1. Protocol Title

Tofacitinib Hypothesis-generating, Pilot Study for Corticosteroid-Dependent Sarcoidosis

2. Objectives

This study will enroll 5 subjects with corticosteroid dependent pulmonary sarcoidosis.

The purpose of this pilot study is to determine if further research is warranted to assess if tofacitinib is an effective steroid sparing treatment for pulmonary sarcoidosis. The primary end point for this study is a 50% or greater reduction in corticosteroid requirement. We hypothesize that 60% of the patients will have a 50% or greater reduction in their steroid requirement without a significant decrease in pulmonary function testing and with a similar quality of life. We further hypothesize that STAT-1 dependent gene expression studies will show a significant decrease after tofacitinib treatment.

Objective 1: Test the hypothesis that the addition of tofacitinib will allow patients with sarcoidosis to have 50% or greater reduction in their corticosteroid requirement without a significant decrease in pulmonary function testing, and with a similar quality of life as measured by a validated questionnaire (1).

Objective 2: Test the hypothesis that the addition of tofacitinib will result in significantly decreased expression of STAT-1 dependent gene expression.

3. Background

Sarcoidosis is an inflammatory disorder of unclear etiology with a prevalence that has been estimated to be as high as 300/100,000. (2) The mainstay of treatment is oral corticosteroids. However, this therapy has numerous side effects and has been linked to increased relapses and poor quality of life, particularly at high doses. (3, 4) Furthermore, there is a subset of patients with persistent disease despite corticosteroid treatment. This has led to multiple trials evaluating various immunomodulatory agents for steroid sparing treatment in sarcoidosis. Our group and others have previously shown upregulation of the STAT1 pathway including the downstream cytokines in tissue, whole blood and lymph nodes of patients with sarcoidosis. (5-7)

Tofacitinib is a janus kinase (JAK) inhibitor with a predominant effect on JAK1 and JAK3 which in turn decreases STAT1 activation. (8) Tofacitinib is currently FDA approved for treatment of psoriatic arthritis and rheumatoid arthritis and has recently shown superiority when compared to methotrexate as front-line therapy. It is similar to TNF-alpha inhibition when added as an adjunctive therapy. (9, 10) Other trials have shown efficacy in a number of other inflammatory disorders including ulcerative colitis. (11, 12)

Given the need for improved therapeutics, and the role of STAT1 in the pathogenesis of sarcoidosis, we propose a study examining the reduction in steroid use in patients who are dependent on a stable dose (defined as same dose for 4 weeks) of 15 mg/day to 30 mg/day of prednisone or its equivalent to control their disease. A recent query of OHSU's electronic medical record identified over 800 adult patients with sarcoidosis, generally 10-30% of patients with sarcoid require chronic treatment for an expected population of 80-240 eligible patients in our system. (13) We intend to enroll 5 patients with pulmonary sarcoidosis, age 18 or older of either gender in an open label proof-of-concept study design and treat with 5 mg of Tofacitinib BID for 16 weeks as a steroid sparing agent. We hypothesize that 60% of patients will have a 50% or greater reduction in their steroid requirements without a significant decrease (defined as less than 15% reduction in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) or diffusing capacity for carbon monoxide (DLCO)) in pulmonary function testing and a similar quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ).(1) A clinically significant change is defined as >4 units in the SGRQ. (14) Patients who respond by these criteria will be allowed to continue on the study drug for additional time up to 52 weeks. This small study will serve as a pilot and safety study; larger trials will ultimately be necessary to validate these results.

