



Consent Version: 05/18/2020

Consent to Participate in Research

TITLE: A PHASE 2 MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF IFETROBAN IN PATIENTS WITH DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS OR SYSTEMIC SCLEROSIS-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

PROTOCOL NO.: CPI-IFE-004
WCG IRB Protocol #20170961
CRP17032
2006738640

SPONSOR: Cumberland Pharmaceuticals Inc.

INVESTIGATOR: C. Kent Kwoh, MD
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**STUDY-RELATED
PHONE NUMBER(S):** Daytime Phone Number: 520-626-8379
24 Hours Phone Number: 520-694-6000

RESEARCHER'S STATEMENT

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide if you want to be in the study. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or the form that is not clear. When we have answered all of your questions, you can decide if you want to be in the study or not. This process is called 'informed consent.' We will give you a copy of this form for your records.

This is a consent form for research participation. It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate. Participation is voluntary. You may choose not to



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participate or to withdraw later with no penalties or loss of benefits to which you are otherwise entitled.

The University receives compensation from the sponsor of this study for the conduct of this study. If you have any questions, please discuss this with your study doctor.

This consent form may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss the study with family or friends before making your decision.

In this consent form, “you” always refers to the subject.

PURPOSE OF THE STUDY

You are being asked to take part in this research study because you have systemic sclerosis, also called scleroderma. Systemic sclerosis is an autoimmune disease. Autoimmune diseases occur when the body’s own immune system does not work properly and attacks the body’s own tissues and organs. Systemic sclerosis is a group of rare diseases that involve the hardening and tightening of the skin and connective tissues (the fibers that provide the framework and support for your body).

In some people, systemic sclerosis affects only the skin. However, in many people, systemic sclerosis also harms the body beyond the skin. It can affect joints, tendons, skeletal muscles, blood vessels, and internal organs; including the lungs, heart, stomach, and kidney. Signs and symptoms of systemic sclerosis vary, depending on which structures are affected. Systemic sclerosis affects women more often than men and most commonly occurs between the ages of 30 and 50.

Currently, there are no drugs approved in the United States for the treatment of systemic sclerosis. The current treatment for systemic sclerosis focuses on treatments that ease the symptoms or improve quality of life.

Ifetroban sodium (ifetroban) is an investigational drug, meaning that it is not approved by the United States Food and Drug Administration (FDA). Ifetroban has been studied in 24 clinical studies in over 1300 people. These studies included both healthy volunteers and patients with various cardiovascular diseases. Cumberland Pharmaceutical (Cumberland) has also recently conducted clinical studies using ifetroban in patients with liver and respiratory diseases. The purpose of this study is to find out if ifetroban would be a safe and effective treatment in patients with systemic sclerosis.

This study is being done at approximately 6 sites in the United States. Thirty-four (34) patients with systemic sclerosis will be enrolled into the study.

Eligibility Criteria:

To be eligible to enter the study, you **must**:

- Be an adult male or female;

- Be at least 18 years of age but less than 80 years of age; and
- Have diffuse systemic sclerosis (SSc) or systemic sclerosis-pulmonary arterial hypertension (SSc-PAH) that meets the one of the two following criteria:

