DAIT/Rho STATISTICAL ANALYSIS PLAN
Version 1.0

ITN075AI BRAVOS: Brentuximab Vedotin for Systemic Sclerosis

VERSION: **1.0**

DATE: **17Jul2023**

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ITN075AI BRAVOS: Brentuximab Vedotin for Systemic Sclerosis

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Document History

Version	Date	Change(s)	Author
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LIST OF ABBREVIATIONS

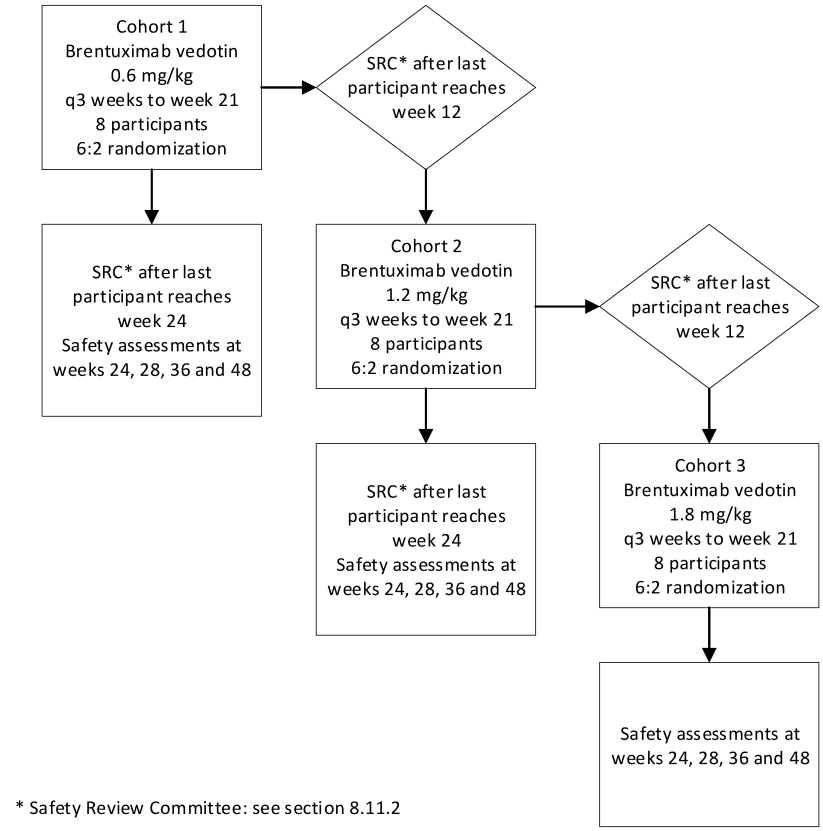
ABVD	Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine
AE	Adverse Event
ALCL	Anaplastic Large Cell Lymphoma
ALT	Alanine Aminotransferase
ANA	Anti-Nuclear Antibodies
ASCT	Autologous Stem Cell Transplant
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC	Centers for 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
HAQ-DI	Health Assessment Questionnaire-Disability Index
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. PROTOCOL 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.

2. INTRODUCTION

This statistical analysis plan (SAP) only includes analyses related to the clinical endpoints outlined in the protocol. Mechanistic analyses will be performed at the Immune Tolerance Network (ITN), and a separate analysis plan will be created to detail the planned analyses. Relevant clinical data from the study will be submitted to the ITN Biomarker and Discovery Research (BDR) and ITN Bioinformatics Groups (BiG) to augment the mechanistic analyses.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (%)."

- Numeric variables will be summarized using n, mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data. The level of precision may be modified on specific displays based on clinical judgment.

- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.

- Test statistics including *t* and *z* test statistics will be reported to two decimal places.

- *P*-values will be reported to three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as "<0.001." A *p*-value can be reported as "1.000" only if it is exactly 1.000 without rounding. A *p*-value can be reported as "0.000" only if it is exactly 0.000 without rounding.

- All analyses will be performed using the SAS System version 9.4 or higher.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

4. ANALYSIS SAMPLES

The **safety sample** is defined as all participants 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.

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.

Participants who terminate early from the study will be excluded from subsequent PP samples. A blinded data review panel will evaluate deviations from the protocol for impact on assessments and exclusion from the PP samples. Reasons for exclusion may include, but are not limited to, violations of entry criteria, departures from assigned treatment regimen, modifications of concurrent therapy, or administration of study procedures outside the specified visit windows.

