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Study Participant Initials

A Randomized, Double-Blind, Placebo-Controlled study of Belimumab and Rituximab Combination Therapy for the Treatment of Diffuse Cutaneous Systemic Sclerosis

January 14, 2019
NCT# Pending

HOSPITAL FOR SPECIAL SURGERY
535 East 70th Street
New York, NY 10021

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY INVOLVING GENETIC TESTING

You are being asked to participate in a research study conducted by the Hospital for Special Surgery (HSS). This form is designed to provide you with information about the Study, which you should know and understand. After reading this form, you will have an opportunity to ask any questions you may have

NOTE: Only the current IRB-stamped approved consent form may be used.

IRB#:2018-2011

Principal Investigator: Robert Spiera, MD Telephone (212) 774-2048

NAME OF RESEARCH STUDY: A Randomized, Double-Blind, Placebo-Controlled study of Belimumab and Rituxan Combination Therapy for the Treatment of Diffuse Cutaneous Systemic Sclerosis

The sponsor(s) of the study is/are: Hospital for Special Surgery (Funding provided by GSK)

Subject Population: Inpatient: _____ Outpatient: __X____ Other:_____

We expect to enlist the following number of subjects for this study: ____30_____

Your participation will involve this many visits: _____17_____

Each of these visits is expected to take the following amount of time: Day 0, week 2 (7-8 hours), Week 4 (5-6 hours), Screening (3 hours), all other visits (2-3 hours).

Will there be reimbursement for participation in this study? Yes__X__ No_____
(If yes, complete below)

For your participation in this study you will be paid $___25___ per study visit for a total of up to $____425_____ for completing the study.

If you do not complete the study, you will be paid $____25____ for each completed study visit.

IRB Administrative Use Only

Hospital for Special Surgery Institutional Review Board Approval
1/14/2019 Thru 12/17/2019

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

INTRODUCTION:

You are being asked to participate in a research study being conducted at Hospital for Special Surgery (the "Hospital") that involves genetic testing. This consent form provides you with the information you will need when considering whether to participate in this research study and in the aspects of the study that relate to genetic testing.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks, possible benefits and alternatives of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. If you decide to participate in this research study, you will be asked to sign and date this consent form, to indicate that you agree to participate. This process is called informed consent. You will be given a copy of this form to keep.

1. STUDY PURPOSE – WHY IS THIS STUDY BEING DONE:

Systemic sclerosis (scleroderma) is a chronic autoimmune disease that can involve the skin, the blood vessels, the muscles and other connective tissues, and major organs including the lungs, kidneys, gastrointestinal tract, and heart. The exact cause of this disorder is not known at this time. Similar to other rheumatic disorders, scleroderma is an autoimmune disease. It is believed that the immune system stimulates fibroblasts, a certain type of cell in the body, to overproduce collagen, and the collagen forms thick connective tissue that builds up around the cells of the skin and internal organs.

To date there is no drug that has been definitively proven to cure or modify the course of scleroderma. While much effort has gone into addressing the various problems that people with scleroderma have, further research is needed to develop a way of slowing the progression of the underlying disease process. Medications frequently used to treat scleroderma include corticosteroids (like prednisone), methotrexate, mycophenolate mofetil (MMF or Cellcept), and cyclophosphamide (Cytoxan). These medications have variable degrees of success in treating scleroderma as well as varying degrees of toxicity.
There is retrospective data on the use of MMF in scleroderma with improvement in the skin thickening over twelve months of observation. Additionally there is experience using MMF with Belimumab in SLE patients with acceptable safety, and belimumab and MMF in scleroderma with acceptable safety.

The purpose of this study is to determine whether the Rituximab (Rituxan) and Belimumab (Benlysta) combination therapy with Mycophenolate Mofetil (MMF, Cellcept) background therapy will improve fibrosis in Systemic Sclerosis skin when compared to treatment with

placebo and Mycophenolate Mofetil in a group of patients with early Systemic Sclerosis. Belimumab has been approved by the Food and Drug Administration (FDA) for the treatment of Systemic lupus erythematosus (SLE), a related autoimmune, rheumatologic disease. This combination therapy is not FDA approved to treat scleroderma at this time. This medication is administered as a subcutaneous injection.

A total of 30 subjects will participate in this study at HSS.

Rituximab is approved by the U.S. Food and Drug Administration (FDA) to treat some types of cancer, rheumatoid arthritis and vasculitis. Rituximab works by decreasing one type of immune system cells called B cells in your body. B cells are known to have a role in Systemic Sclerosis. Once these cells are removed, your disease may become less active or even inactive. However, your body will make new B cells. These new B cells may cause your disease to become active again. Belimumab works by decreasing the new B cells your body makes and may even change the type of type of B cells that your body makes.

Neither rituximab nor belimumab is approved by the FDA to treat Systemic Sclerosis.

Treatment with a combination of rituximab infusion and subcutaneous belimumab injection with background MMF has not been studied in patients with Systemic Sclerosis.

The main purpose of this randomized controlled clinical trial is to learn about the safety of the experimental treatment of Systemic Sclerosis with the combination of rituximab, belimumab and background MMF. This study may or may not be able to show whether this is an effective treatment for Systemic Sclerosis. Your overall participation will be over a period of 16 months.

In this study blood and skin will be collected to help determine whether this therapy is safe and effective and to improve our understanding of scleroderma. Different research tests will be done on the blood and skin now and in the future that may or may not include genetic testing. It is not the aim of this research study to provide you with clinically relevant genetic information that could be used to guide you or your physicians in making health care decisions. Genetic counseling, which is available for established genetic tests, is not offered through participation in this research study, as this is a research study and counseling for results of testing in this study is not possible. (We tell you this because New York law requires us to advise you of the availability of genetic counseling prior to your signing this consent form and participating in this study.)

2. WHO SHOULD NOT BE IN THE STUDY:

1. Inability to render informed consent in accordance with institutional guidelines.
2. Disease duration of greater than 3 years.
3. Patients with mixed connective tissue disease or “overlap” unless the dominant features of the illness are diffuse systemic sclerosis.
4. Limited scleroderma.