Diffuse Cutaneous SSc Inclusion Criterion

1. Adults with diagnosed diffuse cutaneous SSc within 7 years following initial diagnosis

SSc-PAH Inclusion Criteria

1. Adults with confirmed SSc-PAH
2. Stable oral therapy for PAH for at least 30 days
3. NYHA Class I-III Heart Failure

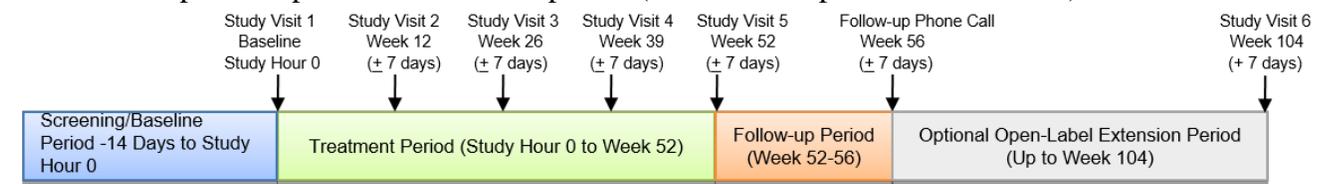
You also **must not:**

- Have a type of SSc known as sclerosis sine scleroderma;
- be less than 18 years of age or greater than 80 years of age;
- be pregnant or nursing a child (if you are able to bear children, you must be using an effective form of birth control if you are sexually active during the study);
- have started prostanoid therapy or changed your dose within the last 3 months if you have PAH (prostanoid therapy is not permitted if you have diffuse SSc);
- have current or planned treatment with pirfenidone;
- have used of rituximab in the last 3 months;
- have used of mycophenolic acid (Myfortic, CellCept) at a stable dose for less than 3 months;
- have current or planned corticosteroid therapy greater than 15mg per day prednisone or prednisone equivalent;
- have significant lung disease, defined as FVC (Forced Vital Capacity) less than 50% predicted or DLCO (Diffusion Capacity of Carbon Monoxide) less than 40% predicted;
- have significant kidney disease, defined as Glomerular Filtration Rate [GFR] less than 60 ml/min;
- have moderate or severe liver disease;
- have a contraindication to have an MRI procedure performed (e.g. implanted magnetic material, claustrophobia);
- have a known hypersensitivity to gadolinium;
- have a cause of pulmonary hypertension other than WHO Group I associated with SSc;
- have used aspirin more than 81 mg per day in the last two weeks;
- have used warfarin, heparin, or other anticoagulant in the past 30 days;
- have had a recent (within 6 weeks) myocardial infarction or persistent atrial arrhythmias;
- be allergic to the study drug;
- have taken another experimental or investigational drugs within the last 30 days; and
- have any other reason why the study doctor believes it is not in your best interest for you to take part in this study.

PROCEDURES

The study will be conducted in three periods with an optional open-label extension period.

1. The screening and baseline period (which can be done up to 14 days before the first dose of study drug, with the exception of the baseline CMR which can be done up to 3 months before);
2. The treatment period (will last for 52 weeks); and,
3. The follow-up period (will last up to 4 weeks)
4. The optional open-label extension period (will last for up to 52 more weeks)



Screening Period

To see if you can take part in the study, the study staff will ask you some questions about your past medical history and do a physical exam. They will also record information such as your:

- Age, gender, race, and ethnicity;
- Any medicine you have recently taken (including prescription, over-the counter, and herbal medications), and;
- Any information about your family history of autoimmune disease.

In addition to asking you about your past medical history, a member of the research team will do the following procedures.

- If you are female (and could have a child) you may have a pregnancy test and be asked what kind of birth control you are using. You must be using an effective form of birth control, if you are sexually active during the study.

Baseline Period

During the baseline period, a member of the research team will do the following assessments or procedures:

- Physical examination.
- They will record your vital signs, including your current heart rate, breathing rate, temperature, and blood pressure;
- A cardiac magnetic resonance imaging (MRI) to evaluate the structures and function of your heart and the adjacent vessels (which can be done up to 3 months before Study Hour 0);
- A cardiac echocardiogram to evaluate the structures and function of your heart;
- A pulmonary function test to evaluate how well your lungs function;
- An oxygen saturation measurement. This test will give the study doctor an estimate of the amount of oxygen in the blood.

- A New York Heart Association (NYHA) Functional Classification assessment. This assessment will tell the study doctor if you have and the extent of any heart failure.
- A Six-Minute Walk Test. This assessment will tell the study doctor the extent of your exercise tolerance in chronic respiratory disease and heart failure.
- Skin Biopsy of Biomarker Analysis. During this test, a sample of lesional skin will be taken from the forearm and analyzed to see if biomarkers (a measure of activity and type of activity) of disease can be identified to predict a response to an experimental treatment. If no lesions are present on the forearm, a biopsy will not be collected.
- A sample of blood (approximately 50 mL or 3 1/3 tablespoons) will be collected for biomarker analysis and erythrocyte sedimentation rate (ESR).
 - Biomarker Analysis: For this test, blood samples will be collected and analyzed to see if biomarkers (a measure of activity and type of activity) of disease can be identified to predict a response to an experimental treatment.
 - ESR: For this test a sample of blood will be collected and analyzed to measure the degree of inflammation present in your body.
- A Urine Prostaglandin Analysis: For this assessment, you will be asked to provide a urine sample at each study visit. This is similar to urine samples collected at routine health assessments except the urine collection will be used for an analysis of prostaglandin levels which may be a biomarker of disease activity.
- A Digital Ulcer Assessment: Active digital tip count and patient VAS assessment of digital ulcer pain. The digital ulcer assessment consists of one procedure and, if necessary, a self-completed pain assessment. The assessment will identify if you have digit (finger) tip ulcers. If digit ulcers are present; then, you will be asked to perform a self-completed pain assessment of the pain that you are feeling in the hand (or hands) due to the digital ulcers.
- A Modified Rodnan Skin Thickness Score. During this assessment, the study doctor, by meaning of feeling with their fingers, will measure the changes in your skins thickness at 17 different sections of your body. Changes in skin thickness is a measure of disease severity.
- Health Questionnaires: You will be asked to complete a series of questionnaires. The questionnaires will be used to determine the extent of your health and quality of life based upon your current disease status. These questionnaires include the:
 - Scleroderma Health Assessment Questionnaire (SHAQ);
 - Medical Outcomes Study Questionnaire Short Form 36 Health Survey (RAND SF-36);
 - A Quality of Life Questionnaire (the WHODAS 2.0); and
 - UCLA Scleroderma Clinical Trial Consortium. Gastrointestinal Tract Instrument (UCLA SCTC GIT 2.0);
- Daily Raynaud's Condition Score: you will be asked to complete the Raynaud's Phenomenon Attack diary once a day to record the frequency and duration of any attacks.
- A sample of blood (approximately 30 mL or 6 teaspoons) will be collected for clinical chemistry, hematology, and coagulation. These tests will give the study doctor important information about the current status of your kidneys, liver, electrolytes, blood sugar, blood proteins, blood cells, and the blood's ability to clot.
- Record all medications that you are currently taking, including medications that you have taken in the 14 days prior to Study Hour 0.

