ≥ 4 points at screening and at baseline.

The subject must have failed at least one of the following treatments for SLE after a trial of at least 3 months:

- mycophenolate mofetil or mycophenolic acid, azathioprine, methotrexate, leflunomide, 6-mercaptopurine, calcineurin inhibitors, cyclophosphamide;
- belimumab, other B cell activating factor pathway antagonists, or abatacept; or
- antimalarials, such as hydroxychloroquine, in combination with prednisone of at least 10 mg/day or equivalent.

Test Product, Dose and Mode of Administration:

Brentuximab vedotin, 0.3 to 1.8 mg/kg administered by IV infusion over 30 minutes every 3 weeks for a total of 4 doses during the treatment period.

Reference Therapy, Dose, and Mode of Administration:

Matching placebo.

Criteria for Evaluation:

Efficacy Measures: British Isles Lupus Assessment Group (BILAG) Assessments, SLEDAI, Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), swollen joint count (SJC), tender joint count (TJC), Patient's Global Assessment of Pain (PtGP), Patient's Global Assessment of Disease Activity (PtGA), Physician's Global Assessment of Disease Activity (PhGA), Health Assessment Questionnaire-Disability Index (HAQ-DI), Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Lupus Quality of Life (LupusQoL), and high-sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR).

Pharmacokinetic Measurements: brentuximab vedotin, total antibody (TAb), and monomethyl auristatin E (MMAE) concentrations and PK parameters (when determinable: area under the concentration-time curve [AUC], clearance [CL], maximum observed concentration [C_{max}], and half-life [$t_{1/2}$]); antitherapeutic antibodies.

Pharmacodynamic Measurements: analysis of flow cytometry, inflammatory markers, antinuclear antibodies, anti-double-stranded deoxyribonucleic acid antibodies, antibody panel, complement studies, cytokines, and ribonucleic acid (RNA) analysis; optional lymph node or tonsil biopsies.

Safety: adverse events (AEs), vital signs, physical and neurological examinations, electrocardiograms, clinical laboratory evaluations, and PML monitoring.

Name of Sponsor/Company:	Seattle Genetics, Inc.
Name of Finished Product:	Brentuximab vedotin
Name of Active Ingredient:	Brentuximab vedotin

Statistical Methods:

Determination of Sample Size

Since no prior studies in SLE have been conducted with brentuximab vedotin, the primary objective of this study is to evaluate the safety and tolerability of brentuximab vedotin in this patient population. As such, the number of subjects planned has been based on clinical judgment, to provide sufficient experience upon which to design a larger efficacy (Phase 2) study. Study measurements of efficacy, safety, PK, and PD will be listed and summarized by dose and treatment group. Comparisons between brentuximab vedotin-treated subjects and placebo-treated controls will be performed, where applicable.

Statistical Considerations

For qualitative parameters, descriptive statistics (number, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum values) will be presented for each treatment. Geometric means and correlation of coefficient will be included as deemed relevant. Frequency and percentage of subjects for each treatment will be presented for categorical data.

A detailed description of all statistical analyses will be provided in a separate Statistical Analysis Plan.

Analysis Populations

Full Analysis Set (FAS): The FAS (Intent-to-Treat [ITT] Population) includes all randomized subjects. Subjects will be analyzed according to the treatment assigned.

Per-Protocol (PP): The PP Population includes all randomized subjects who have received at least 1 dose of study drug, have both the baseline and Day 85 SLE Responder Index (SRI) and have no protocol violations. Subjects will be analyzed according to the actual treatment received.

Safety: The Safety Population includes all subjects who received at least 1 dose of study drug.

Pharmacokinetic: The Pharmacokinetic Population will include all subjects who received at least 1 dose of brentuximab vedotin and for whom at least 1 plasma or serum sample was obtained for PK analysis.

Analyses of secondary efficacy endpoints will be performed on the ITT Population. Supportive analyses may be repeated using the PP Population. The PD endpoints will be analyzed using the ITT population only. All safety analyses will be based on the Safety Population. All PK analyses will be based on the Pharmacokinetic Population.

Primary Efficacy Endpoint (not applicable)

Secondary Efficacy Endpoints

The number and percentage of subjects achieving SRI response will be presented with 95% exact binomial confidence intervals (CIs). Comparisons between the active treatments and placebo will be performed through a Fisher's exact test. The nominal p-value and 95% CI for the treatment effect will be presented.

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Exploratory Efficacy Endpoints

For each continuous endpoint based on change from baseline, descriptive statistics (number, mean, median, standard deviation, minimum, maximum, and 95% CI) will be generated for each treatment group.

The overall difference between the 2 treatments in the changes from baseline will be tested using an analysis of covariance (ANCOVA) model controlling for baseline. The treatment effect will be estimated by the placebo versus brentuximab vedotin difference in least-squares means from the ANCOVA model described above. If the assumptions underlying the ANCOVA model are not met, then a nonparametric ANCOVA or a Wilcoxon Mann-Whitney test will be performed as a supplemental analysis of the parametric ANCOVA model. The nominal p-value and 95% CI for the treatment effect will be presented.

For each binary endpoint based on proportion, the number of subjects as well as the percentage within each group will be presented. Comparisons between treatments will be performed through a Fisher's exact test.

Safety

Adverse Events: Adverse events will be coded using the Medical Dictionary for Regulatory Activities and will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. Furthermore, a summary for serious AEs and summaries by severity (according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03) and relationship to study drug will be presented. Most frequent AEs and drug-related AEs will also be provided. In addition, AEs of special interest (including, but may not be limited to, PML and neuropathy) will be summarized.

Subject death due to any cause and subjects with AEs leading to study drug discontinuation will be listed and summarized.

Proportion of subjects who discontinue study drug or dose interruption due to treatment-emergent AEs will be summarized by treatment.

Laboratory values: Laboratory data will be summarized as mean change from baseline to endpoint. Shift tables will also be produced describing changes from normal to abnormal (high and low) levels or abnormal (high and low) to normal levels.

Vital Signs, Physical Findings, and Other Safety Evaluations: Vital signs will be listed and summarized over time by treatment and overall. Changes from baseline will also be summarized. Notable values and changes will be tabulated.

Electrocardiogram evaluations will be summarized by treatment and visit.

Individual listings presenting subjects with flags will be created for both changes and absolute values.

Physical and neurological examination findings will be displayed in a descriptive manner for each subject.

Interim Analysis

An SMC will review and evaluate blinded interim safety data after the final subject of each cohort has been evaluated at the Day 43 and Day 85 visits. The data from a given cohort may be unblinded for preliminary data analyses after completion of all subjects for the cohort (Day 85 and/or Day 127).

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	American College of Rheumatology
ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANCOVA	analysis of covariance
anti-dsDNA	anti-double-stranded deoxyribonucleic acid
anti-RNP	anti-ribonucleoprotein antibodies
anti-Sm	anti-Smith antibodies
anti-SSA	anti-Sjögren's Syndrome A antibodies
anti-SSB	anti-Sjögren's Syndrome B antibodies
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BAFF	B cell activating factor
BICLA	BILAG-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
CBC	complete blood count
C_{eoi}	observed concentration at end of infusion
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
C_{max}	maximum observed concentration
CNS	central nervous system
CRF	case report form
CT	computed tomography
C_{trough}	observed concentration at the end of the dosing interval
CYP3A4	cytochrome P450 enzyme 3A4
ECG	electrocardiogram

eGFR	estimated glomerular filtration rate
ERB	Ethical Review Board
ESR	erythrocyte sedimentation rate
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
HbA1c	glycosylated hemoglobin
HIV	human immunodeficiency virus
HL	Hodgkin's lymphoma
hpf	high-power field
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonization
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous(ly)
IWRS	Interactive Web Response System
JAK	Janus kinase
JCV	John Cunningham virus
LupusQoL	Lupus Quality of Life
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug
PCS	Physical Component Summary
PD	pharmacodynamic(s)

P-gp	P-glycoprotein
PhGA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PP	Per-Protocol
PtGA	Patient's Global Assessment of Disease Activity
PtGP	Patient's Global Assessment of Pain
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
sCD153	soluble CD153
sCD30	soluble CD30
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SF-36	Short Form-36
SJC	swollen joint count
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedures
SRI	SLE Responder Index
$t_{1/2}$	half-life
TAb	total antibodies
Th	T helper
TJC	tender joint count
TNF	tumor necrosis factor
TWEAK	cytokine TNF-like weak inducer of apoptosis
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

2.0 INTRODUCTION

2.1 Background

Systemic lupus erythematosus (SLE) is a chronic, multisystem, disabling autoimmune condition, which predominantly affects women of childbearing years. Its prevalence in the United States (US) is estimated to be approximately 52.2/100,000, with the highest incidence between 15 to 44 years of age at a female-to-male ratio as high as 12:1.[1-4] Clinical manifestations can involve multiple organ systems, including rash and alopecia, renal disease, inflammatory arthritis, serositis, vasculitis, autoimmune cytopenias, cognitive dysfunction and other central nervous system (CNS) involvement, and constitutional symptoms, all leading to significant morbidity including reduced physical function, employment loss, lower health-related quality of life, and reduced lifespan.[5-7]

Treatment options for SLE remain relatively limited. Some, particularly milder, cases of SLE may respond to treatment with oral antimalarial agents such as hydroxychloroquine[8,9], but moderate-to-severe disease, particularly involving critical systems such as renal or CNS, often involves immunosuppressive therapies, including oral immunosuppressants such as mycophenolate mofetil or azathioprine, as well as cyclophosphamide, calcineurin inhibitors, and B cell depleting therapy with rituximab.[10] The anti-B lymphocyte stimulator therapy, belimumab, may be particularly helpful in patients with mucocutaneous and/or musculoskeletal manifestations, but the treatment effect remains relatively small.[11] Regardless of the specific therapy chosen, the majority of patients continue to require long-term corticosteroid therapy, resulting in long-term morbidity and mortality.[6,12] Novel therapeutic options, therefore, are urgently needed.

2.2 CD30 and Systemic Lupus Erythematosus

CD30 (TNFRSF8) is a 120kD type I membrane glycoprotein of the tumor necrosis factor (TNF) receptor superfamily whose expression is largely restricted to activated T, B, and NK cells, in contrast to its ligand CD30 ligand (TNFSF8, CD153), which is expressed on many hematopoietic cells, including myeloid-derived cells, megakaryocytes, and erythroid precursors, as well as activated T cells. Signaling through CD30 may result in cellular proliferation, activation, differentiation, or apoptosis, depending on the cell type and biological context, influencing T cell tolerance, immune response contraction, and activation phenotype.[13] CD30 may play a particular role in T cell costimulation, such as during the generation and effector phases of helper T cell function[14], including T helper (Th) type 1 (Th1), Th2, and Th17 responses, and may also play a role in effector B cell differentiation,

such as during the development of plasmablasts and plasma cells – all of which have been implicated in the pathogenesis of SLE.[15-22]

Indeed, increased soluble CD30 (sCD30) levels and/or CD30+ T cells have been observed in SLE, correlating with disease activity as assessed by indices such as the European Consensus Lupus Activity Measurement.[23-27] In addition, CD30 ligand directed therapy with either a neutralizing or neutralizing and depleting antibody against CD30 ligand has been demonstrated to reduce renal disease and autoantibody production in lupus-prone NZB/W F1 mice, as well as T-dependent class-switched antibody responses.[28-30] CD30 and/or CD30 ligand expression may therefore identify a subset of pathogenic lymphocytes in SLE, and intervention upon the CD30 pathway and/or CD30+ cells may be of therapeutic benefit.

2.3 Brentuximab Vedotin

Brentuximab vedotin is an antibody-drug conjugate (ADC) consisting of: 1) the chimeric immunoglobulin (Ig) G1 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. Upon binding to the surface of CD30-expressince cells, the ADC-CD30 complex is internalized, leading via proteolytic cleavage to the release of MMAE, whose binding to tubulin disrupts the microtubule network within the cell. Brentuximab vedotin has been extensively studied and used in multiple oncology settings, particularly relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL), where CD30 is prominently expressed, and for which brentuximab vedotin is currently indicated for therapeutic use in the US, Europe, and other countries. In the Phase 2 (pivotal) studies, objective responses (complete or partial remissions) were seen in 75% of HL and 86% of ALCL. Nearly all patients (> 90%) in both studies experienced a reduction in tumor volume. Treatment-emergent adverse events (AEs) occurring in ≥ 20% of HL and systemic ALCL patients in the Phase 2 studies were peripheral sensory neuropathy (45%), fatigue (43%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (31%), neutropenia (21%), and vomiting (20%). These events were primarily Grade 1 or 2, with the exception of neutropenia, for which Grade 3 and 4 events were reported for 13% and 7% of patients, respectively. Similar patterns and incidences of AEs were generally observed for HL and ALCL patients.[31]

Additional information on the nonclinical and clinical studies conducted may be found in the Investigator's Brochure.

2.4 Rationale for the Study

Since CD30 and/or CD30-expressing immune cells appear to play key roles in the pathogenesis of SLE, brentuximab vedotin may be an efficacious therapy. At the time of writing this protocol, no prior studies have formally evaluated brentuximab vedotin in patients with SLE. However, prior to this study, the Sponsor received reports of several patients with SLE whose pre-existing autoimmune disease activity improved significantly, in the opinion of the treating rheumatologist, during brentuximab vedotin therapy administered for HL or ALCL. Therefore, this study intends to explore the potential for brentuximab vedotin as a therapy for SLE.

This first study in SLE will include patients with active disease irrespective of specific organ involvement, because it remains unclear if CD30-related immune functions play particular roles in specific end-organ manifestations. Studies in the NZB/NZW F1 lupus-prone mouse model demonstrated efficacy of intervention upon CD30 ligand upon renal endpoints[28-30], but pathogenic autoantibody production was also reduced in general. In addition, the clinical anecdotes received by the Sponsor have indicated improvement in several organ systems, including mucocutaneous and musculoskeletal. As such, there may be a more global, systemic potential for benefit. The preliminary findings from this study may help guide subsequent studies, which may focus on end organ-specific manifestations, such as nephritis.

2.5 Discussion of Study Design and Dose Selection

This will be a randomized, blinded, placebo-controlled, multiple-ascending-dose study of brentuximab vedotin in patients with SLE who have moderate to severe disease and who have failed at least one conventional therapy.

A multiple-ascending-dose design has been selected because the optimal dose regimen of brentuximab vedotin has not been determined in patients with SLE. The current standard dose regimen of brentuximab vedotin given for HL and ALCL is 1.8 mg/kg intravenously (IV) every 3 weeks, continued until disease progression or unacceptable toxicity. The tolerability of this regimen is well-understood in the oncology population and the most common adverse effects warranting treatment withdrawal or dose reduction are peripheral sensory neuropathy (45%) and neutropenia (21%).

However, partial and complete responses have been observed with brentuximab vedotin at 0.6 and 1.2 mg/kg every 3 weeks, respectively, where clinically significant peripheral neuropathy and neutropenia were not observed.[32] As such, doses of brentuximab vedotin lower than the current oncology dose of 1.8 mg/kg may prove efficacious in SLE, with less or no toxicity. Furthermore, the risks of such complications may be lower in the SLE

population due to a reduced number of prior and/or ongoing myelosuppressive and/or neuropathic medications. Simulations based on a population pharmacokinetics (PK) model developed using data from oncology patients predict that the first proposed dose level of 0.3 mg/kg will achieve serum brentuximab vedotin ADC observed concentration at the end of the dosing interval (C_{trough}) levels greater than the in vitro half-maximal inhibitory concentration (IC_{50}) against Th1 cells with 94% probability, but is expected to achieve a C_{trough} greater than the in vitro IC_{50} against Th17 cells with only 11% probability, which may be insufficient to induce remission consistently in SLE. The fourth doses of 0.3, 0.6, 1.2, and 1.8 mg/kg given every 3 weeks are expected to achieve C_{trough} greater than the in vitro IC_{50} against Th17 cells with 22%, 48%, 72%, and 83% probability, respectively, the latter of which may be sufficient, in addition to Th1 inhibition, to translate into disease remission. Therefore, 4 doses of up to 1.8 mg/kg may be appropriate to achieve sufficient brentuximab vedotin exposures in patients with SLE. As such, this study will be the first to explore the effects and tolerability of escalating doses of brentuximab vedotin in SLE; it is anticipated that the results of this study will inform the design of a longer-term, efficacy-focused Phase 2 study, since SLE often requires chronic, maintenance therapy.

In oncology patients, the median time to onset of neuropathy with brentuximab vedotin was 12.4 (HL) to 15.0 (ALCL) weeks, and the majority of neutropenia (82%) occurred within the first 4 treatment cycles, during a 1.8 mg/kg every 3 weeks dosing regimen. Given this experience, the present study proposes to examine the tolerability of a 12-week course of brentuximab vedotin (4 doses when given every 3 weeks) in patients with SLE.

