Evaluation of Brentuximab Vedotin for Diffuse Cutaneous Systemic Sclerosis: A Phase 1/2 Multicenter Randomized, Double Blinded, Safety Study

Protocol ITN075AI

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PROTOCOL APPROVAL

Trial ID: ITN075AI	**Protocol Version: 5.0**
	Dated: December 10, 2021
IND # 132661	**Protocol Chairs:** David Fox, MD; Dinesh Khanna, MD, MSc

Short Title: *Brentuximab Vedotin for Systemic Sclerosis*

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of good clinical practice (GCP) as described in the US Code of Federal Regulations (CFR)—45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in the International Conference on Harmonization (ICH) document entitled *Integrated Addendum to ICHE6(R1): Guideline for Good Clinical Practice E6(R2)*. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the principal investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without written permission of the NIAID.

_____

Principal Investigator (Print)

_____ _____

Principal Investigator (*Sign*) **Date**

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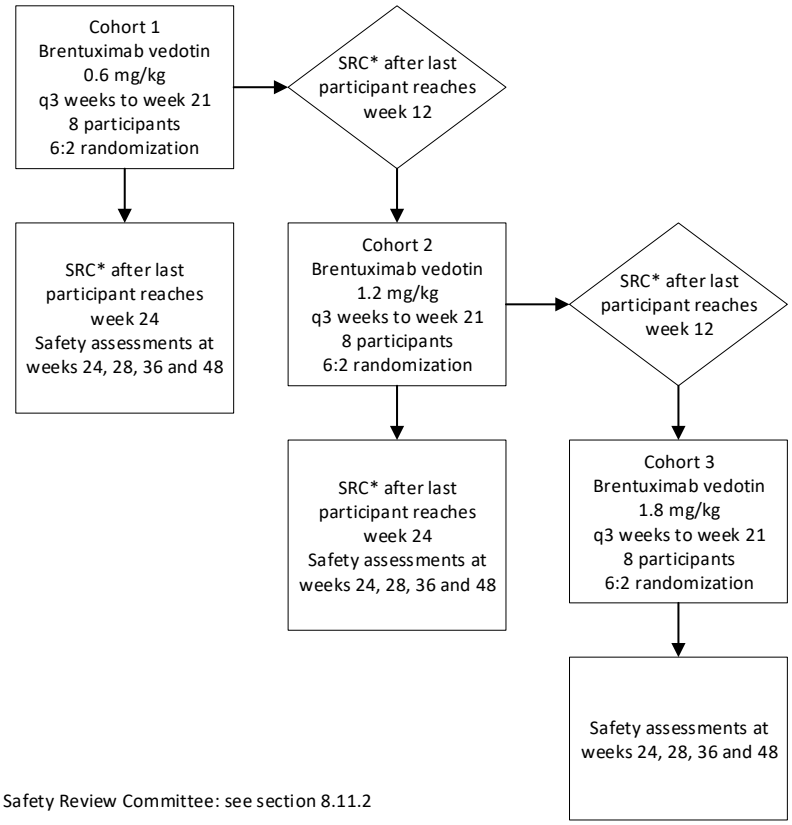
SYNOPSIS

Title	**Evaluation of Brentuximab Vedotin for Diffuse Cutaneous Systemic Sclerosis: A Phase 1/2 Multicenter Randomized, Double Blinded, Safety Study**
IND Sponsor	DAIT NIAID
Conducted by	Immune Tolerance Network
Protocol Chair(s)	David Fox and Dinesh Khanna
Accrual Objective	24 participants who receive sufficient doses of the investigational medication to assess safety
Study Treatment	Three ascending dose cohorts will receive brentuximab vedotin or placebo equivalent
Study Design	This trial will be conducted as a multicenter prospective double blind placebo-controlled dose escalation safety study with brentuximab vedotin and stable background immunosuppressive therapy in adult individuals with dcSSc. Adult male and female participants with dcSSc will be recruited by a collaborative group of clinical sites in the United States. Participants who meet the eligibility criteria will be enrolled without regard to gender, race, or ethnicity. Eligible participants will be randomly assigned to study treatment, either brentuximab vedotin or placebo equivalent in a 6:2 ratio favoring brentuximab vedotin. Three dose cohorts are planned with 8 participants in each cohort, for a total of 24 participants who receive sufficient doses of the investigational medication to assess safety. The doses planned for each ascending dose cohort include 0.6mg/kg, 1.2 mg/kg, and 1.8 mg/kg brentuximab vedotin or placebo equivalent. All cohorts will receive intravenous administration of study medication every 3 weeks for 21 weeks, for a total of eight doses. Following completion of treatment, participants will undergo follow-up visits at weeks 24, 28, 36 and 48. After completion of the first 12 weeks of treatment for each of the first two cohorts of 8 participants, an interim safety analysis will be conducted and reviewed by an independent Safety Review Committee, as described in Section 8.11.2. Approval by the Safety Review Committee following the 12-week interim safety analysis will be required before proceeding to the next higher dose of brentuximab vedotin. Interim safety analysis will also be conducted at 24 weeks following completion of study treatment for each of the first two cohorts of 8 participants. Following either the week 12 or the week 24 interim safety

reviews, the Safety Review Committee can recommend actions regarding study conduct, as described in Section 8.11.2.



Study Duration

Total study duration target is 308 weeks:

- Enrollment phase duration target is 260 weeks.
- Study participation phase for each participant is 48 weeks, which includes a treatment phase of 21 weeks and a follow-up phase of 27 weeks.

Primary Objective

To assess the safety and tolerability of brentuximab vedotin in diffuse cutaneous systemic sclerosis (dcSSc).

Primary Endpoint

The primary endpoint will be the proportion of participants who experience at least one Grade 3 or higher adverse event at or before week 48.

Secondary Endpoints

Safety Endpoints:

1. The proportion of participants who experience at least one Grade 3 or higher adverse event at or before weeks 12, 24, and 36.

2. The proportion of participants who experience at least one Grade 2 or higher adverse event at or before weeks 12, 24, 36, and 48.
3. The proportion of participants with Grade 2 or higher peripheral neuropathy at or before weeks 12, 24, 36, and 48.
4. The proportion of participants with Grade 3 or higher neutropenia at or before weeks 12, 24, 36, and 48.
5. The proportion of participants with any of the following Grade 3 or higher adverse events at or before week 48:
   a. Peripheral neuropathy.
   b. Neutropenia.
   c. Infectious adverse events.
   d. Infusion reactions, including anaphylaxis and new onset rash consistent with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other drug reaction.
   e. PML.

Exploratory Efficacy Endpoints:

1. Modified Rodnan Skin Score (mRSS) at weeks 12, 24, and 48.
2. Provisional American College of Rheumatology Combined Response Index in Systemic Sclerosis (CRISS) at weeks 24 and 48.
3. Percent predicted Forced Vital Capacity (FVC) at weeks 24 and 48 weeks.
4. Physician's global assessment on a Likert scale at weeks 24 and 48.
5. Patient's global assessment on a Likert scale at weeks 24 and 48.
6. Health-related quality of life (HRQOL) assessed by PROMIS-29 version 2.0 at weeks 24 and 48.
7. Physical function assessed by the Scleroderma Health Assessment Questionnaire-Disability Index (SHAQ-DI) at weeks 24 and 48.

Inclusion Criteria

1. Classification of systemic sclerosis (SSc), as defined using the 2013 American College of Rheumatology/European Union League Against Rheumatism classification of SSc.
2. Diagnosis of dcSSc, as defined by LeRoy and Medsger.

3. Disease duration ≤ 60 months (defined as time from the first non-Raynaud phenomenon manifestation).
4. mRSS units ≥ 15 and ≤ 45, and both of the following:
   a. At least mild skin thickening (≥ 1+ mRSS) of the forearm, and
   b. At least moderate skin thickening (≥ 2+ mRSS) at the planned forearm skin biopsy site.
5. Documentation of at least 12 weeks of ongoing immunosuppressive therapy for SSc at the time of enrollment, and at least 4 weeks at a stable dose, of one of the following:
   a. Methotrexate ≤ 25 mg/week, or
   b. Mycophenolate mofetil ≤ 3 grams/day or mycophenolate sodium ≤ 2.16 grams/day, or
   c. Azathioprine ≤ 3mg/kg/day.
6. Age 18-70 years inclusive.
7. Completion of primary SARS-CoV-2 vaccination series is required at least 14 days prior to the first infusion of study medication at Visit 0. The dose and schedule of the vaccine is defined according to current FDA approval or Emergency Use Authorization at the time of screening.
8. Ability to provide informed consent.

Exclusion Criteria

1. Rheumatic disease other than dcSSc; it is acceptable to include patients with osteoarthritis, fibromyalgia, sicca symptoms, and scleroderma-associated myopathy.
2. Limited cutaneous SSc or sine scleroderma.
3. Pulmonary disease with FVC ≤ 60% of predicted, or DLCO (corrected for hemoglobin) ≤ 60% of predicted.
4. Pulmonary hypertension (PH) or moderate to severe left ventricular dysfunction defined as one of the following:
   a. Transthoracic echocardiography demonstrating at least one of the following (unless subsequent right heart catheterization does not demonstrate PH; or unless prior right heart catheterization within one year did not demonstrate PH and echocardiography results are not significantly changed):

i. Tricuspid regurgitation jet >2.8 m/sec or estimated right ventricular systolic pressure > 42 mm Hg, or

ii. At least one of the following:

1. Abnormality of right atrial size, shape, or wall thickness consistent with PH, or
2. Abnormality of right ventricular size, shape, or wall thickness consistent with PH, or
3. Abnormal septal wall shape consistent with PH.

iii. Left Ventricular Ejection Fraction (LVEF) < 50%.

b. Right heart catheterization showing mean pulmonary artery pressure ≥25 mm Hg at rest.

c. Current use of approved medications for PH. It is acceptable to use phosphodiesterase type 5 (PDE-5) inhibitors for Raynaud's, digital ulcers, and intermittently for erectile dysfunction.

5. Active scleroderma renal crisis within the 4 months prior to enrollment.
6. History of moderate-to-severe lower gastrointestinal dysmotility such as current use of parenteral nutrition and/or recent history of intestinal pseudo-obstruction within 3 months prior to enrollment.
7. The following medications:
   a. Oral corticosteroids >10 mg/day of prednisone or equivalent within 2 weeks prior to enrollment.
   b. Treatment with intravenous immunoglobulin (IVIG) within 12 weeks prior to enrollment.
   c. Treatment with cyclophosphamide within 6 months prior to enrollment.
   d. Use of investigational biologic or non-biologic medication within the past 90 days, or 5 half-lives prior to enrollment, whichever is greater, except for SARS-CoV-2 vaccines, and medications used for prevention and treatment of COVID-19, per FDA Emergency Use Authorization.

e. Use of anti-TNF medication or other biologic medications within the past 90 days, or 5 half-lives prior to enrollment, whichever is greater.

f. Prior treatment with anti-CD20 if either of the following are true:

   i. B cells ≤ lower limit of normal (LLN), or

   ii. Treatment with anti-CD20 has been within 12 months prior to enrollment.

g. Any prior treatment with cell-depleting therapies other than anti-CD20, including investigational agents, including but not limited to, CAMPATH®, anti-CD4, anti-CD5, anti-CD3, anti-CD19.

h. Any prior treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation.

8. Receipt of a live-attenuated vaccine within 3 months of study enrollment.
9. Concomitant malignancies or a history of malignancy, with the exception of adequately treated basal and squamous cell carcinoma of the skin, or carcinoma in situ of the cervix.
10. Major surgery (including joint surgery) within 8 weeks prior to enrollment.
11. History of solid organ or hematopoietic stem cell transplantation.
12. History of primary immunodeficiency.
13. Comorbidities requiring systemic corticosteroid therapy, including those which have required three or more courses of systemic corticosteroids within the 12 months prior to enrollment.
14. Current substance abuse or history of substance abuse within 12 months prior to enrollment.
15. History of severe depression or severe psychiatric condition.
16. Lack of peripheral venous access.
17. Known hypersensitivity to brentuximab vedotin, a component thereof, or the excipient contained in the drug formulation.
18. Severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, or neurological disease (or, in the investigator's opinion, any other concomitant medical condition that places the

participant at risk by participating in this study), including but not limited to:

a. Uncompensated congestive heart failure (New York Heart Association Class III or VI).
b. Clinically significant active coronary artery disease (e.g., unstable angina or acute myocardial infarction within 6 months prior to enrollment).
c. Recently active cerebrovascular disease (e.g., stroke or transient ischemic attack within 6 months prior to enrollment).
d. Uncontrolled systemic hypertension.
e. Confirmed diagnosis of diabetes mellitus.
f. Pancreatitis within 30 days prior to enrollment.
g. History or presence of peripheral neuropathy, such as mononeuritis multiplex, acute or chronic inflammatory demyelinating polyneuropathy, axonal sensorimotor neuropathies, or drug related neuropathy or neuritis.

19. Evidence of infection:
    a. Any infected ulcer at enrollment.
    b. Active bacterial, viral, fungal, or opportunistic infections requiring systemic anti-infective therapy.
    c. Evidence of current or prior infection with tuberculosis
        i. Positive QuantiFERON® – TB Gold or TB Gold Plus test results. Purified protein derivative (PPD) tuberculin test may be substituted for QuantiFERON® – TB Gold or TB Gold Plus test.
        ii. Indeterminant QuantiFERON® – TB Gold or TB Gold Plus test results, unless followed by a subsequent negative PPD or negative QuantiFERON® and clearance by local Infectious Disease department.
    d. Evidence of current or prior infection with
        i. Human immunodeficiency virus (HIV), or
        ii. Hepatitis B (as assessed by hepatitis B surface antigen, HBsAg and antibody to hepatitis B core antigen, anti-HBc), or
        iii. Hepatitis C (HCV), except adequately treated HCV with documentation of sustained

virologic response defined as undetectable HCV RNA at least 12 weeks after the end of treatment.

e. History of progressive multifocal leukoencephalopathy (PML).

f. Hospitalization for treatment of infections, or parenteral (intravenous or intramuscular) antibacterial, antivirals, anti-fungal, or anti-parasitic agents within the past 60 days prior to enrollment.

g. Chronic infection that is currently being treated with systemic suppressive antibiotic or antiviral therapy, including but not limited to tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster, and atypical mycobacteria.

h. History of significant infection or recurrent infection that, in the investigator's opinion, places the participant at risk by participating in this study.

i. Positive PCR test for SARS-CoV-2 within the two weeks prior to enrollment.

20. The following laboratory abnormalities:

a. Neutropenia (absolute neutrophil count <1500/mm^3).

b. Thrombocytopenia (platelets <100,000/mm^3).

c. Moderately severe anemia (hemoglobin, Hgb < 10 g/dL).

d. Liver function test (aspartate aminotransferase [AST], alanine aminotransferase [ALT], or alkaline phosphatase) results that are ≥ 1.5 times the upper limit of normal.

e. Serum total bilirubin > 1.5 times the upper limit of normal, or > 3 times the upper limit of normal in the presence of Gilbert's syndrome.

f. Serum amylase and serum lipase > 1.5 times the upper limit of normal.