5. Systemic sclerosis-like illness associated with environmental or ingested agents such as toxic rapeseed oil, vinyl chloride, or bleomycin.
6. The use of other anti-fibrotic agents including colchicine, D-penicillamine, or tyrosine kinase inhibitors (nilotinib, imatinib, dasatinib) in the month prior to enrollment.
7. Use in the prior month of corticosteroids at doses exceeding the equivalent of prednisone 10 mg daily. Use of corticosteroid at $\leq$ 10 mg of prednisone can continue during the course of the study.
8. Concurrent serious medical condition which in the opinion of the investigator makes the patient inappropriate for this study such as uncontrollable CHF, arrhythmia, severe pulmonary or systemic hypertension, severe GI involvement, hepatic impairment, serum creatinine of greater than 2.0, active infection, severe diabetes, unstable atherosclerotic cardiovascular disease, malignancy, HIV, or severe peripheral vascular disease.
9. A positive pregnancy test at entry into this study. Men and women with reproductive potential will be required to use effective means of contraception through the course of the study, such as (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) double-barrier methods (such as a condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)(3) an intrauterine device (IUD) or intrauterine system (IUS) (4) estrogenic vaginal ring (5) percutaneous contraceptive patches, or (6) implants of levonorgestrel or etonogestrel. Approved hormonal contraceptives (such as birth control pills, patches, implants or injections) may interact with and reduce the effectiveness of MMF so women receiving MMF who are using oral contraceptives for birth control should employ an additional method (e.g. barrier method). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use.
10. Women not willing to use effective birth control for the duration of the study
11. Breastfeeding.
12. Participation in another clinical research study involving the evaluation of another investigational drug within ninety days of entry into this study.
13. The presence of severe lung disease as defined by a diffusion capacity of less than 30% of predicted or requiring supplemental oxygen and forced vital capacity (FVC) of less than 45% of predicted.
14. Grade 3 hypogammaglobulinemia
15. Have a significant IgG deficiency (IgG level < 400 mg/dL)
16. Have an IgA deficiency (IgA level < 10 mg/dL)
17. Have a historically positive HIV test or test positive at screening for HIV
18. Neutrophils <1.5X10E9/L
19. Hepatitis status:
    a) Serologic evidence of current or past Hepatitis B (HB) infection based on the results of testing for HBsAg and HBcAb as follows:

1. Patients positive for HBsAg or HBcAb are excluded

b) Positive test for Hepatitis C antibody

20. Known active bacterial, viral, fungal, mycobacterial, or other infection or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening, or oral antibiotics within 2 weeks prior to screening
21. Infection history:
    a) Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)
    b) Hospitalization for treatment of infection within 60 days of Day 0.
    c) Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of Day 0
22. Suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes zoster and atypical mycobacteria)
23. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
24. Prior use of Belimumab, Rituximab, or other B-Cell depleting therapies ever
25. The use of other biologics including TNF inhibitors, abatacept, or tocilizumab within the washout period mandated in the table below for each particular drug:

Drug	**Washout Period**
Tocilizumab	1 month for patients on 2mg/kg or 4 mg/kg. 2 months for patients on 8mg/kg.
Cyclophosphamide (oral or IV)	3 months
Abatacept	2.5 months
TNF Inhibitors	Etanercept – 1 mo Infliximab – 2 mo Adalimumab – 2.5 mo
Any biologic investigational agent (e.g., abetimus sodium, anti CD40L antibody, BG9588/ IDEC 131)	365 days prior to belimumab
Any non-biologic investigational agent	30 days prior to belimumab

26. Have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation in the last 2 months or who in the investigator's judgment, pose a significant suicide risk.
27. Current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0.

28. History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies
29. Live vaccines within 30 days prior to baseline
30. Have a history of malignant neoplasm within the last 5 years with the exception of basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma in situ of the uterine cervix treated locally and with no evidence of metastatic disease for 3 years
31. Have a history of a primary immunodeficiency
32. Have any other clinically significant abnormal laboratory value in the opinion of the investigator
33. Have any intercurrent significant medical or psychiatric illness that the investigator considers would make the candidate unsuitable for the study
34. Non English Speakers

3. STUDY PROCEDURES – WHAT YOU WILL BE ASKED TO DO:

Before you enter into the study, you will have a screening visit where you will have several tests to see if you are a good fit to join the study. It is possible that you may not be eligible for this study. We estimate that 75% of patients who will go through the screening visit will be randomized in this study.

Once you enter into the study, you will be in this study for a total of about 16 months.

There are two different experimental treatment groups in this study. One group will receive active treatment of Belimumab and Rituximab infusions with background MMF while the other group will receive two placebo infusions with background MMF. After you have completed your screening and the investigator verifies your eligibility to participate in this study, you will be randomly assigned to an experimental group by a computer program. Randomization will occur in a 2:1 manner, favoring your placement into the treatment group. This means that you will have a 66.67% chance to receive treatment with rituximab and belimumab.

The following describes how you will receive study drug in each of the 2 treatment groups:

- Group 1 - Two infusions of 1000 mg of Rituximab , weekly subcutaneous injections of 200 mg of Belimumab, and background MMF, 2-3 g a day.
- Group 2 (10 patients) - Two placebo infusions, weekly subcutaneous injections, and background MMF, 2-3 g a day.

Visits

If you are eligible and decide to be in this study, the following routine and/or experimental procedures will be performed (the description below includes the scheduled number of visits/procedures):

Including both the screening and treatment phases of the study, your total participation in this study will be 17 visits over the course of about 16 months. A full review of your history and physical, clinical laboratories, as well as review of medical records will be performed at the screening visit. The study physician will ask you to have a full pulmonary function test (PFT) before your next visit to confirm entry into the study. All women of childbearing potential will have to undergo a urine pregnancy test every study visit. You will also be asked to complete a Modified Rodnan Skin Score (MRSS) questionnaire. At the baseline visit, two 3 mm punch skin biopsies, and other patient derived endpoints will be performed. At this visit, you will be started on mycophenalate mofetil (MMF) 2-3 g once daily unless you are already on this medication.

After this, you will be randomized to treatment with either Rituximan/Belimumab or placebo/placebo in the dosing regimen of two infusions of 1000 mg of Rituximab or placebo at day 0 and week 2 followed by weekly subcutaneous injections of 200 mg Belimumab or placebo starting at week 4. The first subcutaneous injection of Belimumab includes a 3 hour observation. You will be evaluated additionally at the initiation of treatment, every two weeks for the 2 infusions and every 4 weeks for 48 weeks total of Belimumab/placebo treatment. The placebo infusions will be of normal saline. A follow up study visit will be completed 4 weeks after the last dose of Belimumab/placebo and MMF.

At each study visit, a history and physical exam will be performed by the physician investigator, and basic laboratory data collected. The Modified Rodnan Skin Score (MRSS) will be performed at screening, at start of rituximab/belimumab or placebo/placebo treatment , at the start of Belimumab/placebo, and then at every visit, including the follow up.

Pulmonary function tests (PFTs) will occur at day 0 and at visit 5. Two 3 mm punch biopsies of skin affected by scleroderma will be obtained at baseline and at 9 months. This procedure will be conducted at New York Presbyterian Hospital by a dermatologist at Weill Cornell Medical College. At the conclusion of the study, the tissue sample will be analyzed by a trained dermatopathologist. All tissue samples will be stored at HSS until the time of analysis. Other data collected at each study visit will include the physician and patient-derived outcome measures, including scleroderma health assessment questionnaire (sHAQ), SF-36 (quality of life assessment), Raynaud's Condition Score, physician global assessment of disease activity, and patient global assessment of disease activity

You and/or your insurance will be responsible for any costs of all procedures performed that are standard of care, that is, care that you would receive even if you were not in this study.

We ask you to complete the following visits.

