A Phase 2 Randomized Double-Blinded Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Sarilumab in Improving the Quality of Life in Subjects with Indolent Systemic Mastocytosis

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List of Abbreviations

AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST	Aspartate transaminase
BTRIS	Biomedical Translational Research Information System
CBC/diff	Complete blood count with differential
CC	Clinical Center
CFR	Code of Federal Regulations
CRIMSON	Clinical Research Information Management System of the NIAID
CRP	C-reactive protein
CSO	Clinical Safety Office
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450 isozyme
DCR	Division of Clinical Research
DMARD	Disease-modifying antirheumatic drug
DSMB	Data and safety monitoring board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GRIS	Genomic Research Integration System
GTT	Green top tube
HRPP	Human Research Protections Program
ICH	International Council on Harmonisation
IL-6	Interleukin 6
IL-6R	Interleukin 6 receptor
IND	Investigational new drug
IRB	Institutional review board
ISM	Indolent systemic mastocytosis
ITT	Intent to treat
IV	Intravenous(ly)
LAD	Laboratory of Allergic Diseases
LTT	Lavender top tube
MC-QoL	Mastocytosis Quality of Life Questionnaire
mITT	Modified intent to treat
mITT2	Second modified intent to treat
mITT3	Third modified intent to treat
MQLQ	Mastocytosis Quality of Life Questionnaire
MSAF	Mastocytosis Symptom Assessment Form
MSAS	Memorial Symptom Assessment Scale
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections

OHSRP	Office of Human Subjects Research Protections
PCR	Polymerase chain reaction
PI	Principal investigator
PP	Per protocol
PT/PTT	Prothrombin/partial thromboplastin time
Q2W	Once every 2 weeks
QoL	Quality of life
SAE	Serious adverse event
SAR	Suspected adverse reaction
SC	Subcutaneous(ly)
SCORMA	Scoring of mastocytosis index
SERF	Safety expedited report form
SRCP	Safety review and communications plan
SST	Serum separator tube
SUSAR	Serious and unexpected suspected adverse reaction
ULN	Upper limit of normal
UP	Unanticipated problem

Protocol Summary

Full Title:	A Phase 2 Randomized Double-Blinded Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Sarilumab in Improving the Quality of Life in Subjects with Indolent Systemic Mastocytosis
Short Title:	Sarilumab for Treatment of ISM
Clinical Phase:	2
IND Sponsor:	OCRPRO/DCR/NIAID/NIH
Conducted by:	LAD/NIAID
PI:	Hirsh Komarow, MD
Sample Size:	N = 30
Accrual Ceiling:	N = 60
Study Population:	Participants will be aged 18 to 74 years-old who have been diagnosed with indolent systemic mastocytosis (ISM).
Accrual Period:	5 years
Study Design:	This will be a randomized, placebo-controlled double-blinded study. Thirty participants will be randomized (1:1) to receive 8 subcutaneous (SC) injections of 200 mg of sarilumab (trade name Kevzara) or placebo once every 2 weeks (Q2W) for 16 weeks. Participants will be evaluated at each study visit for improvement of symptoms of ISM and safety. Study visits for dose 4, 6, and 8 of study agent administration may be self administered at home without study assessments. After a 12-week washout period, all participants will be offered the opportunity to continue 200-mg sarilumab SC Q2W for 52 more weeks, with regular safety checkups.
Study Duration:	Start Date: October 2018 End Date: July 2027 Participants will be on study for up to 91 weeks, from screening through the end of the 1-year for open-label administration.
Study Agent/ Intervention Description:	Kevzara (sarilumab, Sanofi/Genzyme [Cambridge, MA. USA]), 200 mg/dose or placebo via SC injection Q2W for 16 weeks

	(8 doses), with the option to continue sarilumab at 200 mg Q2W for 52 more weeks.
Primary Objective:	To determine the efficacy and safety of 8 doses of sarilumab in improving the quality of life (QoL) in participants with ISM.
Secondary Objectives:	1. To assess the need for symptomatic relief with standard medicines. 2. To assess the effect of sarilumab on serum tryptase. 3. To investigate the effect of sarilumab on the allelic frequency of D816V *KIT* in peripheral blood. 4. To investigate the effects of sarilumab on bone marrow mast cell infiltrates.
Exploratory Objectives:	1. To assess the effect of sarilumab on end-organ targets of mastocytosis. 2. To evaluate the effect of sarilumab on skin manifestations. 3. To evaluate the effect of sarilumab on markers of bone marrow resorption and deposition. 4. To determine the long-term safety of sarilumab in participants with ISM.
Primary Endpoints:	1. QoL at 16 weeks post-initiation of study drug/placebo using the Mastocytosis Quality of Life Questionnaire (MC-QoL). 2. Frequency and severity of adverse events (AEs) during the randomized double-blinded placebo-controlled treatment period.
Secondary Endpoints:	1. Percent improvement in QoL from baseline to 16 weeks post-initiation of study drug/placebo using the MC-QoL. This is computed as [(Baseline QoL – 16-week QoL)/Baseline QoL] × 100. 2. Percent improvement in QoL using scoring of mastocytosis index (SCORMA), Memorial Symptom Assessment Scale (MSAS) the Mastocytosis Quality of Life Questionnaire (MQLQ), and the Mastocytosis Symptoms Assessment Form (MSAF). 3. Reduction in use of medicines for symptomatic relief. 4. Reduction in serum levels of tryptase. 5. Decrease in the allelic frequency of D816V using allele-specific polymerase chain reaction (PCR). 6. Reduction in percentage infiltrating mast cells in bone marrow.
Exploratory Endpoints:	1. Reduction in size of liver and spleen, as visualized by ultrasound. 2. Reduction in number of cutaneous lesions, as determined by SCORMA and photography.

3. Assessment of metabolic bone disease and bone turnover as determined by the peripheral blood markers, bone-specific alkaline phosphatase, osteocalcin, N terminal propeptide of type I procollagen, and crosslinked telopeptides of type I collagen.
4. Frequency and severity of AEs during the open-label treatment period.

Précis

Systemic mastocytosis is a disorder caused by clonal mast cell proliferation and release of mast cell mediators including tryptase. As a result, mast cell numbers may increase and affect target organs including the dermis (maculopapular cutaneous mastocytosis/urticaria pigmentosa, flushing), gastrointestinal tract (abdominal pain, diarrhea), skeletal system (osteoporosis), hematological system (anemia, thrombocytopenia), and spleen and liver (organomegaly). Patients with indolent (non-aggressive) systemic mastocytosis (ISM) are not candidates for cytoreductive therapy and are generally treated with symptomatic therapy that only partly decreases symptoms. There is, however, a documented association between severity of mastocytosis and elevated serum levels of interleukin (IL)-6. Furthermore, mast cells have been shown to double their rate of division and exhibit increased reactivity and release of mediators when cultured in the presence of IL-6. In addition, in an animal model of mastocytosis, anti-IL-6 has been shown to slow disease progression. In this study, adults with ISM will thus be randomized and treated with sarilumab, a recombinant monoclonal antibody directed against the IL-6 receptor, or receive placebo. Sarilumab is marketed in the United States as Kevzara (Sanofi/Genzyme [Cambridge, MA, USA]) and is approved by the Food and Drug Administration for the treatment of rheumatoid arthritis. Binding of sarilumab to the IL-6 receptor inhibits IL-6-associated human mast cell signaling and proliferation with a resultant decrease in proliferation and reactivity (decreased mediator release), and therefore is a rational choice for the treatment of ISM.

In this study, participants will be randomized with approximately half of the participants receiving study drug, which will be administered at 200 mg via subcutaneous (SC) injection once every 2 weeks (Q2W) for a total of 16 weeks. The other participants will receive a placebo administered via SC injection Q2W for 16 weeks. Participants will return for a follow-up visit 2 weeks after the final dose (treatment peak), and then again 12 weeks later. Evaluations at study visits will include quality of life and symptom assessments and measurement of serum tryptase levels. Bone marrow examination will be performed at the onset and conclusion of the study. After the week 28 visit, all participants will have the option to continue sarilumab for 52 more weeks, at 200 mg administered via SC injections. Participants will continue to be monitored on a regular basis for safety concerns, as instructed in the study drug’s package insert.

1 Background Information and Scientific Rationale

1.1 Background on Mastocytosis

Mastocytosis is clonal disorder of mast-cell proliferation that results in an increase in mast cells in the skin, bone marrow, and other organs systems.[1] Clinical features of mastocytosis include flushing, pruritus, abdominal pain, diarrhea, hypotension, syncope, and musculoskeletal pain. These features are attributed to both the local and systemic release of mast-cell mediators. The skin is almost always involved in adult patients with ISM in addition to the clinical features described. Greater than 90% of adult patients with ISM have an activating mutation in *KIT*, the receptor for stem cell factor (mast cell growth factor), which results in ligand-independent activation of KIT that is associated with disease pathogenesis. Life-threatening forms of mastocytosis including aggressive mastocytosis, systemic mastocytosis associated with a hematologic neoplasm, and mast cell leukemia are treated with cytoreductive therapy targeting this receptor, which may prolong life, but does not result in disease remission.

ISM, in contrast, is a less severe systemic variant, and patients with ISM are generally managed over the long term with symptomatic therapy that includes mediator blocking agents like H1 and H2 anti-histamines and leukotriene antagonists. Patients with ISM are not candidates for cytoreductive agents due to potential toxic side effects that outweigh the benefits. Unfortunately, symptomatic therapy is often unsuccessful in controlling symptoms and in most cases, disease continues to progress with both an increase in mast cell burden and symptoms.

Interleukin 6 (IL-6) is a pleiotropic cytokine involved in inflammation, infection, and cancer. IL-6 is produced by a number of cells including T cells, mast cells, and macrophages in response to infection and acute inflammation.[2] It facilitates interaction between stromal and immune cells, and has been associated with the pathogenesis of several human mast cell–related diseases.[3] IL-6 levels in peripheral blood have been correlated with severity of disease not only in systemic mastocytosis, but also in acute and chronic urticaria, and asthma.[4-8] Increased IL-6 levels in mastocytosis are correlated with bone marrow pathology, organomegaly, osteoporosis, levels of tryptase,[4] and risk for progression of systemic disease.[7] In vivo, IL-6 has also been shown to promote mast-cell maturation, proliferation, reactivity, and down-regulation of the soluble IL-6 receptor (IL-6R), thus promoting inflammation,[9] and IL-6 inhibition reduced oxidative stress in mutant mast cells.[10] Treatment of ISM with an IL-6 antagonist is thus a logical approach toward decreasing mast cell mediator release and the associated symptoms.

Based on this approach, we treated one patient who had severe cutaneous disease and ISM with tocilizumab for 6 months (8 mg/kg/month). This patient had been experiencing significant skin symptoms (pruritus, flushing) and gastrointestinal (GI) manifestations (daily vomiting, diarrhea, bloating, and abdominal pain) in addition to daily fatigue and joint pain. The patient tolerated the medication without any treatment-related AEs and showed a dramatic clinical response as assessed monthly using the MC-QoL.[11] Percentage improvement in comparison to baseline

assessment was determined to be between 67%-80% in the four QoL categories assessed (general, emotions, skin, social life) and total QoL scores. This response exceeded our expectation as defined by a primary endpoint of 50% improvement in overall QoL parameters. An improvement of 50% in QoL has been identified as clinically meaningful in other studies using tocilizumab in rheumatoid arthritis.[12] Our findings in this patient support the need for a blinded study that can more definitively provide data on efficacy and safety.

1.2 Sarilumab

As developed by Sanofi/Genzyme, sarilumab is a fully human anti-IL-6Rα monoclonal antibody that binds membrane-bound and soluble human IL-6R and has been shown to inhibit IL-6 signaling.[13] In 2017, the United States Food and Drug Administration (FDA) approved sarilumab for the treatment of rheumatoid arthritis. The drug's mechanism of action, in addition to its application in related inflammatory disorders[14] (eg, ankylosing spondylitis[15] and uveitis[16]) positions it as a plausible candidate for treatment of patients with systemic mastocytosis.

1.3 Scientific Rationale

Current treatment for ISM is directed at reduction of symptoms and improvement of QoL. The role of IL-6 in mast-cell proliferation and mediator release[9] suggests antagonist therapy has the potential to treat ISM, as well. Antagonist therapy with anti-IL-6R would be expected to decrease the release of mediators from mast cells and possibly mast cell number, thus providing a significant relief of symptoms. This is supported by our experience treating one ISM patient with the IL-6R antagonist tocilizumab, an FDA-approved treatment for rheumatoid arthritis, another disorder associated with IL-6-associated disease. Sarilumab, which is also an anti-IL-6R antibody that is indicated for treatment of rheumatoid arthritis, demonstrates a similar safety profile to tocilizumab. Sarilumab has also demonstrated a greater affinity for human IL-6R compared with tocilizumab,[17] so a clinical study to investigate its use in treating ISM is timely.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study will be to determine the efficacy and safety of 8 doses of sarilumab in improving QoL in participants with ISM.

2.2 Secondary Objectives

The secondary objectives will be:

1. To assess the need for symptomatic relief with standard medicines.
2. To assess the effect of sarilumab on serum tryptase.