5. STUDY PARTICIPANTS

5.1. Disposition of Participants

The disposition of all participants will be summarized in tables by treatment group and cohort. A listing of disposition for randomized participants will also be created.

The numbers and percentages of participants randomized, in each analysis sample, and completing study will be presented. For participants terminating early from the study, the reasons for early termination will be presented. For participants discontinuing study treatment early, the reasons for discontinuing study treatment early will be presented.

5.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for the safety sample. Demographic and baseline characteristics will also be presented in data listings by treatment group and cohort.

Demographic characteristics and general health include:

- Sex,
- Race,
- Ethnicity,
- Age,
- Height,
- Weight, and
- BMI.

Baseline characteristics include:

- Disease duration (for both onset of Raynaud's and non-Raynaud's symptoms)
- mRSS total score
- FVC % predicted and in units of mL
- DLCO % predicted, adjusted for hemoglobin
- Patient's global assessment (PGA)
- Physician's global assessment (PhGA)
- HAQ-DI total score
- Use of prednisone
- Use of methotrexate
- Use of mycophenolate mofetil or mycophenolate sodium
- Use of azathioprine

Baseline (Visit 0) results will be presented; if a measurement is missing for a participant at baseline, the screening value (Visit -1) will be used.

6. STUDY OPERATIONS

6.1. Protocol Deviations

Major protocol deviations will be listed by site and participant with information including type of deviation, date of occurrence, details of the deviation, the reason for the deviation, and whether the deviation was COVID-19 related. Additionally, protocol deviations will be summarized in tabular format by type of deviation.

6.2. Treatment Adherence

Participants will receive IV infusions of either 0.6 mg/kg or 1.2 mg/kg brentuximab vedotin or placebo every 3 weeks for 21 weeks, for a total of up to 8 infusions. A third dosing cohort with a dose of 1.8 mg/kg of brentuximab vedotin or placebo was originally planned, but the study closed after enrolling cohort 2 (1.2 mg/kg) due to enrollment challenges.

Since study drug is administered at the study visits, compliance is monitored by the medical staff and documented on the eCRF.

Study drug infusion data will be listed for each participant with information such as number and % of infusions received, date of infusion, whether the infusion was given, reason the infusion was withheld, and the prescribed dose. A table will be created to summarize the number of infusions received by treatment group and cohort.

7. ENDPOINT EVALUATION

7.1. Overview of Safety and Efficacy Analysis Methods

7.1.1. Multicenter Studies

Study participants were recruited from 9 study sites. However, 2 of the 9 sites did not screen any participants, and 4 sites never randomized any participants. Due to the small number of participants in the study, study data will be analyzed as a whole, and no formal accommodation for site-to-site variation will be made.

7.1.2. Endpoints

Table 7-1 Table of Endpoints and Analysis Methods

Endpoint	Method 1	Method 2
Primary Endpoint		
Proportion of participants who experienced a Grade 3 or higher AE at or before week 48 (Sample: safety)	***Analysis:*** *Estimate proportions and derive 95% CI using Clopper-Pearson exact method for each treatment group and dosing cohort*	***Analysis:*** *Treatment group comparison using Fisher's exact test (separate test for each cohort)*
Proportion of participants who experienced a Grade 3 or higher AE at or before week 48 (Sample: PP48)	***Analysis:*** *Estimate proportions and derive 95% CI using Clopper-Pearson exact method for each treatment group and dosing cohort*	***Analysis:*** *Treatment group comparison using Fisher's exact test (separate test for each cohort)*
Secondary Safety Endpoints		
Proportion of participants who experienced a Grade 3 or higher AE at or before weeks 12, 24, 36	*Same as primary*	*Same as primary*
Proportion of participants who experienced a Grade 2 or higher AE at or before weeks 12, 24, 36, 48	*Same as primary*	*Same as primary*
Proportion of participants who experienced a Grade 2 or higher peripheral neuropathy at or before weeks 12, 24, 36, 48	*Same as primary*	*Same as primary*
Proportion of participants who experienced a Grade 3 or higher neutropenia at or before weeks 12, 24, 36, 48	*Same as primary*	*Same as primary*

