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

GSK – Investigator Initiated Study

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NCT# Pending

Protocol Synopsis

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study of Belimumab and Rituximab Combination Therapy for the Treatment of Diffuse Cutaneous Systemic Sclerosis
Supporter	GSK, Investigator Initiated Study
Site	Hospital for Special Surgery 535 East 70th Street United States of America, New York, NY, 10021
Research Hypothesis:	In this randomized controlled study, we will test the hypothesis that Rituximab and Belimumab combination therapy with Mycophenolate Mofetil background therapy will improve fibrosis in SSc skin when compared to treatment with placebo and Mycophenolate Mofetil (MMF, Cellcept) in a group of patients with early SSc
Study Schema:	Two infusions of 1000 mg of rituximab two weeks apart and Belimumab subcutaneous once every week (200 mg) and background MMF (2-3 g po, qd) vs two placebo Rituximab infusions two weeks apart and placebo Belimumab subcutaneous once every week and background MMF (2-3 g po, qd) administered over a 12 month period.
Study objectives:	
Primary Safety	The proportion of participants who experience at least one Grade 3 or higher adverse event at or before 12 months
Primary Efficacy	• Change in the CRISS at 12 months
Secondary Safety and Efficacy	• Proportion of patients who experience at least one grade 2 or higher adverse event • All infectious adverse events • All infusion reactions • All injection site reactions • All adverse events • Change in the CRISS at 6 months • Change in the MRSS at 6 and 12 months • Change in Forced Vital Capacity (FVC) • Change in the short form-36 (SF-36) • Change in the scleroderma health assessment questionnaire-disability index (sHAQ-DI) • Change in PROMIS-29 • Change in GIT score • Change in Scleroderma Skin Questionnaire • Change in the DAS-28 • Change in joint count • Change in CDAI • Change in Global Combined Response Index

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Introduction

Overall Risk/Benefits Assessment

This is a randomized, double-blind, placebo-controlled study to assess efficacy of Rituximab and Belimumab combination therapy in patients with diffuse cutaneous Systemic sclerosis (SSc, Scleroderma). Scleroderma is a significant rheumatic disease, and is associated with substantial morbidity and disability, and many detrimental effects on health-related quality of life. There are currently no Food and Drug Administration (FDA) approved drugs for SSc.

Research Hypothesis

In this randomized controlled study, we will test the hypothesis that Rituximab and Belimumab combination therapy with Mycophenolate Mofetil background therapy will improve fibrosis in SSc skin when compared to treatment with placebo and Mycophenolate Mofetil (MMF, Cellcept) in a group of patients with early SSc without internal organ complications.

Study Rationale

Scleroderma is a multi-system inflammatory disease where dysregulated fibrosis, autoimmunity, and vasculopathy lead to disability, organ failure, and accelerated mortality. There are two main subtypes of SSc: limited cutaneous (lc) SSc and diffuse cutaneous (dc) SSc, with disease subtype determined by distribution of skin involvement and with different patterns of internal organ involvement observed in the two subtypes. SSc has an estimated prevalence of 276 per million in the United States,[1] and the ten-year mortality rates range from 23 percent to 45 percent.[1,2] There is currently no satisfactory disease modifying agent for this potentially devastating disease. Frequently employed treatments include cyclophosphamide,[3] methotrexate,[4] and mycophenalate mofetil[5] and improved therapy for SSc is an urgent and unmet need.

B-Cell abnormalities are part of the immune dysregulation seen in systemic sclerosis. Belimumab (Benlysta) decreases B-Cell survival and is a therapeutic agent with high potential in SSc.

Anti–B-cell therapy has already been shown to be effective in treating rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), chronic graft-versus-host disease and other related autoimmune diseases. Recent assessment has indicated that B-cells function as immunoregulatory cells in the induction and maintenance of systemic autoimmunity. These cells display a variety of functions, including antigen presentation, production of cytokines, lymphoid organogenesis, differentiation of T-effector cells and modulation of dendritic cell function through cytokine production, and in the activation of T cells in addition to production of autoantibodies.[6] Abnormalities in B-cell development and/or function could contribute to autoimmunity in addition to or independently of autoantibody production.

Several investigations have shown that B cells play an important role in the pathogenesis of SSc. The presence of antinuclear antibodies (ANAs) has been detected in 90% of patients with SSc and is thought to be a central feature of immune activation in the disease.[7] Specific autoantibodies (e.g. anti-Scl70, anti-centromere and anti-RNA polymerase III antibodies) associate strongly with individual disease phenotypes, and their presence is evidence of abnormal B-cell activation in patients with SSc.[8] Hypergammaglobulinemia, hyperactivity of polyclonal and memory B-lymphocytes and altered B-cell homeostasis have been detected in SSc patients.[9,10] In addition, gene expression analysis using DNA

microarrays has revealed an upregulation of B-cell related genes in SSc skin lesions.[11] Immunochemical analysis suggests that the B lymphocyte signature observed on these arrays is from CD20+ B cells.

Perivascular B-cell infiltration has been found in the skin of SSc patients,[12] and B-Cells have been observed in the lungs of patients with SSc-related interstitial lung disease.[13] Levels of circulating naive B cells (CD27-) are increased in SSc patients, while memory B cells (CD27 medium), although reduced in number, show markers of activation (CD 80, 86, 95).[14] Both naïve and memory B cell populations exhibit increased expression of CD19, a critical cell surface signal transduction molecule expressed by early pre-B cells from the time of heavy chain rearrangement until plasma cell differentiation. Flow-cytometric analyses of blood from patients with scleroderma have indicated that surface CD19 density in scleroderma B cells are 20% higher than those from healthy controls.[15]

Polymorphisms of the CD19 promoter region were found to correlate with higher CD19 expression on B cells, whereas polymorphisms of CD22, a negative regulator of B-cell receptor signaling, led to decreased CD22 surface expression on B cells in SSc patients.[15,16] In the tight skin (TSK) mouse, a commonly employed murine model of systemic fibrosis, B-cells exhibit a hyper responsive phenotype with decreased IgM expression and increased IgG and autoantibody production. CD19 signaling is augmented in this model, and knock-out of CD19 leads to decreased skin fibrosis.[17] In addition, CD19 deficiency correlates with hyperg-globulinemia and elevated autoantibody levels including anti-topoisomerae I antibody. Reciprocally, in transgenic mice overexpressing CD-19, antitopoisomerase I antibody levels are significantly increased.[17] CD 19–null mice treated with bleomycin show a reduced fibrotic response in the skin and lungs as well as reduced levels of the profibrotic cytokines IL-6 and TGF-β. However, TSK mice with increased expression of CD19 do not exhibit increased skin thickness. Thus, exaggerating B-cell activation through the increase of CD19 does not lead to further skin fibrosis though silencing B-cell activation can reduce skin fibrosis.[17]

