Interleukin-1 Blockade for Treatment of Cardiac Sarcoidosis

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Interleukin-1 blockade in cardiac sarcoidosis

Unique Protocol Identification Number: MAGiC ART

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Principal Investigator: Jordana Kron

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Summary of Changes from Previous Version: 10012020 v 2.001

Affected Section(s)	Summary of Revisions Made	Rationale
1.1	Study duration increased to 36 months.	The duration of the study will continue for 36 months, in part due to COVID-19 pandemic-related delays.
5.1, 6.5	Changed inclusion criteria, added 4. to indicated need for 'stable medical therapy for cardiac sarcoidosis for at least 30 days'.	This is to clarify that it is important to avoid changes in background therapies would influence the findings of the study.
5.2, 6.5, 8.2.2	Changed exclusion criteria, added 8. to include only Tumor Necrosis Factor-α blockers as contra-indicated medications. This is also clarified in Concomitant Medications and Risks Reduction Strategies for Anakinra treatment.	This is consistent with the Food & Drug Administration Prescribing Information for Anakinra (Kineret®) that allows the drug to be prescribed with other immunomodulating medications other than Tumor Necrosis Factor-α blockers. This will reduce the number of screen failures among the patients being considered.
8.1.1	Changes to biomarkers, added the use of additional exploratory cytokine bioassays available through LabCorp. We deleted the plan for storage of samples at VCU as part of this study.	The additional cytokine bioassays may provide insight into the pathobiology of the disease.

Summary of Changes from Previous Version: 070720 v 1.011

Affected Section(s)	Summary of Revisions Made	Rationale

1.1, 1.2, 4.1, 6.1, 6.2, 6.3, 7.1, 9.1, 9.2, 9.3	Change from double-blind to open-label study design	Lack of availability placebo syringes.
1.1	Added in the Synopsis that Interval changes in CRP represents a secondary endpoint in this feasibility study but also the primary efficacy endpoint.	Clarification needed for consistency between the different sections of the protocol.
1.3	Explanation of time window for baseline assessments; added comment on flexibility related to COVID-19 pandemic emergency.	Provide explanation about planned timing for interventions.
8.1.3	Minor reformatting to indicate that ECG Holter monitoring will be performed both at VCU and UMich. Also added that operators interpreting the study will be blinded to treatment allocation.	Clarification and adding blinded assessment piece.
8.1.4	Comment added that cardiac magnetic resonance operators interpreting the study will be blinded to treatment allocation.	Clarification and adding blinded assessment piece.

Additional minor changes throughout the text to maintain consistent in terminology used.

Summary of Changes from Previous Version: 061020 v 1.010

Affected Section(s)	Summary of Revisions Made	Rationale
1.2, 6.2.4	Eliminating the 14 day drug dispensing visit.	We have now access to placebo syringes allowing to prepare a 28-day supply and not requiring re-dosing after 14 days.
1.1, 1.2, 1.3, 3.0, 8.1.5, 8.2.3, 9.1	Eliminating cardiopulmonary exercise testing.	Increased risk for aerosol transmission of viral particles, need for PCR testing before each test. Of note this is only a test done for a sub-study at VCU only.
5.2	Evidence of COVID-19 within the last 60 days or recent (21 days) exposure to close personal contact with COVID-19.	Exclude patients with COVID-19 or at risk for COVID-19.
10.1.6	DSMB Liaison has been transitioned to Amy Ladd, PhD.	Chris DeWilde has left VCU.

Summary of Changes from Previous Version: 020420 v 1.009

Affected Section(s)	Summary of Revisions Made	Rationale
1.1	Clarified that arrhythmia assessment will be done at both VCU and Michigan.	Accurate representation of events.
1.2	Schema figure updated. Figure shows that Holter will be performed at both centers; the figure no longer specifies which diagnostic criteria since both HRS and Japanese criteria may be used.	Accurate representation of events.
1.2	Protocol schematic revised to show that labs will not be drawn at 6 months.	Accurate representation of events.
5.1	Clarification of inclusion criteria to include to include the Japanese Diagnostic criteria as an alternative to the Heart Rhythm diagnostic criteria.	It is common clinical practice to use Japanese criteria specifically to diagnose isolated cardiac sarcoidosis.
8.1.1	Added that samples will be collected at baseline at VCU for a cardiac sarcoidosis repository and stored unidentified.	Accurate representation of events.
8.1.3	Clarification of potential need for a chest radiograph in selected patients to determine the presence of fractured or retained device leads.	It is common clinical practice to obtain chest radiograph prior to cardiac magnetic resonance when presence of fractured or retained device leads cannot be excluded.
8.2.3	Clarification of risk related to chest radiograph for selected patients.	Description of risk.

Summary of Changes from Previous Version: 010720 v 1.008

Affected Section(s)	Summary of Revisions Made	Rationale
1.3	Clarified that arrhythmia assessment will be done at both VCU and Michigan	Research plan includes arrhythmia assessment at both centers.
1.3	Clarified which safety labs and which inflammation labs will be drawn including pregnancy test (if applicable).	Specific labs drawn at each time point had not been specified.
5.2	Clarified which other immunosuppression therapies patients may be on.	Allowed and excluded concomitant therapies was not clear.

5.2	Clarified that patients with severe kidney disease will be excluded.	To optimize safety, patients with severe renal disease will be excluded.
6.5	Clarified that stable doses of steroids is defined as > 1 month and allowed dose is <0.5 mg/kg/day.	Allowed dose of concomitant steroids was not clear.

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Statement of Compliance

Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below. If the study is an ***intramural*** *NIH study, use the second statement below:*

1. The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

    - United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

    National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.
    OR
2. The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the [specify NIH Institute or Center (IC) [Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.
    For either option above, the following paragraph would be included:
    The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Interleukin-1 blockade in cardiac sarcoidosis

Study Description: A Randomized Open-label Feasibility and Safety Pilot Study

Objectives:

Primary Objective: To determine feasibility of recruitment and tolerability of treatment with anakinra on top of standard anti-inflammatory therapy in patients with cardiac sarcoidosis

Secondary Objectives: 1) To determine the effects of anakinra on systemic inflammation measured by plasma-derived inflammatory biomarkers in patients with cardiac sarcoidosis (Primary Efficacy Endpoint).
2) *To longitudinally detect and monitor myocardial inflammation and fibrosis in cardiac sarcoidosis patients with cardiac magnetic resonance (CMR) and positron emission tomography (PET) imaging[Imaging Substudy @ VCU].*

Endpoints:

Primary Endpoint:

- *Number of subjects enrolled, stratified by race/ethnicity [Feasibility Endpoint]*
- *Interval changes in inflammatory biomarkers (CRP and IL-6) after 4 weeks of treatment with anakinra [Efficacy Endpoints].*

Secondary Endpoints:

- *Clinical outcomes:*
  - *incidence of death (cardiac and non-cardiac)*
  - *hospitalization (for cardiac and non-cardiac reasons)*
  - *change in medication use for sarcoidosis (number and doses)*
  - *change in medication use for heart disease (number and doses)*
  - *Adverse events at 28, 60, and 180 days*

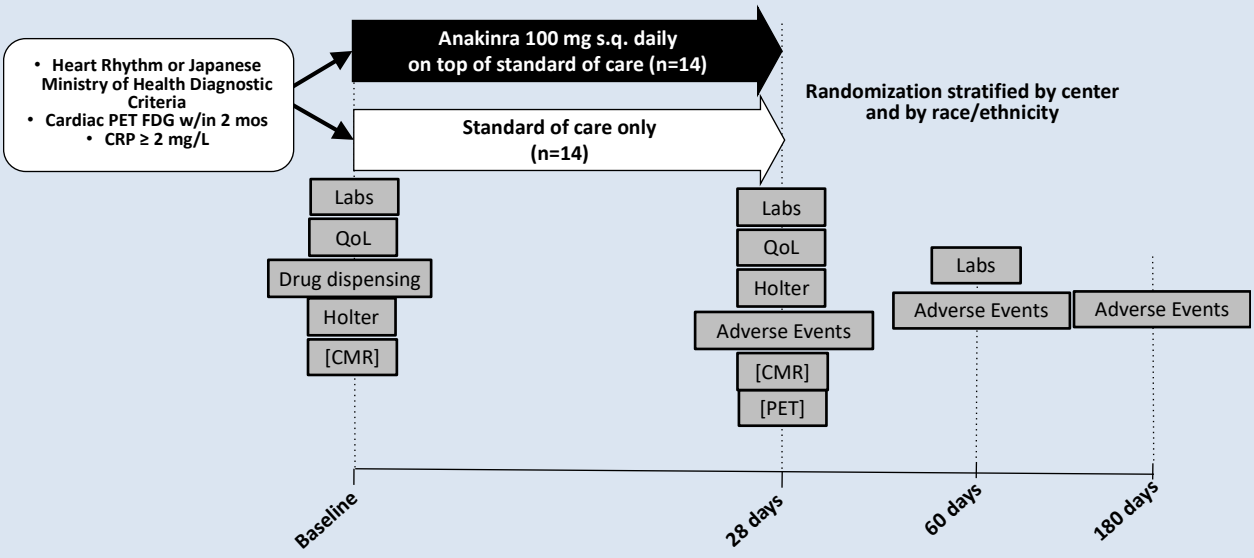
- *24 hour Holter arrhythmia assessment:*
    - *Number, duration, and rate of sustained VT*
    - *Number, duration, and rate of non-sustained VT*
    - *absolute number and percentage of premature ventricular contractions*
    - *number and type of AV blocks*
    - *number and duration of sinus pauses*
    - *occurrence of atrial arrhythmias*
- *Quality of life assessment with Sarcoidosis Assessment Tool*