RES= Research procedures

SOC= Standard of care (care you would receive if you were not participating in this study)

Visit	Screening	Baseline 1	Rituximab infusion 1/ Baseline 2	Rituximab infusion 2	Visit 1	Between visits (monthly)	Visit 2	Between visits (monthly)	Visit 3	Between visits (monthly)	Visit 4	Between visits (monthly)	Visit 5 (end of study visit)	Follow-up
Time	**Month -1 to 0**	**Month -1 to 0**	**Day 0**	**Week 2 +/- 3 days**	**Week 4 +/- 3 days**		**Month 3 +/- 7 days**		**Month 6 +/- 7 days**		**Month 9 +/- 7 days**		**Month 12 +/- 7 days**	**Month 15 +/- 7 days**
Informed Consent	RES													
Review of inclusion/exclusion criteria	RES													
Demographics	RES													
Medical History	RES													
Physical Exam (including joint count)	RES	RES	RES	RES	RES		RES		RES		RES		RES	RES
MRSS	RES		RES		RES		RES		RES		RES		RES	RES
Hep B, Hep C test, HIV, IgA	RES													
Quantitative IgG	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	
Urine pregnancy test (for women of childbearing potential)	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES
CBC, CMP	SOC	SOC	SOC*	SOC*	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	
ESR, CRP		RES											RES	
CPK	RES		RES	RES			RES		RES		RES		RES	
LFT	SOC		SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	
CD-19									RES				RES	
Patient and physician global assessments, SF-36, SHAQ-DI, PROMIS-29, SSPRO, CSSRS	RES	RES	RES	RES	RES		RES		RES		RES		RES	RES
DAS-28, CDAI, tender joint counts		RES											RES	

Full PFT and DLCO			SOC										SOC	
FVC ONLY									SOC					
Two 3mm punch biopsies ***		RES									RES			
MMF dosing**		RES												
Daily stable MMF			RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	
Rituximab infusion			RES	RES										
Subcutaneous Belimumab injections weekly					RES****	RES	RES	RES	RES	RES	RES	RES	RES	

* Lab tests must be performed prior to rituximab/placebo infusions, can be performed up to one week before the study visit.
**If you are not yet on MMF, you will begin taking it here, increasing until on a stable 2-3 g a day dose before baseline 2.
***These will be performed at Weill Cornell Medical Center by Dr. Horatio Wildman.
****The first belimumab injection includes a 3 hour observation.

Screening Visit (Visit 0, Day -28 to Day 0)

You will undergo procedures to establish inclusion/exclusion criteria and will sign the informed consent form. The following clinical assessments and laboratory evaluations will be performed during this visit:

- Informed Consent
- Inclusion and Exclusion criteria
- Collection of patient questionnaires (SF-36, SHAQ-DI, PROMIS-29, SSPRO, CSSRS, UCLA SCTC GIT 2.0)
- Patient & Physician Global Assessments
- Demographics
- Medical history (including scleroderma history and medication review)
- Physical exam with height, weight and vital signs
- Serum IgG and IgA
- Hepatitis B, hepatitis C, HIV antibody
- Laboratory tests including CBC, CMP
- Modified Rodnan Skin Score measurement
- Review of medical records
- If a pulmonary function test (FVC) has not been performed within 6 months of screening or if the physician advises repeat testing, the test(s) will be scheduled before the next visit (Baseline 1)

Baseline 1 (Visit 1, Day 1, may occur over 2 days)

During the first MMF treatment visit (baseline visit), the following clinical research procedures will be conducted:

- Review of medical history, including a detailed medication review
- Collection of patient questionnaires (SF-36, SHAQ-DI, PROMIS-29, SSPRO, CSSRS, UCLA SCTC GIT 2.0)
- Patient & Physician Global Assessments
- Two 3 mm punch biopsies of involved skin on the forearm
- Physical exam with height, weight and vital signs
- Laboratory tests including CBC, CMP, LFT, Serum IgG and urine pregnancy test in WOCBP, CD-19 **(must be done before rituximab infusion, can be done up to one week before study visit), PBMC**
- Modified Rodnan Skin Score measurement
- Dispensation of MMF, wash in period begins. Patients will spend the next 4 weeks increasing their dose, week by week, to the final 2-3 g per day dose.

  - **If patients are already on the appropriate MMF dose, they will remain on the same dose for the remainder of the study and will not complete a Baseline 1 visit.**
- **Full PFT with DLCO will be performed at this visit**

Baseline 2/Rituximab Infusion 1 (Visit 2, 4 weeks after baseline 1)

During the Rituximab treatment visit, the following clinical research procedures will be conducted:

- Review of medical history, including a detailed medication review
- Collection of patient questionnaires (SF-36, SHAQ-DI, PROMIS-29, SSPRO, CSSRS, UCLA SCTC GIT 2.0)
- Patient & Physician Global Assessments
- Physical exam with height, weight and vital signs
- Laboratory tests including CBC, CMP, LFT, Serum IgG and urine pregnancy test in WOCBP
- Modified Rodnan Skin Score measurement, tender joint count
- Dispensation of MMF
- Rituximab infusion
- **Full PFT with DLCO will be performed at this visit**

The patient should be on their final, stable (2-3 g a day) MMF dose by this visit.

Infusion 2 (Visit 2, 2 weeks after infusion 1)

During the Rituximab treatment visit, the following clinical research procedures will be conducted:

- Review of medical history, including a detailed medication review
- Collection of patient questionnaires (SF-36, SHAQ-DI, PROMIS-29, SSPRO, CSSRS, UCLA SCTC GIT 2.0)
- Patient & Physician Global Assessments
- Physical exam with height, weight and vital signs
- Laboratory tests including CBC, CMP, LFT, Serum IgG and urine pregnancy test in WOCBP
- Modified Rodnan Skin Score measurement, tender joint count
- Dispensation of MMF
- Rituximab infusion

Study Visits (Visit 1, Visit 2, Visit 3, Visit 4)

- Review of medical history, including a detailed medication review
- Collection of patient questionnaires (SF-36, SHAQ-DI, PROMIS-29, SSPRO, CSSRS, UCLA SCTC GIT 2.0)
- Patient & Physician Global Assessments
- Physical exam with height, weight and vital signs
- Laboratory tests including CBC, CMP, LFT, Serum IgG and urine pregnancy test in WOCBP
- Modified Rodnan Skin Score, tender joint count
- Dispensation of MMF
- Dispensation of Belimumab
    - First two subcutaneous injections will be performed under the supervision of a healthcare professional. The rest of the injections will be done at home.
- **FVC will be completed at Visit 3**
- **PBMC at visit 2 and 3**

NOTE: Between study visits, subjects will make trips monthly (two times before the next study visit) to the study center for CBC, CMP, LFT, Serum IgG, and pregnancy tests (if a woman is of childbearing potential).

End of Study Visit– Visit 5

No drug will be dispensed at this visit.