In addition to the aforementioned B-cell abnormalities, serum BAFF levels have been shown to be elevated in SSc patients when compared to healthy controls, these levels correlated positively with extent of skin fibrosis, and decreasing BAFF levels were accompanied by improvement in the MRSS. BAFF receptor expression on B cells was increased in SSc patients relative to healthy controls.[18,19] BAFF mRNA expression was found to be up-regulated in the affected skin of patients with early dcSSc (as defined as less than three years of disease duration from the first non-Raynaud's symptom of SSc) when compared to those with late dcSSc, scar tissue, or healthy controls. Furthermore, serum BLyS levels were found to be elevated in the tight skin (TSK/+) mouse,[20] a genetic model for SSc. A BLyS antagonist downregulated the expression of fibrogenic type 2 cytokines, such as IL-6 and IL-10, and inhibited autoantibody generation, development of skin fibrosis and hyper-gammaglobulinemia in the TSK/+ mouse. Skin fibrosis in TSK mice is improved with a parallel reduction in IL-6 production from B cells (20). BAFF induced IL-6 production by TSK B cells could play an important role in the development of skin fibrosis, and BAFF antagonist attenuates skin fibrosis with a decrease in IL-6 production.[18,19] BAFF stimulation enhances CD19 expression and also phosphorylation of CD19 by B cell antigen receptor. Thus, excess BAFF may contribute to B cell hyperactivity through the overexpression of CD19.[21]

As new studies shed light on the pathogenic roles of B-cells in SSc, there have been promising initial investigations looking at Rituximab, a chimeric mAB against human CD20 that depletes peripheral B-cells, in the treatment of SSc with four small published trials[4,5,22] to date. The medication was found to be

tolerable in all of the studies, with little associated toxicity and no reported serious adverse events attributable to Rituximab. Three of the studies showed improvement in the MRSS, and potential improvement in pulmonary function was shown as well. Daoussis, et al performed a randomized, controlled trial, open-label trial with 14 patients which showed an improved FVC (improvement of 10.25% in treated vs deterioration of 5.04% in controls) and DLCO (improvement of 19.46% in the treated group vs deterioration of 7.5% in the control group.) In this study the MRSS improved from 13.5 +/- 6.84 vs 8.37 +/- 6.45 at baseline vs 1 year, respectively, P = 0.0003). There was no significant change in the control group. In Lafyatis, et al. a study which recruited all patients with less than 18 months disease duration, no significant change was seen in 15 patient in the MRSS. This group did observe depletion of cutaneous B-Cell infiltrates. In an open label study by Smith, et al. the MRSS improved from 24.8 to 14.3 which was a mean improvement of 43%, $p<0.001$. Significant improvements were noted in the dermal hyalinised collagen content and dermal myofibroblast numbers as well. As a whole these studies point favorably to B-Cell directed therapies for this incurable disease.

Belimumab (Benlysta®), a recombinant, fully human monoclonal antibody, has been FDA approved as an add on therapy to SoC in sero-positive SLE. Belimumab binds to soluble human B lymphocyte stimulator (BLyS) with high affinity and inhibits its biologic activity. The background above provides a robust rationale for the investigation of belimumab in the treatment of dcSSc.

In a recently completed double-blind, placebo-controlled pilot study completed by our center, the safety and efficacy of belimumab was tested in patients with early dcSSC treated with background MMF. Patients were then randomized 1:1 to either intravenous belimumab or placebo. In both treatment groups, an improvement in mRSS was observed, and although the median difference was greater in the actively treated as compared to the placebo group, this did not achieve statistical significance in this relatively small study. However, significant decreases in expression of B-cell signaling and pro-fibrotic genes and pathways was observed in patients with improved MRSS in the belimumab group but not in the placebo group.[23]

The clinical and translational findings of this pilot trial strongly support potential efficacy of belimumab in the treatment of dcSSc and further exploration of anti-B cell strategies in this rheumatic disease.

In recent years, there has been an increasing interest in treating patients with SSc with rituximab, especially for patients with interstitial lung disease (ILD). One randomized controlled trial focused on patients with SSc <2 years, and found that rituximab treatment, in comparison to the placebo group, caused a small improvement in lung function, but this difference did not reach statistical significance.[23] A chart review of 14 late disease SSc-ILD patients demonstrated that the median forced vital capacity increased compared to baseline, although not statistically significant, and skin scores remained stable at the end of follow-up.[24] In a series of 10 case reports (5 patients with early disease, 5 with late disease), rituximab was found to be most effective in treating early and rapidly progressive forms of SSc.[25] These studies demonstrate the need for further studies analyzing rituximab and especially its usage in early disease.

Utilizing belimumab and rituximab as a combination therapy in SSc has not previously been studied, but this approach has been considered in other autoimmune disorders. A completed study of rituximab and belimumab for SLE was successful in proving this combination therapy superior to placebo.[27]Case reports

have demonstrated efficacy of belimumab after rituximab as maintenance therapy in several patients with SLE.[27] Additionally, there is an ongoing study focusing on this combination therapy in Sjogren's, and another study is planned for ANCA Associated Vasculitis. We propose similarly administering two infusions of 1000 mg of rituximab two weeks apart in this SSc trial. This dosing regimen has been demonstrated in a previous uncontrolled pilot trial conducted by Lafayatis et al. to deplete B cells in both peripheral blood and skin for patients with SSc. Importantly, a significant reduction of the myofibroblast score in the skin biopsies of the RTX was demonstrated, and safety and tolerability was acceptable. This same Rituximab dosing strategy was used in the ongoing trial of Rituximab, Belimumab and Cyclophosphamide combination therapy in SLE (CALIBRATE).

This combination is of interest to us as an option for patients with SSc.

There is no standard treatment for patients with dcSSc. Treatments employed commonly include methotrexate, MMF, and cyclophosphamide.[3,5,28] None of these treatment options have a high level of evidence or a dramatic benefit. MMF has been used in conjunction with Belimumab in SLE as has methotrexate. Because of no clear superior treatment (MTX vs MMF in SSc) in the literature, the investigators have chosen MMF as baseline therapy due to a perceived balance of benefit in SSc as well as experience using it with Belimumab. All patients are offered active treatment with MMF.

In this 52 week, single center, randomized, double-blind, placebo-controlled study, we will address the following specific aims:

1. Determine whether Belimumab used in combination with Rituximab (Rituxan), compared to placebo in the context of background therapy with mycophenolate mofetil (MMF, Cellcept) is safe and tolerable in the treatment of patients with early diffuse cutaneous (dc)SSc (Disease duration < 3 years) as assessed by comparison of adverse and serious adverse effects.

2. Determine whether Belimumab used in combination with Rituximab is more effective than placebo when used in combination with MMF, as measured by change in modified Rodnan Skin Score (mRSS), forced vital capacity (FVC), hemoglobin corrected diffusion capacity (DLCO), Medsger Severity Scale (MSS), and by other physician and patient derived outcome measures.

3. Determine the biological activity of rituximab/belimumab/mmf vs placebo/placebo/mmf as assessed by effect on histology of skin, gene expression of skin and blood, change in B-Cell profiles including assessment of B regulatory cells, effect on BLyS levels, and effect on serological and cutaneous biomarkers of disease activity.