21. Renal dysfunction, defined as either one of the following:

a. Serum creatinine > 1.5 times the upper limit of normal.

b. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m2.

22. Pregnancy.

23. Breastfeeding.

24. Unwillingness to use two forms of medically acceptable contraception methods by participants and their partners (if of reproductive potential) during the study and for at least 6 months after last dose of study drug.
25. Inability to comply with study and follow-up procedures.

ABBREVIATIONS

ABVD	Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine
AE	Adverse Event
ALCL	Anaplastic Large Cell Lymphoma
ALT	Alanine Aminotransferase
ANA	Anti-Nuclear Antibodies
ASCT	Autologous Stem Cell Transplant
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CRISS	Combined Response Index in Systemic Sclerosis
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
dcSSC	Diffuse Cutaneous Systemic Sclerosis
DAIT	Division of Allergy, Immunology, and Transplantation
DSC	Discontinuation Visit
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EKG	Electrocardiogram
ELISPOT	Enzyme-linked Immunospot
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration

FEV1	Forced Expiratory Volume 1
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GVHD	Graft Versus Host Disease
HBsAg	Hepatitis B Surface Antigen
HBc	Hepatitis B Core Antigen
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HRQOL	Health-related quality of life
HL	Hodgkin's lymphoma
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ICOS	Inducible Costimulator
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
ISH	In Situ Hybridization
ITN	Immune Tolerance Network
IVIG	Intravenous Immunoglobulin
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl Auristatin E
mRSS	Modified Rodnan Skin Score
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases

NIH	National Institutes of Health
NK	Natural Killer
OHRP	Office for Human Research Protections
OSHA	Occupational Safety and Health Administration
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PDE-5	Phosphodiesterase type 5
P-gp	P-glycoprotein
PH	Pulmonary Hypertension
PML	Progressive Multifocal Leukoencephalopathy
PP	Per Protocol
PPD	Purified Protein Derivative
RA	Rheumatoid Arthritis
REMS	Risk Evaluation and Mitigation Strategy
RNA	Ribonucleic Acid
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCID	Severe Combined Immunodeficiency
SHAQ-DI	Scleroderma Health Assessment Questionnaire-Disability Index
SLE	Systemic Lupus Erythematosus
SNP	Single Nucleotide Polymorphisms
SOP	Standard Operating Procedure
SSc	Systemic Sclerosis

SRC	Safety Review Committee
ULN	Upper Limit of Normal
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND

Systemic sclerosis (SSc) is a rare autoimmune condition characterized by fibrosis, inflammation, and micro vasculopathy affecting multiple organ systems. Prevalence of SSc is reported at approximately 3/10,000 in the United States [3]. The disease is more common in females but appears to be more severe in males [1, 2]. Morbidity and mortality are high, and there is no effective approved therapy. The diffuse cutaneous form of systemic sclerosis (dcSSc), defined by widespread skin involvement, has a poor prognosis, with estimated 55% mortality at 10 years [2, 4]. It typically presents as Raynaud's phenomenon and is characterized by sclerodactyly, digital ulcers, and proximal cutaneous involvement, complicated by pain, infection, and diminished function. Pulmonary involvement includes interstitial lung disease and pulmonary hypertension and is the leading cause of mortality. Esophageal, articular, and cardiac manifestations are also common. Renal involvement is less common but life-threatening due to severe hypertension and scleroderma renal crisis [4, 5].

There is no Food and Drug Administration (FDA)-approved treatment for dcSSc. Treatment options are extremely limited, and include general immunosuppressive agents such as methotrexate, mycophenolate mofetil, cyclophosphamide, azathioprine, and glucocorticoids [6]. Autologous stem cell transplantation is more efficacious than pulse cyclophosphamide for severe systemic sclerosis but is associated with treatment-related mortality [7-10]. Biologic therapies are under investigation, and rituximab and tocilizumab show promise. Case series with rituximab have reported skin score improvements [11], but no placebo-controlled trial data is available. A recent phase II randomized controlled trial of tocilizumab did not meet its primary endpoint, but exploratory analyses suggested benefit in terms of pulmonary function, and a phase III trial is in progress [12, 13].

In summary, there is significant unmet need for effective treatment options for dcSSc, a highly morbid disease associated with life-threatening complications. The present study will be a dose-escalation safety trial of brentuximab vedotin, a drug-antibody conjugate approved for the treatment of lymphoma and targeted to the CD30 molecule expressed on activated T and B lymphocytes. There is evidence for CD30 involvement in SSc, which will be described in section 1.2. The study presented in this protocol represents the first step in determining safety and tolerability of brentuximab vedotin in SSc, prior to proceeding to a future placebo-controlled efficacy study.

1.2 SCIENTIFIC RATIONALE

SSc is characterized by organ fibrosis, with evidence for an underlying autoimmune pathogenesis [14]. Anti-nuclear antibodies (ANA) are nearly universal in SSc, and often are present with other clinically–associated autoantibodies, including anti-centromere, anti-ribonucleic acid (RNA) polymerase 3 and anti-topoisomerase 1 [15]. Autoantibodies are typically present at a stage of disease prior to full expression of the clinical

phenotype. Only 6.4% of SSc patients are ANA-negative, and these patients may have milder disease [16].

Substantial evidence supports the concept that T cells play a key role in the pathogenesis and fibrotic complications of SSc. Skin biopsies obtained from SSc patients early in their disease demonstrate a perivascular, mononuclear cell infiltrate comprised of T cells and macrophages [17, 18]. T cells are the dominant population of lymphocytes in the skin, and are activated [17]. T cell infiltration correlates with skin thickening, suggesting a relationship between inflammation and fibrosis. The expression of inducible costimulator (ICOS), expressed on activated T cells, is elevated in patients with early dcSSc [19]. Also, the T lymphocytes in SSc tissue overexpress TNF receptor II and these cells, when costimulated with TNF-α, trigger collagen production by releasing profibrotic cytokines [20]. Th2 cells, defined by their production of IL-4, have been implicated in SSc because some of their cytokine products, such as IL-13, are pro-fibrotic [21-23]. Recently, a novel mechanism has been identified by which the production of IL-4, the signature Th2 cytokine, leads to fibrosis, through activation of secretion by myeloid cells of pro-fibrotic factors that alter the program of gene expression in adjacent fibroblasts in the skin, leading to collagen fibril cross-linking [24].

CD30 is a target of interest for treatment in SSc. CD30 and its ligand, CD153, are members of the TNF-R and TNF families respectively and are expressed on various subsets of hematopoietic cells. CD30 is expressed on activated T and B lymphocytes and on natural killer cells, while CD153 is more broadly expressed on myeloid, erythroid, megakaryocytic and some lymphoid cells. CD30 has been reported to be preferentially expressed on Th2 cells [25], a subpopulation implicated in fibrosis [21-23]. Signal transduction through CD30 has a variety of consequences in T and B cells, including co-stimulation, effector cell differentiation, and survival of antigen specific memory cells [26, 27], and thus may influence immune cell activation and tolerance. CD30 is required for development of autoimmune disease in a Foxp3-deficient autoimmune mouse model, possibly related to CD30's role in T and B cell memory responses [28, 29]. Moreover, an antibody to the CD30 ligand prevented the development of spontaneous diabetes in the NOD mouse model [30].

Membrane CD30 exists in 105kDa and 120kDa forms, which can be proteolytically cleaved to release an 88kDa soluble form of CD30. Soluble CD30 is elevated in SSc, and levels correlate with clinical features such as number of skin lesions and number of involved body areas [31-34]. CD30 has been detected on CD4+ T cells in SSc skin biopsies, along with high expression of the Th2 cytokine IL-4 in SSc skin [31]. Soluble CD30 is also elevated in a number of other autoimmune conditions including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Hashimoto's thyroiditis, primary biliary cirrhosis, Sjogren's syndrome, and Wegener's granulomatosis, and in some cases CD30 is expressed on cells in blood and tissues in these conditions [35-44]. Lesional skin-infiltrating T lymphocytes express CD30 in acute atopic dermatitis, but not in acute contact dermatitis [45]. The association of CD30 with the pro-fibrotic Th2 phenotype and

the elevated levels observed in autoimmune diseases, including SSc, support a rationale for targeting CD30 as a treatment strategy for SSc.

1.3 PRECLINICAL AND CLINICAL EXPERIENCE

Brentuximab vedotin, also known as SGN-35, is an antibody-drug conjugate, or immunotoxin, developed for the treatment of Hodgkin's lymphoma (HL) and anaplastic large cell lymphoma (ALCL) based on expression of CD30 on these tumors [46, 47]. The ongoing manufacturer development portfolio includes 21 completed and 9 ongoing clinical trials. Brentuximab vedotin consists of a chimeric IgG1 monoclonal antibody directed to CD30 coupled by way of a protease-cleavable linker to the antimitotic toxin monomethyl auristatin E (MMAE) [48]. The immunotoxin is internalized by clathrin-mediated endocytosis upon antibody binding to target cells, followed by cathepsin-mediated release of the toxin component. Free intracellular MMAE then binds to tubulin, thereby disrupting the microtubule network which results in interruption of the cell cycle and cell apoptosis [48]. MMAE is also believed to cause bystander killing by way of diffusion into the tumor microenvironment [48, 49]. Other possible mechanisms of action of brentuximab vedotin include apoptosis via CD30 ligation [50], and antibody dependent cellular phagocytosis [51].

1.3.1 Preclinical Studies

SGN-35 (brentuximab vedotin) was shown to prevent lymphoma tumor growth in Severe Combined Immunodeficiency (SCID) mice xenografted with human CD30+ Hodgkin's lymphoma cells or anaplastic large cell lymphoma cells [52, 53]. Tumor growth was delayed even if SGN-35 was administered after the tumors were established. Combining SGN-35 with the chemotherapeutic regimen ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or with gemcitabine was more effective in treating lymphoma tumors in mice than SGN-35 alone or chemotherapy alone [53]. No studies have been conducted with brentuximab vedotin in animal models of autoimmunity since the antibody component of the immunotoxin does not cross-react with CD30 on murine cells.

Toxicology studies conducted with brentuximab vedotin in cynomologus monkeys demonstrated toxicities in hematopoietic compartments consistent with MMAE, including lymphoid depletion, bone marrow hypocellularity, and neutropenia [54]. Studies in rats showed impaired fertility in males, lethal embryo and fetal effects, and teratogenicity, resulting in the assignment of Pregnancy Category D [54].

1.3.2 Clinical Studies

1.3.2.1 Clinical studies with brentuximab vedotin for CD30-positive lymphomas.

Brentuximab vedotin is approved for previously untreated Stage III or IV classical HL in combination with chemotherapy, for HL at high risk of relapse or progression following autologous stem cell transplant (ASCT), and for HL after failing ASCT or after failing at least two multi-agent chemotherapeutic regimens when transplant is not an option [55].

Brentuximab vedotin is also approved for previously untreated systemic ALCL or other CD-30 expressing peripheral T cell lymphoma in combination with chemotherapy, for systemic ALCL after failing at least one multi-agent chemotherapeutic regimen, and for primary cutaneous ALCL and CD30-expressing mycosis fungoides after receiving prior systemic treatment [55]. Accelerated approval was obtained in 2011 based on the results of two single arm phase II clinical trials in HL and ALCL [54].

In a pivotal phase II trial in relapsed or refractory HL following ASCT, 102 participants received intravenous brentuximab vedotin 1.8 mg/kg every three weeks for up to 16 doses [56]. The overall disease control rate (complete remission + partial remission + stable disease) was 96%, with a median progression-free survival of 5.6 months. Complete remission was observed in 34% of participants, and the median progression-free survival in these complete remission participants was 20.5 months. Durable remission was reported in approximately half of the participants who achieved complete remission after a median of 53 months of follow-up [57].

In a second pivotal phase II trial in relapsed or refractory ALCL, 58 participants received intravenous brentuximab vedotin 1.8 mg/kg every three weeks for up to 16 doses [58]. Complete remission was achieved in 57% of participants, and partial remission was achieved in 29% of participants. The estimated median duration of progression-free survival was 13.4 months.

Of note, in a phase II trial of brentuximab vedotin monotherapy in treatment-naïve participants with HL who were age 60 and older, 73% of participants achieved complete remission and 100% of participants achieved stable disease or better [59]. Brentuximab vedotin was generally well-tolerated in this older group of participants (median age 78) who were not eligible for or who had declined conventional combination chemotherapeutic regimens.

A phase III trial of brentuximab vedotin as consolidation therapy in 329 HL patients considered to be at risk for relapse or progression following ASCT demonstrated significant improvement in progression-free survival compared to placebo [60].

Ongoing studies with brentuximab vedotin include monotherapy or combination with standard of care for treatment of HL, ALCL, CD30-positive cutaneous T cell lymphoma, CD30-positive mature T-cell lymphoma, and diffuse large B cell lymphoma.

1.3.2.2 Clinical studies with brentuximab vedotin in graft versus host disease.

A phase 1 trial of brentuximab vedotin for treatment of established steroid-refractory graft versus host disease (GVHD) was undertaken based on the observation that an increased percentage of central memory CD8 T cells express CD30 and soluble CD30 is elevated at the onset of acute GVHD [61]. This trial is completed (NCT01596218), and early results demonstrated a 37% response rate including some complete responses [62]. In contrast, a phase 1 trial of brentuximab vedotin for prevention of GVHD was stopped early due to the occurrence of GVHD in the participants [63].

1.3.2.3 Clinical studies with brentuximab vedotin in autoimmune disease.

Seattle Genetics has received case reports of improvement in comorbid autoimmune disease manifestations in a number of individuals treated for lymphoma with brentuximab vedotin. The majority of reports indicate improvements in relatively common diseases such as RA and SLE, including one published case report in RA [64]. This report describes a 76-year-old woman with long-standing RA inadequately controlled on TNF inhibitor and methotrexate therapy, who experienced a complete remission of RA while treated with brentuximab vedotin for Stage IV Hodgkin's lymphoma, despite discontinuation of TNF inhibitor therapy, methotrexate, and steroids. Improvements have also been observed in a number of less common autoimmune conditions, including SSc and interstitial lung disease. Based on the reports of improvement in SLE and other autoimmune conditions in patients treated with brentuximab vedotin for lymphoma, Seattle Genetics initiated a dose escalation phase 2a trial of brentuximab vedotin in SLE [65]. Seattle Genetics terminated the study before completion due to revised business portfolio prioritization (NCT02533570).

1.4 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS FOR HUMAN PARTICIPANTS

1.4.1 Risks

Brentuximab vedotin is associated with a number of known toxicities as summarized in the prescribing information [55]. A safety review of brentuximab vedotin for HL has been published [66]. Brentuximab vedotin has been tested and approved for relapsed or refractory HL and ALCL following at least one prior high dose multi-agent regimen of chemotherapy, and prior autologous stem cell transplant in the case of HL. As such, the adverse events described below have generally occurred in the setting of prior or concurrent high dose chemotherapy.