If you chose to take part in the study it is your responsibility to answer all questions completely and honestly. These tests and procedures will establish a baseline of your condition. Future tests and procedures will be compared to the baseline to determine if and how the study drug affects your condition.

Treatment Period – Study Visit 2 through Study Visit 5

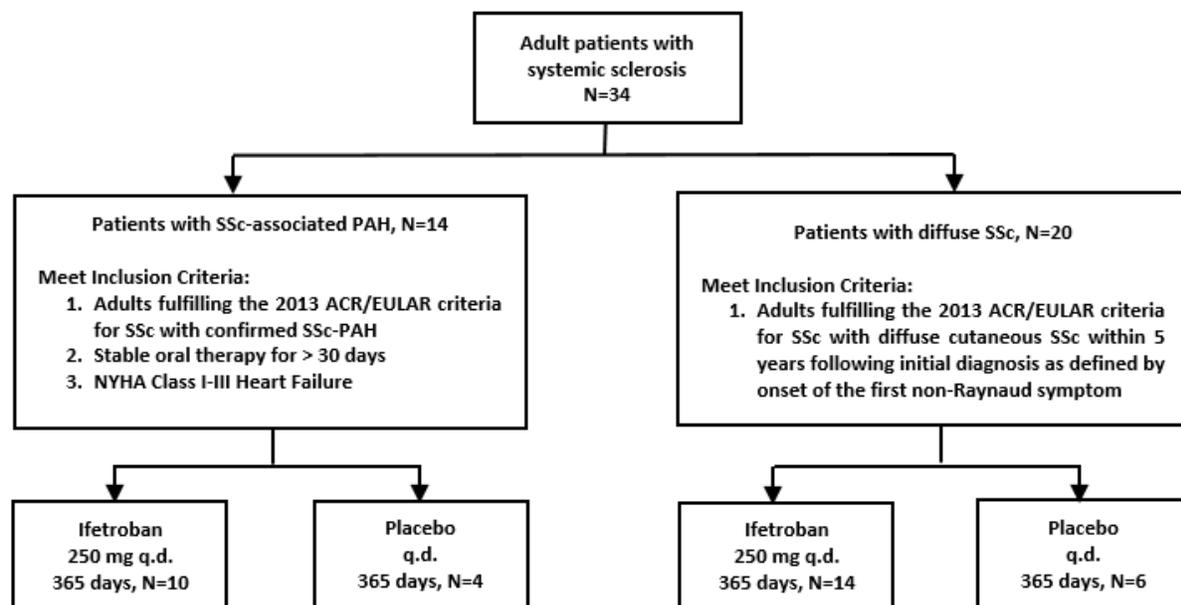
Treatment Assignment

If you agree to take part in the study, you will be randomly assigned to a study treatment group. Randomization means that you are assigned to a study treatment group by chance. The study treatment will be unknown to you, the doctor, the research team, and the study sponsor. This is known as “blinding”. Blinding is done to decrease the bias in a study. By not knowing which treatment you will receive, it decreases the researcher’s and the sponsor’s ability to form an opinion about the study treatment before all the data has been collected and analysed properly. However, this information is available to the study doctor if needed in an emergency.

If you agree to take part in this study, you will be grouped with other subjects based on whether you have diffuse cutaneous systemic sclerosis (SSc) or systemic sclerosis with pulmonary arterial hypertension (SSc-PAH).

For subject enrolling with SSc-PAH, fourteen (14) subject will take part in this study. Ten (10) will receive ifetroban and four will receive a matching placebo.

For subjects enrolling with diffuse cutaneous SSc, twenty (20) subjects will take part in the study. Fourteen (14) will receive ifetroban and six (6) will receive a matching placebo.



Dosing

If you are in the ifetroban treatment group, you will be asked to take five 50 mg capsules (total daily dose is equal to 250 mg) by mouth per day, for 365 days.

If you are in the placebo treatment group, you will be asked to take five matching placebo capsules by mouth per day for 365 days.

Dietary Restrictions

Regardless of which group you are assigned, you should take all five tablets (at one time) while you are in a fasting state. You will be asked not to eat any food for at least 6 hours before taking the study drug and to not eat any food for at least 30 minutes after taking the study drug. Drinking a small amount of liquids to take the tablets is okay.

