CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-blind, Placebo-controlled, Phase 2a Study with an Open-label Cohort to Assess the Safety, Tolerability, and Efficacy of Namilumab in Subjects with Active Cardiac Sarcoidosis
Protocol Number:	KIN-1902-2002
Protocol Name:	RESOLVE - Heart
Compound Name and/or Number:	Namilumab
Sponsor:	Kinevant Sciences GmbH Kinevant Sciences GmbH (KSG), a Swiss Limited Liability Company, is the Sponsor of this study. Kinevant Sciences, Inc. (KSI), a Delaware corporation and an affiliate of KSG, has been engaged by KSG to manage the day-to-day operations of the study. All references to "Sponsor" contained herein shall refer to KSI, acting pursuant to a services agreement with KSG. Kinevant Sciences GmbH Viaduktstrasse 8 CH-4051 Basel Switzerland Kinevant Sciences, Inc. 151 West 42nd Street, 15th floor New York, NY, 10036 USA
Development Phase:	2a
Indication:	Cardiac Sarcoidosis
Current Version and Effective Date:	Version 2.0 (Amendment 1): 14-April-2022
Study Director:	PPD Telephone: PPD Email: PPD

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SPONSOR SIGNATURE PAGE

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Protocol Number: KIN-1902-2002

This protocol has been approved by a representative of Kinevant Sciences, Inc. The following signature documents this approval.

PPD

PPD

Date

INVESTIGATOR SIGNATURE PAGE

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Protocol Number: KIN-1902-2002

- I confirm agreement to conduct the study in compliance with the protocol and International Conference on Harmonisation-Good Clinical Practice (ICH/GCP) guidelines;
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study;
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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PROTOCOL SYNOPSIS

Title of Study	A Randomized, Double-blind, Placebo-controlled, Phase 2a Study with an Open-label Cohort to Assess the Safety, Tolerability, and Efficacy of Namilumab in Subjects with Active Cardiac Sarcoidosis
Indication	Treatment of cardiac sarcoidosis (CS)
Study Centers	Approximately 20 sites within the US
Study Objective(s)	**Primary Objectives:** The primary objective of this study is: • To determine the safety and tolerability of namilumab in subjects with CS based on treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations. **Secondary Objectives:** The secondary objectives of this study include the following: • To evaluate other measures of safety and tolerability of namilumab; • To evaluate the efficacy of namilumab on cardiac inflammation determined by [18-F] fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) (FDG-PET/CT); • To assess the effect of namilumab on cardiac arrhythmia burden; • To assess the effect of namilumab on cardiac function; • To assess the effect of namilumab on cumulative oral corticosteroid (OCS) use and OCS toxicity; • To assess the effect of namilumab on use of rescue therapy; • To assess the effect of namilumab on patient-reported outcomes (PROs): o King's Sarcoidosis Questionnaire (KSQ); o Fatigue Assessment Scale (FAS); o Subject Global Assessment (SGA). • To assess the population pharmacokinetics (PPK) and exposure-response (E-R) relationships for efficacy and safety of namilumab.
Study Rationale	Sarcoidosis is a multi-organ autoimmune disease characterized by non-necrotizing granulomas believed to be formed from an exaggerated immune response to unidentified antigens. Granulomas are tight clusters of monocytes/macrophages and multinucleated giant cells (MGCs) interspersed with CD4+ T cells. Patients with CS have non-necrotizing granulomas affecting the heart and represent 5% of the total sarcoidosis population (approximately 10,000 people in the US).

	Granulocyte-macrophage colony-stimulating factor (GM-CSF), a pro-inflammatory cytokine and myeloid cell growth factor, is thought to play a key role in the granulomatous response by stimulating the fusion of macrophages into MGCs, activating the mobilization of monocytes/macrophages into tissue, and supporting the crosstalk between CD4+ T cells and myeloid cells. Successful late-phase clinical trials in rheumatoid arthritis, giant cell arteritis, and severe coronavirus disease 2019 (COVID-19) have solidified the pathogenic role of GM-CSF in aberrant immune responses. Human tissue and mouse model studies over the past 3 decades have implicated GM-CSF in the formation of normal granulomas and sarcoid granulomas. GM-CSF neutralization with namilumab has the potential to improve outcomes in CS by downregulating the granulomatous response that drives the disease.
Study Population	This study will include adult subjects with active CS.
Number of Planned Subjects	Approximately 30 total subjects are planned for this study in 2 cohorts; Cohort A will enroll 20 subjects; Cohort B will enroll 10 subjects.
Study Design	Cohort A will be 34-weeks duration, and will be double-blinded, randomized, and placebo-controlled. Twenty subjects will be enrolled; 10 subjects per arm will receive either namilumab or placebo. All subjects will also be treated with prednisone 25-60 mg/day, or equivalent, in addition to other immunosuppressive therapy (IST) they may already be receiving. The Investigator will determine the starting dose of OCS. Subjects will be treated with prednisone at a dose ranging between 25-60 mg/day, or equivalent. Subjects should begin OCS treatment any time after the completion of the screening PET scan through completion of the Baseline Visit. Note the timing requirement for the OCS and PET scan pertains to the intended study dose of OCS (25-60 mg/day of prednisone or equivalent) and not to any pre-existing treatment of ≤10 mg/day of prednisone or equivalent. Subjects must agree to taper OCS over 22 weeks after randomization. Cohort B is 34 weeks in duration, open-label, and with a single arm. Ten subjects will be enrolled. Eligible subjects for Cohort B are those who otherwise qualify for Cohort A but prefer not to receive high-dose OCS, or, in the opinion of the Investigator, are not suitable candidates to take prednisone 25-60 mg/day. The reason for not providing high-dose OCS should be documented in the subject's chart and source records. Subjects will receive open-label namilumab in addition to their background therapy without change to any ongoing OCS dose (≤10 mg/day of prednisone or equivalent) or IST medication(s) and dose(s).