Study Objectives

Primary Safety Objectives

The primary safety outcome of the study is as follows:

- The proportion of participants who experience at least one Grade 3 or higher adverse event at or before 12 months

Primary Efficacy Objectives

The primary efficacy outcome of the study is as follows:

- Change in the CRISS at 12 months

Secondary Objectives

Secondary safety and efficacy endpoints will include:

- Proportion of patients who experience at least one grade 2 or higher adverse event
- All infectious adverse events
- All infusion reactions
- All injection site reactions
- All adverse events
- Change in the CRISS at 6 months
- Change in the MRSS at 6 and 12 months
- Change in Forced Vital Capacity (FVC)
- Change in the short form-36 (SF-36)
- Change in the scleroderma health assessment questionnaire-disability index (sHAQ-DI)
- Change in PROMIS-29
- Change in GIT score
- Change in Scleroderma Skin Questionnaire
- Change in the DAS-28
- Change in joint count
- Change in CDAI
- Change in Global Combined Response Index

Tertiary Objectives

- Change in gene expression in the skin as assessed by DNA microarray

- Change in B-Cell subsets as assessed by flow cytometry
- Change in gene expression in the PBMC
- Change in histopathology

Ethical Considerations

Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the participant informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure).

Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigators will have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials/process (e.g., advertisements), and any other written information to be provided to participants. The investigator or sponsor should also provide the IRB/IEC with a copy of the Package Insert or product labeling information to be provided to participants, and any updates.

The investigator will provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

Informed Consent

The consent process will occur in a private clinic room at HSS at the beginning of the patient's screening visit. Informed consent will be obtained before any study procedures are performed. The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

Confidentiality

The Investigator will ensure that the subject's confidentiality is maintained. On the case report forms or other documents, subjects will be identified by unique initials and a subject study number only. Documents that are not for submission to the Sponsor or designee (e.g., signed informed consent/assent forms) will be kept in strict confidence by the Investigator.

Investigational Plan

Study Design and Duration

This study is a randomized, double-blind, placebo-controlled study. Eligible participants will be randomized 2:1 to favor active treatment. The active treatment is two infusions of 1000 mg of Rituximab two weeks apart followed by 200 mg of subcutaneous Belimumab once a week for 48 weeks vs two placebo infusions two weeks apart, followed by placebo subcutaneous injections once a week for 48 weeks. All patients will be on background Mycophenolate Mofetil (2-3 g a day).

Study Population

Before any study procedures are performed, participants will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if participants consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

This study will enroll 30 patients total.

For entry into the study, the following criteria MUST be met:

Inclusion Criteria

1. Age greater than or equal to eighteen years and less than or equal to 80.
2. Classification of systemic sclerosis (SSc), as defined using the 2013 American College of Rheumatology/European Union League Against Rheumatism classification of SSc.
3. Diagnosis of dcSSc, as defined by LeRoy and Medsger.
4. Disease duration of less than or equal to 3 years as defined by the date of onset of the first non-Raynaud's symptom.
5. A modified Rodnan Skin Score (mRSS) of > 14

Exclusion Criteria

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

Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- A two-times increase in modified Rodnan Skin Score within 6 months
- Progressive Systemic Sclerosis related Interstitial Lung Disease at 6 months, defined as:
    - Absolute decline in FVC % predicted, attributable to SSc-ILD, by >15%, and
    - Absolute decline in DLCO% predicted, attributable to SSc-ILD, by >20%, and
- Must be confirmed by repeat pulmonary function testing within 1 month.
- Presence of new inflammatory infiltrates on HRCT, which are deemed SSc-related by study investigators

- Onset of new Scleroderma Renal Crisis
- Onset of new heart failure
- Investigator decision that removal from trial is in subject's best interest
- Neutrophils <1X10E9/L.

Any subject removed from the trial will continue to be seen according to protocol and will be treated by the best medical decision of the investigators. A minimum of 2 follow-up visits will be documented when a patient is removed from the study.

Subjects will be monitored for late onset neutropenia at 6 months post rituximab or other immunosuppressive agent. Monitor patients for signs and symptoms of infection, monitor laboratory values, request that patients report signs of infection. Treat infections immediately and appropriately.

Contraceptive requirements for women of childbearing potential

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%.

Therefore, these women must have a negative serum pregnancy test at screening, and agree to 1 of the following:

- Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent (Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
  OR
- 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.

Special Considerations: Mycophenolate Mofetil

- Mycophenolate can cause fetal harm when administered to a pregnant female. Use of mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations.
- Mycophenolate affects the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving MMF who are using oral contraceptives for birth control should employ an additional method (e.g., barrier method) resulting in two reliable forms of contraception being used simultaneously before starting study treatments, during therapy, and for 6 weeks after stopping therapy; unless abstinence is the chosen method of contraception
- For women of childbearing potential, two serum or urine pregnancy tests are required, separated by 8 – 10 days and with the second immediately preceding initiation of study related therapy
- For sexually active men, condoms should be used during, and for at least 90 days after cessation of mycophenolate treatment. No sperm donation should be made during this period of time. For female partners of male subjects, it is recommended to use highly effective contraception during treatment and for 90 days after the last dose of mycophenolate
- No blood donation should be made by the study subjects during mycophenolate treatment and for at least 6 weeks after stopping mycophenolate treatment

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

If PML is suspected, this should be immediately reported to GSK. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

Combination anti-B cell therapy considerations

- All subjects should be monitored closely for infection
- Serum IgG levels should be measured monthly in this situation
- Stopping / withdrawal criteria:
    - Benlysta should be discontinued in subjects with IgG levels <400 mg/dL associated with a severe or serious infection.
    - If a subject experiences any IgG levels < 250 mg/dL not associated with severe or serious infection, the dose of study agent must be withheld and GSK must be consulted before administering any subsequent dose of study agent. Increased vigilance for infection is required. Clinical judgment should be applied with respect to the appropriateness of continuing study therapy in these subjects.

If a subject experiences a clinically significant, potentially life-threatening (Grade 4) adverse event (AE) that the investigator believes is definitely, possibly or probably related to study agent, then treatment with study agent will be discontinued. The subject should be withdrawn from study agent and followed at regularly scheduled study visits as specified by protocol or until resolution of the AE(s), whichever is longer.

Liver Chemistry Stopping Criteria

Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

- ALT Absolute: ALT ≥ 8xULN
- ALT Increase:
  - ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
  - ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
- Bilirubin: ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)
  - Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury
  - All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
- INR: ALT ≥ 3xULN and INR>1.5, if INR measured
- Cannot Monitor:
  - ALT ≥ 5xULN but <8xULN and labs cannot be monitored weekly for ≥2 weeks
  - ALT ≥ 3xULN but <5xULN and labs cannot be monitored weekly for ≥4 weeks
- Symptomatic: ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
  - New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

Required Actions, Monitoring and follow up Assessments following ANY Liver Stopping Event

Actions

- Immediately discontinue study treatment
- Report the event to GSK within 24 hours
- Perform liver event follow up assessments (as stated below)

- Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
- Do not restart/rechallenge subject with study treatment

Monitoring

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline
- A specialist or hepatology consultation is recommended

For All other criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs
- Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

Follow Up Assessments:

- Viral hepatitis serology (Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody)
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin□2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
- Record use of concomitant medications including acetaminophen, herbal remedies, other over the counter medications
- Record alcohol use

For bilirubin or INR criteria:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins)
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009])
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease

Increased Monitoring Criteria with Continued Therapy

Criteria

- If ALT ≥5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks
  OR
- ALT ≥3xULN and <5xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks

Required Actions

- Notify GSK within 24 hours of learning of the abnormality to discuss subject safety
- Subject can continue study treatment
- Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event
- If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

Treatments

Study Treatment

Definition of Investigational Product

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In this protocol, the investigational products are Rituximab and Benlysta.