Since the efficacy and tolerability of brentuximab vedotin in SLE is unknown, and many of the AEs observed with brentuximab vedotin in the oncology population may coincide with disease manifestations of SLE (eg, neuropathy or leukopenia), this study will involve a placebo comparator in a randomized, double-blind fashion. The randomization scheme proposed is anticipated to produce a cohort of placebo-treated patients comparable in size with the brentuximab vedotin cohorts, analogous to previously executed studies in SLE.[33-34]

2.6 Risk Assessment

In 2011, brentuximab vedotin (ADCETRIS®) was approved for marketing in the US for the treatment of patients with HL and ALCL, and in 2012, the product label was revised to include a Boxed Warning for progressive multifocal leukoencephalopathy (PML) and a contraindication for concomitant use of brentuximab vedotin and bleomycin. The product label dated March 2016 may be found in Appendix 4. Should the product label be updated during conduct of the current study, a revised version will be provided to the Investigators.

Primary safety concerns with brentuximab vedotin include peripheral neuropathy and neutropenia. In the pivotal trials in HL and ALCL, neutropenia of Grade 3 or higher developed after a median of 2 doses administered at 1.8 mg/kg every 3 weeks, while the median time to Grade 3 neuropathy was 36.1 to 38.0 weeks. Therefore, neutropenia appears to be a more sensitive measure of serious toxicity, and should be evident by 6 weeks in the majority of treated subjects.

A Safety Monitoring Committee (SMC) will review and evaluate unblinded interim safety data after the final subject of each cohort has been evaluated at the Day 43 (Week 6) visit. Initiation of enrollment at the next dose level will only commence after endorsement of the SMC. When available from each full cohort, the SMC will review all Day 85 safety data and may recommend that an already enrolled succeeding dose cohort be discontinued, or its treatment regimen truncated.

The peripheral neuropathy associated with brentuximab vedotin is predominantly sensory; however, cases of peripheral motor neuropathy have also been reported. Collective data suggest that peripheral neuropathy is an effect of cumulative exposure to brentuximab vedotin. In the pivotal trials in HL and ALCL, neuropathy of Grade 3 or higher developed in 13% of patients after a median of 36.1 to 38.0 weeks of brentuximab vedotin administered at 1.8 mg/kg every 3 weeks, and resolved and/or improved after a median of 16 weeks. The first onset of any grade peripheral neuropathy increased incrementally with increasing numbers of cycles, and a trend toward increased incidence of first onset of Grade 3 peripheral neuropathy and peripheral motor neuropathy in later cycles was apparent. In line with these observations, the incidences of peripheral neuropathy were highest in later cycles. Subjects in the current study will be limited to exposures of brentuximab vedotin < 12 weeks, but nonetheless will be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness.

Neutropenia was the most common hematological AE reported in the pivotal trials in HL and ALCL, where Grade 3 or higher neutropenia developed in 20% of patients after a median of 2 doses administered at 1.8 mg/kg every 3 weeks, and lasted a median of 1 week. Less than half of the patients with Grade 3 or 4 neutropenia had temporally associated infections, and the majority of temporally associated infections were Grade 1 or 2. Febrile neutropenia has been reported with brentuximab vedotin treatment. In the current study, subjects will be monitored throughout for cytopenias through routine laboratory testing.

Some cases of PML have been reported during treatment with brentuximab vedotin in the oncology setting, but a causal relationship remains unclear. As of 18 August 2014, a total of 7 cases of PML had been reported out of 14,614 patients treated, of which 3 were confirmed as PML by an independent adjudication committee, 2 were confirmed as not PML, and

2 were unable to be adjudicated. This corresponds to a rate (0.048%) not higher than the published background rate of PML in patients with lymphoproliferative disorders treated with chemotherapy (0.07% to 0.52%).[35-37] Studies on the risk of PML with other therapies, specifically natalizumab, indicate that the risk of PML is primarily increased in patients treated continuously for prolonged periods, ie, more than 12 months[38], and in subjects known to be seropositive for John Cunningham virus (JCV) antibody.[39] The present study is limited to 4 doses of brentuximab vedotin administered over 12 weeks, and will test all subjects for JCV seropositivity at screening. These results will be available to the Investigator and subject before randomization to facilitate an informed decision to proceed in the study. During the study, a clinical monitoring plan for PML, including neurological examinations, will be implemented to monitor closely for signs and symptoms suggestive of PML, which may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia, or seizures, which may occur over weeks to months.

Other warnings and precautions for the use of brentuximab vedotin, which are pertinent to a population of patients with SLE, include infusion-related reactions (including anaphylaxis), serious and opportunistic infections, Stevens-Johnson syndrome, and embryo-fetal toxicity. All doses of study drug will be administered in the clinic by appropriately trained personnel and women who are pregnant are not allowed to participate in the study. In this study, subjects will be closely monitored throughout the study for the emergence of signs or symptoms suggestive of infection or other conditions of concern.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of brentuximab vedotin in adults with active SLE.

3.2 Secondary Objectives

The secondary objectives of the study are:

- to explore the PK and pharmacodynamics (PD) of brentuximab vedotin in adults with active SLE; and
- to explore the efficacy of brentuximab vedotin in adults with active SLE.

4.0 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This is a multicenter, randomized, placebo-controlled, double-blind, multiple-ascending-dose study to evaluate the safety and tolerability of brentuximab vedotin in subjects with active SLE. Approximately 40 subjects in 4 dosing cohorts (10 subjects per cohort) are planned for study participation at approximately 20 study sites in the US. Subjects who meet inclusion and exclusion criteria will be randomly assigned in a 4:1 ratio within each dosing cohort to receive IV brentuximab vedotin or placebo every 3 weeks (Days 1, 22, 43, and 64) for a total of 4 doses. The following doses are planned for each ascending dose cohort:

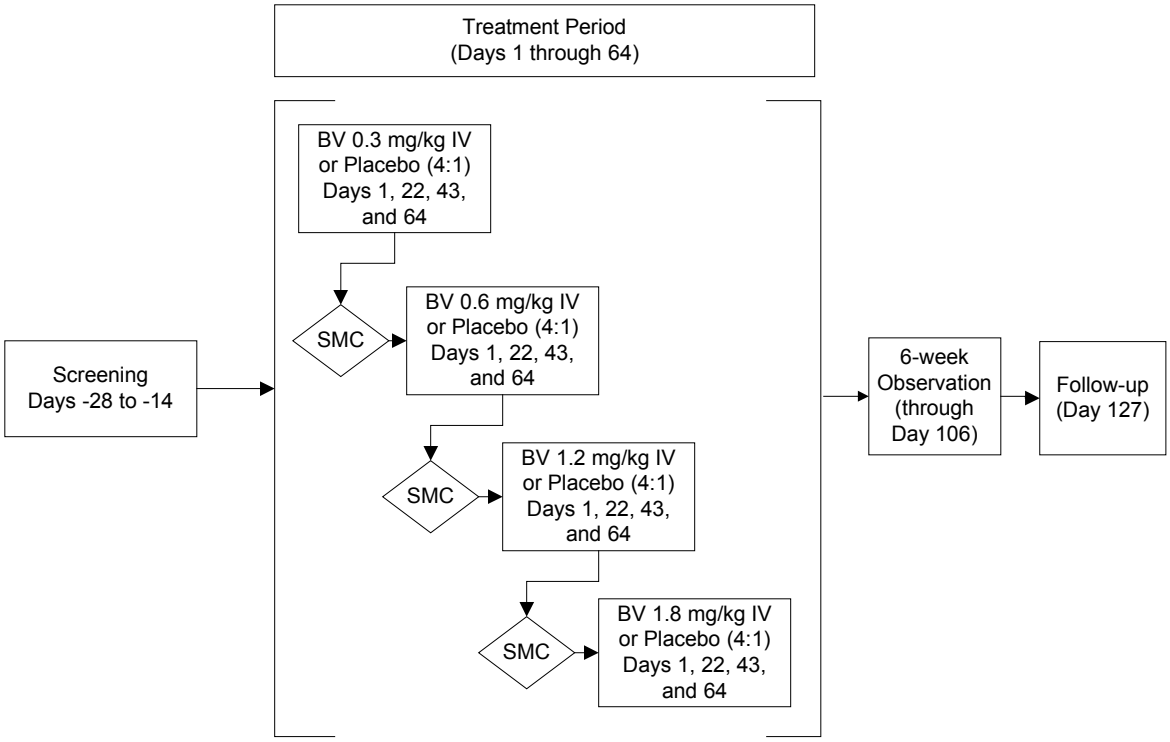
- 0.3 mg/kg IV every 3 weeks for 4 doses;
- 0.6 mg/kg IV every 3 weeks for 4 doses;
- 1.2 mg/kg IV every 3 weeks for 4 doses; and
- 1.8 mg/kg IV every 3 weeks for 4 doses.

There will be a total of 10 subjects in each dose cohort with 8 subjects randomly assigned to each of the 4 brentuximab vedotin doses and 2 subjects to placebo (for a total of 8 placebo subjects overall). Initiation of enrollment at the next dose level will only commence after the final subject of each cohort has been evaluated at the Day 43 visit, and upon endorsement of the SMC following review of the safety data. Depending on the findings, the SMC may recommend additional enrollment of subjects at specific dose levels to better characterize the safety of a particular dose, or may recommend different dose regimens based on the emerging safety data. When available from each full cohort, the SMC will review all Day 85 safety data and may recommend that an already enrolled succeeding dose cohort be discontinued, or its treatment regimen truncated. Doses are not to exceed 1.8 mg/kg IV every 3 weeks or equivalent. Up to 20 subjects total may be enrolled via additional SMC-recommended cohorts for a total of up to 60 subjects.

Assessments for safety (including PML monitoring, see Section 6.3.3), efficacy, PK, and PD will be performed at the times indicated in the schedule of events (see Table 3). Following the last dose of study drug, there will be a 6-week observation period (through Day 106) and a follow-up visit will take place at Day 127.

A flowchart of the study design is presented in Figure 1.

Figure 1 Flowchart of Study Design for Protocol SGN35-022



BV = brentuximab vedotin; IV = intravenous; SMC = Safety Monitoring Committee.

Randomization will occur on Day 1 prior to the first dose.

An SMC will review and evaluate blinded interim safety data after the final subject of each cohort has been evaluated at the Day 43 visit. Initiation of enrollment at the next dose level will only commence after endorsement of the SMC and Sponsor.

4.2 Discussion of Study Design

A discussion of the study design may be found in Section 2.5.

4.3 Study Periods

All study assessments will be performed at the times indicated in the Schedule of Events in Table 3.

4.3.1 Screening (Days -28 to -14)

After providing written informed consent, subjects will be screened for study participation between 28 and 14 days prior to study start, to allow for results of laboratory testing to be available prior to study enrollment. Subjects who fail the initial screening assessments may be rescreened, as judged appropriate by the Medical Monitor. Individual assessments (ie, clinical laboratory tests) may be repeated within the initial screening window. If the

initial screening window has passed, a full rescreening may be conducted at a later date, with agreement from the Medical Monitor. Screening assessments will include the following:

- review of inclusion and exclusion criteria (see Section 4.4);
- demographics;
- medical history;
- concomitant medications, including previously failed or intolerated SLE therapy;
- British Isles Lupus Assessment Group (BILAG), SLE disease activity index (SLEDAI), Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), swollen joint count (SJC)/tender joint count (TJC), Patient's Global Assessment of Pain (PtGP), Patient's Global Assessment of Disease Activity (PtGA), and Physician's Global Assessment of Disease Activity (PhGA) assessments (to be performed prior to other study procedures);
- chest x-ray or chest computed tomography (CT) (if not performed and documented within the last 3 months);
- physical and neurological examinations;
- height;
- measurement of vital signs (blood pressure, pulse rate, respiratory rate, temperature, and weight);
- clinical laboratory assessments (complete blood count [CBC] with differential, chemistry panel, glycosylated hemoglobin [HbA1c], B cell [CD19+] count [if applicable], urinalysis, viral serologies [including sample for JCV testing], tuberculosis testing, and serum pregnancy test for women of childbearing potential [WOCBP] only);
- collection of blood samples for flow cytometry, antinuclear antibodies (ANA), anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies, autoantibody panel, complement studies, cytokines, and ribonucleic acid (RNA) analysis; and
- recording of AEs/serious AEs (SAEs).

4.3.2 Treatment Period (Days 1 to 71)

4.3.2.1 Baseline (Day 1)

Prior to study drug administration on Day 1, subjects will be assessed to confirm that no new criteria have been met since the screening visit that would exclude the subject from entering

the study. Eligible subjects will be randomly assigned to treatment (see Section 5.3) and the following baseline assessments will be performed prior to dosing:

- BILAG, SLEDAI, CLASI, SJC/TJC, PtGP, PtGA, PhGA, Health Assessment Questionnaire-Disability Index (HAQ-DI), Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Lupus Quality of Life (LupusQoL) assessments (to be performed prior to other study procedures);
- physical and neurological (PML assessment) examinations;
- measurement of vital signs (blood pressure, pulse rate, respiratory rate, temperature, and weight);
- clinical laboratory assessments (CBC with differential, chemistry panel, B cell [CD19+] count [if applicable], fasting lipid panel, urinalysis, and urine pregnancy test for WOCBP only);

  (Note: The results of the CBC must be available prior to dosing and testing may be done by a local laboratory to facilitate availability of the results. In addition, a separate CBC sample for central laboratory testing should also be collected. Urine pregnancy testing will be performed locally only and results must be available prior to dosing.)
- 12-lead electrocardiogram (ECG);
- collection of blood samples for PK analysis (predose and end of infusion) and antitherapeutic antibodies (predose only);
- collection of blood samples for flow cytometry, inflammatory markers, ANA, anti-dsDNA antibodies, autoantibody panel, complement studies, cytokines, and RNA analysis;
- collection of pharmacogenetic sample (if applicable);
- optional lymph node or tonsil biopsy; and
- recording of AEs/SAEs and concomitant medication use.

Following completion of predose procedures, subjects will receive either brentuximab vedotin or matching placebo as an IV infusion over approximately 30 minutes. Blood samples for PK analysis will be collected prior to and at the end of the infusion; samples for antitherapeutic antibodies will be collected prior to dosing only.

4.3.2.2 Treatment

4.3.2.2.1 Days 2 and 3

On Days 2 and 3, blood samples for PK analysis, flow cytometry, anti-dsDNA antibodies, and RNA analysis will be collected. Adverse events and concomitant medication use will be recorded.

4.3.2.2.2 Day 8 (±1 day)

On Day 8 (±1 day), blood samples for PK analysis, flow cytometry, inflammatory markers, anti-dsDNA antibodies, complement studies, cytokines, and RNA analysis will be collected. In addition, blood samples for clinical laboratory assessments (CBC with differential and chemistry panel) will be collected. Adverse events and concomitant medication use will be recorded.

4.3.2.2.3 Day 15 (±2 days)

On Day 15 (±2 days), blood samples for PK analysis, flow cytometry, inflammatory markers, anti-dsDNA antibodies, complement studies, and RNA analysis will be collected. In addition, blood samples for clinical laboratory assessments (CBC with differential and chemistry panel) will be collected. Adverse events and concomitant medication use will be recorded.

4.3.2.2.4 Day 22 (±2 days)

On Day 22 (±2 days) prior to study drug administration, the following assessments will be performed:

- BILAG, SLEDAI, CLASI, SJC/TJC, PtGP, PtGA, and PhGA assessments;
- physical and neurological (PML assessment) examinations;
- measurement of vital signs (blood pressure, pulse rate, respiratory rate, temperature, and weight);
- clinical laboratory assessments (CBC with differential, chemistry panel, fasting lipid panel, urinalysis, and urine pregnancy test for WOCBP only);

  (Note: The results of the CBC must be available prior to dosing and testing may be done by a local laboratory to facilitate availability of the results. In addition, a separate CBC sample for central laboratory testing should also be collected. Urine pregnancy testing will be performed locally only and results must be available prior to dosing.)

- collection of blood samples for PK analysis (predose and end of infusion) and antitherapeutic antibodies (predose only);
- collection of blood samples for flow cytometry, inflammatory markers, ANA, anti-dsDNA antibodies, complement studies, cytokines, direct Coombs test, and RNA analysis; and
- recording of AEs/SAEs and concomitant medication use.

Following completion of predose procedures, subjects will receive either brentuximab vedotin or matching placebo as an IV infusion over approximately 30 minutes. Blood samples for PK analysis will be collected prior to and at the end of the infusion; samples for antitherapeutic antibodies will be collected prior to dosing only.

4.3.2.2.5 Day 29 (±2 days)

Approximately 1 week following the administration of study drug (Day 29 ±2 days), blood samples for clinical laboratory assessments (CBC with differential and chemistry panel) will be collected.

4.3.2.2.6 Day 43 (±2 days)

On Day 43 (±2 days) prior to study drug administration, the following assessments will be performed:

- BILAG, SLEDAI, CLASI, SJC/TJC, PtGP, PtGA, PhGA, HAQ-DI, SF-36, FACIT-F, and LupusQoL assessments;
- physical and neurological (PML assessment) examinations;
- measurement of vital signs (blood pressure, pulse rate, respiratory rate, temperature, and weight);
- clinical laboratory assessments (CBC with differential, chemistry panel, fasting lipid panel, urinalysis, and urine pregnancy test for WOCBP only);

  (Note: The results of the CBC must be available prior to dosing and testing may be done by a local laboratory to facilitate availability of the results. In addition, a separate CBC sample for central laboratory testing should also be collected. Urine pregnancy testing will be performed locally only and results must be available prior to dosing.)
- ECG;
- collection of blood samples for PK analysis (predose and end of infusion) and antitherapeutic antibodies (predose only);

- collection of blood samples for flow cytometry, inflammatory markers, ANA, anti-dsDNA antibodies, autoantibody panel, complement studies, and RNA analysis; and
- recording of AEs/SAEs and concomitant medication use.