[For the Imaging Substudy @ VCU]

- *Cardiac magnetic resonance imaging*
    - *change in left ventricular ejection fraction*
    - *change in late gadolinium enhancement*
- *Cardiac FDG PET*
    - *change in intensity of tracer uptake*

Study Population:	28 patients (age >21 years) with a clinical diagnosis of cardiac sarcoidosis, cardiac uptake on FDG-PET within 2 months, CRP high-sensitivity assay ≥ 2 mg/L
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	Virginia Commonwealth University, Richmond, VA University of Michigan, Ann Arbor, MI
Description of Study Intervention:	Two-center, randomized, open-label, clinical trial with allocation to Anakinra Anakinra 100 mg daily on top of standard of care or standard of care only in 1:1 ratio for 28 days
Study Duration:	36 months
Participant Duration:	180 days

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening visit (within 30 days)	Randomization / Treatment day 1	28±3 days	60±7 days	180±7 days
Inclusion/Exclusion criteria and Informed Consent	**X**	**X**			
Clinical Assessment (history and physical exam)	**X**	**X**	**X**		
Safety laboratory tests (CBC with diff, CMP, [urine pregnancy at randomization as applicable])	**X**		**X**	**X**	
Inflammatory biomarkers (hsCRP, IL-6)	**X**		**X**		
Quality of life (QoL) assessment	**X**		**X**		
Investigational drug dispensing (education on storage and self-administration)		**X** for anakinra group			
Assessment for adverse events (in-person or by telephone)			**X**	**X**	**X**

Arrhythmia assessment with 24-hour ECG Holter	**X**	**X** ±14 days
[Cardiac magnetic resonance]	***[X]***	***[X]*** ±14 days
[Cardiac PET scan]	***[X]*** within 60 days	***[X]*** ±14 days

Procedures indicated in [brackets] denote additional testing done as part of the VCU Imaging Substudy.

*_indicates complete blood cell count with differential and comprehensive metabolic profile at each time point, and pregnancy test at initial visit (if applicable)

Considering the ongoing COVID-19 pandemic emergency, the PI will consider potential deviation to the protocol if needed to promote the safe conduct of the research.

2 INTRODUCTION

2.1 STUDY RATIONALE

The current study is designed to test the hypothesis that *IL-1 activation represents a shared molecular mechanism common to different forms of cardiomyopathy*, and that **IL-1 blockade with anakinra can safely modulate systemic and cardiac inflammation in patients with a rare form of sarcoidosis affecting the heart.**

2.2 BACKGROUND

Cardiac sarcoidosis is a rare presentation of sarcoidosis involving the heart that disproportionately affects young people, more commonly African-American women than other groups. Cardiac sarcoidosis can cause serious arrhythmic complications leading to death. Corticosteroids are the standard treatment for sarcoidosis yet the evidence for efficacy is largely lacking and their use is associated with significant toxicities. *There is no proof of survival benefit* from corticosteroids and **there have been no randomized clinical trials for patients with cardiac sarcoidosis.**

There is a dearth of safe, targeted anti-inflammatory therapies for patients with cardiac sarcoidosis. Interleukin-1 is the prototypical pro-inflammatory cytokine that is involved in virtually every acute process. Studies suggest IL-1 plays a role in the pathogenesis of sarcoidosis and we have demonstrated the presence of the inflammasome, a macromolecular structure that produces cytokines including IL-1, in the granulomas of heart tissue in patients with cardiac sarcoidosis. While IL-1 plays a role in the pathogenesis of granuloma formation in sarcoidosis, the effects of IL-1 blockade have never been evaluated as a potential therapeutic agent for cardiac sarcoidosis. IL-1 blockers have been widely studied in patients with heart disease, showing a low rate of predictable complications, making it the preferred anti-inflammatory agent to be studied in cardiac sarcoidosis.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Anakinra is a recombinant human IL-1 receptor antagonist that has been FDA-approved for the treatment of inflammatory disorders such as rheumatoid arthritis for many years. In pilot clinical trials, anakinra has led to improved cardiovascular function in patients with rheumatoid arthritis, ST-segment elevation acute myocardial infarction, and chronic systolic heart failure. The use of anakinra as an anti-inflammatory treatment for cardiac sarcoidosis is justified by anakinra's relatively low risk/benefit ratio. Anakinra has been used in more than 150,000 patients with rheumatoid arthritis with a favorable risk profile.[1]

Anakinra is given as a subcutaneous injection of 100 mg (0.67 mL) daily or every other day in patients with severe impairment in renal function. There is no loading dose and no dose-adjustments needed with age, weight, or liver failure. Drug-to-drug interactions have not been reported. There are no known toxic effects of anakinra in pregnancy (category B), however pregnant women will be excluded from this research study. In a study following patients with rheumatoid arthritis for up to 3 years, anakinra was generally well-tolerated with few side effects.

The most likely side effects associated with the use of anakinra include:

- Injection site reaction (>10%, up to 50%, but infrequently leading to interruption of treatment <5%)
- Serious Infection (1.8% in anakinra vs 0.6% in placebo in clinical trial of rheumatoid arthritis);
- Headache, generally mild and self-limiting (1-10%);
- Diarrhea, generally mild and self-limiting (1-10%);
- Nausea, generally mild and self-limiting (1-10%);
- Hypersensitivity reaction (rash, anaphylaxis, arthritis)(rare, 1-2%).
- Neutropenia (rare, <1%, reversible).

The injection site reactions are by far the most common adverse reaction.[2] The reactions present as painful irritation/redness at the site of injection usually occurring 1-2 weeks after start of treatment. They are responsive to topical steroids and/or antihistamine therapy. The reactions are common (up to 50%) but rarely cause of discontinuation of therapy (<5%).

Despite the increase in risk of serious infection with anakinra, such events are rather rare (<2% during chronic treatment in patients with rheumatoid arthritis already on other immunomodulating drugs [observational data]). Anakinra is indeed not associated with an increase in infection-related mortality, nor associated with opportunistic infection. In clinical trials with anakinra, the infection rates did not differ between active treatment and placebo. Anakinra may, however, mask some of the signs of infection such as fever and leukocytosis, and therefore education on the need to be aware of risk of infection is warranted. Nevertheless, when given to patients with sepsis in the setting of a clinical trial, anakinra had no negative effect on survival. While anakinra is postulated to prevent inflammatory-based hypercoagulability, anakinra has not been associated with any appreciable bleeding risk in pre-clinical, clinical, or post-marketing surveillance (including animal studies at >100X the clinically relevant dose).

2.3.2 KNOWN POTENTIAL BENEFITS

In a series of phase II studies led by the PI of this proposal, Dr. Abbate [VCU], treatment with anakinra was shown to be safe and associated with reduced incidence of heart failure in patients with ST-segment elevation MI (STEMI)[3]and with improved cardiorespiratory fitness and quality of life in patients with systolic heart failure.[4], [5]In the large CANTOS trial of 10,061 patients with previous myocardial infarction and elevated CRP (≥2 mg/L), canakinumab, a monoclonal antibody blocking interleukin- 1beta, led to a 15% significantly lower rate of atherothrombotic events[6], a 36% reduction in need for coronary revascularization[6] and a dose-dependent reduction in hospitalization for heart failure.[7] In a small CANTOS substudy completed here at VCU by Dr. Abbate's team, patients with systolic heart failure treated with canakinumab experienced a significant improvement in cardiorespiratory fitness (peak VO2) and cardiac function (LVEF).[8] In all instances, the clinical improvement correlated with reduction of the systemic inflammatory biomarkers, namely CRP, showing a dose-response relationship between CRP reduction and benefits observed.