Study Treatments	**Cohort A:** • Treatment Arm 1: Namilumab administered subcutaneously (SC): 150 mg on Day 1, Day 15 (Week 2), and then every 4 weeks (Q4W) thereafter through Week 30. • Treatment Arm 2: Placebo administered to match namilumab dosing. Subjects randomized to Treatment Arm 1 or 2 will also be treated with prednisone 25-60 mg/day, or equivalent, in addition to any other background IST they are already receiving. **Cohort B:** • Namilumab administered SC: 150 mg on Day 1, Day 15 (Week 2), and then Q4W thereafter through Week 30. Subjects enrolled in Cohort B must continue their background therapy without change to any ongoing OCS dose (≤10 mg/day of prednisone or equivalent) or ISTs.
Treatment and Study Duration	Participation will be approximately 44 weeks (308 days) as follows: • Up to 6-week (42 days) Screening Period; • 34-week (238 days) Treatment Period (with steroid tapering during the first 22 weeks for subjects participating in Cohort A); • Follow-up phone call approximately 4 weeks (28 days) after the End-of-Treatment (EOT) Visit (approximately 8 weeks [56 days] after the last dose of study drug at Week 30).
Study Endpoint(s)	**Primary Endpoints:** The primary endpoint of this study includes the following: • Incidence and severity of TEAEs, SAEs, and adverse events (AEs) leading to discontinuation. **Secondary Endpoints:** • Other safety endpoints including: o Incidence and magnitude of treatment-emergent laboratory abnormalities; o Change from baseline in vital signs; o Change from baseline in electrocardiogram (ECG) parameters.

	• Mean change from baseline in PET maximum standardized update value (SUVmax), SUVmean, and total glycosylation; • Cumulative arrhythmia burden and hospitalization for cardiac events; • Mean change from baseline in left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) on transthoracic echocardiogram (TTE); • Cumulative oral steroid use, modified glucocorticoid toxicity index (mGTI), and mean change from Baseline in glycosylated hemoglobin (HbA_{1C}); • Proportion of subjects requiring rescue therapy (either cohort) and proportion of subjects successfully achieving steroid taper without requiring rescue therapy (Cohort A); • Mean change from baseline in KSQ (General and sub-domains), Fatigue Assessment Scale (FAS), and Subject Global Assessment (SGA); • Assessments of PPK and E-R relationships for safety and efficacy if data permit. **Note:** For endpoints defined as mean change from baseline, the primary assessment will be at Week 34.
Inclusion Criteria	**An individual will be eligible for participation in this study only if all the following inclusion criteria are met:** 1. Male or female age ≥18 years. 2. Able and willing to provide written informed consent, which includes compliance with study requirements and restrictions listed in the consent form. 3. History of documented sarcoidosis (must include histological confirmation, from any organ, in the subject's medical history or records). 4. Meet Heart Rhythm Society Cardiac Sarcoid Diagnostic Criteria (modified). 5. PET SUVmax ≥3 at Screening and scan consistent with active CS on central over-read. 6. If receiving OCS, dose must have been ≤10 mg of prednisone or equivalent, and dose must have been stable for at least 4 weeks prior to completion of the screening PET scan. 7. For subjects in Cohort A: subjects must agree to be treated with high-dose OCS and agree to taper their OCS at the time of randomization. 8. If receiving methotrexate and/or other IST, dose must have been stable for ≥3 months prior to completion of the screening PET scan.

