A Phase II, Single-Site, Double-Blind, Placebo-Controlled Randomized Withdrawal Study Assessing the Efficacy and Safety of Sarilumab in Patients With Glucocorticoid-Dependent Sarcoidosis

Study Protocol and Statistical Analysis Plan

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TITLE: A phase II, single-site, double-blind, placebo-controlled randomized withdrawal study assessing the efficacy and safety of sarilumab in patients with glucocorticoid-dependent sarcoidosis

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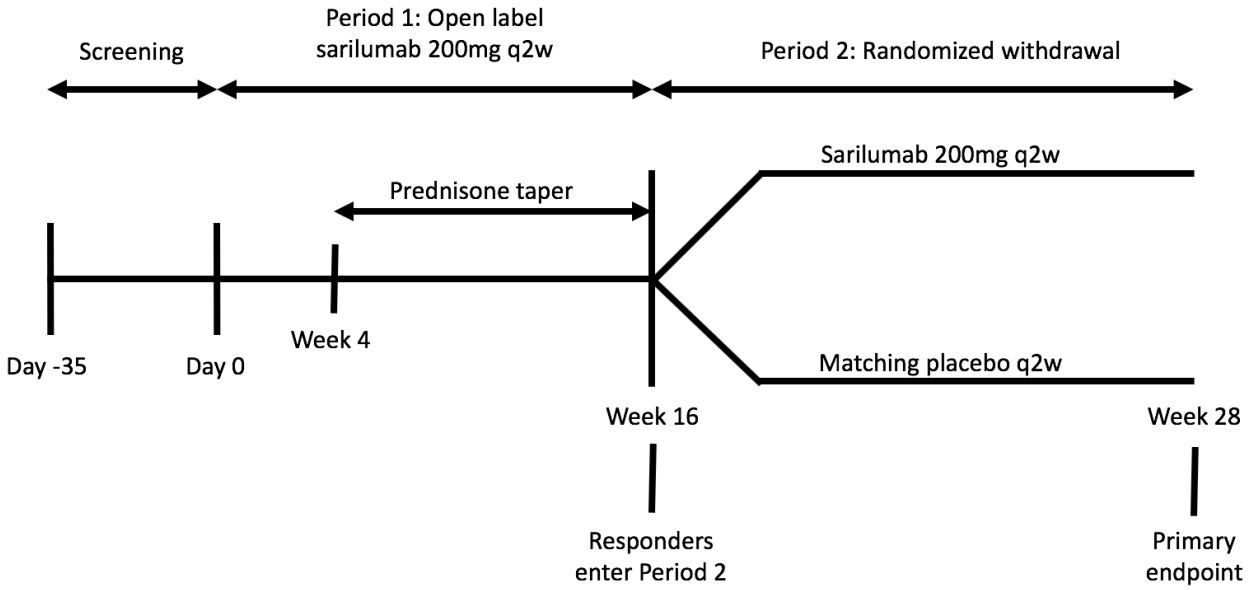
PROTOCOL SYNOPSIS

TITLE	A phase II, single-site, double-blind, placebo-controlled randomized withdrawal study assessing the efficacy and safety of sarilumab in patients with glucocorticoid-dependent sarcoidosis
STUDY PHASE	Phase IIb
INDICATION	Glucocorticoid-dependent sarcoidosis
INVESTIGATIONAL PRODUCT OR PROCEDURE	Sarilumab
PRIMARY OBJECTIVE(S)	To demonstrate that sarilumab treatment is effective for inducing and maintaining glucocorticoid-free remission in male or female patients aged 18 to 75 with biopsy proven, active, glucocorticoid-dependent sarcoidosis
SECONDARY OBJECTIVE(S)	To determine the number of patients in glucocorticoid-free remission and the change in prednisone dose compared to baseline at Week 16, after the open-label period (Period 1) of the study. Additional secondary objectives at both Week 16 and Week 28 are to demonstrate that sarilumab treatment is effective for reducing disease manifestation-specific metrics, for improving laboratory parameters, and for reducing cumulative prednisone dose. An important secondary objective is to demonstrate safety in this patient population.
TREATMENT SUMMARY	During Period 1 of this study, fifteen patients will receive sarilumab 200mg subcutaneously every two weeks in an open-label fashion. Subjects will continue their background disease modifying anti-rheumatic drug (DMARD) therapies and current glucocorticoid dose (prednisone ≥ 10 mg and ≤ 60 mg daily or alternate glucocorticoid equivalent is required for study entry). During the screening period, all patients will change their glucocorticoid to prednisone with stable dosing for at least 14 days before their baseline visit. If a patient is on a prednisone dose between 40 mg daily and 60 mg daily, the dose will be

	reduced to 40 mg daily by the end of week 3 at the clinician's discretion. Starting at week 4, all patients will begin a scheduled prednisone taper that will take place from week 4 until week 16. Patients will be required to adhere to this tapering protocol. If a violation in the tapering schedule occurs, the patient will be deemed a nonresponder. Patients will be required to fill out a daily steroid diary to clearly document their daily prednisone intake. All attempts will be made to perform a pill count at each visit. During Period 2 of the study (starting at Week 16), the patients that responded in Period 1 will be randomized to withdraw from sarilumab. Patients will be assigned in a blinded, 1:1 fashion to receive either sarilumab 200mg subcutaneously every two weeks or matching placebo.
SAMPLE SIZE	15 patients
STATISTICAL CONSIDERATIONS	The sample size for Period 1 of the trial of 15 patients was calculated based on the assumption that 80% of the patients will respond to open-label sarilumab, allowing for 12 patients to enroll in the randomized withdrawal Period 2 of the study. The sample size of 12 for Period 2 was calculated based on the assumption that 85% of the placebo group (roughly 5 out of 6) will flare (i.e., require reinitiation of prednisone) over the subsequent 12 weeks compared to 15% (roughly 1 out of 6) in the sarilumab group. This relative hazard of 0.20 gives a power of 80% with an alpha of 0.05 to detect a difference between treatment groups assuming Kaplan-Meier analysis. A sample size of 15 was deemed recruitable at Stanford after searching the Stanford medicine Research data Repository (STARR), which is a clinical data warehouse containing all patients seen at Stanford Hospital and Clinics. A search for patients

	between the ages of 18 and 75 who were given the diagnosis code for sarcoidosis on at least two separate occasions within the last year and who are currently on prednisone, yields 200 potential patients. Assuming half of these are coded correctly, and one-third of those truly have glucocorticoid-dependent, refractory disease, that leaves roughly 30 patients to screen, half of which we anticipate will be eligible for, and willing to participate in, the study. Our IRB will allow us to identify specific patients within STARR whom we can contact to determine their interest in the study.