Treatment Period Evaluations:

The Treatment Period begins with the first dose of study drug and continues for one year (52 weeks). On most days during the Treatment Period there are no study procedures except for taking the daily doses of study drug; however, at certain times during the study, you will be asked to return to study research center to repeat certain assessments and procedures. These study visits will occur at:

- Week 12 (plus or minus 7 days);
- Week 26 (plus or minus 7 days);
- Week 39 (plus or minus 7 days); and
- Week 52 (plus or minus 7 days).

In addition to the scheduled study visits, a member of the research team will contact you by phone and ask you a few questions. These phone calls will occur about every other week at the start of the study; then about every four weeks later during the study. The phone calls are to see how you are doing and should take just a few minutes of your time.

During each of the study visits, many of the procedures that were done during the screening and baseline visits will be repeated. This will include:

- Pregnancy test, if applicable. **This procedure will not be done at Study Visit 5;**
- A physical examination;
- A cardiac magnetic resonance imaging (MRI). **This procedure will not be done at Study Visits 2 and 4;**
- An echocardiogram. **This procedure will not be done at Study Visits 2 and 4;**
- A pulmonary function test. **This procedure will not be done at Study Visit 4;**
- Vital Signs and a measurement of oxygen saturation;
- A New York Heart Association (NYHA) Functional Classification assessment;
- A Six-Minute Walk Test;
- Skin Biopsy of Biomarker Analysis. **This procedure will not be done at Study Visits 2 and 4;**
- Urine collection for prostaglandin analysis;
- A sample of blood (approximately 5 mL or 1 teaspoon) for biomarker analysis and ESR;

- A Digital Ulcer Assessment;
- A Modified Rodnan Skin Thickness Score;
- The SHAQ;
- The SF-36;
- The WHODAS 2.0;
- The UCLA SCTC GIT 2.0;
- Raynaud's Phenomenon Attack Diary
- A sample of blood for clinical chemistry, hematology, and coagulation.

In addition to these assessments, a member of the research team will ask you about and record:

- All medications that you are currently taking; and.
- Any adverse events that occurred since the previous visit.

Post-Treatment Period – Follow-up Phone Call (Week 56)

Post-Treatment Period Evaluations:

During the post-treatment period, a member of the research team will contact you by phone and perform certain tasks. These will include asking and recording information about:

- The drugs that you are currently taking, including the study drug.
- Any adverse events that occurred since the previous visit.

Optional Open-Label Extension Period

Optional Open-Label Extension Period Evaluations:

After completing 52 weeks of treatment, a member of the research team will ask whether you are interested in participating in the open-label extension. All eligible participants will receive study drug for an additional 12 months (52 weeks).

During the extension period, a member of the research team will contact you by phone at Weeks 64, 78 and 91 (plus or minus 3 days) to confirm you are currently taking the study drug and record any adverse events that occurred since the previous visit or call. You will visit the study center at the end of the extension period (Week 104 +/- 7 days) and have the following procedures repeated:

- Pregnancy test, if applicable.
- A physical examination;
- A cardiac magnetic resonance imaging (MRI).
- An echocardiogram.
- A pulmonary function test.
- Vital Signs and a measurement of oxygen saturation;
- A New York Heart Association (NYHA) Functional Classification assessment;
- A Six-Minute Walk Test;

- Skin Biopsy of Biomarker Analysis
- Urine collection for prostaglandin analysis;
- A sample of blood (approximately 5 mL or 1 teaspoon) for biomarker analysis and ESR;
- A Digital Ulcer Assessment;
- A Modified Rodnan Skin Thickness Score;
- The SHAQ;
- The SF-36;
- The WHODAS 2.0;
- The UCLA SCTC GIT 2.0;
- Raynaud's Phenomenon Attack Diary
- A sample of blood for clinical chemistry, hematology, and coagulation.

RISKS, STRESSES, AND DISCOMFORTS

Study Drug

Ifetroban has been given to over 1300 subjects in single and multiple dose research studies. The majority of these studies were done in healthy volunteers and in adult subjects with various heart and blood vessel related diseases. In these studies, safety was assessed by reviewing adverse events (side effects), vital signs, and laboratory measurements.

The most frequently reported side effects in other studies with this drug were:

- PTT ratio (prolonged blood clotting test) (24%)
- high CPK (heart muscle damage) levels (19.1%)
- low hemoglobin (or iron in your red blood cells) levels (7.6%)
- low protein levels (7.3%)
- headache (8.4%)
- musculoskeletal pain (5.0%)
- angina pectoris (chest pain) (3.5%)
- bradycardia (slow heart rate) (3.3%)

Less common side effects include:

- myocardial infarction (heart attack) (2.9%)
- nausea/vomiting (2.6%)
- dyspepsia (upset stomach) (2.5%)
- upper respiratory infection (2.5%),
- hematoma or blood clot (2.4%)
- abdominal pain (2.1%)
- anxiety/nervousness (2.0%)

Most of these side effects were reported in studies of patients with cardiovascular or heart diseases.

Some previous subjects who took ifetroban and who also had cardiac events or whose hearts did not pump enough blood experienced other adverse events that were judged to be related to their heart disease.