Adverse events occurring in greater than or equal to 10% of participants in the pivotal phase II trial in HL included peripheral sensory neuropathy, nausea, fatigue, neutropenia, diarrhea, pyrexia, vomiting, arthralgia, pruritus, myalgia, peripheral motor neuropathy, and alopecia [56]. Treatment emergent hyperglycemia has been reported at 5.4% to 12.1% across studies, with associated risk factors being pre-existing hyperglycemia and high body mass index greater than 30 kg/m^2 [65]. Serious events of hyperglycemia reported in people treated with brentuximab vedotin include new onset hyperglycemia, exacerbations of pre-existing diabetes mellitus, and ketoacidosis (including fatal outcomes) [65]. The prescribing information highlights specific warnings for peripheral neuropathy, anaphylaxis and infusion reactions, neutropenia, thrombocytopenia, anemia, serious and opportunistic infections, hepatotoxicity, pulmonary toxicity, gastrointestinal complications, Stevens-Johnson syndrome, toxic epidermal necrolysis, and fetal harm, with a black box warning for progressive multifocal leukoencephalopathy (PML).

1.4.1.1 Risk of Peripheral Neuropathy

Peripheral sensory neuropathy is the most commonly known risk of brentuximab vedotin, with peripheral motor neuropathy reported at a lower incidence. In the phase II pivotal clinical trial in HL, peripheral sensory neuropathy occurred in 42% of participants and peripheral motor neuropathy occurred in 11% of participants [56]. In this trial, brentuximab vedotin was administered every three weeks for a maximum of 16 doses. Peripheral neuropathy was the most common adverse event leading to treatment discontinuation or dose reduction. The majority of events were Grade 1 or Grade 2 peripheral sensory neuropathy events, consisting of numbness and tingling of fingers and toes. The median time to onset of any peripheral neuropathy event was 12.4 weeks, to Grade 2 events was 27.3 weeks, and to Grade 3 events was 38.0 weeks. The peripheral neuropathy events improved by at least one grade in 80% of those affected and resolved completely in 50% [56].

Similar results were reported in the phase II pivotal trial in ALCL and a phase III placebo-controlled trial of brentuximab vedotin for consolidation therapy after ASCT for HL [58, 60]. There were no Grade 4 peripheral neuropathy events in any of these three studies, however peripheral motor neuropathy events were categorized as serious in 4% of participants in the pivotal phase II HL trial [54]. Of note, in the pivotal phase II trials, 24% of participants had pre-existing peripheral neuropathy at baseline.

As described in the Investigator's Brochure (IB), the median duration of treatment was approximately 48 weeks in the phase III trial of consolidation therapy following ASCT in HL patients [60]. Worsening of neuropathy was mitigated by reduction and delay in dosing. Peripheral neuropathy events tended to worsen with longer treatment exposure, with the first onset at approximately 12 weeks after the first dose of brentuximab vedotin. Grade 3 peripheral neuropathy events occurred at a median of approximately 34 weeks. The majority of events improved or resolved by a median of approximately 23 weeks.

Patients enrolled in a retreatment or extension treatment trial had more peripheral neuropathy at baseline compared to the pivotal phase II studies, and also developed more peripheral neuropathy events [65].

As of August 2020, a search of the clinical trial database found treatment emergent peripheral neuropathy (sensory and motor) occurred in 1394 participants (55%). Most of the events (1177, or 47%) were ≤ Grade 2 [65].

The prescribing information for brentuximab vedotin as monotherapy reports 62% of patients experienced any grade of neuropathy. The median time to onset was three months (range 0-12). Of patients experiencing neuropathy, 62% had complete resolution of symptoms, 24% had partial improvement, and 14% had no improvement at the time of the last evaluation. The prescribing information recommends temporary discontinuation and subsequent dose modification for Grade 2 or Grade 3 peripheral neuropathy, and permanent discontinuation for Grade 4 peripheral neuropathy [55]. In the trial described in this protocol, the dose of brentuximab vedotin will be suspended if a participant

develops Grade 2 peripheral neuropathy and restarted at a lower dose if the peripheral neuropathy resolves. Brentuximab vedotin will be permanently discontinued for Grade 3 or greater peripheral neuropathy (see section 5.2). Participants will be excluded if they are older than 70 years of age, if they have diabetes, or if they have pre-existing peripheral neuropathy (see section 4.2). In addition, participants will be monitored for peripheral neuropathy throughout the trial.

1.4.1.1.1 Risk of peripheral neuropathy in participants age 60 and older

In a small trial of 27 participants age 60 and older with HL (median age 78), peripheral neuropathy events occurred in a higher proportion of participants than observed in the pivotal phase II trials [59]. Treatment emergent peripheral neuropathy adverse events occurred in 89% of participants, with Grade 3 peripheral neuropathy occurring in 30%. Peripheral neuropathy events improved or resolved in 58% of affected participants.

Comorbid risk factors for peripheral neuropathy adverse events included diabetes, hypothyroidism and pre-existing peripheral neuropathy. Of 13 participants with diabetes and/or hypothyroidism, 6 participants developed Grade 3 peripheral neuropathy, compared to 2 of the 14 participants without diabetes and/or hypothyroidism. The first onset of grade 3 peripheral neuropathy occurred earlier in this older population compared to the onset observed in the pivotal phase II trials, at a median of 16.6 weeks for older participants with comorbid risk factors, and a median of 15.4 weeks for older participants without comorbid risk factors [59].

1.4.1.2 Risk of Cytopenia, Serious Infections, and PML.

Neutropenia was the most common Grade 3 or Grade 4 adverse event in the pivotal phase II trials of brentuximab vedotin in HL and ALCL, occurring in 26% of participants. Grade 3 or greater thrombocytopenia and anemia were also reported [54, 56, 58]. The prescribing information for brentuximab vedotin recommends temporary discontinuation and consideration of G-CSF for grade 3 or grade 4 neutropenia, and permanent discontinuation or dose reduction for grade 4 neutropenia that recurs [55]. In this protocol, brentuximab vedotin will be discontinued for Grade 3 or greater neutropenia or thrombocytopenia (section 5.2).

Although serious infections were not common in the pivotal phase II trials, one participant in an early dose finding study died after developing febrile neutropenia and sepsis. This participant received 3.6 mg/kg brentuximab vedotin (twice the dose that was subsequently approved) [46]. Other fatal infectious adverse events included influenzal pneumonia and cytomegalovirus infection [65]. Pneumocystic carinii pneumonia has also occurred [65]. Although rare, PML has been reported in 5 individuals receiving brentuximab vedotin [67, 68], resulting in the addition of a black box warning for PML to the prescribing information [55]. The incidence of PML in cancer patients treated with brentuximab vedotin was < 0.05% [65].

In the phase III trial of brentuximab vedotin as consolidation therapy following high dose immunotherapy and autologous stem cell transplantation for refractory HL, serious

infections were reported in 15 participants (9%) in the brentuximab vedotin arm and 7 participants (4%) in the placebo arm, with pneumonia as the most common serious infection [65]. Herpes simplex and herpes zoster infections occurred more commonly in the brentuximab vedotin arm, while other opportunistic infections were rare. Overall, in the pivotal studies serious infections were reported in 10% of patients. Treatment-related serious adverse events included pneumonia, urinary tract infection, staphylococcus bacteremia, and pneumocystis carinii pneumonia. Grade 1 or Grade 2 upper respiratory infection was the infection with the highest incidence [65].

In a phase III trial of brentuximab vedotin compared to physician's choice of methotrexate or bexarotene for CD-30 positive cutaneous T cell lymphoma, serious infectious adverse events related to study drug occurred in 4 participants. These included Grade 3 impetigo, Grade 3 diverticulitis, and Grade 3 cellulitis [65]. All three serious infectious adverse events resolved without sequelae. One participant in each arm of the trial had infectious adverse events associated with Grade 3 or Grade 4 neutropenia.

1.4.1.2.1 Risk of SARS-CoV-2 infection

There is a risk of SARS-CoV-2 infection during study conduct. Participants will be educated and advised about the importance of strict adherence to the Centers for Disease Control and Prevention (CDC) recommendations for reducing the risk of SARS-CoV-2 infection, including mask wearing, social distancing, and hand washing. Completion of a primary SARS-CoV-2 vaccination series is required 14 days prior to the first infusion of study medication. The dose and schedule of the vaccine is defined according to current FDA approval or Emergency Use Authorization at the time of screening. Additional doses of SARS-CoV-2 vaccines are permitted if authorized by the FDA during study conduct.

Participants are required to have a negative SARS-CoV-2 PCR test prior to enrollment.

Study medication will be suspended if the participant develops symptomatic or asymptomatic SARS-CoV-2 infection, or any other infection that the investigator judges to be significant. Participants with confirmed mild or moderate SARS-CoV-2 infection will be evaluated for treatment with a monoclonal antibody product authorized by the FDA for the treatment of COVID-19, as soon as possible following confirmation of the infection and within 10 days of symptom onset [69-71]. Additionally, any participant who has close contact with a SARS-CoV-2 infected individual should be evaluated for post-exposure prophylaxis as soon as possible after exposure [69, 70]. Use of other therapeutic agents for the treatment of SARS-CoV-2 that have been authorized or approved by the FDA may also be considered, depending on the clinical circumstance.

1.4.1.3 Risk of Pancreatitis, Hepatotoxicity, and Other Gastrointestinal Complications

Eight cases of pancreatitis have been reported to be associated with brentuximab vedotin, including two fatal cases. All cases presented with abdominal pain, nausea, and elevated lipase [72]. One case of acute pancreatitis was also reported in the phase III placebo-controlled trial of brentuximab vedotin consolidation therapy after HSCT for HL [60]. In clinical trials the incidence of acute pancreatitis is ≤0.3% and ≤0.2% in the post-marketing setting [65].

Hepatotoxicity has been reported in association with brentuximab vedotin, in some cases fatal. The majority of events were mild to moderate asymptomatic transaminase elevations. The reported incidence of hepatobiliary disorder is < 2% in clinical studies and post-marketing experience [65].

Other gastrointestinal complications were reported to be common in trials with brentuximab vedotin, including nausea, vomiting, abdominal pain, and diarrhea, although the majority of these adverse events were Grade 2 or less [54, 56, 58]. Additional serious gastrointestinal complications have been reported, including perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus.

1.4.1.4 Risk of Infusion Reactions, Pulmonary Toxicity, and Skin and Subcutaneous Tissue Disorders

Two cases of anaphylaxis occurred in phase 1 trials with brentuximab vedotin. Grade 1 or Grade 2 infusion reactions were reported in 12% of participants in the pivotal phase II trials, including chills, nausea, dyspnea, pruritis, fever, and cough [54].

Pulmonary toxicity associated with brentuximab vedotin has been reported, primarily when combined with bleomycin [73]. Pulmonary adverse events were also reported in both the brentuximab vedotin group and the placebo group in a phase III trial of consolidation therapy following ASCT for HL, including two deaths in the brentuximab vedotin group resulting from acute respiratory distress syndrome [60]. Fatal and serious events of non-infectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome have been reported with brentuximab vedotin monotherapy. Although a causal relationship has not been established, pulmonary toxicity related to brentuximab vedotin monotherapy has not been ruled out [65].

Although rare, fatal and serious Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with brentuximab vedotin [54, 65, 74]. Rash and alopecia were common adverse events reported in the pivotal phase II clinical trials [54, 56, 58].

1.4.1.5 Risk of Embryo and Fetal Harm and Impaired Fertility

Decreased embryo viability and teratogenicity, including fetal malformations, have been described in animal studies. Brentuximab vedotin may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Hence women receiving

brentuximab vedotin and female partners of men receiving brentuximab vedotin should take measures to prevent pregnancy during treatment with brentuximab vedotin and for at least six months after the final dose of brentuximab vedotin. Requirements for contraception are outlined in protocol section 5.3.1.2. Decreased male fertility has also been associated with brentuximab vedotin in animal studies [54, 55, 65].

1.4.1.6 Risk of Drug Interaction with Cytochrome P450 3A4 Inhibitors or Inducers, or P-glycoprotein Inhibitors

Concomitant use of strong Cytochrome P450 3A4 (CYP3A4) inhibitors or inducers, or P-glycoprotein (P-gp) inhibitors, has the potential to affect the exposure to MMAE. Participants who are receiving strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, should be closely monitored for adverse reactions [55]. A specific precaution for potential drug interactions is provided in Section 5.3.4.1, and examples are provided in Appendix 3. These agents will be avoided whenever possible.

1.4.2 Benefits

As noted in section 1.1, there are no FDA-approved therapies for dcSSc, and immunosuppressive drugs do not adequately control disease [6]. Although individual participants in this trial should not anticipate direct benefit, a dose escalation safety study is the first step in evaluating brentuximab vedotin as a treatment for dcSSc. A future placebo-controlled clinical trial testing the efficacy of brentuximab vedotin for dcSSc could then lead to benefit for individuals suffering from this morbid and life-threatening condition.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

To assess the safety and tolerability of brentuximab vedotin in diffuse cutaneous systemic sclerosis (dcSSc).

2.2 SECONDARY OBJECTIVES

Safety Objectives

1. To assess safety events that occur during and following brentuximab vedotin administration in dcSSc.
2. To assess peripheral neuropathy and neutropenia during and following brentuximab vedotin administration in dcSSc.

Exploratory Efficacy Objectives

1. To assess cutaneous, pulmonary, and other clinical manifestations of dcSSc during and following brentuximab vedotin administration.
2. To assess patient-reported quality of life measures in dcSSc during and following brentuximab vedotin administration.

2.3 EXPLORATORY MECHANISTIC OBJECTIVES

1. To analyze immune cell populations and cytokines in the skin and blood during and following brentuximab vedotin administration.
2. To analyze autoantibodies and soluble CD30 during and following brentuximab vedotin administration.
3. To analyze genetic signatures of disease, inflammation, and fibrosis during and following brentuximab vedotin administration.

3. STUDY DESIGN

3.1 DESCRIPTION

This trial will be conducted as a multicenter prospective double blind placebo-controlled dose escalation safety study with brentuximab vedotin and stable background immunosuppressive therapy in adult individuals with dcSSc. Adult male and female participants with dcSSc will be recruited by a collaborative group of clinical sites in the United States. Participants who meet the eligibility criteria will be enrolled without regard to gender, race, or ethnicity. Eligible participants will be randomly assigned to study treatment, either brentuximab vedotin or placebo equivalent in a 6:2 ratio favoring brentuximab vedotin. Three dose cohorts are planned with 8 participants in each cohort, for a total of 24 participants who receive sufficient doses of the investigational medication to assess safety (Section 4.5).

The doses planned for each ascending dose cohort include 0.6mg/kg, 1.2 mg/kg, and 1.8 mg/kg brentuximab vedotin or placebo equivalent. All cohorts will receive intravenous administration of study medication every 3 weeks for 21 weeks, for a total of eight doses. Following completion of treatment, participants will undergo follow-up visits at weeks 24, 28, 36 and 48.

After completion of the first 12 weeks of treatment for each of the first two cohorts of 8 participants, an interim safety analysis will be conducted and reviewed by an independent Safety Review Committee, as described in Section 8.11.2. Approval by the Safety Review Committee following the 12-week interim safety analysis will be required before proceeding to the next higher dose of brentuximab vedotin.