The hypothesis being tested is that Anakinra (Kineret) will inhibit the systemic inflammatory response in patients with cardiac sarcoidosis. As with all clinical trials, there is no guarantee that there is a benefit with anakinra. If anakinra treatment reduces inflammatory biomarkers, this could have a substantial potential benefit on the disease severity.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Importance of the Knowledge to be Gained

Cardiac sarcoidosis is a condition of deregulated inflammatory response in the heart, causing a granulomatous response. A role for IL-1 in the local and systemic inflammatory response in cardiac sarcoidosis has been proposed. IL-1 targeted therapies are available to treat several chronic inflammatory diseases. Clinical trials have shown a benefit of IL-1 blockade in acute myocardial infarction and heart failure. No targeted anti-IL-1 therapies have been tested in patients with cardiac sarcoidosis. The unanswered question remains whether IL-1 is a key mediator (versus a manifestation) of systemic and cardiac inflammation in cardiac sarcoidosis. This proposal will investigate whether IL-1 blockade can reduce systemic inflammatory biomarkers. The findings will then form the basis for the subsequent design of a phase II-III clinical trials.

Risks reduction strategies for Anakinra treatment

The risks associated with Anakinra appear to be mostly related to risk of infection (1.8% vs 0.6% of serious infections in a rheumatoid arthritis study), and injection site reactions. To better estimate the risk, one needs to place the estimates in context: the estimated 2% risk of serious infection with anakinra quoted in the FDA approved package insert refers to the use of anakinra/Kineret as second line agent for the treatment of rheumatoid arthritis, in which anakinra was used in addition to corticosteroids or other disease-modifying agents further increasing infectious risk. The risk of infection of anakinra monotherapy is not known, but it does not appear to be high. In a study cohort of patients with Neonatal Onset Multisystem Inflammatory Disease, another autoinflammatory condition for which anakinra is indicated, no dose limiting toxicities were reported for anakinra over the 148.1 patient-year study period: there were only 3 serious infections reported (2 wound infections and 1 gastroenteritis) and in all 3 cases, treatment

with anakinra was considered possibly related to the event, however treatment was not discontinued and patients improved with antibiotics. Moreover, if one considers the 'excess risk' of serious infection with anakinra to evenly distributed through the year, a treatment of 1 month, would lead to an excess risk that is less than then 1.2% difference reported in the prescribing information. Nevertheless, the inherent anti-inflammatory activity of anakinra may potentially mask some of the signs of infection such as fever and leukocytosis. In the CANTOS trial, canakinumab, another IL-1 blocker was associated with a 0.1% excess risk of life-threatening infection per year compared with placebo – canakinumab, at difference with anakinra, is long-acting and it cannot be stopped in case of infection, and therefore one would consider the risk of life-threatening infections with anakinra given for 1 month to be 10-fold lower than canakinumab for 1 year.

To reduce the risk of infections with anakinra we plan to follow the following strategies:

- Exclude patients with acute or chronic infections at time of screening;
- Exclude patients with concomitant biologic immunomodulating medications, such as TNF-a blockers;
- Exclude patients who are neutropenic;
- Educate patients on the possibility that symptoms or signs of infections may be less evident with taking the investigational drug;
- Provide patient with 24/7 phone access to investigators to discuss potential symptoms or signs of infection;

With this plan in place we have not seen any issues with severe infections since our first clinical trial with anakinra in acute STEMI in 2008 including now over 200 patients.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the feasibility of recruitment and tolerability of treatment with anakinra on top of standard anti-inflammatory therapy in patients with cardiac sarcoidosis.	Number of subjects screened, enrolled and treated, stratified according to race/ethnicity.	We have established target enrollment for minority representation of >40%, of which >30% African-American.
Secondary		
To determine the effects of anakinra on systemic inflammation measured by plasma-derived inflammatory biomarkers in patients with cardiac sarcoidosis.	Interval change in inflammatory biomarkers (CRP and IL-6) after 4 weeks of treatment with anakinra.	CRP and IL-6 are systemic inflammatory biomarkers that are surrogate for cardiovascular outcomes.
Tertiary/Exploratory		
To longitudinally detect and monitor myocardial inflammation and fibrosis in cardiac sarcoidosis patients with cardiac magnetic resonance (CMR) and positron emission tomography (PET) imaging[Imaging Substudy @ VCU].	We will measure changes in T1 and T2 mapping at CMR and in signal intensity at PET over time in the cohort.	T1 and T2 mapping at CMR are promising techniques for tissue level characterization of cardiomyopathies.

4 STUDY DESIGN

4.1 OVERALL DESIGN

We designed a randomized open-label study of anakinra 100 mg daily once daily for 28 days on top of standard of care in patients with cardiac sarcoidosis, cardiac FDG uptake on PET scan, and CRP ≥2 mg/L.

The study is composed of 2 treatment arms:

1. Anakinra 100 mg/0.67 mL daily subcutaneous injection on top of standard of care for 4 weeks [active treatment];
2. Standard of care only [control group].

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We chose to perform a pilot study a randomized, open label trial of 28 patients of anakinra 100 mg daily on top of standard of care versus standard of care only for 28 days to determine whether IL-1 blockade with anakinra is associated with a biological signal or not, based on surrogate endpoints of changes in systemic inflammatory biomarkers.

We believe that this small pilot study is a necessary initial step to determine feasibility and estimate the effect size of anakinra in a phase II study, to be followed by an appropriately powered multicenter RCT if the results of this pilot study prove promising.

This pilot study is structured to provide the necessary and sufficient information to make this determination.

4.3 JUSTIFICATION FOR DOSE

Anakinra is available for use with a label indication for rheumatoid arthritis and cryopyrin-associated periodic syndromes[9] and it has a very favorable safety profile.[10] The 100 mg daily subcutaneously is the currently approved dose on the FDA label, that has been shown to be efficacious across a wide range of clinical conditions, including heart failure,[11],[12] and also meets conditions for an IND exemption according to the criteria listed in § 312.2(b) of the federal regulation (see letter from FDA official). Treatment for 2-4 weeks has been shown to be efficacious in reducing inflammatory plasma biomarkers and improving exercise capacity in patients with systolic heart failure with New York Heart Association class II-IV symptoms.[4],[5],[13],[14],[15] We also recently completed a phase IB/II study in patients with pulmonary arterial hypertension and right ventricular failure treated with anakinra showing a significant reduction in inflammatory biomarkers after 2 weeks.[8] Anakinra 100 mg daily for 14 days was also as effective as 100

mg twice daily for 14 days in quenching the acute inflammatory response associated with ST segment elevation MI (Abstract presented at the ESC 2019).

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patients with sarcoidosis will be screened according to the following **criteria** *(all 3 criteria need to be met):*

Clinical diagnosis of cardiac sarcoidosis according to either the
Heart Rhythm Society Diagnostic Criteria based on one of the 2 diagnosis pathways (see below):

1. *Histological diagnosis from myocardial tissue* – cardiac sarcoidosis is diagnosed in the presence of non-caseating granuloma on histologic examination of myocardial tissue with no alternative cause identified (including negative stain for microorganisms – as applicable);

2. *Clinical diagnosis from invasive and/or non-invasive studies* – it is probable that there is cardiac sarcoidosis if there is (a) histological diagnosis of extracardiac sarcoidosis and (b) one or more of the following: steroid +/- immunosuppressant responsive cardiomyopathy or heart block; unexplained reduction in LVEF (<40%); unexplained sustained (spontaneous or induced) ventricular tachycardia; Mobitz type II 2nd degree or 3rd degree AV block; patchy uptake on dedicated cardiac PET (in a pattern consistent with cardiac sarcoidosis); late gadolinium enhancement on cardiac magnetic resonance (in a pattern consistent with cardiac sarcoidosis); positive gallium uptake (in a pattern consistent with cardiac sarcoidosis) and (c) other causes for the cardiac manifestation(s) have been reasonable excluded.

or the diagnostic guidelines for cardiac sarcoidosis based on New CS Guidelines in Japan (see below):

1. *Histological diagnosis group* (those with positive myocardial biopsy findings)
   Cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas.
2. *Clinical diagnosis group* (those with negative myocardial biopsy findings or those not undergoing myocardial biopsy)
   The patient is clinically diagnosed as having sarcoidosis:
   (1) When epithelioid granulomas are found in organs other than the heart and clinical findings strongly suggestive of the above-mentioned cardiac involvement are present (Table 1); or
   (2) When the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis; at least 2 of the 5 characteristic laboratory findings of a sarcoidosis (Table 2); and clinical findings strongly suggest the above-mentioned cardiac involvement (Table 1)

TABLE 1. Clinical findings defining cardiac involvement
Cardiac findings should be assess based on the major criteria and the minor criteria. Clinical findings that satisfy the following 1) or 2) strongly suggest the presence of cardiac involvement.
(1) 2 or more of the 5 major criteria (a)-(e) are satisfied.
(2) 1 of the 5 major criteria (a)-(e) and 2 or more of the 3 minor criteria (f)-(h) are satisfied.