Following completion of predose procedures, subjects will receive either brentuximab vedotin or matching placebo as an IV infusion over approximately 30 minutes. Blood samples for PK analysis will be collected prior to and at the end of the infusion; samples for antitherapeutic antibodies will be collected prior to dosing only.

4.3.2.2.7 Day 50 (±2 days)

Approximately 1 week following the administration of study drug (Day 50 ±2 days), blood samples for clinical laboratory assessments (CBC with differential and chemistry panel) will be collected.

4.3.2.2.8 Day 64 (±2 days)

On Day 64 (±2 days) prior to study drug administration, the following assessments will be performed:

- BILAG, SLEDAI, CLASI, SJC/TJC, PtGP, PtGA, and PhGA assessments;
- physical and neurological (PML assessment) examinations;
- measurement of vital signs (blood pressure, pulse rate, respiratory rate, temperature, and weight);
- clinical laboratory assessments (CBC with differential, chemistry panel, fasting lipid panel, urinalysis, and urine pregnancy test for WOCBP only);

  (Note: The results of the CBC must be available prior to dosing and testing may be done by a local laboratory to facilitate availability of the results. In addition, a separate CBC sample for central laboratory testing should also be collected. Urine pregnancy testing will be performed locally only and results must be available prior to dosing.)
- collection of blood samples for PK analysis (predose and end of infusion) and antitherapeutic antibodies (predose only);
- collection of blood samples for flow cytometry, inflammatory markers, ANA, anti-dsDNA antibodies, complement studies, cytokines, direct Coombs test, and RNA analysis; and
- recording of AEs/SAEs and concomitant medication use.

Following completion of predose procedures, subjects will receive either brentuximab vedotin or matching placebo as an IV infusion over approximately 30 minutes. Blood samples for PK analysis will be collected prior to and at the end of the infusion; samples for antitherapeutic antibodies will be collected prior to dosing only.

4.3.2.2.9 Day 71 (±2 days)

Approximately 1 week following the administration of study drug (Day 71 ±2 days), blood samples for clinical laboratory assessments (CBC with differential and chemistry panel) will be collected.

4.3.2.3 Observation

4.3.2.3.1 Day 85 (±2 days)

On Day 85 (±2 days), the following assessments will be performed:

- BILAG, SLEDAI, CLASI, SJC/TJC, PtGP, PtGA, PhGA, HAQ-DI, SF-36, FACIT-F, and LupusQoL assessments;
- physical and neurological (PML assessment) examinations;
- measurement of vital signs (blood pressure, pulse rate, respiratory rate, temperature, and weight);
- clinical laboratory assessments (CBC with differential, chemistry panel, fasting lipid panel, urinalysis, and urine pregnancy test for WOCBP only);
- ECG;
- collection of blood samples for PK analysis and antitherapeutic antibodies;
- collection of blood samples for flow cytometry, inflammatory markers, ANA, anti-dsDNA antibodies, autoantibody panel, complement studies, cytokines, and RNA analysis;
- optional lymph node or tonsil biopsy; and
- recording of AEs/SAEs and concomitant medication use.

4.3.2.3.2 Day 106 (±2 days)

On Day 106 (±2 days), the following assessments will be performed:

- BILAG, SLEDAI, CLASI, SJC/TJC, PtGP, PtGA, and PhGA assessments;
- physical and neurological (PML assessment) examination;

- measurement of vital signs (blood pressure, pulse rate, respiratory rate, temperature, and weight);
- clinical laboratory assessments (CBC with differential, chemistry panel, fasting lipid panel, and urinalysis);
- collection of blood samples for PK analysis and antitherapeutic antibodies;
- collection of blood samples for flow cytometry, inflammatory markers, ANA, anti-dsDNA antibodies, complement studies, direct Coombs test, and RNA analysis; and
- recording of AEs/SAEs and concomitant medication use.

4.3.3 Follow-up or Early Discontinuation (±7 days)

The final study visit will be conducted 3 weeks (Day 127 ±7 days) following the last observation visit or at early study termination. The following assessments will be performed:

- BILAG, SLEDAI, CLASI, SJC/TJC, PtGP, PtGA, PhGA, HAQ-DI, SF-36, FACIT-F, and LupusQoL assessments;
- physical and neurological (PML assessment) examinations;
- measurement of vital signs (blood pressure, pulse rate, respiratory rate, temperature, and weight);
- clinical laboratory assessments (CBC with differential, HbA1c, chemistry panel, and urinalysis);
- collection of blood samples for PK analysis and antitherapeutic antibodies;
- collection of blood samples for flow cytometry, inflammatory markers, ANA, anti-dsDNA antibodies, autoantibody panel, complement studies, cytokines, and RNA analysis; and
- recording of AEs/SAEs and concomitant medication use.

4.4 Selection of Study Population

4.4.1 Inclusion Criteria

Subjects may be entered in the study only if they meet all of the following criteria:

1. Subject is able to provide written, informed consent.

2. Subject is an adult, aged ≥ 18 years.

3. Women of childbearing potential or male subjects with a WOCBP partner, will use 2 forms of highly-effective contraception method during the study through 6 months following the last dose of study drug. Women of childbearing potential includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as amenorrhea ≥ 12 consecutive months without another cause, or documented follicle-stimulating hormone level > 35 mIU/mL for women with irregular menstrual periods and on hormone replacement therapy (HRT). Acceptable forms of effective contraception include: established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods of contraception (condom or occlusive cap) with spermicidal foam/gel/film/cream/suppository; male sterilization; and true abstinence. Women of childbearing potential taking concomitant mycophenolate and oral contraceptives must use a barrier method of contraception along with their oral contraceptives.

4. If subject is a WOCBP, a serum pregnancy test result at screening and urine pregnancy test result at baseline must be negative.

5. Subjects must have a documented diagnosis of SLE for at least 6 months prior to screening according to both of the following:

    a. fulfills at least 4 of 11 of the 1997 Update of the 1982 American College of Rheumatology (ACR) Revised Criteria for Classification of SLE; and

    b. has a history of positive ANA (≥ 1:80) or anti-dsDNA (≥ 30 IU/mL) test prior to screening.

6. Subjects must have a positive ANA (≥ 1:80) or anti-dsDNA (≥ 30 IU/mL) test at screening (a single rescreening of previously positive subjects who were negative at screening will be allowed).

7. Subjects must demonstrate active SLE as indicated by a SLEDAI score ≥ 4 points at screening and at baseline.

8. Subject has failed (defined as inadequate response, such as worsening or continued disease activity while on treatment) at least one of the following treatments for SLE after a trial of at least 3 months:

a. mycophenolate mofetil or mycophenolic acid, azathioprine, methotrexate, leflunomide, 6-mercaptopurine, calcineurin inhibitors, cyclophosphamide;

b. belimumab, other B cell activating factor (BAFF) pathway antagonists, or abatacept; or

c. antimalarials, such as hydroxychloroquine, in combination with prednisone of at least 10 mg/day or equivalent.

9. If taking the following medications, the subject must be on a stable dose prior to the baseline visit for at least the durations indicated and be willing and able to continue at stable doses throughout the study, unless otherwise allowed by this protocol:

   a. corticosteroids (up to 40 mg/day prednisone or equivalent): 4 weeks;

   b. hydroxychloroquine or other antimalarials: 3 months;

   c. mycophenolate mofetil or mycophenolic acid, azathioprine, methotrexate, leflunomide, or 6-mercaptopurine: 3 months; or

   d. nonsteroidal anti-inflammatory drugs (NSAIDS) or COX-2 inhibitors at or below the maximum approved dose: 2 weeks.

4.4.2 Exclusion Criteria

Subjects will not be entered in the study for any of the following reasons:

1. The subject has any serious health condition, which, in the opinion of the Investigator, would place the subject at undue risk from the study, including:

   a. uncompensated congestive heart failure (New York Heart Association Class III or IV);

   b. clinically significant active cardiac disease (eg, unstable angina or acute myocardial infarction within 3 months);

   c. recently active cerebrovascular disease (eg, stroke or transient ischemic attack within 3 months);

   d. uncontrolled hypertension, unless attributable to SLE disease activity;

   e. uncontrolled diabetes;

f. pancreatitis within the past 14 days prior to screening, unless attributable to SLE disease activity; if recent pancreatitis, must have normal amylase and lipase for 7 days prior to screening;

g. known clinically significant immunodeficiency;

h. substance abuse, such as alcoholism or drug abuse;

i. history of a known peripheral neuropathy, such as mononeuritis multiplex, acute or chronic inflammatory demyelinating polyneuropathy, axonal sensorimotor neuropathies, drug-related neuropathy or neuritis, or diabetic neuropathy;

2. Subject has had recent serious or ongoing infection, or risk for serious infection, including:

   a. active or latent tuberculosis, as suggested by chest x-ray or CT scan within the 3 months prior to screening and/or QuantiFERON-TB Gold/tuberculin purified protein derivative testing at screening (subjects with a history of latent tuberculosis with documented completed treatment by a Centers for Disease Control-recommended regimen are allowed);

   b. known history of chronic hepatitis B or hepatitis C, as suggested by serological testing;

   c. seropositivity for human immunodeficiency virus (HIV);

   d. history of PML;

   e. use of antibiotics within 2 weeks of baseline; or

   f. live vaccinations within 8 weeks of baseline.

3. Subject has screening laboratory abnormalities of any of the following criteria:

   a. hemoglobin < 10.0 g/dL;

   b. absolute neutrophil count < 1500/μL (< 1.5×10^9/L);

   c. platelet count < 100,000/μL (< 100×10^9/L);

   d. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5x upper limit of normal (ULN);

   e. serum total bilirubin > 1.5x ULN, or > 3x ULN for patients with Gilbert's syndrome;

f. serum creatinine > 1.5x ULN or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2; or

g. serum amylase or lipase > 1.5x ULN.

4. Subject has a history of new or recurrent malignancy within the past 5 years, except basal cell carcinoma of the skin, squamous cell skin cancer, or in situ carcinoma that has been adequately treated with no evidence of recurrent disease for 12 months.

5. The subject is pregnant and/or breastfeeding.

6. The subject is unable or unwilling to complete the study protocol.

7. The subject fulfills diagnostic criteria for another rheumatic (overlap) disease that may confound clinical assessments in the study. Secondary sicca or Sjögren's syndrome, antiphospholipid antibody syndrome, and overlap with rheumatoid arthritis ("rhupus") are allowed.

8. The subject is receiving treatment with any of the following within the timeframes indicated before baseline, if not otherwise previously dosed longer term according to Inclusion Criterion 9:

   a. corticosteroids: 2 weeks;

   b. cyclosporin, tacrolimus, methotrexate, leflunomide, azathioprine, 6-mercaptopurine, cyclophosphamide, tofacitinib, or other Janus kinase (JAK) inhibitors: 4 weeks;

   c. biologic therapies, including belimumab, abatacept, interleukin (IL)-6, and TNF-α (eg, infliximab, adalimumab, certolizumab pegol, or golimumab) antagonists: 8 weeks;

   d. rituximab or other B cell depleting therapies: 6 months (subjects who have been exposed to B cell depleting therapies must have a normal peripheral B cell count at baseline, if not demonstrated before); or

   e. other drugs or biologics, including investigational products: 8 weeks or 5 half-lives, whichever is longer.

9. The subject has urgent, severe SLE disease activity, which, in the opinion of the Investigator, warrants immediate immunosuppressive therapy and would not be appropriate for the study (eg, severely active neuropsychiatric SLE warranting immediate pulse corticosteroids and/or immunosuppressants such as cyclophosphamide, which makes the possibility of receiving placebo an inappropriate risk).

10. The subject has ongoing participation in another therapeutic clinical trial.

11. The subject has a known hypersensitivity to brentuximab vedotin, component thereof, or excipient contained in the drug formulation.

4.4.3 Disease Diagnostic Criteria

For participation in the study, subjects must:

- have a documented diagnosis of SLE for at least 6 months prior to screening according Inclusion Criterion 5;
- must demonstrate active SLE at screening and at baseline, as indicated in Inclusion Criterion 7; and
- have failed at least one of the treatments for SLE as listed in Inclusion Criterion 8.

4.4.4 Subject Withdrawal

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be withdrawn from the study, and the Sponsor and Quintiles must be contacted.

In addition, subjects will be withdrawn from study drug and from the study in the following circumstances:

- The Investigator decides that the subject should be withdrawn. If this decision is made because of an intolerable AE or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The Sponsor and Quintiles are to be notified immediately.
- The subject experiences a clinically significant worsening of SLE warranting a significant change in therapy according to the Investigator. The Sponsor and Quintiles are to be notified immediately.
- The subject experiences signs or symptoms suggestive of PML.
- The subject experiences any Grade 3 or higher infection.
- The subject experiences any Grade 3 (according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI-CTCAE]) or higher neutropenia (ie, absolute neutrophil count < 1.0 $\times 10^9$/L), thrombocytopenia (ie, platelet count

< 50 $\times 10^9$/L), anemia (ie, hemoglobin < 8.0 g/dL or transfusion indicated), or liver function test abnormal (ie, ALT or AST > 5x ULN) that does not correct to Grade 1 or better before the next scheduled dose of brentuximab vedotin.

- The subject experiences any Grade 3 or higher neuropathy. Dosing will be withheld for any subject who experiences Grade 2 neuropathy, but decisions to resume dosing will be made on a case-by-case basis in consultation with the Medical Monitor (see Section 5.1).
- The subject has missed more than 1 dose.
- The subject is unwilling to continue in the study.
- The subject exhibits a lack of compliance with protocol.
- The Investigator or the Sponsor, for any reason, stops the study.

Subjects who discontinue the study early will have early termination procedures performed as shown in the schedule of events (Table 3). Subjects who are withdrawn from the study will not be replaced.

4.5 Safety Monitoring Committee

An SMC consisting of Sponsor representatives as well as members independent from the Sponsor will be established. The membership should include at least 1 Sponsor representative, 1 member independent from the Sponsor, and 1 rheumatologist. The SMC will review and evaluate the blinded interim safety data after the final subject of each cohort has been evaluated at the Day 43 visit. Initiation of enrollment at the next dose level will only commence after endorsement of the SMC and Sponsor. In addition, the SMC will review neurological AEs and other safety events during the study as considered necessary. When available from each full cohort, the SMC will review all Day 85 safety data and may recommend that an already enrolled succeeding dose cohort be discontinued, or its treatment regimen truncated.

The SMC will be responsible for making recommendations as to whether it is scientifically and ethically appropriate to continue enrollment, discontinue treatment groups, or discontinue the study. Only the SMC is authorized to evaluate unblinded interim efficacy and safety analyses prior to the completion of each dosing cohort, if appropriate. Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

Details of the SMC and interim analyses will be documented in an SMC charter and SMC analysis plan. All Investigators and subjects will remain blinded to the original treatment assignments before final database lock.

5.0 STUDY TREATMENTS

5.1 Treatments Administered

Eligible subjects will receive 4 doses of either brentuximab vedotin 0.3, 0.6, 1.2, or 1.8 mg/kg IV or matching placebo, given every 3 weeks (Days 1, 22, 43, and 64) during the treatment period.

Individual doses are based on subject weight (see Section 5.5) and will be administered as an IV infusion over approximately 30 minutes. The study drug cannot be mixed with other medications.

Dose reductions are not permitted; however, dosing will be withheld if a subject experiences Grade 2 neuropathy. Resumption of dosing will be decided on a case-by-case basis by the Medical Monitor. Subjects who experience Grade 3 or higher neuropathy or who miss more than a single dose will be withdrawn from the study (see Section 4.4.4).

Further instructions on the dose preparation and administration will be provided in the Pharmacy Manual.

5.2 Identity of Investigational Product

Study drug will be provided by the Sponsor in individual kits containing four 50-mg vials. Each vial of active study drug contains 55 mg for injection (brentuximab vedotin), trehalose, sodium citrate, and polysorbate 80. The 5-mg overfill in each vial is to ensure that the labeled quantity of 50 mg may be withdrawn. Vials containing placebo are identical in appearance. The vials will be reconstituted with the appropriate amount of Sterile Water for Injection. The pH of reconstituted product is approximately 6.6. Vials and reconstituted study drug should be stored at 2° to 8°C. 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 time of use. Reconstituted vials and solutions must not be shaken.

Additional information on the storage, handling, and destruction of study drug will be provided in the Pharmacy Manual.

5.3 Method of Assigning Subjects to Treatment Group

Once the subject meets inclusion and exclusion criteria and has provided written informed consent, the study site will request the study medication assignment using the Interactive Web Response System (IWRS).

A total of 10 subjects in each dose cohort will be randomly assigned in a 4:1 ratio, resulting in 8 subjects assigned to each of the 4 brentuximab vedotin dose cohorts and a total of 8 subjects assigned to placebo (2 per cohort).