- Review of medical history, including a detailed medication review
- Physical exam with height, weight and vital signs
- Two 3mm punch biopsies of involved skin on forearm
- PBMC
- Modified Rodnan Skin Score, tender joint count
- Collection of patient questionnaires (SF-36, SHAQ-DI, PROMIS-29, SSPRO, CSSRS, UCLA SCTC GIT 2.0)
- Physical & Patient Global Assessments
- Laboratory tests including CBC, CMP, LFT, Serum IgG and urine pregnancy test in WOCBP
- **Full PFT with DLCO will be performed at this visit**

3-month Follow-up

- Review of medical history, including a detailed medication review

- Physical exam with height, weight and vital signs
- Modified Rodnan Skin Score, tender joint count
- Collection of patient questionnaires (SF-36, SHAQ-DI, PROMIS-29, SSPRO, CSSRS, UCLA SCTC GIT 2.0)
- Patient & Physician Global Assessments
- Laboratory tests including CBC, CMP, LFT, Serum IgG and urine pregnancy test in WOCBP

Extra or unplanned visits

You may be asked to see your study doctor in-between the visits mentioned above if your doctor believes that your disease may be getting worse. At these visits, the study staff will ask you about any medications you are taking or have used since your last visit. You will have a physical exam and vital signs will be checked (blood pressure, pulse, temperature and breathing rate). In addition, blood samples will be taken for your general health. No more than 3 tablespoons of blood will be taken at the visit.

Medications you are allowed to take during this study

You are able to to take their medications for underlying comorbidities, including pain medication.

Medications you are not allowed to take during this study

You should not take any other anti-fibrotic agents including colchicine, D-penicillamine, or tyrosine kinase inhibitors (nilotinib, imatinib, dasatinib)

4. STUDY RISKS – WHAT ADVERSE (BAD) EFFECTS CAN HAPPEN TO YOU BY PARTICIPATING IN THE STUDY:

Rituximab Risks

The following risks were reported in studies with rituximab in adults with Rheumatoid Arthritis. There is no reason to believe that risks will be different for people with Systemic Sclerosis. There may be other risks that are unknown to us at this time.

Most common, > 10%	Other common, 1% - 9%	Serious, rare, < 1%
fever chills nausea/vomiting tongue or throat swelling headache tiredness itching runny nose joint pain	hives wheezing or difficulty breathing low blood pressure dizziness rash muscle pain fluid in the legs or swelling flushing sweating and worsening chest pain low blood count worsening irregular heart beat or heart failure	low blood pressure breathing difficulty throat swelling arthritis disorders of the blood vessels lung disorders eye disorders severe skin reactions that may result in death severe lung and heart infusion-related reactions resulted in death reported in people with tumors

Your body may react to the rituximab by thinking it does not belong in your body and your immune system will develop specific proteins (antibodies) to destroy the rituximab. This may prevent you from receiving this or other antibody therapies in the future due to your body's sensitivity to this medication. Your immune system may develop quick allergic reactions to rituximab at the time when you receive the infusion of rituximab. These allergic reactions can include hives, swelling in face, lowing blood pressure, and breathing difficulty and can be severe although very rare. To decrease the risk of allergic reactions, you will be given medications before the infusion to prevent the allergic reactions, you will be monitored closely during the infusion and rituximab will be given very slowly.

B-cells are important cells in the immune system and help the body to fight infection. Rituximab decreases the number of B cells in the blood and other tissues, which is the reason it is being studied for the treatment of your disease. A slight increase in the number of serious and non-serious infections has been seen in rheumatoid arthritis patients treated with rituximab in some, but not all, studies. Therefore if you have a sore throat or a cold that lasts longer than normal you should seek medical attention and let your study doctor know as soon as possible.

Your doctor will monitor your blood counts at each study visit because a drop in blood counts has been seen in patients on rituximab being treated for cancer.

Some patients developed new serious viral infections or had a worsening of chronic viral infections. Most, but not all, of these patients had cancer and they were on other anti-

cancer treatments which made them more at risk. In some cases, these infections occurred over one year after rituximab treatment and resulted in death. A rare and severe viral infection called PML (progressive multifocal leukoencephalopathy), which can cause brain damage such as memory loss, trouble thinking and blindness, and is almost always fatal, has occurred in patients who received rituximab. The majority of these patients received rituximab in combination with chemotherapy (drugs that treat cancer) or as part of a bone marrow transplant.

Two patients with SLE who received rituximab developed PML, which resulted in death. It is estimated that about 10,000 patients with SLE were treated with rituximab during the time that these two patients developed PML. These two patients received several rituximab treatments and also received other immune suppressing drugs for lupus. It is therefore unclear whether treatment with rituximab increased the risk for this infection. Tell your study doctor immediately if you, your family members or your other doctors notice any new or worsening medical problems, such as a new or sudden change in thinking, walking, strength, vision, or other problems that have lasted over several days.

Low neutrophils (one type of white blood cells), including severe and late onset have been reported in recent studies in rheumatoid arthritis and other autoimmune disease after rituximab treatment. Although these events are not common and usually mild, some have been associated with fatal infections.

Some patients with cancer who were treated with rituximab and chemotherapy had bowel problems including blockage and in some cases the bowel developed holes, which sometimes resulted in death. There have been some cases of bowel problems including blockage and in some cases the bowel developed holes, in patients who have received rituximab for rheumatoid arthritis (RA), however this was not more frequent than expected in RA patients.

Also, in the rheumatoid arthritis clinical trials, more patients who received rituximab had problems with the heart and blood vessels such as heart attacks and strokes compared to patients who received placebo.

Belimumab Risks

Most common, > 10%	Other common, 1% - 9%	Serious, rare, < 1%
nausea diarrhea fever common cold bronchitis insomnia pain in arms and legs depression migraine sore throat anxiety	pneumonia urinary tract infection skin infection bronchitis	swelling of the face, lips, mouth, or tongue; wheezing, difficulty in breathing or shortness of breath; rash or itchy raised bumps (welts or hives), slow heart beat, high or low blood pressure, or dizziness

Belimumab has mostly been studied in patients with systemic lupus erythematosus (also called "lupus" or "SLE").
In patients with diseases other than lupus, there is very little or nothing known about the side effects of belimumab although in a pilot study done here at HSS, the safety did not appear different than what is seen in lupus. Safety information from lupus patients is given here.

Allergic Reactions to Belimumab

Some patients (up to 1 out of 100) have more severe side effects. These may happen because of an allergic reaction. Patients who have had allergic reactions before may be more likely to have allergic reactions to belimumab. These reactions happen most often on the day of or the day after the first or second belimumab dose is given. These reactions can be very serious and can cause death. With these reactions there may be swelling of the face, lips, mouth, or tongue; wheezing, difficulty in breathing or shortness of breath; rash or itchy raised bumps (welts or hives), slow heart beat, high or low blood pressure, or dizziness. Get medical help right away if you get any of these problems during the study.

