Research Consent Form Template

<u>Protocol Title</u>: Evaluation of Brentuximab Vedotin for Diffuse Cutaneous Systemic Sclerosis: A Phase I/II Multicenter, Randomized, Double-Blinded Safety Study (Protocol ITN075AI)

<u>Short Title</u>: Brentuximab Vedotin in Diffuse Cutaneous Systemic Sclerosis (BRAVOS)

Key Study Information

This consent contains information that will help you decide if you want to take part in this research study. We encourage you to read the entire document. All the information is important, but here are some key points to help you understand the study, which is described in more detail later in this form. Taking part in this study is your decision and is completely voluntary. There will be no penalties or loss of benefits to which you are otherwise entitled if you do not want to take part in the study or if you decide to discontinue early.

- This is a one-year research study for people with diffuse cutaneous systemic sclerosis (scleroderma, SSc, dcSSc) on stable background immunosuppressive medication with moderate skin disease.

- The study will evaluate the safety and tolerability of 3 doses of brentuximab vedotin, a medication that targets a part of the immune system involved with inflammation and fibrosis (scarring), present in autoimmune diseases including SSc.

- Brentuximab vedotin has been approved to treat several kinds of hematologic malignancies (cancers of the blood including Hodgkin's lymphoma). There have been reports of patients with autoimmune diseases, including rheumatoid arthritis and SSc, having an improvement of autoimmune symptoms when taking this drug for cancer. This has not been studied in scleroderma or other autoimmune diseases until now.

- The study involves 13 scheduled visits over a one-year period: a screening visit; 8 treatment visits; 4 follow-up visits, but you may be seen for extra visits if needed for active disease or side effects. The visits can range from 2-6 hours (treatment visits are 4-6 hours each).

- Procedures in the study include pulmonary function tests, echocardiograms, skin biopsies, blood tests, physical examinations, and questionnaires. There is a placebo control in this study, which means that of every 8 participants

enrolled, 2 receive infusions with saline (salt fluid) (an inactive substance not containing the study medication).

- There are risks with the study medication as outlined in the table and text in the **RISKS AND/OR DISCOMFORTS** section.

- There is compensation for your time and expenses in this study as described in the **PAYMENTS (REIMBURSEMENT)** section.

- There may be no direct medical benefit to you by being in this study. The information learned from this study may someday benefit people with systemic sclerosis.

- Before you decide whether to take part in this research, we would like you to carefully review this informed consent form. You will be given a copy of the signed form for your records.

INTRODUCTION / BACKGROUND

Diffuse cutaneous systemic sclerosis (dcSSc, also known as progressive scleroderma) is an autoimmune disease. In autoimmune disease, the body's immune system attacks its own body. In dcSSc, a person's own immune cells attack the skin and can also attack the internal organs, including the joints, lungs, heart, intestinal tract, and kidneys. This type of scleroderma causes tightness and thickening of the skin and can affect the hands, fingers, arms, legs, and torso (chest and back). Available treatments that suppress or weaken the immune system may decrease symptoms and slow disease progression. However, none of these medicines have shown significant long term benefit and they all have side effects.

CD30 is a protein (chemical) found at low levels on the surface of normal healthy white blood cells. These white blood cells are involved in the body's fight against disease and infection. However, in diseases like certain types of cancer, more of this protein is seen on overactive immune cells and cancer cells. It has also been shown that levels of CD30 may be higher on cells involved with inflammation (swelling) and fibrosis (scarring) in dcSSc and other autoimmune diseases. Therefore, CD30 may be a good target for the immune cells involved in disease activity.

Brentuximab vedotin (BV) is a drug that attaches to the CD30 protein and releases a toxin (poison) into the cell. This causes the cell to die. Studies have been performed using this drug in cancer. BV is now approved by the U.S. Food and Drug Administration (FDA) for the treatment of Hodgkin's and other lymphomas (cancers of the lymph system). Some cancer patients who also have the autoimmune disease have reported improvements in their autoimmune disease symptoms after treatment with BV. The autoimmune diseases have included rheumatoid arthritis, systemic lupus erythematosus

(lupus) and, dcSSc.

Until now, research studies evaluating the effect of BV in autoimmune disease have not been done. Before we can study whether BV can treat autoimmune disease, we need to determine whether it is safe. We think BV may work by attaching to the immune cells that cause autoimmune disease causing them to die. However, because CD30 is also found on normal cells there is the risk that BV could harm these normal cells too. There is also the risk that the toxin (poison) that is part of the drug may leak into spaces next to the immune cell targets which could damage normal cells and tissues. A few people with lupus were treated with low doses of BV as part of a study conducted by the company that makes BV. No safety concerns were identified. The study was not completed. The study we are asking you to participate in is a safety study of BV in individuals with dcSSc.

PURPOSE OF THE STUDY

- To evaluate the safety and tolerability of brentuximab vedotin (BV) in your disease, dcSSc
- To measure/check if this new drug decreases symptoms associated with dcSSc
- To examine the effect on the immune system by looking at blood and skin samples.