SCHEMA


Screening
Period 1: Open label
sarilumab 200mg q2w
Period 2: Randomized withdrawal
Sarilumab 200mg q2w
Prednisone taper
Week 4
Day -35
Day 0
Matching placebo q2w
Week 16
Week 28
Responders
enter Period 2
Primary
endpoint

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACE	Angiotensin converting enzyme
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Anti-nuclear autoantibody
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BSA	Body surface area
CBC	Complete blood count
CIB	Clinical investigation brochure
CK	Creatinine kinase
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
DMARDs	Disease modifying anti-rheumatic drugs
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
FACIT	Functional assessment of chronic illness therapy
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
IL-6	Interleukin-6
IL-6-R	Interleukin-6 receptor
IP	Investigational product
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
NSAIDs	Non-steroidal anti-inflammatory drugs
OS	Overall survival
PFTs	Pulmonary function tests
PK	Pharmacokinetic
PLT	Platelet
PR	Partial response
QD	Once daily
RBC	Red blood cells
RF	Rheumatoid factor
RR	Response rate
SAE	Serious adverse event
SD	Standard deviation
SEM	Standard error of the mean

SJC	Swollen joints count
TB	Tuberculosis
TEAEs	Treatment emergent adverse events
TJC	Tender joints count
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

1.1. Primary Objective

The primary objective of this study is to determine if sarilumab treatment is effective for inducing and maintaining glucocorticoid-free remission in male or female patients aged 18 to 75 with biopsy proven, active, glucocorticoid-dependent sarcoidosis affecting any organ other than the heart or the central nervous system.

1.2. Secondary Objectives

Secondary objectives of this study are to determine the number of patients in glucocorticoid-free remission and the change in prednisone dose compared to baseline at Week 16, after the open-label period (Period 1) of the study. Additional secondary objectives at both Week 16 and Week 28 are to demonstrate that sarilumab treatment is effective for reducing disease manifestation-specific metrics, for improving laboratory parameters, and for reducing cumulative prednisone dose. An important secondary objective is to demonstrate safety in this patient population.

2. BACKGROUND

2.1 Sarcoidosis

Sarcoidosis is a rare disease, but one that carries a high risk of morbidity and mortality with a 5 and 10-year mortality rate of 4 and 9% [1]. The prevalence is estimated at 10-20 per 100,000 of the general population, with roughly 50,000 people affected in the United States [2]. The incidence varies by region and ethnicity; the disease is roughly four times more common in blacks. Sarcoidosis typically presents between the ages of 20 and 60 and a higher mortality exists in patients older than 55, non-Hispanic African Americans, and women [1]. The lungs are affected in the vast majority of patients (~90%), leading to fatigue, dyspnea, and often pulmonary fibrosis which can result in death. When the liver is affected, it can cause hepatic failure requiring transplantation. Ocular inflammation can permanently damage the eye, skin rashes are disfiguring, enlarged lymph nodes and glands can be painful, and inflammatory arthritis can be debilitating.

Sarcoidosis is often chronic, requiring long-term immunosuppression. There are no established guidelines for the treatment of sarcoidosis, but the mainstay therapy is glucocorticoids. It is well established that prolonged use of glucocorticoids has a number of harmful effects, including glucose intolerance, osteoporosis, weight gain, hypertension, hyperlipidemia, infection, insomnia, cataracts, gastrointestinal perforation, and mood changes [3-5]. Thus, it is essential for patients who do not respond to glucocorticoids to be treated with additional agents in hopes of minimizing exposure to steroids. Typically, a disease modifying anti-rheumatic drug (DMARD), such as methotrexate or azathioprine, is added to prednisone. When this fails, and for severe manifestations, more potent drugs are used such as cyclophosphamide or a biologic drug such as a TNF-inhibitor. Despite these therapies, many patients have ongoing sarcoidosis symptoms and organ injury.

2.2 Sarilumab

Sarilumab is a recombinant human monoclonal antibody of the immunoglobulin G1 (IgG1) kappa isotype directed against the interleukin-6 receptor α-subunit (IL-6Rα). Sarilumab binds to human

IL-6Rα and has been demonstrated to block interleukin-6 (IL-6) mediated signaling. Sarilumab, formulated for subcutaneous (SC) injection at doses of 150 and 200 mg every 2 weeks (q2w), was approved for the treatment of RA in Canada on 12 January 2017, the United States (US) on 22 May 2017, European Union (EU), Norway, Iceland, and Liechtenstein on 23 June 2017, and Japan on 27 September 2017. Sarilumab is also in Phase 2 development for the treatment of polyarticular-course juvenile idiopathic arthritis (pcJIA) in pediatric patients.

As of 12 January 2018, the global sarilumab RA clinical development program consisted of 10 Phase 1clinical pharmacology studies and 9 Phase 2/3 studies.

Phase 1 studies:
Of the 10 Phase 1 clinical pharmacology studies, 8 studies were conducted in patients with RA receiving methotrexate (MTX) and 1 study was conducted in healthy subjects. All but 2 of these studies (TDR10805/6R88-RA-0802 and INT12684) were single dose studies.

Phase 2/3 studies in RA:
Of the 9 Phase 2 and 3 studies of the global RA program, 5 studies have been completed (EFC11072/SARIL-RA-MOBILITY, EFC10832/SARIL-RA-TARGET, SFY13370/SARIL-RA-ASCERTAIN, EFC13752/ SARIL-RA-ONE, MSC12665/SARIL-RA-EASY); 2 were prematurely terminated (ACT11575 and EFC11574/SARIL-RA-COMPARE) due to the operational feasibility and lack of ability to provide a timely result versus the plan but not due to any safety issue; and 2 studies are ongoing: the open-label extension part of EFC14092/SARIL-RA-MONARCH (double-blind part of this study has been completed) and the uncontrolled extension Phase 3 study LTS11210 (SARIL-RA-EXTEND) that enrolled patients from studies EFC11072, EFC10832, EFC13752, SFY13370, and ACT11575.

The global RA program has enrolled patients with RA from over 40 countries worldwide, who required alternatives to oral disease-modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor alpha (TNF-α) antagonists because of inadequate control of disease activity or intolerance to these agents. This program entered Phase 2/3 with an operationally seamless study, EFC11072, consisting of a combined dose-ranging (Phase 2) part and a confirmatory (Phase 3) part, which was conducted in patients with active RA who were inadequate responders to MTX therapy.

In the dose-ranging part of the study (EFC11072/Part A), 5 dose regimens (100 mg q2w, 150 mg q2w, 200 mg q2w, 100 mg every week [qw], and 150 mg qw) and placebo were tested in 306 randomized patients. The demographic and disease characteristics at baseline were similar across all treatment groups.

Based on an in-depth analysis of the Phase 2 study results, the 150 mg q2w and 200 mg q2w doses were selected for evaluation in 2 pivotal Phase 3 trials in RA (EFC11072 Part B and EFC10832) where sarilumab was tested as a combination therapy with a conventional DMARD.