In this study, belimumab will be administered as an injection (under the skin). In a study in lupus patients using the injection form of belimumab (under the skin), skin reactions in the area of injection occurred in less than one in 10 people, and were mild or moderate in severity. No serious reactions occurred. Your study doctor or study nurse will watch you closely in the clinic for 3 hours after the first and second times you are given belimumab for any signs of a reaction. After your first supervised injection and at the discretion of your study doctor/nurse you may be

allowed to self-administer all subsequent doses at home, following the instructions provided you. If at any time, you do not feel adequately trained with self-injection, you may return to the site for further training. If you are unable to self-administer the study agent, you must have surrogate, such as a caregiver, to administer the subcutaneous injection for you. You or your caregiver(s) should not administer the study drug until proper training in subcutaneous injection technique is received.

Sometimes allergy medicines or medicines like acetaminophen (Tylenol) or paracetamol are given before a belimumab dose. It is not known if this helps keep someone from having allergic side effects to belimumab or not, or if it keeps allergic side effects from being as severe.

The side effects that may warn of an allergic reaction include:

- Swelling of the face, lips, mouth, or tongue
- Wheezing, difficulty in breathing or shortness of breath
- Rash
- Itchy raised bumps or hives

Get medical help right away if you have any of these side effects.

Delayed-type allergic reactions can occur with belimumab. These types of reactions generally occur 5-10 days after a dose of medication (but can occur before or after that time) and include a combination of symptoms such as rash, nausea, fatigue, muscle aches, headache, and/or facial swelling. If you experience these symptoms, particularly if you experience a combination of such symptoms contact your doctor or nurse.

In previous clinical trials with belimumab in lupus, a very small number of people became depressed and even committed suicide. During the trial, we will ask you to tell your doctor if you become depressed. If you become depressed or suicidal a referral for psychological counseling will be made.

One case of rare and severe viral infection called PML (progressive multifocal leukoencephalopathy), which can cause brain damage such as memory loss, trouble thinking and blindness, and is almost always fatal, has been reported in an SLE patient treated with belimumab in combination with mycophenolate mofetil (MMF also known as CellCept®) and prednisone.

Your chance of getting PML may be higher if you are treated with medicines that weaken your immune system, including belimumab. Tell your doctor right away if you have memory loss, trouble thinking, difficulty with talking or walking, loss of vision, or similar problems. There may be other risks that are unknown to us at this time.

Risks of taking belimumab after rituximab

If you are assigned to study group 2, you will receive rituximab followed by belimumab. Because both of these drugs affect B cells, you may have low B cells count in your blood and body for a long time after you finish the treatments. Also, immunoglobulin, a protein made by B cells to fight infection, may be decreased. It is not clear if the decrease of immunoglobulin in your blood increases the risk of infection. Your doctor will measure your immunoglobulin level during the study and if the level is too low, belimumab will be held.

There is safety data on this combination from a CALIBRATE trial conducted here at HSS among other sites. In that study, SLE patients received cyclophosphamide and high dose steroids in addition to Rituximab and belimumab (meaning a more toxic background therapy) and there was no increase in number of grade 3 or higher infectious adverse events or hypogammaglobulinemia (low levels of protective blood immunoglobulins) in patients in the active treatment arm. There are presently two large industry sponsored trials ongoing, including the BLISS- BELIEVE trial in SLE (which has been active for 1 year) and a trial in Sjogren's. Both trials have had a committee, known as a Data Safety Monitoring Board (DSMB), established to review safety data. After regular DSMB oversight, neither trial has halted enrollment due to safety concerns. An open label published study of 16 patients with SLE similarly demonstrated acceptable safety.

Side Effects of MMF include in order of frequency, >20%:

Cardiovascular: high blood pressure, low blood pressure, swelling, chest pain, fast heart rate
Central nervous system: pain, insomnia, fever, dizziness, anxiety
Dermatologic: Rash
Endocrine & metabolic: high blood sugar, high cholesterol, low magnesium, low potassium, low calcium, high potassium
Gastrointestinal: abdominal pain, diarrhea, nausea, constipation, vomiting, low appetite, upset stomach
Genitourinary: Urinary tract infection
Hematologic: low white blood cell count, anemia (low red blood cell count) , high white blood cell count, low platelet count
Hepatic: abnormal liver function tests, fluid in abdomen
Neuromuscular & skeletal: Back pain, weakness, tremor, numbness or tingling
Renal: kidney function abnormal
Respiratory: shortness of breath, infection, fluid around lung, cough
Miscellaneous: infections

3% to <20%:

Chest pain, abnormal heart rhythm, dizziness, blood clots
Central nervous system: Sleepiness, dizziness, confusion, depression, mood change,

Dermatologic: rash, hair loss, too much hair, itchiness, skin cancer
Endocrine & metabolic: abnormal acid level in blood, elevated sugar, change in sodium level, change in chloride level, change in phosphorus level, elevated uric acid
Gastrointestinal: Abdomen enlarged, pain with swallowing, flatulence, stomach inflammation, stomach infection, bleeding, yeast infection, weight gain/loss
Genitourinary: Impotence, increased urination, pelvic pain, prostatic disorder, swelling, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder
Hematologic: Coagulation disorder, bleeding, low white blood cell count, anemia
Hepatic: Abnormal liver tests including: alkaline phosphatase increased, bilirubinemia, gall bladder infection, gallstones, Increased Gamma-glutamyl Transpeptidase (GCT), hepatitis, jaundice, liver damage, transaminases increased
Local: Abscess
Neuromuscular & skeletal: joint pain, muscle pain, cramps, neuropathy
Ocular: Amblyopia, cataract, conjunctivitis, eye hemorrhage, tearing disorder, vision abnormal
Otic: Deafness, ear disorder, ear pain, ringing in ear
Renal: protein in urine, creatinine increased, pain with urination, hematuria, decreased urine, kidney infection, kidney failure
Respiratory: Apnea, asthma, bronchitis, nose bleeding, coughing blood, hiccups, hyperventilation, low oxygen, respiratory acidosis, throat infection, pneumonia, pneumothorax, pulmonary edema, pulmonary hypertension, respiratory yeast infection, rhinitis, sputum increased, voice alteration
Miscellaneous: yeast infection, Cytomegalovirus CMV virus infection, shingles, herpes virus infection, sweatiness/flushing, flu-like syndrome, healing abnormal, hernia, ileus infection, cancer, peritoneal infection, thirst
Postmarketing and/or case reports: Atypical mycobacterial infection, BK virus-associated nephropathy, colitis, gastrointestinal perforation, infectious endocarditis, interstitial lung disorder, intestinal villous atrophy, lymphoma, lymphoproliferative disease, malignancy, meningitis, pancreatitis, progressive multifocal leukoencephalopathy (sometimes fatal), pulmonary fibrosis (fatal), pure red cell aplasia, tuberculosis.

<u>Risk of Infection</u>
Because of the type of medicine it is, belimumab may make it easier for you to get an infection. These infections can be serious and fatal. Tell your doctor if you get chills or a fever or any other sign that makes you think you may have an infection. If you have any infection that keeps coming back or is hard to get rid of, you should not be treated with belimumab. Make sure you talk to your study doctor if you have or get these kinds of infections.