STUDY DESCRIPTION/ PROCEDURES

This study is a randomized, double-blind, placebo-controlled trial, which means that brentuximab vedotin (BV) is compared to a placebo (an inactive substance). Neither you nor your study doctor knows which you are receiving although your doctor can find out if needed for your safety. There is a 3 to 1 chance of receiving the study drug BV. This means three out of every four participants get BV. Your treatment group is determined by chance (like a flip of a coin). The study design, of three participants getting the drug for everyone participant who does not, allows for an objective (fair) evaluation of the drug. Three doses of BV are being studied over time: 0.6 mg/kg, 1.2 mg/kg, and 1.8 mg/kg (1.8 mg/kg is the approved dose for cancer treatment).

The study will enroll participants in three groups. Each group will include 8 participants who get enough medication to assess the safety of this drug. The lowest dose is tested in the first group with the dose increased in later groups. Before entering anyone into the next higher dose group a full safety review is conducted. The dosing group you are assigned to is the one that is enrolling at the time you enter the study.

Whatever group you are in the study drug is given to you 8 times. Each dose is given about every 3 weeks for 21 weeks (just over 5 months) for 4 additional visits through one year (described later in this form). You may be asked to return to the study site more often if needed for your safety. You are to continue taking your usual medications for dcSSc while you participate in the study. The COVID-19 pandemic may affect how we conduct the study. If needed, the study team may conduct some visits virtually. We do not know whether this will happen, or which visits will be impacted.

This study plans to include approximately 24 adults between the ages of 18 and 70 who meet all other entry criteria and are able to complete most of the infusions. We may need to enroll more than 24 participants but not more than 40 participants.

Approximately 9 study sites in the United States are participating. Each site is expected to enroll approximately 4-5 study participants.

The study has a screening phase, a study drug administration phase, and a safety follow-up phase as described below. The study is sponsored (supported) in part by funding from the National Institute of Allergy and Infectious Diseases (NIAID), of the National Institutes of Health (NIH). The Immune Tolerance Network (ITN) is conducting the study. Seattle Genetics, Inc. is the manufacturer of BV and is providing the study drug for the trial.

Screening Phase

If you decide to participate and sign this form, the study screening phase begins to determine if you qualify to become a study volunteer. This phase lasts up to 1 month and evaluations may be scheduled over more than one visit. During this time, you are asked questions about your illness and other health history questions and what medications and supplements you take. A clinical evaluation is done, consisting of the studies listed below.

- **Physical Exam:** (including weight and vital signs- temperature, blood pressure, heart rate, and breathing rate). This includes a detailed examination of your skin and joints.
- **Echocardiogram:** an ultrasound that uses sound waves to create pictures of the heart. The ultrasound waves rebound or "echo" of the heart and show the size, shape, and movement of the heart's valves and chambers as well as the flow of blood through the heart and surrounding blood vessels.
- **Electrocardiogram (ECG):** This test measures the rate and regularity of your heartbeat, as well as the size and position of the right ventricle in your heart. Electrodes (pieces of metal attached to wires) are attached to your arms, legs, and chest to record the electrical activity of your heart.
- **Tuberculosis Test (PPD Skin Testing or QuantiFERON®-TB Gold Plus Blood Test):**
    - For the PPD skin test you receive a small injection under the skin of your forearm to determine if you have been exposed to tuberculosis (TB). You return to the study site 48-72 hours after the test for the results to be read.
    - If tested with the QuantiFERON®-TB Gold Plus Test method 3 mL (1 teaspoon) of blood is drawn.

  This testing may not be necessary if you have already had it done in the last month and we can obtain documentation of the results from your physician.
- **SARS-CoV-2 Test**- This test will be performed to check if you have COVID-19.

If your test results are positive, you may not be able to participate in the study. Also, if you have tested Positive for SARS-CoV-2 within the two weeks prior to participating in this study, you may not be able to participate.

- **COVID Vaccination**: You are required to complete the primary SARS-CoV-2 vaccination series before screening. All doses of your vaccination series including the booster or additional dose must be completed at least 14 days prior to your first infusion of the study medication. Your study doctor will review with you the doses you have received and confirm that you are up to date with the most recent FDA and CDC recommendations.

- **Pulmonary Function Tests (PFTs)**: a test to measure lung function in which you breathe in and out of a machine. This test measures how well your lungs inhale and exhale air.
- **Routine Blood Tests:** approximately 20 mL (4 Teaspoons) of blood and a urine sample are collected to evaluate your disease status and overall health. This includes a pregnancy test (for women of child-bearing potential) to confirm that you are not pregnant. All participants are tested for infectious diseases which include HIV testing described below:

If you agree to participate in this study your blood is tested for Human Immunodeficiency Virus (HIV), the virus which causes AIDS. If your test results are positive, you cannot participate in the study. Your HIV test result is given to you in person, not over the phone. Your medical records are kept confidential to the extent permitted by law. If you have any questions regarding the HIV testing or the information provided above, you are encouraged to discuss them with your study doctor.