3. To investigate the effect of sarilumab on the allelic frequency of D816V *KIT* in peripheral blood.
4. To investigate the effects of sarilumab on bone marrow mast cell infiltrates.

2.3 Exploratory Objectives

The exploratory objectives will include:

1. To assess the effect of sarilumab on end-organ targets of mastocytosis.
2. To evaluate the effect of sarilumab on skin manifestations.
3. To evaluate the effect of sarilumab on markers of bone marrow resorption and deposition.
4. To determine the long-term safety of sarilumab in participants with ISM.

3 Study Design

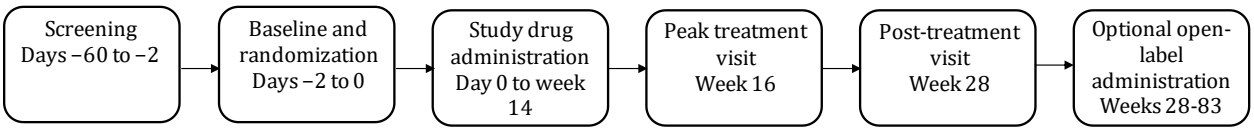
3.1 Description of the Study Design

This is a phase 2, double-blinded, randomized, placebo-controlled study to evaluate the efficacy of sarilumab as treatment for ISM. Patients with ISM will receive either 200 mg of sarilumab or placebo via SC injection Q2W for a total of 16 weeks (8 doses). Participants will return for a follow-up visit 2 weeks after the final dose (treatment peak), and then again 12 weeks later. Participants will be evaluated for clinical improvement of ISM-related symptoms, drug-related AEs, and molecular markers of ISM. After the week 28 visit, all participants will have the option to continue sarilumab for 52 more weeks, at 200 mg administered via SC injections. Participants will continue to be monitored on a regular basis for safety concerns, as instructed in the study drug's package insert.

Throughout the study, if a participant's lab results meet pausing criteria (section 12.6), then at the discretion of the PI, CSO, and data and safety monitoring board (DSMB), the dose may be temporarily reduced to 150 mg until the lab values return to normal.

A schematic of the study design is presented in Figure 1.

Figure 1 Study Schedule



3.2 Study Endpoints

3.2.1 Primary Endpoints

1. QoL at 16 weeks post-initiation of study drug/placebo using the MC-QoL.
2. Frequency and severity of AEs during the randomized double-blinded placebo-controlled treatment period.

3.2.2 Secondary Endpoints

1. Percent improvement in QoL from baseline to 16 weeks post-initiation of study drug/placebo using the MC-QoL. This is computed as [(Baseline QoL − 16-week QoL)/Baseline QoL] × 100.
2. Percent improvement in QoL using SCORMA, MSAS and MQLQ/MSAF.
3. Reduction in use of medicines for symptomatic relief.
4. Reduction in serum levels of tryptase.
5. Decrease in the allelic frequency of D816V using allele-specific PCR.
6. Reduction in percentage infiltrating mast cells in bone marrow.

3.2.3 Exploratory Endpoints

1. Reduction in size of liver and spleen, as visualized by ultrasound.
2. Reduction in number of cutaneous lesions, as determined by SCORMA and photography.
3. Assessment of metabolic bone disease and bone turnover as determined by the peripheral blood markers, bone-specific alkaline phosphatase, osteocalcin, N-terminal propeptide of type I procollagen, and crosslinked telopeptides of type I collagen.
4. Frequency and severity of AEs during the open-label treatment period.

4 Study Population

4.1 Recruitment Plan

All participants will be recruited from the NIAID study 02-I-0277, “Regulation of the Proliferation and Survival of Normal and Neoplastic Human Mast Cells.” Participants will also be screened on that study.

Recruitment of NIH staff: NIH staff, NIH contractors, NIH fellows and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the “NIH Information Sheet on Employee Research Participation.”

For NIH staff members:

- NIH staff may be a vulnerable class of participants.
- Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the participant's employment or work situation.
- The employee participant's privacy and confidentiality will be preserved in accordance with NIH CC and NIAID policies, which define the scope and limitations of the protections.
- For NIH staff participants, consent will be obtained by an individual independent of the staff member's team. Those in a supervisory position to any staff member and co-workers of the staff member will not obtain consent.
- The importance of maintaining confidentiality when obtaining potentially sensitive and private information from co-workers or subordinates will be reviewed with the study staff at least annually and more often if warranted.

4.2 Participant Inclusion Criteria

Participants must meet all of the following criteria to be enrolled in this study:

1. Male or female participant ≥ 18 and < 75 years of age at screening.
2. Enrolled on NIAID protocol 02-I-0277.
3. Documented pathologic diagnosis of ISM.
4. MC-QoL score of at least 25% (which suggests participant is at least somewhat affected by all McQoL questions).
5. Willing and able to undergo a bone marrow biopsy and aspirate.
6. Absolute neutrophil count (ANC) ≥ 2000/μL.
7. Hemoglobin ≥ 12.0 g/dL (males), ≥ 11 g/dL (females).
8. Platelet count ≥ 150,000/μL.
9. Alanine transaminase (ALT) and aspartate transaminase (AST) < 1.5 times the upper limit of normal (ULN).
10. Willing to allow storage of blood and bone marrow for future use in medical research.
11. Willing to allow genetic testing on biospecimens.
12. Able to provide informed consent.
13. Participants who can become pregnant must agree to use adequate contraception when engaging in sexual activities that can result in pregnancy. Adequate contraception must be used consistently, beginning at least 1 month before the beginning of dosing and lasting until 3 months after the final dose of study drug. Acceptable methods of contraception include the following:
    - Hormonal contraception (non-oral only).
    - Male or female condom with spermicide.
    - Diaphragm or cervical cap with a spermicide.

- Intrauterine device.

4.3 Participant Exclusion Criteria

Individuals meeting any of the following criteria will be excluded from study participation:

1. Any abnormality that would be scored as a Grade 4 toxicity on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Only clinically significant lab results will deem the subject ineligible
2. Infected with HIV or has other known immunodeficiency.
3. Has an active infection, including localized infection.
4. Active diverticulitis.
5. Active or chronic viral hepatitis.
6. Active or latent tuberculosis.
7. Use of any other anti-IL-6 or anti-IL-6R agent within 1 year prior to the date informed consent was obtained.
8. Use of cytoreductive therapy for mastocytosis within 1 year prior to the date informed consent was obtained.
9. Known lymphoma or advanced and metastatic solid tumors on active therapy (including chemotherapy) within 1 year prior to the date informed consent was obtained.
10. Use of chemotherapy within 1 year prior to the date informed consent was obtained.
11. Receipt of any marketed (eg, omalizumab) or investigational biologic or monoclonal antibody reported to affect mast cell activation within 5 half-lives prior to date informed consent was obtained.
12. Receipt of intravenous (IV) immunoglobulin within 30 days prior to the date informed consent was obtained.
13. Receipt of live attenuated vaccines within 30 days prior to the date informed consent was obtained.
14. History of alcohol or drug/abuse within 12 months prior to date informed consent was obtained.
15. Is allergic to any component of the sarilumab formulation.
16. Pregnant or breastfeeding.
17. Any condition that, in the opinion of the investigator, contraindicates participation in this study.

Co-enrollment guidelines: Co-enrollment in other trials is restricted, other than enrollment on observational studies. Study staff should be notified of co-enrollment as it may require the approval of the investigator.

4.4 Justification for Exclusion of Special Populations

Exclusion of pregnant women: It is not known whether this drug can cause fetal harm or adversely affect reproductive capacity in humans. The limited human data with this drug in pregnant women are not sufficient to inform drug-associated risk for major birth defects and miscarriage. Monoclonal antibodies are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero–exposed infant. Levels of immunoglobulin G, in response to antigen challenge, may be reduced in the fetus/infant of treated mothers. Therefore, to reduce risk, pregnant participants are excluded from this study.

Exclusion of breastfeeding women: There is an unknown but potential risk for sarilumab to be excreted in human milk, so there is the potential risk of AEs in nursing infants. Therefore, breastfeeding must have been discontinued before treatment with sarilumab begins.

Exclusion of children: Mastocytosis that is diagnosed in children often resolves by 18 years of age. This drug has also not been evaluated in pediatric patients. Therefore, the risk-benefit ratio would not justify targeting this population.

5 Study Agent/Interventions

5.1 Disposition and Dispensation

Sanofi/Genzyme will supply pre-filled syringes of sarilumab and placebo. Study agent and placebo will be distributed via the NIH pharmacy according to standard pharmacy procedures.

5.1.1 Formulation, Packaging, and Labeling

Each package will be individually labeled in the NIH pharmacy with the patient ID number, dosing instructions, recommended storage conditions, the name and address of the manufacturer, and that the agent should be kept out of reach of children.

5.2 Study Agent Storage and Stability

Syringes of sarilumab should be stored at 2°C-8°C and away from the light. Do not freeze. Syringes may also be stored in their outer carton at room temperature (< 25°C) for up to 14 days. The drug should not be used past the expiration date printed on the carton.[13]

5.3 Randomization and Blinding/Unblinding Procedures

Eligible participants will be allocated 1:1 to study agent or placebo. A randomization scheme will be generated by the study statistician who will provide a randomized list of arm assignments to the NIH CC Pharmacy. A permuted block approach, with varying block sizes, will be used for the randomization process.

The participants, the investigators, and all who are involved in the evaluation of the study participants including study monitors and central laboratory personnel are blinded to a participant's treatment assignment until all participants have completed the week 16 visit. The NIH research pharmacist is identified as the unblinded third party who will be in charge of treatment assignment, maintaining study supplies/inventory list, and preparing the blinded study medication for each participant. The NIH research pharmacist will be independent of any study assessments. To maintain blinding, any discussion of the treatment assignment between the clinicians and the pharmacy staff is prohibited until the study is unblinded. Unblinding will occur when the final participant completes their week 28 visit (section 6.2.5), or in the case of early termination or study drug discontinuation, after the participant's final study visit.

Participants will be assigned a screening number after completion of the protocol consent for enrollment in the study in the Clinical Research Information Management System of the NIAID (CRIMSON). The study statistician will generate the randomization codes. These codes will be maintained by the NIH research pharmacist. A study allocation number (1, 2, etc) will be assigned when the participant is ready to be randomized. Randomization is defined as the time that the pharmacy is notified that this new participant, with this study allocation number, is being enrolled. This should coincide with the day that the first dose of study drug is administered. Randomization will continue until there are 30 participants who initiate study drug and have at least the first post-baseline QoL measurement at 4 weeks. Note that participants who do not meet these criteria still remain in the study, and attempts to obtain subsequent QoL measures should be made.

5.3.1 Emergency Unblinding

If a participant experiences an AE whose management (eg, diagnostic procedures, treatment) in the opinion of the principal investigator (PI) or designee would differ depending on the study arm, or in the case of pregnancy, then the PI or designee will contact the NIH CC Pharmacy for release of the randomization code. The sponsor and DSMB executive secretary will be informed within 1 business day of any request for unblinding. The participant will remain enrolled in the study and the data will be used for analysis.

5.4 Preparation, Administration, and Dosage of Sarilumab and Placebo

Sarilumab is supplied in single-use pre-filled syringes (150 or 200 mg/1.14 mL) for SC injection. Placebo will be supplied by Sanofi/Genzyme in the same fashion in pre-filled syringes. The volume of the placebo dose is also 1.14 mL.

The pausing criteria are described in section 12.6. Participants who resume after a pause as a result of lab abnormalities may have their dose temporarily reduced from 200 to 150 mg, at the discretion of the PI (in consultation with the CSO), until these values return to stated thresholds (section 12.6.2), per the sarilumab package insert.[13]

5.5 Study Product Accountability Procedures

The NIH pharmacy will maintain accurate drug accountability records. A binder containing instructions and the required accountability documentation will be provided to the study pharmacist. When the study is completed, the accountability documentation will be maintained at the NIH CC per standard procedures. All unused study drug must be disposed of upon authorization by NIAID or its designee. All records regarding the disposition of study drug must be available for inspection by the study monitors and regulatory authorities.

5.6 Concomitant Medications and Procedures

All concomitant prescription and nonprescription (including over-the-counter) medications taken during study participation will be recorded. Reduction in medication use will be noted and documented based on clinic intake and participants will be required to maintain a medication change diary (Appendix H) for monitoring of medications. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

Various in vitro and limited in vivo human studies have shown that cytokines and cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes and therefore have the potential to alter the pharmacokinetics of concomitantly administered drugs that are substrate of these enzymes. Liver CYPs are downregulated by IL-6, so inhibition of IL-6 may restore liver CYP activity. Drug doses therefore may need to be modified in light of increased CYP-mediated metabolism, especially in drugs with a narrow therapeutic index. The effect of sarilumab on CYPs can persist for weeks after sarilumab therapy ends.[13] Therefore, drugs with a narrow therapeutic that are CYP metabolized will be identified and monitored for clinical effects and blood levels if necessary.