In the Phase 3 confirmatory part of EFC11072 (Part B), both sarilumab dose groups showed clinically relevant and statistically significant ($p<0.0001$) improvements compared with placebo in all 3 co-primary endpoints: improvement in signs and symptoms of RA at 24 weeks (as defined by 20% improvement on American College of Rheumatology [ACR] definition of improvement

criteria [ACR20]), improvement in physical function (as assessed by Health Assessment Questionnaire Disability Index [HAQ-DI]) at Week 16 and inhibition of progression of structural damage at Week 52. Study EFC11072 Part B, Cohort 2 (where patients were randomized to either placebo or one of 2 selected doses: 150 mg q2w or 200 mg q2w) demonstrated that sarilumab 200 mg q2w and 150 mg q2w inhibited the 1-year rate of radiographic progression by 91% and 68% relative to placebo, respectively.

In addition to study EFC11072, efficacy of sarilumab was demonstrated in study EFC10832, conducted in patients who had an inadequate response or intolerance to one or more TNF-α antagonists. For the primary endpoints of ACR20 at Week 24 and HAQ-DI at Week 12, significant improvement was observed in patients treated with sarilumab 200 mg q2w and 150 mg q2w compared with placebo, showing that patients who previously had an inadequate response or intolerance to TNF-α antagonists responded to treatment with sarilumab.

Although demonstration of efficacy was not the primary objective for the other Phase 3 clinical trials in RA where sarilumab was administered either as monotherapy (EFC13752, EFC14092) or with concomitant DMARD therapy (SFY13370 and MSC12665), clinical efficacy profiles in these studies were consistent with results from the active-controlled Phase 3 studies in the global program (EFC11072 Part B, and EFC10832).

Patients who completed studies EFC11072, EFC10832, EFC13752, and SFY13370 had the option to enroll in the ongoing long-term extension study LTS11210 at the highest tested dose (200 mg q2w). In this study, the efficacy of sarilumab administered concomitantly with DMARDs was sustained for the duration of the available follow-up period: approximately 3.8 years and 2.1 years for patients initially randomized in EFC11072 Part B and EFC10832, respectively. The persistence of efficacy was consistent across all the domains of treatment of RA, namely signs and symptoms, structural damage, and physical function.

Safety:
For the patients treated with sarilumab and concomitant DMARD, a higher incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to discontinuation were observed in the sarilumab treatment groups compared to the placebo group. The incidence of TEAEs leading to death was similar in sarilumab and placebo groups.

In the placebo-controlled population, compared to the placebo group, higher incidences of TEAEs, SAEs, and TEAEs leading to discontinuation were observed in sarilumab 200 mg q2w or 150 mg q2w + DMARD treatment groups relative to the placebo + DMARD group. These differences were generally attributable to higher rates of the AESIs associated with IL-6 blockade, specifically infections and laboratory abnormalities (including decrease in absolute neutrophil count (ANC) and platelet count, increase in transaminase and lipids) in the sarilumab + DMARD groups.

The observations with regards to adverse event (AE) and laboratory parameters with long-term administration were consistent with what was observed in the placebo-controlled population, and no safety findings were identified as attributable to long-term administration.

Other diseases:
Sarilumab was studied in ankylosing spondylitis (AS) patients in the DRI11073 study. Patients who completed the DRI11073 study had the possibility of enrolling in the LTS11298 long-term safety study if appropriate. The DRI11073 study failed to demonstrate clinical efficacy and the clinical development in this indication has been terminated. Consequently the LTS11298 study was prematurely discontinued. Overall, the safety observations from these studies conducted in patients with AS were consistent with has been observed in patients with RA.

Sarilumab was also evaluated in a randomized double-blind Phase 2 study of patients with noninfectious uveitis (NIU) (ACT13480/SARIL-NIU-SATURN). Although the primary efficacy endpoint of a 2 step reduction in vitreous haze (VH) or reduction in steroid dose was not met, significant improvements were observed for key secondary endpoints such as change from baseline in adjudicated VH at Week 16, change from baseline in best-corrected visual acuity (BCVA) at Week 16, and change from baseline central retinal thickness (CRT) at Week 16. Furthermore, changes in adjudicated VH, BCVA, and CRT were maintained at Week 52. No new safety signals have been detected with sarilumab use in NIU compared with other indications. The AEs and laboratory changes were consistent with results observed in studies with sarilumab in RA patients and with IL-6 inhibition.

The FDA has approved sarilumab for the treatment of rheumatoid arthritis. It is not FDA approved for the treatment of sarcoidosis, however this clinical investigation is exempt from an IND as it meets the following requirements:

- Sarliumab is lawfully marketed in the United States
- The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug
- The investigation is not intended to support a significant change in the advertising for the drug
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk associated with the drug
- The investigation is conducted in compliance with the requirements for review by the Stanford IRB and with the requirements for informed consent
- The investigation is not intended to promote or commercialize the drug

2.3 Rationale

Sarcoidosis is a chronic illness, requiring long-term immunosuppression. There are no established guidelines for the treatment of sarcoidosis, but the mainstay therapy is glucocorticoids. It is well established that prolonged use of glucocorticoids has a number of harmful effects, including glucose intolerance, osteoporosis, weight gain, hypertension, hyperlipidemia, infection, insomnia, cataracts, gastrointestinal perforation, and mood changes [3-5]. Thus, it is essential for patients who do not respond to glucocorticoids to be treated with additional agents in hopes of minimizing exposure to steroids. Typically, a disease modifying anti-rheumatic drug (DMARD), such as methotrexate or azathioprine, is added to prednisone. When this fails, and for severe manifestations, more potent drugs are used such as cyclophosphamide or a biologic drug such as a TNF-inhibitor. Despite these therapies, many patients have ongoing sarcoidosis symptoms and organ injury.

Interleukin-6 (IL-6) is elevated in the blood and bronchoalveolar (BAL) fluid of patients with sarcoidosis [6, 7]. This inflammatory cytokine leads to B cell differentiation into antibody-secreting cells. Patients with sarcoidosis have elevated blood levels of immunoglobulins, consistent with B cell hyperactivation [7]. In addition, these activated B cells can serve as highly affinity-matured antigen presenting cells for T cells. IL-6 also stimulates T cells directly and specifically induces Th17 T cell development. Th17 cells are elevated in sarcoidosis and likely contribute to disease pathogenesis through secretion of IL-17 and interferon-gamma (IFN-γ) [8-10]. IL-6 additionally inhibits Treg differentiation, thereby decreasing the population of cells responsible for restraining the effector T cell response [11].