To randomly assign a subject to treatment, the study site will use the internet to access the IWRS. Subjects will be assigned their 6-digit subject number, starting with a 3-digit site number followed by a hyphen and a 3-digit sequential number (eg, 101-001). The IWRS will provide the study drug kit number(s) of the blinded study drug to be dispensed.

5.4 Selection of Doses in the Study

The doses selected for administration in this study are at or below those used for the standard regimen of brentuximab vedotin when given for HL and ALCL. See Section 2.5 for additional discussion of the dose selection.

5.5 Selection and Timing of Dose for Each Subject

Dosing is based on subject weight at baseline; however, doses will be adjusted for subjects who experience a ≥ 10% change in weight from baseline. Actual weights will be used except for subjects weighing > 100 kg; the dose for these subjects will be calculated based on 100 kg. Rounding is permissible within 5% of the nominal dose.

Subjects will receive 4 doses of study drug (either brentuximab vedotin or placebo according to the randomized treatment) given 3 weeks apart during the treatment period (Days 1, 22, 43, and 64).

5.6 Blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. Brentuximab vedotin and placebo solutions for IV administration will be identical in physical appearance. The treatment each subject will receive during the treatment period will not be disclosed to the Investigator, study site personnel, subject, Sponsor, or Quintiles. Upon request, treatment assignments will be revealed to the Investigators when the clinical study report is final. The SMC will review and evaluate blinded interim safety data after the final subject of each cohort has been evaluated at the

Day 43 visit. The data for a given cohort may be unblinded for preliminary data analyses after completion of all subjects for the cohort (Day 85 and/or Day 127).

The process for breaking the blind will be handled through the IWRS. Investigators are strongly discouraged from requesting the blind be broken for an individual subject, unless there is a subject safety issue that requires unblinding and would change subject management. Any site that breaks the blind under inappropriate circumstances may be asked to discontinue its participation in the study. If the blind is broken, it may be broken for only the subject in question and the subject must be withdrawn from the study.

The Sponsor and Quintiles must be notified immediately if a subject and/or Investigator is unblinded during the course of the study. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents and case report forms (CRFs).

5.7 Prior and Concomitant Treatments

A concomitant treatment is any drug or substance administered from the time of the subject's written informed consent until the subject's last study visit, including over-the-counter medications, herbal medications, vitamins, NSAIDS, and mineral supplements. The use of all concomitant treatments during the study, including the start and stop dates, must be recorded on the subject's CRF, according to instructions for CRF completion.

If there are changes to a concomitant medication or if the subject requires concomitant therapy for an AE, it must be reported on the appropriate CRF page and in the source medical records.

Previously failed or intolerated treatments for SLE will be recorded in the subject's CRF as a prior medication.

5.7.1 Excluded Medications

Treatment with any of the following within the timeframes indicated before baseline (if not otherwise previously dosed longer term according to Section 5.7.2) are not allowed:

- colchicine or corticosteroids: 2 weeks;
- cyclosporin, tacrolimus, methotrexate, leflunomide, azathioprine, 6-mercaptopurine, cyclophosphamide, tofacitinib, or other JAK inhibitors: 4 weeks;
- biologic therapies, including belimumab, abatacept, IL-6, and TNF-α (eg, infliximab, adalimumab, certolizumab pegol, or golimumab) antagonists: 8 weeks;

- rituximab or other B cell depleting therapies: 6 months (subjects who have been exposed to B cell depleting therapies must have a normal peripheral B cell count at baseline, if not demonstrated before);
- other drugs or biologics, including investigational products: 8 weeks or 5 half-lives, whichever is longer;
- antibiotics: 2 weeks; or
- live vaccinations: 8 weeks.

Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity (see Appendix 4); therefore, the administration of bleomycin is not allowed during this study.

5.7.2 Allowed Medications

If taking the following medications, the subject must be on a stable dose prior to the baseline visit for at least the durations indicated and be willing and able to continue at stable doses throughout the study:

- corticosteroids (up to 40 mg/day prednisone or equivalent): 4 weeks;
- hydroxychloroquine or other antimalarials: 3 months;
- mycophenolate mofetil, mycophenolic acid, azathioprine, methotrexate, leflunomide, or 6-mercaptopurine: 3 months;
- NSAIDS and COX-2 inhibitors at or below the maximum approved dose: 2 weeks; or
- Oral, injected, or implanted hormonal methods of contraception, as well as HRT: 3 months.

Temporary increases in corticosteroid dosage ("bursts") are permissible during the study as follows.

- The maximum duration of a burst is limited to 14 days duration on no more than 2 occasions.
- The corticosteroid dose must return to the preburst dose or lower at least 1 week before the 12-week assessments.
- The maximum dosage during a burst is up to 0.5 mg/kg prednisone, or equivalent, including any other steroids being given.

- The specific dose and taper schedule is at the discretion of the Investigator.

No increases in corticosteroid dosage outside of bursts are permitted. Decreases in the maintenance corticosteroid dose are allowed.

MMAE is primarily metabolized by cytochrome P450 enzyme 3A4 (CYP3A4), and is a substrate of P-glycoprotein (P-gp). Caution should be used in co-administering drugs which strongly inhibit CYP3A4 or P-gp, since increased MMAE exposures may result.

Required Premedication and Postmedication

Medication should not be administered for the prevention of infusion-related reactions prior to the first dose of brentuximab vedotin. However, subjects who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent brentuximab vedotin infusions with premedication as described in Section 6.3.2.

5.8 Treatment Compliance

All doses of study drug (including placebo) will be administered in the clinic under the supervision of the Investigator or designee and recorded in the CRFs. Therefore, no assessment of treatment compliance is planned.

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the CRFs.

5.9 Study Drug Accountability

The Investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study drug using the Drug Accountability Form. These forms must be available for inspection at any time.

6.0 EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS

6.1 Schedule of Events

A schedule of events is presented in Table 3.

6.2 Efficacy Measures

6.2.1 Response Assessments

The following response assessments will be performed at the time points indicated in the schedule of events (Table 3):

- BILAG 2004;
- SLEDAI-2K;
- CLASI[40];
- SJC – 66 joints;
- TJC – 68 joints;
- PtGP;
- PtGA;
- PhGA;
- HAQ-DI;
- SF-36;
- FACIT-F;
- LupusQoL; and
- high-sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR).

Details of these scales and assessments will be provided in the study reference manual.

6.2.2 Response Definitions

The following definitions will be used to evaluate the response assessments.

- **BILAG Clinical Response** is defined as (must meet both criteria):
  - BILAG C scores or better in all organ domains; and
  - no new BILAG A or B scores in any organ domain.
- **Systemic Lupus Erythematosus Responder Index** (SRI) definition of response includes:
  - reduction in Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI of at least 4 points;
  - no new BILAG A organ domain scores and no more than 1 new BILAG B score; and
  - no worsening (increase of < 0.3) in PhGA versus baseline.
- **BILAG-based Combined Lupus Assessment** (BICLA) definition of response includes:
  - BILAG-2004 improvement (all A scores at baseline improved to B/C/D, and all B scores improved to C or D);
  - no worsening in disease activity (no new BILAG-2004 A scores and ≤ 1 new B score);
  - no worsening of total SLEDAI-2K score from baseline;
  - no significant deterioration (< 10% worsening) in 100 mm visual analogue PhGA; and
  - no treatment failure (defined as nonprotocol treatment [ie, new or increased immunosuppressives or antimalarials or increased or parenteral corticosteroids] or premature discontinuation from study treatment).
- **Active renal disease** is defined as either:
  - both of urinary protein:creatinine ratio ≥ 0.5 and active urinary sediment as defined by at least one of the following (in the absence of urinary tract infection):
    - more than 5 red blood cells (RBCs)/high power field (hpf) (or above the reference range for the laboratory),

  - more than 5 white blood cells (WBCs)/hpf (or above the reference range for the laboratory), or
  - presence of cellular casts (RBC or WBC); or
- isolated severe proteinuria without active sediment (eg, ≥ 3.5 grams/day or equivalent).

- **SELENA SLE flare** definitions include:
  - SELENA mild/moderate flare:
    - a change in SLEDAI ≥ 3 points,
    - new/worse skin, stomatitis, serositis, arthritis, or fever,
    - increased prednisone < 0.5 mg/kg/day,
    - added NSAID/hydroxychloroquine, or
    - ≥ 1.0 increase in PhGA (on a 0 to 3 scale);
  - SELENA severe flare:
    - change in SLEDAI > 12,
    - new/worse CNS-SLE, vasculitis, nephritis, myositis, platelet count < 60,000/μL, hemolytic anemia with hemoglobin < 7 mg/dL, requiring doubling or > 0.5 mg/kg/day prednisone,
    - hospitalization for SLE,
    - prednisone > 0.5 mg/kg/day,
    - new immunosuppressive, or
    - increased PhGA to > 2.5.
- **BILAG SLE flare** definitions include:
  - BILAG flare:
    - development of any new BILAG A domain score, or
    - ≥ 2 new BILAG B domain scores;
  - BILAG severe flare: development of any new BILAG A domain score.

- **Renal flare** is defined as any of these 3 events:
  - increased proteinuria, as defined by:
    - a urinary protein:creatinine ratio > 0.5, provided the 24-hour urine protein (if done) contains a total of at least 500 mg of protein, OR
    - a reproducible increase in 24-hour urine protein levels to:
      - > 1,000 mg if the baseline value was < 200 mg,
      - > 2,000 mg if the baseline value was between 200 and 1,000 mg, or
      - more than twice the value at baseline if the baseline value was > 1,000;
  - impaired renal function, as defined by a reproducible decrease in eGFR of > 20%, accompanied by proteinuria (> 1,000 mg/24 hours), hematuria (≥ 4 RBCs/hpf or above the reference range for the laboratory), and/or cellular (RBC and WBC) casts; or
  - new hematuria, as defined by a new, reproducible hematuria (≥ 11 to 20 RBCs/hpf) or a reproducible increase in hematuria by 2 grades compared with baseline, associated with > 25% dysmorphic RBCs, glomerular in origin, exclusive of menses, accompanied by either an 800 mg increase in 24-hour urinary protein levels or new RBC casts.

6.2.3 Efficacy Endpoints

6.2.3.1 Primary

Not applicable to this study.

6.2.3.2 Secondary

The secondary endpoint is the proportion of subjects achieving an SRI response at Day 85.

6.2.3.3 Exploratory

Exploratory efficacy outcomes include the following:

- proportion of subjects achieving a BICLA response at Day 85;
- proportion of subjects achieving a BILAG clinical response at Day 85
- proportion of subjects achieving a BILAG partial clinical response at Day 85, defined as BILAG C scores or better;

- proportion of subjects achieving a BILAG partial clinical response at Day 85, defined as a maximum of 1 BILAG B score or better;
- proportion of subjects achieving a SLEDAI clinical response at Day 85, defined by a ≥ 4 point improvement from baseline;
- proportion of subjects achieving organ-specific BILAG clinical response and partial clinical responses at Day 85 as determined by organ domain-specific scores;
- proportion of subjects achieving 20%, 50%, 70%, and n% (ACR20, ACR50, ACR70, and ACRn, respectively) improvement in SJC and TJC at Days 22, 43, 64, 85, 106, and 127;
- mean and median of observed and percentage change from baseline in SLEDAI, CLASI, TJC, SJC, PtGP, PtGA, PhGA, hsCRP, and ESR at Days 22, 43, 64, 85, 106, and 127;
- mean and median of observed and percentage change from baseline in organ domain-specific SLEDAI scores at Days 22, 43, 64, 85, 106, and 127;
- mean and median of observed and percentage change from baseline in HAQ-DI, SF-36, SF-36 Physical Component Summary (PCS), SF-36 Mental Component Summary (MCS), and FACIT-F at Days 43, 85, and 127;
- mean and median of observed and percentage change from baseline in urinary sediment (cellular casts, pyuria, hematuria), proteinuria (protein/creatinine ratio), and eGFR at Days 22, 43, 64, 85, 106, and 127; and
- mean and median of observed and percentage change from baseline in urinary sediment (cellular casts, pyuria, hematuria), proteinuria (protein/creatinine ratio), and eGFR at Days 22, 43, 64, 85, 106, and 127 in subjects with active renal disease at baseline.

Additional possible exploratory efficacy outcomes include the following:

- median time to treatment failure as defined by:
  - death or need for additional immunosuppressive therapy, or
  - death, end-stage renal disease, doubling of serum creatinine, or SLE or renal flare;
- incidence at Days 22, 43, 64, 85, 106, and 127 of SLE flares using the SELENA and BILAG definitions;
- median time to first mild/moderate and severe SLE flares using SELENA and BILAG definitions;
- incidence at Days 22, 43, 64, 85, 106, and 127 of renal flares;

- median time to first renal flare;
- mean and median of observed and percentage change from Day 85 in SLEDAI, CLASI, TJC, SJC, PtGP, PtGA, PhGA, hsCRP, and ESR to Days 106 and 127;
- mean and median of observed and percentage change from Day 85 in HAQ-DI, SF-36, SF-36 PCS, SF-36 MCS, and FACIT-F to Day 127;
- mean and median of observed and percentage change from Day 85 in urinary sediment (cellular casts, pyuria, hematuria), proteinuria (protein/creatinine ratio), and eGFR to Days 106 and 127; and
- mean and median of observed and percentage change from Day 85 in urinary sediment (cellular casts, pyuria, hematuria), proteinuria (protein/creatinine ratio), and eGFR to Days 106 and 127 in subjects with active renal disease at baseline.

6.3 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs, including SAEs; recording of concomitant medications; physical and neurological examination findings; ECG recordings; and measurements of vital signs and protocol-specified laboratory tests. In addition, subjects will be closely monitored for signs and symptoms suggestive of neuropathy or PML.

6.3.1 Adverse Events

6.3.1.1 Definitions

Adverse Event

According to the International Council for Harmonization (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient 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 CRF.

- All AEs and SAEs, including AEs of special interest (eg, new-onset neuropathy or suspected cases of PML), that occur from the time of informed consent through the follow-up visit should be recorded.

- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in an SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record "anemia" rather than "low hemoglobin").

Adverse Events of Special Interest

For this study, AEs of special interest include any treatment-emergent neuropathy and suspected cases of PML (see Section 6.3.1.3 for reporting of AEs). These events will be followed until significant changes return to baseline, the event stabilizes or is no longer considered clinically significant by the Investigator, the subject dies or withdraws consent, or the study is closed.

Subjects who experience a Grade 2 neuropathy will have dosing withheld (see Section 5.1); subjects with Grade 3 or higher neuropathy will be withdrawn from the study (see Section 4.4.4).

See Section 6.3.3 for additional information on PML monitoring and Section 6.3.2 for management of infusion reactions.

Serious Adverse Event

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

- Fatal: The AE resulted in death.
- Life-threatening: The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
- Hospitalization: The AE 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 SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the

underlying study target disease need not be captured as SAEs.

- Disabling/ incapacitating: The AE 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: The AE was an adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
- Medically significant: The AE did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

Adverse Event Severity

Adverse event severity should be graded using the NCI-CTCAE, version 4.03. These criteria will be provided in the study manual.

The 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 Event).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to brentuximab vedotin should be evaluated by the Investigator using the following criteria:

- Related: There is evidence to suggest a causal relationship between the study drug and the AE, such as:
  - an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, or Stevens-Johnson syndrome); or
  - an event that is not commonly associated with study drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture).
- Unrelated: Another cause of the AE 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 AE and administration of the study drug, or a causal relationship is considered biologically implausible.

6.3.1.2 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 nondirected 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; and
- outcome.

Diagnosis Versus Signs or Symptoms

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

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI-CTCAE terms of ‘cytokine release syndrome,’ ‘acute infusion reaction,’ or ‘allergic or hypersensitivity reaction.’ Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms

occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

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

The following should be considered when recording SAEs:

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

Pregnancy

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

Collection of data on the CRF: All pregnancies (as described above) that occur within 28 days of the last dose of study drug(s), 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 in Section 6.3.1.1) should be reported as SAEs.

6.3.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from date of consent through the follow-up visit. 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. In addition, new-onset neuropathy, suspected PML, or other AEs/SAEs of interest will be reported until the end of the follow-up period.

Serious AEs 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 nonserious AEs will be followed through the safety reporting period. Certain nonserious AEs of special interest may be followed until resolution, return to baseline, the event stabilizes or is no longer considered clinically significant by the Investigator, the subject dies or withdraws consent, or study closure.

6.3.1.4 Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE or suspected case of PML, Investigators are to report the event to the Sponsor at the fax number below, regardless of the relationship of the event to the study treatment regimen.

SAE Fax: +1 (425) 527-4308

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; and
- study treatment, if known.

The completed SAE Form and SAE Fax Cover Sheet are to be faxed to the Sponsor's Drug Safety Department within 24 hours (see fax number above and as specified on the SAE report form).

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

6.3.1.5 Emergency Medical Contacts

To ensure the safety of study subjects, an Emergency Medical Call Center Help Desk will access the Quintiles Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the Investigator with a Quintiles Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. A primary global contact number and additional back up number for the Help Desk and Medical Monitor contact information will be distributed to all Investigators.