Interim safety analysis will also be conducted at 24 weeks following completion of study treatment for each of the first two cohorts of 8 participants. Following either the week 12 or the week 24 interim safety reviews, the Safety Review Committee can recommend actions regarding study conduct, as described in Section 8.11.2.

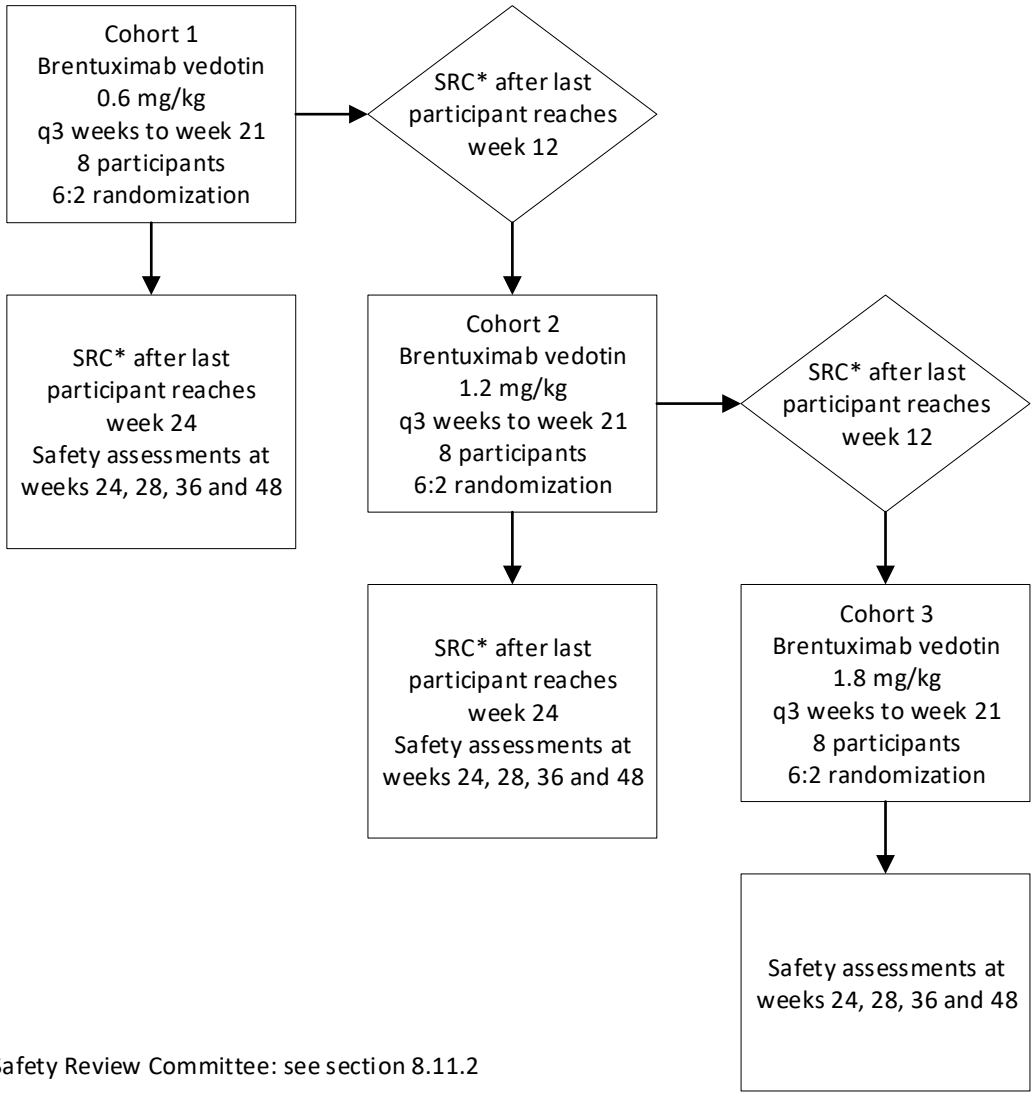


Figure 1. Study Schema

3.2 STUDY REGIMEN

Brentuximab vedotin or placebo.

- Cohort 1: Intravenous brentuximab vedotin 0.6 mg/kg or placebo every three weeks for eight doses.
- Cohort 2: Intravenous brentuximab vedotin 1.2 mg/kg or placebo every three weeks for eight doses.
- Cohort 3: Intravenous brentuximab vedotin 1.8 mg/kg or placebo every three weeks for eight doses.

3.3 STUDY DURATION

Total study duration target is 308 weeks:

- Enrollment phase duration target is 260 weeks.
- Study participation phase for each participant is 48 weeks, which includes a treatment phase of 21 weeks and a follow-up phase of 27 weeks.

3.4 STUDY ENDPOINTS

3.4.1 Primary Endpoint

The primary endpoint will be the proportion of participants who experience at least one Grade 3 or higher adverse event at or before week 48.

3.4.2 Secondary Endpoints

Safety Endpoints:

1. The proportion of participants who experience at least one Grade 3 or higher adverse event at or before weeks 12, 24 and 36.
2. The proportion of participants who experience at least one Grade 2 or higher adverse event at or before weeks 12, 24, 36, and 48.
3. The proportion of participants with Grade 2 or higher peripheral neuropathy at or before weeks 12, 24, 36, and 48.
4. The proportion of participants with Grade 3 or higher neutropenia at or before weeks 12, 24, 36, and 48.
5. The proportion of participants with any of the following Grade 3 or higher adverse events at or before week 48:
   a. Peripheral neuropathy.
   b. Neutropenia.
   c. Infectious adverse events.
   d. Infusion reactions, including anaphylaxis and new onset rash consistent with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other drug reaction.
   e. PML.

Exploratory Efficacy Endpoints:

1. Modified Rodnan Skin Score (mRSS) at weeks 12, 24, and 48.
2. Provisional American College of Rheumatology Combined Response Index in Systemic Sclerosis (CRISS) [75] at weeks 24 and 48.
3. Percent predicted Forced Vital Capacity (FVC) at weeks 24 and 48 weeks.
4. Physician's global assessment on a Likert scale at weeks 24 and 48.
5. Patient's global assessment on a Likert scale at weeks 24 and 48.

6. Health-related quality of life (HRQOL) assessed by PROMIS-29 version 2.0 at weeks 24 and 48.
7. Physical function assessed by the Scleroderma Health Assessment Questionnaire-Disability Index (SHAQ-DI) at weeks 24 and 48.

3.5 RATIONALE FOR SELECTION OF DRUG, ROUTE, DOSE, AND REGIMEN

The brentuximab vedotin route, dose, and regimen was selected based on the suggested dosing and administration of brentuximab vedotin for relapsed or refractory classical Hodgkin's lymphoma and systemic anaplastic large cell lymphoma [55]. The dose recommended in the prescribing information is 1.8 mg/kg administered intravenously every three weeks for a maximum of 16 doses.

Since the current study is a dose escalation safety evaluation in a non-oncology indication, the first cohort will receive one third of the recommended dose of brentuximab vedotin (0.6 mg/kg) for eight doses, the second cohort will receive two thirds of the recommended dose of brentuximab vedotin (1.2 mg/kg) for eight doses, and the final cohort will receive the recommended oncology dose of brentuximab vedotin (1.8 mg/kg) for eight doses.

Of note, Seattle Genetics undertook a dose escalation study of brentuximab vedotin in SLE [65]. The trial was planned as a blinded randomized safety study in a total of 40 adult participants with active SLE, with each cohort of 10 participants receiving one of four escalating doses of brentuximab vedotin or placebo. The primary outcome measures were the number and percentage of participants experiencing adverse events over a 127-day time frame. Although no safety concerns were noted in the first two dosing cohorts, Seattle Genetics terminated the study before completion due to revised business portfolio prioritization (NCT02533570).

4. ELIGIBILITY

4.1 INCLUSION CRITERIA

Patients must meet *all* of the following criteria to be eligible for this study:

1. Classification of systemic sclerosis (SSc), as defined using the 2013 American College of Rheumatology/European Union League Against Rheumatism classification of SSc [76].
2. Diagnosis of dcSSc, as defined by LeRoy and Medsger [77].
3. Disease duration ≤ 60 months (defined as time from the first non-Raynaud phenomenon manifestation).
4. mRSS units ≥ 15 and ≤ 45, and both of the following:
   a. At least mild skin thickening (≥ 1+ mRSS) of the forearm, and

b. At least moderate skin thickening (≥ 2+ mRSS) at the planned forearm skin biopsy site.

5. Documentation of at least 12 weeks of ongoing immunosuppressive therapy for SSc at the time of enrollment, and at least 4 weeks at a stable dose, of one of the following:
   a. Methotrexate ≤ 25 mg/week, or
   b. Mycophenolate mofetil ≤ 3 grams/day or mycophenolate sodium ≤ 2.16 grams/day, or
   c. Azathioprine ≤ 3mg/kg/day.
6. Age 18-70 years inclusive.
7. Completion of primary SARS-CoV-2 vaccination series is required at least 14 days prior to the first infusion of study medication at Visit 0. The dose and schedule of the vaccine is defined according to current FDA approval or Emergency Use Authorization at the time of screening.
8. Ability to provide informed consent.

4.2 EXCLUSION CRITERIA

Patients who meet any of the following criteria will *not* be eligible for this study:

1. Rheumatic disease other than dcSSc; it is acceptable to include patients with osteoarthritis, fibromyalgia, sicca symptoms, and scleroderma-associated myopathy.
2. Limited cutaneous SSc or sine scleroderma.
3. Pulmonary disease with FVC ≤ 60% of predicted, or DLCO (corrected for hemoglobin) ≤ 60% of predicted.
4. Pulmonary hypertension (PH) or moderate to severe left ventricular dysfunction, defined as one of the following:
   a. Transthoracic echocardiography demonstrating at least one of the following (unless subsequent right heart catheterization does not demonstrate PH; or unless prior right heart catheterization within one year did not demonstrate PH and echocardiography results are not significantly changed):
      i. Tricuspid regurgitation jet >2.8 m/sec or estimated right ventricular systolic pressure > 42 mm Hg, or
      ii. At least one of the following:
         1. Abnormality of right atrial size, shape, or wall thickness consistent with PH, or
         2. Abnormality of right ventricular size, shape, or wall thickness consistent with PH, or
         3. Abnormal septal wall shape consistent with PH.
      iii. Left Ventricular Ejection Fraction (LVEF) < 50%.

b. Right heart catheterization showing mean pulmonary artery pressure ≥25 mm Hg at rest.
c. Current use of approved medications for PH. It is acceptable to use phosphodiesterase type 5 (PDE-5) inhibitors for Raynaud's, digital ulcers, and intermittently for erectile dysfunction.

5. Active scleroderma renal crisis within the 4 months prior to enrollment.
6. History of moderate-to-severe lower gastrointestinal dysmotility such as current use of parenteral nutrition and/or recent history of intestinal pseudo-obstruction within 3 months prior to enrollment.
7. The following medications:
   a. Oral corticosteroids >10 mg/day of prednisone or equivalent within 2 weeks prior to enrollment.
   b. Treatment with intravenous immunoglobulin (IVIG) within 12 weeks prior to enrollment.
   c. Treatment with cyclophosphamide within 6 months prior to enrollment.
   d. Use of investigational biologic or non-biologic medication within the past 90 days, or 5 half-lives prior to enrollment, whichever is greater, except for SARS-CoV-2 vaccines, and medications used for prevention and treatment of COVID-19, per FDA Emergency Use Authorization.
   e. Use of anti-TNF medication or other biologic medications within the past 90 days, or 5 half-lives prior to enrollment, whichever is greater.
   f. Prior treatment with anti-CD20 if either of the following are true:
      i. B cells ≤ lower limit of normal (LLN), or
      ii. Treatment with anti-CD20 has been within 12 months prior to enrollment.
   g. Any prior treatment with cell-depleting therapies other than anti-CD20, including investigational agents, including but not limited to, CAMPATH®, anti-CD4, anti-CD5, anti-CD3, anti-CD19.
   h. Any prior treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation.
8. Receipt of a live-attenuated vaccine within 3 months of study enrollment.
9. Concomitant malignancies or a history of malignancy, with the exception of adequately treated basal and squamous cell carcinoma of the skin, or carcinoma in situ of the cervix.
10. Major surgery (including joint surgery) within 8 weeks prior to enrollment.
11. History of solid organ or hematopoietic stem cell transplantation.
12. History of primary immunodeficiency.

13. Comorbidities requiring systemic corticosteroid therapy, including those which have required three or more courses of systemic corticosteroids within the 12 months prior to enrollment.
14. Current substance abuse or history of substance abuse within 12 months prior to enrollment.
15. History of severe depression or severe psychiatric condition.
16. Lack of peripheral venous access.
17. Known hypersensitivity to brentuximab vedotin, a component thereof, or the excipient contained in the drug formulation.
18. Severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, or neurological disease (or, in the investigator's opinion, any other concomitant medical condition that places the participant at risk by participating in this study), including but not limited to:
    a. Uncompensated congestive heart failure (New York Heart Association Class III or VI).
    b. Clinically significant active coronary artery disease (e.g., unstable angina or acute myocardial infarction within 6 months prior to enrollment).
    c. Recently active cerebrovascular disease (e.g., stroke or transient ischemic attack within 6 months prior to enrollment).
    d. Uncontrolled systemic hypertension.
    e. Confirmed diagnosis of diabetes mellitus.
    f. Pancreatitis within 30 days prior to enrollment.
    g. History or presence of peripheral neuropathy, such as mononeuritis multiplex, acute or chronic inflammatory demyelinating polyneuropathy, axonal sensorimotor neuropathies, or drug related neuropathy or neuritis.
19. Evidence of infection:
    a. Any infected ulcer at enrollment.
    b. Active bacterial, viral, fungal, or opportunistic infections requiring systemic anti-infective therapy.
    c. Evidence of current or prior infection with tuberculosis
        i. Positive QuantiFERON® – TB Gold or TB Gold Plus test results. Purified protein derivative (PPD) tuberculin test may be substituted for QuantiFERON® – TB Gold or TB Gold Plus test.
        ii. Indeterminant QuantiFERON® – TB Gold or TB Gold Plus test results, unless followed by a subsequent negative PPD or negative QuantiFERON® and clearance by local Infectious Disease department.
    d. Evidence of current or prior infection with
        i. Human immunodeficiency virus (HIV), or

ii. Hepatitis B (as assessed by hepatitis B surface antigen, HBsAg and antibody to hepatitis B core antigen, anti-HBc) or

iii. Hepatitis C (HCV), except adequately treated HCV with documentation of sustained virologic response defined as undetectable HCV RNA at least 12 weeks after the end of treatment.

e. History of progressive multifocal leukoencephalopathy (PML).

f. Hospitalization for treatment of infections, or parenteral (intravenous or intramuscular) antibacterial, antivirals, anti-fungal, or anti-parasitic agents within the past 60 days prior to enrollment.

g. Chronic infection that is currently being treated with systemic suppressive antibiotic or antiviral therapy, including but not limited to tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster, and atypical mycobacteria.

h. History of significant infection or recurrent infection that, in the investigator's opinion, places the participant at risk by participating in this study.

i. Positive PCR test for SARS-CoV-2 within 14 days prior to enrollment.