5.7 Prohibited Medications and Procedures

Participants may not receive any live vaccine while they are being treated with sarilumab because inhibition of IL-6 may obstruct the normal immune response.[13]

6 Study Schedule

All visits will take place at the NIH CC. Study participation will include an optional inpatient stay for approximately 3 days (baseline testing, randomization, and first dose administration), two full clinic days (screening and peak treatment, which both include a bone marrow examination), 4 half clinic days (doses 3, 5, 7, final study visit), and 4 short clinic visits (doses 2, 4, 6, 8) for AE assessment and injection only. For subjects opting to self administer study agent at home at doses 4, 6, and 8, a visit to NIH will not take place. No history, physical exam, AE collection, pregnancy test or diary review will take place for these subjects. A table of the study

schedule and procedures/evaluations is provided in Appendix A. A table of blood volumes to be collected at each visit is provided in Appendix B.

6.1 Screening (Days −60 to −2)

Informed consent will be obtained before the following screening tests are conducted:

1. Physical exam with vital signs, including height and weight.
2. Medical history/medication overview.
3. Assessment of ISM symptoms.
4. Blood draw for clinical evaluations:
   a. Complete blood count with differential (CBC/diff).
   b. Acute care, hepatic, and mineral panels.
   c. Serum tryptase.
   d. Prothrombin/partial thromboplastin time (PT/PTT).
   e. HIV test (anti-HIV-1/2 antibodies).
   f. Hepatitis B and C antibody test, B DNA, and C RNA.
   g. QuantiFERON Gold tuberculosis test.
5. Serum or urine pregnancy test (participants of childbearing potential only).
6. MC-QoL.
7. SCORMA.
8. MSAS.
9. MQLQ/MSAF
10. Bone marrow biopsy and aspirate (if not done at NIH within the last 150 days on protocol 02-I-0277).
11. *KIT* D816V mutation analysis on bone marrow and blood (if not done at NIH within the last 150 days)
12. Flow cytometry on bone marrow and blood (if not done at NIH within the last 150 days).
13. Ultrasound of abdomen.
14. Photography of affected areas.

6.2 Randomized, Double-Blinded, Placebo-Controlled Treatment Period

6.2.1 Baseline (Days −2 to 0)

After eligibility has been confirmed, participants will visit the NIH CC for baseline testing. Participants may be admitted as inpatients and will be randomized to receive sarilumab or placebo. The following procedures will then be done at baseline:

1. Physical exam with vital signs.
2. Overview of medical/medication history.
3. Assessment of baseline symptoms of ISM.

4. Assessment of AEs.
5. Blood draw for clinical evaluations:
   a. CBC/diff.
   b. Acute care, hepatic, and mineral panels.
   c. PT/PTT.
   d. Total protein.
   e. Lipid panel.
   f. Serum tryptase.
   g. C-reactive protein (CRP).
6. Urine or serum pregnancy test (for participants of childbearing potential only).
7. Blood draw for DNA and RNA collection.
8. Collection of serum (8 mL serum separator tube [SST]) for storage.
9. Serum IL-6 levels.
10. Serum markers of bone marrow resorption and deposition.
11. Plasma for storage (10 mL green top tube [GTT]).
12. Whole blood for storage (3 mL lavender top tube [LTT]).
13. MC-QoL.
14. SCORMA.
15. MSAS.
16. MQLQ/MSAF.
17. *KIT* D816V mutation analysis on blood.
18. Flow cytometry on blood.
19. Photography of affected areas (optional).
20. Skin punch biopsy (optional).

6.2.2 First Dose (Day 0)

Participants will receive either 200 mg of sarilumab or placebo via SC injection (see section 5.4). The participant will be monitored during administration and for 1 hour after to observe for any immediate drug-related AEs. Participants of childbearing potential must have had a negative pregnancy test at baseline before dose administration. Participants will be discharged after postdose monitoring if they have not experienced any serious hypersensitivity reactions. Hypersensitivity reactions will be treated as clinically appropriate. Before discharge, participants will be provided with a side effect and medication change diary (Appendix H), with instructions to fill it out in between visits as appropriate, and to bring it in for review to all future study visit.

6.2.3 Doses 2-8 (weeks 2, 4, 6, 8, 10, 12, 14 ± 4 days)

Participants will return to the NIH CC once every 2 weeks (± 4 days) to receive their next dose of study drug or placebo. The exception will be subjects at doses 4, 6, and 8 who have not experienced reactions to the agent. These subjects may opt to self-administer the study agent at home. At each visit where agent will be administered at NIH, before dose administration, the

participant will undergo a physical exam with vital signs, overview of medical history, diary review, and assessment of AEs. At each visits where participants of childbearing potential receive study agent at NIH, they will also have a urine or serum pregnancy test, which must be negative before administration of the study drug. In addition, at the visits for doses 3, 5, and 7 (weeks 4, 8, and 12), participants will undergo the following procedures before dose administration:

1. Blood draw for clinical evaluations:
    a. CBC/diff.
    b. Acute care, hepatic, and mineral panels.
    c. PT/PTT.
    d. Total protein.
    e. Lipid panel.
    f. Serum tryptase.
    g. CRP.
2. Collection of serum (8 mL SST) for storage.
3. Serum IL-6 levels.
4. Plasma for storage (10 mL GTT).
5. Whole blood for storage (3 mL LTT).
6. MC-QoL.
7. SCORMA.
8. MSAS.
9. MQLQ/MSAF.
10. Photography of affected areas (optional).

As at the first dose visit, participants will be monitored during their injection and for 1 hour after the injection to observe for any immediate drug-related AEs and hypersensitivity reactions. Hypersensitivity reactions will be treated as clinically appropriate.

Participants who have not experienced reactions to the injection after the second dose may, at the request of the participant and the discretion of the PI, be trained to self-inject the study drug/placebo for the fourth, sixth, and eighth doses (weeks 6, 10, and 14). There is no known increase in risks for self injection. Subjects will be provided with dosing materials to take home and instructions for storage and administration. These participants will not have study visits (including pregnancy test, AE evaluation, study diary review or history and physical exam at the NIH for these doses. When a dose is to be self-injected at home, study staff will contact subject to ensure administration took place, and document this in the NIH medical record.

6.2.4 Peak Treatment (Week 16 ± 7 days)

Two weeks (± 7 days) after the eighth and final dose of sarilumab, the participant will return to the NIH CC and undergo the following procedures. This visit will take 1-2 days, and participants will be seen as outpatients.

1. Physical exam with vital signs.
2. Overview of medical/medication history.
3. Assessment of AEs.
4. Blood draw for clinical evaluations:
   a. CBC/diff.
   b. Acute care, hepatic, and mineral panels.
   c. PT/PTT.
   d. Total protein.
   e. Lipid panel.
   f. Serum tryptase.
   g. CRP.
5. Urine or serum pregnancy test (for participants of childbearing potential only).
6. Blood draw for RNA collection.
7. Collection of serum (8 mL SST) for storage.
8. Serum IL-6 levels.
9. Serum markers of bone marrow resorption and deposition.
10. Plasma for storage (10 mL GTT].
11. Whole blood for storage (3 mL LTT).
12. MC-QoL.
13. SCORMA.
14. MSAS.
15. MQLQ/MSAF
16. Bone marrow biopsy and aspirate.
17. *KIT* D816V mutation analysis on blood and bone marrow.
18. Flow cytometry on bone marrow and blood.
19. Ultrasound of abdomen.
20. Photography of affected areas.
21. Skin punch biopsy (optional).
22. Diary review.

6.2.5 Post-treatment Visit (Week 28 ± 7 days)

The participant will return to the NIH CC for a post-treatment visit 12 weeks (± 7 days) after the peak treatment follow-up visit (section 6.2.4). The participant will undergo the following procedures:

1. Physical exam with vital signs.
2. Overview of medical/medication history.
3. Assessment of AEs.
4. Blood draw for clinical evaluations:
    a. CBC/diff.
    b. Acute care, hepatic, and mineral panels.
    c. PT/PTT.
    d. Total protein.
    e. Lipid panel.
    f. Serum tryptase.
    g. CRP.
5. Pregnancy test (serum or urine, for participants of childbearing potential only).
6. Collection of serum (8 mL SST) for storage.
7. Serum IL-6 levels.
8. Serum markers of bone marrow resorption and deposition.
9. Plasma for storage (10 mL GTT).
10. Whole blood for storage (3 mL LTT).
11. MC-QoL.
12. SCORMA.
13. MSAS.
14. MQLQ/MSAF
15. KIT D816V mutation analysis on blood.
16. Flow cytometry on blood.
17. Photography of affected areas.
18. Diary review.

At the end of this visit, participants who continue to meet all eligibility criteria (sections 4.2 and 4.3) will be offered the opportunity to continue on sarilumab for another 52 weeks. Prior to beginning the open-label treatment, a safety assessment of any AEs that may have occurred during the randomized treatment period will be reviewed with the participant. Participants who decline will end their participation after this visit. Those who accept will continue on the study as described below (section 6.3).

6.2.6 Early Termination Visit

All effort will be made to conduct an early termination visit for participants who withdraw from the study during the randomized, double-blinded portion. This visit will include all of the procedures performed at the normal peak treatment visit (see section 6.2.4).

6.3 Optional Open-label Treatment Period

For the optional open-label portion of the study, participants will receive 200-mg sarilumab SC Q2W for 52 weeks (26 doses). Participants will be trained by the study team to self-administer the injection at home. The first dose will be given following the post-treatment visit (section 6.2.5), which will be considered week 1 for this portion of the study. Therefore, the final dose will be administered on week 51. The participant will be provided with a memory aid (Appendix I), in addition to the side effect/medication change diary, to keep track of self-administered doses of sarilumab.

For this first dose, the participant will be monitored during administration and for 1 hour after to observe for any immediate drug-related AEs. Participants will be discharged after postdose monitoring if they have not experienced any serious hypersensitivity reactions. Hypersensitivity reactions will be treated as clinically appropriate.

6.3.1 Open Administration Follow-up Visits (week 7 ± 7 days, and weeks 19, 31, and 43 all ± 14 days)

Participants will return for follow-up visits approximately 6 weeks after starting this treatment period, and every 3 months thereafter. The following procedures will be done at each visit:

1. Physical exam with vital signs.
2. Overview of medical/medication history.
3. Assessment of AEs.
4. Blood draw for clinical evaluations:
   a. CBC/diff.
   b. Acute care, hepatic, and mineral panels.
   c. Serum tryptase
   d. Lipid panel (weeks 7 and 31 only).
5. Pregnancy test (serum or urine, for participants of childbearing potential only).
6. Diary and memory aid review.

After these procedures, the participant will receive their dose of sarilumab, administered by themselves or by study staff. As at the first open-label dose, participants will be monitored during their injection and for 1 hour after the injection to observe for any immediate drug-related AEs and hypersensitivity reactions. Hypersensitivity reactions will be treated as clinically appropriate.

6.3.2 Final Study Visit (week 55 ± 14 days)

A final study visit will be done approximately 1 month after the last dose, and the following procedures will be done:

1. Physical exam with vital signs.
2. Overview of medical/medication history.
3. Assessment of AEs.
4. Blood draw for clinical evaluations:
   a. CBC/diff.
   b. Acute care, hepatic, and mineral panels.
   c. Serum tryptase
5. Pregnancy test (serum or urine, for participants of childbearing potential only).
6. Diary and memory aid review.

Participation in this study ends after this visit.

6.3.3 Early Termination Visit

All effort will be made to conduct an early termination visit for participants who withdraw from the study during the open-label treatment portion. This visit will include all of the procedures performed at the final study visit (see section 6.3.2).

6.4 Pregnancy

- If a participant becomes pregnant during the course of the study, then they will discontinue the study agent and research procedures but continue to be followed for safety assessments. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to KEVZARA during pregnancy. Pregnant women will be encouraged to register themselves by calling 1-877-311-8972 and MotherToBaby@ucsd.edu. If the study team is informed before a pregnant woman registers, the study team will enroll participant in pregnancy registry.

7 Study Procedures/Evaluations

Blood draw: Blood will be collected for clinical safety evaluations (CBC/diff; acute care, hepatic, and mineral panels; total protein; PT/PTT; lipids; serum tryptase; and CRP), storage, collection of DNA and RNA, and to examine serum IL-6 levels and markers of bone marrow resorption and deposition. Blood will also be used to test for HIV, hepatitis B, hepatitis C, and tuberculosis, to determine if the participant's blood cells carry the D816V mutation in the *KIT* gene, which is characteristic of adult ISM and for markers of ISM using flow cytometry. The amount of blood drawn for research purposes will be within the limits allowed for adult research participants by the NIH CC (Medical Administrative Policy 95-9, Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf).

Bone marrow biopsy/aspirate: Bone marrow specimens will be evaluated to determine if the participant's bone marrow carries the D816V mutation in the *KIT* gene and for evaluation of the extent of mast cell infiltration, markers, and morphology.

Abdominal ultrasound: Ultrasound of the participant's abdominal area will be conducted to evaluate enlargement of the liver and spleen.