Primary: [redacted]
Secondary:

6.3.1.6 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the Sponsor (see Section 6.3.1.4).

The Sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements.

6.3.2 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 administering medications for infusion-related reactions.

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

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

6.3.3 Progressive Multifocal Leukoencephalopathy Assessment

Study site personnel and subjects will be educated regarding the signs and symptoms of PML. Close monitoring during the course of the study for any new symptoms or signs suggestive of PML will be performed, with regular neurologic examinations (including evaluation of cranial nerves, motor and sensory function, coordination, and mental status). The PML assessment will be conducted by a qualified individual and will be performed at screening and as indicated on the schedule of events (see Table 3).

If a subject has a positive finding on the PML assessment or if there is strong clinical suspicion for PML, the event should be expeditiously reported as an AE of special interest within 24 hours (see Section 6.3.1.4). If PML is suspected, dosing with study drug for that subject will be suspended and the subject should be promptly referred to a neurologist. Following formal evaluation by a neurologist, further work up will include brain magnetic resonance imaging performed with and without contrast. If PML cannot be ruled out, a

lumbar puncture with cerebrospinal fluid analysis for JCV by polymerase chain reaction may be performed. If JCV is detected, the subject should be treated as a PML case, permanently discontinue study drug, and transfer to safety follow-up. Dosing with study drug can only be resumed in subjects where PML has been ruled out.

6.3.4 Anaphylaxis

Anaphylaxis will be defined by the criteria discussed in the statement paper from the Second Symposium on the Definition and Management of Anaphylaxis[41] and reproduced in Table 1.

Table 1 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a <u>likely</u> allergen for that patient* (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *<u>known</u> allergen for that patient* (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

BP = blood pressure; PEF = peak expiratory flow.

* Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

6.3.5 Clinical Laboratory Evaluations

Samples will be drawn for both central and local laboratories. Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions.

The following laboratory assessments will be performed by the central laboratory (unless otherwise specified) to evaluate safety at scheduled time points (see Table 3) during the course of the study:

- CBC with differential: hemoglobin, hematocrit, RBC count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, WBC count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count;

  Note: The results of the CBC must be available prior to administration of each dose; therefore, testing at these time points may be done by a local laboratory to facilitate availability of the results. In addition, separate CBC samples at all specified time points should be collected for central laboratory testing.

- B cell count as quantified by CD19+ cells on flow cytometry, if applicable (for subjects with prior B cell depletion therapy, see Table 3);

- HbA1c;

- chemistry panel: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, uric acid, albumin, eGFR, glucose, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase, amylase, lipase, and creatine phosphokinase;

- eight-hour fasting lipid panel: total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein;

- urinalysis: dipstick urinalysis, spot urinary protein and creatinine, and microscopic examination of the urinary sediment; and

- pregnancy test for WOCBP (Note: testing will be performed locally only and results will be available prior to dosing).

In addition, viral serology (HIV, hepatitis B surface antigen, anti-hepatitis B surface antibody, anti-hepatitis B core antibody, hepatitis C, and JCV) and tuberculosis (QuantiFERON-TB Gold or tuberculin purified protein derivative) tests will be performed at screening only.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the laboratory value abnormality is consistent with a current diagnosis, it may be documented accordingly.

6.3.6 Vital Signs, Physical Findings, and Other Safety Assessments

Measurement of vital signs, physical examinations, and 12-lead ECG recordings will be performed at the time points indicated in the schedule of events (see Table 3) and recorded in the subject's medical records and CRF. New or worsened abnormalities from baseline should be reported as AEs, as appropriate.

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature after the subject has been seated for 5 minutes. Weight in kilograms will be measured in indoor clothing without shoes; height in centimeters is measured at screening only.

Complete physical examinations should include, but are not limited to, an assessment of head, eye, ear, nose, and throat, and cardiovascular, respiratory, gastrointestinal, musculoskeletal, dermatological, and neurological systems. See Section 6.3.3 for additional information on PML monitoring and neurological examinations.

Standard 12-lead ECGs will be recorded after the subject has rested in a supine position for at least 10 minutes and should be obtained from the same machine whenever possible. The Investigator or designee should review, sign, and date the ECG tracings. Paper copies will be filed in the subject's records at the site.

6.4 Pharmacokinetic Measurements

6.4.1 Plasma Concentrations

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

Samples for PK analysis will be collected within 30 minutes prior to study drug administration and at the end of infusion (within 5 minutes) on study drug administration days (Days 1, 22, 43, and 64). Samples will also be collected between the first and second doses on Days 2, 3, 8, and 15 at approximately the same time of day as the end-of-infusion sample on Day 1, if possible. Additional samples will be collected any time on the day of collection during the observation period (Days 85 and 106) and at the follow-up visit on Day 127.

Up to approximately 700 mL of whole blood will be obtained from each subject for PK, PD, and safety assessments during the study.

The following information will be captured for blood sample collection in each subject's CRF:

1. subject's number and initial;
2. time and date of dose administration; and
3. time and date of each blood sample collected for PK analysis.

Please refer to the Laboratory Manual for sample collection and storage procedures.

6.4.2 Antitherapeutic Antibodies

Serum samples will be collected for the detection and characterization of antibodies against brentuximab vedotin in all subjects at the time points indicated in the schedule of events (see Table 3). Samples will be analyzed using validated assays.

6.5 Pharmacodynamic Measures

Pharmacodynamic assessments will be performed as specified in the schedule of events (Table 3) and include the following:

- flow cytometry for specific lymphocyte populations that may include, but are not limited to, the following:
  - naïve T, TEM, TCM: CD4, CD30, CD45RA, CD153, CD3, CD197, and CD8;
  - Treg/Th1/Th2/Th17: CD4, CD30, CD127, CD183, CD153, CD25, CD3, CD196, CD8, and CD194;
  - naïve B, plasmablasts, plasma cells, memory B: CD19, CD30, CD38, IgD, CD153, CD10, CD27, CD138, and CD20;
  - macrophages, NK cells DCs: CD30/CD19, CD30, HLA-DR, CD16, CD153, CD11c, CD7, CD123, CD56, and CD14; and
- inflammatory markers, including: ESR, hsCRP, sCD30, and soluble CD153 (sCD153);
- autoantibody assays including, but not limited to:
  - ANA, as assessed by indirect immunofluorescence titer;
  - anti-dsDNA;
  - anti-C1q;

  - anti-Smith antibodies (anti-Sm), anti-ribonucleoprotein (anti-RNP), anti-Sjögren's Syndrome A antibodies (anti-SSA), and anti-Sjögren's Syndrome B antibodies (anti-SSB);
  - anticardiolipin, anti-β-2-glycoprotein I, lupus anticoagulant;
  - direct Coombs test; and
  - quantitative IgG, IgM, IgA, and IgE;
- complement studies: C1q, C3, C4, and CH50;
- lymph node or tonsil biopsies (optional):
  - T cell subpopulations such as, but not limited to:
    - CD4+ and CD4+CD30+, and subpopulations of each, such as: CD25+ or Foxp3+, interferon (IFN)γ+ or CXCR3+, IL-4+ or CCR4+, and IL-17+ or CCR7+;
    - CD8+ and CD8+CD30+;
  - B cell subpopulations such as, but not limited to, naïve and memory, plasmablasts and plasma cells; and
  - germinal center structure.

In addition, a serum sample will be collected for possible future testing of SLE-related cytokines, such as, but not necessarily limited to, IFN-α, BAFF, and cytokine TNF-like weak inducer of apoptosis (TWEAK).

Also, RNA sampling as specified in the schedule of events (Table 3) will consist of retention of a peripheral blood RNA sample for possible future testing of genome-wide SLE-related inflammatory gene expression patterns, such as via microarray or RNA-seq.

6.6 Pharmacogenetic Sampling

For subjects who provide additional consent, a de-identified blood sample will be collected at baseline for potential future research.

6.7 Appropriateness of Measurements

All efficacy, safety, PK, and PD assessments used in this study are widely used and generally recognized as reliable, accurate, and relevant.

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of Good Clinical Practice (GCP) (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s);
- central laboratories for clinical laboratory parameters and ECGs;
- site initiation visit;
- early site visits post enrollment;
- routine site monitoring;
- ongoing site communication and training;
- data management quality control checks;
- continuous data acquisition and cleaning;
- internal review of data; and
- quality control check of the final clinical study report.

In addition, the Sponsor and/or Quintiles Clinical Quality Assurance Department may conduct periodic audits of the study processes including, but not limited to, study site, site visits, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

7.1 Monitoring

The Sponsor has engaged the services of a contract research organization, Quintiles, to perform all monitoring functions within this clinical study. Quintiles' monitors will work in accordance with Sponsor or Quintiles' SOPs and have the same rights and responsibilities as

monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study site, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in CRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study site. They will arrange for the supply of study drug and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to the United States CFR Title 21 parts 50, 56, and 312 and ICH Guideline for GCP. Monitoring visits will be made to each site while subjects are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the CRFs will be compared with the original source documents (source data verification). For all items, this check will be 100%.

7.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of Quintiles. The data will be inspected for inconsistencies by performing validation checks.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary. Concomitant diseases will be coded using MedDRA.

7.3 Quality Assurance Audit

Study sites, the study database, and study documentation may be subject to a Quality Assurance audit during the course of the study by the Sponsor or Quintiles on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

8.0 STATISTICS

8.1 Determination of Sample Size

Since no prior studies in SLE have been conducted with brentuximab vedotin, the primary objective of this study is to evaluate the safety and tolerability of brentuximab vedotin in this patient population. As such, the number of subjects planned has been based on clinical judgment, to provide sufficient experience upon which to design a larger efficacy (Phase 2) study. Study measurements of efficacy, safety, PK, and PD will be listed and summarized by dose and treatment group. Comparisons between brentuximab vedotin-treated subjects and placebo-treated controls will be performed, where applicable.

8.2 Statistical Methods

Data will be analyzed by Quintiles Inc. biostatistical staff. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the Statistical Analysis Plan prepared by Quintiles and approved by the Sponsor before database lock.

Summaries for safety and efficacy data collected will be presented for each treatment group, ie, for brentuximab vedotin 0.3, 0.6, 1.2, or 1.8 mg/kg IV every 3 weeks and placebo at each scheduled visit/assessment. Placebo subjects across cohorts will be aggregated for analysis. Subjects will be evaluated according to the treatment received.

For qualitative parameters, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of parameters will be presented. Quantitative parameters will be summarized by the population size (N for sample size and n for available data), the mean, the standard deviation, the median, 25th percentile, 75th percentile, the minimum, and the maximum values. Geometric means and coefficients of variation will be included as deemed relevant.

A nominal significance level of 5% will be used for exploratory inference testing.

8.2.1 Analysis Populations

Assignment of subjects into the Safety, Per-Protocol (PP), Intent-to-Treat (ITT), and Pharmacokinetic Populations will be conducted prior to the database lock.

Full Analysis Set (FAS): The FAS (ITT Population) includes all randomized subjects. Subjects will be analyzed according to the treatment assigned.

Per-Protocol: The PP Population includes all randomized subjects who have received at least 1 dose of study drug, have both the baseline and Day 85 SRI and have no protocol violations. Subjects will be analyzed according to the actual treatment received.

Safety: The Safety Population includes all subjects who received at least 1 dose of study drug.

Pharmacokinetic: The Pharmacokinetic Population will include all subjects who received at least 1 dose of brentuximab vedotin and for whom at least 1 plasma or serum sample was obtained for PK analysis.

Analyses of secondary efficacy endpoints will be performed on the ITT Population. Supportive analyses may be repeated using the PP Population. The PD endpoints (see Section 6.2.3 for a description of the endpoints) may be analyzed using the ITT population only. All safety analyses will be based on the Safety Population. All PK analyses will be based on the Pharmacokinetic Population.

8.2.2 Missing Data

No imputation will be performed on any missing assessments.

8.3 Subject Disposition

The numbers of subjects who receive each treatment and the duration of exposure will be summarized for the Safety Population.

Prior and concomitant therapies will be listed. The frequency and percentage of subjects who used prior or concomitant medication will be summarized by Anatomic, Therapeutic, and Chemical classification (WHO Drug) and treatment. Concomitant medications will also be checked for protocol deviations.

Subjects who took prohibited concomitant medications will be noted in the summary of protocol deviations.

8.4 Subject Characteristics

Subject demographics will include (but are not limited to) age, sex, race, ethnicity, height, weight, and body mass index.

Continuous variables will be presented with mean, median, 25th percentile, 75th percentile, standard deviation, minimum, maximum, and (if appropriate) the number of nonmissing observations.

Categorical data will be displayed via absolute and relative frequencies for each category (including a category labeled as 'missing' when appropriate).

Furthermore, all protocol deviations will be summarized with the number (%) of subjects by deviation and listed by subject.

8.5 Efficacy Analyses

8.5.1 Primary Analyses

Not applicable to this study.

8.5.2 Secondary Analyses

The number and percentage of subjects achieving SRI response will be presented with 95% exact binomial confidence intervals (CIs). Comparisons between the active treatments and placebo will be performed through a Fisher's exact test. The nominal p-value and 95% CI for the treatment effect will be presented.

8.5.3 Exploratory Efficacy Endpoints

For each continuous endpoint based on change from baseline, descriptive statistics (number, mean, median, standard deviation, minimum, maximum, and 95% CI) will be generated for each treatment group.

The difference in the changes from baseline between the active and placebo treatments will be tested using an analysis of covariance (ANCOVA) model controlling for baseline. The treatment effect will be estimated by the difference in least-squares means (brentuximab vedotin at each dose level and overall minus placebo) from the ANCOVA model described above. If the assumptions underlying the ANCOVA model are not met, then a nonparametric ANCOVA or a Wilcoxon Mann-Whitney test will be performed as a supplemental analysis of the parametric ANCOVA model. The nominal p-value and 95% CI for the treatment effect will be presented.

For each binary endpoint based on proportion, the number of subjects as well as the percentage within each group will be presented. Comparisons between treatments will be performed through a Fisher's exact test.

8.5.4 Subgroup Analysis

Given the small sample size in this study, no subgroup analyses will be performed.

8.6 Safety

The assessment of safety will be based on the analyses of AEs, vital signs, physical examinations, ECGs, and clinical laboratory evaluations.

8.6.1 Adverse Events

Adverse events will be coded using the MedDRA dictionary and will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each system organ class, and having each individual AE as reported by preferred term. Furthermore, a summary for SAEs and summaries by severity (according to the NCI-CTCAE, version 4.03) and relationship to study drug will be presented. Most frequent AEs and drug-related AEs will also be provided. In addition, AEs of special interest will be summarized.

All percentages will be based on the number of patients in the Safety Population.

In the summaries, AEs will be counted only once per subject. If a subject reports the same AE more than once, it will be counted with its worst severity and closest relationship to study drug. Only those AEs that began between start and end of the study will be summarized.

Adverse events will also be listed by subject and treatment.

Subject death due to any cause and subjects with AEs leading to study drug discontinuation will be listed and summarized.

The proportion of subjects who discontinue study drug or dose interruption due to AEs will be summarized by treatment.

8.6.2 Clinical Laboratory Tests

Proportions of subjects who develop laboratory abnormalities of interest will be summarized by treatment.

Summary statistics over time will be presented for the continuous laboratory parameters. Descriptive statistics of changes from baseline by study visits will also be presented.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

All laboratory data will be listed with abnormal values flagged.

8.6.3 Vital Signs, Physical Findings, and Other Safety Evaluations

Observed and change-from-baseline vital signs will be listed and summarized over time by treatment. Changes from baseline will also be summarized. Notable values and changes will be tabulated.

Electrocardiogram evaluations will be summarized by treatment and visit.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum values) of the continuous ECG parameters will be presented by treatment group and overall at each assessment visit for the raw data and change from baseline data. Frequency counts will be presented per treatment for both change and absolute values.

Individual listings presenting subjects with flags will be created for both change and absolute values.

Physical and neurological examination findings will be displayed in a descriptive manner for each subject.

8.7 Pharmacokinetic Analyses

Pharmacokinetic endpoints include the following (when determinable):

- PK parameters for brentuximab vedotin (ADC), eg, maximum observed concentration (C_{max}) (concentration at the end of infusion [C_{eoi}]), area under the concentration-time curve (AUC), clearance (CL), and half-life ($t_{1/2}$);
- PK parameters for TAb, eg, C_{max} (C_{eoi}), AUC, CL, and $t_{1/2}$;
- PK parameters for MMAE, eg, C_{max}, AUC, and $t_{1/2}$; and
- the incidence of antitherapeutic antibodies.

8.8 Pharmacodynamic Analyses

Observed, change from baseline, and percentage change from baseline for all PD assessments will be listed and summarized over time by treatment. Corresponding figures for summary measures over time will be presented as relevant.

The incidence of positivity for the following will also be summarized: ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-SSA, anti-SSB, anticardiolipin, anti-β-2-glycoprotein I, lupus anticoagulant, anti-C1q, and direct Coombs test.

8.9 Interim Analyses

An SMC will review and evaluate blinded interim safety data after the final subject of each cohort has been evaluated at the Day 43 visit (see Section 4.5). The data from a given cohort may be unblinded for preliminary data analyses after completion of all subjects for the cohort (Day 85 and/or Day 127).