4. Study Design

This is a 16-week open-label, interventional, proof of concept, hypothesis-generating study. This study will enroll five subjects over the course of two years. Patients recruited for this study must have histologically proven sarcoidosis, evidence of pulmonary disease on chest imaging, and an FVC >50%. They must require a stable dose (defined by 4 weeks or more) of prednisone at least 15 mg/day or equivalent corticosteroid prior to enrollment in the study. The prednisone dose cannot exceed 30 mg/day. The above criteria should insure that this is a relatively uniform group of subjects. All subjects will receive Tofacitinib 5mg twice daily for 16 weeks. After four weeks on Tofacitinib, the corticosteroid will be tapered per a pre-defined protocol (attached); once a reduction of 50% has been achieved, any further taper will be per physician discretion. The schedule for corticosteroid taper is based on 30 plus years of experience and customary practice at the Oregon Health & Science University. The experience of the investigators has consistently demonstrated an inability to taper corticosteroid dosage in many patients with sarcoidosis unless an effective, alternative immunosuppressive has been added to the patient's regimen. Furthermore, higher doses of corticosteroids have consistently been correlated with the risk of infection. (15) Throughout the trial we will be monitoring blood counts, liver function tests, lipids, renal function, and pulmonary function testing. We will also evaluate STAT-1 activity through measurement of CXCL10 levels and RNA-Seq measurement of selected transcripts (see below) before and after Tofacitinib therapy. The primary endpoint is a 50% or greater reduction in steroids with no significant decrease in pulmonary function or quality of life. After 16 weeks, subjects who meet the primary end-point will be permitted an optional one year open-label extension.

5. Study Population

a. Number of Subjects

Five subjects with histologically proven sarcoidosis with pulmonary involvement and corticosteroid dependence will be enrolled in this trial.

b. Inclusion and Exclusion Criteria

Inclusion Criteria: Subjects age 18 and older of either sex will be included. Subjects must meet the WASOG definition of pulmonary sarcoidosis. (16) They must have histologically proven sarcoidosis, evidence of Pulmonary sarcoidosis on chest radiograph (Stage I, II, III or IV) (17), an FVC >50%, and can have concomitant extrapulmonary disease. Subjects must require 15 mg to 30 mg/day prednisone or equivalent corticosteroid to control their sarcoidosis. Dose of prednisone must be stable for 4 weeks prior to enrollment in the study. Subjects may be taking methotrexate, but may not be taking other immunosuppressive or immunomodulatory treatments (see below).

Exclusion Criteria:

- Patients taking immunomodulatory medications other than methotrexate in the two months prior to the study period will not be included. This includes but is not limited to azathioprine, cyclophosphamide, leflunomide, mycophenolate mofetil, cyclosporine, tacrolimus, and biologic medications.
- Patients requiring >30 mg/day prednisone or its equivalent.
- Pregnant or lactating women will not be included.
- Subjects with the following blood dyscrasias will not be included:
    - Hemoglobin <9g/dL or Hematocrit <30%
    - White blood cell count <3.0 K/cu mm
    - Absolute neutrophil count <1.2 K/cu mm
    - Platelet count <100 K/cu mm
- Subjects with an estimated GFR ≤40 ml/min
- Subjects with a total bilirubin, AST, or ALT more than 1.5 times the upper limit of normal at screening.

- Severe, progressive, or uncontrolled chronic liver disease including fibrosis, cirrhosis, or recent or active hepatitis.
- History of any lymphoproliferative disorder such as Epstein Barr virus (EBV) related lymphoproliferative disorder, history of lymphoma, leukemia, or signs and symptoms suggest of current lymphatic disease.
- Current malignancy or history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.
- Have or have had an opportunistic infection (e.g., herpes zoster [shingles], cytomegalovirus, Pneumocystis carinii, aspergillosis and aspergilloma, histoplasmosis, or mycobacteria other than TB) within 6 months prior to screening.
- Have a known infection with human immunodeficiency virus (HIV)
- Have current signs and symptoms of systemic lupus erythematosus, or severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac (New York Heart Association class III or IV), neurologic, or cerebral diseases (with the exception of sarcoidosis).

Screening: Subjects will be recruited through the Oregon Health and Science University (OHSU) pulmonary, ophthalmology, rheumatology, and internal medicine clinics in addition to local community pulmonology clinics by referral. Review of OHSU medical records and Epic query will also be used to identify potential subjects. Pre-screening will take place first through chart review and then telephone interview. Subjects who are eligible for the trial after pre-screening will then be screened in person. At the screening visit subjects will receive informed consent as below. Health history and medications will be reviewed. Blood and/or urine samples will be collected, and pulmonary function testing will be done as per the baseline visit plan detailed below. Data from subjects who fail screening will be destroyed at the end of the study.

c. Vulnerable Populations

This study will not include children, pregnant women, neonates, prisoners, or decisionally impaired adults.

d. Setting

Subjects will be consented and samples will be drawn at the OHSU specialty clinics on the 3rd and 4th floors of the Physician's Pavilion. Spirometry will be performed in the pulmonary function lab in Multnomah Pavilion or Physician's Pavilion. Samples will be stored in a central repository as part of Dr. Jim Rosenbaum's laboratory.