Progressive multifocal leukoencephalopathy (PML) is a serious and life threatening brain condition. Your chance of getting PML may be higher if you are treated with medicines that weaken your immune system, including belimumab. Tell your doctor immediately if you have memory loss, trouble thinking, difficulty with talking or walking, loss of vision, or similar problems

Risk of Cancer
Because of the type of medicine it is, belimumab may make it easier for you to get cancer. So far, patients who get belimumab have not gotten cancer more often than patients who do not get belimumab.

Vaccines
Vaccines help your body fight infections. If you get a vaccine while you are taking belimumab, the vaccine might not work as well as if you weren't taking belimumab. Also, some types of vaccines may not be safe for you to get while you are taking belimumab. Make sure you check with your study doctor before getting any vaccine.

Pregnancy
You should not take part in this study if you are pregnant. Mothers should not breastfeed a baby while on this study.
You should not get pregnant while you are in this study. If you are a woman who is able to get pregnant you must agree to use a type of birth control that works well. You will have to use an approved method of birth control while you are in this study and for at least 4 months after the last dose of study medicine you get. Your doctor will tell you about the choices of birth control that you can use in this study. Even if you are using birth control, you will have pregnancy testing at every visit during the study.

Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of levonorgestrel or etonogestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

Suicidality
Tell your study doctor if you have been depressed, worried or anxious, or have been thinking about suicide or hurting yourself. Tell your doctor even if these problems are not bothering you a lot right now. Also tell your study doctor if you are having any mood problems, are not acting or feeling like yourself, or are having behavior problems. If your family or friends have told you that they think you have these problems, tell your doctor, even if you don't agree.

Side Effects from Pre-Medications Prior to Rituximab/Placebo Infusions
Short term use of corticosteroids (such as prednisone) may be associated with side effects which include an increase in blood pressure and mood swings.
The chances of side effects from the acetaminophen (Tylenol®) and diphenhydramine (Benadryl®) given pre-infusion are very small and may include rare allergic reactions. Benadryl® is known to make you feel drowsy, and for this reason you must not drive the day of either study drug infusion.

Risks of Vaccinations
Risks of vaccine injection are infection, pain, redness, bruising, bleeding, and swelling at the injection site. Occasional flu-like symptoms have been reported. Allergic reactions, which appear as rash, itching, swelling, and difficulty breathing, have very rarely been described. There is a possibility that you will not be fully immunized following the vaccinations.

Risks of Other Study Procedures
Administering the study medication into a vein and collecting blood samples at each visit may involve temporary discomfort or bruising, possibly fainting, and, very rarely inflammation (swelling) or clotting of the vein being used, or infection at the site where the needle is inserted. If the rituximab leaks from the vein into the surrounding tissue, it may cause temporary pain and damage to the surrounding tissue.

Risks to Pregnancy or Breastfeeding
The risks to the unborn fetus and newborn from rituximab are not known. Because rituximab may be secreted in breast milk, a nursing infant may also be exposed. The endothelin receptor antagonists (bosentan (Tracleer®) or ambrisentan (Letairis) may cause damage to an unborn fetus. Therefore, women who are pregnant or nursing a child may not participate in this trial. If you become pregnant during the treatment phase of the trial, your therapy will be discontinued. It is necessary that every effort be made to avoid the possibility of pregnancy or fathering a child while receiving rituximab therapy and for a minimum of twelve months after treatment. Women of child-bearing potential must have a negative pregnancy test prior to each treatment with rituximab. It is important that individuals enrolled in this study who are of child-bearing potential (i.e. not post-menopausal or surgically sterile) use a medically acceptable form of birth control before beginning treatment. Because the rituximab antibody may stay in the body for up to twelve months after treatment, study participants of both sexes will be expected to continue using a reliable method of birth control for a minimum of twelve months after the last treatment with rituximab. The study doctor will discuss appropriate birth control measures with you.
If you suspect that you (or your partner) have become pregnant during the trial, you must notify the study doctor immediately.

Blood Draws

The risks for this procedure are minimal and rare. They include:

• Minor discomfort, bleeding, and bruising at the needle site. These symptoms often get better without medical help.

• Feeling faint (like "passing out") during the blood draw. If this occurs, the blood draw technician and other trained staff will be available to help you.

• Due to the amount of blood being drawn during the course of study, there is also a risk of developing anemia (low blood count).

• With any medical test, such as a blood test, there is always a small risk that the results may be viewed by an unauthorized (without permission) person and linked to you.

• Access to genetic test results by an authorized person could possibly cause you problems with your family (having a family member learn about a disease that may be passed to them), or problems with getting a job or insurance.

Modified Rodnan Skin Score

Although this is a non-invasive procedure, you may experience minor discomfort when the treating physician places the skin between his/her fingers to assess its thickness.

Punch biopsies

There is always a slight risk that the dermatologist performing the punch biopsy procedure will not be able to close the skin opening with stitches. If this is the case, the dermatologist will use a chemical to stop bleeding. Additionally, the procedures may leave you with small scars.

Measures taken to treat/minimize infection risk:

- We have excluded patients from participating who have a chronic or persistent infection that could be worsened by treatment with rituximab.
- A PPD test, either a skin test or blood test, will be performed to determine if you had TB (tuberculosis) or are at risk of developing TB as described in Study Description: Screening/Baseline Phase.
- You may be vaccinated before beginning study therapy as described under Study Description: Screening/Baseline Phase. After receiving study treatment, you should not receive live vaccines until your B cell count has returned to normal.
- You should notify your doctor immediately if you have any signs of an infection such as fever, cough, or changes in mental status (like weakness, inability to concentrate, difficulty walking, changes in vision, etc.).
- If you have a fever or an infection at the time that you are scheduled to receive an infusion, the infusion may be delayed for several days until the infection has resolved or you have received a course of antibiotic therapy. Very rarely, if repeated infections happen while your B cells are low you may need treatment with intravenous immunoglobulin.
- Rarely, rituximab has been associated with anemia (low red blood cell count), reduced numbers of cells that help fight infection (white blood cells), and reduced numbers of

cells that help your blood to clot (platelets). It is important that you inform the study doctors of any past problem you may have had with bleeding.

Inflammation in many parts of the body has been reported to occur rarely (less than 1 in a 1,000) in patients following the completion of rituximab infusions including arthritis inflammation of the blood vessels, the lung, the eyes and the skin. Rarely, the skin reactions have been so severe that they have resulted in death. In addition some people have developed inflammation affecting many parts of their bodies at the same time including serum sickness (a hypersensitive reaction like an allergy – may include fever, arthritis, hives, itching, fatigue – occurring up to 7 to 14 days after receiving the rituximab) and lupus-like symptoms such as joint pain and swelling, rash, or fatigue.