9.0 ETHICS

9.1 Institutional Review Board or Independent Ethics Committee

The Investigator will provide the Sponsor or Quintiles with documentation of Institutional Review Board (IRB)/Ethical Review Board (ERB) approval of the protocol and informed consent before the study may begin at the study sites. The Investigator will supply documentation to the Sponsor or Quintiles of required IRB/ERB's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/ERB, any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/ERB annually, or more frequently if requested by the IRB/ERB. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

9.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (2013), the applicable guidelines for GCP, or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

9.3 Subject Information and Informed Consent

The informed consent form will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The informed consent form contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug. The Investigator will provide each subject with a copy of the signed and dated consent form and will document in the subject's source notes that informed consent was given.

10.0 STUDY ADMINISTRATION

10.1 Administrative Structure

Table 2 provides a list of key individuals and their roles from the Sponsor and Quintiles that will contribute to this study.

Table 2 Study Administration Structure

Sponsor Representative: [redacted]	**Quintiles Medical Advisor:** [redacted]
Central Clinical Laboratory: [redacted]	**Quintiles Medical Emergency Contact:** [redacted] **Serious Adverse Event Reporting:** [redacted]

10.2 Data Handling and Record Keeping

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

The Investigator must maintain essential study documents (protocol and protocol amendments, completed CRFs, signed informed consent forms, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period if required by Sponsor; the applicable regulatory requirements; or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

10.3 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

The Investigator will allow the Sponsor, Quintiles, and authorized regulatory authorities to have direct access to all documents pertaining to the study.

10.4 Investigator Information

10.4.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (1997); the United States CFR Title 21 parts 50, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

A summary of Investigator obligations is provided in Appendix 3.

10.4.2 Protocol Signatures

The Investigator must sign the Investigator Signature Page of the Protocol (Appendix 1). By signing the protocol, the Investigator confirms in writing that he/she has read, understands, and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any site where the Investigator has not signed the protocol.

11.0 REFERENCES

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12.0 APPENDICES

APPENDIX 1: SIGNATURE OF SPONSOR AND INVESTIGATOR

SIGNATURE OF SPONSOR

PROTOCOL TITLE: A Multi-center, Randomized, Double-blinded, Placebo-controlled, Multiple-ascending-dose Study of Brentuximab Vedotin in Adults With Active Systemic Lupus Erythematosus

PROTOCOL NO: SGN35-022

Signature of Sponsor's authorized representative:

[redacted]

Date: 25 July 2016

Seattle Genetics, Inc.
21823 30th Drive SE
Bothell, WA 98021, United States

SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Multi-center, Randomized, Double-blinded, Placebo-controlled, Multiple-ascending-dose Study of Brentuximab Vedotin in Adults With Active Systemic Lupus Erythematosus

PROTOCOL NO: SGN35-022

This protocol is a confidential communication of Seattle Genetics, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Seattle Genetics, Inc.

Instructions to the Investigator: Please SIGN and DATE both copies of this signature page. PRINT your name, title, and the name of the center/address in which the study will be conducted on both copies. Return one of the signed copies to Seattle Genetics, Inc., and retain the second signed copy for the study files.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature Principal Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Multi-center, Randomized, Double-blinded, Placebo-controlled, Multiple-ascending-dose Study of Brentuximab Vedotin in Adults With Active Systemic Lupus Erythematosus

PROTOCOL NO: SGN35-022

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Instructions to the Investigator: Please SIGN and DATE both copies of this signature page. PRINT your name, title, and the name of the center/address in which the study will be conducted on both copies. Return one of the signed copies to Seattle Genetics, Inc., and retain the second signed copy for the study files.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature Principal Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

APPENDIX 2: SCHEDULE OF EVENTS

Table 3 Schedule of Events

		Screening	Baseline	Treatment										Obser-vation		Follow-up/ Early Term
	Day(s)	-28 to -14	1 (1)	2	3	8	15	22	29	43	50	64	71	85	106	127
	Visit Window					±1d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d
General	Informed consent	X														
	Inclusion/exclusion	X	X[a]													
	Demographics	X														
	Medical history	X														
	Physician present	X	X					X		X		X		X	X	X
	Clinic visit	X	X					X		X		X		X	X	X
	Home or clinic visit			X	X	X	X		X		X		X			
Safety Assessments	Physical examination	X	X					X		X		X		X	X	X
	PML assessment	X	X					X		X		X		X	X	X
	Vital signs[b]	X	X					X		X		X		X	X	X
	Height	X														
	CBC with differential[c]	X	X			X	X	X	X	X	X	X	X	X	X	X
	B cell (CD19+) count[d]	X	X													
	HbA1c	X														X
	Chemistry panel[e]	X	X			X	X	X	X	X	X	X	X	X	X	X
	Fasting lipid profile[f]		X					X		X		X		X	X	
	Viral serologies[g]	X														
	Tuberculosis testing[h]	X														
	Urinary studies[i]	X	X					X		X		X		X	X	X

Table 3 Schedule of Events

	Day(s)	Screening	Baseline	Treatment										Obser-vation		Follow-up/ Early Term
		-28 to -14	1 (1)	2	3	8	15	22	29	43	50	64	71	85	106	127
	Visit Window					±1d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d
	Pregnancy test (WOCBP)[j]	X	X					X		X		X		X		
	Chest x-ray[k]	X														
	Electrocardiogram		X							X				X		
PK/PD	Pharmacokinetic sample[Error Reference source not found.]		X	X	X	X	X	X		X		X		X	X	X
	Antitherapeutic antibodies[m]		X					X		X		X		X	X	X
	Flow cytometry[n]	X	X	X	X	X	X	X		X		X		X	X	X
	Inflammatory markers[o]		X			X	X	X		X		X		X	X	X
	ANA[p]	X	X					X		X		X		X	X	X
	Anti-dsDNA antibodies	X	X	X	X	X	X	X		X		X		X	X	X
	Autoantibody panel[q]	X	X					X[r]		X		X[r]		X	X[r]	X
	Complement studies[s]	X	X			X	X	X		X		X		X	X	X
	Cytokines[t]	X	X			X		X				X		X		X
	RNA sample[u]	X	X	X	X	X	X	X		X		X		X	X	X
	Lymph node or tonsil biopsy[v]		X											X		
Pharmaco-genetic	DNA sample[w]		X													
Efficacy Assessments[x]	BILAG	X	X					X		X		X		X	X	X
	SLEDAI	X	X					X		X		X		X	X	X
	CLASI	X	X					X		X		X		X	X	X

Table 3 Schedule of Events

	Day(s)	Screening	Baseline	Treatment										Obser-vation		Follow-up/ Early Term
		-28 to -14	1 (1)	2	3	8	15	22	29	43	50	64	71	85	106	127
	Visit Window					±1d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d
	SJC/TJC	X	X					X		X		X		X	X	X
	PtGP, PtGA, PhGA	X	X					X		X		X		X	X	X
	HAQ-DI, SF-36, FACIT-F, LupusQoL		X							X				X		X
General Monitoring	Concomitant medications	X	X	X	X	X	X	X		X		X		X	X	X
	Adverse events	X	X	X	X	X	X	X		X		X		X	X	X
Treatment	Randomization		X													
	Study drug administration[Error Reference source not found.,y]		X					X		X		X				

ALT = alanine aminotransferase; ANA = antinuclear antibodies; anti-dsDNA = anti-double-stranded deoxyribonucleic acid; anti-RNP = anti-r bonucleoprotein; anti-Sm = anti-Smith ant body; anti-SSA = anti-Sjögren's Syndrome A antibodies; anti-SSB = anti-Sjögren's Syndrome B antibodies; AST = aspartate aminotransferase; BAFF = B cell activating factor; BILAG = British Isles Lupus Assessment Group; CBC = complete blood count; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI = Health Assessment Questionnaire-Disability Index; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IFN = interferon; Ig = immunoglobulin; JCV = John Cunningham virus; LupusQoL = Lupus Quality of Life; PD = pharmacodynamic; PhGA = Physician's Global Assessment of Disease Activity; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PtGA = Patient's Global Assessment of Disease Activity; PtGP = Patient's Global Assessment of Pain; RBC = red blood cell; RNA = r bonucleic acid; sCD153 = soluble CD153; sCD30 = soluble CD30; SF-36 = Short Form-36; SJC = swollen joint count; SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; TJC = tender joint count; TNF = tumor necrosis factor; TWEAK = cytokine TNF-l ke weak inducer of apoptosis; WBC = white blood cell; WOCBP = women of childbearing potential.

[a] Continuing study eligibility will be confirmed at the Baseline Visit.

[b] Vital signs include blood pressure, pulse rate, respiratory rate, temperature, and weight.

[c] Complete blood count with differential to include hemoglobin, hematocrit, RBC count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distr bution width, WBC count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count. Results must be available prior to dosing; therefore, an additional sample may be collected for local laboratory testing on Days 1, 22, 43, and 64. The predose sample on these days should still be collected for central laboratory testing.

[d] B cell count for subjects with prior B cell depletion therapy, such as rituximab. Baseline testing may be omitted for subjects with normal counts at screening.

[e] Chemistry panel includes: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, a bumin, eGFR, glucose, total and direct bilirubin, ALT, AST, a kaline

Table 3 Schedule of Events

		Screening	Baseline	Treatment										Obser-vation		Follow-up/ Early Term
	Day(s)	-28 to -14	1 (1)	2	3	8	15	22	29	43	50	64	71	85	106	127
	Visit Window					±1d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d

phosphatase, lactate dehydrogenase, uric acid, amylase, lipase, and creatine phosphokinase.

[f] Eight-hour fasting lipid profile includes total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein.

[g] Viral serologies include tests for HIV, hepatitis B (surface antigen, surface antibody, and core antibody), hepatitis C, and JCV.

[h] Tuberculosis testing involves QuantiFERON-TB Gold or tuberculin purified protein derivative.

[i] Urinary studies include dipstick urinalysis, spot urinary protein and creatinine, and microscopic examination. Urine samples will be collected and stored for future exploratory analysis.

[j] Urine pregnancy tests will be performed by the local laboratory only.

[k] Chest x-ray or CT scan at screening, unless documented within the last 3 months.

[l] Pharmacokinetic samples will be collected within 30 minutes prior to dosing and within 5 minutes after the end of infusion on study drug administration days (Days 1, 22, 43, and 64). On Days 2, 3, 8, and 15, PK samples will be collected at approximately the same time of day as the end of infusion sample on Day 1, if possible. On Days 85, 106, and 127, PK samples may be collected at any time of day.

[m] Samples for antitherapeutic antibodies are collected prior to dosing only.

[n] Flow cytometry includes assessments for lymphocyte populations. A separate peripheral blood mononuclear cell sample will be retained for future exploratory analysis.

[o] Inflammatory markers include ESR, hsCRP, sCD30, and sCD153. A replicate serum sample will be retained for future exploratory analysis.

[p] Antinuclear antibodies consists of immunofluorescence testing. A replicate serum sample will be retained for future exploratory analysis.

[q] Autoantibody panel includes anti-Sm, anti-RNP, anti-SSA, anti-SSB, lupus anticoagulant, anti-β-2-glycoprotein I, anticardiolipin, anti-C1q, direct Coombs test, and quantitative IgG, IgM, IgA, and IgE.

[r] Direct Coombs test only.

[s] Complement studies include C3, C4, CH50, and C1q.

[t] Cytokines indicates retention of a serum sample for poss ble future testing of SLE-related cytokines, such as IFN-α, BAFF, or TWEAK.

[u] Sample consists of retention of a peripheral blood RNA sample for possible future testing of genome-wide SLE-related inflammatory gene expression patterns, such as via microarray or RNA-seq.

[v] Optional. For each subject, location of this tissue collection should remain consistent throughout the study. May include analyses of CD30+ T and B cell populations and germinal center structure.

[w] Optional sample for subjects who have provided separate informed consent. The sample will be collected in a Vacutainer™ tube containing ethylenediaminetetraacetic acid as an anticoagulant and stored frozen until use.

[x] Quality of life questionnaires should be completed prior to other study assessments scheduled for the same visit.

[y] Randomization occurs prior to study drug administration.

APPENDIX 3: INVESTIGATOR RESPONSIBILITIES

Per Good Clinical Practices 21CFR312.53

The Investigator:

- Will conduct the study in accordance with the relevant, current protocol and will only make changes in the protocol after notifying the Sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;
- Will comply with all requirements regarding the obligations of clinical Investigators and all other pertinent requirements;
- Will personally conduct or supervise the described investigation;
- Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and Institutional Review Board (IRB) review and approval are met.
- Will report to the Sponsor adverse experiences that occur in the course of the investigation in accordance with Section 312.64;
- Has read and understands the information in the Investigator's Brochure, including the potential risks and side effects of the drug; and
- Will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

Per Good Clinical Practices 21CFR312.60

General Responsibilities of Investigators:

An Investigator is responsible for ensuring that an investigation is conducted according to the signed Investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of drugs under investigation. An Investigator shall, in accordance with the provisions of part 50, obtain the informed consent of each human subject to whom the drug is administered, **except as provided in CFR50.23.**

Obligations of the Investigator

The Investigator Shall:

- Maintain IRB approval to conduct the clinical trial and report to the IRB as required. The IRB must assume continued responsibility for the study and review the research on at least an annual basis;
- Maintain a file of all communications with the IRB on issues related to the clinical trial;
- Complete, sign, and return to Quintiles a Food and Drug Administration (FDA) Form 1572 including a current curricula vitae (CV) for the Principal Investigator and Sub-Investigator(s), if listed;
- Conduct the study in strict adherence to the protocol;
- Supervise the use of the study drug as outlined in the protocol. The study drug may only be provided by staff working under the supervision of the Investigator;
- Store the study drug in a secure and locked area with limited access. The storage and custody of the study drug are the responsibilities of the Investigator;
- Maintain adequate records of the receipt and disposition of all study drug (including dates, quantities, and use by study subjects);
- Inform each subject of the risks and benefits of participating in the study and obtain a properly signed, dated, and witnessed (if applicable) informed consent form for each subject before he or she begins any study-related procedures;
- Document all adverse events on the case report forms (CRFs); document all serious adverse events (SAEs) on the SAE Form and immediately notify Sponsor and Quintiles via phone and fax;
- Report all SAEs to the IRB;
- Maintain a master log of all subjects screened for the study and establish a system to alert clinic staff of scheduled follow-up visits; provide clinic staff with a system for contacting study subjects who do not return for scheduled follow-up;
- Document and maintain accurate CRFs for all subjects. As required, sign forms ascertaining the accuracy of data recorded. Storage and custody of all study-related records are the responsibility of the Investigator;
- Retain the copies of the CRFs, the original informed consent forms, and all study-related documentation at the study site for a period of fifteen (15) years after termination of the

study unless Quintiles authorizes, in writing, earlier destruction. Notify Quintiles before destroying any study records after the required retention period. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained;

- Make available all study subjects' records to staff and representatives from Quintiles, Sponsor and FDA or other Regulatory Agency personnel;
- Return to Sponsor or their agent, study materials (which may include unused study supplies) following completion, discontinuation, or suspension of the study;
- Be thoroughly familiar with the properties of the investigational agent as described in the Clinical Investigator Brochure;
- Ensure that sufficient time is allotted to conduct and complete the study; ensure adequate staff and facilities are available for the duration of the study; and ensure that other studies do not divert essential subjects or facilities from the study at hand;
- Provide information to all staff members involved with the study or with other elements of the subject's management;
- Notify Quintiles and Sponsor in the event the blind is broken; and
- Ensure that the confidentiality of all information about subjects and the information supplied by Quintiles and Sponsor is respected by all persons.

APPENDIX 4: ADCETRIS (BRENTUXIMAB VEDOTIN) PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADCETRIS safely and effectively. See full prescribing information for ADCETRIS.

ADCETRIS® (brentuximab vedotin) for injection, for intravenous use

Initial U.S. approval: 2011

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
See full prescribing information for complete boxed warning.

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS (5.9, 6.1).

RECENT MAJOR CHANGES

Indications and Usage (1.2)	08/2015
Dosage and Administration (2.1)	08/2015
Warnings and Precautions (5)	03/2016

INDICATIONS AND USAGE

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for treatment of patients with:

- Classical Hodgkin lymphoma (HL) after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates (1.1).
- Classical HL at high risk of relapse or progression as post-auto-HSCT consolidation (1.2).
- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen (1.3).

  Accelerated approval was granted for the sALCL indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION

- Administer only as an intravenous infusion over 30 minutes every 3 weeks.
- The recommended dose is 1.8 mg/kg (2).
- Reduce dose in patients with mild hepatic impairment (2).

DOSAGE FORMS AND STRENGTHS

For injection: 50 mg lyophilized powder in a single-use vial (3).

CONTRAINDICATIONS

Concomitant use with bleomycin due to pulmonary toxicity (4).