Study Drug Phase

If you qualify for the study, you move on to the study drug phase. There are 8 study drug doses (infusions), each given intravenously (in a vein, IV) every 3 weeks. You are admitted to the infusion center on the morning of each scheduled dose of the study drug. After completion of the pre-infusion evaluations, you will have an IV catheter (thin, plastic tube) inserted in a vein in your arm or hand. Each dose of the study drug is given over approximately 30 minutes, and you are closely monitored for safety during and after the infusion. You should expect to be in the infusion center for approximately 4-6 hours on each of the infusion days.
The following evaluations occur before the study drug infusions:

- **Physical Exam**: a brief physical examination, including vital signs and weight.
- **Pulmonary Function Test (PFT)**: at Week 12 before the 5th study drug dose. You may be required to have a SAR-CoV-2 test done before you come in for this procedure

- **Safety Blood and Urine Tests:** approximately 15 mL (1 Tablespoon) of blood is

drawn to look at your disease status and overall health within 3 days of each study drug dose. This is done to make sure it is safe to give the next dose. Women of childbearing potential have a urine pregnancy test.

- **Research Blood Tests (Baseline before 1st dose and Week 12 before the 5th dose):** approximately 105 mL (7 Tablespoons) of blood is drawn for research purposes to study your immune system, your dcSSc disease status, and the response to the study drug. A portion of the blood is used for genetic tests to identify and study the genes of your immune system relating to your disease and the study treatment. Also, we ask your permission to store unused samples for future use which may involve genetic testing (this is described at the end of this form before the signature page).

- **Skin Biopsies (Baseline before 1st dose and Week 12 before the 5th dose):** Skin biopsies are taken using a tiny circular blade (punch biopsy) on the skin of your forearm. Before the 1st and 5th doses of the study drug, two 3-millimeter (mm) punch biopsies are collected, removing small cylinders of skin. For all biopsies, the skin is injected with a local anesthetic (lidocaine) to numb the area to minimize pain and discomfort. Each biopsy procedure takes approximately 15-20 minutes. The wounds usually heal in 7-10 days and during that time you may feel some mild discomfort. If needed, an over-the-counter pain reliever may be recommended by your study doctor. Rarely sutures (stitches) may be needed to close the biopsy sites. If required, the sutures are removed 10-14 days after the biopsy, either at the study site or by your primary care doctor closer to home.

- **Disease Activity/Quality of Life Questionnaires (baseline before 1st dose):** you are asked to complete several questionnaires and surveys about your disease and its impact on your life. They should take approximately 20 minutes to complete.

Follow-Up Phase

Contact with the study site continues for approximately one year after starting the study drug. The first follow-up visit is scheduled 3 weeks after the last study drug infusion, at Week 24 and then at Weeks 28, 36, and 48. You may be asked to come in more often depending on your health status, if necessary, for your safety. The evaluations and procedures are listed below (see a full description of each under the **Screening and Study Drug Administration Phase** descriptions):

- **Physical Exam:** (including weight and vital signs- temperature, blood pressure, heart rate, breathing rate, and oxygen saturation) is conducted at each visit. This includes a detailed examination of your skin and joints at the Week 24 and Week 48 visits.
- **Pulmonary Function Tests (PFTs):** repeated at the Week 24 and Week 48 visits. You may be required to have a SARS -CoV-2 test done before you come in for this procedure
- **Echocardiogram:** repeated at the Week 24 visit.

- **Blood Tests:**
    - **Routine Blood and Urine Tests:** a total of approximately 10 mL (2 teaspoons) of blood is collected at all 4 follow-up visits to evaluate your disease condition and overall health. Women of childbearing potential have a urine pregnancy test.
    - **Research Blood Tests:** a total of approximately 105 mL (7 Tablespoons) of blood is collected at the Week 24 and Week 48 visits for research purposes as previously outlined under the **Treatment Phase.**
    - **At Week 28**: This visit may be conducted virtually. Your study team will decide how this visit will be done and inform you.
- **Skin Biopsies:** repeated at the Week 24 visit.
- **Disease Activity/Quality of Life Questionnaires:** repeated at the Week 24 and Week 48 visits.

The table below outlines the study visits for the 3 study phases.

Study Phase	Screening	Treatment								Follow-Up				
Visit Number	1	2	3	4	5	6	7	8	9	10	11**	12	13	14
Visit Week	-4	0	3	6	9	12	15	18	21	24	28	36	48	Unscheduled
Physical Examination and Vital Signs	X	X	X	X	X	X	X	X	X	X		X	X	X
Blood Tests	X	X	X	X	X	X	X	X	X	X		X	X	X
Urine Pregnancy Test (as applicable)		X	X	X	X	X	X	X	X	X		X	X	X
Echocardiogram	X									X				
Pulmonary Function Test*	X*					X*				X*			X*	
Electrocardiogram	X													
Infectious Disease Testing (includes HIV, TB, and SARS-CoV-2)	X													
Questionnaires		X								X			X	
Skin Biopsies		X				X				X				
Study Drug Administration		X	X	X	X	X	X	X	X					
Review medications and health status	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*You may be required to have a SARS-CoV-2 test before this procedure. Your study team will advise when and what to do before this visit.