Sarilumab binds the IL-6 receptor and prevents its activity. It has been studied extensively in rheumatoid arthritis (RA), and has been shown to improve disease activity, radiographic findings, and markers of inflammation [12-15]. Given sarilumab's efficacy and favorable safety profile, it is now FDA-approved for the treatment of RA. Sarilumab has never been tested in sarcoidosis patients, and we believe it will have similar efficacy when given to this patient population. There are limited options in the management of sarcoidosis, and determining whether novel approaches such as sarilumab are useful for improving patients' quality of life and for decreasing morbidity and mortality is critical.

2.4 Study Design

The primary purpose of this study is to evaluate sarilumab in the treatment of sarcoidosis. The first period of this trial, Period 1, is single-arm and open-label, in which all patients will receive sarilumab. The second period, Period 2, is a two-arm, randomized withdrawal study in which half of the patients will receive sarilumab and half will receive matching placebo. Period 2 will be double blind. The primary outcome of the study is designed to evaluate efficacy of sarilumab in the treatment of sarcoidosis.

2.5 Correlative Studies Background

A plasma sample (5 ml) will be collected for future biomarker analysis at Baseline, Week 16, and Week 28. This will be used to study cytokines including IL-6 levels. Peripheral blood mononuclear cells will also be collected at Baseline, Week 16, and Week 28. These will be used to characterize the immune response before and after treatment.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

(1.) Men and women of all races and ethnicities age 18 to 80.
(2.) Biopsy proven non-caseating granulomas consistent with sarcoidosis, with negative infectious studies including AFB and fungal stains, and with compatible clinical and/or radiographic manifestations of sarcoidosis.
(3.) Involvement of the lungs (stage II or III pulmonary sarcoidosis), lymph nodes, liver, kidneys, spleen, bone, soft tissues, skin, and/or eyes.
(4.) At least one active manifestation, defined by the need for ongoing glucocorticoid treatment to control a sign or symptom of sarcoidosis, which requires treatment with prednisone (or equivalent

corticosteroid) ≥ 10 mg and ≤ 60 mg daily (i.e. glucocorticoid dependence), with stable dosing for ≥ 28 days prior to baseline. If patients are taking a glucocorticoid other than prednisone, they will be changed to prednisone at the equivalent dose and take this daily for ≥ 14 days prior to baseline.
(5.) DMARDs including methotrexate, leflunomide, azathioprine, mycophenolate mofetil, and/or anti-malarials (i.e. hydroxychloroquine) will be permitted, but the regimen must be stable for ≥ 28 days prior to baseline and remain stable during follow-up.
(6.) Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

(1.) Patients < 18 years of age or > 80 years of age.
(2.) Stage IV pulmonary sarcoidosis.
(3.) Central nervous system sarcoidosis.
(4.) Cardiac sarcoidosis.
(5.) Prior treatment with an anti-IL-6 therapy.
(6.) Treatment with a biologic agent including rituximab, belimumab, TNF inhibitors, abatacept, or IL-17 inhibitors administered within 28 days prior to baseline (6 months for rituximab).
(7.) Treatment with cyclophosphamide within 3 months prior to baseline.
(8.) Treatment with prednisone < 10 mg or > 60 mg daily.
(9.) Known hypersensitivity or allergy to the study drug.
(10.) History of, or current, inflammatory or autoimmune disease other than sarcoidosis which would present a safety issue or confound interpretation of the data.
(11.) Prior or current history of other significant concomitant illness that, according to the investigator's judgment, would adversely affect the patient's participation in the study. These include, but are not limited to, cardiovascular (including stage III or IV cardiac failure according to the New York Heart Association classification), neurological (including demyelinating disease), active infectious diseases, or history of diverticulitis or gastrointestinal perforation.
(12.) Patients currently pregnant or breast-feeding.
(13.) Women of childbearing potential (WOCBP) who are unwilling to utilize adequate contraception and unwilling to not become pregnant during the full course of the study (must be willing to be tested for pregnancy). Adequate contraceptive measures include oral contraceptives (continuous use, as per prescription, for 2 or more cycles prior to screening), intrauterine devices, contraceptive sponges, condoms or diaphragms plus foam, or jelly, or surgical procedures such as bilateral tubal ligation or vasectomy in partner.
(14.) Administration of a live/attenuated vaccine within 30 days.
(15.) Evidence of active tuberculosis, HIV, or hepatitis B or C infection.
(16.) History of cancer other than non-melanoma skin cancer.
(17.) Patients with any of the following laboratory abnormalities at the screening visit: hemoglobin <8.5 g/dL, white blood cells <3000/mm3, neutrophils <2000/mm3, platelet count <150,000 cells/mm3, aspartate aminotransferase (AST) or ALT >1.5 x ULN, and/or bilirubin (total) above the upper limit of normal (unless Gilbert's disease has been determined by genetic testing and documented).
(18.) Presence of severe uncontrolled hypercholesterolemia (>350 mg/dL, 9.1 mmol/L) or hypertriglyceridemia (>500 mg/dL, 5.6 mmol/L) at screening or baseline.
(19.) Patients with calculated creatinine clearance <30 mL/minute (using Cockroft-Gault formula).
(20.) History of alcohol or drug abuse within 5 years prior to the screening visit.
(21.) Participation in any clinical research study evaluating another investigational drug or therapy

within 5 half-lives or 60 days of first investigational medicinal product (IMP) administration, whichever is longer.
(22.) Any patient who has had surgery within 4 weeks prior to the screening visit or with planned surgery during the course of the study.

3.3 Informed Consent Process

All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant will receive a copy of the signed and dated consent document. The original signed copy of the consent document will be retained in the medical record or research file.

3.4 Randomization Procedures

In Period 2 of the study, patients will be randomized to sarilumab or matching placebo. This will be done by our administrative assistant Angelica Aberia using a computer-generated random number. An odd number will be assigned to sarilumab and an even number will be assigned to placebo. Only Angelica will be aware of the assignment and she will communicate this directly to the Investigational Pharmacy. The investigators and patients will remain blinded. The codebook with the patient assignments will be stored by Angelica in a secure, locked file cabinet.

3.5 Study Timeline

Primary Completion:
The study will reach primary completion 15 months from the time the study opens to accrual.

Study Completion:
The study will reach study completion 24 months from the time the study opens to accrual.

4. TREATMENT PLAN

At Screening, vital signs will be obtained, a physical examination performed, and complete medical history obtained. **Routine clinical laboratory tests** (including a chemistry panel, complete blood count, urinalysis, spot urine protein and creatinine, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), urine pregnancy test), **sarcoidosis-related laboratory tests** (including angiotensin converting enzyme (ACE), total immunoglobulins (IgG), urine calcium, 25-hydroxy vitamin D, and **safety laboratory tests** (including serum pregnancy test for females, HIV test, hepatitis B test, hepatitis C test, and quantiferon test for tuberculosis) will be performed. An electrocardiogram and chest x-ray will also be obtained. At Baseline and Week 16, routine clinical laboratory tests and sarcoidosis-related laboratory tests will be repeated, and in addition the following tests will be performed at Baseline (and only repeated at Week 16 if abnormal at Baseline): pulmonary function tests, chest computed tomography, creatinine kinase (CK), aldolase, and lactose dehydrogenase (LDH). At Week 28, routine clinical laboratory tests and sarcoidosis-related laboratory tests will be repeated. At visits 3-11, vital signs, a physical examination, a medical history, and routine clinical laboratory tests will be obtained, urine pregnancy test for WOCBP. At Baseline, Week 16, and Week 28 the ePOST, global patient VAS, global physician VAS, HAQ, and FACIT-F will be assessed. Also at Baseline, Week 16, and Week 28, eight green

top tubes will be collected and processed for plasma and peripheral blood mononuclear cells, which will be stored at -80°C for future research.