WARNINGS AND PRECAUTIONS

- Peripheral neuropathy: Monitor patients for neuropathy and institute dose modifications accordingly (5.1).
- Anaphylaxis and infusion reactions: If an infusion reaction occurs, interrupt the infusion. If anaphylaxis occurs, immediately discontinue the infusion (5.2).
- Hematologic toxicities: Monitor complete blood counts prior to each dose of ADCETRIS. Closely monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses (5.3).
- Serious infections and opportunistic infections: Closely monitor patients for the emergence of bacterial, fungal or viral infections (5.4).
- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor or high tumor burden (5.5).
- Hepatotoxicity: Monitor liver enzymes and bilirubin (5.8).
- Pulmonary toxicity: Monitor patients for new or worsening symptoms (5.10).
- Serious dermatologic reactions: Discontinue if Stevens-Johnson syndrome or toxic epidermal necrolysis occurs (5.11).
- Gastrointestinal complications: Monitor patients for new or worsening symptoms (5.12).
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy (5.13).

ADVERSE REACTIONS

The most common adverse reactions (≥20%) were:

- Relapsed classical HL and relapsed sALCL: neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting (6.1).
- Classical HL post-auto-HSCT consolidation: neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough, and diarrhea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Seattle Genetics, Inc. at 1-855-473-2436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE) (7.1).

USE IN SPECIFIC POPULATIONS

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use (5.6, 5.7, 8.6, 8.7).

Lactation: Breastfeeding not recommended (8.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS *[see Warnings and Precautions (5.9), Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Classical Hodgkin Lymphoma (HL)

ADCETRIS is indicated for treatment of patients with classical HL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.

1.2 Classical Hodgkin Lymphoma (HL) Post-auto-HSCT Consolidation

ADCETRIS is indicated for the treatment of patients with classical HL at high risk of relapse or progression as post-auto-HSCT consolidation *[see Clinical Studies (14.1)]*.

1.3 Systemic Anaplastic Large Cell Lymphoma (sALCL)

ADCETRIS is indicated for treatment of patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen.

The sALCL indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Recommendations

Administer ADCETRIS as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. See Table 1 for the recommended starting dosage.

For classical HL post-auto-HSCT consolidation treatment, initiate ADCETRIS treatment within 4–6 weeks post-auto-HSCT or upon recovery from auto-HSCT. These patients should continue treatment until a maximum of 16 cycles, disease progression, or unacceptable toxicity.

Table 1: Recommended ADCETRIS Dosage

	Recommended Starting Dosage
Normal renal and hepatic function	1.8 mg/kg up to 180 mg
Renal impairment	
Mild (creatinine clearance >50–80 mL/min) or moderate (creatinine clearance 30–50 mL/min)	1.8 mg/kg up to 180 mg
Severe (creatinine clearance less than 30 mL/min)	Avoid use *[see Warnings and Precautions (5.6)]*
Hepatic impairment	
Mild (Child-Pugh A)	1.2 mg/kg up to 120 mg
Moderate (Child-Pugh B) or severe (Child-Pugh C)	Avoid use *[see Warnings and Precautions (5.7)]*

2.2 Dose Modification

Peripheral Neuropathy: For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. For Grade 4 peripheral neuropathy, ADCETRIS should be discontinued.

Neutropenia: The dose of ADCETRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Consider G-CSF prophylaxis for subsequent cycles in patients who experience Grade 3 or 4 neutropenia in the previous cycle**.** In patients with recurrent Grade 4 neutropenia despite the use of G-CSF prophylaxis, consider discontinuation or dose reduction of ADCETRIS to 1.2 mg/kg.

2.3 Instructions for Preparation and Administration

Administration

- Administer ADCETRIS as an intravenous infusion only.
- **Do not mix ADCETRIS with, or administer as an infusion with, other medicinal products.**

Reconstitution

- Follow procedures for proper handling and disposal of anticancer drugs *[see References (15)]*.
- Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
- Determine the number of 50 mg vials needed based on the patient's weight and the prescribed dose *[see Dosage and Administration (2.1)]*.
- Reconstitute each 50 mg vial of ADCETRIS with 10.5 mL of Sterile Water for Injection, USP, to yield a single-use solution containing 5 mg/mL brentuximab vedotin.
- Direct the stream toward the wall of vial and not directly at the cake or powder.
- Gently swirl the vial to aid dissolution. **DO NOT SHAKE**.

- Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates.
- Following reconstitution, dilute immediately into an infusion bag. If not diluted immediately, store the solution at 2–8°C (36–46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**
- Discard any unused portion left in the vial.

Dilution

- Calculate the required volume of 5 mg/mL reconstituted ADCETRIS solution needed.
- Withdraw this amount from the vial and immediately add it to an infusion bag containing a minimum volume of 100 mL of 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection to achieve a final concentration of 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin.
- Gently invert the bag to mix the solution.
- Following dilution, infuse the ADCETRIS solution immediately. If not used immediately, store the solution at 2–8°C (36–46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**

3 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder in a single-use vial for reconstitution.

4 CONTRAINDICATIONS

ADCETRIS is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation) *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative. In the relapsed classical HL and sALCL clinical trials, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCETRIS *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.2 Anaphylaxis and Infusion Reactions

Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management

instituted. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

5.3 Hematologic Toxicities

Prolonged (≥1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with treatment with ADCETRIS. Complete blood counts should be monitored prior to each dose of ADCETRIS and more frequent monitoring should be considered for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCETRIS doses *[see Dosage and Administration (2.2)]*.

5.4 Serious Infections and Opportunistic Infections

Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Patients should be closely monitored during treatment for the emergence of possible bacterial, fungal, or viral infections.

5.5 Tumor Lysis Syndrome

Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.6 Increased Toxicity in the Presence of Severe Renal Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment [creatinine clearance (CLcr) <30 mL/min] *[see Use in Specific Populations (8.6)]*.

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Use in Specific Populations (8.7)]*.

5.8 Hepatotoxicity

Serious cases of hepatotoxicity, including fatal outcomes, have occurred in patients receiving ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADCETRIS or after ADCETRIS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin.

Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

5.9 Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity

Events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

5.11 Serious Dermatologic Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

5.12 Gastrointestinal Complications

Fatal and serious gastrointestinal (GI) complications including perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus have been reported in ADCETRIS-treated patients. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

5.13 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCETRIS in pregnant women. Brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations, in animals at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every three weeks.

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. If ADCETRIS is used during pregnancy or if the patient becomes pregnant during ADCETRIS treatment, the patient should be apprised of the potential risk to the fetus *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Peripheral Neuropathy *[see Warnings and Precautions (5.1)]*
- Anaphylaxis and Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Hematologic Toxicities *[see Warnings and Precautions (5.3)]*
- Serious Infections and Opportunistic Infections *[see Warnings and Precautions (5.4)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.5)]*
- Increased Toxicity in the Presence of Severe Renal Impairment *[see Warnings and Precautions (5.6)]*
- Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment *[see Warnings and Precautions (5.7)]*
- Hepatotoxicity *[see Warnings and Precautions (5.8)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.9)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.10)]*
- Serious Dermatologic Reactions *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Complications *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to ADCETRIS as monotherapy in 327 patients with classical Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL), including 160 patients in two uncontrolled single-arm trials (Studies 1 and 2) and 167 patients in one placebo-controlled randomized trial (Study 3).

In Studies 1 and 2, the most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting. The most common adverse reactions occurring in at least 10% of patients in either Study 1 or 2, regardless of causality, using the NCI Common Toxicity Criteria (CTC) Version 3.0, are shown in Table 2.

In Study 3, the most common adverse reactions (≥20%) in the ADCETRIS-treatment arm, regardless of causality, were neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough,

and diarrhea. The most common adverse reactions occurring in at least 10% of patients, using the NCI CTC Version 4, are shown in Table 3.

Experience in Classical Hodgkin Lymphoma

Summary of Clinical Trial Experience in Relapsed Classical HL (Study 1)

ADCETRIS was studied in 102 patients with classical HL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 9 cycles (range, 1–16) *[see Clinical Studies (14.1)]*.

The most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, upper respiratory tract infection, nausea, diarrhea, anemia, pyrexia, thrombocytopenia, rash, abdominal pain, cough, and vomiting.

Summary of Clinical Trial Experience in Classical HL Post-auto-HSCT Consolidation (Study 3)

ADCETRIS was studied in 329 patients with classical HL at high risk of relapse or progression post-auto-HSCT in a randomized, double-blind, placebo-controlled clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks or placebo for up to 16 cycles. Of the 329 enrolled patients, 327 (167 brentuximab vedotin, 160 placebo) received at least one dose of study treatment. The median number of treatment cycles in each study arm was 15 (range, 1–16) and 80 patients (48%) in the ADCETRIS-treatment arm received 16 cycles *[see Clinical Studies (14.1)]*.

Standard international guidelines were followed for infection prophylaxis for herpes simplex virus (HSV), varicella-zoster virus (VZV), and *Pneumocystis jiroveci* pneumonia (PCP) post-auto-HSCT. Overall, 312 patients (95%) received HSV and VZV prophylaxis with a median duration of 11.1 months (range, 0–20) and 319 patients (98%) received PCP prophylaxis with a median duration of 6.5 months (range, 0–20).

Experience in Systemic Anaplastic Large Cell Lymphoma

Summary of Clinical Trial Experience in Relapsed sALCL (Study 2)

ADCETRIS was studied in 58 patients with sALCL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 7 cycles (range, 1–16) *[see Clinical Studies (14.2)]*.

The most common adverse reactions (≥20%), regardless of causality, were neutropenia, anemia, peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea, and pain.

Table 2: Most Commonly Reported (≥10%) Adverse Reactions in Studies 1 and 2

	Classical HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Blood and lymphatic system disorders						
Neutropenia*	54	15	6	55	12	9
Anemia*	33	8	2	52	2	-
Thrombocytopenia*	28	7	2	16	5	5
Lymphadenopathy	11	-	-	10	-	-
Nervous system disorders						
Peripheral sensory neuropathy	52	8	-	53	10	-
Peripheral motor neuropathy	16	4	-	7	3	-
Headache	19	-	-	16	2	-
Dizziness	11	-	-	16	-	-
General disorders and administration site conditions						
Fatigue	49	3	-	41	2	2
Pyrexia	29	2	-	38	2	-
Chills	13	-	-	12	-	-
Pain	7	-	-	28	-	5
Edema peripheral	4	-	-	16	-	-
Infections and infestations						
Upper respiratory tract infection	47	-	-	12	-	-
Gastrointestinal disorders						
Nausea	42	-	-	38	2	-
Diarrhea	36	1	-	29	3	-
Abdominal pain	25	2	1	9	2	-
Vomiting	22	-	-	17	3	-
Constipation	16	-	-	19	2	-
Skin and subcutaneous tissue disorders						
Rash	27	-	-	31	-	-
Pruritus	17	-	-	19	-	-
Alopecia	13	-	-	14	-	-
Night sweats	12	-	-	9	-	-
Dry skin	4	-	-	10	-	-

	Classical HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Respiratory, thoracic and mediastinal disorders						
Cough	25	-	-	17	-	-
Dyspnea	13	1	-	19	2	-
Oropharyngeal pain	11	-	-	9	-	-
Musculoskeletal and connective tissue disorders						
Arthralgia	19	-	-	9	-	-
Myalgia	17	-	-	16	2	-
Back pain	14	-	-	10	2	-
Pain in extremity	10	-	-	10	2	2
Muscle spasms	9	-	-	10	2	-
Psychiatric disorders						
Insomnia	14	-	-	16	-	-
Anxiety	11	2	-	7	-	-
Metabolism and nutrition disorders						
Decreased appetite	11	-	-	16	2	-
Investigations						
Weight decreased	6	-	-	12	3	-

*Derived from laboratory values and adverse reaction data

Table 3: Most Commonly Reported (≥10% in the ADCETRIS arm) Adverse Reactions in Study 3

	ADCETRIS Total N = 167 % of patients			Placebo Total N = 160 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Blood and lymphatic system disorders						
Neutropenia*	78	30	9	34	6	4
Thrombocytopenia*	41	2	4	20	3	2
Anemia*	27	4	-	19	2	-
Nervous system disorders						
Peripheral sensory neuropathy	56	10	-	16	1	-
Peripheral motor neuropathy	23	6	-	2	1	-
Headache	11	2	-	8	1	-

	ADCETRIS Total N = 167 % of patients			Placebo Total N = 160 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infections and infestations						
Upper respiratory tract infection	26	-	-	23	1	-
General disorders and administration site conditions						
Fatigue	24	2	-	18	3	-
Pyrexia	19	2	-	16	-	-
Chills	10	-	-	5	-	-
Gastrointestinal disorders						
Nausea	22	3	-	8	-	-
Diarrhea	20	2	-	10	1	-
Vomiting	16	2	-	7	-	-
Abdominal pain	14	2	-	3	-	-
Constipation	13	2	-	3	-	-
Respiratory, thoracic and mediastinal disorders						
Cough	21	-	-	16	-	-
Dyspnea	13	-	-	6	-	1
Investigations						
Weight decreased	19	1	-	6	-	-
Musculoskeletal and connective tissue disorders						
Arthralgia	18	1	-	9	-	-
Muscle spasms	11	-	-	6	-	-
Myalgia	11	1	-	4	-	-
Skin and subcutaneous tissue disorders						
Pruritus	12	1	-	8	-	-
Metabolism and nutrition disorders						
Decreased appetite	12	1	-	6	-	-

*Derived from laboratory values and adverse reaction data

Additional Important Adverse Reactions

Peripheral neuropathy

In Studies 1 and 2, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of

the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation.

In Study 3, 67% of patients treated with ADCETRIS experienced any grade of neuropathy. The median time to first onset of any grade was 14 weeks (range, 0.1–47), of Grade 2 was 27 weeks (range, 0.4–52) and of Grade 3 was 34 weeks (range, 7–106). The median time from onset to resolution or improvement of any grade was 23 weeks (range, 0.1–138), of Grade 2 was 24 weeks (range, 1–108), and of Grade 3 was 25 weeks (range, 2–98). Of the patients who reported neuropathy, 59% had complete resolution and 41% had residual neuropathy (26% partial improvement, 15% no improvement) at the time of their last evaluation.

Infusion reactions

Two cases of anaphylaxis were reported in the dose-finding trials. There were no Grade 3 or 4 infusion-related reactions reported in Studies 1 and 2; however, Grade 1 or 2 infusion-related reactions were reported for 19 patients (12%). In Studies 1 and 2, the most common adverse reactions (≥2%) associated with infusion-related reactions were chills (4%), nausea (3%), dyspnea (3%), pruritus (3%), pyrexia (2%), and cough (2%).

In Study 3, infusion-related reactions were reported in 25 patients (15%) in the ADCETRIS-treated arm and 3 patients (2%) in the placebo arm. Grade 3 events were reported in 3 of the 25 patients treated with ADCETRIS who experienced infusion-related reactions. No Grade 4 infusion-related reactions were reported. The most common adverse reactions (≥2%) associated with infusion-related reactions were nausea (4%), chills (4%), dyspnea (2%), headache (2%), pruritus (2%), rash (2%), back pain (2%), and vomiting (2%).

Pulmonary Toxicity

In a trial in patients with classical HL that studied ADCETRIS with bleomycin as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCETRIS with bleomycin is contraindicated *[see Contraindications (4)].*

Cases of pulmonary toxicity have also been reported in patients receiving ADCETRIS. In Study 3, pulmonary toxicity was reported in 8 patients (5%) in the ADCETRIS-treated arm and 5 patients (3%) in the placebo arm. A causal association with single-agent ADCETRIS has not been established.

Serious adverse reactions

In Studies 1 and 2, serious adverse reactions, regardless of causality, were reported in 31% of patients receiving ADCETRIS. The most common serious adverse reactions experienced by patients with classical HL include peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and

pyrexia (2%). The most common serious adverse reactions experienced by patients with sALCL were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%). Other important serious adverse reactions reported include PML, Stevens-Johnson syndrome, and tumor lysis syndrome.

In Study 3, serious adverse reactions, regardless of causality, were reported in 25% of ADCETRIS-treated patients. The most common serious adverse reactions were pneumonia (4%), pyrexia (4%), vomiting (3%), nausea (2%), hepatotoxicity (2%), and peripheral sensory neuropathy (2%).

Dose modifications

Adverse reactions that led to dose delays in more than 5% of patients in Studies 1 and 2 were neutropenia (14%) and peripheral sensory neuropathy (11%) *[see Dosage and Administration (2.2)]*.

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients in Study 3 were neutropenia (22%), peripheral sensory neuropathy (16%), upper respiratory tract infection (6%), and peripheral motor neuropathy (6%) *[see Dosage and Administration (2.2)]*.

Discontinuations

Adverse reactions led to treatment discontinuation in 21% of patients in Studies 1 and 2. Adverse reactions that led to treatment discontinuation in 2 or more patients with classical HL or sALCL were peripheral sensory neuropathy (8%) and peripheral motor neuropathy (3%).

Adverse reactions led to treatment discontinuation in 32% of ADCETRIS-treated patients in Study 3. Adverse reactions that led to treatment discontinuation in 2 or more patients were peripheral sensory neuropathy (14%), peripheral motor neuropathy (7%), acute respiratory distress syndrome (1%), paraesthesia (1%), and vomiting (1%).

6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ADCETRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: febrile neutropenia *[see Warnings and Precautions (5.3)]*.