**This visit may be conducted remotely, unless you are being followed-up due to new onset of disease related to study drug use.

Collection and Storage of Samples/Information
For this project, we collect, store, and use blood and skin samples and study information (data).
The samples and data are used for research now and in the future. Some of this research is for genetic tests, including analysis of deoxyribonucleic acid (DNA). Genetic tests study an individual's inherited characteristics, found in DNA, which is present in each of the cells of your body. Blood and skin samples collected will be used for research tests including analysis of deoxyribonucleic acid (DNA). DNA contains information needed to build and operate the human body. Your samples are coded with a number so that your name and personal information are not labeled on them. Only your study doctor has the code that directly links you to your specimens. Samples sent to outside labs for analysis will only have this coded number. All data are kept confidential and lab workers testing the DNA will not have any of your traditional identifiers (i.e., initials, birthdate, address, etc.).

Your confidentiality is protected to the extent permitted by law. Although we remove identifiers, we cannot guarantee confidentiality. For example, if the research is for genetic testing there is a chance that it could be traced back to you because your genes are specific to you.

The genetic studies described are for research purposes only. Results from these tests will not be provided to you or your doctor. It is not the purpose of these studies to look for or provide you with any medical information or diagnoses relating to your present condition or any other disease or illness.

Samples and data may be shared with other investigators. If you agree to participate, your samples are stored in a secure central location at the Immune Tolerance Network (ITN) laboratories until the testing for this study can be carried out. Results from the study and related health information are stored in a secure database. Details of how your identity is protected will be described later in this form. Also, at the end of this form, you are asked to consider allowing storage of unused samples for future use which may not be directly related to this study.

RISKS AND/OR DISCOMFORTS

The risks of the study drug based on the current information are described below. Given the limited experience with giving the drug for AD including dcSSc, most of this information comes from experience in people with cancer. The treatments and procedures involved in this research project may involve risks that are unknown or not possible to predict. You will be notified immediately of any new significant findings during the research which may affect your willingness to continue in the study.

Risks Associated with Brentuximab Vedotin (BV):

More common and serious risks are numbered and described in more detail below the table.

Table 2: Risks of BV when used without other cancer drugs

Very Common side effects (≥ 10%)	Common side effects (≥1% to<10%)	Uncommon side effects (≥0.1 to < 1%)	Rare Side Effects (≥0.01 to<0.1%)	Very Rare Side Effects (<0.01%)
Hair loss (Alopecia) [1]Peripheral neuropathy [3]Neutropenia [4]Infections • Upper respiratory tract infection Fever Cough Tiredness [9] Abdominal complications • nausea, vomiting, diarrhea, and constipation Feeling out breath Joint pains (Arthralgia) Headache [7]Itching, rash	Back pain Chills Dizziness High blood sugar (Hyperglycemia) [3] Febrile neutropenia, Thrombocytopenia (low platelets) Muscle pain [9] Abdominal complications • Abdominal pain, distension, dyspepsia, weight loss [4]Infections • nasopharyngitis, bronchitis, influenza, oral candidiasis, shingles (Herpes zoster), pneumonia, sepsis, sinusitis, urinary tract infection. High levels of liver enzymes (Elevated ALT/AST) [7]Skin complications • hives Oropharyngeal pain (throat pain)	[2] Sudden and serious infusion related reaction [9] Abdominal complications • gastrointestinal hemorrhage, intestinal perforation, ileus [8]Damage to the liver [6]Lung damage (pulmonary toxicity) [4]Infection	[9]Acute pancreatitis [9] Neutropenic colitis [5]PML (Progressive Multifocal Leukoencephalopathy) [7] Skin complications • Stevens-Johnson syndrome/toxic epidermal necrosis	Immune response to the drug (Drug specific antibody response) [9] Enterocolitis [4]Opportunistic infections

[1]Peripheral Neuropathy

There have been reports of neuropathy (abnormal functioning of the nerves) of the arms and legs in individuals who received BV. Neuropathy can involve either the sensory nerves (that control feeling touch, pain, temperature) or motor nerves (that control movement like gripping, lifting, or walking). Sensory neuropathy was more common than the motor, and in most cases was reversible after the dose was lowered or treatment was stopped. Patients older than 60 reported more pain, weakness, or unusual sensations in their hands and feet. More older patients had severe cases of peripheral neuropathy than younger patients after being given BV. This could be because of age, or it could be because of other diseases more common in this age group associated with neuropathy, like diabetes. This study is excluding people from participating who have diabetes or a history of peripheral neuropathy no matter what the cause.