1. Major criteria
   (a) High-grade AV block (including complete AV block) or fatal ventricular arrhythmia (e.g., sustained VT and VF)
   (b) Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional wall thickening
   (c) Left ventricular contractile dysfunction (LVEF < 50%)
   (d) ^{67}Ga citrate scintigraphy or ^{18}F-FDG PET reveals abnormally high tracer accumulation in the heart
   (e) Gadolinium-enhanced MRI revealed delayed contrast enhancement of the myocardium
2. Minor criteria
   (f) Abnormal ECG findings: Ventricular arrhythmias (nonsustained VT, multifocal or frequent premature ventricular contractions, bundle branch block, axis deviation, or abnormal Q waves
   (g) Perfusion defects on myocardial perfusion scintigraphy (SPECT)
   (h) Endomyocardial biopsy: Monocyte infiltration and moderate or severe myocardial interstitial fibrosis

Table 2. Characteristic laboratory findings of sarcoidosis

1. Bilateral hilar lymphadenopathy
2. High serum angiotensin-converting (ACE) activity or elevated serum lysozyme levels
3. High serum soluble interleukin-2 receptor (sIL-2R) levels
4. Significant tracer accumulation in 67Ga citrate scintigraphy or 18F-FDG PET
5. A high percentage of lymphocytes with a CD4CD8 ration of >3.5 in BAL fluid.

or the Diagnostic guidelines for isolated cardiac sarcoidosis based on New CS Guidelines in Japan

Diagnostic guidelines for isolated cardiac sarcoidosis

Prerequisite

3. No clinical findings characteristic of sarcoidosis are observed in any organs other than the heart. (The patient should be examined in detail for respiratory, ophthalmic, and skin involvement of sarcoidosis. When the patient is symptomatic, other etiologies that can affect the corresponding organs must be ruled out.)
4. ^{67}Ga scintigraphy or ^{18}F-FDG PET reveals no abnormal tracer accumulation in any organs other than the heart.
5. A chest CT scan reveals no shadow along the lymphatic tracts in the lungs or no hilar and mediastinal lymphadenopathy (minor axis>10 mm).

(1) Histological diagnosis group
Isolated cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas.

(2) Clinical diagnosis group
Isolated cardiac sarcoidosis is diagnosed clinically when criterion (d) and at least 3 other major criteria (a)-(e) are satisfied. (Table 1)

2. Cardiac fluoro-deoxyglucose uptake on recent PET (performed within the prior 60 days)

3. CRP high-sensitivity assay ≥2 mg/l (performed within the prior 60 days)

4. **On stable medical therapy for cardiac sarcoidosis for at least 30 days prior to randomization**

5.2 EXCLUSION CRITERIA

Subjects will not be eligible if they meet any one of the following exclusion criteria.

1. Age<21 years;
2. Pregnancy;
3. Inability to obtain consent from patient or legally authorized representative;
4. Contraindications to treatment with Anakinra (Kineret)(i.e. prior allergic reaction to the drug or to E. coli derived products or severe allergy to latex);
5. Severe anemia (*Hgb<8 g/dl - due to the need of more frequent blood sampling with this study*).
6. Acute or chronic active infections (*not including treated/cured HCV with negative viral load*).
7. Acute or chronic inflammatory disease other than sarcoidosis.
8. Treatment with Tumor Necrosis Factor-α blockers.
9. Active acute or chronic psychiatric illness that in the opinion of the investigator may prevent from complying with study instructions;
10. Limited English Proficiency that in the opinion of the investigator may prevent from understanding the content of the informed consent form or safely completing the study procedures.
11. Live vaccination within the prior month
12. Neutropenia (defined as absolute neutrophil count < 1,500/ml or <1,000/ml if subject is African American)
13. History of malignancy within the prior 5 years (with exception of basal cell skin cancer, carcinoma in-situ of the cervix or low risk prostate cancer after curative therapy)
14. Participation in another concurrent intervention study within 30 day or treatment with an investigational drug within 5 half-lives prior to randomization
15. *Severe kidney disease (GFR <30 mL/min/1.73m^2)*
16. *Evidence of COVID-19 within the last 60 days or recent (21 days) exposure to close personal contact with COVID-19.*
17. *[Chronic, moderate-to-severe kidney disease (GFR <60 mL/min/1.73m^2) or acute kidney injury, or history of severe hypersensitivity reactions to gadolinium-based contrast agents] – For VCU Imaging Substudy*

5.3 LIFESTYLE CONSIDERATIONS

There are no specific lifestyle considerations of restrictions required of patients during this study.

5.4 SCREEN FAILURES

Screen failures will not be included in the trial. Reasons for screening failure will be recorded. Individuals who do not meet the criteria for participation in this trial (screen failure) because of may be rescreened if the subsequently meet all inclusion criteria and do not have any exclusion criteria. Rescreened participants will be assigned a new participant number.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Virginia Commonwealth University

The VCU Sarcoidosis Clinic is an interdisciplinary, collaborative clinic established in 2014. Dr. Kron is a founding member of this clinic, which provides sarcoidosis patients evaluation by cardiology, pulmonary, and rheumatology specialists. The VCU Sarcoidosis Clinic was recognized as a World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG) Sarcoidosis Clinic in 2017. The multidisciplinary approach is unique in the region and one of only a few such clinics nationwide. The clinic provides care to a large volume of sarcoidosis patients in Richmond and Central Virginia and receives referrals from throughout the mid-Atlantic region. Since 2010, VCU has treated more than 1600 individual sarcoidosis patients in 12,160 patient encounters.

Dr. Kron has a dedicated cardiac sarcoidosis clinic each week, to our knowledge the only such clinic in the country. Over the past 4 years, Dr. Kron has enrolled 80 patients from the Sarcoidosis Clinic to participate in the Cardiac Sarcoidosis Consortium prospective registry. Of the more than 20 international sarcoidosis centers, VCU is in the top 2 for patient enrollment to the registry. In 2016, Dr. Kron enrolled 25 CS patients to participate in a prospective study evaluating circulating fibrocytes. Based on clinic volume and track record of patient enrollment, we feel we can recruit 8-10 patients per year to participate in the current study. We will monitor recruitment and we will quickly intervene to add referrals from nearby providers if needed. Dr. Kenneth Bilchick, University of Virginia Cardiac Electrophysiologist, has committed to support the study with patient referrals from the Charlottesville region.

University of Michigan

The University of Michigan Sarcoidosis Clinic is also recognized as a WASOG Sarcoidosis Clinic. Our team of physicians, which includes UMich investigators, Drs. Crawford and Bogun, works in concert to provide expert care to patients with this multi organ disease. It is a collaboration of providers from cardiac

electrophysiology and heart failure, as well we pulmonology, rheumatology, dermatology, and others. Cardiac patients are discussed at monthly cardiac sarcoidosis conferences, during which electrophysiologists, heart failure specialists, pulmonologists, and radiologists review cases and develop diagnostic and treatment plans for the reviewed patients. Due to the relatively high volume of the patients diagnosed with this rare disorder through the concerted effort of the physicians in the Sarcoidosis Clinic, UMich has enrolled almost 100 patients in the prospective International Cardiac Sarcoidosis Registry. A significant number of patients, who are strongly suspected of having the disorder due to their clinical presentation and imaging studies, but who lack the pathognomonic tissue biopsy, are also followed. Based on the clinic volume of the cardiac sarcoidosis patients and the interest of a number of physicians from various specialties, we feel confident that we will be well suited to enroll at least 8-10 patients annually in the proposed pilot study.

Retention Strategies

The patients are regularly followed in clinic and will be chosen for their compliance. The proposed study is also designed to be short, only 4 weeks. All study participants will receive cards with 24-hour/7-day contact number for study team members. This approach has been sufficient to achieve a 90% retention on average in prior studies of IL-1 blockade in HF at VCU. We will also implement a patient reimbursement for each completed study visit up to $100 for the completion of all study visits. We believe this may overcome some financial barriers that our patients at VCU Health and Michigan Medicine (formerly University of Michigan Health System) may experience related to the time and cost of travel. We will collect data on enrollment and retention barriers to help enhance the success of a future

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

We will select 28 patients and randomly assign them to treatment with anakinra 100 mg subcutaneously daily on top of standard of care or standard of care only for 4 weeks (1:1 ratio).

6.1.2 DOSING AND ADMINISTRATION

The study is composed of 2 treatment arms:

1. Anakinra 100 mg/0.67 mL daily subcutaneous injection for 4 weeks on top of standard of care [active treatment];
2. Standard of care only [control group].

6.2 Preparation/Handling/Storage/Accountability

6.2.1 ACQUISITION AND ACCOUNTABILITY

Anakinra dispensed in small syringes (0.67 mL) will be provided to the patient for daily subcutaneous injection.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Anakinra will be provided as commercially available Kineret® product.

6.2.3 PRODUCT STORAGE AND STABILITY

Anakinra should be stored in the refrigerator at 2 degrees C to 8 degrees C (36 degrees F to 46 degrees F). Anakinra should not be frozen or shaken. Anakinra should be protected from light.

6.2.4 PREPARATION

After completion of all baseline testing, patients randomized to anakinra will be given a 28-day supply of anakinra and will also receive instruction from the investigators regarding self-injection technique.