Endpoint	Method 1	Method 2
Proportion of participants who experienced certain Grade 3 or higher AEs at or before week 48 [see section 7.3.5 for list]	*Same as primary*	*Same as primary*
Exploratory Efficacy Endpoints[1]		
mRSS at weeks 12, 24, and 48	***Analysis:*** *Wilcoxon Signed Rank test (within treatment group analysis)*	***Analysis:*** *Wilcoxon Rank Sum Test (between treatment group analysis)*
Revised CRISS at weeks 24 and 48	***Analysis:*** *Estimate proportions of responders and derive 95% CI using Clopper-Pearson exact method for each treatment group and dosing cohort*	***Analysis:*** *Treatment group comparison using Fisher's exact test (separate test for each cohort)*
FVC% predicted at weeks 24 and 48	***Analysis:*** *Wilcoxon Signed Rank test (within treatment group analysis)*	***Analysis:*** *Wilcoxon Rank Sum Test (between treatment group analysis)*
FVC in units of mL at weeks 24 and 48	***Analysis:*** *Wilcoxon Signed Rank test (within treatment group analysis)*	***Analysis:*** *Wilcoxon Rank Sum Test (between treatment group analysis)*
Physician's global assessment at weeks 24 and 48	***Analysis:*** *Wilcoxon Signed Rank test (within treatment group analysis)*	***Analysis:*** *Wilcoxon Rank Sum Test (between treatment group analysis)*
Patient's global assessment at weeks 24 and 48	***Analysis:*** *Wilcoxon Signed Rank test (within treatment group analysis)*	***Analysis:*** *Wilcoxon Rank Sum Test (between treatment group analysis)*
PROMIS-29 at weeks 24 and 48 (8 domains)[1]	***Analysis:*** *Wilcoxon Signed Rank test (within treatment group analysis)*	***Analysis:*** *Wilcoxon Rank Sum Test (between treatment group analysis)*
SHAQ-DI (8 domains of HAQ-DI, total score for HAQ-DI, and 6 VAS) at weeks 24 and 48[1]	***Analysis:*** *Wilcoxon Signed Rank test (within treatment group analysis)*	***Analysis:*** *Wilcoxon Rank Sum Test (between treatment group analysis)*
Dose-response relationship[2] for discrete endpoints	***Analysis:*** *Exact Cochran-Armitage test for trend*	**--**
Dose-response relationship[2] for continuous endpoints	***Analysis:*** *Spearman correlation*	**--**

[1] All components of the PROMIS-29 and SHAQ-DI are described in more detail in sections 7.3.11 and 7.3.12 respectively.
[2] There will be 3 dose levels in these analyses: placebo (0.0 mg/kg), and brentuximab vedotin at low (0.6 mg/kg) and medium (1.2 mg/kg) dose. See section 7.3.13 for more details on the dose-response analyses.

7.2. 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.

7.2.1. Computation of the Primary Endpoint

The denominator for the proportions will be the number of participants in the safety and PP48 samples. The numerator will be the number of these participants with a Grade 3 or higher AE.

7.2.2. Primary Analysis of the Primary Endpoint

Proportions will be estimated by treatment group together with their 95% confidence intervals derived using the Clopper-Pearson exact method.

A treatment group comparison within each dosing cohort will be performed using Fisher's exact test.

Proportions and confidence intervals will also be presented for the treatment groups pooled across cohorts.

7.3. Secondary and Exploratory Endpoints

For all treatment group comparisons the null hypothesis is that there is no difference between the treatment groups. All secondary inferential analyses are considered supportive; p-values will be presented without adjustment for multiple comparisons.

All analyses will be performed on the safety sample and on the PP sample that corresponds with each endpoint.

7.3.1. Proportion of participants who experience at least one Grade 3 or higher AE at or before weeks 12, 24, and 36

Analyses will be performed on the safety sample and at each study week using the corresponding PP12, PP24, and PP36 samples. This endpoint will be analyzed the same way as the primary endpoint (section 7.2.2).

7.3.2. Proportion of participants who experience at least one Grade 2 or higher AE at or before weeks 12, 24, 36, and 48.

Analyses will be performed on the safety sample and at each study week using the corresponding PP12, PP24, PP36, and PP48 samples. This endpoint will be analyzed the same way as the primary endpoint (section 7.2.2).

7.3.3. Proportion of participants with Grade 2 or higher peripheral neuropathy at or before weeks 12, 24, 36, and 48.

Analyses will be performed on the safety sample and at each study week using the corresponding PP12, PP24, PP36, and PP48 samples. This endpoint will be analyzed the same way as the primary endpoint (section 7.2.2).