MC-QoL assessment: The MC-QoL is a validated health-related QoL survey for adult patients with mastocytosis that consists of 27 items and is divided into four domains: symptoms, social life/functioning, emotions, and skin.[11] The overall disease impairment on QoL is measured by assessing both the total score and the scores of each domain. The MC-QoL is provided in Appendix C.

SCORMA assessment: SCORMA evaluates three measures of mastocytosis in a semi-quantitative fashion: extent of skin involvement, lesion activity, and subjective symptoms.[18] The SCORMA chart is provided in Appendix D.

MSAS assessment: The MSAS is used to evaluate a patient's experience with 32 symptoms over the course of the previous week.[19] Symptoms are evaluated by severity and distress for eight of the symptoms, and also for frequency for the remaining 24. The MSAS is provided in Appendix E.

MQLQ/MSAF assessment: The MQLQ is disease specific quality of life questionare valided in mastocytosis consisting of 49 questions to assess the effect of mastoctyosis on daily life. It is complemented with the MSAF which is a symptom scoring form. The MQLQ is provided in Appendix F and the MSAF is in Appendix G.

Photographs: Photographs will be taken at screening, at baseline before study drug is administered (optional), at the treatment peak, and at the post-treatment visit, and may also be taken at other visits to document physical findings. Identifiable photographs will be kept in a secure database. Participants will sign the standard NIH photography consent form before photos are taken.

Skin punch biopsy (optional) : The biopsy site may be numbed using a cream or spray before a local anesthetic is injected. A small circle of skin (2-5 mm) will be removed using a punch and the area will then be closed with gel foam, steri-strips, or non-absorbable sutures and covered with a dressing.

Research evaluation on biopsies will include immunohistologic staining to detect the presence and number of mast cells and/or maculopapular cutaneous mastocytosis and may include genetic studies.

8 Potential Risks and Benefits

8.1 Potential Risks

Sarilumab: Adverse reactions (ARs) have been determined in clinical trials conducted primarily in patients with rheumatoid arthritis and on combination therapy with disease-modifying antirheumatic drugs (DMARDs, eg, Imuran, cyclophosphamide, and methotrexate). Our patients with ISM in general are not being treated with DMARDs. In clinical trials as reported in the package insert[13] and summarized below and in Table 1, the most frequent ARs (occurring in at least 3% of patients treated with sarilumab in combination with DMARDs) were neutropenia, increased liver enzymes, injection site erythema, upper respiratory infections, and urinary tract infections.

Premature discontinuation due to ARs occurred in 8%, 6%, and 3% of patients treated with sarilumab at 200 mg, sarilumab at 150 mg, and placebo, respectively. The most common ARs (greater than 1%) that resulted in discontinuation of therapy with sarilumab was neutropenia.

The most commonly reported infections (2%-4% of patients) were upper respiratory tract infections, urinary tract infections, and nasopharyngitis. The most frequently observed serious infections included pneumonia and cellulitis. There is a theoretical risk for tuberculosis activation or shingles reactivation.

Reports of GI perforation were primarily reported as complications of diverticulitis including lower GI perforation and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs) or corticosteroids. The contribution of these concomitant medications relative to sarilumab in the development of GI perforations is not known.

Injection site reactions were reported in 7% of patients receiving sarilumab at 200 mg, 6% receiving sarilumab at 150 mg, and 1% receiving placebo. These injection site reactions (including erythema and pruritus) were mild in severity for the majority of patients and necessitated drug discontinuation in 2 (0.2%) patients receiving sarilumab.

Table 1: Common Adverse Reactions in Adults with Moderately to Severely Active Rheumatoid Arthritis

Preferred Term	Placebo + DMARD (N = 579)	Sarilumab 150 mg + DMARD (N = 579)	Sarilumab 200 mg + DMARD (N = 582)
Neutropenia	0.2%	7%	10%
ALT increased	2%	5%	5%
Injection site erythema	0.9%	5%	4%
Injection site pruritus	0.2%	2%	2%
Upper respiratory tract infection	2%	4%	3%
Urinary tract infection	2%	3%	3%
Hypertriglyceridemia	0.5%	3%	1%
Leukopenia	0%	0.9%	2%

Adverse reactions occurring in 2% or more in the 150 mg sarilumab + DMARD or 200 mg sarilumab + DMARD groups and greater than observed in placebo + DMARD. Pre-rescue, placebo-controlled population.
ALT = alanine transaminase; DMARD = disease-modifying antirheumatic drug.

Laboratory Abnormalities

Decreased neutrophil count less than 1000/μL occurred in patients on combination therapy and occurred in 6% and 4% of patients in the 200-mg sarilumab + DMARD and 150-mg sarilumab + DMARD groups, respectively, compared to no patients in the placebo + DMARD groups. Decrease in ANC was not associated with the occurrence of infections, including serious infections. Decreases in platelet counts less than 100,000/μL occurred in 1% and 0.7% of patients on 200- and 150-mg sarilumab + DMARD, respectively, compared to no patients on placebo + DMARD, without associated bleeding events. Liver enzyme elevations in the pre-rescue placebo-controlled population (sarilumab + DMARD or placebo + DMARD) are summarized in Table 2.

Liver elevation was not associated with clinically relevant increases in direct bilirubin or clinical evidence of hepatitis or hepatic impairment.

Lipid abnormalities (low-density lipoproteins, high-density lipoproteins, and triglycerides) were observed at 4 weeks after initiation of therapy with no additional increases observed thereafter.

Table 2: Incidence of Liver Enzyme Elevations in Adults with Moderately to Severely Active Rheumatoid Arthritis

	Placebo + DMARD N = 579	Sarilumab 150 mg + DMARD N = 579	Sarilumab 200 mg + DMARD N = 582
AST			
> 1× ULN to 3× ULN	15%	27%	30%
> 3× ULN to 5× ULN	0%	1%	1%
> 5× ULN	0%	0.7%	0.2%
ALT			
> 1× ULN to 3× ULN	25%	38%	43%
> 3× ULN to 5× ULN	1%	4%	3%
> 5× ULN	0%	1%	0.7%

Phase 3 placebo-controlled safety population through the pre-rescue period. ALT = alanine transaminase; AST = aspartate transaminase; DMARD = disease-modifying antirheumatic drug; ULN = upper limit of normal.

Malignancies

In the 52-week placebo-controlled population, 9 malignancies (exposure-adjusted event rate of 1.0 event per 100 patient-years) were diagnosed in patients receiving sarilumab + DMARD compared to 4 malignancies in patients in the control group (exposure-adjusted event rate of 1.0 event per 100 patient-years).

Other Adverse Reactions

Because sarilumab is a monoclonal antibody, there is the risk of allergic or anaphylactic reactions. The most frequent hypersensitivity reactions observed in clinical trials were rash at the injection site rash or other parts of the body and urticaria.

While there are no nonclinical data suggesting risks to fertility or embryofetal development, sarilumab has not be evaluated in pregnant humans. There is an unknown but potential risk for sarilumab to be excreted in human milk. Therefore, participants should not be pregnant, planning to become pregnant, or breastfeeding while participating in this study.

There may be additional risks of sarilumab that are currently unknown.

Bone marrow biopsy/aspirate: Bone marrow biopsy and aspirate are commonly performed medical procedures that are associated with low risk, which includes the potential for some bleeding or infection at the site that may or may not require antibiotic treatment. There is usually some pressure-like discomfort during needle insertion, and the procedure may also result in a bruise and/or some discomfort at the site or surrounding tissue for a day or two after the anesthetic wears off. Standard procedures will be followed for all bone marrow biopsies and aspirates to minimize pain and the possibility of infection from the procedure.

Conscious sedation: Participants may request conscious sedation in addition to local anesthesia for bone marrow biopsy and aspirate. Sedative drugs will be provided by experienced

anesthesiologists of the NIH CC and IV administered. Side effects from sedative medications include cardiovascular and respiratory depression, manifested by bradycardia, hypotension, respiratory acidosis, and apnea. Additional ARs reported with these drugs are stinging or pain at the injection site, hiccoughs, nausea, vomiting, postoperative drowsiness and headache, and hypersensitivity reactions. Participants will be closely monitored and appropriate countermeasures will be taken as necessary.

Skin punch biopsy: Pain or discomfort may occur during and after the biopsy, even with the use of the local anesthetic. There may be a mild burning sensation when the numbing medicine is injected into the skin. The anesthetic may irritate the skin or rarely cause an allergic reaction, which can be treated with medicine. There may be bleeding at the biopsy site, which would require application of pressure to stop the bleeding. Rarely, biopsy sites become infected. In certain individuals, the biopsy will heal with a keloid. This is more likely to occur if it has happened in the past.

Blood draw and insertion of IV catheter: The risks of drawing blood and inserting an IV catheter for administration of sedative drugs include pain, swelling, redness, bruising, bleeding, and, rarely, fainting or infection.

Photographs: Taking pictures of the face and body may be embarrassing to some people. These photographs may be published in medical journals, without identifying the participant. We will attempt to preserve the anonymity of the participant as much as possible, while providing the information needed to support the research being published. Participants may decline photographs or place restrictions on their use. Participants will be given the opportunity to discuss this with the investigator.

8.2 Potential Benefits

Participants may not receive any benefit from this study. There is the potential that a 16-week treatment regimen of sarilumab will alleviate or resolve symptoms related to ISM. The results of this study may improve the investigators' understanding of anti-IL-6 therapy as treatment for ISM.

9 Research Use of Stored Human Samples, Specimens, or Data

Intended Use: Samples, specimens, and data collected under this protocol may be used to study mastocytosis. Genetic testing may be performed in the future.

Storage: All the stored study research samples are labeled by a code that only the investigators can link to the participant. Samples are stored in LAD storage space, which is a secure facility with limited access. Data will be kept in password-protected computers. Only investigators or their designees will have access to the samples and data.

Tracking: Samples and data acquired under this protocol will be tracked using the CRIMSON database system.

Disposition at the Completion of the Protocol:

- In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. If the planned research falls within the category of "human subjects research" on the part of the NIH researchers, IRB review and approval will be obtained. This includes the NIH researchers sending out coded and linked samples or data and getting results that they can link back to their participants.
- At the time of protocol termination, samples will either be destroyed or, after IRB approval, transferred to another existing protocol. Data will be archived by the study team in compliance with requirements for retention of research records; alternatively, after IRB and study sponsor approval, the data may be either destroyed or transferred to another repository.

Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:

- Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that meets the definition of a reportable event will be reported to the NIH IM IRB according to NIH Human Research Protections Program (HRPP) Policy 801.
- Additionally, participants may decide at any point not to have their samples stored. In this case, the PI will destroy all known remaining samples and report what was done to both the participant and to the IRB. This decision will not affect the individual participant's participation in this protocol or any other protocols at NIH.

10 Data Sharing Plan

Human data generated in this study will be shared for future research as follows:

- De-identified data in an NIH-funded or approved public repository.
- De-identified data in another public repository.
- Identified data in the Biomedical Translational Research Information System (BTRIS, automatic for activities in the CC) and the Genomic Research Integration System (GRIS).
- De-identified or identified data with approved outside collaborators under appropriate agreements.

When will the data be shared?

Data may be shared with Sanofi/Genzyme shortly before publication.

11 Remuneration Plan for Participants

All participants may be reimbursed for travel and lodging, as per the NIAID policy. Participants will not receive any other remuneration.

12 Assessment of Safety

12.1 Definitions

The NIAID Clinical Safety Office (CSO) is responsible for sponsor safety oversight of this study, and the definitions below comply with CSO requirements.

Adverse Event: An AE is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (eg, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the individual's participation in the research, whether or not considered related to the research.

Adverse Reaction: An AE that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR): An AE for which there is a reasonable possibility that the investigational agent caused the AE. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than AR, which implies a high degree of certainty.

Serious Adverse Event (SAE): An SAE is an AE that results in one or more of the following outcomes:

- death
- a life-threatening event (places the participant at immediate risk of death from the event as it occurred)
- an inpatient hospitalization or prolongation of an existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unexpected Adverse Event: An AE is unexpected if it is not listed in the investigator's brochure or package insert (for marketed products) or is not listed at the specificity or severity that has been observed. It is the responsibility of the IND sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR): A SUSAR is an SAR that is both serious and unexpected.

Unanticipated Problem: A UP is any event, incident, experience, or outcome that meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research risks that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and (b) the characteristics of the participant population being studied; and
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others (which may include research staff, family members, or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or expected. (Per the IND sponsor, an AE with a serious outcome will be considered increased risk.)

Unanticipated Problem that is not an Adverse Event (UPnonAE): A UP that does not fit the definition of an AE, but which may, in the opinion of the investigator, involve risk to the participant, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered non-serious UPs. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

Protocol Deviation: Any change, divergence, or departure from the IRB-approved research protocol.

1. Major deviations: Deviations from the IRB-approved protocol that have, or may have the potential to, negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
2. Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study.

Non-compliance: Failure of investigator(s) to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the IRB, whether intentional or not.

1. Serious non-compliance: Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject.

Non-compliance that materially affects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.

2. Continuing non-compliance: A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different noncompliant events. Such non-compliance may be unintentional (e.g., due to lack of understanding, knowledge, or commitment), or intentional (e.g., due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).