Definition of Non-Investigational Product

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care. In this protocol, the non-investigational product is MMF, which all patients will be on a stable dose of throughout the trial.

Handling and Dispensing

Upon receipt, the shipment of medications and placebo will be stored in a secure area. At each study office visit, patients will be dispensed enough study medication to last them until their next study office visit. Institutional Pharmacy Accountability Logs may be used to document receipt of study drug and dispensing of drug to participants via the Study Coordinator. The investigator is responsible for ensuring that it is dispensed only to study participants and only from the official study site by authorized personnel.

The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity), as described below:

MMF pills (tablet or capsule) and corresponding placebo should be stored in a closed container at room temperature, away from heat, moisture, and direct light. Keep the medicine tightly closed.

Care should be taken when handling the drug products that are used in this protocol. Proper aseptic techniques must be used when preparing and administering products. Products should be inspected visually for particulate matter prior to administration. Refer to the Package Insert for additional information regarding handling, preparation, and storage of Benlysta and MMF.

If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact the DCC immediately.

Drug Ordering and Accountability

Initial Orders
After study activation occurs, the initial drug supply will be sent to the site.

Re-Supply
Subsequent drug supply will be shipped to HSS based on study activity.

Method of Assigning Subjects to Treatment
Patients will be assessed at an initial screening visit during which time a history and physical examination will take place as well as a full review of medical records. A full review of the patient's history and physical, clinical laboratories, as well as review of records will be performed at the screening visit. The physician will require a PFT within the last 6 months of the patient's Baseline 1 visit. The physician may order repeat tests to confirm the patient's entry into the study. During the baseline visit, eligible patients will be seen for a baseline visit when PFTs, MRSS, skin biopsy, and patient derived endpoints will be performed. Safety assessments will be performed at every visit.

After patients maintain a dose of MMF for at least 1 month, patients will be randomized to treatment with either Belimumab & Rituximab or placebo. Patients will be receiving Belimumab subcutaneously and Rituximab intravenously. Placebo injections and infusions will be of normal saline.

Patients will be randomized after all screening assessments have been completed and the investigator has verified that eligibility criteria have been met. At the time of randomization, patients will be assigned a unique randomization number; no participant may begin treatment prior to randomization. Eligible participants will be randomized to one of 2 groups:

- Group 1 (20 patients):Two infusions of 1000 mg of Rituximab , weekly subcutaneous injections of 200 mg of Benlysta, and background MMF, 1000 -1500 mg twice daily.
- Group 2 (10 patients): Two placebo infusions, weekly placebo subcutaneous injections, and background MMF, 1000 -1500 mg twice daily.

Randomization into each group is done in a 2:1 manner, Group 1:Group 2. The statistician Jackie Finik will prepare the randomization schedule, using computer-generated block randomization with the block sizes. A secure web-based application will be built that will be used by the coordinators to enter participant information (e.g., participant ID) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the site pharmacists.

Blinding/Unblinding

This is a double-blind study. The study staff and the patient are blinded to the treatment assignment.

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in a participant, **in which knowledge of the investigational product is critical to the participant's management**, the blind **for that participant** may be broken.

The DSMB will be blinded to study therapy that subjects have been assigned during the course of the study, but may recommend un-blinding as needed.

Before breaking the blind of an individual participant's treatment, the investigator should have determined that the information is necessary, i.e., that it will alter the participant's immediate management. A discussion with the protocol chairs will occur and authorization to proceed or not with unblinding will be given to the investigator. In many cases, particularly when the emergency is not investigational product-related, the problem may be properly managed by assuming that the participant is receiving active product without the need for unblinding.

Concomitant Treatments

Patients are allowed to take their medications for underlying comorbidities, including pain medication. Full exclusionary medications are listed under the exclusion section of this protocol.

Other Restrictions and Precautions

Physicians will exercise caution when considering the use of study medication in patients with a history of recurrent infections, underlying conditions which may predispose them to infections, or chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment in this study will be monitored closely with administration of study drug discontinued if a patient develops a serious infection.

Study Assessments and Procedures

Study Outcome Assessments

Study-related procedures and outcome measures that will be performed as part of this protocol are listed below. Specific times at which each test will be performed are summarized in the schedule of events table.

Complete medical history. Medical history will be performed as per standard medical care.

Physical examination. A standard complete physical examination will be performed, with the addition of the assessment of modified Rodnan Skin Score (MRSS), 28-tender joint count, 28-swollen joint count, tendon friction rubs, joint contractures and digital ulcers.

Vital signs. Vital signs will include: pulse, blood pressure, respiratory rate, temperature (C º), height (cm), weight (kg) and body mass index.

Pulmonary function tests (PFTs) Spirometry: Carried out by either certified pulmonary function technologists (National Board of Respiratory Care) or experienced staff that meets American Thoracic Society (ATS) recommendations. All spirometry equipment and procedures will conform to the most recently published standards of the ATS/ERS Task Force. Forced expiratory maneuvers will be performed

at least in triplicate with the minimal requirement that three maneuvers are "acceptable" and that two of these maneuvers meet end-of-test and repeatability criteria for FVC and FEV1.

Skin Biopsies: Skin biopsies will be performed at baseline 1, and Visit 5. The skin biopsies will consist of 2 3-mm punch biopsies of involved skin on the forearm. Skin biopsies will be subjected to histopathology, immunohistochemistry, and RNA extraction for gene expression analysis by qPCR and microarray. Additionally, a blinded investigator will compare the pre and post dose biopsies to determine change in inflammation and fibrosis.

Blood: Blood will be drawn for both clinical labs and translational blood tests. Studies on blood will include flow cytometry to assess B-Cell subsets on PBMC, gene expression analysis on peripheral blood mononuclear cells (PBMC), assessment of biomarker and cytokine levels including autoantibodies, CRP, ESR, CMP, CBC and CPK.

Urine pregnancy tests: All women of childbearing potential will have to undergo a urine pregnancy test every study visit. The results of the pregnancy test must be available prior to each dosing.