20. The following laboratory abnormalities:

a. Neutropenia (absolute neutrophil count <1500/mm^3).

b. Thrombocytopenia (platelets <100,000/mm^3).

c. Moderately severe anemia (hemoglobin < 10 g/dL).

d. Liver function test (aspartate aminotransferase [AST], alanine aminotransferase [ALT], or alkaline phosphatase) results that are ≥ 1.5 times the upper limit of normal.

e. Serum total bilirubin > 1.5 times the upper limit of normal, or > 3 times the upper limit of normal in the presence of Gilbert's syndrome.

f. Serum amylase and serum lipase > 1.5 times the upper limit of normal.

21. Renal dysfunction, defined as either one of the following:

a. Serum creatinine > 1.5 times the upper limit of normal.

b. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2.

22. Pregnancy.

23. Breastfeeding.

24. Unwillingness to use two forms of medically acceptable contraception methods by participants and their partners (if of reproductive potential) during the study and for at least 6 months after last dose of study drug.

25. Inability to comply with study and follow-up procedures.

4.3 PREMATURE DISCONTINUATION OF STUDY THERAPY

Study treatment, defined as the dosing and administration of study medication according to study specification, will be discontinued for an individual participant if any of the following occurs:

- A toxicity management discontinuation criterion is met for brentuximab vedotin (Section 5.2).
- The participant's dose of methotrexate, mycophenolate mofetil, azathioprine, or prednisone exceeds the allowed dose (Section 5.3.1.1 and section 5.3.3).
- The investigator or the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor determines that it is in the participant's best interest to discontinue treatment for any reason, including non-adherence to the protocol.
- The participant requests that treatment be halted.
- The participant becomes pregnant (see section 8.8 Reporting Pregnancy).

Further care will be provided according to the judgment and practice of the principal investigator.

At this time the participant will complete all assessments listed for the discontinuation visit (DSC). The participant will be asked to return for safety follow-up visits at weeks 12, 24, 36, and 48, if these visits have not already occurred.

If study treatment is discontinued, the NIAID Medical Monitor should be notified.

4.4 PREMATURE TERMINATION OF A PARTICIPANT FROM THE STUDY

Withdrawal of consent. Participants who withdraw consent will be asked to complete an end-of-study visit to include the assessments listed in visit 11.

Failure to return. Participants who do not return for visits and who do not respond to repeated attempts by the site staff to have them return will be considered lost to follow-up.

Investigator decision. The investigator or the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor determines that participation in the study is no longer in the best interest of the participant.

4.5 REPLACEMENT OF STUDY PARTICIPANTS

Participants will be replaced if they do not receive 1 full dose of study medication, or if they discontinue before receiving 6 of 8 doses for a reason unrelated to treatment or the disease. A maximum of 8 extra participants may be enrolled in a single dosing cohort under these criteria. The procedures in section 4.3 will be followed for participants who receive any part of an infusion of study medication.

5. STUDY THERAPIES, MEDICATIONS AND PROCEDURES

5.1 INVESTIGATIONAL MEDICATION: BRENTUXIMAB VEDOTIN

5.1.1 Formulation and Packaging

Brentuximab vedotin 50 mg is supplied as a sterile, white to off-white lyophilized, preservative-free cake or powder in a single-use vial for reconstitution. The pH of reconstituted product is approximately 6.6. Brentuximab vedotin will be provided by the manufacturer. Brentuximab vedotin will be distributed to sites by a designated drug distributor under contract to NIAID.

5.1.2 Placebo Preparation

Brentuximab vedotin placebo consisting of 0.9% Normal Saline will be prepared by the site pharmacist.

5.1.3 Dosage, Handling, Preparation, and Administration

5.1.3.1 Dosage

Brentuximab vedotin dose will be determined based on the participant's weight. Rounding is permissible within 5% of the nominal dose. Weight from the previous visit may be used to calculate the brentuximab vedotin dose unless the weight was obtained more than 30 days previously. Actual weight will be used except for participants weighing greater than 100kg; the dose for participants with weight greater than 100 kg will be calculated based on 100 kg.

Brentuximab vedotin or placebo will be administered every 3 weeks from study week 0 through study week 21, according to the schedule described in Section 3.1:

- Cohort 1 will receive 0.6 mg/kg brentuximab vedotin or placebo (to a maximum dose 60 mg).
- Cohort 2 will receive 1.2 mg/kg brentuximab vedotin or placebo (to a maximum dose 120 mg).
- Cohort 3 will receive 1.8 mg/kg brentuximab vedotin or placebo (to a maximum dose 180 mg).

5.1.3.2 Storage Conditions and Handling Precautions

Brentuximab vedotin is an anti-neoplastic product, and must be handled and disposed according to guidelines provided by Occupational Safety and Health Administration (OSHA) for hazardous drugs [78]. Handling precautions include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

Brentuximab vedotin vials must be stored at 2-8^{o} C and protected from light in the original container prior to reconstitution.

Following reconstitution and dilution, brentuximab vedotin solution can be stored at 2-8° C and administered within 24 hours of reconstitution and dilution.

Do not freeze.

5.1.3.3 Preparation

5.1.3.3.1 Reconstitution

Brentuximab vedotin will be reconstituted according to the prescribing information [55]. The number of 50 mg vials of brentuximab vedotin needed will be calculated based on the participant's weight, as described in section 5.1.3.1. Each vial will be reconstituted with 10.5mL of Sterile Water for Injection USP, to yield a single-use solution containing 5mg/ml brentuximab vedotin.

The stream of Sterile Water will be directed toward the wall of the vial and not directly at the cake or powder. Gently swirl the vial to aid dissolution. Do not shake. Upon inspection, the reconstituted solution should be clear to slightly opalescent, colorless, and free of particulate matter.

Reconstituted brentuximab vedotin will be immediately diluted into an infusion bag. If not diluted immediately, reconstituted brentuximab vedotin will be stored according to section 5.1.3.2.

The unused portion of brentuximab vedotin vials will be discarded according to guidelines provided by OSHA for hazardous drugs [78].

5.1.3.3.2 Dilution

Reconstituted brentuximab vedotin will be diluted according to the prescribing information [55]. The required volume of 5 mg/mL brentuximab vedotin will be calculated based on the participant's weight. This volume will be withdrawn from the vials and immediately added to an infusion bag containing a minimum volume of 0.9% Normal Saline Injection, 5% Dextrose Injection, or Lactated Ringer's Injection. The infusion bag will be gently inverted to mix.

Following dilution, brentuximab vedotin will be infused immediately according to the instruction in section 5.1.3.4. If not infused immediately, brentuximab vedotin will be stored according to section 5.1.3.2.

5.1.3.4 Administration and Monitoring

5.1.3.4.1 Pre-medication

Routine premedication for brentuximab vedotin is not indicated [55]. However, premedication should be administered to any participant who experienced a Grade ≤ 2 infusion reaction during or following a previous brentuximab vedotin administration. These participants should receive premedication one hour (plus or minus approximately 15 minutes) prior to the brentuximab vedotin infusion with oral acetaminophen 650 mg, oral diphenhydramine 50 mg or equivalent antihistamine, and intravenous methylprednisolone 20 mg or equivalent corticosteroid.

5.1.3.4.2 Monitoring

Brentuximab vedotin infusions will occur in a setting with access to ACLS certified personnel, resuscitative drugs, monitoring devices, and CPR equipment. Vital signs must be assessed prior to the infusion, approximately every 15 minutes during the infusion, at the end of the infusion, and 1 hour after the completion of the infusion. After the infusion is complete, the intravenous line must remain in the participant for at least 1 hour to facilitate administration of medical management if needed.

5.1.3.4.3 Administration

Brentuximab vedotin or placebo will be administered as an intravenous infusion over approximately, but no less than, 30 minutes, as described in the prescribing information at study weeks 0 through 21. Hematology and serum chemistry results must be obtained within 72 hours prior to infusions at study weeks 3 through 21.

Brentuximab vedotin must not be administered as an intravenous (IV) push or bolus. Do not mix brentuximab vedotin, or administer as an infusion, with any other medicinal products. If an infusion related reaction occurs, the infusion should be interrupted and medical management instituted as needed (e.g., corticosteroids, epinephrine, bronchodilators, or oxygen). In cases of mild reactions (≤ Grade 2), the infusion can be resumed at a 50% rate reduction when symptoms have resolved and are no longer deemed a threat to the participant's well-being. If anaphylaxis occurs, immediately and permanently discontinue brentuximab vedotin and administer emergency medical therapy.

5.2 TOXICITY MANAGEMENT OF BRENTUXIMAB VEDOTIN

5.2.1 SARS-CoV-2 Infection or Exposure

Suspend brentuximab vedotin or placebo administration if the participant develops symptomatic or asymptomatic SARS-CoV-2 infection:

- Participants with mild or moderate SARS-CoV-2 infection should be evaluated for treatment with a monoclonal antibody product authorized by the FDA for the treatment of COVID-19, as soon as possible following confirmation of the infection and within 10 days of symptom onset [69-71]. Use of other FDA authorized or approved therapeutic agents should also be considered as they become available, depending on the clinical circumstance.

- Brentuximab vedotin may be restarted at the next scheduled dose, if symptoms have been absent for at least 10 days, or in the case of asymptomatic infection at least 10 days have passed since the positive SARS-CoV-2 test. In addition, a negative PCR test for SARS-CoV-2 must be obtained prior to restarting brentuximab vedotin or placebo administration.

- Any participant who has close contact with a SARS-CoV-2 infected individual should be evaluated for post-exposure prophylaxis as soon as possible after exposure [69, 70].

5.2.2 Other Infection or AE

Suspend brentuximab vedotin or placebo administration if the participant develops any other infection or AE that the investigator judges to be significant. If the infection or AE resolves, brentuximab vedotin may be restarted at the next scheduled dose.

5.2.3 Peripheral Neuropathy

Suspend brentuximab vedotin administration if the participant develops a Grade 2 peripheral neuropathy. If the peripheral neuropathy resolves, brentuximab vedotin may be restarted at a lower dose as follows: the affected participant in Cohort 1 will restart brentuximab vedotin at 0.3 mg/kg/dose, in Cohort 2 will restart brentuximab vedotin at 0.6 mg/kg/dose, and in Cohort 3 will restart brentuximab vedotin at 1.2 mg/kg/dose.

5.2.4 Permanent Discontinuation of Study Medication for Toxicity

Permanently discontinue brentuximab vedotin if any of the following occurs:

- The participant misses > 3 doses of brentuximab vedotin.
- Grade 2 peripheral neuropathy recurs after brentuximab vedotin suspension and dose modification, as described above.
- Grade 3 or greater peripheral neuropathy.
- Grade 3 or greater neutropenia or thrombocytopenia.
- Grade 3 or greater infusion reaction.
- Anaphylaxis, defined as a serious allergic reaction that is rapid in onset and may cause death (see Appendix 2) [79].
- New onset rash consistent with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other drug reaction.
- eGFR < 30 ml/min/1.73m^2.
- Potential drug-induced liver injury, defined as all three of the following:
    - ALT or AST elevation > 3 times upper limit of normal (ULN), and
    - Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), and
    - No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including but not limited to viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drugs known to be hepatotoxic.
- Two or more Grade 3 or greater infections, or one Grade 4 infection.

- A suspected case of PML.

A diagnosis of PML should be considered in any participant presenting with new-onset or deteriorating neurological signs and symptoms. The participant should be referred to a neurologist or other appropriate specialist for evaluation. If PML is suspected, this should be immediately reported to the NIAID Medical Monitor. The appropriateness of continuing study medication, while the case is being assessed, should be discussed.

If brentuximab vedotin is discontinued, the procedures in Section 4.3 should be followed.

5.3 CONCOMITANT MEDICATIONS

5.3.1 Required Medications

5.3.1.1 Required Immunosuppression

Participants are required to be on one of the following medications at study entry:

- Methotrexate ≤ 25 mg/week.
- Mycophenolate mofetil ≤ 3 grams/day or mycophenolate sodium ≤ 2.16 grams/day.
- Azathioprine ≤ 3mg/kg/day.

It is recommended that these medications are maintained at a stable dose, however dose reductions are allowed for toxicity associated with these medications or in case of infection, per investigator judgment.

5.3.1.2 Contraception

Use of two methods of medically acceptable contraception are required for participants and their partners (if of reproductive potential) during the study and for at least 6 months after 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 for 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.

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. Female participants of childbearing potential taking concomitant mycophenolate and oral contraceptives must use a barrier method of contraception along with their oral contraceptives.

Mycophenolate Risk Evaluation and Mitigation Strategy (REMS). It is strongly recommended that investigators with female participants of childbearing potential taking mycophenolate mofetil enroll them in the Mycophenolate REMS program, as described in section 8.8.

5.3.2 Recommended Prophylactic Medication

Folic acid supplementation is strongly recommended for participants on methotrexate.

5.3.3 Permitted Medications

Use of hydroxychloroquine ≤ 400 mg/day is permitted at study enrollment and continuing during the study. Initiation of hydroxychloroquine during the study is not permitted.

Oral corticosteroids ≤ 10 mg/day prednisone or the equivalent are permitted.

Corticosteroids may be increased for SSc or non-SSc indications on two separate occasions for a period of ≤14 days. Increases for SSc indications are not to exceed prednisone 20 mg per day or the equivalent and increases for non-SSc indications are not to exceed prednisone 0.5 mg/kg/day or the equivalent. Corticosteroid dose may be increased one time between study weeks 0 and 24 and one time between study weeks 24 and 48.

Corticosteroids are also allowed as premedication for infusion reactions, as described in section 5.1.3.4.1.

5.3.4 Prohibited Medications and Vaccines

Participants may not use immunosuppressive or immunomodulatory medications, including biologics, except those specified in the protocol. Increases above the dose at study enrollment are prohibited for the following medications:

- Methotrexate.
- Mycophenolate mofetil.
- Azathioprine.

The use of any investigational drug or investigational treatment other than those specified in the protocol is prohibited during study participation. SARS-CoV-2 vaccines and medications used for prevention and treatment of COVID-19, as authorized by the FDA for emergency use, are not prohibited.

The use of live attenuated vaccines is prohibited during treatment with study medication and for 12 weeks following treatment.

Concomitant administration of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity; therefore, bleomycin administration during the study is prohibited.

5.3.4.1 Special Precautions for Cytochrome P450 3A4 Inhibitors or Inducers, or P-glycoprotein Inhibitors

Concomitant use of strong Cytochrome P450 3A4 (CYP3A4) inhibitors or inducers, or P-glycoprotein (P-gp) inhibitors, has the potential to affect the exposure to MMAE. Participants who are receiving strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, should be closely monitored for adverse reactions [55]. See Appendix 3 for examples [80]. These medications should be avoided, and alternatives used whenever possible.