Adherence to the investigational treatment will be addressed by count of syringes and completion of all study visits. All concomitant medications will also be recorded at each clinic visit.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDED ASSESSMENT

Randomization will be handled by a member of the research team not involved in the consenting process using a dedicated randomization algorithm, stratified by center (VCU / UMich) and by race/ethnicity (Caucasian / Others).

Assessment of ECG Holter and of imaging, for substudy, will be performed by operators who are blinded to treatment allocation.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to the investigational treatment will be addressed by count of syringes and completion of all study visits. All concomitant medications will also be recorded at each clinic visit.

6.5 CONCOMITANT THERAPY

All concomitant medications and dosages will be recorded at each clinic visit.

Patients may be on stable [at least 30 days] doses of steroids (< 0.5 mg/kg/day) or steroid-sparing agents including methotrexate but not tumor necrosis factor-alpha (TNF-alpha) blockers.

6.5.1 RESCUE MEDICINE

The investigational treatment in this study is viewed as treatment to be added on top of current treatment on patients considered to be stable. If at any time, the subject requires intensification of the treatment for sarcoidosis including a drug that would be render the patient no longer a candidate for the study, the subject may choose to discontinue to study treatment and initiate the new treatment without delay. The subject may however not be able to continue the investigational drug treatment if a new immunosuppressive or biologic agent is added.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Reasons for discontinuation of treatment

Reasons for discontinuation of Anakinra:

- Systemic infection (sepsis)*;
- Surgery*;
- New diagnosis of cancer that requires local or systemic treatment;
- Hypersensitivity reaction (rash, anaphylaxis, arthritis);
- Severe injection site reactions*;
- Need for immunosuppressant therapy or treatment with a biologic agent (i.e. TNF-alpha blocker);
- Acute myocardial infarction or stroke*;
- Severe neutropenia (<1,000/mm3) if there is a perception of increased infectious risk by the provider*.

In the cases labelled by * treatment may be restarted by investigators after the condition is resolved.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patient withdrawal

Patients may withdraw from the study at any time. The investigators can withdraw any patient at any time from the study if medically necessary. Missing data will not be inputted. The decision regarding continuation or termination of the study will be solely based on safety data. Interim analyses will be performed by the DSMB as indicated below.

It will be documented whether or not each patient completed the study. If for any reason the study treatment or observations were discontinued, the reasons will be recorded and the IRB will be informed.

Reasons for early termination of the study

The decision regarding continuation or termination of the study will be solely based on safety data, and will be made by the DSMB. Interim analyses will be performed by the DSMB.

Halting rules

The study will be temporarily suspended if any of the following conditions are met:

- *Any serious adverse event that probably or definitely related to the investigational product*;

- The number of subjects experiencing a *serious* adverse event considered *unrelated or only possibly related* to the investigational product exceeds 50% (after the first 3 or more subjects are enrolled);

- The number of subjects experiencing *either a serious adverse event considered unrelated or only possibly related* to the investigational product or *a non-serious adverse event of at least moderate intensity that is probably or definitely related* to the investigational product exceeds 75%.

If any of these conditions are met, the enrollment is halted until the DSMB is given the opportunity to review the data. After the assessment of the DSMB, a discussion with the PI and the Sponsor (NCATS) should be held prior to the final decision to resume or permanently stop the study.

Example of data provided to the DSMB:

- [____] of subjects with serious AE considered probably or definitely related, if >0, halting rule

- [____] of subjects with serious AE considered unrelated or only possibly related, if >50%, halting rule

- [____] of subjects with serious AE unrelated or only possibly related + [_____] number of subjects with non-serious AE of at least moderate intensity probably or definitely related, if >75%, halting rule

7.3 LOST TO FOLLOW-UP

The investigational treatment will be given for 28 days. Participants will be followed for 180 days. The patients are regularly followed in clinic and will be chosen for their compliance. The proposed study is also designed to be short, only 4 weeks. All study participants will receive cards with 24-hour/7-day contact number for study team members. This approach has been sufficient to achieve a 90% retention on average in prior studies of IL-1 blockade in HF at VCU.

We will also implement a patient reimbursement of $100 for each of 3 compled study visits (Randomization Visit, 28-day Visit, and 60-day Visit) up to a total of $300 for completion of these study visits.

We believe this may overcome some financial barriers that our patients at VCU Health and Michigan Medicine (formerly University of Michigan Health System) may experience related to the time and cost of travel. We will collect data on enrollment and retention barriers to help enhance the success of a future phase 3 trial. The power analysis has also taken into account a potential loss of data at follow up to 20%. Missing data will not be inputted.

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 Biomarkers

Blood samples will be taken from a peripheral vein at time of screening, randomization visit and the 28-day visit, and used for analysis of inflammatory markers - high-sensitivity C reactive protein (CRP) and Interleukin-6 (IL-6).

Samples will be processed by the Department of Pathology at VCU or UMich, as standard of care tests are processed.

We will compare interval changes in CRP and IL-6 between the 2 groups using an analysis of variance (ANOVA) for repeated measures and assessing for time_x_group interaction.

Additional exploratory analyses will be conducted on cytokines from sera of patients with bioassays available through LabCorp.

8.1.2 Quality of life questionnaires

Quality of life (QoL) scores will be measured at randomization and 28-day visit with the disease-specific Sarcoidosis Assessment Tool (SAT), which has been shown to be reliable and consistent in sarcoidosis-specific patient reported outcomes at baseline and at 28 days. The 51 question SAT requires about 5 to 10 minutes to complete and is thus ideal for use in clinical settings. The SAT will be electronically administered as a REDCap survey on a printed format or a tablet during study visits with results directly built to a database. The scoring will be performed using a code provided by Dr. Marc Judson at University of Albany.

We will compare interval changes in SAT QoL scores between the 2 groups using an analysis of variance (ANOVA) for repeated measures and assessing for time_x_group interaction.

The following assessments of efficacy will be performed at VCU only as part of an imaging substudy.

8.1.3 ECG Holter Monitor

Cardiac sarcoidosis is associated with a high arrhythmia burden and an increased risk of sudden death. Even if asymptomatic, patients with cardiac sarcoidosis often have abnormal ECG Holter recordings. A 24-hour ECG Holter will be performed within 30 day of randomization and 28$\pm$14 days follow-up to quantitate arrhythmias. Arrhythmia data collected will include: (1) number, duration, and rate of sustained ventricular tachycardias; (2) number, duration, and rate of non-sustained ventricular

tachycardias; (3) absolute number and percentage of premature ventricular contractions; (4) number and type of AV blocks; (5) number and duration of sinus pauses; and (6) occurrence of atrial arrhythmias. Cardiac devices including defibrillators and pacemakers will be interrogated at baseline and at 28 days follow up to detect atrial and ventricular arrhythmia burdens, percentage of atrial and ventricular pacing, and any device malfunction. Operators blinded to treatment assignment will interpret the ECG Holter.

8.1.4 [Cardiac Magnetic Resonance – part of Imaging Substudy @VCU]

[Cardiac magnetic resonance will be performed within 30 days of randomization and after 28±14 days of randomization visit. Cardiac function (left ventricular volumes, mass, and strain) will be assessed with a steady-state free precession (SSFP) cine stack in the short axis plane covering the heart from base to apex. Orthogonal long axis SSFP cines will be acquired to quantify long axis strain and 3D circumferential strain obtained with the short axis images. Tissue characterization of scar and inflammation will also be included in the cardiac magnetic resonance imaging protocol. Prior to contrast, short axis slices of the left ventricle (basal, mid-cavity, apical) will be acquired to produce native T1 and T2 maps. Following gadolinium contrast administration, post-contrast T1 maps will be repeated and late gadolinium enhancement (LGE) images will be acquired in short axis slices covering the heart. When necessary, a wideband LGE acquisition will be used to improve image quality and reduce artifacts associated with implanted cardiac devices. All images will be acquired on a 1.5T Siemens Aera scanner and images will be post-processed using Circle CVI 42 software. In selected patients a chest radiograph may be necessary to determine the presence of fractured or retained device leads. Operators blinded to treatment assignment will interpret the ECG Holter.]

8.2 SAFETY AND OTHER ASSESSMENTS

This study involves greater than minimal risk related to treatment with an investigational drug, execution of non-invasive testing that are associated with a small, yet measurable risk, performance of multiple blood draws, risk of loss of privacy and confidentiality, and the possibility of incidental findings during the study investigations that may affect clinical care. The risk reduction strategies are presented herein. The risk/benefit ratio is discussed considering the potential beneficial effects of IL-1 blockade with anakinra in patients with recently decompensated systolic heart failure.