Schedule of Assessments

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	X													
Review of inclusion/exclusion criteria	X													
Demographics	X													
Medical History	X													
Physical Exam (including joint count)	X	X	X	X	X		X		X		X		X	X
MRSS	X		X		X		X		X		X		X	X
Hep B, Hep C test, HIV, IgA	X													
Quantitative IgG	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test (for women of childbearing potential)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PBMC		X					X		X				X	X
CBC, CMP	X	X	X*	X*	X	X	X	X	X	X	X	X	X	
ESR, CRP		X											X	
CPK	X		X	X			X		X		X		X	
LFT	X		X	X	X	X	X	X	X	X	X	X	X	
CD-19									X				X	
Patient and physician global assessments, SF-36, SHAQ-DI, PROMIS-29, SSPRO, CSSRS	X	X	X	X	X		X		X		X		X	X

DAS-28, CDAI, tender joint counts		X							X				X	
Full PFT and DLCO			X										X	
FVC ONLY									X					
Two 3mm punch biopsies ***		X									X			
MMF dosing**		X												
Daily stable Cellcept			X	X	X	X	X	X	X	X	X	X	X	
Rituximab infusion			X	X										
Subcutaneous Belimumab injections weekly					X****	X	X	X	X	X	X	X	X	

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

Schedule of Events (List)

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

Participants 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)

II. 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**

III. 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) Cellcept dose by this visit.

IV. 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

V. 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).

VI. 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**

VII. 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

Safety Assessments

Safety assessments will include the evaluation of adverse events, lab assessments, and physical examination.

- An adverse event is any occurrence or worsening of an undesirable or unintended symptom, sign, laboratory result, radiological finding, or disease state that is temporally associated with the use of a medical product, whether or not related to the medical product. Adverse events will be categorized by body system; general, CNS, cutaneous, cardiovascular, ENT. Gastrointestinal, genitourinary, hematologic, pulmonary, musculoskeletal, and PNS. The major categories of adverse events are mortality, hospitalizations, infections, malignancies, and drug-induced cystitis. The presence of these adverse events will be checked for and recorded at each visit. All adverse events will be appropriately collected, graded and reported by the study investigators. Throughout the study, the physician investigator will treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize.
- Unexpected adverse events are those that are not listed or identified in the package insert or in the investigator's protocol
- Serious adverse events (SAE) or reaction is defined as any adverse event occurring at any dose that suggests a significant hazard, contraindication, side effect or precaution. This includes, but may not be limited to, death, life-threatening occurrences, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect, or any event that required intervention to prevent permanent impairment or damage. Adverse events classified as serious according to the definition set forth by the health authorities will be reported promptly to the appropriate health authorities.

Efficacy Assessments

Primary Efficacy Assessments

American College of Rheumatology Composite Response Index in Diffuse Cutaneous Systemic Sclerosis (ACR CRISS): The primary efficacy assessment is the change in CRISS at 1 year. The ACR CRISS was developed using expert consensus and data driven approaches for use in clinical trials (Khanna et al, 2016). The exponential algorithm determines the predicted probability of improvement from baseline, incorporating change in the mRSS, FVC percent predicted, physician and patient global assessments, and HAQ-DI. The outcome is a continuous variable between 0.0 and 1.0 (0 – 100%). A higher score indicates greater improvement. Subjects are not considered improved (ACR CRISS score = 0) if they develop new: 1) renal crisis; 2) decline in FVC% predicted by 15% (relative) from baseline and confirmed after 1 month; or 3) left ventricular failure (systolic ejection fraction < 45%); or 4) new pulmonary artery hypertension on right heart catheterization requiring treatment.

Secondary Safety and Efficacy Assessments

The Modified Rodnan skin score: The MRSS is a validated physical examination method for estimating skin induration. It is correlated with biopsy measures of skin thickness and reflects prognosis and visceral involvement, especially in early disease2, 4. It is scored on a 0 (normal) to 3+ (severe induration) ordinal scales over 17 body areas, with a maximum score of 51 and is used to categorize severity of SSc. Minimally clinically significant difference in MRSS is 3-5 points (Amjadi et al., American College of

Rheumatology; Aug 2009; 2493-2494) It has been extensively used as primary/ secondary outcome in RCT with Scleroderma. This will be collected at every study visit.

Patient global assessment for Overall Health (PtGA): This assessment represents the patient's assessment of the patient's global scleroderma on a 0-10 Likert scale. "On a scale of 0-10, how was your overall health in the last week? 0=Excellent; 10=Extremely Poor. Assessed at every study visit.

Physician global assessment for overall disease (MDGA): This assessment represents the physician's assessment of the patient's current disease activity on a 0-10 Likert scale. "On a scale of 0-10, how was your patient's overall health in the last week? 0=Excellent; 10=Extremely Poor". Assessed at every study visit.

Scleroderma Health Assessment Questionnaire – Disability Index (SHAQ-DI): The SHAQ-DI is a disease-targeted, musculoskeletal-targeted measure intended for assessing functional ability in scleroderma. It is a self-administered 20-question instrument that assesses a patient's level of functional ability and includes questions that involve both upper and lower extremities. The SHAQ-DI score ranges from 0 (no disability) to 3 (severe disability). It has a 7 day recall period and has been extensively used in SSc65, 67. 5 visual analog scales are included in the scleroderma-HAQ assessing burden of digital ulcers, Raynaud's, gastrointestinal involvement, breathing, and overall disease 68. Assessed at every study visit.

Pulmonary function tests, Forced Vital Capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO): Forced expiratory maneuvers will be performed at least in triplicate with the minimal requirement that three maneuvers are "acceptable" and that two of these maneuvers meet end-of-test and repeatability criteria for FVC and FEV1. DLCO is a measure of lung disease severity. Lung testing will be performed at visits Baseline 1, Visit 3, Visit 5, with a full PFT with DLCO being measured at Baseline 1, and Visit 5.

Short Form-36 (SF-36): On Short Form-36 (SF-36) forms, individuals with SSc score significantly lower than healthy controls in domains of physical component score, mental component score, physical functioning, role-physical, bodily pain, general health, and mental health (Iudici et al, 2013).

PROMIS-29: The PROMIS-29 Short Form, most current version (currently Version 2.0), will be used to assess patient-reported state of health on Visits 1, 3, and 5. The National Institutes of Health established the Patient Reported Outcomes Measurement Information System (PROMIS) (www.nihpromis.org) to create a standardized and uniformly scored set of patient-reported-outcomes instruments. The PROMIS network developed item (question) banks and short forms in more than 20 health domains as well as a set of global health items and 29-, 43-, and 57-item profile measures. To create a brief, practical-yet-inclusive short profile, a consensus-building process was used to identify 7 of these 20 domains to produce the PROMIS-29. The 7 domains specifically relate to physical, mental and social health and cover the most relevant areas of self-reported health for most people with chronic illness: pain, fatigue, depression, anxiety, sleep, physical function, and sexual function. The PROMIS-29 includes 4 items each from these 7 core PROMIS domains as well as one 11-point rating scale for pain intensity. Norm-based scores have been calculated for each domain, such that a score of 50 represents the mean of the general population (standard deviation = 10). High scores represent more of the domain being measured. Thus, on symptom-oriented domains of PROMIS-29 (anxiety, depression, fatigue, pain interference, and sleep disturbance), higher scores represent worse symptomatology. On the function-oriented domains (physical functioning and social role), higher scores represent better functioning.