There may be side effects which are unknown at this time.

Other Study-Related Potential Risks

What are the risks to pregnant women?

Being a part of this study while pregnant may expose an unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be not be allowed to take part in the study. If you are a woman of childbearing potential, a pregnancy test will be done and it must be negative before you can continue in this study. The pregnancy test may be done by collecting either a urine or blood sample. If the pregnancy test is done by a blood sample then approximately 1 teaspoon of blood drawn will be drawn from a vein by needle-stick.

If you are sexually active, you must agree to use appropriate contraceptive measures for the duration of the study and for one month after you quit taking the study drug. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

What are the risks to men fathering a child?

Your participation in this research may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for one month afterward. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should promptly notify her doctor.

Cardiac MRI

Magnetic resonance imaging (MRI) is a safe, noninvasive test that creates detailed pictures of your organs and tissues, in this instance, of your heart. "Noninvasive" means that no surgery is done and no instruments are inserted into your body. MRI uses radio waves, magnets, and a computer to create pictures of your heart. Unlike other imaging tests, MRI does not use ionizing radiation or carry any risk of causing cancer. A cardiac MRI is usually completed in less than 90 minutes once the procedure has started but may be shorter or longer depending on what the initial images show.

Cardiac MRI scan poses almost no risk to the average patient when appropriate safety guidelines are followed. There is a very slight risk of an allergic reaction if contrast material is used. For this procedure, a contrast agent called gadolinium will be used. Nephrogenic systemic fibrosis, is a fibrotic disease of the skin and internal organs is a rare complication of cardiac MRI when high doses of gadolinium contrast material is used in patients with very poor kidney function.

Allergic Reaction

An allergic reaction is the body's response to a substance. Allergic reactions can happen from something like pollen but it can also happen when taking any drug. You could have an allergic reaction to the drugs you get in this study.

Allergic reactions may be mild or severe. Mild reactions may include hives (itchy red spots on the skin), itching, nasal congestion (also known as rhinitis), rash, scratchy throat, or watery or itchy eyes. Severe reactions may include flushing of the face, swelling of the face, eyes, or tongue, throat or chest tightness, difficulty breathing, difficulty swallowing, dizziness, low blood pressure, or unconsciousness. In rare cases, a severe reaction could cause death.

Echocardiography

Ultrasound (or sonography) echocardiography is a test that uses high-frequency sound waves to show what is inside your body. You will lie on a cushioned table and gel will be applied to your skin. The gel acts as a conductor. A transducer (a hand-held device that sends and receives ultrasound signals) will be moved over the area of your body being imaged. Images instantly are seen on a television-like monitor and sent to film or videotape for a specialist to review and interpret. The procedure typically takes anywhere from 20-60 minutes. The gel may be sticky but the test should not cause any pain or discomfort.

Pulmonary Functions Test

Pulmonary Functions Test or spirometry is a test that shows how your lungs work by measuring how much and how fast air moves out of your lungs. During the tests, you will be asked to wear a nose clip and forcefully blow into a tube hooked to a machine. The procedure typically takes anywhere from 10-30 minutes to perform. There are few risks associated with spirometry. It may make you cough or feel lightheaded; however, these will usually go away shortly after the test is finished.

Oxygen Saturation

Pulse oximetry is a simple and noninvasive procedure used to measure the level of oxygen (or oxygen saturation) in the blood. The blood's percentage of oxygen can be measured using a clip-like sensor device that is placed on a thin part of your body, such as an earlobe, nose, or the finger.

Oxygen saturation should always be above 95 percent. However, oxygen saturation may be lower if you have a respiratory disease or a certain type of heart disease. Oxygen saturation typically takes just a few seconds to perform and there are no risks associated with measuring oxygen saturation.

New York Heart Association Function Class

The New York Heart Association (NYHA) Functional Classification is a measure of a patient's symptoms and functional capacity, which is an estimate of what the patient's heart will allow the patient to do. The doctor will classify your level of heart failure according to the severity of the symptoms you display.

Six Minute Walk Test

A 6-minute walk test (6MWT) is used to find out how far you can walk on a flat surface for 6 minutes. The 6MWT only takes 6 minutes to perform; however, the entire procedure may take longer because you should be allowed time to rest before the procedure is performed.

There are few risks to this test because you decide how fast you will walk depending on your ability. Changes in your breathing, blood pressure, heart rate, and fainting can happen, and in very rare cases, heart attack or stroke. Trained staff and emergency equipment will be available if needed.

Skin Biopsy

A skin biopsy is a simple medical procedure where a small piece of skin is removed from and tested in a lab. The sample size is often very small. Generally, there is little risk from a skin biopsy; however, possible risks may include: a reaction to anesthetic (numbing medicine), excessive bleeding, bruising, infection, and excessive scarring.