5.4 DRUG ACCOUNTABILITY

Under federal regulations (21CFR 312.62) an investigator is responsible for delegating this responsibility to a qualified pharmacist of record (PoR) at every study site. The PoR is required to maintain adequate records of the disposition of the investigational product, including the date and quantity of drug that was received, the participants to whom drug was dispensed (participant by participant accounting), and an account of any drug accidentally or deliberately destroyed. The investigator will ensure that the investigational product supplies are stored as specified in the protocol and pharmacy manual in a secured area, with access limited to authorized study personnel as described in the clinical study agreement.

Records for receipt, storage, use, and disposition of the study drug will be maintained by the study sites. A drug-dispensing log will be kept current for each participant and will contain the identification of each participant and the date and quantity of drug dispensed. All remaining unused investigational product will be returned to the sponsor or sponsor's representative after study termination or destroyed with the permission of the sponsor in accordance with applicable law and study site procedures. If investigational product is to be destroyed locally, the investigator will provide documentation in accordance with sponsor's specifications.

All records regarding disposition of the investigational product will be available for inspection by the clinical trial monitor.

5.5 ASSESSMENT OF COMPLIANCE WITH STUDY MEDICATION

All study medications will be administered at sites by trained medical staff. Therefore, compliance will be monitored by the site and documented on the eCRF.

6. STUDY ASSESSMENTS AND WINDOWS

6.1 VISIT WINDOWS

6.1.1 Scheduled Visits

Appendix 1 presents the schedule of events for this trial. Visit 0 must occur within 28 days of Visit –1. All other scheduled study visits must occur within the time limits specified below:

Visits 1 through 8: +/-3 days

Visit 9: +/- 7 days
Visits 10 and 11: +/- 14 days

6.1.2 Window for Administration of Study Medication

The schedule for administration of study medication is described in Appendix 1. Study medication infusions must occur at least 18 days after the prior infusion.

6.1.3 Unscheduled Visits

Unscheduled visits may be performed to document any symptoms or to document a scleroderma flare during the study. Unscheduled visits may also be performed for Neurologist assessment in the event of suspected peripheral neuropathy. Assessments for an unscheduled visit are listed in Appendix 1. Some of the assessments may be omitted at the discretion of the investigator if they are not indicated.

6.2 RANDOMIZATION, BLINDING, AND UNBLINDING

6.2.1 Randomization

Participants who meet the eligibility criteria will be randomly assigned to a study treatment group, either brentuximab vedotin or placebo control. Enrollment is defined as the time of random assignment. Participants will be randomly assigned to their treatment group utilizing a centralized, automated randomization system. Randomization will not be stratified.

6.2.2 Blinding

Blinding will be maintained for all study participants and trial personnel, with the exception of the site pharmacist from the time of randomization throughout the study.

6.2.3 Unblinding

Unblinding before the study is completed will occur only if a participant's well-being is threatened and the site investigator believes unblinding is necessary to protect the participant. Unblinding may also occur in the event of pregnancy in a female participant or a male participant's partner.

Whenever possible, before treatment assignment for an individual participant is unblinded, the site investigator must confer with the NIAID medical monitor and the protocol chair. The NIAID medical monitor will notify the study management team.

If emergency unblinding is required for a subject's well-being during non-business hours, the site principal investigator or designee (i.e., sub-investigator specified on Form FDA 1572) must notify the investigative pharmacy of the need for the treatment assignment. The emergency unblinding will be recorded and reported to the DSMB. A full account of the event will be recorded, including the date and time of the emergency, the reason for the decision to unblind, and the names of the medical monitor and others who were notified of the emergency. During site visits, the site monitor must verify that the medical monitor was notified and that a written account was completed. The reasons for unblinding of a participant's treatment will be included in the final study report.

Immune Tolerance Network (ITN) and NIAID approval is required for unblinding the treatment of an individual participant or subgroups of participants for unplanned interim analyses to support DSMB reviews and final analysis.

An exception to the above rule is that Investigational New Drug (IND) Safety Reports will be reported to the health authorities, DSMB, and Institutional Review Boards (IRB) or ethics review committee in an unblinded fashion as requested by current ICH and local guidance.

6.3 GENERAL ASSESSMENTS

- Informed consent. Written informed consent will be obtained before any study assessments or procedures are performed.
- Eligibility criteria: Eligibility for study participation will be assessed during the screening period.
- Randomization.
- Demographics: age and ethnicity.
- Medical history. A history will be taken to determine if the participant has had any clinically significant diseases or medical procedures other than the disease under study.
- Scleroderma history. A history will be taken to determine the date of diagnosis of disease.
- Comprehensive physical examination.
- Limited physical examination. A physical examination focused on participant's current complaints and clinical status at the study visit will be conducted.
- Peripheral neuropathy assessment, including
    - Pin sensibility.
    - Vibration sensibility.
    - Muscle strength.
    - Motor symptoms (dexterity, walking, climbing, activities of daily life).
    - Sensory symptoms (paresthesia, numbness, neuropathic pain).
    - Autonomic symptoms
- Vital signs. Weight, temperature, blood pressure, respiration, and pulse will be obtained at all visits. Height will be obtained at visit -1. Temperature, blood pressure, respiration, and pulse will be obtained immediately before study drug infusion, approximately every 15 minutes during the infusion, at the end of the infusion and 60 minutes after the infusion is completed.
- Adverse events. Participants will be assessed for AEs.

- Concomitant medications. All concomitant medications and their indications will be recorded.

6.4 CLINICAL LABORATORY ASSESSMENTS

- Hematology (complete blood count, differential and platelet count).
- Serum chemistry: Blood urea nitrogen (BUN), creatinine, eGFR and liver panel (AST, ALT, alkaline phosphate, direct and total bilirubin). eGFR will be calculated according to the CKD-EPI formula [81].
- Serum amylase and lipase.
- HIV, unless test has been performed within 30 days of visit -1 and documented test results are available.
- Hepatitis B (surface antibody, core antibody, and surface antigen), unless test has been performed within 30 days of visit -1 and documented test results are available.
- Hepatitis C (RNA and antibody), unless test has been performed within 30 days of visit -1 and documented test results are available.
- Erythrocyte sedimentation rate (ESR).
- Serum Human Chorionic Gonadotropin (HCG) for women of childbearing potential (see section 5.3.1.2).
- STAT Urine Human Chorionic Gonadotropin (HCG) for women of childbearing potential (see section 5.3.1.2).
- QuantiFERON®-TB Gold or TB Gold Plus, unless test has been performed within 30 days of visit -1 and documented test results are available. (PPD tuberculin skin test may be substituted for the QuantiFERON®-TB Gold or TB Gold Plus).
- PCR test for SARS-CoV-2 within 14 days prior to enrollment.

6.5 GENERAL CLINICAL ASSESSMENTS

- Electrocardiogram (EKG).
- Echocardiogram.

6.6 DISEASE-SPECIFIC ASSESSMENTS

- Pulmonary function testing. Spirometry (FVC and FEV1) with DLCO. DLCO will be calculated according to the Global Lung Function Initiative (GLI) all-age reference values and corrected for hemoglobin [82, 83].
- Modified Rodnan Skin Score (mRSS).
- Physician global assessment.
- Patient reported outcomes (patient global assessments, PROMIS-29, SHAQ-DI) [84].

6.7 MECHANISTIC ASSESSMENTS

- Punch skin biopsies will be collected from fibrotic-skin areas.
- Plasma/Serum assays.
- PBMC assays.
- Whole blood DNA genotyping.
- Whole blood gene expression analysis.

7. MECHANISTIC ASSAYS

7.1 MECHANISTIC HYPOTHESES AND RATIONALE

SSc is characterized by fibrosis, inflammation, and micro vasculopathy in multiple organ systems, and there is substantial evidence linking these symptoms to an underlying autoimmune pathogenesis [14]. Nearly all patients diagnosed with SSc have anti-nuclear antibodies as well as other clinically–associated autoantibodies present in circulation [15]. Furthermore, biopsies taken from skin of SSc patients show infiltration of activated T cells [17], and this infiltration correlates with skin thickening, suggesting a relationship between fibrosis in the skin and inflammation. Recent data also suggests a key role for Th2 cells in skin fibrosis in which production of pro-fibrotic cytokines by Th2 cells ultimately leads to altered gene expression in skin fibroblasts [24].

CD30 is expressed on several immune cell subsets, but reports suggest that the subpopulation of Th2 cells implicated in SSc skin fibrosis may preferentially express CD30 [25, 31]. Therefore, the primary mechanistic hypothesis is that brentuximab vedotin will alter the balance of pro- versus anti-fibrotic effects of autoreactive T cells by impacting pathogenic Th2 cell populations expressing CD30 in the skin and/or peripheral blood. Brentuximab vedotin may also alter functional properties of new and/or pre-existing T cell subtypes not eliminated by treatment in skin or blood. Given that CD30 is also expressed by activated B cells and natural killer (NK) cells [27, 85] it is possible brentuximab vedotin will alter the frequency and/or functional properties of these immune cell types in skin and/or blood as well. Mechanistic studies will address multiple questions but will be prioritized based on the amount of tissue and blood available.

In this study, skin and blood samples will be collected with the objective of analyzing cellular infiltration and circulating immune cell populations, cytokine levels both in skin and circulation, autoantibodies, soluble CD30, and genetic signatures of disease, inflammation, and fibrosis. It is hypothesized that treatment with brentuximab vedotin may result in: 1) impact on CD30 expressing cells resulting in alterations in the number, proportion, and/or functional status of effector and regulatory T cells in peripheral blood and affected skin [25, 86-92], 2) favorable changes in gene expression in affected skin, specifically, downregulation of inflammatory and pro-fibrotic gene signatures and the expression of specific genes that have clinically-predictive value [93-96]. The following hypotheses will also be explored: 1) changes in the presence and titer of antinuclear

antibodies and other SSc-associated autoantibodies, 2) changes in the levels of circulating soluble CD30.

7.2 PLANNED MECHANISTIC ASSAYS

Two skin biopsies will be collected from fibrotic-skin areas at weeks 0, 12, and 24. One biopsy will be used for RNA isolation and one biopsy for immunohistochemical analysis. Blood will be collected at week 0, 12, 24 and 48 in ABI Tempus™ blood collection tubes for gene expression analysis, in serum clot tubes for serum assessments, and in heparinized tubes for PBMC isolation and plasma characterization.

7.2.1 Local Immune Responses in the Skin

7.2.1.1 Immunohistochemistry/In Situ Hybridization (IHC/ISH)

One of the two skin biopsies will be preserved for IHC/ISH upon collection. Skin sections may be stained with antibodies directed against T-cells and cytokines. Cellular infiltration can be compared between treatment groups to evaluate the efficacy of treatment on reducing the Th2 subsets and associated inflammatory and pro-fibrotic cytokines.

7.2.1.2 Gene expression of RNAlater® biopsies

CD30+ Th2 cells are critical to the pathogenesis of SSc and can be detected in lesional skin and blood [27, 34]. Treatment with brentuximab vedotin may impact CD30+ Th2 cells in affected skin resulting in reduced lesional levels of pro-fibrotic Th2 cytokines such as IL-4, and stabilization or reduction in molecular signatures of active fibrosis in SSc lesions.

Skin biopsies will be collected from enrolled participants to evaluate transcriptional changes following treatment with brentuximab vedotin. One of the two skin biopsies will be submerged in RNAlater® upon collection for evaluation of gene expression profiles. RNA will be isolated, and gene expression of selected cytokines and other immune regulatory molecules will be further evaluated using methods such as microarray, Nano string or RNA-seq.

Biopsy tissue will be compared pre- and post-treatment to determine the effect of treatment on the global gene expression in participants with SSc. Care will be taken in the interpretation of data comparing participants since the drug effects of immunosuppressive therapy for SSc at the time of enrollment may confound mechanistic observations. Therefore, comparisons at baseline will be performed to evaluate inflammatory signatures in the participants prior to treatment with brentuximab vedotin.

7.2.2 Cellular Assays

7.2.2.1 Peripheral Blood Mononuclear Cell (PBMC) preparation

All blood samples collected for PBMC isolation will be shipped from the clinical sites to the ITN core facility for processing using ITN standard operating procedures (SOPs) for PBMC separation and freezing. This will ensure that standardized procedures are used,

and that high quality material is obtained for testing. PBMCs will be stored in the vapor phase of liquid nitrogen until use.

7.2.2.2 Multi-parameter immunoprofiling of PBMC

Flow cytometry or mass cytometry may be done at ITN laboratories to analyze the impact of treatment on the frequency and functional status of specific immune cell populations in viably cryopreserved PBMC. We will investigate the hypothesis that treatment with brentuximab vedotin will impact CD30-expressing cells in peripheral blood. This may alter the proportion of activated effector T cell subtypes in the CD4 and CD8 T cell compartments, the ratio of effector T cell subsets to regulatory T cells, and/or the proportion of activated B cells and NK cells in the peripheral blood.

7.2.2.3 Quantification of autoreactive B cells

Activated B cells may express CD30 on their surface, thus treatment with brentuximab vedotin may have an impact on circulating B cells, specifically autoreactive B cells. Enzyme-linked immunospot (ELISPOT) assays may be used to quantify B cells with reactivity towards nuclear antigens. The kinetics of this response may be measured, and comparisons could be made between baseline and the time points following treatment.

7.2.2.4 Epigenetic analysis of PBMC

Recent data has emphasized the importance of epigenetic modifications in the pathogenesis of many disorders, including SSc [97, 98]. Current evidence demonstrates alterations in DNA methylation and histone code modifications in cells from patients with SSc [99]. While studies have revealed the significant role of epigenetic modifications in the pathogenesis of SSc, the causal nature of epigenetic alterations in SSc pathogenesis, as well as the effects of specific treatments, remains elusive. Epigenetic studies may therefore be designed to investigate correlations with disease progression and therapeutic response.

7.2.3 Serum and Plasma Assays

7.2.3.1 Serum cytokine assays

Alterations in presence or function of effector T cell populations due to treatment with brentuximab vedotin may result in changes in the gene expression profile in SSc patients [93-96]. Participant serum/plasma may be analyzed to investigate the impact of treatment on circulating levels of cytokines and inflammatory mediators. Longitudinal assessment of serum cytokines and inflammatory mediators may be performed using immunoassay platforms. Additionally, the impact of treatment on levels of cytokines and inflammatory mediators could be evaluated for correlations with changes in immune cell populations and/or gene expression in peripheral blood and skin.

7.2.3.2 Autoantibody titers

SSc is associated with several autoantibodies that may be clinically relevant in determining the diagnosis and prognosis of affected individuals [100]. Given that activated B cells may express CD30, treatment with brentuximab vedotin may impact

autoantibody production [27, 85]. To explore the impact of treatment on autoantibody titers, participant serum may be analyzed for circulating levels of antinuclear or other autoantibodies by ELISA or similar method. Longitudinal assessment of autoantibody levels could be compared between baseline and the time points following treatment.

7.2.3.3 Soluble CD30 levels

Circulating levels of soluble CD30 in patients with SSc have been shown to correlate with disease activity of SSc [32, 33]. Elimination of CD30+ cells may lower sCD30, which could be a biomarker of response to brentuximab vedotin. In order to explore the impact of treatment on soluble CD30, participant serum may be analyzed for circulating levels of soluble CD30. Circulating levels of soluble CD30 could be compared between baseline and the time points following treatment.