Approximately 80% of individuals in the cancer studies who experienced peripheral neuropathy showed resolution or improvement in symptoms after stopping BV, with approximately 60% of those having complete resolution of all neuropathy symptoms. Some of the symptoms of neuropathy may seem similar to the symptoms seen in Raynaud's syndrome which is common in dcSSc. You are checked for neuropathy throughout the study, and it is important to notify the study team immediately if you notice any change in feeling in your hands and/or feet (such as burning sensation, pain, numbness or tingling, or loss of feeling) or weakness in your arms or legs affecting your movement (ability to grip, lift, walk, etc.).

[2]Infusion-Related Reactions

Infusion reactions during or soon after receiving BV treatment have been reported. Not all infusion reactions are true allergic reactions. Most of the infusion reactions have been mild or moderate in severity and none have been life-threatening in patients receiving only BV. The allergic reactions included chills, nausea, cough, itching, and shortness of breath. Rare but more serious reactions occurred in cancer patients receiving both BV and chemotherapy. Though unlikely, there is a chance that you could have a life-threatening allergic reaction (anaphylaxis) that requires immediate medical attention and stopping study treatment. Symptoms of anaphylaxis could include itching/hives; trouble breathing; chest tightness; feeling faint; and swelling of your tongue, face, or throat. You are monitored closely during and after each study drug infusion and quickly treated if a reaction occurs. If you experience a mild or moderate infusion reaction you will receive medications (diphenhydramine (Benadryl®) and acetaminophen (Tylenol®)) before any additional doses to help prevent it from happening again.

[3]Low Number of Blood Cells

Treatment with BV has been associated with neutropenia, which is a drop in the number of a type of white blood cells called neutrophils. White blood cells are an important part of the immune system to fight infection and having a low number of these cells may make it easier for you to get sick. In patients receiving both BV and chemotherapy, there were reports of very low white blood cells with fever (febrile neutropenia) that were life-threatening. Low numbers of red blood cells and platelets have also been reported with treatment with BV. A low number of red blood cells can cause anemia and fatigue which could make you feel tired or need a blood transfusion. Platelets are blood cells responsible for clotting of the blood and a low number of these cells can cause bleeding. You are monitored closely with blood tests before and after each dose of the study drug. Your dose is lowered, and your infusions are held or stopped permanently if needed for your safety. You should notify your study doctor immediately with any signs of infection, unexpected bleeding, or unusual fatigue (tiredness or weakness).

[4]Infections

There have been reports of increased infections with BV. Upper Respiratory Tract Infections (URIs) were the most common infections reported in more than 10 out of 100 of patients receiving BV, while sepsis, herpes zoster, pneumonia, candidiasis, pneumonitis, nasopharyngitis (swelling and redness in your throat and nose), bronchitis, sinusitis, influenza, and oral candidiasis (a yeast infection in your mouth, sometimes called "thrush") were common infections in people taking BV**.** Among these infections, the following may become serious infections- pneumonia, pneumonitis, influenza, and herpes zoster and can be life threatening.

You could get sick from something that doesn't usually cause problems, like a virus or a germ due to weakened immune system (opportunistic infections). This may happen because your immune system isn't as strong as usual. Opportunistic infections may occur, but very rarely because the immune system is weakened by BV.

You should contact the study team immediately if you get a fever, sore throat, cough, sinus problems, headache or have trouble breathing and/or develop painful sores (ulcers) in/on the mouth or skin.

Risk of COVID-19 infection

BV may increase your risk of getting COVID-19. The infection could be more severe as a result of receiving this drug. To decrease your risk of infection with SARS-CoV-2, and to protect yourself and others, we strongly recommend that you follow the Centers for Disease Control (CDC) recommended measures which include wearing a mask, practicing social distancing, and frequent handwashing/use of hand sanitizer. These measures are outlined on the CDC website at the following link: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html.

You must complete the primary SARS-CoV-2 vaccination series with one of the FDA authorized or licensed SARS-CoV-2 vaccines at the time of screening. Booster doses can be completed during screening, but 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.

You must have a negative COVID-19 test before your second visit at week 0 also known as first day of infusion.

If you develop COVID-19 infection during your participation in the study, the infusions of BV will be stopped until you have recovered from the infection. Infusions may be restarted at the next scheduled dose, if your symptoms have been absent for at least 10 days, or if in the case that you didn't have any symptoms of the infection at least 10 days should have passed since you tested positive for COVID-19.

You will need to have a negative test before the infusions can be restarted.

We strongly recommend that you notify your study doctor immediately if you get exposed to someone with known COVID-19 infection or have a positive test. If you test positive for COVID 19, with or without symptoms, you should report to your study doctor immediately and within 10 days from the first day of your symptom onset. Your study doctor may prescribe FDA approved or authorized COVID-19 treatments such as monoclonal antibodies. If you get exposed, you may be advised to receive other therapies as they become available for either treatment or prophylaxis.