7.3.4. Proportion of participants with Grade 3 or higher neutropenia at or before weeks 12, 24, 36, and 48.

Analyses will be performed on the safety sample and at each study week using the corresponding PP12, PP24, PP36, and PP48 samples. This endpoint will be analyzed the same way as the primary endpoint (section 7.2.2).

7.3.5. Proportion of participants with any of the following Grade 3 or higher AEs at or before week 48: peripheral neuropathy, neutropenia, infectious adverse events, infusion reactions (including anaphylaxis and new onset rash consistent with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other drug reaction), or PML.

This analysis will be performed on the safety sample and PP48 sample. This endpoint will be analyzed the same way as the primary endpoint (section 7.2.2).

7.3.6. Modified Rodnan Skin Score (mRSS) at weeks 12, 24, and 48.

Summary statistics of mRSS total score will be presented in a table by cohort, treatment group, and visit for the safety sample. The mRSS results for each body location and the total score will be listed.

Within each dose level of treatment (0.6 mg/kg, 1.2 mg/kg), the Wilcoxon Signed Rank test will be used to compare the change in the total score at each study week with baseline. The change from baseline for the treatment groups within each cohort will be compared using the Wilcoxon Rank Sum test. Analyses will be performed on the safety sample and at each study week using the corresponding PP12, PP24, and PP48 samples.

7.3.7. Provisional American College of Rheumatology Combined Response Index in Systemic Sclerosis (CRISS) at weeks 24 and 48.

The revised CRISS categorizes participants as responders or non-responders. The proportion of responders in each cohort and treatment group will be presented in a table. The same analysis as the primary endpoint will be performed on the proportion of responders: proportions will be estimated by treatment group together with their 95% confidence intervals derived using the Clopper-Pearson exact method. Additionally, a between-group comparison within each dosing cohort will be performed using Fisher's exact test.

Analyses will be performed on the safety sample and at each study week using the corresponding PP24 and PP48 samples.

Definitions for responders and non-responders are below:

- If the participant develops any of the Step 1 criteria, they are considered a non-responder. Step 1 criteria are below.
    - RENAL: New scleroderma renal crisis
    - ILD: Decline in forced vital capacity (FVC)% predicted ≥15% (relative) in established ILD and FVC %predicted below 80% predicted
    - HEART: New onset of left ventricular failure (defined as left ventricular ejection fraction ≤45%) requiring treatment
    - CARDIOPULMONARY: New onset of pulmonary arterial hypertension on right heart catheterization requiring treatment
    - GASTROINTESTINAL: Dysmotility requiring enteral or parenteral nutrition
    - DIGITAL ISCHEMIA: Gangrene, amputation, or hospitalization requiring treatment

- A responder is a participant who has improved in at least 2 of the 5 core set measures without worsening in more than one core set measure. The 5 core set measures are:
  - mRSS: improvement must be at least 25% decrease from baseline
  - HAQ-DI (total score): improvement must be at least 25% decrease from baseline
  - Patient Global Assessment: improvement must be at least 25% decrease from baseline
  - Physician Global Assessment: improvement must be at least 25% decrease from baseline
  - FVC % predicted: improvement must be at least 5% increase from baseline
- Worsening for each component is the same magnitude as improvement, but in the opposite direction.

Note: scoring of core set measures with floor values of 0 (mRSS, HAQ-DI, PGA and PhGA) are performed as follows: cases where the baseline result is 0 and follow-up result is >0 are defined as worsening; cases where the baseline result is >0 and follow-up result is 0 are defined as improvement. Cases where both the baseline and follow-up results are 0 are defined to be neither worsening nor improvement.

A heat map will be created to show improvement, worsening, or neither for each core set measure for each participant.

7.3.8. Forced Vital Capacity (FVC) at weeks 24 and 48.

Summary statistics of percent predicted FVC and FVC in units of mL will be presented in a table by cohort, treatment group, and visit for the safety sample. The FVC data (both raw data in units of mL and % predicted) will be listed with the other spirometry data (section 8.5.5).

Within each dose level of treatment (0.6 mg/kg, 1.2 mg/kg), the Wilcoxon Signed Rank test will be used to compare the change in percent predicted FVC and FVC in units of mL at each study week with baseline. The change from baseline for the treatment groups within each cohort will be compared using the Wilcoxon Rank Sum test. Analyses will be performed on the safety sample and at each study week using the corresponding PP24 and PP48 samples.

7.3.9. Physician's global assessment on a Likert scale at weeks 24 and 48.

Summary statistics of physician's global assessment will be presented in a table by cohort, treatment group, and visit for the safety sample. This data will also be listed.