8.2.1 Potential risks associated with anakinra

Anakinra is a recombinant human IL-1 receptor antagonist that has been FDA-approved for the treatment of inflammatory disorders such as rheumatoid arthritis for many years. In pilot clinical trials, anakinra has led to improved cardiovascular function in patients with rheumatoid arthritis, ST-segment elevation acute myocardial infarction, and chronic systolic heart failure. The use of anakinra as an anti-inflammatory

treatment for cardiac sarcoidosis is justified by anakinra's relatively low risk/benefit ratio. Anakinra has been used in more than 150,000 patients with rheumatoid arthritis with a favorable risk profile.[16]

Anakinra is given as a subcutaneous injection of 100 mg (0.67 mL) daily or every other day in patients with severe impairment in renal function. There is no loading dose and no dose-adjustments needed with age, weight, or liver failure. Drug-to-drug interactions have not been reported. There are no known toxic effects of anakinra in pregnancy (category B), however pregnant women will be excluded from this research study. In a study following patients with rheumatoid arthritis for up to 3 years, anakinra was generally well-tolerated with few side effects.

The most likely side effects associated with the use of anakinra include:

- Injection site reaction (>10%, up to 50%, but infrequently leading to interruption of treatment <5%)
- Serious Infection (1.8% in anakinra vs 0.6% in placebo in clinical trial of rheumatoid arthritis);
- Headache, generally mild and self-limiting (1-10%);
- Diarrhea, generally mild and self-limiting (1-10%);
- Nausea, generally mild and self-limiting (1-10%);
- Hypersensitivity reaction (rash, anaphylaxis, arthritis)(rare, 1-2%).
- Neutropenia (rare, <1%, reversible).

The injection site reactions are by far the most common adverse reaction.[17] The reactions present as painful irritation/redness at the site of injection usually occurring 1-2 weeks after start of treatment. They are responsive to topical steroids and/or antihistamine therapy. The reactions are common (up to 50%) but rarely cause of discontinuation of therapy (<5%).

Despite the increase in risk of serious infection with anakinra, such events are rather rare (<2% during chronic treatment in patients with rheumatoid arthritis already on other immunomodulating drugs [observational data]). Anakinra is indeed not associated with an increase in infection-related mortality, nor associated with opportunistic infection. In clinical trials with anakinra, the infection rates did not differ between active treatment and placebo. Anakinra may, however, mask some of the signs of infection such as fever and leukocytosis, and therefore education on the need to be aware of risk of infection is warranted. Nevertheless, when given to patients with sepsis in the setting of a clinical trial, anakinra had no negative effect on survival. While anakinra is postulated to prevent inflammatory-based hypercoagulability, anakinra has not been associated with any appreciable bleeding risk in pre-clinical, clinical, or post-marketing surveillance (including animal studies at >100X the clinically relevant dose).

8.2.2 Risks reduction strategies for Anakinra treatment

The risks associated with anakinra appear to be mostly related to risk of infection (1.8% vs 0.6% of serious infections in a rheumatoid arthritis study[18]), and injection site reactions. To better estimate the risk, one needs to place the estimates in context: the estimated 2% risk of serious infection with anakinra quoted in the FDA approved package insert refers to the use of anakinra/Kineret as second line agent for the treatment of rheumatoid arthritis, in which anakinra was used in addition to corticosteroids or other disease-modifying agents further increasing infectious risk. The risk of infection of anakinra monotherapy is not known, but it does not appear to be high. In a study cohort of patients with Neonatal Onset Multisystem Inflammatory Disease, another autoinflammatory condition for which anakinra is indicated, no dose limiting toxicities were reported for anakinra over the 148.1 patient-year study period: there were only 3 serious infections reported (2 wound infections and 1 gastroenteritis) and in all 3 cases, treatment with anakinra was considered possibly related to the event, however treatment was not discontinued and patients improved with antibiotics. Moreover, if one considers the 'excess risk' of serious infection with anakinra to evenly distributed through the year, a treatment of 1 month, would lead to an excess risk that is less than then 1.2% difference reported in the prescribing information. Nevertheless, the inherent anti-inflammatory activity of anakinra may potentially mask some of the signs of infection such as fever and leukocytosis. In the CANTOS trial, canakinumab, another IL-1 blocker was associated with a 0.1% excess risk of life-threatening infection per year compared with placebo – canakinumab, at difference with anakinra, is long-acting and it cannot be stopped in case of infection, and therefore one would consider the risk of life-threatening infections with anakinra given for 1 month to be 10-fold lower than canakinumab for 1 year.

To reduce the risk of infections with anakinra we plan to follow the following strategies:

- Exclude patients with acute or chronic infections at time of screening;
- Exclude patients on TNF-alpha blockers;
- Exclude patients who are neutropenic;
- Educate patients on the possibility that symptoms or signs of infections may be less evident with taking the investigational drug;
- Provide patient with 24/7 phone access to investigators to discuss potential symptoms or signs of infection.

With this plan in place we have not seen any issues with severe infections since our first clinical trial with anakinra in acute STEMI in 2008 including now over 200 patients.

8.2.3 Testing Risks and Risk Reduction Strategies

There is a social/psychological risk in this study of breaching confidentiality and having a patient's diagnosis discovered. The likelihood of this occurring, however, is very low, and will be further lowered by creating a secure database that does not link patient identity with clinical data. Loss of confidentiality is also a potential risk. However, except when required by law, patients will not be identified by name,

social security number, address, telephone number or any other personal identifier. The number of study visits could impact some aspects of the patients' social lives.

All study procedures will be performed in standard clinical settings with established protections for patient privacy. To protect patient confidentiality, all records will be stored in a locked office and/or password protected encrypted files. All patient identifiers will be removed in any presentations or publications.

Vulnerable populations (i.e. prisoners, children) will not be eligible for participation. We will not include pregnant women.
Considering the small size and the pilot nature of this study, the uncertainties of the benefit, and the potential challenges of communication regarding side effects, we plan to exclude subjects with limited English proficiency.

The following risks pertain to the different tests that are being used for monitoring the treatment responses:

- Blood draw: minor bleeding (rare) and infection (extremely rare) at puncture site.
- Clinical assessment: no greater than minimal risk.
- Quality of life assessment: no greater than minimal risk.
- Adverse event assessment: no greater than minimal risk

While the results of the FDG-PET are used to determine inclusion criteria, FDG-PET is considered standard of care and only one test will be necessary for the study and not be performed for study purposes alone.

The ECG Holter monitoring has very little risk. The use of electrodes on the skin placed for 24 –or 48 hours can cause irritation to the skin.
All the tests are either no greater than minimal risk or rather low risk. Only trained and skilled personnel will be performing study procedures thus reducing the risk of error.
There is always the possibility of incidental findings of cardiac or non-cardiac abnormalities during the completion of the tests. The results will be reviewed by the PI and the other investigators, and when considered clinically significant the results will be communicated to the patient and documented in the electronic health record.

<u>The risks described below apply to the imaging substudy being completed at VCU alone:</u>
The risks associated with undergoing cardiac magnetic resonance include:
During the CMR, the patient may feel mild vibrations throughout the body. The machine will produce a loud knocking noise. The participant will be given earplugs to protect the ears. Some people, especially those who tend to feel uncomfortable in small or closed spaced, may feel "closed in" and become anxious

while in the scanner. The CMR will require a catheter to be inserted into one of the participant's veins in order to inject the CMR contrast agent. This may cause skin irritation, bleeding, and/or infection. The participant may have an allergic reaction to the contrast agent.

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF), a progressive fibrosis disease of the skin and internal organs, among patients with impaired elimination of the drugs. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2) as well as patients with acute kidney injury – patients with chronic moderate-to-severe kidney disease or acute kidney injury will be excluded from this study.

The magnetic field used in CMR scanning may harm people who have metal in their bodies (neurostimulators, certain clips, or staples from surgery). Gadolinium based contrast agents may remain in patients' bodies, including the brain, for months to years after receiving these drugs. Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function.
The participant's defibrillator will be FDA approved to undergo CMR and the defibrillator will be turned to CMR mode for the CMR. The risks are rare (<1% chance that this will happen) and include:

- *Abnormal fast or slow heart beats caused by the CMR.*
- *Discomfort due to slight movement or heating of the defibrillator.*
- *Fainting or passing out, worsening of heart failure.*
- *Mechanical damage to the defibrillator or leads caused by the CMR.*
- *Irregular defibrillator function caused by the CMR.*
- *Interruption of normal pacing or pacing too fast caused by the CMR.*
- *Device pacing irregularly or not continuously.*
- *Device not able to shock the heart.*
- *Increased pacing electricity needed to make the heart beat.*
- *Movement of the defibrillator or leads.*
- *Difficulty with the defibrillator being able to see your normal heart beat.*
- *Symptoms from the defibrillator making your heart beat at a slightly faster and fixed rate on purpose during the CMR.*
- *Death.*
- *For some devices, coming into contact with the strong magnetic field of a CMR scanner will likely damage the Beeper function on the defibrillator such that it may no longer be heard (Likely, > 50% chance that this will happen).*

- *The heart doctor can explain the potential risks of loss of beeper function. For example: The device will no longer beep when the battery is low and it is time to replace. However, the heart doctor will be able to check the battery status with a programmer at every clinic visit to make sure the device is replaced before the battery runs out - or - The device will no longer beep for certain patient conditions or device malfunctions. However, the physician can use a programmer to identify and react to these situations. Home monitoring systems will also identify such conditions and alert the heart doctor.*

- *There is a risk that the CMR will detect an unrelated health problem that may need to be evaluated and treated.*

In selected patients, there may be a need for a chest radiograph to exclude the presence of retained or fractured device leads. A chest radiograph exposes the patient to a very low dose of radiation, a negligible increased risk to health.