RNA extraction and gene expression analyses will be performed by the OHSU Gene Profiling Shared Resource and the Massively Parallel Sequencing Shared Resource under the guidance of Dr. Christina Harrington.

e. Recruitment Methods

Subjects will be recruited through the OHSU rheumatology, pulmonary, ophthalmology, and internal medicine clinics. Subjects referred from outside clinicians/scientists or self-referral will be allowed, but is expected to account for a minority of subjects. Postings on internet support groups for people living with sarcoidosis will also be used for recruitment. An Epic and medical record query will be used to identify potential subjects. Subjects will be contacted by phone. A copy of the phone script is attached.

f. Consent Process

The consent process will take place in the OHSU pulmonary clinic or other appropriate OHSU clinic prior to any study procedures. Dr. Marcia Friedman, Dr. Janelle Stevens, or a member of their research team will be responsible for discussing the study and consent documents with study participants. Ample time will be provided to ask and answer questions. It will be emphasized that participation is entirely voluntary and that this will not affect ongoing clinical care. If needed, an interpreter will be provided for the consent process and subsequent study visits. There are no current plans to provide a translated consent. Written consent will be verified by study staff prior to any research procedures. The signed form will be kept in study binders.

6. Procedures Involved

- Blood draw: A blood draw will be done at baseline and at weeks 2, 4, 8, 12, 16 (end of treatment). We estimate that the blood draw at baseline and week 16 will be approximately 15ml. We estimate that the blood draw at weeks 2, 4, 8, and 12 will be approximately 7.5ml.
- Urinalysis: Women will have a baseline urine pregnancy test.
- RNA Seq: at baseline and week 16 blood will be drawn for blood levels of CXCL10 and RNA-Seq to assess change in STAT1-dependent gene expression using a known STAT1 pathway analysis. This is genetic testing. Consent will be obtained using the attached consent from. We have chosen RNA-Seq because this is a discovery protocol and because we have expertise in the implementation of this technology with two funded, NIH RO1 proposals dependent on it. However, because this study is based on just 5 paired samples and we wish to minimize multiple statistical comparisons, we will perform a paired T test on 14 transcripts which we have previously shown to be up regulated in the blood of patients with sarcoidosis and which are downstream of STAT-1 (including STAT-1 itself).[7] These transcripts are A2M, WARS, CCND1, STAT-1, MT-1, TRH, CD64, IRF1, PSMB9, MHC2TA, OPRM1, Pim-1, CXCL9, and CDKN1A. The thousands of additional transcripts detected by RNA Seq will be analyzed, but in all cases, changes in expression will be considered as a preliminary observation which requires validation.
- Pulmonary function testing: At baseline and at the end of treatment (week 16), we will measure spirometry with DLCO. At weeks 4, 8, and 12 we will measure spirometry only.
- Study drug: Tofacitinib 5 mg twice daily will be given from week 0 to week 16 to treat sarcoidosis. Tofacitinib is FDA approved for the treatment of rheumatoid arthritis but is not FDA approved for the treatment of sarcoidosis.
- Questionnaires: At each visit, quality of life will be measured with the Saint George Respiratory Questionnaire (SGRQ), and assessment of involved organ systems will be measured via the WASOG sarcoidosis organ assessment instrument.
- Subjects should have had a chest x-ray within one year of enrollment and will have a repeat chest x-ray after the 16 weeks of treatment.