During Period 1 (Baseline through Week 16), all subjects will receive 200mg of sarilumab subcutaneously every two weeks. During Period 2 (Week 16 through Week 28), half of the subjects who responded in Period 1 will receive 200mg of sarilumab subcutaneously every two weeks and half of the subjects will receive matching placebo in a double-blinded fashion.

4.1 General Concomitant Medication and Supportive Care Guidelines

Patients will be allowed to continue background DMARDs including methotrexate, leflunomide, azathioprine, mycophenolate mofetil, and/or anti-malarials. These are standard drugs used in the treatment of sarcoidosis. The regimen must be stable for ≥ 28 days prior to baseline and remain stable during follow-up. Patients will also be on ≥ 10 mg and ≤ 60 mg daily of prednisone or equivalent glucocorticoid to be eligible for the study and will follow a scheduled taper. Patients will undergo blood draws during the study. During blood draws, a patient may have pain and/or bruising at the place on his/her arm where blood is taken. Blood clots may form and infections may occur, but these events are rare. He or she may feel faint or lightheaded. They will also have an electrocardiogram. There may be minor discomfort and/or skin irritation at the site where the electrodes (sticky pads) are placed on the skin for the recording of the ECG. They will also have a chest x-ray. Radiation exposure from a chest x-ray is equivalent to the amount of radiation exposure one would experience from 10 days of natural radiation (such as sunlight). They will also have a non-contrast chest computed tomography. Radiation exposure from a computed tomography of the chest is equivalent to roughly 70 times the amount of radiation from a chest x-ray. They will undergo pulmonary function testing. There may be minor discomfort from the deep breathing required to complete pulmonary function testing. If they have known or suspected ocular sarcoidosis, they will have an ophthalmologic evaluation with fluorescein angiography. This will involve dilating the pupils, which often makes it difficult to see clearly and in bright lights after the eye exam for a few hours. For the angiography, patients will receive an injection of a dye called fluorescein. There may be minor discomfort from the needle at the site of injection. There may also be bruising at the site of injection. The most common side effects of this dye are nausea and vomiting; however, occasional allergic reactions, fainting, breathing difficulties, or shock may occur. The dye may stain your skin and urine; which may last approximately for 1 day. Mild reactions such as itching, swelling, or redness near where the dye is put in your vein are more common and have been estimated to happen in about 1 out of 100 times. Rare severe allergic reactions can also happen during the fluorescein dye test. People allergic to shellfish may be at increased risk for an allergic reaction to fluorescein or other dye. However, individuals with allergies to shellfish can receive a medication before the dye test to minimize allergic responses. Serious allergic reactions such as severe swelling and difficulty breathing can happen in 1 out of 10,000 patients and about 1 out of 222,000 patients can have a heart attack, stroke, or even die from the fluorescein dye administration.

4.2 Criteria for Removal from Study

The study will be placed on hold for safety monitoring board review in the case of a death, a serious adverse event related to the drug, or a Grade 4 treatment emergent adverse event or laboratory

abnormality. The safety monitoring committee will determine if the study can resume and if the patient should remain in the study or be removed. A patient may withdraw from the study at any time if they choose to withdraw their consent.

4.3 Alternatives

Risks to the patient will be minimized through frequent clinic visits and appropriate laboratory testing. In addition, all data will be reviewed by the investigators, as well as the safety monitoring board, which will meet every 6 months.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Sarilumab

Sarilumab (SAR153191), also designated as REGN88, is co-developed by Sanofi and Regeneron. Sarilumab is a recombinant human monoclonal antibody of the IgG kappa isotype directed against the alpha subunit of the IL-6 receptor (IL-6Rα). Sarilumab is a potent and specific inhibitor of IL-6 mediated signaling. By binding to IL-6Rα with high affinity, sarilumab blocks the binding of IL-6 and interrupts the cytokine-mediated signaling cascade. Interleukin-6 is a key element in the etiology of rheumatic conditions and inhibition of its signaling is a critical part of the mechanism of action of sarilumab.

For complete information on mechanism of action, summaries of animal and clinical studies, non-clinical and clinical pharmacokinetics, major route of elimination, safety profile, please see the Investigator's Brochure.

5.1.1 Summary of nonclinical studies

Sarilumab has been evaluated in a series of in vitro experiments to quantify the affinity of the antibody for IL-6Rα and the ability to block the binding and signaling of IL-6. In addition, the role of the Fc effector function in the mechanism of action of the antibody was evaluated in vitro. The equilibrium binding affinity (KD) of sarilumab to human IL-6Rα was determined by surface plasmon resonance (SPR) Biacore to be approximately 54 pM. Similar studies with cynomolgus monkey IL-6Rα indicate a KD of 123 pM. The similar affinities of sarilumab for monkey and human IL-6Rα indicate that monkeys are a relevant species for performing nonclinical studies. In contrast, no binding of sarilumab to murine IL-6Rα was observed, suggesting that rodents are not a useful model system for pharmacology or toxicology studies. In vitro, sarilumab completely blocked the binding of a 200 nM concentration of human IL-6 to human IL-6Rα, as demonstrated by SPR-Biacore; in a competition enzyme-linked immunosorbent assay, sarilumab blocked binding of a 100 pM constant concentration of dimeric human IL-6Rα to human IL-6 with an IC50 of 108 pM. In vitro cell-based assays demonstrate that sarilumab blocks IL-6-dependent signal transducer and activator of transcription 3 (STAT3) activation in the HepG2 human hepatocarcinoma cell line, and blocks trans-signaling induced by a combination of IL-6 and soluble IL-6Rα in an engineered human embryonic kidney 293 (HEK-293) cell line that overexpresses gp130 but does not express IL-6Rα. No detectable Fc effector function activity was associated with sarilumab, as determined in vitro in cell-based assays for antibody-dependent cell-mediated cytotoxicity and complement-

dependent cytotoxicity. In total, these in vitro data are consistent with sarilumab exerting its actions through blockade of the IL-6/IL-6Rα interaction.