7.2.4 Whole Blood Assays

7.2.4.1 Whole blood DNA genotyping

It is reasonable to assume that treatment may not be equally effective in all individuals and that genetic differences may, in part, determine response. DNA may be isolated from whole blood collected from all consenting participants, and the ITN may perform genotyping for HLA Class I/II alleles or single nucleotide polymorphisms (SNPs) in selected immune response genes to investigate correlations with disease progression and therapeutic response.

7.2.4.2 Gene expression in peripheral blood.

Systemic treatment with biologic medications has been shown to modulate gene expression in autoimmune disease; therefore, whole blood can be used to evaluate changes in the peripheral circulation due to immunomodulation of the disease or the systemic nature of the treatment. Whole blood will be collected from enrolled participants and may be used to evaluate global changes in gene expression during and after treatment. Gene expression of selected cytokines and other immune regulatory molecules may be further investigated using quantitative methods.

7.3 RETENTION OF SAMPLES

A major priority of the Immune Tolerance Network, in partnership with the National Institute of Allergy and Infectious Diseases of the NIH, USA, is the development of novel immunoassays in order to better understand mechanisms of tolerance and to develop biomarkers to predict the development and maintenance of clinical tolerance. As in all Immune Tolerance Network-funded clinical trials, informed consent will be obtained from all participants for their samples to be stored for use in future studies. Biological specimens collected in this trial will be stored long-term in order to re-evaluate biologic responses as new research tools to study tolerance become available. The specimens will therefore be stored at the ITN sample repository for a minimum of 10 years. Residual specimens may be used by the investigators for development of new immunologic assays or for cross-trial comparisons. Although specimens in this protocol

are described in the context of assays to be performed, it should be noted that not necessarily all assays will be performed for all participants at each time point. Decisions to perform assays will be made based on statistical and scientific planning, hypotheses to be tested, and technologies available. Finally, clinical outcomes will be taken into account to determine the potential value of the assays. For example, if a clinical effect fails to occur, it may be decided that there is minimal value in performing certain mechanistic assays. The ITN sample sharing policy will apply for the provision of samples to study or outside investigators (www.immunetolerance.org).

8. SAFETY MONITORING AND REPORTING

8.1 OVERVIEW

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 8.5, Reporting of Adverse Events and Serious Adverse Events/Events of Special Interest) to the sponsor (DAIT/NIAID). Appropriate notifications will also be made to the Immune Tolerance Network (ITN), site principal investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (November 27, 2017): https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

8.2 DEFINITIONS

8.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

8.2.2 Adverse Reaction and Suspected Adverse Reaction (SAR)

Suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the investigational drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal

relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a) and ICH E2A).

An adverse reaction (AR) is any adverse event caused by the study drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

8.2.3 Unexpected Adverse Event/Reaction

A SAR is considered "expected" when it is listed in the investigator brochure, the package insert, or the protocol. A SAR is considered "unexpected" when its nature (specificity), severity, or rate of occurrence is not consistent with applicable product information as described in the safety information provided in the investigator brochure, the package insert, or the protocol (21 CFR 312.32(a) and ICH E2A). A serious unexpected suspected adverse reaction is referred to as a SUSAR. For this study, expectedness will be determined by product information provided in the investigator brochure, package insert, and protocol for brentuximab vedotin.

8.2.4 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor (DAIT/NIAID) it results in any of the following outcomes [21 CFR 312.32(a), and ICH E2A].

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor (DAIT/NIAID) its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations are not to be reported as an SAE unless hospitalization is prolonged due to complications.

8.3 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

8.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (November 27, 2017), except for the grading of liver chemistry abnormalities, which is described in Section 8.3.2. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events if related to a study-mandated procedure, treatment, or change in treatment (but are not treatment-emergent). If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

8.3.2 Grading of Liver Chemistry Abnormalities

For this study, AEs related to liver function testing will be graded relative to the upper limit of normal (ULN) as follows:

- Aspartate aminotransferase [AST] increased
    - Grade 1: > ULN – 3.0x ULN
    - Grade 2: > 3.0x ULN - 5.0x ULN

- Grade 3: > 5.0x ULN - 20.0x ULN
- Grade 4: > 20.0x ULN

- Alanine aminotransferase [ALT] increased
  - Grade 1: > ULN – 3.0x ULN
  - Grade 2: > 3.0x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN

- Alkaline phosphatase [ALP] increased
  - Grade 1: > ULN – 2.5x ULN
  - Grade 2: > 2.5x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN

- Blood bilirubin increased
  - Grade 1: > ULN – 1.5x ULN
  - Grade 2: > 1.5x ULN - 3.0x ULN
  - Grade 3: > 3.0x ULN - 10.0x ULN
  - Grade 4: > 10.0x ULN

8.3.3 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE eCRF. Final determination of attribution for safety events that may be eligible for expedited reporting to the health authorities will be determined by the sponsor, DAIT/NIAID. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 1.

Table 1 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Not related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.

3	Related	The adverse event is clearly related.

8.4 COLLECTING AND RECORDING ADVERSE EVENTS

8.4.1 Collection Period

All adverse events, regardless of NCI-CTCAE severity grade should be recorded in the study source documentation per the criteria below:

- Adverse events will be collected from the time the subjects signs the informed consent until he/she initiates study intervention or until he/she is determined to be ineligible to receive study intervention, if the investigator determines that the adverse event is related to a study-mandated procedure, treatment, or change in treatment.
- For all participants, adverse events will be collected from the time of initiation of study intervention until he/she completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

8.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject (e.g., using a checklist, structured questioning, diary, etc.).
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 8.3.1.

8.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 8.2, Definitions) on the appropriate electronic CRF regardless of the relationship to study therapy regimen or study procedure. Events grade 2 or higher will be recorded on the appropriate AE case report form (eCRF) for this study. The only exception to the above is that Grade 1 or higher SARS-CoV-2 infection will be recorded.

Once recorded, an AE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

An SAE will be followed until it resolves with or without sequelae OR until 30 days after the end of study participation.

If the AE is related to a laboratory or diagnostic evaluation, the evaluation that produced the value or result should be repeated until that value or result returns to normal or can be explained and the participant's safety is not at risk.

8.5 REPORTING ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND EVENTS OF SPECIAL INTEREST TO SPONSOR: DAIT/NIAID

8.5.1 Reporting Adverse Events

This section describes the responsibilities of site investigators to report adverse events to the study sponsor (DAIT/NIAID) via the DAIT- Statistical and Clinical Coordinating Center (DAIT-SACCC). Timely reporting of adverse events of NCI-CTCAE Grade 2 and higher is required.

Unless otherwise noted below in Section 8.5.2 for serious adverse events and events of special interest, AEs must be recorded on the AE eCRF within five (5) days of discovery of the event. Whenever possible, a diagnosis should be provided, rather than compilation of signs/symptoms, with grade of the event dictated by highest grade of the sign/symptom component.

8.5.2 Reporting of Serious Adverse Events and Events of Special Interest

This section describes the responsibilities of the site investigator to report serious adverse events and events of special interest to the sponsor via the electronic CRF (eCRF). Timely reporting of adverse events is required by 21 CFR Part 312.32, and ICH E6 guidelines.

The adverse events outlined below must be reported by the site investigators to DAIT/NIAID via the DAIT-SACCC regardless of relationship or expectedness to study intervention within 1 business day of discovery of the event:

- All SAEs per 21 CFR 312.32 definitions (see Section 8.2.4, Serious Adverse Events).
- The following events of special interest regardless of drug relationship:
    - Grade 3 or higher peripheral neuropathy.
    - Grade 3 or higher neutropenia or thrombocytopenia.
    - Grade 3 or higher infusion reaction.
    - Anaphylaxis, defined as a serious allergic reaction that is rapid in onset and may cause death (see Appendix 2) [79].
    - New onset rash consistent with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other drug reaction.

- eGFR < 30 ml/min/1.73m^2.
- Potential drug-induced liver injury, defined as all three of the following:
  - ALT or AST elevation > 3 times ULN, and
  - Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), and
  - No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including but not limited to viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drugs known to be hepatotoxic.
- Grade 3 or greater infection.
- A suspected case of PML.

- All other Clinical events with an NCI-CTCAE Grade 3 or greater severity deemed possibly or definitely related to brentuximab vedotin.

Note: clinical events include signs/symptoms, diagnoses, and laboratory abnormalities with clinical consequence (defined as the requirement for intervention, correction, increased monitoring, or further evaluation).

When a site investigator identifies a serious adverse event or event of special interest specified above, he or she must notify DAIT/NIAID via the DAIT-SACCC within 1 business day. Site investigators are to report these events on the SAE eCRF in EDC. Should EDC become unavailable/ inaccessible, the site investigator should notify DAIT/NIAID via the DAIT-SACCC email at Rho_productsafety@rhoworld.com. This email can serve as the initial notification; however, within the next business day the SAE eCRF must be completed.

All requested information on the SAE eCRF should be provided. Unavailable details of the event at time of initial report should not delay submission of known information. The initial report should include at a minimum: AE term, relationship to brentuximab vedotin, and reason why event is serious (per definitions). Supplementary CRF pages including medical history, concomitant medications, demographics, study drug administration, and death must be provided. As additional details become available, the SAE eCRF should be updated and submitted. With each iteration of the form, the investigator (or designated sub-investigator) must sign the form electronically.

For additional information regarding SAE reporting, contact Rho Product Safety (DAIT-SACCC):

Rho Product Safety
2635 E NC Hwy 54
Durham, NC 27713

Toll-free-(888)-746-7231
SAE Fax Line: 1-888-746-3293
Email: Rho_productsafety@rhoworld.com

8.6 REPORTING TO HEALTH AUTHORITIES

After an adverse event requiring 1 business day reporting (per Section 8.5.2, Reporting of Serious Adverse Events of Special interest) is submitted by the site investigator and assessed by DAIT/NIAID, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities (Annual Reporting and Expedited Reporting).

8.6.1 Annual Reporting

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions
- Serious and not a suspected adverse reaction
- Pregnancy

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

8.6.2 Expedited Safety Reporting

This option applies if the adverse event is classified as one of the following:

- Serious and unexpected suspected adverse reaction [SUSAR]:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug
    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

The sponsor (DAIT/NIAID) will notify the appropriate health authorities (FDA) and all participating investigators of Expedited Safety Reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) will be reported as soon as possible or within 7 calendar days.

Final Study Report: A complete summary of safety information (including both Standard and Expedited reports as defined above) is included in the final study report to be submitted to both US FDA at the closure of the protocol.

8.7 REPORTING OF ADVERSE EVENTS TO IRBS

All investigators shall report AEs and SAEs, including IND safety reports, in a timely fashion to their respective IRBs in accordance with applicable regulations and guidelines.

8.8 REPORTING PREGNANCY

The investigator shall be informed immediately of any pregnancy in a study subject or a partner of a study subject. A pregnant subject shall be instructed to stop taking study medication. The investigator shall counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject shall continue until the conclusion of the pregnancy.

The investigator shall report to the sponsor (DAIT/NIAID) via the DAIT-SACCC any pregnancy in a study subject or a partner of a study subject within one business day of becoming aware of the event according to the procedures specified in section 8.5.2. The pregnancy eCRF will be used to submit the information for tracking purposes only, as the pregnancy itself is not considered an SAE. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy information must be updated and submitted to the DAIT-SACCC via the eCRF form as new information becomes available. When possible, similar information should be obtained for a pregnancy occurring in a partner of a study subject.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion should be submitted on the SAE eCRF form.

Mycophenolate REMS Program. It is strongly recommended that investigators with female participants of childbearing potential taking mycophenolate mofetil (MMF) enroll them in the Mycophenolate Risk Evaluation and Mitigation Strategy (REMS) program (www.mycophenolaterems.com). Under this program, an investigator will be required to report any pregnancy occurring in a female participant while she is taking MMF or within the first 6 weeks following discontinuation of MMF treatment to the Mycophenolate Pregnancy Registry, which

is part of the MMF REMS program. Study participants will be encouraged to participate in the MMF REMS program as well.

8.9 REPORTING UNANTICIPATED PROBLEMS

An investigator must promptly notify the sponsor (DAIT/NIAID) via the DAIT-SACCC if an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event.

8.10 REVIEW OF SAFETY INFORMATION

8.10.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the DAIT-SACCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate eCRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received from the DAIT-SACCC.

8.11 DATA SAFETY AND MONITORING BOARD REVIEW

8.11.1 Routine DSMB Reviews

The progress of the study will be monitored by the NIAID Data and Safety Monitoring Board (NIAID DSMB). The NIAID Autoimmune DSMB will be chartered to review safety data and to make recommendations to NIAID regarding continuation, termination, or modification of the study. The DSMB will review the safety data 6 months after the first participant is treated. Following the initial review, the DSMB will review the safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB chair will be informed of any Expedited Safety Reports in a timely manner in order to make a recommendation for an ad hoc full board review and /or protocol suspension. Discontinuation of study treatment will also be periodically reported to the DSMB. In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the NIAID medical monitor or protocol co-chairs to warrant review, or when an event occurs that could contribute to a stopping rule.

8.11.2 Protocol-Defined Interim Safety Reviews

Interim safety reviews will be undertaken by a Safety Review Committee (SRC) comprised of a subgroup of the DSMB. The study design (section 3.1) specifies interim safety analysis and review by the SRC after each of the first two dosing cohorts have completed 12 weeks of therapy. Approval by the SRC is required following review of the 12-week interim safety data prior to proceeding to the next higher dosing cohort.

Interim safety analysis will also be conducted after each of the first two dosing cohorts have completed 24 weeks of therapy.

Following each protocol-specified interim safety review, the SRC can recommend actions regarding study conduct, including, but not limited to, the following:

1. Continue the study as planned.
2. Add participants to an existing dosing cohort.
3. Reduce the number of weeks of study drug administration for the next higher dosing cohort.
4. Stop the study.

8.11.3 Ad hoc DSMB Reviews (Stopping Rule Guidance)

If any of the following events occur, the chair of the DSMB will be notified and a review of the safety data will be performed. The DSMB will have the discretion to recommend actions regarding study conduct, and will determine if enrollment in the study should be stopped and/or administration of investigational study medication should be halted:

1. Any death that is at least possibly related to use of the investigational study medication.
2. Any life-threatening infusion reactions during infusion of study medication or within the observation period after study medication that lead to permanent discontinuation of the infusion, including anaphylaxis.
3. One case of PML.
4. Any grade 4 adverse event that is at least possibly related to use of the investigational study medication.
5. Two or more Grade 3 or higher peripheral neuropathy events involving different participants.

If stopping rule 1, 2, or 3 is met, then no new participants will be consented, and no new participants will be enrolled, until after the DSMB completes review of the safety data. Participants in the screening phase of the study may continue to undergo minimal risk procedures.