Within each dose level of treatment (0.6 mg/kg, 1.2 mg/kg), the Wilcoxon Signed Rank test will be used to compare the change in the assessment at each study week with baseline. The change from baseline for the treatment groups within each cohort will be compared using the Wilcoxon Rank Sum test. Analyses will be performed on the safety sample and at each study week using the corresponding PP24 and PP48 samples.

7.3.10. Patient's global assessment on a Likert scale at weeks 24 and 48.

Summary statistics of patient's global assessment will be presented in a table by cohort, treatment group, and visit the safety sample. This data will also be listed.

Within each dose level of treatment (0.6 mg/kg, 1.2 mg/kg), the Wilcoxon Signed Rank test will be used to compare the change in the assessment at each study week with baseline. The change from baseline for the treatment groups within each cohort will be compared using the Wilcoxon Rank Sum test. Analyses will be performed on the safety sample and at each study week using the corresponding PP24 and PP48 samples.

7.3.11. Health-related quality of life (HRQOL) assessed by PROMIS-29 v2.0 at weeks 24 and 48.

Summary statistics of each domain of the PROMIS-29 will be presented in a table by cohort, treatment group, and visit for the safety sample.

- The domains are: Physical Function, Anxiety, Depression, Fatigue, Sleep Disturbance, Social Roles and Activities, Pain Interference
- Two scores are available for each PROMIS domain listed above: the total raw score and transformed score (T-score). To find the total raw score for a domain, all items must be answered. The total raw score will be derived as the sum of the values associated with the response to each question. The total raw summed score can range from 4 to 20 for each domain. The total raw summed score will then be translated into a T-score [2]. The T-score will be summarized in tables and analyzed.
- The 8th domain, Pain Intensity, is scored by participants on a scale of 1 to 10.

The responses to each question in each domain as well as the total scores, T-scores, and standard errors will be shown in listings.

Within each dose level of treatment (0.6 mg/kg, 1.2 mg/kg) and PROMIS-29 domain, the Wilcoxon Signed Rank test will be used to compare the change in the T-score at each study week with baseline. The change from baseline in the T-scores for each domain for the treatment groups within each cohort will be compared using the Wilcoxon Rank Sum test. These same analyses will be performed for the pain intensity result. Analyses will be performed on the safety sample and at each study week using the corresponding PP24 and PP48 samples.

7.3.12. Physical function assessed by the Scleroderma Health Assessment Questionnaire-Disability Index (SHAQ-DI) at weeks 24 and 48.

Summary statistics for the SHAQ scores will be presented in a table by cohort, treatment group, and visit for the safety sample. SHAQ consists of HAQ-DI and 6 VAS. The HAQ-DI total score and results from each domain and the results of the 6 VAS will be listed. For each domain, the score is computed as the maximum value over all variables in the domain ("Alternative Disability Index"). The total score is computed as the mean over all the non-missing domain scores. If less than 6 domain scores are available, the total score is missing. Details on the HAQ-DI can be seen in [3].

The domains are: Dressing and Grooming, Arising, Eating, Walking, Hygiene, Reach, Grip, Activities

- The 6 VAS questions are below:
    - How much pain have you had because of your illness IN THE PAST WEEK?
    - IN THE PAST WEEK, how much have your intestinal problems interfered with your daily activities?
    - IN THE PAST WEEK, how much have your breathing problems interfered with your daily activities?
    - IN THE PAST WEEK, how much has Raynaud's interfered with your daily activities?
    - IN THE PAST WEEK, how much have your finger ulcers interfered with your daily activities?
    - Overall, considering how much pain, discomfort, limitations in your daily life and other changes in your body and life, how severe would you rate your disease today?

Within each dose level of treatment (0.6 mg/kg, 1.2 mg/kg), the Wilcoxon Signed Rank test will be used to compare the change in the total score and VAS results at each study week with baseline. The change from baseline in the total scores and VAS results for the treatment groups within each cohort will be compared using the Wilcoxon Rank Sum test. Analyses will be performed on the safety sample and at each study week using the corresponding PP24 and PP48 samples.

7.3.13. Analysis of Dose-Response Relationship

These analyses will be performed on the safety sample and PP48 sample. There will be 3 dose levels for these analyses: placebo (0.0 mg/kg), and brentuximab vedotin at low (0.6 mg/kg) and medium (1.2 mg/kg) dose.