Your body may react to the rituximab by thinking it does not belong in your body, causing your immune system to develop specific proteins (antibodies) to destroy the drug. This is a rare effect (happens less than 1% of the time). The presence of antibodies to rituximab could prevent you from safely receiving other similar drugs in the future.
The long-term risks of taking rituximab on development of cancer, as well as its effects on potential fertility in men and women, are unknown.

Genetic Testing

One additional risk from this study is that it may generate information about you or your family that could relate to your genetic predisposition to specific diseases or medical conditions. Although every effort will be made to ensure that any information about you will not be wrongly disclosed or used, there is always the possibility that it may be inadvertently disclosed, which could cause emotional distress to you or your family. As described below, however, in the section entitled "Confidentiality and Privacy," we will take major precautions to protect your medical information from being wrongly used or disclosed.

Biological specimens, skin and blood, that you contribute for this study will be maintained for as long as it is deemed useful for research purposes, after which time the specimen will be destroyed. If your specimen is used for any future studies, it will either be completely stripped of any information that could be used to identify you, or it will be coded in such a way as to protect your identity, under the supervision of the Hospital's research review committee. You have the right to withdraw your consent to the storage and/or future genetic testing of your biological specimens at any time by contacting the Principal Investigator of this study, Dr. Robert Spiera at the following phone number (212) 774-2048. If you do so, any portion of your specimen that has not already been used for research purposes will be destroyed. Once your specimen has been stripped of all information that could identify you, however, it will not be possible to remove your specimen from those specimens that are stored for future research.

If the Hospital, the Hospital's Institutional Review Board, and the company or

government agency funding the research agree, study information, genetic information, and biological materials may be transferred to other hospitals and research institutions. This could happen if one or more of the investigators in this study relocates to another institution, or if HSS, in consultation with the investigators, believes that transferring these materials will allow important scientific research to be done.

You should be aware that insurance companies sometimes use information on medical testing to evaluate whether a person should be able to purchase a life, health or disability insurance policy, and an insurance carrier may request, or condition benefits upon, disclosure by you to them of certain medical information. Because this study likely will not provide you with any clinically meaningful genetic information about yourself, participation in this study should in no way affect your ability to obtain insurance coverage. If asked by an insurance carrier whether participation in this study provided you with any information regarding your vulnerability or predisposition to certain illnesses, you should respond that it did not.

5. THERAPEUTIC OBJECTIVES (to be checked by HSS Investigator):

__x___This study includes experimental/investigational procedures which may not give you immediate or any benefits. It is hoped the knowledge gained will be of benefit to others in the future.

__x___This study is planned to select your treatment by chance, since you will be assigned at random to one or more groups of people in the study who will receive different treatments, or no treatment. It is not known if any treatment you receive will be of benefit to you.

6. STUDY BENEFITS:

You are not expected to benefit personally from this research study. Participation in this study will not provide you with any therapeutic benefits, nor will it provide you with information regarding whether you are genetically predisposed to developing any known illnesses.

Benefits for society may include providing further information about the genetic basis of scleroderma as well as the development of safe and effective therapies for that illness.

7. ALTERNATIVES TO PARTICIPATING IN THE RESEARCH STUDY:

You are not required to participate in this study, and you have the alternative of not participating at all. If you do not want to participate in the study, your decision will not affect in any way your ability to continue to receive care at the Hospital and from Hospital doctors. You can and

should speak to your treating physician about other therapies used to treat patients with scleroderma, including the possibility of being treated with mycophenolate alone outside of this study.

8. COSTS TO THE PARTICIPANT and COMPENSATION:

HSS is committed to providing financial assistance when financially warranted and consistent with its resources, regardless of age, gender, religion, race or sexual orientation. So if you do not have health insurance, or if your health insurance does not pay for your medical care, you may seek financial assistance from HSS. Eligibility determinations are made on a case-by-case basis in accordance with HSS's financial assistance policy. You will be responsible for any costs not covered by financial assistance, which could be all of the costs (if HSS determines that you are not eligible for financial assistance) or some of the costs (if financial assistance awarded by HSS does not cover all of the costs). For more information about the Financial Assistance Program or to request a Financial Assistance Application call (212) 606-1505 to speak with a Financial Assistance Counselor or you can visit the following site: http://www.hss.edu/patient-financial-assistance-notice.asp.

You will be paid $25 per visit (for a total of $425 if you complete the study) for your participation in this study. You will not be reimbursed for any other expenses. You are required to provide a valid Social Security Number in order to receive payment for your participation or reimbursement for travel. Payment will be completed in the form of a check mailed to you at the address you listed in your medical records.

Depending on the amount of payments you receive from HSS over the year, tax law may require the HSS Finance Department to report that amount to the Internal Revenue Service (IRS) or other federal and state agencies, as applicable. Generally this reporting would take place if you receive payments that equal $600 or more from HSS in a calendar year. You would be responsible for the payment of any tax that may be due

There are no charges or expenses associated with your participation in this study. Nor will you receive money or any other form of compensation in return for such participation; participation is voluntary. Those research procedures listed in Section 2 (marked as "RES") will be covered by the study and will not be your financial responsibility.

As indicated in Section 2, those costs which are considered Standard of Care for your treatment here at Hospital for Special Surgery will be your/or your insurance's responsibility. You will be responsible for any co-pays, deductibles, and co-insurance associated with your medical care, just as you would be for any costs billed to your health insurance outside of this study. You will also be financially responsible for any medical care costs not covered by your health insurance.

There are no plans to compensate you for the use of the findings of this study, or any of the information or biologic materials (such as blood or tissue) collected from you during the study, even if they are used to develop or make a commercial product (such as a drug, device, biologic substance, or test).

9. COMPENSATION FOR INJURY:

All medical interventions--whether the routine care you receive in your physician's office or the experimental treatments you receive when participating in a research study--involve some risk of injury. In addition, there may be risks associated with this research study that are presently unknown and unforeseeable. If you sustain any injury during the course of the research or experience any adverse reaction to a study drug or procedure, please contact the Principal Investigator, **Dr. Spiera**, at the following telephone number: **212 774-2048**. If such a complication arises, the researchers will assist you in obtaining appropriate medical treatment. Such treatment is of course available to you at the Hospital, or you could go to any other facility of your choosing. The costs of the care that you receive at the Hospital for research-related injuries will be billed to your insurance carrier or managed care plan in the ordinary manner. You will be responsible for any co-pays or deductibles required by your insurer or managed care plan. Financial compensation for lost wages and other non-medical costs will not be provided by the Hospital or the research staff. Signing this document does not waive your rights in the event of negligence on the part of the Hospital or research staff.

10. CONFIDENTIALITY and PRIVACY:

Any and all information about you obtained through this study, including any results of genetic testing, is private and confidential, and will not be disclosed, unless permitted or required by law or by this consent form and the related authorization form you will sign. If a disclosure of information is not authorized by law or by this consent form, that disclosure will not be made without your further written informed consent.

Medical and research records will be confidential to the extent permitted by law. Information that does not become part of the subject's medical record will be identified by a code, and personal information from the patient's records will not be released without their written permission. Patients will not be identified in any publication about this study.