Procedures	Baseline	Week 0*	Week 2	Week 4	Week 8	Week 12	Week 16
Informed Consent	X						
Screening labs**: Quantiferon, HIV, HBsAg, HBcAB, HCV ab,	X						
Urine pregnancy test (women only)	X						
Start study drug		X					
End study drug							X
Start steroid taper				X			
Physical Exam	X		X	X	X	X	X
Spirometry with DLCO	X***						X
Spirometry				X	X	X	
Labs: CBC, LFT, Lipid measurement, BMP.	X***		X	X	X	X	X
Labs: CRP	X						X
Labs: CXCL10 level	X						X
RNA Seq	X						X
Questionnaires: SGRQ, WASOG	X		X	X	X	X	X

Adverse event reporting			X	X	X	X	X
Medication Reconciliation			X	X	X	X	X
Chest Xray	X**						X

* There should be no more than 4 weeks between baseline and start of study drug (week 0)
**If screening labs or Chest Xray have been done within the past one year, they do not need to be repeated here.
***If these tests have been done within 4 weeks of baseline visit, they do not need to be repeated. HIV: human immunodeficiency virus, HBsAG: hepatitis B surface antigen, HBcAB: hepatitis B core antibody, HCV: hepatitis C virus, PFT: pulmonary function testing, CBC: complete blood count, LFT: liver function test, BMP: basic metabolic panel, CPR: C-reactive protein, SCGQ: Saint George Respiratory Questionnaire

All of the above procedures, testing, and study drug will be billed to the study. Patients and their insurance will not be billed for any of the above procedures during the 16 week study. Patients continuing on to long-term follow up may have laboratory testing billed to insurance as below under "Long term follow-up".

Long term follow-up: Patients who do not meet the primary end point will not be followed long term. Patients who meet the primary endpoint will be continued on study drug for up to one year. During that one year they will be followed with labs (CBC, BMP, liver function panel, lipid panel) every two months, and the above questionnaires and adverse event reporting by phone every three months. A clinic visit will be required every 6 months. Labs done during the one-year extension period will be billed to the patient's insurance; study drug will be covered by Pfizer.

Voluntary withdrawal from the study: Subjects may withdraw from the intervention (study drug Tofacitinib) at any time. For subjects who choose to withdraw from the intervention we will collect the following data two weeks after withdrawal from the intervention: CBC, lipid measurement, LFT, BMP, adverse event reporting.

Treatment with Tofacitanib to be discontinued and the patient withdrawn from this study for:

- Serious infections (those requiring parenteral antimicrobial therapy or hospitalization)
- A decline in glomerular filtration rate of 33% or greater
- An increase in liver function tests (LFTs) >2.5x the upper limit of normal
- Neutrophil counts <1000 neutrophils/mm3
- Platelet counts <100,000 platelets/mm3
- Any single hemoglobin value <8.0 g/dL or one that drops ≥2 gm/dL below baseline
- Other serious or severe AEs that the investigator believes are sufficient to discontinue the medication
- Extrapulmonary disease such as uveitis with substantial worsening despite tofacitinib therapy as determined by another health care provider

7. Data and Specimens

a. Handling of Data and Specimens

Clinical case report forms and signed consent forms will be kept on paper in locked filing cabinets in restricted access offices at OHSU. Electronic data is stored on restricted drives on the OHSU network through encrypted computers, and using OCTRI's installation of REDCap. Samples will be stored in Dr. Jim Rosenbaum's laboratory on the second floor of the Biomedical Research Building. Dr. Friedman, Dr. Stevens or their study staff will verify that consent has been given to participate in genetic research prior to collecting any samples for genetic studies (see study consent). The PAXGene Blood tubes will be transported by the study coordinator to the Gene Profiling Shared Resource in Richard Jones Hall where the RNA extraction will be performed. Case report forms will be kept for three years after study completion and then destroyed. After three years, electronic data and samples will be de-identified and encrypted and stored in a repository as discussed below under "Data and

Specimen Banking". Dr. Friedman or Dr. Stevens will be responsible for receipt and transmission of data and specimens.

Data for this project will be stored in OCTRI's installation of REDCap, a highly secure and robust web-based research data collection and management system.