Sarilumab does not bind to mouse IL-6R; therefore, the surrogate REGN844 antibody (an IL-6R antibody that cross reacts with mouse receptor) was used for the murine model experiments. In vitro, REGN844 binds specifically to mouse IL-6Rα with high affinity and inhibits IL-6 stimulated mouse B-cell proliferation. A study with sarilumab was performed in double-humanized (IL-6hu/hu IL-6Rαhu/hu) mice expressing human IL-6 and the human ectodomain of IL-6Rα instead of the equivalent mouse gene products. In double-humanized IL-6/IL-6Rα mice, sarilumab prevents turpentine-induced elevation of serum amyloid A (SAA), a key biomarker of the acute phase inflammatory response. For studies in wild type mice, REGN844 was tested. In concordance with the PD activity of sarilumab in double-humanized mice, REGN844 prevents turpentine-induced elevation of SAA and mitigated disease incidence, severity and bone erosion in a collagen induced arthritis model.

5.1.2 Summary of clinical studies

As of 12 January 2018, the global sarilumab RA clinical development program consisted of 10 Phase 1clinical pharmacology studies and 9 Phase 2/3 studies.

Phase 1 studies:
Of the 10 Phase 1 clinical pharmacology studies, 8 studies were conducted in patients with RA receiving methotrexate (MTX) and 1 study was conducted in healthy subjects. All but 2 of these studies (TDR10805/6R88-RA-0802 and INT12684) were single dose studies.

Phase 2/3 studies in RA:
Of the 9 Phase 2 and 3 studies of the global RA program, 5 studies have been completed (EFC11072/SARIL-RA-MOBILITY, EFC10832/SARIL-RA-TARGET, SFY13370/SARIL-RA-ASCERTAIN, EFC13752/ SARIL-RA-ONE, MSC12665/SARIL-RA-EASY); 2 were prematurely terminated (ACT11575 and EFC11574/SARIL-RA-COMPARE) due to the operational feasibility and lack of ability to provide a timely result versus the plan but not due to any safety issue; and 2 studies are ongoing: the open-label extension part of EFC14092/SARIL-RA-MONARCH (double-blind part of this study has been completed) and the uncontrolled extension Phase 3 study LTS11210 (SARIL-RA-EXTEND) that enrolled patients from studies EFC11072, EFC10832, EFC13752, SFY13370, and ACT11575.

The global RA program has enrolled patients with RA from over 40 countries worldwide, who required alternatives to oral disease-modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor alpha (TNF-α) antagonists because of inadequate control of disease activity or intolerance to these agents. This program entered Phase 2/3 with an operationally seamless study, EFC11072, consisting of a combined dose-ranging (Phase 2) part and a confirmatory (Phase 3) part, which was conducted in patients with active RA who were inadequate responders to MTX therapy.

In the dose-ranging part of the study (EFC11072/Part A), 5 dose regimens (100 mg q2w, 150 mg q2w, 200 mg q2w, 100 mg every week [qw], and 150 mg qw) and placebo were tested in 306 randomized patients. The demographic and disease characteristics at baseline were similar

across all treatment groups.

Based on an in-depth analysis of the Phase 2 study results, the 150 mg q2w and 200 mg q2w doses were selected for evaluation in 2 pivotal Phase 3 trials in RA (EFC11072 Part B and EFC10832) where sarilumab was tested as a combination therapy with a conventional DMARD.

In the Phase 3 confirmatory part of EFC11072 (Part B), both sarilumab dose groups showed clinically relevant and statistically significant ($p<0.0001$) improvements compared with placebo in all 3 co-primary endpoints: improvement in signs and symptoms of RA at 24 weeks (as defined by 20% improvement on American College of Rheumatology [ACR] definition of improvement criteria [ACR20]), improvement in physical function (as assessed by Health Assessment Questionnaire Disability Index [HAQ-DI]) at Week 16 and inhibition of progression of structural damage at Week 52. Study EFC11072 Part B, Cohort 2 (where patients were randomized to either placebo or one of 2 selected doses: 150 mg q2w or 200 mg q2w) demonstrated that sarilumab 200 mg q2w and 150 mg q2w inhibited the 1-year rate of radiographic progression by 91% and 68% relative to placebo, respectively.

In addition to study EFC11072, efficacy of sarilumab was demonstrated in study EFC10832, conducted in patients who had an inadequate response or intolerance to one or more TNF-α antagonists. For the primary endpoints of ACR20 at Week 24 and HAQ-DI at Week 12, significant improvement was observed in patients treated with sarilumab 200 mg q2w and 150 mg q2w compared with placebo, showing that patients who previously had an inadequate response or intolerance to TNF-α antagonists responded to treatment with sarilumab.

Although demonstration of efficacy was not the primary objective for the other Phase 3 clinical trials in RA where sarilumab was administered either as monotherapy (EFC13752, EFC14092) or with concomitant DMARD therapy (SFY13370 and MSC12665), clinical efficacy profiles in these studies were consistent with results from the active-controlled Phase 3 studies in the global program (EFC11072 Part B, and EFC10832).

Patients who completed studies EFC11072, EFC10832, EFC13752, and SFY13370 had the option to enroll in the ongoing long-term extension study LTS11210 at the highest tested dose (200 mg q2w). In this study, the efficacy of sarilumab administered concomitantly with DMARDs was sustained for the duration of the available follow-up period: approximately 3.8 years and 2.1 years for patients initially randomized in EFC11072 Part B and EFC10832, respectively. The persistence of efficacy was consistent across all the domains of treatment of RA, namely signs and symptoms, structural damage, and physical function.

Safety:
For the patients treated with sarilumab and concomitant DMARD, a higher incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to discontinuation were observed in the sarilumab treatment groups compared to the placebo group. The incidence of TEAEs leading to death was similar in sarilumab and placebo groups.

In the placebo-controlled population, compared to the placebo group, higher incidences of

TEAEs, SAEs, and TEAEs leading to discontinuation were observed in sarilumab 200 mg q2w or 150 mg q2w + DMARD treatment groups relative to the placebo + DMARD group. These differences were generally attributable to higher rates of the AESIs associated with IL-6 blockade, specifically infections and laboratory abnormalities (including decrease in absolute neutrophil count (ANC) and platelet count, increase in transaminase and lipids) in the sarilumab + DMARD groups.

The observations with regards to adverse event (AE) and laboratory parameters with long-term administration were consistent with what was observed in the placebo-controlled population, and no safety findings were identified as attributable to long-term administration.

Other diseases:
Sarilumab was studied in ankylosing spondylitis (AS) patients in the DRI11073 study. Patients who completed the DRI11073 study had the possibility of enrolling in the LTS11298 long-term safety study if appropriate. The DRI11073 study failed to demonstrate clinical efficacy and the clinical development in this indication has been terminated. Consequently the LTS11298 study was prematurely discontinued. Overall, the safety observations from these studies conducted in patients with AS were consistent with has been observed in patients with RA.