The endpoints listed below will each be analyzed using the exact version of the Cochran-Armitage test for trend.

- The primary endpoint (proportion of participants who experience at least one Grade 3 or higher AE)
- The proportion of participants who experience at least one Grade 2 or higher AE
- The proportion of participants with a Grade 2 or higher peripheral neuropathy
- The proportion of participants with a Grade 3 or higher neutropenia
- The proportion of participants with any of the following Grade 3 or higher adverse events: peripheral neuropathy, neutropenia, infectious adverse events, infusion reactions (including anaphylaxis and new onset rash consistent with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other drug reaction), or PML
- The proportion of participants who are responders per the revised CRISS.

The endpoints listed below will each be analyzed using Spearman correlation to determine if there is an association in the change from baseline with the dose level.

- mRSS total score
- FVC (% predicted)
- FVC (mL)
- Physician’s global assessment
- Patient’s global assessment
- Each domain of the PROMIS-29
- HAQ-DI total score

8. SAFETY EVALUATION

8.1. Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample defined in Section 4 unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site.

Safety will be analyzed in each treatment group through the reporting of adverse events (AEs), vital signs, physical examination findings, and changes in routine laboratory values.

Listings will be prepared for all safety measurements. All listings will be sorted by cohort and treatment.

8.2. Adverse Events

All AEs will be classified by system organ class (SOC) and preferred term, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 23.0). The severity of AEs will be classified using the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0, except for the grading of liver chemistry abnormalities, which is described in protocol section 8.3.2. Each AE is entered on the electronic case report form (eCRF) once at the highest severity. As such, no additional data manipulation is needed to identify events.

For participants who screen fail, AEs are collected from the time a participant signs informed consent until the participant is determined to be ineligible to receive study medication if the AE is determined to be related to a study-mandated procedure, treatment, or change in treatment. For randomized participants, AEs will be collected from the time a participant signs informed consent until the participant completes the study, or until 30 days after the participant prematurely withdraws from the study (without withdrawing consent).

Treatment-emergent AEs will be identified as those with an onset date on or after the first dose of study medication. If the AE onset date and treatment start date are the same, the site will be queried to confirm whether the AE began before or after the first dose of study drug was given. If the start of the AE in relation to the start of study medication cannot be established (e.g., the start date for the AE is missing), then the AE will be considered treatment-emergent. All data tabulations will be of only treatment-emergent events while non treatment-emergent AEs will be listed separately.

Relationship to study drug will be shown in listings. An assessment of the relationship of an adverse event to study therapy is made by site personnel who are blinded to the study treatment.

COVID-19 adverse events will be collected in the following manner: any cases of COVID-19 that have been confirmed by a positive PCR test or serology will be called "COVID-19 confirmed". For other adverse events that are not confirmed cases of COVID-19, typical reporting procedures will be used to describe a diagnosis if available, or a list of symptoms if no diagnosis is available. A listing of confirmed COVID-19 cases will be created if any occur.

An overall summary table will be developed to report the number of events and the number and percentage of participants having at least one event in the following categories:

- AEs
- AEs indicated as serious
- AEs of special interest
- AEs that were reported as being related (possibly related or related) to a study drug
- AEs reported by severity
- AEs that lead to study drug discontinuation
- AEs with an outcome of death

In addition, AEs classified by MedDRA SOC and preferred term will be summarized for each treatment group and overall for each of the following:

- All AEs
- AEs leading to discontinuation of study drug
- AEs by maximum severity
- AEs by relationship to study drug

Summary tables will present the total number of events as well as the number and percentage of participants experiencing the events. If a participant experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of participants experiencing the events, a participant will only be counted once if they experience an event within the particular SOC or preferred term. Percentages will be based on the number of participants in the safety population.

8.3. Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be summarized in the overall AE summary table and in a separate table by SOC and preferred term. A listing showing all SAEs and AEs of special interest (AESIs) will be created. Separate displays listing and summarizing death will be created if a death occurs.

8.4. Clinical Laboratory Evaluation

Clinical laboratory measurements include serum chemistry, hematology, and ESR. Results will be converted to standardized units where possible. For numeric laboratory results, descriptive statistics of laboratory values and the change from baseline of laboratory values will be presented for each treatment group and overall for each cohort. There were no categorical lab results collected in this study.

Laboratory data will be plotted to show patterns over time. For each cohort and lab test, spaghetti plots will show the results over time. Participant lines will be colored by treatment group, and grade 2 or higher results will be annotated.