	9. Female subjects must agree to use an approved highly effective birth control (BC) method (<1% failure rate per year) for at least 28 days prior to randomization, throughout the study, and for at least 8 weeks (56 days) post last dose of study drug, unless documented to have a reproductive status of nonchildbearing potential or is postmenopausal: • Non-childbearing potential defined as pre-menopausal female with medical history of bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries), bilateral salpingectomy, bilateral tubal ligation, bilateral hysteroscopic sterilization, or total hysterectomy at least 3 months prior to Screening. • Postmenopausal defined as 12 months of spontaneous amenorrhea; otherwise, a follicle-stimulating hormone (FSH) confirmation will be required. For females with questionable menopausal history (e.g., irregular menstrual periods and age >40 years), a documented serum FSH level must be ≥30 mIU/mL. • Woman of childbearing potential (WCBP) who is already using an established method of highly effective contraception or agrees to use one of the allowed BC methods, for at least 28 days prior to randomization, throughout the study, and for 8 weeks (56 days) following the last dose of study drug. 10. Male subjects must agree to, and attest that, female partners of childbearing potential are using one of the allowed highly effective methods of contraception as described above for at least 28 days prior to randomization/enrollment, throughout the study, and for 8 weeks (56 days) following the last dose of study drug. 11. Body Mass Index (BMI) ≤40 kg/m^2 at Screening. 12. Vaccination for COVID-19 with completion of the primary series at least 2 weeks prior to randomization.
Exclusion Criteria	1. Hospitalized for any respiratory or cardiac illness ≤30 days prior to Screening. 2. Known pulmonary hypertension requiring therapy. 3. Systemic (oral or parenteral) antibiotic or pulse OCS treatment for any indication within 42 days prior to randomization. 4. Autoimmune disease other than sarcoidosis likely to require treatment during the subject's participation in this study. 5. Symptoms and/or signs of extracardiac sarcoidosis that are likely to warrant treatment in addition to that required for the subject's cardiac disease. 6. Estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 (Modification of Diet in Renal Disease

	[MDRD] equation) or requiring renal replacement therapy. 7. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >2 × upper limit of normal (ULN). 8. Platelet count <100,000 per mm^3. 9. Hemoglobin ≤9.5 g/dL. 10. Absolute neutrophil count <1,000 per mm^3. 11. Serum albumin-corrected calcium >3.5 mmol/L (14 mg/dL). 12. Positive anti-GM-CSF autoantibody, or history of pulmonary alveolar proteinosis (PAP). 13. Use of any biologic immunomodulator (approved or investigational) within the 6 months prior to Screening. Allergens for hypersensitivity desensitization or vaccines are not excluded per this criterion. Treatment with immunoglobulin within 6 months prior to Screening. Treatment with any investigational immunomodulator (e.g., Neuropilin 2 [NRP2] modulator) within 6 months prior to Screening. 14. Treatment with any Janus kinase (JAK) inhibitor within 3 months prior to Screening. 15. Participation in another interventional clinical trial within 6 months prior to Screening and throughout the duration of participation in this study. 16. History of left ventricular ejection fraction (LVEF) ≤30% or NYHA class III or IV heart failure. 17. Fridericia corrected QT interval (QTcF) >480 msec on the 12-lead ECG at Screening; if QTcF exceeds 480 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF measures should be used to determine eligibility. Note: If a subject has a pre-existing bundle branch block (BBB), the QTcF exclusion cutoff will be >500 msec. 18. Systolic blood pressure (SBP) <90 or >180 mm Hg; Diastolic blood pressure (DBP) <60 or >110 mm Hg at Screening. 19. Has documented laboratory-confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as determined by polymerase chain reaction (PCR) or other approved clinical testing ≤3 months prior to randomization. 20. Administration of any fully live virus or bacterial vaccinations within 3 months prior to Screening or administration of non-live or live-attenuated vaccine within 2 weeks of randomization. Note: COVID-19 booster and influenza vaccinations are allowed to be completed during the study. 21. History of mycetoma or fungal respiratory infection. 22. History of or planned solid organ or hematopoietic cell transplantation.