Sarilumab was also evaluated in a randomized double-blind Phase 2 study of patients with noninfectious uveitis (NIU) (ACT13480/SARIL-NIU-SATURN). Although the primary efficacy endpoint of a 2 step reduction in vitreous haze (VH) or reduction in steroid dose was not met, significant improvements were observed for key secondary endpoints such as change from baseline in adjudicated VH at Week 16, change from baseline in best-corrected visual acuity (BCVA) at Week 16, and change from baseline central retinal thickness (CRT) at Week 16. Furthermore, changes in adjudicated VH, BCVA, and CRT were maintained at Week 52. No new safety signals have been detected with sarilumab use in NIU compared with other indications. The AEs and laboratory changes were consistent with results observed in studies with sarilumab in RA patients and with IL-6 inhibition.

5.1.3 Intervention

In Period 1, patients will all receive sarilumab in an open-label fashion. They will be provided with prefilled syringes containing 1.14 mL of sarilumab (equally 200mg), which they will administer subcutaneously every two weeks. This dose was chosen based on studies in rheumatoid arthritis that showed efficacy at this dose, and this is the FDA approved dose for the treatment of rheumatoid arthritis. In Period 2 of the study, patients will be randomized to withdraw from sarilumab and receive placebo or continue sarilumab. Sarilumab and placebo will be provided in identically matched glass prefilled syringes. Each prefilled syringe will contain 1.14 mL of sarilumab or matching placebo.

5.2 Availability

Sarilumab and matching placebo will be provided by Regeneron.

5.3 Agent Ordering

Study IP and matching placebo will be sent from Regeneron to the Stanford University Hospital investigational pharmacy where it will be appropriately stored in a locked facility. The drug shipment address is Stanford Health Care, Attention: Investigational Drug Service, 300 Pasteur Drive, Room H0302, Stanford, CA 94305. Phone: 650-736-1990.

5.4 Agent Accountability

All investigational drug supplies will be kept in appropriate, secure area (a locked refrigerator in the locked pharmacy room) under the responsibility of the Stanford Investigational Pharmacy and will be stored separately from other medication and in the original carton as per specification mentioned on the label.

6. DOSE MODIFICATIONS

Sarilumab will be provided as a subcutaneous injection of 200 mg every two weeks. There will be no dosage modifications.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

The adverse drug reactions in Phase 3 trials (i.e., events potentially associated with sarilumab administration) are upper respiratory tract infection, nasopharyngitis, oral herpes urinary tract infection, neutropenia, leukopenia, thrombocytopenia, hypertriglyceridemia, injection site erythema, injection site rash, rash, urticaria, increased aspartate aminotransferase, and increased ALT.

Based on the preclinical and clinical studies of sarilumab as well as the safety profile of another IL-6 inhibitor (tocilizumab) and other biological DMARDs, hypersensitivity reactions, serious infections, and neutropenia, are an important identified risk with sarilumab administration. Important potential risks are thrombocytopenia and the potential risk of bleeding, clinically evident hepatic injury, an impact on CV outcome (MACE) secondary to LDL elevation, GI perforations, and malignancy.

7.2 Adverse Event Reporting

All AEs regardless of seriousness or relationship to IMP/NIP, spanning from the signature of the informed consent form, until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) included in the CRF. Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP. Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if they are medically relevant: symptomatic or requiring either corrective treatment or consultation or leading to discontinuation or modification of

dosing and/or fulfilling a seriousness criterion and/or is defined as an AE with pre-specified monitoring.

7.2.1 Serious Adverse Events

In the case of a serious adverse event the Investigator must immediately:

- ENTER (within 24 hours of knowledge) the information related to the SAE in the CRF and notify the DSMC.
- SEND a copy of all examinations carried out and the dates on which these examinations were performed, to Regeneron. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly mentioned on any copy of source document. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the CRF as appropriate, and further documentation as well as additional information (for Lab data, concomitant Medication, patient status) should be sent (by fax or e-mail) to the Monitoring Team within 24 hours of knowledge. In addition, any effort should be made to further document each Serious AE that is fatal or life threatening within the week (7 days) following initial notification.
- Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Laboratory Correlative Studies

Patient blood will be drawn in the Stanford phlebotomy lab and transported to the main clinical lab in the Stanford University Hospital for processing. The following blood and urine tests will be performed per the study calendar: chemistry panel, complete blood count with differential, erythrocyte sedimentation rate, C-reactive protein, angiotensin converting enzyme, quantitative immunoglobulins, 25-hydroxy vitamin D, serum pregnancy test, HIV-1/2 serology, hepatitis B serology, hepatitis C serology, quantiferon TB test, creatinine kinase, aldolase, lactate dehydrogenase, urine pregnancy test, urinalysis, urine protein/creatinine, and urine calcium. In addition, roughly 40 mL of research blood will be collected in heparin containing tubes and sent to the Stanford Clinical and Translational Research Unit (CTRU). Plasma and peripheral blood mononuclear cells (PBMCs) will be extracted. Plasma samples will be stored at -70 degrees for future study. PBMCs will be stored in liquid nitrogen for future study.

9. STUDY CALENDAR

	Screen Day -35 to 0	Baseline Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 18	Week 20	Week 24	Week 28	Week 34	ET	Unscheduled visit
Written IC	X													
Randomization		X												
Medical history	X													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete PE	X											X	X	
Limited PE		X	X	X	X	X	X	X	X	X	X			X
ePOST		X					X				X		X	
Global VAS patient		X					X				X		X	
Global VAS physician		X					X				X		X	
FACIT-F and HAQ		X					X				X		X	
Routine clinical labs:														
Chemistry panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/diff	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis, urine P/C	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR, CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy		X	X	X	X	X	X	X	X	X	X	X	X	X
Sarcoidosis labs:														
ACE level	X	X					X				X		X	
Immunoglobulins	X	X					X				X		X	
Urine calcium	X	X					X				X		X	
25-hydroxy vit D	X	X					X				X		X	
Safety labs:														
Serum pregnancy	X													
HIV-1/2 serology	X													
Hepatitis B serology	X													
Hepatitis C serology	X													
QuantiFERON TB	X													
Screening tests:														
EKG	X													
Chest x-ray	X													
Sarcoid-specific tests:														
Pulm Function Test		X					X							
CT chest		X					X							
CK, aldolase, LDH		X					X							
Research labs:														
Plasma		X					X				X			
PBMCs		X					X				X			
Review AEs and meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensing		X		X	X	X	X		X	X	X			
Drug accountability			X	X	X	X	X	X	X	X	X		X	

10. MEASUREMENTS

10.1 Primary and Secondary Outcome measures

Primary endpoint: The primary endpoint is the flare-free survival of sarilumab-treated patients compared to placebo-treated controls in the double-blind randomized withdrawal period (Period 2) from Week 16 to Week 28. Patients will be considered to have flared if they receive rescue medication including increased glucocorticoids, or if they discontinue the study treatment in order to start a different therapy.