Biopsies take about 10-15 minutes to perform. After the numbing medicine wears off there may be some soreness at the biopsy site that may last for a few hours. A small scar will develop at the site of the biopsy. Numbing medicines, like xylocaine, generally do not cause allergic reactions (such as causing rash); however, an allergic reaction is possible, and you will not be given xylocaine if you have a history of such a reaction. Xylocaine will be given by a small injection into the skin at the site of the skin biopsy.

If necessary, to speed healing, one or two stitches (sutures) will be placed where the biopsy is taken, which may be removed 5 - 7 days later. To assist in healing, the doctor who takes the biopsy will provide instruction on biopsy skin care. Infection rarely occurs and is largely prevented by the use of an aseptic (or sterile) biopsy technique and proper wound care. If an infection does occur, you will be instructed on how to treat the infection. If the infection persists, antibiotics may be prescribed.

Digital Ulcer Assessment

The digital ulcer assessment consists of two parts: 1) an active digital tip count, and 2) if digital ulcers are present, a self-conducted assessment of pain.

Active digital tip count and self-conducted assessment of pain. During these assessments the study doctor will examine your fingertips for changes in the blood vessels that affect your tissues; specifically, changes that may lead to ulcers (dying tissue). If ulcers are present, the study doctors will ask that you evaluate the amount of pain that you are currently experiencing. The digital ulcer assessment typically takes just a few minutes to perform. There are few risks associated with the digital ulcer assessments.

Modified Rodnan Skin Score

The modified Rodnan skin score (mRSS) is a physical examination of the skin. The skin surface area is examined at 17 different areas: fingers, hands, forearms, upper arms, feet, legs, and thighs, and face, chest, and abdomen. In each of these areas, the skin score is evaluated by manual palpation (touching the skin). The skin score is used to evaluate the amount of skin fibrosis, which in turn correlates with the extent of fibrosis and dysfunction of the internal

organs, such as the heart, lung, kidney, and stomach. The mRSS typically takes between 15-30 minutes. There are few risks associated with the MRSS.

Blood Draws

Blood samples will be taken at various times for laboratory assessments. Drawing blood from a vein in your arm may cause temporary discomfort and/or bruising. Infection, excessive bleeding, clotting or fainting are also possible, although unlikely.

Unknown/Unforeseen Risks

It is possible that other rare side effects could occur which are not described in this consent form. It is also possible that you could have a side effect that has not occurred before.

There may be unknown risks to taking ifetroban. Every person is different, and there is no way to know how the study drug will work in everyone. Sometimes people have allergies to medicines. Allergic reactions are rare but can happen. Allergic reactions can be life threatening. This study drug could also interact with another medication you are taking and that can be harmful.

Ifetroban has been well tolerated in other clinical trial. Analysis of the safety data did not show any unexpected safety issues. Although this data did not reveal any safety concerns, patients enrolled in this study may be monitored carefully for bleeding events such as spontaneous hemorrhage (or bleeding), decreased hemoglobin (iron in the red blood cells), and/or prolonged bleeding time (increased time to form a blood clot).

This is particularly important in studies in which ifetroban is used in combination with thrombolytic (clot dissolving or blood thinning) therapy. The major risks of currently available thrombolytic agents include hemorrhage (increased bleeding), neurologic (nerve) events, immunologic complications, systemic low blood pressure and myocardial (heart) rupture. Thromboembolic or bleeding events and cardiac rhythm disturbances are rare with these agents. In addition, significant bleeding events are uncommon in patients without an underlying vascular disease. If you are taking an anticoagulant or blood thinner you cannot take part in this study. If you are taking an anticoagulant or blood thinner it is important that you tell the study doctor.

If you believe that you are having side effects or an adverse reaction from the study drug or study related procedures, please contact Dr. Kwoh immediately and he will either treat you or refer you for treatment.

NEW FINDINGS

We will provide any new information found during the study that might affect your willingness to take part in the study. We will also tell you about any changes to the way the research will be performed.

A blinded and unblinded medical reviewer will be reviewing the data from this research throughout the study. We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to remain in this study.

BENEFITS

This study is not being done to treat your disease. The study is being done to determine if ifetroban will have an effect on your disease. You may feel better or live longer as a result of being in the study, however there is no guarantee of this. We believe that the study drug will help patients with scleroderma; however, it is unknown if it will help. The study is being done in the hope that it will provide information that will improve the treatment of people with fibrotic diseases in the future.

If you receive the placebo, there will be no benefit to you. However, the information gained from your taking part in the study may help doctors find better ways to treat patients with fibrotic diseases, such as scleroderma in the future.

Many of the assessment performed during the study (echocardiogram, PFT, etc.) are standard of care assessments that are performed in the diagnosis and care of patients with SSc. The test are also used to predict this and other disease processes. During the study, these tests will be done more often than during the normal course of routine care.

What are the Costs of taking part in this study?

The study drug Ifetroban and services performed for research only will be provided at no charge to you and/or your insurance company.