[5]Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a rare, life-threatening brain infection caused by the John Cunningham Virus (JC Virus) This virus is carried by the majority of people and is harmless except among those with lowered immune defenses when it can become activated. The disease occurs in patients undergoing immunosuppressive therapy and/or chemotherapy for cancer and organ transplant, and there have been rare reports in individuals with autoimmune diseases. Cases of PML have been reported in cancer patients receiving BV, usually in combination with other immunosuppressive drugs. PML can result in death or severe disability. Contact your study doctor immediately if you have any of the following or if anyone close to you notices these symptoms: confusion or problems thinking, loss of balance or problems

walking, problems speaking, decreased strength or weakness on one side of your body, blurred vision, or loss of vision.

[6]Lung Damage (Pulmonary Toxicity)
Interstitial lung disease (ILD), or scarring of the lung tissue, is a condition found in dcSSc. ILD has been reported in patients receiving BV. Because some individuals may have ILD when starting the study, it may be difficult to evaluate the effect of BV on the condition. Pneumonitis and Adult Respiratory Distress Syndrome (ARDS) are two other lung conditions that have been seen. In some cases, these conditions have been fatal. Symptoms include cough and shortness of breath. This study limits the amount of lung disease that a person can have to participate, and you are closely monitored for this throughout your participation. If you have breathing problems including a new or worsening cough or shortness of breath you should notify your study doctor immediately.

[7] Skin Toxicities
Skin complications including rashes, itching, flushing, patchy red skin, and hives were reported commonly in people taking BV.

Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis is a serious painful rash that occurs rarely in people who take BV. It is a reaction to the medication and causes a rash that spreads to most of your skin. SJS can cause, blisters, hives, swollen tongue, peeling and can cause death.

[8]Hepatotoxicity
Temporary stress to your liver may occur but recovers once the drug is stopped. However, uncommonly this damage can be more severe and permanent, and very rarely fatal. In this study your liver function blood tests will be checked frequently, and the drug will be held or stopped if necessary for your safety. You may or may not have symptoms which could include yellow eyes or skin, feeling tired, nausea, or vomiting. You could have belly pain, bleeding that doesn't stop, sudden weight gain, and/or swollen hands or feet. If this happens, get emergency medical help right away.

[9] Abdominal Complications or Gastrointestinal Toxicities
The following list of abdominal complications were reported as very common including nausea, vomiting, diarrhea, and constipation. Abdominal distension (stomach swelling), pain and upset stomach were reported as common. More severe abdominal complications happen less frequently as listed in table 2. In the event of new or worsening abdominal symptoms, report to your doctor immediately.

Potential Drug Interactions
There is a risk for a potential drug interaction between BV and a few specific medications as reported by the drug manufacturer. These include certain antibiotics and antifungals used to treat infections. It is important to notify the study doctor if you have been prescribed a new medication before starting to take it to make sure it is not one of these drugs to be avoided.

Pregnancy, Breastfeeding, and Fertility
In animal studies, BV caused miscarriages and birth defects. The risks in humans to the unborn fetus and newborn from BV are unknown. Given what is known about how the drug works, there is a chance that BV can cause fetal harm when given to a pregnant woman. Because BV may be secreted in breast milk, a nursing baby may also be exposed. Therefore, women who want to become pregnant within the next year should not participate. Women who are pregnant or nursing a child may not participate in this trial. Women of child-bearing potential must have a negative pregnancy test before each dose of the study drug and urine pregnancy tests will continue to be checked through the last follow-up visit. BV also affects the testes (sperm-producing organs) in male animals.

Two methods of medically acceptable birth control are required for participants and their partners (if of reproductive potential) during the study and for at least 6 months after last dose of the study drug. Your study doctor will discuss appropriate birth control measures with you. If you or your partner become pregnant during the study, you must

notify your study doctor immediately. If this happens during the treatment phase the study drug will be discontinued. The study doctor will want to follow the outcome of pregnancy affecting any participant and his partner.

Decreased male fertility has been associated with BV in animal studies.

Risks Associated with Skin Biopsies:
The skin biopsies may result in temporary discomfort during the procedure and for a short time afterward. There is a small risk of bleeding, infection, and rarely, allergic reaction to the local anesthetic. The biopsy sites usually heal with minimally visible scars.

Risks Associated with Blood Drawing/IV Insertion:
Drawing blood samples and inserting an IV may involve temporary discomfort or bruise, possibly fainting, and very rarely inflammation (swelling), infection, or clotting of the vein.

Risks Associated with Stored and Shared Blood and Information:
Traditional identifiers (such as your name, address, or social security number) are not placed into any scientific database. The **Confidentiality Section** later in this form describes the safeguards used to code information that could link results back to you. Every effort is made to protect your privacy to the extent permitted by law. It would be very hard for anyone to tell whom the data belongs to.