12.2 Documenting, Recording, and Reporting Adverse Events

All AEs occurring from the baseline visit through the final study visit will be documented, recorded, and reported.

At each contact with the participant, information regarding AEs will be elicited by appropriate questioning and examinations and will be:

- immediately documented in the participant's medical record/source document,
- recorded in CRIMSON, and
- reported as outlined below (eg, IND sponsor, IRB, and FDA).

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

A laboratory abnormality will not be reported as an AE if ALL of the following criteria are met:

- It is no more than "Grade 1" or "Mild" per the protocol-specified toxicity table (or investigator assessment if not listed on the table); AND
- It does NOT require an intervention (eg, discontinuation of treatment, dose reduction/delay, additional assessments, or treatment); AND
- It is assessed by the PI as NOT related to the study agent(s); AND
- It is assessed by the PI as NOT clinically significant (eg, the abnormal value does NOT suggest a disease or organ toxicity).

All abnormal laboratory findings will be reviewed on a routine basis by the PI to identify potential safety signals. An abnormal lab not included on the toxicity table should be assessed in a similar fashion to the criteria above.

12.3 Investigator Assessment of Adverse Events

The investigator will assess all AEs with respect to seriousness (criteria listed above), severity (intensity or grade), and causality (relationship to study agent and relationship to research) according to the following guidelines.

12.3.1 Severity

The Investigator will grade the severity of each AE according to the CTCAE v 5.0, which can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

12.3.2 Causality

Causality (likelihood that the event is caused by the study agent) will be assessed considering the factors listed under the following categories:

Definitely Related

- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related

- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related

- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related

- does not have a reasonable temporal relationship
  OR
- good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship
  OR
- definitely due to an alternative etiology

Note: Other factors (eg, dechallenge, rechallenge) should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

12.4 Investigator Reporting Responsibilities to the Sponsor

12.4.1 Adverse Events

AE data will be submitted to the IND sponsor when requested for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

12.4.2 Serious Adverse Events

All SAEs (regardless of relationship and whether or not they are also UPs) must be reported on the safety expedited report form (SERF) and sent to the CSO by fax or email attachment. Deaths and immediately life-threatening SAEs must be reported to the CSO within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

CSO CONTACT INFORMATION:

Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
E-mail: rchspsafety@mail.nih.gov

SAEs that have not resolved by the end of the follow-up period are followed until final outcome is known. If it is not possible to obtain a final outcome for an SAE (eg, the participant is lost to follow-up), the reason a final outcome could not be obtained will be recorded by the investigator on the AE case report form and the SERF.

SAEs that occur after the final study visit that are reported to and are assessed by the investigator to be possibly, probably, or definitely related to study drug must be reported to the CSO.

12.4.3 Unanticipated Problems

Ups that are also AEs must be reported to the CSO by fax or e-mail attachment using the NIH Problem Report Form no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the CSO.

12.4.4 Pregnancy

All pregnancies will be reported on the Pregnancy Notification/Outcome Form to the CSO within 1 business day from site awareness.

Pregnancy outcome data (eg, delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within 3 business days of the site's awareness.

Although pregnancy itself is not an AE, events that meet SAE criteria during pregnancy, delivery, or in the neonate (eg, congenital anomaly/birth defect) are reportable on the SERF.

In the event of pregnancy, the following steps will be taken:

- Discontinue the study agent and procedures but continue to follow-up for safety.
- Unblind the participant.
- Study team will enroll participant in pregnancy registry.
- Report to the DSMB.
- Advise research participant to notify the obstetrician of study participation and study agent exposure.

12.5 Sponsor's Reporting Responsibilities

SUSARs, as defined in Title 21 of the United States Code of Federal Regulations (CFR) Part 312.32 and determined by the IND sponsor, will be reported to FDA and all participating investigators as IND Safety Reports.

The IND sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

12.6 Pausing Rules for Individual Participants

Pausing is the suspension of administration of study agent to a single participant until a decision is made whether or not to resume administration of the study agent.

The pausing criteria for a single participant in this study include any of the following:

- A participant experiences an SAE that is unexpected and possibly, probably, or definitely related to a study agent.
- A participant experiences two grade 3 or greater AE that is unexpected and possibly, probably, or definitely related to a study agent.
- A participant develops a serious infection or an opportunistic infection, per the sarilumab package insert.[13]
- A participant develops one of the following lab abnormalities, per the sarilumab package insert:[13]

- ANC < 1000/µL.
- Platelet count < 100,000/µL.
- ALT or AST > 3.0 × ULN.

- Any safety issue that the site investigator determines should pause administration of a study agent to a single participant.

12.6.1 Reporting a Pause

If a pausing criterion is met, then a description of the AE(s) or safety issue must be reported by the PI or designee within 1 business day to the CSO and the DSMB by fax or email, and to the IRB according to their requirements.

12.6.2 Resumption of a Paused Participant

The CSO, in collaboration with the PI, will determine whether or not it is safe to resume administration of the study agent to the participant. The PI will notify the IRB of the decision on resumption of the study agent. If the pause was initiated because of lab abnormalities, then per the sarilumab package insert upon resumption, the sarilumab dose may be reduced from 200 to 150 mg after lab values return to stated thresholds.[13] The decision to modify the dose will be made by the PI in consultation with the CSO, and reported to the DSMB. The sarilumab dose can be raised to 200 mg again as clinically appropriate, at the discretion of the PI, CSO, and/or DSMB.

12.6.3 Discontinuation of Study Agent for Individual Participants

Permanent discontinuation of study drug will occur per the sarilumab package insert if:[13]

- ANC < 500/mL.
- Platelet count < 50,000/µL.
- ALT > 5 × ULN

Participants who do not resume study agent during the randomized, double-blind portion of the study will continue to be followed for 16 weeks, and then be encouraged to have an early termination visit (section 6.2.6). Participants who do not resume study agent during the open-label portion will be encouraged to have an early termination visit (section 6.3.3) shortly after the decision is made not to resume.

12.7 Halting Rules for the Protocol

Halting the study requires immediate discontinuation of study agent administered for all participants and suspension of enrollment until a decision is made whether or not to continue enrollment and study agent administration.

The halting rules are:

- 2 or more participants experience the same or similar SAEs that are unexpected and possibly, probably, or definitely related to the study agent;

OR

- 2 or more of the same or similar AEs in different participants that are grade 3 or above and are unexpected and possibly, probably, or definitely related to the study agent;

OR

- any safety issue that the PI determines should halt the study.

The PI and/or CSO will determine if the study should be halted. In addition, the FDA may halt the study at any time following review of any safety concerns.

12.7.1 Reporting a Study Halt

If a halting rule is met, then a description of the AE(s) or safety issue must be reported by the PI or designee within 1 business day to the CSO and the DSMB by fax or email, and to the IRB according to their requirements.

12.7.2 Resumption of a Halted Study

The IND sponsor, in collaboration with the PI, the DSMB, and any specified safety review team will determine if it is safe to resume the study. The PI will notify the IRB of the decision on resumption of the study.

12.7.3 Discontinuation of Study Agent

Participants who do not resume study agent during the randomized, double-blind portion of the study will continue to be followed for safety for 16 weeks, and then be encouraged to have an early termination visit (section 6.2.6). Participants who do not resume study agent during the open-label portion will be encouraged to have an early termination visit (section 6.3.3) shortly after the decision is made not to resume.

12.8 Withdrawal Criteria for an Individual Participant

An individual participant will be withdrawn for any of the following:

- An individual participant's decision. (The investigator should attempt to determine the reason for the participant's decision.)
- Non-compliance with study procedures to the extent that it is potentially harmful to the participant or to the integrity of the study data.
- A participant misses more than 1 dose of study drug during the randomized portion of the study.

- The investigator determines that continued participation in the study would not be in the best interest of the participant.

Participants who wish to withdraw from the study will be encouraged to have an early termination visit (sections 6.2.6 or 6.3.3).

12.8.1 Additional Participant Randomization Following Withdrawn Participant or Participants Who Discontinue Study Treatment

Any participant who does not complete the study or misses a dose or requires dose reduction through the post-treatment visit (section 6.2.5) may be replaced by an additional randomized participant. However, all randomized participants will be strongly encouraged to complete all study follow-up, and all randomized participants will be included in the data set for analysis even if their follow-up assessments are incomplete.

12.9 Safety Oversight

12.9.1 Safety Review and Communications Plan

A safety review and communications plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

12.9.2 Sponsor Medical Monitor

A medical monitor, representing the IND sponsor (OCRPRO), has been appointed for oversight of safety in this clinical study. The sponsor medical monitor will be responsible for performing safety assessments as outlined in the SRCP.

12.9.3 Data and Safety Monitoring Board

The NIAID intramural DSMB includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interests as defined by NIAID policy. The DSMB will review the study prior to initiation and twice a year thereafter, and may convene additional reviews as necessary. The board will review the study data to evaluate the safety, efficacy, study progress, and conduct of the study. These reports will be confidential to the DSMB, with data partially unblinded (ie, by treatment group with dummy labels). All SAEs, all Ups, and all IND Safety Reports will be reported by the PI to the DSMB at the same time they are submitted to the IND sponsor. The PI will notify the DSMB of any cases of intentional or unintentional unblinding in writing within 1 business day after site awareness and as soon as possible via email to the DSMB mailbox (niaiddsmbia@niaid.nih.gov) outlining the reason for the unblinding and the date it occurred. The PI will notify the board at the time pausing or

halting criteria are met and obtain a recommendation concerning continuation, modification, or termination of the study.

13 Reporting Procedures

13.1 Reporting to the NIH IM IRB

UPs, non-compliance, and other reportable events will be reported to the NIH IM IRB according to NIH HRPP Policy 801.

13.2 Reporting to the NIAID Clinical Director

The principal investigator will report UPs, major protocol deviations, and deaths to the NIAID clinical director according to institutional timelines.

14 Site Monitoring Plan

According to the International Council on Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) guidelines section 5.18, and 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines." Monitors under contract to the NIAID/OCRPRO will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the consent process for each monitored participant; 2) to verify the prompt and accurate recording of all monitored data points in CRIMSON and prompt reporting of all SAEs; 3) to compare abstracted information entered into CRIMSON with individual participants' records and source documents (participants' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original participant information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections [OHRP], FDA) and applicable guidelines (ICH GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (eg, consent forms, CRIMSON data abstracts) and pertinent hospital or clinical records, including CRIMSON, readily available for inspection by the local IRB, FDA, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

15 Statistical Considerations

15.1 Study Hypotheses

The primary hypothesis is that the MC-QoL at 16 weeks will be different in the sarilumab-treated participants than in the placebo participants. This is a two-sided alpha = 0.05 test and will be covariate-adjusted by the baseline MC-QoL score.

15.2 Sample Size Justification

The sample size of 15 per arm is limited by the number of patients available to study. In this section, statistical power is evaluated for a possible treatment effect. The distribution of the total MC-QoL measurement was informed by Siebenhaar et al.[11] Since the data are not normally distributed and the scale is constrained between 0 and 100, a beta distribution with parameters 1.30, 2.41 (multiplied by 100), to match the mean and standard deviation of 35 and 22 as seen in Table 7 of Siebenhaar was used to simulate power.[11] This distribution appears quite consistent with the box plot shown in Figure 1 of Siebenhaar. The Siebenhaar paper also reports a high intraclass correlation of 0.9 for measurements 2 weeks apart, suggesting a strong correlation between the baseline and 16-week scores is plausible; thus, a correlation of 0.7 was assumed in the simulation. While the treatment effect is unknown, power was determined under the assumption that the percentage decline in MC-QoL in the sarilumab-treated arm would be 60% and 10% in the placebo arm (some improvement was anticipated in the placebo arm because these individuals know they might be getting an active treatment). As noted previously, this difference between the arms on MC-QoL is considered clinically meaningful.

The simulation of the trial data was performed as follows. The first step was to generate bivariate standard normal variables with correlation of 0.7. Then the cumulative distribution function of each of these was applied to an inverse cumulative distribution function of a beta with parameters 1.30 and 2.41, yielding pairs of Beta (1.30, 2.41) variables with approximate correlation of 0.7. For example, if a pair of bivariate standard normal generated is 0.880 and 0.642, then these values are transformed to 0.563 and 0.497, respectively, as the probability that a Beta (1.30, 2.41) variable is less than 0.563 equals Φ (0.880), and 0.497 is determined likewise. All beta variables were multiplied by 100 to match the MC-QoL scale. The first member of the pair represented the baseline MC-QoL, and since the protocol excludes MC-QoL under 25, pairs with baseline < 25 were then excluded from all simulated trials. Within each replication, 15 eligible pairs were assigned to the active drug arm, and 15 to the placebo arm. The second member of each pair was multiplied by (1 – the assumed decline for their respective treatment group), representing the 16-week MC-QoL value. Finally, to reflect the integer scores of the scale, all baseline and 16-week values were rounded to the closest integer.