Routine medical care performed while participating in the study will be billed to you and/or your insurance company. This will include (but is not limited to) tests, procedures, and non-study medications that your study doctor or personal doctor requires as part of your routine care, administration of medications, and the treatment of side effects. Not all insurance companies are willing to pay for services performed in a clinical trial. You will be responsible for any charges that your insurance does not cover including regular co-payments and deductibles. Please speak with your insurance company to find out what you may be financially liable for.

This may include co-payments and deductibles.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?

You will be paid for completed on site study visits starting at Visit 1 as follows:

- \$75/ per study visit for Visits 1, 3, and 5
- \$50/ per study visit for Visit 2 and 4
- \$100 for study Visit 6

You will not be paid for the Screening Visit. Payments are to compensate you for the time you spend for coming to the site to complete the assessments required at each visit and for completing the drug diary that we are asking you to complete between the visits. Ask the study staff about the method of payment that will be used for this study (e.g., check, cash, gift card, direct deposit). If you do not finish the entire study, you will be paid up to the last on site study visit completed.

You are responsible for paying any state, federal, Social Security or other taxes on the payments you receive. You will receive more than \$600.00, a form 1099-MISC in January of the year

following your participation in this study. This form is also sent to the IRS to report any money paid to you. No taxes are kept from your payment.

Compensation for participation in a research study is considered taxable income for you. We are required to obtain your name, address, and Social Security number for federal tax reporting purposes. If your compensation for this research study or a combination of research studies is \$600 or more in a calendar year (January to December), you will receive an IRS Form 1099 to report on your taxes.

ALTERNATIVE TREATMENT

You do not have to be in this study to be treated for SSc. If you choose not to take part in this study, you will get the standard treatment for SSc.

CONSENT FOR STORAGE OF SPECIMENS AND FUTURE RESEARCH

As part of this study, we would like to store the blood and biopsy specimens collected from you for future research on SSc. What we learn about you from this sample will not be put in your medical record. Your test results may be shared with the study doctor but no one else will be given the results from these tests.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password.

Your samples will be kept for an unknown length of time (maybe years) for future research. The samples will be kept until the samples are used.

You will not receive any benefit because of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems. Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study sponsor, and/or others. If this happens, there are no plans to provide money to you.

You do not have to agree to allow your blood and skin samples to be stored in order to be part of this study.

You may request at any time that your research samples be removed from storage and not be used for future research. If you decide you want your samples removed, you may contact Dr. Kwoh at the University of Arizona Arthritis Center at 520-626-8379. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Will your study-related information be shared, disclosed, and kept confidential?

It is anticipated that there will be circumstances where your study related information and PHI will be released to persons and organizations described in this form. If you sign this form, you give permission to the research team to use and/or disclose your PHI for this study. Your

information may be shared or disclosed with others to conduct the study, for regulatory purposes, and to help ensure that the study has been done correctly. These other groups include:

- Office for Human Research Protections or other federal, state, or international regulatory agencies
- US Food and Drug Administration (FDA)
- Banner University Medical Group and Banner Health
- The University of Arizona (UA) and the UA Institutional Review Board
- Western Institutional Review Board
- The sponsor supporting the study, their agents or study monitors
- We may share your health information with your primary care physician or a specialist taking care of your health.

If you agree to take part in this study a copy of this signed informed consent form will be saved into your electronic medical record (EMR) at Banner Health. As a result, healthcare providers and staff who are not working on this study, but who may provide you medical treatment in the future, will know that you are taking part or took part in this study.

Your PHI may no longer be protected under the HIPAA privacy rule once it is disclosed by the research team and may be shared without your permission.

Personnel from the Sponsor and its consultants will be visiting the research facility to monitor the conduct of the study. They will be reviewing your study records and medical records for this purpose.

If reports or articles are written about the study, you will not be identified by name. Your study records may be stored indefinitely after the study ends. You will not have the right to review your research records while the study is ongoing. However, you will be able to review your records after the research has been completed.

Study records can be opened by court order. They may also be produced in response to a subpoena or a request for production of documents.

What study-related information and PHI will be obtained, used or disclosed from your medical record at Banner?

Information related to this research study that identifies you and your PHI will be collected from your past, present, and future hospital and/or other health care provider medical records.

The PHI you are authorizing to be used and/or disclosed in connection with this research study is:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.
- Your Name and Address

- Elements of date (except year) related to an individual (ie. DOB, admission/discharge dates, date of death)
- Telephone number
- Social Security Number
- Medical Record Number
- Any unique identifying number, characteristic or code (a rare disease can be considered a unique id)
- Physician/Clinic Records
- Lab, pathology and/or radiology results
- Biological samples obtained from the subjects
- Hospital/medical records (in- and out-patient)

Demographic information to be disclosed may include, but is not limited to, your name, address, phone number, or social security number. If you receive compensation for participating in this research study, information identifying you may be used or disclosed as necessary to provide that compensation.

You are also giving permission to use and/or disclose PHI related to sexually transmitted disease (STD), acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), other communicable diseases, genetic information (e.g., genetic testing), and treatment of alcohol and/or drug abuse.

Who may use and give out information about you?