Features of REDCap that protect participants' privacy and data security include:

· Physical Security: OCTRI's REDCap software is housed on servers located in ITG's Advanced Computing Center providing locked physical security

· Electronic Security: The REDCap servers are housed behind both the OHSU firewall and a second ACC firewall. All web-based data transmissions are encrypted with industry-standard SSL methods.

· Controlled User Access: REDCap is employs a robust multi-level security system that enables researchers to easily implement "minimum necessary" data access for their research staff, including specification of data fields that are identifiers. This feature includes "single click" ability to provide completely deidentified (removing all identified data fields and shifting dates) for analysis or other purposes. User activities are logged to enable auditing of all data access. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials.

· Data Integrity: REDCap is jointly managed in accordance with OHSU Information Security Directives by ACC staff and members of OCTRI's Biomedical Informatics Program, ensuring fidelity of database configuration and back-ups. User activities are logged to enable auditing of all data changes.

b. Sharing of Results with Subjects

Results of standard tests (CBC, LFT, Lipids, BMP, CRP, pregnancy testing, quantiferon, HIV, Hepatitis B, Hepatitis C, and PFT/spirometry) will be shared with subjects at their request or if deemed clinically necessary. Lab tests evaluating RNA expression and CXCL10, as well as scores on the SGRQ, WASOG-SOAI will not be shared as they are for research purposes only and the RNA-expression and CXCL10 laboratory tests are not CLIA certified.

c. Data and Specimen Banking

After three years, all clinical data and laboratory specimens will be de-identified with an assigned numerical code that will not contain any personal identifiers. The key to associating codes and subjects' personally identifying information will be restricted to the PI and study staff. De-identified data will be stored indefinitely in an encrypted databank. De-identified samples will be stored indefinitely in a repository in Dr. Rosenbaum's laboratory on the second floor of the Biomedical Research Building. De-identified samples may be used for future research including genetic research.

d. Repository

Blood will be obtained from the patient in PAXGene Blood tubes via veinipuncture and be transported by the study coordinator to the Gene Profiling Shared Resource in Richard Jones Hall where the RNA extraction will be performed. Specimens will be accepted only if in appropriate containers with appropriate labeling. Dr. Friedman, Dr. Stevens or their study staff will verify that consent has been given to participate in genetic research and repository prior to collecting any samples for genetic studies (see study consent). Participating in the repository is mandatory for inclusion into the study. Subjects will be assigned a numerical code that will not contain any personal identifiers. The key associating the codes and the subjects personally identifying information will be restricted to the PI and study staff. This code will be used on all clinical case report forms, electronic files for data analysis, and for tracking of specimens. De-identified samples will be stored indefinitely in a locked repository in Dr. Rosenbaum's laboratory on the second floor of the Biomedical Research Building. The Repository Guardian is Dr. James Rosenbaum. His responsibilities include:

- Ensuring that data/specimens are received and released according to OHSU policy and the IRB approved repository protocol.

- Executing a repository sharing agreement each time data or specimens are released for research purposes.
- Ensuring the security and confidentiality of stored data and specimens.
- Ensuring the security and confidentiality of data and specimens during transfer.
- Tracking acquisitions and releases of data and specimens.
- Maintaining methods for identifying data/samples for which consent has been withdrawn and ensuring no future use.
- Identifying data/samples that have limitations on future uses and ensuring that future uses are not contrary to those limits.

A separate IRB approval/determination will be required for each specific human subject research activity that uses identifiable data/specimens from the repository. Material transfer agreements will be used when necessary for the transfer of biological materials. Only de-identified samples will be released to ensure security and confidentiality during the release of data and specimens.

8. Data Analysis

Objective 1:

The primary endpoint will be a 50% reduction in corticosteroid requirement in at least 60% subjects (or 3/5 of the subjects) by week 16, without significant decline in their pulmonary function—defined as a >15% decline in FVC, FEV1, or DLCO relative to the baseline value.

Objective 2:

The secondary endpoints include significant decreases in of peripheral markers of STAT pathway activity using RNA sequencing and CXCL10 levels, both measured before and after 16 weeks of tofacitinib treatment.