8.3 Adverse Events and Serious Adverse Events

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

Grading:

- **Mild:** events require minimal or no treatment and do not interfere with the daily activities.
- **Moderate:** events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and may require local or systemic drug therapy.
- **Severe:** events interrupt a patient's usual daily activity and will likely require systemic drug therapy or other treatment. Severe events are often incapacitating.
- **Serious or life threatening:** any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (it does not include a reaction that had it occurred in a more severe form, might have caused death), or results in hospitalization (or prolongation of a hospitalization), disability or permanent damage, need of a surgical intervention or device implantation to prevent disability, or death.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

Definitely related: The event is temporally related to the administration of the study intervention and, in the opinion of the investigator, no other etiology explains the event.

Probably related: The event is temporally related to the administration of the study intervention and represents, in the opinion of the investigator, the most plausible explanation of the event.

Possibly related: The event is temporally related to the administration of the study intervention but, in the opinion of the investigator, it does not represent the most likely explanation of the event.

Definitely Unrelated: The event is temporally independent of study intervention and/or the event appears, in the opinion of the investigator, to be explained by another etiology.

8.3.3.3 EXPECTEDNESS

Dr. Jordana Kron and/or Dr. Antonio Abbate will be responsible for the initial determination whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Dr. Jordana Kron and/or Dr. Antonio Abbate will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All suspected AEs must have their severity and relationship to study intervention assessed **as soon as possible** (possibly within 24 hours and always within 7 days).

All AE reporting not meeting requirements for required immediate SAE reporting, as described below, will be reported **in aggregate** to the DSMB and NCATS every 6 months and to the IRB every 12 months.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The MAGiC ART is an investigator-initiated study in which, for the purpose of the FDA, the investigator is also the sponsor.
The study is conducted under 21 CFR 312.2(b) regulation for IND exemption (as indicated by pre-IND inquiry 142352 of December 19, 2018 to Dr. Abbate)

All **co-investigators will be instructed to immediately report to the PI (functioning as PI/Sponsor) of any serious adverse event**, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

The PI/Sponsor is responsible to determine if the criteria for reporting to the DSMB/NCATS/FDA are met. The PI/Sponsor is also responsible for following all serious adverse events (SAEs) until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

The PI/Sponsor will be responsible for notifying the DSMB, NCATS, IRB and the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening **suspected adverse reaction** as soon as possible, but **in no case later than 7 calendar days**.

The PI/Sponsor must report any suspected adverse reaction that is both serious and unexpected.
The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, examples are: *(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); (B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); (C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group."*

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Individuals affected by AEs will be debriefed on an individual levels and provided the opportunity to discuss additional diagnostic and therapeutic options, as applicable. These may include discontinuation of investigational therapy, targeted treatments, additional testing. When appropriate, and only if with the consent of the subjects, the primary care physician will also be debriefed and a note will be added to the electronic health record to document the findings.

There will be no sharing of AEs in aggregate, other than what publicly disclosed in publications or presentations.

8.3.8 EVENTS OF SPECIAL INTEREST
Not applicable

8.3.9 REPORTING OF PREGNANCY
Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems **involving risks** to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- 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
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and the DSMB.

The UP report will include the following information:

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DSMB within 5 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DMSB within 5 days of the investigator becoming aware of the problem.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

There will be no prespecified reporting procedure to participants regarding UAP. Any reporting procedure would be discussed with the IRB.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Interval change in CRP levels from baseline to 28 days

We hypothesize that anakinra will reduce systemic inflammation as shown by CRP levels. CRP will be measured with a widely available high-sensitivity assay able to detect values in the normal range (<2 mg/l). Hs-CRP will be measured at randomization visit and again at 28±3 days. We will use ANOVA for repeated measures and assess time_x_group interaction to determine differences between changes in the anakinra on top of standard of care group versus standard of care only group.

- Secondary Efficacy Endpoint(s):

Interval change in IL-6 levels from baseline to 28 days

We hypothesize that anakinra will reduce systemic inflammation as shown by IL-6 levels. IL-6 will be measured with a widely available ELISA assay . IL-6 will be measured at randomization visit and again at 28±3 days. We will use ANOVA for repeated measures and assess time_x_group interaction to determine differences between changes in anakinra group versus control group.

Interval change in QoL scores at SAT

We hypothesize that anakinra will improve QoL scores on SAT questionnaires. QoL SAT will be measured at enrollment and again at 28±3 days. We will use ANOVA for repeated measures and assess time_x_group interaction to determine differences between changes in anakinra group versus control group

- *Additional Efficacy Endpoints(s) for Imaging Substudy available at VCU*

[Interval change in T2 mapping at CMR]

[We hypothesize that anakinra will reduce myocardial edema as measured by T2 mapping at CMR. T2 mapping will be completed within 30 days of randomization and again at 28±14 days. We will use ANOVA for repeated measures and assess time_x_group interaction to determine differences between changes in anakinra versus control.]

[Interval change in cardiac FDG-PET inflammation signal]

[We hypothesize that anakinra will reduce myocardial inflammation as measured by cardiac PET signaling. PET signaling will be completed within 60 days of randomization and again at 28±14 days. We will use ANOVA for repeated measures and assess time_x_group interaction to determine differences between changes in anakinra versus control.]

9.2 SAMPLE SIZE DETERMINATION

Using an informatics-based tool by TriNetX we ran a retrospective analysis of patients seen in the Cardiac Sarcoidosis Clinic at VCU in the past year: we identified 30 subjects with sarcoidosis who had CRP 3-20 mg/L (we excluded patients with CRP>20 mg/L as they may have had concomitant bacterial infection, and therefore could be excluded upon screening). The mean age was 55 years (range 37-82), 55% were men, and 77% were African American. The CRP was 7.64 ±3.74 mg/L (mean±standard deviation). We predict a reduction of CRP by >60% in the anakinra group and no change in standard of care only group. The Table below shows estimated power for CRP reduction between 50% and 75% in the active treatment group (on top of standard of care changes, which are expected to be close to 0), and we evaluated 3 different standard deviation (SD) values starting with 3.74 mg/l which was obtained from our VCU cohort and exploring 0.9x and 1.1x SD.

Power analysis	**CRP reduction** (estimated mean 7.64 mg/l)					
N=28	50%	55%	60%	65%	70%	75%
SD 3.37 mg/l	85%	91%	95%	97%	99%	>99%
SD 3.74 mg/l	77%	84%	90%	94%	97%	98%
SD 4.11 mg/l	69%	77%	84%	89%	93%	96%

9.3 POPULATIONS FOR ANALYSES

We plan to compare the 2 groups (anakinra and control) in an intention-to-treat analysis by which all patients who (1) met all inclusion/exclusion criteria and (2) were randomly assigned to one of the 2 groups were considered as 'treated' independent of whether the patients assigned to anakinra received all or some or any of the investigational treatment after randomization has been completed and treatment assigned. For exploratory purposes we will also perform a per-protocol analysis in which the individual subjects not only will need to meet conditions (1) and (2) but also (3) need to have reported compliance with >75% of investigational drug prescribed.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will compare the change using an ANOVA for repeated measures in which we assess for the significance of the interaction of treatment allocation and time interval (time_x_group interaction) using SPSS 25.0 (Chicago, IL). Additional exploratory endpoints will include absolute CRP values at 28 days, and the percentage of patients with CRP <2 mg/L at each time point. The interval change in CRP levels from baseline to 28 days will be expressed as median and interquartile range. All reporting will be in conjunction with the CONSORT statement.[19]

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

We therefore hypothesize that anakinra will reduce systemic inflammation as shown by CRP. CRP will be measured with a widely available high-sensitivity assay able to detect values in the normal range (<2 mg/l). CRP will be measured at enrollment and again at 28±3 days.

Interval change in CRP levels from baseline to 28 days will represent the primary endpoint.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

We will measure changes in IL-6, an additional inflammatory biomarker as a secondary endpoint. Changes in QoL scores will also be considered a secondary endpoint.

Additional secondary endpoints to be completed as part of the imaging substudy at VCU includes assessment of myocardial edema with T2 mapping at CMR, and myocardial inflammation with cardiac FDG-PET.

9.4.4 SAFETY ANALYSES

The DSMB will monitor the progress of the present trial. The DSMB will meet regularly to review safety data every 6 months or sooner in case of a serious unexpected adverse event that is considered to be possibly, probably or definitely related to the research. All meetings, and specifically any action taken by the committee and the reasons for the actions, will be recorded. These documents will include any data summaries or analyses provided to the DSMB and will remain confidential until the study is concluded. No interim efficacy analyses are planned.