Under the above assumptions, the simulation indicated that a baseline covariate adjusted regression analysis of 16-week MC-QoL value has more than 90% power to show that the

sarilumab-treated arm has superior MC-QoL to the placebo arm. It is noted that this power estimate could be too optimistic, as it is based on limited knowledge of and speculation about the distribution of MC-QoL scores, the correlation between baseline and 16 weeks, and the specific nature of the treatment benefit.

Randomization will continue until there are 30 participants who initiate study drug and have at least the first post-baseline QoL measurement at 4 weeks. Note that participants who do not meet these criteria still remain in the study, and attempts to obtain subsequent QoL measures should be made.

15.3 Description of the Analyses

- Safety analysis: descriptive tabulations of AEs will be constructed. These tabulations will also be stratified by severity.
- Efficacy analysis: the primary analysis of the primary efficacy endpoint will compare treatment groups with a regression analysis, adjusted for baseline QoL. A number of sensitivity analyses are planned for the primary analysis if there are participants with missing data at 16 weeks. Baseline adjusted regression analysis and Wilcoxon rank sum tests will also be applied to a range of efficacy endpoints. Descriptive summaries and graphics will also be provided.

15.4 Planned Interim Analyses

No interim analyses are planned.

15.5 Final Analysis Plan

Several study populations are defined. The intent-to-treat (ITT) population includes all randomized participants. The modified intent-to-treat (mITT) population includes all participants who received at least one dose of sarilumab or placebo. The second modified intent-to-treat (mITT2) population further excludes the participants with no post-baseline data on the MC-QoL. The third modified intent-to-treat (mITT3) population excludes participants without 16-week MC-QoL data. The per protocol (PP) population only includes all participants with available data on 16-week MC-QoL and who report taking more than 80% of study drug.

The primary analysis will compare the groups with respect to the primary endpoint, the 16-week MC-QoL score in the mITT population using linear regression with an indicator for treatment group and the baseline MC-QoL value as a covariate. While the goal is that all participants will have a 16-week MC-QoL regardless of whether they continue drug throughout, the last observed value of MC-QoL will be carried forward to serve as the primary endpoint in the primary analysis for those participants without 16-week values. (This includes carrying the baseline value

forward, if there are no post-baseline measurements). The test will be two-sided with a 0.05 alpha level.

While the goal is to assess all participants at 16 weeks, regardless of whether they continue with study drug, it is possible that some participants will have missing MC-QoL at 16 weeks. The planned primary analysis, using last observation carried forward, implicitly assumes that study participants who stop getting QoL assessments will be in a stable state, such that the last observed measurement is a reasonable imputation for the 16 week visit. However, to assess the robustness of these results, several sensitivity analysis will be conducted, that implicitly make different assumptions. We will conduct a mixed effects model analysis incorporating all available MC-QoL measurements (this will test the treatment effect at week 16; specifically it will analyze the post-baseline visit timepoints as categorical, and will adjust for the baseline QoL as a covariate.). Another approach imputes participants with missing data at 16 weeks as having the worst scores with a Wilcoxon rank sum test on percent improvement, will be conducted in the mITT population. If there is more than 15% missing data on the 16-week MC-QoL in the mITT population, inverse probability weighting approaches to the linear regression analysis will be done as well in the mITT and ITT populations. Additionally, if the results remain unclear due to missing data, pattern mixture analyses allowing for worse than expected outcomes in those with missing data may be explored.

Other sensitivity analyses will be conducted regardless of whether there are missing data at 16 weeks. We will repeat the primary analysis in the PP population, the mITT2 and mITT3 populations. We will repeat the regression analysis but with a log transformation to both QoL values. To be robust from non-normality, a Wilcoxon rank sum test will also be used to compare the 16-week QoL values in the various analysis populations. Finally, graphical representation of each participant's MC-QoL trajectories over time, color coded by treatment assignment will be constructed.

Baseline adjusted linear regression and Wilcoxon rank sum test will also be used for the secondary and exploratory endpoints. If critical to interpretation, some sensitivity analyses may be conducted.

A 95% confidence interval of the difference in median percentage improvement will be calculated using a bootstrap. Similarly, standard normal 95% confidence intervals for difference in mean 16-week values, and difference in the mean change from baseline values will be presented. Graphical presentations of baseline and 16 weeks values changes will be completed.

Exploratory analyses might consider analyses with additional covariates and results within subgroups.

Analyses of AEs will be descriptive by study arm, and will also consider severity of AEs.

16 Ethics/Protection of Human Participants

16.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an ongoing conversation between the human research participant and the researchers which begins before consent is given and continues until the end of the participant's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks, and benefits. Participants will be given the opportunity to ask questions and have them answered.

The participants will sign the informed consent document prior to undergoing any research procedures. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The researcher will document the signing of the consent form in the participant's medical record. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

16.2 Participant Confidentiality

All records will be kept confidential to the extent provided by federal, state, and local law. The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB, the FDA, NIAID, OHRP, the pharmaceutical supporter, or the sponsor's designee.

17 Data Handling and Record Keeping

17.1 Data Capture and Management

Study data will be maintained in CRIMSON and collected directly from participants during study visits and telephone calls or will be abstracted from participants' medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data entry into CRIMSON will be performed by authorized individuals. The investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

17.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP guidelines. Study records will be maintained by the PI according to the timelines specified in 21 CFR 312.62 or a minimum of 5 to 7 years, and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to OCRPRO/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. NIAID will be notified in writing and written OCRPRO/NIAID permission shall be obtained by the site prior to destruction or relocation of research records.

18 Scientific References

1. Horny HP, Metcalfe DD, Akin C, et al. Mastocytosis. In: Swerdlow SH, ed. *WHO classification of tumours of haematopoietic and lymphoid tissues.* Vol 4th ed. Lyon, France: International Agency for Research on Cancer; 2008:62-69.
2. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol.* 2015;16(5):448-457.
3. Mihara M, Hashizume M, Yoshida H, Suzuki M, Shiina M. IL-6/IL-6 receptor system and its role in physiological and pathological conditions. *Clin Sci (Lond).* 2012;122(4):143-159.
4. Brockow K, Akin C, Huber M, Metcalfe DD. IL-6 levels predict disease variant and extent of organ involvement in patients with mastocytosis. *Clin Immunol.* 2005;115(2):216-223.
5. Fujii K, Ohgou N. Up-regulation of IL-6 mRNA in peripheral blood mononuclear cells of patients with acute urticaria. *J Dermatol.* 2004;31(3):242-243.
6. Kasperska-Zajac A, Sztylc J, Machura E, Jop G. Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. *Clin Exp Allergy.* 2011;41(10):1386-1391.
7. Mayado A, Teodosio C, Garcia-Montero AC, et al. Increased IL6 plasma levels in indolent systemic mastocytosis patients are associated with high risk of disease progression. *Leukemia.* 2016;30(1):124-130.
8. Morjaria JB, Babu KS, Vijayanand P, Chauhan AJ, Davies DE, Holgate ST. Sputum IL-6 concentrations in severe asthma and its relationship with FEV1. *Thorax.* 2011;66(6):537.
9. Desai A, Jung MY, Olivera A, et al. IL-6 promotes an increase in human mast cell numbers and reactivity through suppression of suppressor of cytokine signaling 3. *J Allergy Clin Immunol.* 2016.
10. Kim DK, Beaven MA, Kulinski JM, et al. Regulation of Reactive Oxygen Species and the Antioxidant Protein DJ-1 in Mastocytosis. *PloS one.* 2016;11(9):e0162831.
11. Siebenhaar F, von Tschirnhaus E, Hartmann K, et al. Development and validation of the mastocytosis quality of life questionnaire: MC-QoL. *Allergy.* 2016;71(6):869-877.
12. Strand V, Burmester GR, Ogale S, Devenport J, John A, Emery P. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. *Rheumatology.* 2012;51(10):1860-1869.
13. Kevzara [package insert]. Regeneron Pharmaceuticals, Inc., Tarrytown, NY; April 2018. http://products.sanofi.us/kevzara/kevzara.pdf
14. June RR, Olsen NJ. Room for more IL-6 blockade? Sarilumab for the treatment of rheumatoid arthritis. *Expert opinion on biological therapy.* 2016;16(10):1303-1309.
15. Sieper J, Braun J, Kay J, et al. Sarilumab for the treatment of ankylosing spondylitis: results of a Phase II, randomised, double-blind, placebo-controlled study (ALIGN). *Annals of the rheumatic diseases.* 2015;74(6):1051-1057.
16. Lin P. Targeting interleukin-6 for noninfectious uveitis. *Clinical ophthalmology.* 2015;9:1697-1702.
17. Rafique A, Martin J, Blome M, Huant T, Ouyang A, Papadopoulos N. Evaluation of The Binding Kinetics and Functional Bioassay Activity of Sarilumab and Tocilizumab to the

Human IL-6 Receptor (IL-6R) Alpha. Abstract presented at: Annual European Congress of Rheumatology; June 12-15, 2013; Madrid, Spain.

18. Heide R, Middelkamp Hup MA, Mulder PG, Oranje AP, Mastocytosis Study Group R. Clinical scoring of cutaneous mastocytosis. *Acta dermato-venereologica.* 2001;81(4):273-276.
19. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *European journal of cancer.* 1994;30A(9):1326-1336.

Appendix A: Schedule of Procedures/Evaluations

	Screening	Baseline[a]	Study Drug Administration			Peak Treatment Visit	Post-treatment Visit	Early Termination visit
	Day −60 to −2	Day -2 to 0	Day 0	Weeks 2, 6, 10, 14[b]	Weeks 4, 8, 12	Week 16[c]	Week 28	
				± 4 days	± 4 days	± 7 days	± 7 days	
Procedures/Evaluations			Dose 1	Doses 2, (4, 6, 8)[k]	Doses 3, 5, 7			
Assessments								
Informed consent	X[d]							
Randomization[e]		X						
Physical exam with vital signs	X[f]	X		X	X	X	X	X
Medical/medication history	X	X		X	X	X	X	X
Assessment of ISM symptoms	X	X						
Assessment of Aes		X	X	X	X	X	X	X
Study drug administration			X	X[g]	X[g]			
Diary review				X	X	X	X	X
Laboratory Evaluations								
CBC/diff	X	X			X	X	X	X
Acute care, hepatic, mineral panels	X	X			X	X	X	X
PT/PTT	X	X			X	X	X	X
Pregnancy test (serum or urine)	X	X		X	X	X	X	X
Anti-HIV ½ antibody test	X							
Hepatitis B and C antibody test, HBV DNA, and HCV RNA	X							
QuantiFERON tuberculosis test	X							
Total protein		X			X	X	X	X
Lipid panel		X			X	X	X	X
Serum tryptase	X	X			X	X	X	X
CRP		X			X	X	X	X
Ultrasound of abdomen	X					X		X
Research Evaluations								
Blood draw for DNA collection		X						
Blood draw for RNA collection		X				X		X
Serum storage		X			X	X	X	X
Serum for IL-6 levels		X			X	X	X	X
Plasma storage		X			X	X	X	X

	Screening	Baseline[a]	Study Drug Administration			Peak Treatment Visit	Post-treatment Visit	Early Termination visit
	Day −60 to −2	Day -2 to 0	Day 0	Weeks 2, 6, 10, 14[b]	Weeks 4, 8, 12	Week 16[c]	Week 28	
				± 4 days	± 4 days	± 7 days	± 7 days	
Procedures/Evaluations			Dose 1	Doses 2, (4, 6, 8)[k]	Doses 3, 5, 7			
Whole blood storage		X			X	X	X	X
Serum markers of bone marrow resorption and deposition		X				X	X	X
MC-QoL	X	X			X	X	X	X
SCORMA	X	X			X	X	X	X
MSAS	X	X			X	X	X	X
MQLQ/MSAF	X	X			X	X	X	X
Bone marrow biopsy and aspirate	X[h]					X		X
Blood and bone marrow *KIT* D816V mutation analysis	X[h]	X[i]				X	X[i]	X[i]
Blood and bone marrow flow cytometry	X[h]	X[i]				X	X[i]	X[i]
Photography	X	X[j]			X[j]	X	X	X
Skin punch biopsy		X[j]				X[j]		X[j]

AE = adverse event; HBV = hepatitis B virus; HCV = hepatitis C virus; IL = interleukin; ISM = indolent systemic mastocytosis; MC-QoL = Mastocytosis Quality of Life Questionnaire; MSAS = Memorial Symptom Assessment Scale; Q2W = once every 2 weeks; SCORMA = scoring of mastocytosis index; X = to be performed.

A Participants may be admitted as inpatients for this study visit. Procedures will be performed just once during this period.
B At the discretion of the study team, instead of coming to the NIH for study visits on weeks 6, 10 and 14, participants can self-administer study drug at home. No other procedures will be done at these time points for participants who self-administer.
C This visit will take 1-2 days as outpatients.
D Informed consent will be obtained before any study procedures are conducted on this protocol.
E Patients will be randomized to receive sarilumab or placebo.
F The screening physical exam will include measurement of vital signs, height, and weight.
G Sarilumab/placebo will be administered after the other study procedures have been completed.
H Will be done at screening only if not done within the last 150 days on protocol 02-I-0277 or this protocol.
I Only blood will be collected for KIT mutation analysis and flow cytometry at these visits.
j Optional at these visits.
k At visits 4, 6, 8, subjects may self inject at home. At these self administered injection timepoints, no assessments will occur.