RNA sequencing will be done using before the study drug is started, and at week 16. We will evaluate STAT1-dependent gene expression as detected in our prior publication. (18) In our previous study, we found that of the 13/18 genes known to be downstream of STAT1 were upregulated in the peripheral blood of sarcoidosis patients (WARS, A2M, CCND1, CD64, MT-1, TRH, IRF-1, PSMB9, MHC2TA, OPRM1, Pim-1, CXCL9, and CDKN1A). We expect these 13 genes to be upregulated in the blood of pre-treatment subjects, and expect this expression level to significantly decrease in post-treatment subjects. An additional 8 genes in the JAK-STAT pathway were also found to be upregulated (IFNAR1, IFNAR2, IFNAR3, JAK1, JAK2, STAT1, STAT2, and STAT3). In a rheumatoid arthritis study of synovial biopsies before and after tofacitinib, STAT1 and STAT3 were found to be significantly decreased after tofacitinib treatment. (19) Interferon alpha receptors (IFNAR) are located upstream of the JAK-STAT pathway, and whether these expression profiles are expected to change is less clear. Expression of JAK 1, JAK2, STAT1, STAT2, and STAT3 are expected to significantly decrease with tofacitinib therapy. A paired T test will be used to compare expression levels at baseline and after 16 weeks of treatment, where a $p<0.05$ will be considered significant.

Finally, we will be measuring peripheral CXCL10 levels. STAT1 activation leads to CXCL10 transcription, making CXCL10 a valuable peripheral marker of JAK-STAT pathway suppression. (20) Serum levels of CXCL10 have been found to be elevated in the peripheral blood of patients with sarcoidosis, and were also be found to be associated with severity and chronicity of disease. (21) Peripheral expression of CXCL10 in the rheumatoid arthritis has been found to decrease after treatment with tofacitinib. (19) A pair T-test will be used to compare peripheral CXCL10 levels before and after 16 weeks of treatment, where a $p<0.05$ will be considered significant.

9. Privacy, Confidentiality, and Data Security

Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures. Paper files

will be stored in locked filing cabinets in restricted access offices at OHSU. Electronic data is stored on restricted drives on the OHSU network. Access to data/specimens is restricted to study personnel.

Upon completion of the trial, data will be de-identified and stored in a repository. Upon completion of the trial, subjects will be assigned a code that will be used instead of their name, medical record number, or other personally identifying information. Electronic files for data analysis will contain only the subject code. Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN). The key associating the codes and the subjects personally identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive in a limited access folder.

10. Provisions to Monitor the Data to Ensure the Safety of Subjects

See uploaded Data Safety Monitoring Plan form.

11. Risks and Benefits

a. Risks to Subjects

Blood draw: A blood draw may cause bleeding, a bruise, an infection, or fainting. Subjects may feel some pain when blood is drawn.

Pulmonary function testing or spirometry: Pulmonary function testing or spirometry may cause subjects to feel short of breath or dizzy for a few moments after the test.

Genetic testing: Although we will make efforts to protect subjects' identity, there is a small risk of loss of confidentiality. If the results of these studies of genetic makeup were to be accidentally released, it might be possible that the information we will gather could become available to an insurer or an employer, or a relative, or someone else outside the study. Even though there are certain genetic discrimination and confidentiality protections in both Oregon law and federal law, there is still a small chance that a subject could be harmed if a release occurred.

Study drug Tofacitinib:

Tofacitinib has been FDA approved for the treatment of rheumatoid arthritis, but not for the treatment of sarcoidosis. It is possible the risks of this drug in sarcoidosis are different from the risks in rheumatoid arthritis. In rheumatoid arthritis, this drug has been found to have the following risks: (22)

- Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving Tofacitinib. The most common serious infections reported with Tofacitinib included pneumonia, cellulitis, herpes zoster, urinary tract infection, and diverticulitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, esophageal candidiasis, pneumocystosis, multi-dermatomal herpes zoster, cytomegalovirus, and BK virus were reported with Tofacitinib. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids. Other serious infections that were not reported in clinical studies may also occur (e.g., histoplasmosis, coccidioidomycosis, and listeriosis).