If stopping rule 4 or 5 is met, the study will proceed as planned pending DSMB review of the data. However, if two weeks has elapsed and the DSMB has not met, then no new participants will be consented, and no new participants will be enrolled, until after the DSMB completes review of the safety data.

In the event that a temporary halt is placed on consent and enrollment, participants already enrolled in the study will continue to receive study medication if they are not the subject of the DSMB review.

9. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

9.1 ANALYSIS SAMPLES

9.1.1 Analysis Populations

The safety sample is defined as all subjects who receive any amount of the placebo or the brentuximab vedotin study drug. They will be summarized and compared according to the treatment actually received. Because participants receive their assigned medication on the day of randomization, this is conceptually equivalent to the standard intention to treat analysis population.

Supplementary per protocol (PP) analysis samples are defined as follows:

- PP12: Treated participants who receive at least 4 of the 5 infusions over the first 12 weeks, and who have no major protocol deviations that would affect the safety outcomes through the first 12 weeks.
- PP24: Treated participants who receive at least 7 of the 8 infusions over the first 21 weeks, and who have no major protocol deviations that would affect the safety outcomes through the first 24 weeks.
- PP36: Treated participants who receive at least 7 of the 8 infusions over the first 21 weeks, and who have no major protocol deviations that would affect the safety outcomes through the first 36 weeks.
- PP48: Treated participants who receive at least 7 of the 8 infusions over the first 21 weeks, and who have no major protocol deviations that would affect the safety outcomes through the first 48 weeks.

9.2 ANALYSIS OF ENDPOINTS

9.2.1 Primary Endpoint

For each dosing cohort, the primary endpoint is the proportion of participants who experienced at least one Grade 3 or higher adverse event at or before week 48. It will be analyzed using the safety sample and the PP48 analysis sample. Proportions will be estimated by treatment group together with their 95% confidence intervals derived using the Clopper-Pearson exact method. Although this study is not powered to detect it, a between-group comparison within each dosing cohort will be performed using Fisher's exact test.

9.2.2 Secondary and Exploratory Endpoints

Secondary and exploratory endpoints consist of the following:

1. The proportion of participants who experience at least one Grade 3 or higher adverse event at or before weeks 12, 24 and 36.

2. The proportion of participants who experience at least one Grade 2 or higher adverse event at or before weeks 12, 24, 36, and 48.
3. The proportion of participants with Grade 2 or higher peripheral neuropathy at or before weeks 12, 24, 36, and 48.
4. The proportion of participants with Grade 3 or higher neutropenia at or before weeks 12, 24, 36, and 48.
5. The proportion of participants with any of the following Grade 3 or higher adverse events at or before week 48:
   a. Peripheral neuropathy.
   b. Neutropenia.
   c. Infectious adverse events.
   d. Infusion reactions, including anaphylaxis and new onset rash consistent with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other drug reaction.
   e. PML.
6. Modified Rodnan Skin Score (mRSS) at weeks 12, 24, and 48.
7. Provisional American College of Rheumatology Combined Response Index in Systemic Sclerosis (CRISS) at weeks 24 and 48.
8. Percent predicted Forced Vital Capacity (FVC) at weeks 24 and 48 weeks.
9. Physician's global assessment on a Likert scale at weeks 24 and 48.
10. Patient's global assessment on a Likert scale at weeks 24 and 48.
11. Health-related quality of life (HRQOL) assessed by PROMIS-29 version 2.0 at weeks 24 and 48.
12. Physical function assessed by the Scleroderma Health Assessment Questionnaire-Disability Index (SHAQ-DI) at weeks 24 and 48.

All secondary and exploratory endpoints at all study weeks will be analyzed using the safety sample. Additionally, endpoints at weeks 12, 24, 36 and 48 will be analyzed using the corresponding PP12, PP24, PP36 and PP48 analysis samples.

The proportions of participants with peripheral neuropathy and the different types of adverse events will be analyzed and compared in the same manner as described above for the primary endpoint. The numbers of AEs and SAEs will be summarized using simple descriptive statistics. Simple descriptive statistics will be provided overall and by treatment group for FVC and the different disease severity scales. In each dosing cohort, the Wilcoxon Signed Rank test will be used to determine if there was a significant change from baseline to the follow-up evaluations within each treatment group. Between-group comparisons within each dosing cohort will be performed using the Wilcoxon Rank Sum test.

9.2.3 Analysis of Dose-Response Relationship

The 3 dosing cohorts will be merged together to determine if there is a significant dose-response relationship in the endpoints with the amount of brentuximab vedotin received. The 4 dose levels include placebo (0.0 mg/kg), and brentuximab vedotin at low (0.6 mg/kg), medium (1.2 mg/kg), and high dose (1.8 mg/kg). The primary endpoint as well as the proportions of participants with peripheral neuropathy and the different types of adverse events will be analyzed using the exact version of the Cochran-Armitage test for trend. Additionally, these endpoints will be analyzed using a logistic regression model. For FVC and the disease severity scales, the Spearman correlation will be used to determine if there is an association in the change from baseline with the dose level. These analyses will be performed on the safety sample and the PP48 sample.

9.2.4 Missing Data

Standard procedures will be used to ensure that data are as complete and accurate as possible. Due to the fact that this is primarily a safety study and due to the small sample size in each dosing cohort, no imputation for missing data will be done.

9.2.5 Baseline Characteristics and Demographics

Summary statistics for baseline and demographic characteristics will be provided for the safety sample. Demographic data will include age, race, sex, weight, and height. These data will be presented in the following manner:

- Continuous data (i.e., age, weight, and height) will be summarized by mean, standard deviation, median, and range.
- Categorical data (i.e., sex and race) will be presented as counts and percentages.

9.2.6 Safety Analysis

Safety analyses will be performed on the safety sample. Missing safety information will not be imputed. Reports summarizing safety data will be prepared at the end of the study and periodically throughout the study for IND regulatory filings, the DSMB, and for the medical monitor and study management team. Safety reports will be prepared to meet the needs of those groups and individuals responsible for monitoring safety and may include (but are not limited to) summaries and listings of SAEs, AEs, vital signs, laboratory values, physical examination results, events requiring drug discontinuations for individual participants (see Section 4.3), and events listed as study stopping rules (Section 8.11.3). AEs and SAEs in the summary displays and listings will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and/or preferred terms. Severity will be reported using NCI-CTCAE grading criteria. Relationship to study drug will be reported as per Section 8.3.2. Abnormal vital signs and laboratory values will be graded using the NCI-CTCAE criteria and grade will be included in listings.

9.2.7 Interim Analysis of Safety Data

Analysis of safety data is planned after the last participant in each of the first two dosing cohorts of 8 participants has completed the first 12 weeks and the first 24 weeks of treatment and evaluation. A Safety Review Committee (SRC) will review the safety data and make recommendations regarding study conduct, as described in Section 8.11.2.

Tables, listings, and/or figures of all the measures listed in Section 9.2.6 will be presented for each of these interim safety analyses.

9.2.8 Medical History

Medical history within the 12 months prior to screening, including the existence of current signs and symptoms, will be collected for each body system.

9.2.9 Use of Medications

All medications taken by or administered to study participants beginning 30 days before enrollment and continuing throughout the study will be collected. All medications used will be coded according to the World Health Organization (WHO) drug dictionary. A listing of all prior and concomitant medications/therapies will be created. The number and percentage of participants receiving prior and concomitant medications/therapies will be presented overall and by medication class.

9.3 SAMPLE SIZE

No formal power analyses were conducted since all safety and efficacy evaluations are exploratory. The total sample size for this study is 24 participants with 8 participants in each of 3 dosing cohorts including 6 participants receiving brentuximab vedotin and 2 receiving placebo. The ability to detect significant events of certain frequencies was considered. Table 2 illustrates the probability of observing at least 1 significant event in a dosing cohort of 6 participants receiving brentuximab vedotin. A cohort of 3 participants has also been included in case there are partially enrolled cohorts.

Table 2 Probability of Events

	True Probability of Event		
	0.1	**0.2**	**0.3**
Probability of observing at least 1 event in 3 participants	0.27	0.49	0.66
Probability of observing at least 1 event in 6 participants	0.47	0.74	0.88

Additionally, Table 3 displays the upper and lower limits of the exact 95% Clopper-Pearson confidence interval for the primary outcome among the 6 participants treated with brentuximab vedotin in any dosing cohort.

Table 3 Confidence Limits

Number with Grade 3+ AE	Proportion with Grade 3+ AE	Lower Limit for Exact 95% CI	Upper Limit for Exact 95% CI
0	0.000	0.000	0.459
1	0.167	0.004	0.641
2	0.333	0.043	0.777
3	0.500	0.118	0.882
4	0.667	0.223	0.957
5	0.833	0.359	0.996
6	1.000	0.541	1.000

9.4 REPORTING DEVIATIONS FROM THE ORIGINAL STATISTICAL PLAN

The principal features of both the study design and the plan for statistical data analysis are outlined in this protocol and in the statistical analysis plan (SAP). Any change in these features requires either a protocol or an SAP amendment and subject to review by the DSMB, the study sponsor(s), and the health authorities. These changes will be described in the final study report as appropriate.

10. ACCESS TO SOURCE DATA/DOCUMENTS

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants in this clinical trial. Medical and research records should be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational sites must permit authorized representatives of the ITN, sponsor, and health authorities to examine (and to copy when required by applicable law) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (and any personally identifying information must be obscured). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. The investigational sites will normally be notified in advance of auditing visits.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator is required to keep accurate records to ensure that the conduct of the study is fully documented. The principal investigator is required to ensure that all eCRFs are completed for every participant entered in the trial.

The sponsor is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

The eCRFs will be completed online via a web-based EDC system that has been validated and is compliant with Part 11 Title 21 of the Code of Federal Regulations. Data queries will be issued and resolved within the EDC system. Some data cleaning will be performed outside EDC using statistical analysis system (SAS®) software.

Study staff at the site will enter information into the electronic CRFs, and the data will be stored remotely at a central database. Data quality will be ensured through the EDC system's continuous monitoring of data and real-time detection and correction of errors. All elements of data entry (i.e., time, date, verbatim text, and the name of the person performing the data entry) will be recorded in an electronic audit trail to allow all changes in the database to be monitored and maintained in accordance with US and Canadian regulations.

Study staff will enter data from a study visit on the relevant eCRFs within 5 business days following the visit or at the time when data become available.

12. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

12.1 STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, current GCP guidelines — as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance* — and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the sponsor and the appropriate health authorities and ethics review committee (IRB). Any amendments to the protocol or consent materials must also be approved by the Sponsor, the ethics review committee (IRB), and submitted to FDA before they are implemented in the US.

12.2 INFORMED CONSENT

The informed consent form is a means of providing information about the trial to a prospective participant and allows for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form before participating in the study, taking the study drug, and/or undergoing any study-specific procedures. If a participant does not speak and read English, the consent materials must be translated into the appropriate language.

The informed consent form must be updated or revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to a prospective participant for review. The study investigator, in the presence of a witness, will review the consent and answer

questions. The participant will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason.

12.3 PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number. This number, rather than the participant's name, will be used to collect, store, and report participant information.

13. PUBLICATION POLICY

The ITN policy on publication of study results will apply to this study. Authorized participants may find details regarding the policy statement on the ITN internet website at http://www.immunetolerance.org.

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APPENDIX 1. SCHEDULE OF EVENTS

Study Week	-1	0	3	6	9	12	15	18	21	24	28	36	48	DSC	UN
Visit Number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[4]**	**10**	**11**		
General Assessments															
Informed consent	x														
Eligibility criteria	x														
Randomization		x													
Demographics	x														
Medical History	x														
Scleroderma History	x														
Comprehensive physical examination	x									x			x	x	
Limited physical examination		x	x	x	x	x	x	x	x			x			x
Peripheral neuropathy assessment	x		x	x	x	x	x	x	x	x	x[5]	x	x	x	x
Neurologist assessment[1]															x[1]
Vital signs	x	x	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	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical Laboratory Assessments															
Hematology [2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x		x	x	x	x
Serum chemistry [2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x		x	x	x	x
Serum amylase and lipase	x														
HIV	x														
HBV	x														
HCV	x														
ESR	x					x				x			x	x	
Serum HCG[3]	x[3]														
STAT Urine HCG[3]		x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]		x[3]	x[3]	x[3]	x[3]
QuantiFERON Gold, Gold Plus or PPD	x														
PCR test for SARS-CoV-2	x														
General Clinical Assessments															
EKG	x														
Echocardiogram	x									x					
Disease-Specific Assessments															
Spirometry (FVC and FEV1) with DLCO[6]	x					x				x			x	x	
mRSS	x	x				x				x			x	x	
Physician global assessment		x								x			x	x	
Patient global assessment, PROMIS-29, SHAQ-DI		x								x			x	x	
Study Medications															
Study medication administration		x	x	x	x	x	x	x	x						
Mechanistic Assessments															
Skin biopsy		x				x				x					
Plasma/Serum assays		x				x				x			x	x	
PBMC assays		x				x				x			x	x	
Whole blood DNA genotyping		x													
Whole blood gene expression analysis		x				x				x			x	x	

[1] As indicated for suspected peripheral neuropathy
[2] Hematology and serum chemistry results must be obtained within 72 hours prior to infusions at weeks 3 through 21
[3] For women of childbearing potential (see section 5.3.1.2)
[4] Visit 9 will be conducted remotely except if the participant is being followed for a peripheral neuropathy adverse event.
[5] Performed only if the participant is being followed for a peripheral neuropathy adverse event.
[6] Negative SARS-CoV-2 test maybe required prior to PFTs per institutional guidelines.

APPENDIX 2. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any one 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 (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a *likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known 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

PEF, Peak expiratory flow; *BP*, blood pressure.
* 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 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Adapted from the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network [79]

APPENDIX 3. EXAMPLES OF STRONG CYP3A4 INHIBITORS, INDUCERS, AND P-GP INHIBITORS

	Strong CYP3A4 Inhibitors	Strong CYP3A4 Inducers	P-gp inhibitors
Antibiotics	Clarithromycin Telithromycin Azamulin Troleandomycin	Rifampin	Clarithromycin
Antidepressants	Nefazodone		
Anti-epileptic		Phenytoin Carbamazepine	
Antifungals	Itraconazole Ketoconazole Posaconazole Voriconazole		Itraconazole
Cardiovascular	Verapamil Diltiazem		Verapamil Diltiazem Amiodarone Carvedilol Dronedarone Propafenone Quinidine Ranolazine
Protease Inhibitors	Ritonavir[1] Atazanavir Boceprevir Danoprevir Elvitegravir Indinavir Lopinavir Nelfinavir Saquinavir Tipranavir Paritaprevir ombitasvir dasabuvir		Cobicistat Lopinavir Nelfinavir Ritonavir Saquinavir Telaprevir Tipranavir
Vasopressin receptor inhibitor			Conivaptan
Oncology	Idelalisib	Enzalutamide Mitotane	Lapatinib
Other	Grapefruit Juice[2]	St. John's wort[3]	

[1]Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
[2]The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
[3]The effect of St. John's wort varies widely and is preparation dependent.

Adapted from FDA drug development and drug interactions: Table of substrates, inhibitors and inducers [80].