	Open Administration Visits					Final Study Visit	Early Termination Visit
	Week 1[a]	Week 7	Week 19	Week 31	Week 43	Week 55	
Procedures/Evaluations		± 7 days	± 14 days	± 14 days	± 14 days	± 14 days	
Physical exam		X	X	X	X	X	X
Medical/medication history		X	X	X	X	X	X
AE assessment		X	X	X	X	X	X
CBC/diff		X	X	X	X	X	X
Acute care, hepatic, and mineral panels		X	X	X	X	X	X
Lipid panel		X		X			
Pregnancy test (serum or urine)		X	X	X	X	X	X
Serum tryptase		X	X	X	X	X	X
Diary review		X	X	X	X	X	X
Memory aid review		X	X	X	X	X	X
Study drug administration[b]	X	X	X	X	X		

AE = adverse event; CBC = complete blood count.
a Week 1 of the open administration portion of this study immediately follows the post-treatment visit.
b Study drug will be administered after all other procedures have been completed.

Appendix B: Blood Volumes for Specimen Collection

Evaluation	Study visit[a]												
	Randomized, double-blinded, placebo-controlled treatment							Optional open-label treatment					
	Screening (days −60 to −0)	Baseline (days −2 to −0)	W4 (± 4 days)	W8 (± 4 days)	W12 (± 4 days)	W16 (± 7 days)	W28 (± 7 days)	W7 (± 7 days)	W19 (± 14 days)	W31 (± 14 days)	W43 (± 14 days)	W55 (± 14 days)	Early termination visit
HIV test[b,c]	8												
Hepatitis test[c,d]	(8)												
QuantiFERON Gold	1												
Serum pregnancy test	4	4	4	4	4	4	4	4	4	4	4	4	4
CBC/diff[e]	4	4	4	4	4	4	4	4	4	4	4	4	4
Acute care panel[e]	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Hepatic panel[e]	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Mineral panel[e]	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Lipid panel[e]		(4)	(4)	(4)	(4)	(4)	(4)	(4)		(4)			(4)
Total protein[e]		(4)	(4)	(4)	(4)	(4)	(4)						(4)
CRP[e]		(4)	(4)	(4)	(4)	(4)	(4)						(4)
PT/PTT	3	3	3	3	3	3	3						3
Serum tryptase	4	4	4	4	4	4	4	4	4	4	4	4	4
DNA		10											
RNA		10				10							10
Serum storage		8	8	8	8	8	8						8
IL-6 levels		8	8	8	8	8	8						8
Serum markers of bone marrow resorption and deposition		4				4	4						4
Plasma storage		10	10	10	10	10	10						10
Whole blood storage		3	3	3	3	3	3						3
KIT D816V mutation	1	1				1	1						1
Flow cytometry[f]	(1)	(1)				(1)	(1)						(1)
Daily volume (mL)	25	69	44	44	44	59	49	12	12	12	12	12	63
Cumulative volume (mL)	25	94	138	182	226	285	334	346	358	370	382	394	

CBC/diff = complete blood count with differential; CRP = C-reactive protein; IL-6 = interleukin 6 ; PT/PTT = prothrombin/partial thromboplastin time; W = week.

a Blood volumes are presented in mL.

b Anti-HIV-1/2 antibodies test.

c A single volume of blood will be collected for HIV and hepatitis tests.

d Test for anti-hepatitis B and C antibodies, and hepatitis B and C RNA.

e A single volume of blood will be collected for CBC/diff, acute care, hepatic, and mineral panels, CRP, and total protein.

f A single volume of blood will be collected for the *KIT* D816V mutation analysis and flow cytometry.

Appendix C: Mastocytosis Quality of Life Questionnaire

Participant Signature:_____ Date: _____

MC-QoL

Questionnaire Regarding Patient's Quality of Life with Mastocytosis

Instructions: Dear patients, in the following questionnaire you will find a variety of questions regarding your quality of life. Please read through each question carefully and select one of the following five answers that best describes your symptoms. Please do not think too much about your answers but be careful to answer all the questions. Please provide one answer per question, i.e. please mark only one box per question.

	None	Some-what	Moderately	Very	Very Much
How severely were you affected by the following symptoms in **the last 2 weeks**?					
1. Itching	❑	❑	❑	❑	❑
2. Skin Redness/Swelling	❑	❑	❑	❑	❑
3. Sudden feeling of warmth and reddening of the face (Flush episodes)	❑	❑	❑	❑	❑
4. Diarrhea/loose stools	❑	❑	❑	❑	❑
5. Fatigue/Exhaustion	❑	❑	❑	❑	❑
6. Headache	❑	❑	❑	❑	❑
7. Muscle or joint pain	❑	❑	❑	❑	❑
8. Difficulty concentrating	❑	❑	❑	❑	❑

	None	Some-what	Moderately	Very	Very Much
Please indicate how often you have been limited in your daily life in the areas listed below during the **past 2 weeks** because of your mastocytosis.					
9. School/University/Work	❑	❑	❑	❑	❑
10. Sport/Physical Activity	❑	❑	❑	❑	❑
11. Sleep	❑	❑	❑	❑	❑

Participant Signature:_____ Date: _____

12. Sexual activity	❑	❑	❑	❑	❑
13. Leisure time	❑	❑	❑	❑	❑
14. Relationships (Friends, Family, Partner, co-workers)	❑	❑	❑	❑	❑

	Never	**Seldom**	**Occasionally**	**Often**	**Very often**
We would like to further study difficulties and problems that may be associated with your mastocytosis using the following questions. Please answer according to your experiences from the **past 2 weeks**.					
15. In the past 2 weeks, were you tired during the day because you did not sleep well at night?	❑	❑	❑	❑	❑
16. In the past 2 weeks, did you have to change your choices of foods and drinks due to your mastocytosis?	❑	❑	❑	❑	❑
17. Have you felt less capable in the past 2 weeks due to your mastocytosis?	❑	❑	❑	❑	❑
18. Have you been burdened by the symptoms of your mastocytosis in the past 2 weeks?	❑	❑	❑	❑	❑
19. Has your choice of what to wear been restricted in the past 2 weeks due to mastocytosis?	❑	❑	❑	❑	❑
20. In the past 2 weeks, were you ever afraid you might suffer an allergic reaction due to mastocytosis?	❑	❑	❑	❑	❑
21. In the past 2 weeks, were you ever afraid that you might receive the wrong treatment if you became or unconscious or suffered an accident due to your mastocytosis?	❑	❑	❑	❑	❑
22. Have you felt uncomfortable in public during the past 2 weeks due to mastocytosis?	❑	❑	❑	❑	❑
23. In the past 2 weeks, have you ever been afraid of the further worsening of your mastocytosis?	❑	❑	❑	❑	❑

Participant Signature:_____ Date: _____

	Never	Seldom	Occasionally	Often	Very often
In the **past 2 weeks** did you feel					
24. ...a lack of motivation?	❑	❑	❑	❑	❑
25. ...alone with your illness?	❑	❑	❑	❑	❑
26. ...concerned?	❑	❑	❑	❑	❑
27. ...sad?	❑	❑	❑	❑	❑

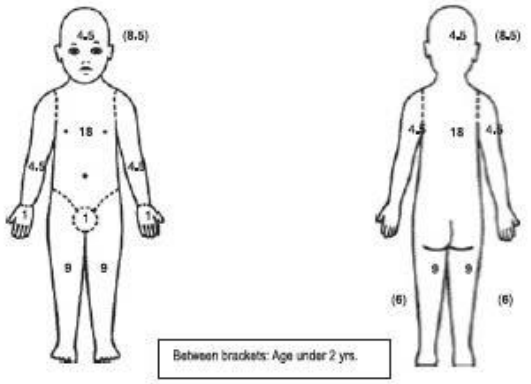
Appendix D: Scoring of Mastocytosis (SCORMA) Index

Participant Signature:_____ Date: _____

MD Signature Date:
:_____

SCORMA INDEX

Institution	:	Name of patient	:
Physician	:	Date of birth	:
Date of visit	:	Patient number	:



Between brackets: Age under 2 yrs.

A: Extent please indicate the area involved [ ]

B: Intensity average representative area [ ]

Criteria	Intensity	Intensity items
1. Pigmentation / erythema	[ ]	0 = absent
2. Vesiculation	[ ]	1 = mild
3. Elevation	[ ]	2 = moderate
4. Positive Darier's sign	[ ]	3 = severe

C: Subjective Symptoms [ ]

	Visual Analog Scale (by parents if child < 5 years)
1. Provoking Factor(s)	0 ---------- 10
2. Flushing	0 ---------- 10
3. Diarrhea	0 ---------- 10
4. Pruritus	0 ---------- 10
5. Localized Bone Pain	0 ---------- 10

Scorma index: A/5 + 5B + 2C/5 [ ]

Figure 1 SCORing MAstocytosis Index.

Appendix E: Memory Symptom Assessment Scale (MSAS)

Participant Signature:_____ Date: _____

MEMORIAL SYMPTOM ASSESSMENT SCALE

Name Date

Section 1

Instructions: We have listed 24 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by circling the appropriate number. If you DID NOT HAVE the symptom, make an "X" in the box marked "DID NOT HAVE."

DURING THE PAST WEEK Did you have any of the following symptoms?	DID NOT HAVE	IF YES How OFTEN did you have it?				IF YES How SEVERE was it usually				IF YES How much did it DISTRESS or BOTHER you?				
		Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not at all	A Little Bit	Somewhat	Quite a Bit	Very Much
Difficulty concentrating		1	2	3	4	1	2	3	4	0	1	2	3	4
Pain		1	2	3	4	1	2	3	4	0	1	2	3	4
Lack of energy		1	2	3	4	1	2	3	4	0	1	2	3	4
Cough		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling nervous		1	2	3	4	1	2	3	4	0	1	2	3	4
Dry mouth		1	2	3	4	1	2	3	4	0	1	2	3	4
Nausea		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling drowsy		1	2	3	4	1	2	3	4	0	1	2	3	4
Numbness/tingling in hands/feet		1	2	3	4	1	2	3	4	0	1	2	3	4
Difficulty sleeping		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling bloated		1	2	3	4	1	2	3	4	0	1	2	3	4
Problems with urination		1	2	3	4	1	2	3	4	0	1	2	3	4
Vomiting		1	2	3	4	1	2	3	4	0	1	2	3	4
Shortness of breath		1	2	3	4	1	2	3	4	0	1	2	3	4
Diarrhea		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling sad		1	2	3	4	1	2	3	4	0	1	2	3	4
Sweats		1	2	3	4	1	2	3	4	0	1	2	3	4
Worrying		1	2	3	4	1	2	3	4	0	1	2	3	4
Problems with sexual interest or activity		1	2	3	4	1	2	3	4	0	1	2	3	4
Itching		1	2	3	4	1	2	3	4	0	1	2	3	4
Lack of appetite		1	2	3	4	1	2	3	4	0	1	2	3	4
Dizziness		1	2	3	4	1	2	3	4	0	1	2	3	4
Difficulty swallowing		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling irritable		1	2	3	4	1	2	3	4	0	1	2	3	4

Participant Signature:_____ Date: _____

Section 2										
INSTRUCTIONS: We have listed 8 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by circling the appropriate number. If you DID NOT HAVE the symptom, make an "X" in the box marked "DID NOT HAVE."										
DURING THE PAST WEEK, Did you have any of the following symptoms?	DID NOT HAVE	IF YES How SEVERE was it usually?				IF YES How much did it DISTRESS or BOTHER you?				
		Slight	Moderate	Severe	Very Severe	Not at all	A little bit	Somewhat	Quite a bit	Very much
Mouth sores		1	2	3	4	0	1	2	3	4
Change in the way food tastes		1	2	3	4	0	1	2	3	4
Weight loss		1	2	3	4	0	1	2	3	4
Hair loss		1	2	3	4	0	1	2	3	4
Constipation		1	2	3	4	0	1	2	3	4
Swelling of arms or legs		1	2	3	4	0	1	2	3	4
"I don't look like myself"		1	2	3	4	0	1	2	3	4
Changes in skin		1	2	3	4	0	1	2	3	4
IF YOU HAD ANY OTHER SYMPTOMS DURING THE PAST WEEK, PLEASE LIST BELOW AND INDICATE HOW MUCH THE SYMPTOM HAS DISTRESSED OR BOTHERED YOU.										
Other:						0	1	2	3	4
Other:						0	1	2	3	4
Other:						0	1	2	3	4

Appendix F: The Mastocytosis Quality of Life Questionnaire (MQLQ)

Participant Signature:_____ Date: _____

The Mastocytosis Quality of Life Questionnaire (MQLQ)

The signs and symptoms of mastocytosis vary from person to person. The following 49 questions are indented to determine the symptoms you have as a result of your mastocytosis and the burden of these symptoms on your daily life. The questions can be answered by checking the box that is most applicable to you. There are seven possible answers:

0 ☐ None, or not applicable	1 ☐ Hardly	2 ☐ Somewhat	3 ☐ Moderately	4 ☐ Considerably	5 ☐ Severely	6 ☐ Worst possible

To what extend does mastocytosis trouble you, because

	0	1	2	3	4	5	6
1. it causes your job to require more energy?	☐	☐	☐	☐	☐	☐	☐
2. it causes you to feel somber?	☐	☐	☐	☐	☐	☐	☐
3. it makes it necessary for you to go to bed earlier on workdays?	☐	☐	☐	☐	☐	☐	☐
4 it reduces your capability or makes you unable to work under stressful conditions?	☐	☐	☐	☐	☐	☐	☐
5. you are required to always carry a epinephrine auto-injector (e.g. Epi-Pen, Jext or Anapen)?	☐	☐	☐	☐	☐	☐	☐
6. you experience (near)fainting during a large mastocytosis attack (anaphylactic reaction)?	☐	☐	☐	☐	☐	☐	☐
7. your family needs to be aware of what to do in the case of a large mastocytosis attack (anaphylactic reaction)?	☐	☐	☐	☐	☐	☐	☐
8. of your immediate wariness when spotting a bee or wasp?	☐	☐	☐	☐	☐	☐	☐
9. of your children's immediate wariness when spotting a bee or wasp?	☐	☐	☐	☐	☐	☐	☐

Participant Signature:_____ Date: _____

0 ☐ None, or not applicable	1 ☐ Hardly	2 ☐ Somewhat	3 ☐ Moderately	4 ☐ Considerably	5 ☐ Severely	6 ☐ Worst possible

To what extend does mastocytosis trouble you, because of

	0	1	2	3	4	5	6
10. your embarrassment for your skin abnormality?	☐	☐	☐	☐	☐	☐	☐
11. your itchy skin?	☐	☐	☐	☐	☐	☐	☐
12. your lower back pain?	☐	☐	☐	☐	☐	☐	☐
13. your physically exhausting flushing attacks?	☐	☐	☐	☐	☐	☐	☐
14. your reduced capability or inability to drink alcohol due to alcohol being a trigger for symptoms?	☐	☐	☐	☐	☐	☐	☐
15. your reduction in height?	☐	☐	☐	☐	☐	☐	☐

To what extend are you troubled by:

	0	1	2	3	4	5	6
16. uncertainty whether or not a symptom is caused by your mastocytosis?	☐	☐	☐	☐	☐	☐	☐
17. uncertainty about the course of your mastocytosis?	☐	☐	☐	☐	☐	☐	☐
18. fear of your mastocytosis progressing to a worse form of mastocytosis?	☐	☐	☐	☐	☐	☐	☐
19. incomprehension of mastocytosis by your social surroundings (friends, family, colleagues)?	☐	☐	☐	☐	☐	☐	☐
20. the difficulty for others to understand mastocytosis?	☐	☐	☐	☐	☐	☐	☐

Participant Signature:_____ Date: _____

Participant Signature:_____ Date: _____

0 ☐ None, or not applicable	1 ☐ Hardly	2 ☐ Somewhat	3 ☐ Moderately	4 ☐ Considerably	5 ☐ Severely	6 ☐ Worst possible

To what extend are you troubled by:

	0	1	2	3	4	5	6
21. an apparent lack of knowledge of mastocytosis by some physicians?	☐	☐	☐	☐	☐	☐	☐
22. your social life suffering from mastocytosis?	☐	☐	☐	☐	☐	☐	☐
23. a large mastocytosis attack (anaphylaxis) being stressful for you?	☐	☐	☐	☐	☐	☐	☐
24. your skin abnormality being cosmetically unappealing?	☐	☐	☐	☐	☐	☐	☐
25. physical stress being a trigger for your mastocytosis symptoms?	☐	☐	☐	☐	☐	☐	☐
26. mental stress being a trigger for your mastocytosis symptoms?	☐	☐	☐	☐	☐	☐	☐
27. a temperature change being a trigger for your mastocytosis symptoms?	☐	☐	☐	☐	☐	☐	☐
28. your skin abnormalities increasing in number or size over time?	☐	☐	☐	☐	☐	☐	☐
29. your skin abnormalities becoming more visible over time?	☐	☐	☐	☐	☐	☐	☐

Participant Signature:_____ Date: _____

0 ☐ None, or not applicable	1 ☐ Hardly	2 ☐ Somewhat	3 ☐ Moderately	4 ☐ Considerably	5 ☐ Severely	6 ☐ Worst possible

How often do you, because of your mastocytosis:

	0	1	2	3	4	5	6
30. suffer from flushing attacks?	☐	☐	☐	☐	☐	☐	☐
31. suffer from a warm, glowing feeling ?	☐	☐	☐	☐	☐	☐	☐
32. suffer from a decrease in stamina?	☐	☐	☐	☐	☐	☐	☐
33. suffer from fatigue?	☐	☐	☐	☐	☐	☐	☐

Do you, because of your mastocytosis:

	0	1	2	3	4	5	6
34. feel worn out despite of only mild exertion?	☐	☐	☐	☐	☐	☐	☐
35. suffer from impaired short term memory?	☐	☐	☐	☐	☐	☐	☐
36. suffer from a lack of mental acuity or a reduced ability to think clearly?	☐	☐	☐	☐	☐	☐	☐
37. have trouble paying attention to conversations?	☐	☐	☐	☐	☐	☐	☐
38. suffer from itchy skin predominantly at night?	☐	☐	☐	☐	☐	☐	☐
39. suffer from stomach aches?	☐	☐	☐	☐	☐	☐	☐
40. suffer from loose stools?	☐	☐	☐	☐	☐	☐	☐
41. suffer from a reduced ability to concentrate?	☐	☐	☐	☐	☐	☐	☐

Participant Signature:_____ Date: _____

0 ☐ None, or not applicable	1 ☐ Hardly	2 ☐ Somewhat	3 ☐ Moderately	4 ☐ Considerably	5 ☐ Severely	6 ☐ Worst possible

Do you, because of your mastocytosis:

42. feel that at one time the lack of knowledge on mastocytosis by doctors has withheld adequate treatment from you?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
43. avoid certain activities (e.g. skating/skiing) for fear of incurring a fracture?	☐	☐	☐	☐	☐	☐	☐
44. avoid strenuous lifting for fear of incurring back pain or fractures?	☐	☐	☐	☐	☐	☐	☐

To what extent are you:

45. afraid that doctors unfamiliar with mastocytosis could prescribe a drug that could trigger an (anaphylactic) attack?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
46. frustrated by the current lack of a curative treatment for mastocytosis?	☐	☐	☐	☐	☐	☐	☐
47. worried about a proper treatment of a (anaphylactic) mastocytosis attack when visiting abroad?	☐	☐	☐	☐	☐	☐	☐
48. afraid to fall due to your greater risk of osteoporosis as a result of your mastocytosis?	☐	☐	☐	☐	☐	☐	☐
49. afraid to incur fractures while exercising due to your greater risk of osteoporosis as a result of your mastocytosis?	☐	☐	☐	☐	☐	☐	☐

Appendix G: The Mastocytosis Symptoms Assessment Form (MSAF)

Participant Signature:_____ Date: _____

The Mastocytosis Symptoms Assessment Form (MSAF)

Please note the severity of your mastocytosis symptoms in the following table. Marking a 0 indicates that the symptom is absent; whereas a 10 indicates that the symptom is very severe. If you suffer from one of the listed symptoms but personally feel that it is not related to mastocytosis then please score it as a 0.

Symptoms	**0** ***(absent)*** **to** **10** ***(very severe)***											**Comment**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Itchy skin												
Dizziness												
Headache												
Fatigue (during the last week)												
Runny nose												
Shortness of breath												
Chest pain/palpitations												
Nausea/vomiting												
Diarrhea, stomach ache, cramps												
Bone pain/ muscle pain												
Concentration problems												
Depression, somberness												
Other, namely: ……..												
Attacks, with or without loss of consciousness.	Frequency per month …….											
Flushing	Frequency per week …….											

Rate with a number from 1 to 10 how much influence fatigue has had, in the last 24 hours, on:												
	0 *(no influence)* **to** **10** *(maximum influence)*											
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Activities (general)												
Mood/temper												
Mobility												
Chores												
Relationships												
Happiness												
Other, namely: ……..												

Appendix H: Side Effect and Medication Change Diary

A Phase 2 Randomized Double-Blinded Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Sarilumab in Improving the Quality of Life in Subjects with Indolent Systemic Mastocytosis

Participant Name _____

If you develop an infection or you need to talk with a member of the study team for any reason, then please contact Dr. Hirsh Komarow at 301-594-2197 or komarowh@mail.nih.gov, or Robin Eisch at 301-443-1720 or Robin.Eisch@niaid.nih.gov. After business hours, please contact Dr. Hirsh Komarow at 301-272-5699 or Dr. Melody Carter at 240-476-0872. For emergencies, immediately call 911.

Instructions

Complete this diary any day you experience a symptom. Only mark which symptoms you have. If you do not have any symptoms on a particular day, then you can skip that day. **Bring all pages with you to every study visit.** We will review the diary at every visit.

Severity

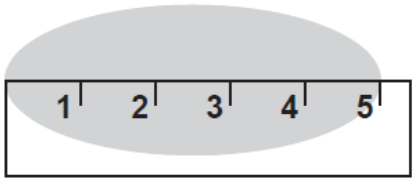
Some people have reactions after receiving their injection of sarilumab or placebo. If you experience any of the symptoms listed in the table, then use the following categories to describe how severe each symptom was:

- 1 = Mild. Minor discomfort that did not affect your usual activities.
- 2 = Moderate. Noticeable discomfort that bothered you enough that you did not do as much as you usually do.
- 3 = Severe. The symptom could not be ignored and stopped you from doing something you wanted or had to do.

Redness or Swelling at Injection Site

Some people experience redness or swelling in the area where they got their injection. If you experience redness or swelling, then measure the area of redness or swelling using the centimeter (cm) ruler at the bottom of this page, and record the measurement in the table.

Example



To measure the area of redness or swelling, measure the widest part of the area from left to right **or** top to bottom.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

A Phase 2 Randomized Double-Blinded Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Sarilumab in Improving the Quality of Life in Subjects with Indolent Systemic Mastocytosis

Participant Name _____

Side Effect Diary

Symptom	Date:	Date:	Date:	Date:	Date:	Date:	Date:
	Severity (1-3)	Severity (1-3)	Severity (1-3)	Severity (1-3)	Severity (1-3)	Severity (1-3)	Severity (1-3)
Injection Site Pain							
Redness at Injection Site *(size in cm)*							
Swelling at Injection Site *(size in cm)*							
Itchiness at Injection Site							
Cold Symptoms *(ex, runny nose, fever)*							
Hives (not at injections site)							
Other *(Describe)*							

A Phase 2 Randomized Double-Blinded Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Sarilumab in Improving the Quality of Life in Subjects with Indolent Systemic Mastocytosis

Participant Name _____

Medication Change Diary

Please complete the following table each time there is a change in your medication. Changes include starting a new medication, stopping a current medication, or changing the dose of a current medication. Record the medication name, what the change was (started taking, stopped taking, or changed dose), the date of the change, the reason why you took it, and the daily dose.

Medication	Change	Change Date	Reason	Daily Dose
Example:				
Aspirin	*Started taking*	*9/1/17*	*Headache*	*81 mg*

Appendix I: Sarilumab Memory Aid

A Phase 2 Randomized Double-Blinded Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Sarilumab in Improving the Quality of Life in Subjects with Indolent Systemic Mastocytosis

Memory aid: Sarilumab injection (150 or 200 mg) once every 2 weeks.

Participant Name _____

*If you develop a serious side effect, or you need to talk with a member of the study team for any reason, then please contact Dr. Hirsh Komarow at 301-594-2197 or komarowh@mail.nih.gov, or Robin Eisch at 301-443-1720 or Robin.Eisch@niaid.nih.gov. After business hours, please contact Dr. Hirsh Komarow at 301-272-5699 or Dr. Melody Carter at 240-476-0872.

STUDY WEEK	DOSE NUMBER	DATE	TOOK SARILUMAB? (Y/N)
1	1		GIVEN AT NIH
3	2		YES ☐ NO ☐
5	3		YES ☐ NO ☐
7	4		GIVEN AT NIH
9	5		YES ☐ NO ☐
11	6		YES ☐ NO ☐
13	7		YES ☐ NO ☐
15	8		YES ☐ NO ☐
17	9		YES ☐ NO ☐
19	10		GIVEN AT NIH
21	11		YES ☐ NO ☐
23	12		YES ☐ NO ☐
25	13		YES ☐ NO ☐
27	14		YES ☐ NO ☐
29	15		YES ☐ NO ☐
31	16		GIVEN AT NIH
33	17		YES ☐ NO ☐
35	18		YES ☐ NO ☐
37	19		YES ☐ NO ☐
39	20		YES ☐ NO ☐
41	21		YES ☐ NO ☐
43	22		GIVEN AT NIH
45	23		YES ☐ NO ☐
47	24		YES ☐ NO ☐
49	25		YES ☐ NO ☐
51	26		YES ☐ NO ☐