BENEFITS

You should not expect a direct benefit from this study. Your disease may improve, stay the same, or worsen during the study.

It is hoped that researchers learn more about the function of the immune system and the response of this disease to treatment with BV. Society may also gain knowledge from this study regarding the safety of using BV for treating patients with dcSSc. We hope the information learned from this study benefits other patients with this disease.

If during the study testing, unexpected (not study-related) information is obtained that would be important for you to know for your well-being, you will be informed of that information with counseling as to appropriate next steps. The study will not cover costs for related follow-up.

New Findings

During your participation in this study, your study doctor will inform you of any new findings from this or other research that may affect your willingness to continue in this study.

PAYMENTS (REIMBURSEMENT)

You will receive approximately $50 per visit to cover travel and other expenses associated with participation in this study. Also, for each of the longer study drug infusion visits, you will receive $20 per hour for up to 4 hours for your stay. Also, for each visit where skin biopsies are obtained, you will receive $50.

Reimbursement for travel expenses that are above $50 per visit may be available. The study staff must first obtain preapproval from the Immune Tolerance Network for any travel expenses that are above $50 per visit.

ALTERNATIVES TO PARTICIPATION

You do not have to participate in this study to receive treatment for your condition. Treatments include other immunosuppressive drugs including methotrexate, azathioprine, mycophenolate, cyclosporine, hydroxychloroquine, and corticosteroids (steroids, Prednisone). Biologic drugs including TNF inhibitors, anakinra, abatacept, and tocilizumab are available as well as B cell targeting drugs (rituximab) and low dose chemotherapy (cyclophosphamide). Stem cell transplantation is another option for

individuals and there may be other research studies involving new therapies for which you may be eligible. Also, you have the option of choosing no therapy. You should talk about other treatments with your study doctor. Make sure that you understand all of your choices before you decide to take part in this study.

WITHDRAWAL FROM THE TREATMENT and/or STUDY

It is important that you understand that ***your participation is completely voluntary*** and that ***you may decide to drop out of the study at any time*** without losing the benefits of your regular medical care to which you are entitled.

Study treatment and/or your participation in this study may be stopped early at any time without your consent. Reasons that might cause this include, but are not limited to, the following:

- The study doctor feels it is not in your best interest to continue.
- You are unable to complete the required study treatments and examinations.
- You experience a serious side effect and your physician determines that it is unsafe for you to continue.
- Your dcSSc and/or general health worsen.
- You need to take a medication that is not allowed while on this study.
- You are unable to comply with the study requirements.
- You become pregnant.
- The study is closed for safety concerns or administrative reasons by the Institution, the Sponsor (the NIAID, NIH), or by National Regulatory Agencies or other health authorities.

If you are either withdrawn from treatment or from the study, you will continue to receive medical care from your primary medical doctor as you did before you participated in this study. Also, your doctor will discuss future treatment and procedures for your continued care. Even if you don't receive all planned doses of the study drug, you are asked to return to the study site to complete any study evaluations necessary for your safety. You may be asked to return for one end of study visit or you may be asked to continue scheduled follow-up visits depending upon the circumstances.

You may withdraw your permission for us to use your data and samples for research. However, you cannot withdraw your samples and information from studies that have already begun. We cannot get samples and information back once they are shared with other researchers.

COSTS

The costs of all medications, tests, and procedures described above that are required by the study will be paid for by the NIAID, NIH through the Immune Tolerance Network. You are responsible for any expenses related to your standard clinical care.

Ask your study doctor about any expected added costs that may result from your participation in this study. Insurance companies and other carriers sometimes refuse to pay the costs of treatment when individuals are participating in research. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may lead to added costs for you or your insurance company.

RESEARCH-RELATED INJURY

If you should be injured as a result of your participation in this study, emergency medical care is available to you, but you or your insurance company will be charged for this treatment. The hospitals and/or treating physicians reserve the right to bill you and/or your insurance provider(s) for services you receive for the injury. No payment or additional compensation is available to you as a result of such injuries. There is no provision for free medical care or monetary compensation from the study sponsor, the NIAID, NIH, nor from Seattle Genetics, Inc. You do not lose any legal rights by signing this form.

CONFIDENTIALITY

Your medical and research records are kept confidential to the extent permitted by law.

All efforts are made to keep your personal information private. However, we cannot always guarantee complete confidentiality.

Information that does not become part of your medical record is identified by a code and personal information from your records will not be released without your written permission. You will not be identified in any publication that results from this research.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- the National Institute of Allergy and Infectious Diseases (NIAID, NIH), sponsor of this research
- NIAID representatives, agents, employees, contractors, grantees, and other persons assisting in the conduct, monitoring, or analysis of this study
- The U.S. Food and Drug Administration (FDA) or representatives of Health Canada
- Representatives of Seattle Genetics, Inc., the pharmaceutical partner supplying the study drug
- Other state and local health and/or regulatory authorities.

These organizations and agencies may also ask permission to look at your medical records from other doctors, hospitals, or other healthcare providers.