The study doctor and the study staff.

Who might get this information?

The sponsor of this research. “Sponsor” means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to make sure that the research was done right.

Will I hear back on any results that directly impact me? Will access to your medical record be limited during the study?

If the results of this study are made public, information that identifies you will not be used. You will not receive any clinically relevant results discovered about you and/or the general subject population.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

Will access to your medical record be limited during the study?

You may not have access to any health information developed as part of this study until it is completed.

When will your authorization expire?

There is no expiration date or event for your authorization. Therefore, unless you cancel this authorization (as instructed below) this authorization will continue to be effective.

Do you have to sign this authorization form?

You do not have to sign this authorization. However, if you decide not to sign, you will not be able to participate in this research study; and it will not affect any non-study Banner Health medical treatment or health care, payment, enrollment in any health plans, or benefits.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission.

WHAT IF I GET HURT OR SICK WHILE I AM IN THIS STUDY?

If you get hurt or sick as a direct result of the study drug or any properly performed study required procedure, the Sponsor will pay for the reasonable costs of medical treatment (including diagnosis, treatment and hospitalization). To ask questions about this, talk to the study doctor or study staff.

The Sponsor will not pay for medical treatment if due to:

- Study doctor and/or study staff failure to follow Protocol directions and/or Sponsor's written instructions
- Study doctor and/or study staff's negligence or misconduct
- The natural progress of your disease or the medical condition you already have, unless it's made worse by participating in the study

The sponsor's policy does not provide payment for any other expenses.

This, however, does not waive your rights in the event of negligence. If you suffer an injury from participating in this study, you should seek treatment. The University of Arizona and Banner Health have no funds set aside for the payment of treatment expenses for this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

What do you need to know if you decide to cancel your authorization?

After signing the authorization, you may decide to cancel your previous authorization for the research team to use your PHI. If you cancel the authorization, you will no longer be able to stay in the research study. Please note that any PHI collected before you cancel the authorization may still be used. You may revoke the authorization by contacting the Principal Investigator in

writing. Contact information is under “Who can answer my questions about this study?” at the end of this document.

The study team or the sponsor may take you off this study at any time without your consent for many reasons including but not limited to:

- an adverse event (side effect) or medical condition which may place you at risk of further complications if you continue to take part,
- an inability to take the study drug,
- you become pregnant,
- an inability to keep scheduled appointments,
- if it is in your best interest,
- if you do not later consent to any future changes that may be made in the study plan, or
- for other reasons.

You may be removed from the study without your consent if the sponsor ends the study, if the study drug is approved by the FDA, if the study doctor decides it is not in the best interest of your health, or if you are not following the study plan.

SOURCE OF FUNDING

Cumberland Pharmaceuticals is paying the study team and/or the University of Washington for the conduct of this study.

QUESTIONS

If at any time you feel you have had a research-related injury, or for questions, concerns, or complaints about the study you may contact Dr. Kwok at 520-626-8379 and 520-694-6000 (24 hours).

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Human Subjects Protection Program at 520-626-6721 or online at <http://rgw.arizona.edu/compliance/human-subjects-protection-program>.

If you have questions about your rights as a research subject or if you have questions, concerns, input, or complaints about the research, you may contact:

WCG Institutional Review Board (WCG IRB)
Telephone: 1-855-818-2289
E-mail: researchquestions@wcgirb.com

An IRB is a group of people who perform review of research.

The WCG IRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact the WCG IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

If you have any questions or concerns about the authorization for access to your PHI, you should contact Sue Colvin, Banner Research Regulatory Affairs Director, at BannerResearchCompliance@bannerhealth.com. You may also request and will be provided a copy of the Notice of Privacy Practices.

To cancel your authorization for access to PHI you must notify the *Principal Investigator/Research Team* in writing at the following address:
1501 North Campbell Avenue, Room 8346
Tucson, AZ 85724

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

SUBJECT'S STATEMENT

I have read the information in this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to take part in this research study.

If I sign this form, I will not lose any of the legal rights that I would otherwise have as a subject in a research study.

Optional Research Activity

The research study you are agreeing to participate in has additional optional research activities. If you choose to participate in the optional research activity, you are also allowing your PHI to be shared for that activity/those activities.

By initialing the line below you agree to allow your information to be used and/or disclosed for the optional Study activity referenced above.

_____ Initials

Signing the consent form

Do not sign this consent form unless you have had a chance to ask questions and have had your questions answered.

If you agree to take part in this study, you will receive a signed and dated copy of this consent form for your records.

I have read (or someone has read to me) this form, and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study **and I authorize the use and/or disclosure of my PHI.**

I am not giving up any legal rights by signing this form. I will be given a signed copy of this form.

Printed name of subject

Signature of subject

Date

Investigator/Study Staff

I have explained the research to the participant before requesting the signature(s) above. There are no blanks in this document. A signed copy of this form has been given to the participant or to the participant's representative.

**Printed name of person
obtaining consent**

Signature of person obtaining consent

Date