    - *Overall Infections:* In the seven controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 20% and 22% in the 5 mg twice daily and 10 mg twice daily groups, respectively, and 18% in the placebo group. The most commonly reported infections with Tofacitinib were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (4%, 3%, and 2% of patients, respectively).

    - *Serious Infections:* In the seven controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who received placebo and

11 patients (1.7 events per 100 patient-years) who received Tofacitinib 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 1.1 (-0.4, 2.5) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily Tofacitinib group minus placebo. In the seven controlled trials, during the 0 to 12 months exposure, serious infections were reported in 34 patients (2.7 events per 100 patient-years) who received 5 mg twice daily of Tofacitinib and 33 patients (2.7 events per 100 patient-years) who received 10 mg twice daily of Tofacitinib. The rate difference between Tofacitinib doses (and the corresponding 95% confidence interval) was -0.1 (-1.3, 1.2) events per 100 patient-years for 10 mg twice daily Tofacitinib minus 5 mg twice daily Tofacitinib. The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection.

- *Tuberculosis:* In the seven controlled trials, during the 0 to 3 months exposure, tuberculosis was not reported in patients who received placebo, 5 mg twice daily of Tofacitinib, or 10 mg twice daily of Tofacitinib. In the seven controlled trials, during the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of Tofacitinib and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of Tofacitinib. The rate difference between Tofacitinib doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily Tofacitinib minus 5 mg twice daily Tofacitinib. Cases of disseminated tuberculosis were also reported. The median Tofacitinib exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days).

- *Opportunistic Infections (excluding tuberculosis*): In the seven controlled trials, during the 0 to 3 months exposure, opportunistic infections were not reported in patients who received placebo, 5 mg twice daily of Tofacitinib, or 10 mg twice daily of Tofacitinib. In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.3 events per 100 patient-years) who received 5 mg twice daily of Tofacitinib and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of Tofacitinib. The rate difference between Tofacitinib doses (and the corresponding 95% confidence interval) was 0 (-0.5, 0.5) events per 100 patient-years for 10 mg twice daily Tofacitinib minus 5 mg twice daily Tofacitinib. The median Tofacitinib exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days)

- <u>Malignancies and Lymphoproliferative Disorders:</u> In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving Tofacitinib with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with Tofacitinib. In Phase 2B, controlled dose-ranging studies in de-novo renal transplant patients, all of whom received induction therapy with basiliximab, high dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with Tofacitinib (2.3%) compared to 0 out of 111 patients treated with cyclosporine. Non-melanoma skin cancers have been reported in patients treated with Tofacitinib and identified as an adverse drug reaction.

  - *Malignancy:* In the seven controlled trials, during the 0 to 3 months exposure, malignancies excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient-years) who received either Tofacitinib 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient-years for the combined 5 mg and 10 mg twice daily Tofacitinib group minus placebo. In the seven controlled trials, during the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily

of Tofacitinib and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of Tofacitinib. The rate difference between Tofacitinib doses (and the corresponding 95% confidence interval) was 0.2 (-0.4, 0.7) events per 100 patient-years for 10 mg twice daily Tofacitinib minus 5 mg twice daily Tofacitinib. One of these malignancies was a case of lymphoma that occurred during the 0 to 12 month period in a patient treated with Tofacitinib 10 mg twice daily. The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma

- Gastrointestinal Perforation: Events of gastrointestinal perforation have been reported in clinical studies with Tofacitinib in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known.

- Laboratory Abnormalities: Treatment with Tofacitinib was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean absolute lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm3 were associated with an increased incidence of treated and serious infections. Treatment with Tofacitinib was associated with an increased incidence of neutropenia (less than 2000 cells/mm3) compared to placebo. Treatment with Tofacitinib was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy.

- Treatment with Tofacitinib was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

    - *Lymphopenia:* In the controlled clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm3 occurred in 0.04% of patients for the 5 mg twice daily and 10 mg twice daily Tofacitinib groups combined during the first 3 months of exposure. Confirmed lymphocyte counts less than 500 cells/mm3 were associated with an increased incidence of treated and serious infections.