Patient confidentiality will be maintained by coding all information, records, blood and tissue samples with a numeric code unique to this study. This code will be linked to the individual names in a log book that will be securely locked in a cabinet. **Only the principal and co-investigators will have access to this information.** Information, records or specimens that are shared with other investigators will always be coded.

After your part in this study has been completed, we would like to be able to contact you, to get more information from you that may be needed for this research, to explain the results of this study, or to notify you of medical information that could help you or your family member. You

have the right, however, not to have us contact you after your part in the study is over. The risks of allowing us to contact you are that we may have information that cause some emotional distress, but the benefits are that we may have information that could help you in your medical planning and decision-making.

Please indicate below whether we have your permission to contact you (and only you) in the future:

☐ **Yes**, you may contact me in the future, after my part in this study is over.

☐ **No**, you may not contact me in the future, after my part in this study is over.

☐ **Yes**, you may ask my next of kin or the representative of my estate for consent to do further testing on my samples after my death and disclose the results to my family.

☐ **No**, you may not ask my next of kin or the representative of my estate for consent to do further testing on my samples after my death and disclose the results to my family.

If you allow us to contact you in the future, we will not disclose your medical information, including any results of genetic tests done as part of the study, to any member of your family for clinical, research or any other purpose, without your further specific written informed consent. If we do think that your family members could benefit from knowing any information we have received about you during this study, we may ask you for permission to contact them, and would explain our reason for wanting to do so. But we will contact no one (other than you yourself) unless and until you specifically tell us to do so. If you do not consent to be contacted in the future, this also means that if you die and we later obtain information that might help your family, we would not be able to contact your family to share that information.

If you consent to participate in this research, your personal information will not be released without your written permission, except as required by law or for regular Hospital treatment, payment, and Hospital management activities. **(We will not, however, release any genetic testing information to any insurance company unless you specifically tell us to do so).** If you agree to participate in this study, the researcher will ask for your separate written permission (on a form called an "authorization") to use and disclose your personal information for certain purposes related to the study. For example, the researcher will ask permission to share your information with the research staff, with the Hospital's research review committee (known as the "Institutional Review Board") and research oversight staff/government agencies that regulate research (OHRP and NY State), with other researchers and scientists working on this study, with your treating physicians or your

other health care providers, and/or with any other people who need your personal information in order to conduct or oversee the study. The researcher will also ask you to allow the sharing of

your personal information with the research sponsor, Human Genome Sciences. Your personal information will usually be shared on research forms without your name or other identifying information, except when your name or other identifying information is necessary to make sure that the information on the research forms is accurate. Your name will not be used in any publication without your prior permission; only the data obtained as a result of your participation in this study will be made public. **Because this study involves drugs, devices or other agents of medical treatment regulated by the U.S. Food and Drug Administration (FDA), the FDA may review your study records and associated health information.**

11. CONFLICT OF INTEREST NOTIFICATION:

HSS is concerned about possible conflicts of interest in research, and has policies that require all investigators and senior research staff to report to HSS significant financial interests (such as stock ownership, royalty payments, and consulting agreements) and relationships (such as membership on a scientific advisory board) that are related to their research studies. When an investigator reports a significant financial interest or relationship that relates to one of his/her studies, HSS's Conflict of Interest Committee for Research reviews the information to evaluate the risk that the interest or relationship might influence how the investigator conducts the study or interprets the results of the study. HSS may also take steps to minimize that risk.

☐ **The Conflict of Interest Committee has determined that there are no conflicts associated with this study.**

☐ **The Conflict of Interest Committee has determined that there is a potential conflict of interest.**

12. VOLUNTARY PARTICIPATION IN, AND WITHDRAWAL FROM, THE STUDY:

Your participation in this study is completely voluntary. You can refuse to participate, or withdraw from the study at any time, and such a decision will not affect your medical care at the Hospital, either now or in the future. Signing this form does not waive any of your legal rights. During the course of the research study, you will be told of any significant new findings or risks that may influence your willingness to continue to participate in the research.

As described earlier in this form, if you agree to participate in this research study, your biological specimens and information will be maintained for as long as it is deemed useful for research purposes, after which time they will be destroyed. You have the right to withdraw your consent to the storage and/or future testing of your specimens at any time, and your specimens that have

not already been used for research will be promptly destroyed. Should you decide to withdraw from the study, or should you decide to participate in the study but to later withdraw your consent to the storage and/or future genetic testing of your specimens, you should contact the Principal Investigator at the telephone number indicated below to let him/her know about this decision.

13. QUESTIONS:

If you have any questions, please ask, and we will do our best to answer them. If you have additional questions in the future, you can reach the Principal Investigator, **Dr. Robert Spiera**, at **(212) 774-2048**. For information about your rights as a research subject, or if you are not satisfied with the manner in which this study is being conducted and would like to discuss your participation with an institutional representative who is not part of this study, please contact the Manager of the Institutional Review Board at (212) 774-7154.

_____
Study Participant Initials

14. STATEMENT OF CONSENT:

I have discussed this study with Dr. Robert Spiera to my satisfaction. I understand that my participation is voluntary and that I can withdraw from the study at any time without prejudice. Signing this form does not waive any of my legal rights. I will be given a copy of this informed consent form for my future reference.

I ACKNOWLEDGE THAT I HAVE READ THE ABOVE EXPLANATION OF THIS STUDY, THAT ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I AGREE TO PARTICIPATE IN THIS RESEARCH STUDY.

_____ _____
Signature of study participant/authorized representative Date and Time signed

I ACKNOWLEDGE THE PROCESS AND/OR SIGNATURE OR STATEMENT SET FORTH ABOVE

_____ _____
Signature of witness (required if consent is presented orally or at the request of the IRB) Date and Time Signed

I CERTIFY THAT I HAVE EXPLAINED FULLY TO THE ABOVE PATIENT THE PURPOSE, PROCEDURES, POSSIBLE RISKS, POTENTIAL BENEFITS AND ALTERNATIVES OF THIS RESEARCH STUDY.

_____ _____
Signature of researcher or designate Date and Time Signed

_____An interpreter in the Study participant's language was provided (check if applicable).

_____
As an HSS representative, please sign here to indicate that you have given a signed copy of this informed consent form to the participant

NOTE TO INVESTIGATORS:

- **THE ORIGINAL OF THIS INFORMED CONSENT FORM MUST BE PLACED IN THE PARTICIPANT'S STUDY FILE.**
- **A SIGNED COPY OF THIS INFORMED CONSENT FORM MUST BE GIVEN TO THE PARTICIPANT.**
- **A COPY OF THE INFORMED CONSENT FORM MUST BE PLACED IN THE PARTICIPANT'S HOSPITAL MEDICAL RECORD IF THE PARTICIPANT IS (OR WILL BE) HOSPITALIZED AT ANY TIME DURING THE STUDY**.

IRB Administrative Use Only

Hospital for Special Surgery Institutional Review Board Approval
1/14/2019 Thru 12/17/2019