The PROMIS-29 includes a single-item pain numerical rating scale for pain, which is a segmented numerical version of a VAS in which the respondent selects a whole number (0-10 integers) that best reflects the intensity of their pain. The numerical rating score is anchored by 2 terms describing average pain severity extremes, “no pain” (score of 0) and “worst pain imaginable” (score of 10). The recall period is 24 hours.
The use of PROMIS-29 has been validated in SSc (Hinchcliff et al, 2011). A single-item numerical rating score for pain in this format has been validated for scleroderma (El-Baalbaki et al, 2011, reviewed in Hawker et al, 2011).

UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Symptoms Questionnaire (UCLA SCTC GIT 2.0): The UCLA SCTC GIT 2.0 is a standardized set of outcome measures developed through literature review, patient focus groups and cognitive debriefing among patients with a variety of gastrointestinal disorders including irritable bowel syndrome, inflammatory bowel disease, other common gastrointestinal disorders, SSc, and a census-based US general population control sample (Khanna et al, 2009). The scale consists of eight domains relating to gastroesophageal reflux (13 items), disrupted swallowing (7 items), diarrhea (5 items), bowel incontinence/soilage (4 items), nausea and vomiting (4 items), constipation (9 items), belly pain (6 items), and gas/bloat/flatulence (12 items). The scales correlated significantly with both generic and disease-targeted legacy instruments, and demonstrate evidence of reliability.

Scleroderma Skin Patient Reported Outcome (SSPRO): The SSPRO includes patient-reported answers to 18 questions about how scleroderma affects the skin and how those skin problems affect how the person feels and does things. Each question is followed by 7 boxes with numbers 0-6, spaced equidistant in between. The boxes are anchored by 2 verbal descriptors, “Not at all” (box labeled 0) and “Very Much” (box labeled 6). The subject selects a box labeled by an integer in response to the question. The recall period is 1 week. The sum of the numbers associated with the answers to each question is the score. A higher score indicates worse skin symptoms.

Disease Activity Score 28 (DAS-28): The DAS28 (Disease Activity Score 28) is a system developed and validated by the EULAR (European League Against Rheumatism) to measure the progress and improvement of Rheumatoid Arthritis. DAS28 is often used in clinical trials for the development of RA. DAS28 values range from 2.0 to 10.0 while higher values mean a higher disease activity. A DAS 28 below the value of 2.6 is interpreted as Remission. The DAS28 is a development of the DAS which is more complex with regards to assessment. "28" describes the number of different joints including in the measurement: proximal interphalangeal joints (10 joints) metacarpophalangeal joints (10) wrists (2) elbows (2) shoulders (2) and knees (2). When looking at these joints, both the number of joints with tenderness upon touching and swelling are counted. In addition, the erythrocyte sedimentation rate is measured. Also, the patient makes a subjective assessment of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible".

Clinical Disease Activity Index (CDAI): The Clinical Disease Activity Index is calculated by adding the swollen joint count, tender joint count, patient global assessment, and the evaluator global assessment.

Global Rank Composite Score: The global rank composite score is an analytic tool that accounts for multiple disease manifestations simultaneously but does not measure disease activity or severity. It reflects how participants compare with one another on the basis of a hierarchy of ordered outcomes: death, event-free survival (survival without respiratory, renal, or cardiac failure), FVC, the score on the Disability Index of the Health Assessment Questionnaire (HAQ-DI; range, 0 to 3, with higher scores indicating more disability), and the modified Rodnan skin score. Participants who were alive at 54 months rank higher than those who died; those who survived event-free rank higher than those who had an event, and so forth down the hierarchy. With the assumption that transplant recipients would have worse early

outcomes but could fare better long-term than participants in the comparison group, the global rank composite score is intentionally constructed to treat early and late deaths (or events of organ failure) as equal, irrespective of timing. Variables that were used to define an event included death, respiratory failure (decrease from baseline of >30% in percent predicted DLco or >20% in percent predicted FVC), renal failure (long-term dialysis or renal transplantation), or cardiac failure (clinical congestive heart failure or left ventricular ejection fraction <30%).

The lowest three components of the global rank composite score are ordinal. They were defined by improvement (increase of ≥10% in the percentage of the predicted FVC, decrease of >0.4 in the HAQ-DI score, or decrease of ≥25% in the modified Rodnan skin score, as compared with baseline values), no change (neither improvement nor worsening), or worsening (decrease from baseline of ≥10% in the percentage of the predicted FVC, increase of >0.4 in the HAQ-DI score, or increase of ≥25% in the modified Rodnan skin score, as compared with baseline values). eft ventricular ejection fraction <30%).

Joint Count: A joint count is the most specific clinical method to quantify abnormalities in patients with rheumatoid arthritis (RA). The swollen joint count reflects the amount of inflamed synovial tissue and the tender joint count is associated more with the level of pain.

American College of Rheumatology Composite Response Index in Diffuse Cutaneous Systemic Sclerosis (ACR CRISS): The ACR CRISS was developed using expert consensus and data driven approaches for use in clinical trials (Khanna et al, 2016). The exponential algorithm determines the predicted probability of improvement from baseline, incorporating change in the mRSS, FVC percent predicted, physician and patient global assessments, and HAQ-DI. The outcome is a continuous variable between 0.0 and 1.0 (0 – 100%). A higher score indicates greater improvement. Subjects are not considered improved (ACR CRISS score = 0) if they develop new: 1) renal crisis; 2) decline in FVC% predicted by 15% (relative) from baseline and confirmed after 1 month; or 3) left ventricular failure (systolic ejection fraction < 45%); or 4) new pulmonary artery hypertension on right heart catheterization requiring treatment.

Columbia Suicide Severity Rating Scale (CSSRS): Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation [Bachen, 2009; Timonen, 2003; Stenager, 1992]. For this reason in studies of patients with autoimmune disease, patients should be clinically assessed for suicidal ideation and/or behavior at each visit. The CSSRS rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent and behaviors." Questions are phrased for use in an interview format, but the C-SSRS may be completed as a self-report measure if necessary. The scale identifies specific behaviors which may be indicative of an individual's intent to complete suicide. An individual exhibiting even a single behavior identified by the scale was 8 to 10 times more likely to complete suicide. The Screener contains 6 "yes" or "no" questions in which respondents are asked to indicate whether they have experienced several thoughts or feelings relating to suicide over the past month and behaviors over their lifetime and past 3 months. Each question addresses a different component of the respondent's suicide ideation severity and behavior. An answer of "yes" to any of the six questions may indicate a need for referral to a trained mental health professional and an answer of "yes" to questions 4, 5 or 6 indicate high-risk.

Adverse Event Reporting

Adverse Events

Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as anAE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

Serious Adverse Events (SAE)

Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

1. Results in death
2. Is life-threatening
3. NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
4. Requires hospitalisation or prolongation of existing hospitalisation
   NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
5. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE
6. Results in disability/incapacity, or
   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
7. Is a congenital anomaly/birth defect
8. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse
9. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT 3xULN and bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants)
   NOTE: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated

with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

Pregnancy

Any pregnancy that occurs during study participation must be reported to GSK. To ensure subject safety, each pregnancy must be reported within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be reported to GSK within 24 hours.

Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of study treatment and until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact.