    - *Neutropenia:* In the controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm3 occurred in 0.07% of patients for the 5 mg twice daily and 10 mg twice daily Tofacitinib groups combined during the first 3 months of exposure. There were no confirmed decreases in ANC below 500 cells/mm3 observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections. In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical trials.

    - *Liver Enzyme Elevations:* Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with Tofacitinib. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of Tofacitinib, or reduction in Tofacitinib dose, resulted in decrease or normalization of liver enzymes. In the controlled monotherapy trials (0-3 months), no differences in the incidence of ALT or AST elevations were observed between the placebo, and Tofacitinib 5 mg, and 10 mg twice daily groups. In the controlled background DMARD trials (0-3 months), ALT elevations greater than 3x ULN were observed in 1.0%, 1.3% and 1.2% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these trials, AST elevations greater than 3x ULN were

observed in 0.6%, 0.5% and 0.4% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. One case of drug-induced liver injury was reported in a patient treated with Tofacitinib 10 mg twice daily for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT greater than 3x ULN and bilirubin elevations greater than 2x ULN, which required hospitalizations and a liver biopsy.

- *Lipid elevations:* In the controlled clinical trials, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure and remained stable thereafter. Changes in lipid parameters during the first 3 months of exposure in the controlled clinical trials are summarized: Mean LDL cholesterol increased by 15% in the Tofacitinib 5 mg twice daily arm and 19% in the Tofacitinib 10 mg twice daily arm. Mean HDL cholesterol increased by 10% in the Tofacitinib 5 mg twice daily arm and 12% in the Tofacitinib 10 mg twice daily arm. Mean LDL/HDL ratios were essentially unchanged in Tofacitinib-treated patients. In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy. In the long-term safety population, elevations in lipid parameters remained consistent with what was seen in the controlled clinical trials.

- *Serum creatinine elevations:* In the controlled clinical trials, dose-related elevations in serum creatinine were observed with Tofacitinib treatment. The mean increase in serum creatinine was <0.1 mg/dL in the 12-month pooled safety analysis; however, with increasing duration of exposure in the long-term extensions, up to 2% of patients were discontinued from Tofacitinib treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

- Other adverse reactions: The following occurred in at least 2% or more of patients and at least 1% greater than that observed in patients on placebo:

	Tofacitinib 5 mg Twice Daily	**Tofacitinib 10 mg Twice Daily***	**Placebo**
Preferred Term	**N = 1336 (%)**	**N = 1349 (%)**	**N = 809 (%)**
Diarrhea	4.0	2.9	2.3
Nasopharyngitis	3.8	2.8	2.8
Upper respiratory tract infection	4.5	3.8	3.3
Headache	4.3	3.4	2.1
Hypertension	1.6	2.3	1.1
N reflects randomized and treated patients from the seven clinical trials			

- Adverse reactions occurring in controlled and open-label extension studies include:
  - Blood and lymphatic system disorders: Anemia
  - Infections and infestations: Diverticulitis
  - Metabolism and nutrition disorders: Dehydration
  - Psychiatric disorders: Insomnia
  - Nervous system disorders: Paresthesia
  - Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion
  - Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea
  - Hepatobiliary disorders: Hepatic steatosis
  - Skin and subcutaneous tissue disorders: Rash, erythema, pruritus
  - Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia, tendonitis, joint swelling

- Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin cancers
- General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

- Pregnancy and Teratogenic effects: Pregnancy Category C. Pregnant and breastfeeding women will not be included in this trial.

b. Potential Benefits to Subjects

The purpose of this trial is to determine if Tofacitinib is an effective therapy in sarcoidosis. If this therapy is effective, subjects may see a symptomatic improvement and a reduction in corticosteroid requirement. Subjects who meet the primary endpoint will go on to a one-year extension where they will be given the study drug free of cost.

12. Resources Available

This study involves RNA extraction and RNA sequencing, which requires special resources through the Gene Profiling Shared Resource (GPSR). Dr. Christina Harrington is the director of the GPSR and will be assisting with this study.

13. Drugs or Devices

We will follow the applicable Research Pharmacy policies and procedures and provide Research Pharmacy with a pharmacy manual for the study.

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