Gastrointestinal disorders:

- Pancreatitis (including fatal outcomes). Consider the diagnosis of pancreatitis for patients presenting with severe abdominal pain.
- Gastrointestinal complications (including fatal outcomes) *[see Warnings and Precautions (5.12)]*.

Hepatobiliary disorders: hepatotoxicity *[see Warnings and Precautions (5.8)]*.

Infections: PML *[see Boxed Warning, Warnings and Precautions (5.9)]*, serious infections and opportunistic infections *[see Warnings and Precautions (5.4)]*.

Metabolism and nutrition disorders: hyperglycemia.

Respiratory, thoracic and mediastinal disorders: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes) *[see Warnings and Precautions (5.10) and Adverse Reactions (6.1)]*.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, including fatal outcomes *[see Warnings and Precautions (5.11)]*.

6.3 Immunogenicity

Patients with classical HL and sALCL in Studies 1 and 2 *[see Clinical Studies (14)]* were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 timepoints) and 30% developed transiently positive antibodies (positive in 1 or 2 post-baseline timepoints). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patient samples that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ADCETRIS with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4/5. *In vitro* data indicate that MMAE is also a substrate of the efflux transporter P-glycoprotein (P-gp).

7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors/Inducers: MMAE is primarily metabolized by CYP3A *[see Clinical Pharmacology (12.3)]*. Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4

inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions. Co-administration of ADCETRIS with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

P-gp Inhibitors: Co-administration of ADCETRIS with P-gp inhibitors may increase exposure to MMAE. Patients who are receiving P-gp inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions.

7.2 Effect of ADCETRIS on Other Drugs

Co-administration of ADCETRIS did not affect exposure to midazolam, a CYP3A4 substrate. MMAE does not inhibit other CYP enzymes at relevant clinical concentrations *[see Clinical Pharmacology (12.3)]*. ADCETRIS is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every three weeks caused embryo-fetal toxicities, including congenital malformations *[see Data]*. Consider the benefits and risks of ADCETRIS and possible risks to the fetus when prescribing ADCETRIS to a pregnant woman.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (≥99%), post-implantation loss (≥99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with classical HL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

Risk Summary

There is no information regarding the presence of brentuximab vedotin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant from ADCETRIS, including cytopenias and neurologic or gastrointestinal toxicities, advise patients that breastfeeding is not recommended during ADCETRIS treatment.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating ADCETRIS therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise females to immediately report pregnancy *[see Use in Specific Populations (8.1)].*

Males

ADCETRIS may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS *[see Nonclinical Toxicology (13.1)].*

Infertility

Males

Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

Safety and effectiveness of ADCETRIS have not been established in pediatric patients.

8.5 Geriatric Use

Clinical trials of ADCETRIS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (CLcr <30 mL/min) *[See Warnings and Precautions (5.6)].*

The kidney is a route of excretion for monomethyl auristatin E (MMAE). The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (CLcr >50–80 mL/min; n=4), moderate (CLcr 30–50 mL/min; n=3) and severe (CLcr <30 mL/min; n=3) renal impairment. In patients with severe renal impairment, the rate of Grade 3 or worse adverse reactions was 3/3 (100%) compared to 3/8 (38%) in patients with normal renal function. Additionally, the AUC of MMAE (component of ADCETRIS) was approximately 2-fold higher in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function.

8.7 Hepatic Impairment

Avoid the use of ADCETRIS in patients with moderate or severe hepatic impairment *[See Warnings and Precautions (5.7)]*.

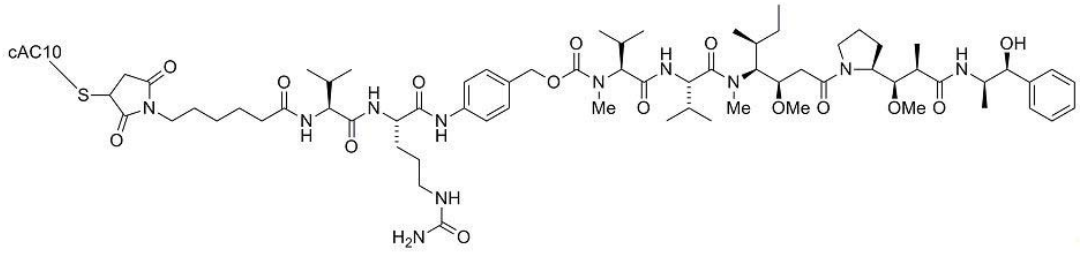
The liver is a route of clearance for MMAE. The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. In patients with moderate and severe hepatic impairment, the rate of ≥Grade 3 adverse reactions was 6/6 (100%) compared to 3/8 (38%) in patients with normal hepatic function. Additionally, the AUC of MMAE was approximately 2.2-fold higher in patients with hepatic impairment compared to patients with normal hepatic function.

10 OVERDOSAGE

There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

11 DESCRIPTION

ADCETRIS (brentuximab vedotin) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30, 2) the microtubule disrupting agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.



Brentuximab vedotin has an approximate molecular weight of 153 kDa. Approximately 4 molecules of MMAE are attached to each antibody molecule. Brentuximab vedotin is produced by chemical conjugation of the antibody and small molecule components. The

antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis.

ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white, preservative-free lyophilized cake or powder in single-use vials. Following reconstitution with 10.5 mL Sterile Water for Injection, USP, a solution containing 5 mg/mL brentuximab vedotin is produced. The reconstituted product contains 70 mg/mL trehalose dihydrate, 5.6 mg/mL sodium citrate dihydrate, 0.21 mg/mL citric acid monohydrate, and 0.20 mg/mL polysorbate 80 and water for injection. The pH is approximately 6.6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brentuximab vedotin is an ADC. The antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a microtubule disrupting agent. MMAE is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of ADCETRIS is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cells.

12.2 Pharmacodynamics

QT/QTc Prolongation Potential

The effect of brentuximab vedotin (1.8 mg/kg) on the QTc interval was evaluated in an open-label, single-arm study in 46 evaluable patients with CD30-expressing hematologic malignancies. Administration of brentuximab vedotin did not prolong the mean QTc interval >10 ms from baseline. Small increases in the mean QTc interval (<10 ms) cannot be excluded because this study did not include a placebo arm and a positive control arm.

12.3 Pharmacokinetics

The pharmacokinetics of brentuximab vedotin were evaluated in early development trials, including dose-finding trials, and in a population pharmacokinetic analysis of data from 314 patients. The pharmacokinetics of three analytes were determined: the ADC, MMAE, and total antibody. Total antibody had the greatest exposure and had a similar PK profile as the ADC. Hence, data on the PK of the ADC and MMAE have been summarized.

Absorption

Maximum concentrations of ADC were typically observed close to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional from 1.2 to 2.7 mg/kg. Steady-state of the ADC was achieved within 21 days with every 3-week dosing of ADCETRIS, consistent with the terminal half-life estimate. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule.

The time to maximum concentration for MMAE ranged from approximately 1 to 3 days. Similar to the ADC, steady-state of MMAE was achieved within 21 days with every 3 week dosing of ADCETRIS. MMAE exposures decreased with continued administration of ADCETRIS with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses.

Distribution

In vitro, the binding of MMAE to human plasma proteins ranged from 68–82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. *In vitro*, MMAE was a substrate of P-gp and was not a potent inhibitor of P-gp.

In humans, the mean steady state volume of distribution was approximately 6–10 L for ADC.

Metabolism

In vivo data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolized. *In vitro* data indicate that the MMAE metabolism that occurs is primarily via oxidation by CYP3A4/5. *In vitro* studies using human liver microsomes indicate that MMAE inhibits CYP3A4/5 but not other CYP isoforms. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

Elimination

MMAE appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. An excretion study was undertaken in patients who received a dose of 1.8 mg/kg of ADCETRIS. Approximately 24% of the total MMAE administered as part of the ADC during an ADCETRIS infusion was recovered in both urine and feces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the feces and the majority of the excreted MMAE was unchanged.

Specific Populations

Renal Impairment: *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment: *[see Use in Specific Populations (8.7)]*.

Effects of Gender, Age, and Race: Based on the population pharmacokinetic analysis; gender, age, and race do not have a meaningful effect on the pharmacokinetics of brentuximab vedotin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with brentuximab vedotin or the small molecule (MMAE) have not been conducted.

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule

disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Fertility studies with brentuximab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies in rats indicate the potential for brentuximab vedotin to impair male reproductive function and fertility. In a 4-week repeat-dose toxicity study in rats with weekly dosing at 0.5, 5, or 10 mg/kg brentuximab vedotin, seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis, and aspermia were observed. Effects in animals were seen mainly at 5 and 10 mg/kg of brentuximab vedotin. These doses are approximately 3 and 6-fold the human recommended dose of 1.8 mg/kg, respectively, based on body weight.

14 CLINICAL STUDIES

14.1 Classical Hodgkin Lymphoma

Clinical Trial in Relapsed Classical HL (Study 1)

The efficacy of ADCETRIS in patients with classical HL who relapsed after autologous hematopoietic stem cell transplantation was evaluated in one open-label, single-arm, multicenter trial. One hundred two patients were treated with 1.8 mg/kg of ADCETRIS intravenously over 30 minutes every 3 weeks. An independent review facility (IRF) performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 102 patients ranged in age from 15–77 years (median, 31 years) and most were female (53%) and white (87%). Patients had received a median of 5 prior therapies including autologous hematopoietic stem cell transplantation.

The efficacy results are summarized in Table 4. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 4: Efficacy Results in Patients with Classical Hodgkin Lymphoma (Study 1)

	N=102		
		Duration of Response, in months	
	Percent (95% CI)	Median (95% CI)	Range
CR	32 (23, 42)	20.5 (12.0, NE*)	1.4 to 21.9+
PR	40 (32, 49)	3.5 (2.2, 4.1)	1.3 to 18.7
ORR	73 (65, 83)	6.7 (4.0, 14.8)	1.3 to 21.9+

*Not estimable

+Follow up was ongoing at the time of data submission.

Randomized Placebo-controlled Clinical Trial in Classical HL Post-auto-HSCT Consolidation (Study 3)

The efficacy of ADCETRIS in patients with classical HL at high risk of relapse or disease progression post-auto-HSCT was studied in a randomized, double-blind, placebo-controlled clinical trial. Three hundred twenty-nine patients were randomized 1:1 to receive placebo or ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks for up to 16 cycles, beginning 30–45 days post-auto-HSCT. Patients in the placebo arm with progressive disease per investigator could receive ADCETRIS as part of a separate trial. The primary endpoint was progression-free survival (PFS) determined by IRF. Standard international guidelines were followed for infection prophylaxis for HSV, VZV, and PCP post-auto-HSCT *[see Clinical Trial Experience (6.1)]*.

High risk of post-auto-HSCT relapse or progression was defined according to status following frontline therapy: refractory, relapse within 12 months, or relapse ≥12 months with extranodal disease. Patients were required to have obtained a CR, PR, or stable disease (SD) to most recent pre-auto-HSCT salvage therapy.

A total of 329 patients were enrolled and randomized (165 ADCETRIS, 164 placebo); 327 patients received study treatment. Patient demographics and baseline characteristics were generally balanced between treatment arms. The 329 patients ranged in age from 18–76 years (median, 32 years) and most were male (53%) and white (94%). Patients had received a median of 2 prior systemic therapies (range, 2–8) excluding autologous hematopoietic stem cell transplantation.

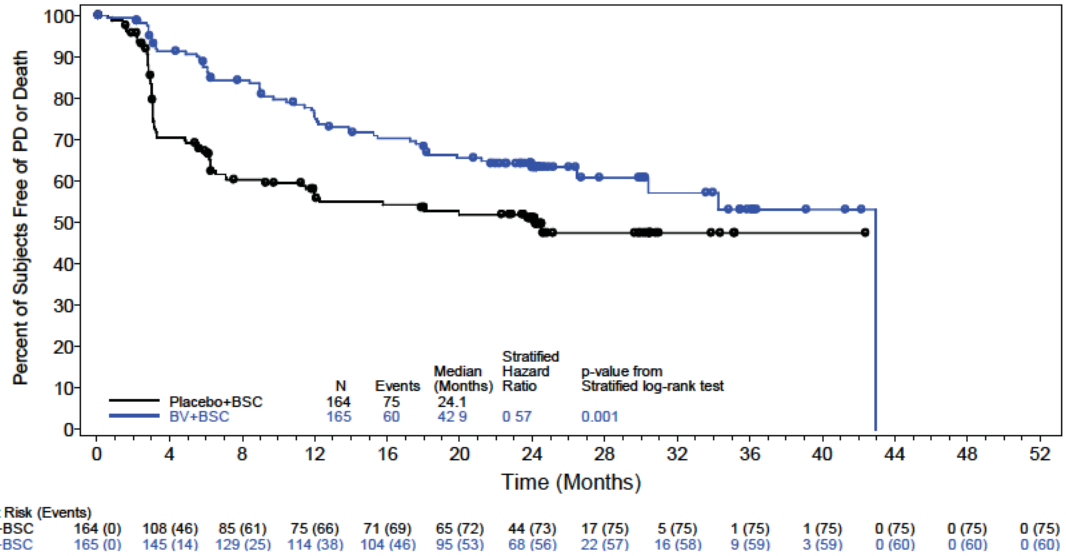
The efficacy results are summarized in Table 5. PFS is calculated from randomization to date of disease progression or death (due to any cause). The median PFS follow-up time from randomization was 22 months (range, 0–49). Study 3 demonstrated a statistically significant improvement in IRF-assessed PFS and increase in median PFS in the ADCETRIS arm compared with the placebo arm. At the time of the PFS analysis, an interim overall survival analysis demonstrated no difference.

Table 5: Efficacy Results in Patients with Classical HL Post-auto-HSCT Consolidation (Study 3)

Progression-free Survival	**ADCETRIS N=165**	**Placebo N=164**
Independent Review Facility		
Number of events (%)	60 (36)	75 (46)
Median months (95% CI)	42.9+ (30.4, 42.9+)	24.1 (11.5, NE*)
Stratified Hazard Ratio (95% CI)	0.57 (0.40, 0.81)	
Stratified Log-Rank Test P-value	P=0.001	

* Not estimable
\+ Estimates are unreliable

Figure 1: Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival (Study 3)



BV: Brentuximab Vedotin; BSC: Best Supportive Care

14.2 Systemic Anaplastic Large Cell Lymphoma

Clinical Trial in Relapsed sALCL (Study 2)

The efficacy of ADCETRIS in patients with relapsed sALCL was evaluated in one open-label, single-arm, multicenter trial. This trial included patients who had sALCL that was relapsed after prior therapy. Fifty-eight patients were treated with 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. An IRF performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 58 patients ranged in age from 14–76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 26% of patients had received prior autologous hematopoietic stem cell transplantation. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative.

The efficacy results are summarized in Table 6. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 6: Efficacy Results in Patients with Systemic Anaplastic Large Cell Lymphoma (Study 2)

	N=58		
		Duration of Response, in months	
	Percent (95% CI)	Median (95% CI)	Range
CR	57 (44, 70)	13.2 (10.8, NE*)	0.7 to 15.9+
PR	29 (18, 41)	2.1 (1.3, 5.7)	0.1 to 15.8+
ORR	86 (77, 95)	12.6 (5.7, NE*)	0.1 to 15.9+

*Not estimable
+ Follow up was ongoing at the time of data submission.

15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. [Accessed on 30 July 2013, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white preservative-free lyophilized cake or powder in individually-boxed single-use vials:

- NDC (51144-050-01), 50 mg brentuximab vedotin.

16.2 Storage

Store vial at 2–8°C (36–46°F) in the original carton to protect from light.

16.3 Special Handling

ADCETRIS is an antineoplastic product. Follow special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

• Peripheral neuropathy

Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbness or tingling of the hands or feet or any muscle weakness *[see Warnings and Precautions (5.1)]*.

• Fever/Neutropenia

Advise patients to contact their health care provider if a fever of 100.5°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops *[see Warnings and Precautions (5.3)]*.

• Infusion reactions

Advise patients to contact their health care provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion *[see Warnings and Precautions (5.2)]*.

• Hepatotoxicity

Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions (5.8)]*.

• Progressive multifocal leukoencephalopathy

Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms *[see Boxed Warning, Warnings and Precautions (5.9)]*:

- changes in mood or usual behavior
- confusion, thinking problems, loss of memory
- changes in vision, speech, or walking
- decreased strength or weakness on one side of the body

• Pulmonary Toxicity

Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath *[see Warnings and Precautions (5.10)]*.

• Pancreatitis

Advise patients to contact their health care provider if they develop severe abdominal pain *[see Adverse Reactions (6.2)]*.

• Gastrointestinal Complications

Advise patients to contact their health care provider if they develop severe abdominal pain, chills, fever, nausea, vomiting, or diarrhea *[see Warnings and Precautions (5.12)]*.

• Females and Males of Reproductive Potential

ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS *[see Use in Specific Populations (8.3)]*.

Advise patients to report pregnancy immediately *[see Warnings and Precautions (5.13)]*.

• Lactation

Advise patients to avoid breastfeeding while receiving ADCETRIS *[see Use in Specific Populations (8.2)]*.

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