After the study is completed, the data are placed in a central storage location or public database. This includes all of the information learned from this study and not just information specific to you. The purpose is to make the study data available to share with other researchers. The information is coded and will not contain your name or other traditional identifying information like social security number or birthday.

Also, a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website does not include information that can identify you. At most, the Web site includes a summary of the results. You can search this Web site at any time.

STUDY CONTACTS: WHO TO CALL WITH QUESTIONS or PROBLEMS

Dr. _____*insert PI name*_____ is the principal investigator at your center who is supervising the research study and following your related treatment and care. If you have questions about the study or experience a research-related injury you should contact Dr. ___*insert PI name*_____ who can be reached at ___*insert phone number*___ during normal business hours. After hours and in emergency situations, the covering physician can be reached by calling the page operator at *insert number*. **If you believe you are experiencing a serious, life-threatening problem then immediately dial 911, go to the nearest emergency room, and notify the study doctor as soon as possible.**

If you have any questions about your rights as a research participant, please contact the Institutional Review Board (*insert name)*_____ at *insert phone number*, or if you prefer, you can direct your questions to _*insert name*_____at the following address: *insert address here*.

OPTIONAL STORAGE OF UNUSED BLOOD SAMPLES FOR FUTURE USE AND SHARING OF INFORMATION

We are asking your permission to store any unused blood and skin tissue from the samples collected to be used in the future for research not yet planned. Since we do not yet know the exact questions that will be studied, we cannot tell you exactly what tests will be done with your samples. As a research participant in this study, you have the option of allowing any unused samples to be stored for future tests that may or may not be related to this study and the disease dcSSc.
Your decision to allow samples and data to be stored and shared is separate from your decision to participate in this study. If you decide to allow storage, your samples and data may be stored for an unknown length of time.

Some of the samples may be used to obtain knowledge about genetic information related to your dcSSc. Genetic tests study an individual's inherited characteristics, found in DNA, which is present in each of the cells of your body. DNA contains information needed to build and operate the human body.

Samples are stored at the Immune Tolerance Network (ITN) laboratories. If you decide to allow storage, your samples and the information learned from them may be stored for an unknown length of time. Any research conducted using your stored blood and skin samples will be approved by an Institutional Review Board. This board is a scientific and ethical group at an institution. Although your stored samples will not be sold, the information obtained from the research using them may in the future lead to the development of commercial products. You will not receive any money from research using your stored samples and the information learned.

We may want to share your samples with researchers at other institutions. Your samples are coded with a number so that your name cannot be identified. Only the investigators of this study at this study site have the code that links you to your specimens. Reports about research done with your samples and the results are not put in your medical record and are kept confidential, to the best of our ability and within state and federal law. Information that does not become part of your medical record is identified by a code, and personal information from your records will not be released without your written permission. You will not be identified in any publication about this study. Reports on these stored samples will not be given to you or your physician(s).

Benefits

There are no direct benefits to you from the collection and storage of these samples and the information learned from their use. However, the use of your samples and information may help researchers learn more about dcSSc and the immune system. The purpose of storing and sharing data is to make information available for use in health research. Collecting, storing, sharing information, and making it available for other studies may help people in the future.

Risks

There may be unknown risks associated with the storage and analysis of your blood and skin samples and the information learned. For example, if future research involves genetic testing there is a chance that it could be traced back to you because your genes are specific to you. We make every effort to protect your confidentiality and to make sure that your personal identity does not become known.

You can change your mind at any time and ask to have your samples destroyed. We ask that you make this request in writing to the study doctor if you choose to do so. If your samples have not already been used for tests, they will be destroyed when your request is received. If your samples have already been used then the information will be used and reported. Your decision regarding the storage of samples or the information learned from the use of your samples in future research does not affect your ability to participate in this study

Please indicate your responses below:

I agree to the storage and sharing of my unused blood and skin samples for future unplanned <u>genetic</u> tests. I agree with the sharing of information learned from this research as described above.

__ Yes __ No _____
Initials of Research Participant

I agree to the storage and sharing of my unused blood and skin samples for future unplanned <u>other</u> tests. I agree to the sharing of information learned from this research as described above.

__ Yes __ No _____
Initials of Research Participant

SIGNATURE PAGE

I confirm that the purpose of the research, the study procedures, and the possible risks and discomforts, as well as potential benefits that I may experience, have been explained to me. Alternatives to my participation in the study also have been discussed. I have read the informed consent and/or it has been explained to me. I was allowed to ask questions about the information, and all of my questions have been answered. My signature below indicates my voluntary willingness to participate in this study.

_____	_____	_____
Research Participant Name *(Typed or printed)*	**Research Participant Signature**	**Date**

Signature of the person explaining and obtaining the consent:

_____	_____	_____
Name and Title *(Typed or printed)*	**Signature**	**Date**

(Note: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the research subject. A copy should be placed in the research subject's medical record, if applicable.)