Interim safety analyses will, however, be performed at each meeting. The DSMB will be provided with data related to adverse events. The DSMB may choose to stop enrollment on the basis of safety data observed. If safety concerns are found, further enrollment will not be allowed until issues are resolved. If no safety concerns are found, enrollment will continue until the target sample size is reached. The following pre-specified halting rules are provided to the DSMB as guidance.

Example of data provided to the DSMB:

- [____] of subjects with serious AE considered probably or definitely related, if >0, halting rule
- [____] of subjects with serious AE considered unrelated or only possibly related, if >50%, halting rule
- [____] of subjects with serious AE unrelated or only possibly related + [_____] number of subjects with non-serious AE of at least moderate intensity probably or definitely related, if >75%, halting rule

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The DSMB will be provided with the number of subjects enrolled, stratified by sex and race/ethnicity. Mean age and range will also be provided.

9.4.6 PLANNED INTERIM ANALYSES

There will be no planned efficacy interim analyses.

9.4.7 SUB-GROUP ANALYSES

Randomization will be stratified by site (VCU and UMich) and by race/ethnicity. Two pre-specified sub-group analyses includes site and race/ethnicity.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable.

9.4.9 EXPLORATORY ANALYSES

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The IRB-approved informed consent form is attached to this protocol as Appendix.

Potential participants will be approached by the investigators during their standard-of-care visits in the VCUHealth or UMich Sarcoidosis Clinic in private patient rooms. The investigator will review the consent form with the patients and invite them ask any questions about the study. All potential participants will be allowed to take the consent form home to review with friends/family or other health care providers. Once the potential participants have had all of their questions answered, they will be invited to sign the consent form.

Participants will not be coerced into participation. They will be advised that their refusal to participate will not affect their standard of care. All potential participants will be allowed to take the consent form home to review with friends/family or other health care providers. Participants will have as much time as needed to decide to participate or not. These are existing sarcoidosis patients that are regularly seen in the VCUHealth or UMich Sarcoidosis clinic.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific

procedures. 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.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, and funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or DSMB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital)

and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at VCU. This will not include the participant's contact or identifying information if the subject was enrolled at UMich. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by VCU research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at VCU.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Virginia Commonwealth University and UMich. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Virginia Commonwealth University. Permission to transmit data to the Virginia Commonwealth University will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at VCU. These samples could be used for research the causes of Sarcoidosis, its complications and other conditions for which individuals with Sarcoidosis are at increased risk, and to improve treatment.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for research.

Access to study data and/or samples will be no longer allowed after study completion.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

SEE DELEGATION LOG ON FILE

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, included in the list below. The DSMB for this study is formed according to the Food and Drug Administration guidance document [OMB Control No. 0910-0581]. The

DSMB liaison and coordinator, Amy Ladd, PhD, will provide the board members with data regarding screening, enrollment, adverse events and withdrawals, and he/she will not participate in the voting. Members of the DSMB are independent from the study conduct and free of conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NCATS.

The DSMB, whose members are independent from the study operations, is composed of 4 clinicians and a biostatistician not involved in the conduct of the study. The DSMB will include Dr. Lynda Rosenfeld (Professor of Medicine, Cardiac Electrophysiology, Yale University), serving as Chair of the board, Dr. Alpha Fowler (Director of VCU Johnson Center for Critical Care and Pulmonary Research), Dr. Melissa Smallfield (Associate Professor of Medicine, Advanced Heart Failure and Transplantation, VCU), and Dr. David Birnie (Deputy Chief and Directory of Research, University of Ottawa), and Le Kang, PhD (VCU Statistician). The DSMB will meet every 6 months or sooner in case of any unanticipated serious adverse events considered to be possibly, probably or definitely related to research.

The DSMB may request an expert opinion by one or more non-members, however only the DSMB members will vote on any individual issue. The DSMB (following positive vote by 3 or more members) may request temporary or permanent halting of the study (see halting rules), or interruption of treatment of one or more patients. The minutes from each meeting will be distributed to the board members, and not to the investigators, unless specifically requested by the DSMB. A brief conclusive statement addressing whether the study should continue as planned or not will be provided to the investigators and the IRB after every meeting which is to occur at least twice yearly.

DSMB Voting Members

Lynda Rosenfeld, MD DSMB Chair
Dr. Rosenfeld is a Professor of Medicine in Cardiology and Pediatrics at Yale University. She is board certified in Internal Medicine and Cardiovascular Disease. She is the Director of the Clinical Cardiac Electrophysiology Fellowship Program.
https://medicine.yale.edu/intmed/profile/lynda_rosenfeld/

Alpha Fowler, MD
Dr. Fowler is a Professor of Medicine in Pulmonary and Critical Care Medicine at VCU. He is board certified in Internal Medicine and Pulmonary Disease. He is the Director of the VCU Johnson Center for Critical Care and Pulmonary Research.
https://www.vcuhealth.org/find-a-provider/find-a-provider/Alpha-Fowler

Melissa Smallfield, MD

Dr. Smallfield is an Associate Professor of Medicine and serves as the Fellowship Program Director for Advanced Heart Failure and Transplantation. She is board certified in Internal Medicine, Cardiovascular Disease, and Advance Heart Failure and Transplant Cardiology.
https://www.vcuhealth.org/find-a-provider/find-a-provider/melissa-smallfield

David Birnie, MD
Dr. Birnie is a Professor of Medicine in Cardiology at the University of Ottawa Health Institute. He is the Deputy Division Head of Cardiology and the Director of Clinical Research for the Division of Cardiology.
https://www.ottawaheart.ca/physician-researcher-profile/birnie-david

Le Kang, PhD
Dr. Kang is an Assistant Professor in the Department of Biostatistics at VCU.
http://wp.vcu.edu/biostats/le-kang/

Non-voting Members
DSMB Liaison

Amy Ladd, PhD DMSB Liaison
Amy Ladd, PhD, CCRP is a Research Regulatory Manager in the Division of Cardiology at VCU.

NCATS Liaison

Pablo Cure, MD, MPH NCATS Liaison
Dr. Cure is the Program Director of the Division of Clinical Innovation at the National Center for Advancing Translational Sciences, NIH. He will be a non-voting member of the DSMB.

10.1.7 CLINICAL MONITORING

The DSMB will monitor the progress of the present trial. The DSMB will meet regularly to review safety data every 6 months or sooner in case of a serious unexpected adverse event that is considered to be possibly, probably or definitely related to the research.

All meetings, and specifically any action taken by the committee and the reasons for the actions, will be recorded. These documents will include any data summaries or analyses provided to the DSMB and will remain confidential until the study is concluded. No interim efficacy analyses are planned.

Interim safety analyses will, however, be performed at each meeting. The DSMB will be provided with data related to adverse events. The DSMB may choose to stop enrollment on the basis of safety data observed. If safety concerns are found, further enrollment will not be allowed until issues are resolved.

If no safety concerns are found, enrollment will continue until the target sample size is reached. The following pre-specified halting rules are provided to the DSMB as guidance.

Halting rules

The study will be temporarily suspended if any of the following conditions are met:

- *Any serious adverse event that probably or definitely related to the investigational product*;
- The number of subjects experiencing a *serious* adverse event considered *unrelated or only possibly related* to the investigational product exceeds 50% (after the first 3 or more subjects are enrolled);
- The number of subjects experiencing *either a serious adverse event considered unrelated or only possibly related* to the investigational product or *a non-serious adverse event of at least moderate intensity that is probably or definitely related* to the investigational product exceeds 75%.

If any of these conditions are met, the enrollment is halted until the DSMB is given the opportunity to review the data and consider the request for unblinding. After the assessment of the DSMB, a discussion with the PI and the Sponsor (NCATS) should be held prior to the final decision to resume or permanently stop the study.

Example of data provided to the DSMB:

- [____] of subjects with serious AE considered probably or definitely related à if >0 --> halting rule
- [____] of subjects with serious AE considered unrelated or only possibly related à if >50% --> halting rule
- [____] of subjects with serious AE unrelated or only possibly related + [_____] number of subjects with non-serious AE of at least moderate intensity probably or definitely related à if >75% --> halting rule

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into OnCore, a 21 CFR Part 11-compliant data capture system provided by the [specify DCC]. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within [specify number] working days of identification of the protocol deviation, or within [specify number] working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NCATS Program Official and Virginia Commonwealth University. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting [specify person or awardee institution or name of data repository].

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design,

conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCATS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMR	Cardiac Magnetic Resonance
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C Reactive Protein
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDG PET	Fluoro-de-oxy-glucose positron emission tomography
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption

IL-6	Interleukin-6
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NCATS	National Center for the Advancing Translational Sciences
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UMich	University of Michigan
UP	Unanticipated Problem
US	United States
VCU	Virginia Commonwealth University

11 REFERENCES

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