Secondary endpoints: The following secondary endpoints will all be assessed at Week 16 and Week 28 compared to baseline as a paired analysis: the change in the extrapulmonary physician organ severity tool (ePOST) score (17 organs rated 0-6, for a total score range of 0-102) [16], the change in global score of sarcoidosis using a visual analogue scale (VAS) by both the patient and physician (distance in mm measured on a 10 cm line), the change in FACIT-F score (fatigue scale ranging from 0-52 with higher score meaning less fatigue), the change in the Health Assessment Questionnaire (HAQ), the change in prednisone dose, the change in serum angiotensin converting enzyme (ACE), serum immunoglobulin G (IgG) levels, serum calcium, urine calcium, and serum 25-hydroxy vitamin D (25-OH-vit D), the change in pulmonary function tests (FVC, FEV1, and DLCO), the change in ALT, AST, and alkaline phosphatase, the change in serum creatinine and urine protein levels, the change in the Sarcoidosis Activity and Severity Index for cutaneous sarcoidosis (7 parameters scored 0-4 for a total score range of 0-28) [17], the change in CK, aldolase, and LDH, and the change in size of sarcoidosis lesions (i.e. enlarged lymph nodes, hepatic nodules, pulmonary nodules) by CT imaging. For patients with known or suspected ocular involvement, the secondary endpoint of change in ophthalmology global assessment of ocular sarcoidosis using a visual analogue scale (VAS) (distance in mm measured on a 10 cm line) [18] will be assessed, as well as the change in any one or more of the following parameters: best corrected visual acuity (BCVA), slit lamp examination (including grading of anterior chamber cells), tonometry, dilated indirect ophthalmoscopy (including grading of vitreous cells and haze), optical coherence tomography (OCT) and OCT angiography, color fundus photography, and fluorescein angiography.

From Week 16 to Week 28, time to flare will be compared between sarilumab-treated patients and placebo-treated controls as well as the proportion of patients in glucocorticoid-free remission at Week 28 between the two groups as additional secondary endpoints.

Safety will be assessed by counting and describing adverse events and abnormal laboratory results.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

We will form a Data and Safety Monitoring Committee (DSMC) consisting of two experience rheumatology clinicians at Stanford University. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

The Protocol Director and his team will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed as paper forms and will be kept in a locked office, only accessible to the research team.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

Patient characteristics including demographics, medical history, and concomitant medications will be summarized. The summaries will be done using descriptive statistics, eg, mean, standard deviation, median, minimum and maximum for quantitative values and counts and percents for qualitative variables.

The primary efficacy analysis of flare-free survival in Period 2 from Week 16 to Week 28 will use the intention-to-treat (ITT) population and will be assessed with Kaplan-Meier methods. **Patients will be considered to have flared in Period 2 if they receive rescue medication including increased glucocorticoids, or if they discontinue the study treatment in order to start a different immunosuppressive therapy.**

For Period 1, secondary endpoint variables will be treated as continuous and the values at Week 16 will be compared to Baseline values using Wilcoxon signed-rank tests. The number of patients in glucocorticoid-free remission at week 16 will be reported. Patients will be considered non-responders in Period 1 if they are unable to complete the glucocorticoid taper, receive rescue medication including increased glucocorticoids, or discontinue the study treatment in order to start a different therapy. For Period 1 secondary efficacy endpoints, non-responders will be included in the analysis only if their prednisone dose is equal to or less than the starting dose and stable for the 4 weeks preceding Week 16. The rationale for this is that patients who flare despite sarilumab therapy might be given high doses of steroids, thus improving their endpoints and falsely attributing the success to sarilumab. As a sensitivity analysis, we will also assess the secondary outcomes using the baseline observation carried forward (BOCF) for those patients deemed non-responders.

For Period 2, time to first flare will be compared using a 2-sided log-rank test. The proportion of patients in glucocorticoid-free remission at week 28 in sarilumab-treated patients compared to placebo controls will be analyzed using a Fisher's exact test. The remaining secondary endpoint variables will be treated as continuous and the values at Week 28 will be compared to Week 16 and to Baseline values using Wilcoxon signed-rank tests. We will not perform any corrections for multiple hypothesis testing due to the exploratory nature of this pilot study which solely aims to generate areas of potential future investigation.

12.2 Randomization

In Period 2 of the study, patients will be randomized to sarilumab or matching placebo. This will be done by our administrative assistant Angelica Aberia. This will be done using a computer-generated random number. An odd number will be assigned to sarilumab and an even number will be assigned to placebo. Only Angelica will be aware of the assignment and she will communicate this directly to the pharmacy. The investigators and patients will remain blinded.

12.3 Sample Size

The sample size for Period 1 of the trial of 15 patients was calculated based on the assumption that 80% of the patients will respond to open-label sarilumab, allowing for 12 patients to enroll in the randomized withdrawal Period 2 of the study. The sample size of 12 for Period 2 was calculated based on the assumption that 85% of the placebo group (roughly 5 out of 6) will flare (i.e. require reinitiation of prednisone) over the subsequent 12 weeks compared to 15% (roughly 1 out of 6) in the sarilumab group. This relative hazard of 0.20 gives a power of 80% with an alpha of 0.05 to detect a difference between treatment groups assuming Kaplan-Meier analysis. There is no published data on the use of sarilumab in sarcoidosis on which to base these assumptions. However, a parallel can be drawn between glucocorticoid-dependent sarcoidosis and glucocorticoid-dependent recurrent pericarditis, as they are both inflammatory and refractory to typical treatments. The latter condition has been studied with Anakinra, an interleukin 1β recombinant receptor antagonist [19]. In that study, 21 out of 21 patients (100%) had a complete response in Period 1 and were subsequently randomized to withdrawal during Period 2. In Period 2, 9 out of 10 (90%) patients receiving placebo had disease recurrence compared to 2 out of 11 patients (18%) receiving Anakinra. Although this is a different disease with a drug targeting a different inflammatory cytokine, there is precedent for a dramatic response in diseases like sarcoidosis using drugs like sarilumab. A sample size of 15 was deemed recruitable at Stanford after searching the Stanford medicine Research data Repository (STARR), which is a clinical data warehouse containing all patients seen at Stanford Hospital and Clinics. A search for patients between the ages of 18 and 75 who were given the diagnosis code for sarcoidosis on at least two separate occasions within the last year and who are currently on prednisone, yields 200 potential patients. Assuming half of these are coded correctly, and one-third of those truly have glucocorticoid-dependent, refractory disease, that leaves roughly 30 patients to screen, half of which we anticipate will be eligible for, and willing to participate in, the study. Our IRB will allow us to identify specific patients within STARR whom we can contact to determine their interest in the study.

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