8.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

8.5.1. Vital Signs

Vital signs of weight, temperature, pulse, respiratory rate, and blood pressure will be obtained at all visits. Additionally, height is collected at Visit -1 only. These vital signs will be displayed in a listing. Vital signs with NCI-CTCAE grading criteria will have the grade included in the listing.

Vital signs will be summarized in a table by treatment group and cohort for each scheduled visit.

Infusion vital signs will be displayed in a separate listing.

8.5.2. Physical Examinations

Either a comprehensive or directed physical examination will be performed at each scheduled study visit. A data listing will be provided for physical examination results that is sorted by cohort, treatment group, participant, and body system. A separate listing of only abnormal physical exam results will also be provided.

8.5.3. Peripheral Neuropathy

Peripheral neuropathy assessment results will be listed. Two listings will be created: one that shows the grade of peripheral neuropathy and action taken for each participant at each study visit. Another listing will display the results of each component of the assessment (pin sensibility, vibration sensibility, muscle strength, motor symptoms, sensory symptoms, and autonomic symptoms).

8.5.4. Echocardiogram

An echocardiogram is performed at screening and Week 24. Results from the echocardiograms will be listed for each participant.

8.5.5. Spirometry

Spirometry data will be listed at each visit for each participant. Actual and % predicted values for FVC, FEV1, and DLCO will be listed. Additionally, predicted FVC will be calculated according to the Global Lung Function Initiative all-age reference values (2017) and predicted DLCO adjusted for hemoglobin will be calculated using the Cotes formula (1972).

8.5.6. Medical History and Scleroderma History

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

Scleroderma history will also be listed. This will include a list of scleroderma symptoms and whether they were ever experienced by the participant.

9. OTHER ANALYSES

9.1. Use of Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary E (version 2017.03). Medications reported on the CRF will be categorized for analysis as prior, concomitant, or after study treatment by comparing the medication start and stop dates with the first and last dose of study medication dates. Medications where both the start and stop dates are prior to the first dose of brentuximab vedotin or placebo will be classified as prior medications. Medications where both the start and stop dates are after the last dose of brentuximab vedotin or placebo will be classified as after study treatment medications. All other medications will be classified as concomitant, indicating that use of the medication overlapped with use of the study medication by at least one day.

The number and percentage of participants receiving prior, concomitant, and after medications will be presented. For each medication type, when reporting the number of participants receiving a medication, a participant will only be counted once if they ever received the medication. Percentages will be based on the number of participants in the safety population.

All medications will also be listed.

9.2. COVID-19 Listing

All visits affected by the COVID-19 pandemic and a description of how they were affected (e.g. out of window, visit done remotely) will be listed.

10. INTERIM ANALYSES AND DATA MONITORING

The progress of the study will be monitored by the Data and Safety Monitoring Board (DSMB). The Autoimmune DSMB will be chartered to review safety data and to make recommendations regarding continuation, termination, or modification of the study. The DSMB will formally review the safety data at least yearly.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor or protocol chair to warrant review, or when an event occurs that could contribute to a predefined stopping rule specified in the protocol.

Findings will be reported to Institutional Review Boards (IRBs) and health authorities.

Additionally, interim safety reviews will be undertaken by a Safety Review Committee (SRC) comprised of a subgroup of the DSMB. The SRC will review the data after all participants in cohorts 1 and 2 complete 12 weeks of study. Approval by the SRC is required before moving to each next higher dosing cohort. The SRC will also review the data after all participants in a cohort reach 24 weeks of study. Due to enrollment challenges, the study stopped enrollment prior to cohort 3 (1.8 mg/kg). The safety review committee will still review the cohort 2 data.

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.

11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Due to enrollment challenges the study team and sponsor decided to not move onto cohort 3 which would have administered the highest dose of 1.8 mg/kg. All analyses and descriptions in the SAP were updated to no longer refer to any analysis of cohort 3. This changed the following planned analyses:

- For the analysis of the dose response relationship across all dose levels, the protocol mentions a logistic regression model will be created, but this analysis was removed since the smaller sample size no longer supports this analysis.

For the exploratory endpoint of CRISS, the revised CRISS will be used, not ACR CRISS (see section 7.3.7 for details on computation of the revised CRISS).

For all endpoints and adverse events, summary statistics of the treatment groups pooled across cohorts will also be presented.