Adverse Events of Special Interest:

In addition to the standard safety protocol language the following adverse events of special interest should be mentioned in the protocol and assessed for frequency in the final report.

- Serious Hypersensitivity or Infusion Reactions
- Serious infections, including herpes zoster and opportunistic infections
- Malignancy
- Suicidal thought, intent or behaviour

Communicating Safety Information: Safety information should be sent via email notification within 24 hours of awareness for all unblinded SAEs reported for subjects who received belimumab, regardless of Investigator/designee/Institution causality assessments to the GSK Central Safety Department: US.NAPS@gsk.com.

    - These SAEs include events reported from open-label studies and from subjects randomized to belimumab in double-blind studies in which the blind was broken (in stream and/or at end of study). Placebo cases should not be reported).
- In addition, all SAEs arising from the study that remain blinded on the Institution database during the course of the study, will be forwarded to GSK retrospectively by Institution using copies of regulatory reports (e.g., CIOMS 1 or MedWatch) and within five working days of Institution database unblinding, where study participants are exposed to belimumab, regardless of Investigator/designee/Institution causality assessments against belimumab.

In single country studies, there may be preference to carry out this reporting through the GSK Local Operating Company (LOC) safety department via their local mailbox. These details may be negotiated

and agreed upon at the time of contract development. Ultimately, there should be one point of contact within GSK to which this reporting is accomplished.. Spontaneous abortions must be reported as an SAE.

Regulatory Reporting Requirements for SAEs by Study Sponsor

The study Sponsor, is responsible for, and undertakes to, assess all clinical safety information arising during the Clinical Trial in order to generate all safety reports as required. Such safety reports will include, but may not be limited to, Individual Case Safety Reports ("ICSRs") for Suspected Unexpected Serious Adverse Reactions ("SUSARs") and, Development Safety Update Report(s) ("DSURs"). The study Sponsor is responsible for submitting such reports to all concerned regulatory authorities in all countries and regions where the Clinical Trial will be conducted, relevant Independent Ethics Committee(s) ("IEC") and individual Clinical Trial investigator(s), as required, within applicable timelines.

Unexpected Adverse Events

Unexpected adverse events are those that are not listed or identified in the package insert or in the investigator's protocol.

Assignment of Adverse Event Intensity

All adverse events will be recorded and classified according to the most recent version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events. The purpose of using this grading system is to provide a standard language to describe toxicities, to facilitate tabulation and analysis of data, and to facilitate the assessment of the clinical significance of all adverse events. Adverse events will be recorded and graded 1 to 5 according the grades provided below:

- Grade 1 = Mild adverse event
- Grade 2 = Moderate adverse event
- Grade 3 = Severe and undesirable adverse event
- Grade 4 = Life-threatening or disabling adverse event
- Grade 5 = Death

Relation to Study Therapy

The relation or attribution of an adverse event to an investigational product will be determined by the investigator and then recorded on the appropriate form. Adverse events will be assessed against the study therapy. Therefore, in determining the relatedness of an adverse event to study therapy, the investigator will have to report it as one of the following categories, also defined by the NCI's Common Terminology Criteria for Adverse Events:

1. Unrelated – the adverse event is clearly not related to the investigational agent.
2. Unlikely – the adverse event is doubtfully related to the investigational agent.
3. Possible – the adverse event may be related to the investigational agent.
4. Probable – the adverse event is likely related to the investigational agent.
5. Definite – The adverse event is clearly related to the investigational agent.

Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. To prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more adverse events.

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the event was administered, it should be recorded in the medical record.

Serious Adverse Event Collecting and Reporting

Following the participant's written consent to participate in the study, all AE/SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

All SAEs will be reported to the IRB within 5 working days of our being made aware of the SAE. Death will be reported immediately to the IRB. Additionally, all SAEs will be reported to the DSMB and GSK within one business day.

Drug Side Effects

Belimumab

The common name of the investigational product is BENLYSTA™. The generic (USAN/INN) name is belimumab.
Belimumab is a recombinant, human, IgG1□□monoclonal antibody specific for soluble human B lymphocyte stimulator (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

Recommended Subcutaneous Dosage Regimen

The recommended dosage is 200 mg once weekly given as a subcutaneous injection in the abdomen or thigh. Subcutaneous dosing is not based on weight. The injection is a clear to opalescent, and colorless to pale yellow solution in a single dose prefilled autoinjector or a single-dose prefilled glass syringe. The syringes will be packaged in a sleeve so that the placebo is not distinguishable from the active drug.

Administration Instructions for Subcutaneous Injection

- When given subcutaneously, It is recommended that the first two subcutaneous injections of belimumab should be under the supervision of a healthcare professional. Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as injection related systemic reactions, and monitor subjects closely. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions. A patient may subsequently self-inject or a patient caregiver may administer belimumab after the healthcare professional determines that it is appropriate
- In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed with intravenous belimumab. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions/injections. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions.
    - In studies utilizing the SC formulation, after the first 2 supervised injections and at the discretion of the investigator, subjects who are adequately trained may self-administer all subsequent doses at home. Comprehensive written instructions on injection technique are required to be provided to the study subject by the investigator. (Appendix 1) After the first and the second doses, subjects who do not feel adequately trained with self-injection may return to the site for further training. Patients who cannot self-administer the study agent must have a reliable resource (eg, a caregiver) to administer the subcutaneous injection. Patients or their caregivers should not administer the study agent until they receive proper training in subcutaneous injection technique.
- Subjects should be made aware of the potential risk of delayed onset acute hypersensitivity, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention in event of its development. For further information, see the belimumab IB.
- Subjects should remain under clinical supervision for 3 hours after completion of the first 2 SC injections. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions. Delayed- type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial edema. Patients treated with belimumab, including those receiving the subcutaneous formulation , should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

Rituximab

Rituxan® (rituximab) is a genetically engineered IgG1 kappa chimeric murine/human monoclonal antibody containing murine light- and heavy-chain variable region sequences and human constant region sequences. The chimeric antibody is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituximab is composed of 1,328 amino acids, and has an approximate molecular weight of 145 kilo Dalton (kD).

The antibody reacts specifically with the CD20 antigen found on the surface of malignant and normal B cells, and established B cell lines. Studies have shown that rituximab binds via its Fc domain to human complement and lyses lymphoid B cell lines by complement dependent cytotoxicity through the induction of apoptosis and via antibody-dependent cell mediated cytotoxicity. The drug is manufactured by Genentech, Inc. and by Biogen IDEC, Inc. Rituximab is supplied as a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials, which must be diluted before administration.

Risks

Given the enhanced B Cell suppression and more profound hypogammaglobulinemia anticipated as result of immunosuppressive combination therapy, potential risks include, but are not limited to, infection (both routine and opportunistic), psychiatric events, malignancy, and possible impact on effect of immunizations. In addition to these events of special interest associated with belimumab, other identified and potential risks for both agents should be considered in the risk mitigation strategy.