12. REFERENCES

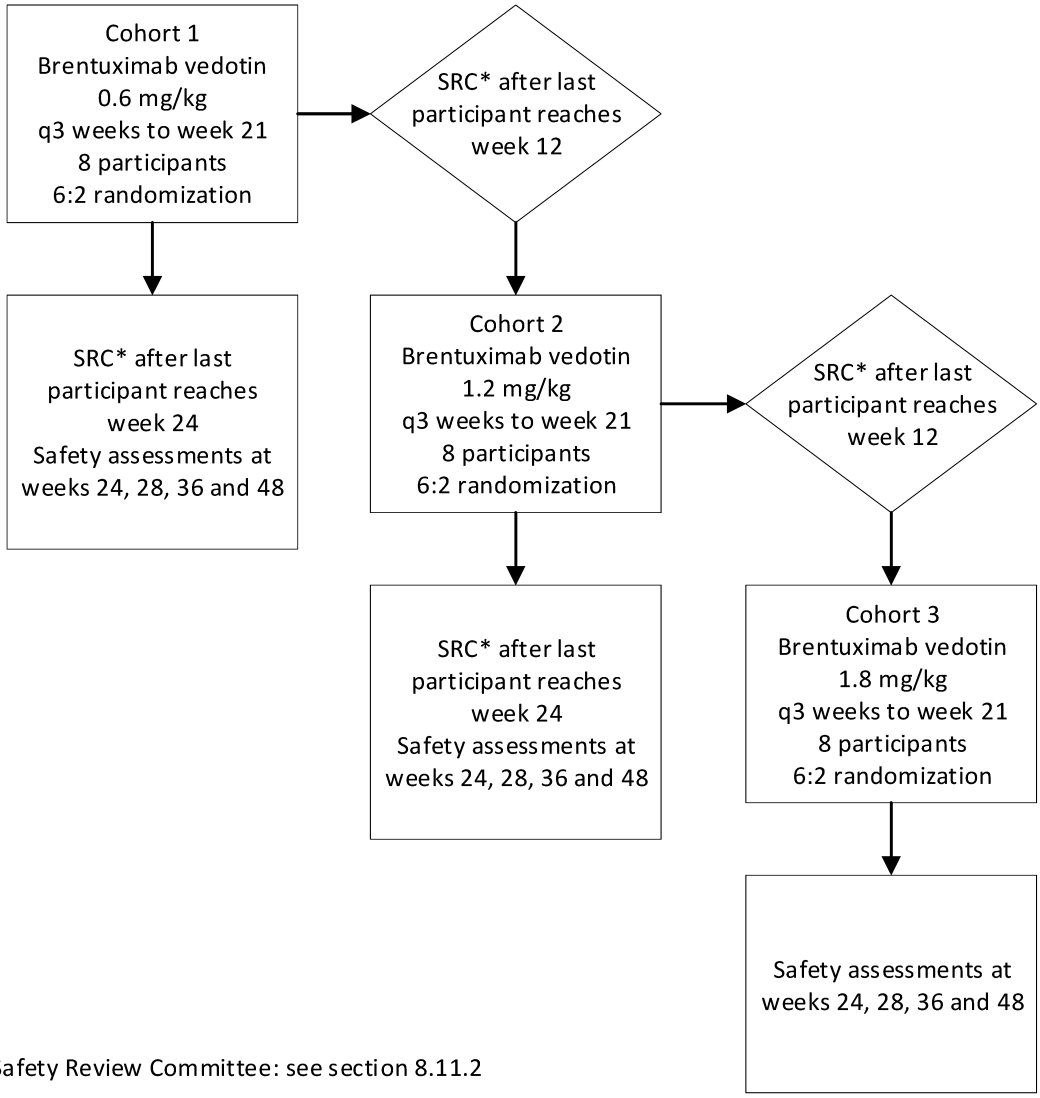
[1] Khanna D, et al. The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis. Arthritis & Rheumatology. 2016;68(2):299-311.

[2] PROMIS Adult Profile Instruments; http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Adult_Profile_Scoring_Manual.pdf

[3] THE HEALTH ASSESSMENT QUESTIONNAIRE (HAQ) DISABILITY INDEX (DI) OF THE CLINICAL HEALTH ASSESSMENT QUESTIONNAIRE (VERSION 96.4): https://www.niehs.nih.gov/research/resources/assets/docs/haq_instructions_508.pdf

13. APPENDICES

13.1. Study Flow Chart



* Safety Review Committee: see section 8.11.2

13.2. 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.