Rituximab: The rate of serious infections with rituximab in the Rheumatoid arthritis (RA) population is 4% per year. Reactivation of hepatitis B has also been very rarely reported in RA patients receiving rituximab. Late onset neutropenia occurs rarely in patients treated with rituximab. Belimumab: The rate of serious infections for SLE is 5% of subjects receiving either belimumab or placebo. Belimumab and Rituximab Coadministration Risks: Infections are expected events for both belimumab and rituximab. Cases of PML have been very rarely reported, including fatal events, for both rituximab and belimumab in autoimmune diseases. There is preclinical evidence for prolonged B cell suppression and more complete B cell depletion as well as effect on IgG1+ plasma cells in the long-lived bone marrow niche thought to be less sensitive to immunotherapy[30] with dual B cell immunotherapy. Assessment of the translatability of the IgG reductions to humans is difficult to make due to species differences in B cell biology and different treatments; however, the mouse data raises the hypothetical risk that immunoglobulin levels may reduce more with co-administration treatment.

Rituximab Dosage and Administration

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Do not infuse rituximab concomitantly with another IV solution or other IV medications.

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Infusion and hypersensitivity reactions may occur. Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of rituximab. Premedication with methylprednisolone 100mg IV x 1 will also be administered. Premedication may attenuate infusion-related events. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.

Administration Guidelines for Adult Patient Population

First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Rituximab infusion should be interrupted for severe reactions. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have completely resolved.

Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of rituximab therapy

Subsequent Infusions: If the subject tolerated the first infusion well, subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the first infusion was not well tolerated, the guidelines for the first infusion should be followed for the subsequent infusions.

Rituximab Storage

Rituximab vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. Rituximab vials should be protected from direct sunlight.

Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 24 hours. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2° to 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

Rituximab Overdose

There has been no experience with overdose of rituximab in human clinical trials.

Data Monitoring

A monitoring plan and data safety monitoring board (DSMB) will be established to review safety data and to make recommendations regarding continuation, termination, or modification of the study. The DSMB will review all safety issues on a quarterly basis or more frequently if required. Safety assessment will be the primary purpose of this quarterly interim analysis. The DSMB will also monitor closely for infections, immunoglobulin levels, and cytopenias. Treatment will be discontinued if immunoglobulin AEs become grade 4. If liver enzymes increase to >3 times the upper limit of normal, we will hold medication and check weekly liver function tests (LFTs) until enzymes return to normal range. The study may be stopped or amended because of significant safety concerns. The safety evaluations will be conducted on conventional safety variables, such as serious adverse events, laboratory tests, and vital sign changes. The DSMB may recommend that the study be stopped only for safety concerns. The DSMB will evaluate the study every quarter. All serious adverse events will be reported to the DSMB within 24 hours of occurrence. As the DSMB will be reviewing frequent safety reports and listing of SAEs, it can request to stop enrollment in the trial or stop study medications. Enrollment in the study will be stopped and administration of all study related medications will be suspended if any of the following occurs:

- One or more deaths within 24 hours of belimumab, rituximab, and/or MMF administration that is felt to be directly related to the medication by the investigator or the DSMB. In the event of such a case, the DSMB would be unblinded to treatment assignment, and only deaths directly related to Belimumab, rituximab, and/or MMF would count towards termination of the trial.
- Two of the first 5 patients enrolled experience Grade IV serious adverse events attributable to study medication
- Two of the first 5 patients enrolled exhibit a greater than 5 point increase in the Modified Rodnan Skin Score in 2 consecutive assessments

Statistical Plan

Sample Size

A total of 30 patients will be enrolled: 20 of whom will receive treatment with Belimumab and Rituximab and 10 of whom will receive placebo. This sample size provides 80% power at an 0.05 significance level to detect a ratio of mean CRISS scores of 1.2 when the ratio under the null hypothesis is 1.0 using a two-sided, two-sample t-test. This power calculation is valid as long as the coefficient of variation (COV) does not exceed 0.2.

For the primary endpoint analysis, the distribution of CRISS scores within each study arm will be assessed using the Shapiro-Wilk test. If scores are not approximately normally distributed, appropriate transformations will be made prior to analysis. Raw scores will be summarized within each study arm by mean ± standard deviation and median [interquartile range]. Comparisons of scores will be made using a two-sided, two-sample t-test.

The safety endpoint will be analyzed by reporting the proportion of patients within each study arm who experience one or more adverse events and who experience one or more serious adverse events. Comparisons will be made using Fisher's exact test. The total number of adverse events and of serious adverse events experienced by each patient will be compared between study arms using the Wilcoxon rank-sum test.

Other secondary endpoints will be evaluated similarly to the primary endpoint, using the Shapiro-Wilk test to determine the distribution of values and appropriately transforming if necessary. Comparisons will be made using two-sided, two-sample t-tests or Wilcoxon rank-sum tests if values cannot be appropriately transformed.

Although self-injection in this population is not expected to be a barrier to adherence, as-treated analysis will be done as well.

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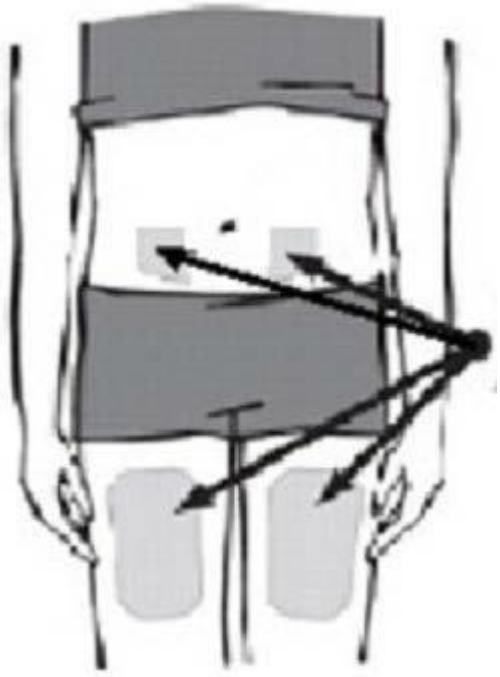
Appendix 1: Patient Subcutaneous Self-dosing instructions (pre-filled syringe)

1. Remove a syringe from the kit allowing it to warm to room temperature for no longer than 30 minutes.
2. Visually inspect the medication in the syringe. Only use the syringe if the:
    - Liquid is clear and free of particles
    - Liquid is colorless to light yellow in appearance
3. Obtain the following:
    - Alcohol swab
    - Sterile gauze
    - Container for syringe disposal
4. Wash your hands thoroughly with soap and water.
5. Choose an injection site: either left or right side of the abdomen or upper thigh. Choose a different site for each injection.



Injectable areas

6. Using a circular motion, clean the injection site with an alcohol swab and allow to dry.
7. Remove the protective cap from the syringe and discard.
8. Hold the syringe in the hand with which you will inject yourself.
9. Using your other hand, gently pinch the skin around the swabbed injection site.
10. Insert the entire needle at a slight angle (45° angle) into the pinched area of the skin.
11. Release the pinched skin and slowly push the plunger down until the entire contents of the syringe is injected.
12. Withdraw the needle from the skin and dispose the syringe in the proper container.
13. Wipe the injection site with gauze.

14. Remember to place used syringes in the container for syringe disposal and return the container to the study site at each visit.