	23. A diagnosis of, or presentation consistent with, Lofgren's syndrome. 24. Significant ischemic heart disease, including myocardial infarction within 6 months, unstable angina, or percutaneous transluminal coronary angioplasty (PTCA)/stent within 1 month prior to Screening; or planned coronary intervention (e.g., coronary artery bypass graft [CABG] or PTCA/stent) during the subject's participation in this study. 25. Significant valvular heart disease known or anticipated to require surgical repair or replacement during the subjects' participation in this study. 26. Subject is indicated for a permanent implantable cardioverter defibrillator (ICD) or permanent pacemaker (per Investigator's opinion) but not yet implanted for any reason, or not planned to be implanted, at least 1 week before initiating treatment with study drug. Subjects with temporary pacing devices or external defibrillator devices are excluded under this criterion even if planned for conversion to a permanent device if that cannot occur at least 1 week prior to treatment with study drug. 27. Known or suspected active and untreated/inadequately treated tuberculosis (TB), human immunodeficiency virus (HIV), hepatitis B or C infection. Subjects with latent TB may be enrolled if anti-TB therapy is commenced prior to randomization. Subjects with positive serology for HIV, hepatitis B or C must have an undetectable viral load by real-time polymerase chain reaction (RT-PCR) prior to randomization. 28. Female subjects who are pregnant or breastfeeding or intend to be, during the study. 29. Prior history of any malignancy (not including fully resected squamous cell carcinoma of the skin, fully resected intra-epithelial neoplasia, or carcinoma in situ of the cervix) or lymphoproliferative disorder within the past 5 years. 30. History of severe allergic or anaphylactic reactions to therapeutic proteins or known sensitivity to namilumab or to its inactive components. 31. History of alcohol or drug abuse, in the Investigator's opinion, unless in full remission for greater than 12 months prior to Screening. 32. Abnormal chest radiograph findings that are inconsistent with a diagnosis of sarcoidosis, or are inconsistent with the subjects past medical history, and that warrant further evaluation in the opinion of the Investigator. 33. Any other acute or chronic medical condition that, in the judgment of the Investigator or Sponsor, may increase the risk

	associated with study participation or investigational product administration, or may interfere with the interpretation of study results, and would make the participant inappropriate for entry into this study.
Database Lock	A final database lock will be performed after last subject's last visit, and final data will be provided for all analyses.
Statistical Analyses	**Determination of Sample Size** The sample size for this study is not based on formal statistical calculations of study power. The planned sample size is considered sufficient to meet the primary objective. **Populations for Analysis** • The Intent-to-Treat (ITT) Population will include all randomized/enrolled subjects. • The modified Intent-to-Treat (mITT) Population will include all randomized/enrolled subjects who receive any amount of study drug and have at least one assessment at baseline or post-baseline for efficacy endpoints defined as changes from baseline. The mITT will be analyzed according to the treatment assigned. All efficacy endpoint analyses will be performed using the mITT Population. • The Per-Protocol (PP) Population will include all subjects in the ITT Population who have no major protocol violations. The PP Population will be used for sensitivity analyses of the efficacy measurements. • The Safety Population (SP) will include all randomized/enrolled subjects who receive any amount of study drug. The SP will be analyzed according to the treatment received. The SP will be used for safety analyses. **Statistical Analyses in General** All statistical analyses will be conducted using SAS, Version 9.3 or later. All the continuous variables, including the changes from baseline, will be summarized by the treatment with the means, standard deviation (SD), medians, and the ranges. All the categorical variables will be summarized by the treatment with numbers and percentages of the subjects. The Data Monitoring Committee (DMC) will be responsible for closely reviewing the unblinded safety data and for providing their recommendations.

	Efficacy Analysis Efficacy analysis will be provided separately for subjects in Cohort A and Cohort B. No hypothesis testing is planned for efficacy endpoints analyses. For continuous efficacy endpoints, summary statistics such as means, medians, and SDs will be provided by treatment groups. Model-based LS means and confidence intervals (CIs) for within treatment estimates and between treatment differences (Cohort A) will also be provided. Categorical efficacy endpoints will be summarized by treatment with counts and percentages of the subjects. CIs for within treatment estimate and between treatment differences (Cohort A) will also be provided. Time to event endpoints will be summarized using the Kaplan-Meier method. **Adjustment of Multiple Comparisons** No hypothesis testing is planned. **Interim Analysis** No formal interim analysis is planned. **Safety Analyses** Safety analysis will be provided separately for subjects in Cohort A and Cohort B, as well as pooled across the 2 cohorts. Safety will be assessed based on the SP for AEs, ECGs, PEs, vital signs, and clinical laboratory tests. Full details will be described in the Statistical Analysis Plan (SAP). **Population Pharmacokinetic and Biomarker Analyses** The PPK and E-R analyses will be performed based on modeling analysis plan (MAP) and reported separately from the final clinical study report. The MAP will be submitted to the Food and Drug Administration (FDA) prior to unblinding subject data for analysis. **Statistical Analysis Plan (SAP)** A detailed SAP will be signed and submitted to the FDA prior to database lock.
Current Version and Effective Date	Version 2.0 (Amendment 1): 14-April-2022
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Study Director	PPD Telephone: PPD Email: PPD

LIST OF ABBREVIATIONS

Abbreviation	Definition
β-hCG	beta human chorionic gonadotropin
ADA	anti-drug antibody
AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BC	birth control
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	contract research organization
CRP	C-reactive protein
CS	cardiac sarcoidosis
CT	computed tomography
DAS	Disease Activity Score
DBP	diastolic blood pressure
DMARD(s)	disease-modifying anti-rheumatic drug(s)
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	End-of-Study
EOT	End-of-Treatment
E-R	exposure-response

ESR	erythrocyte sedimentation rate
ET	Early Termination
FAS	Fatigue Assessment Scale
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte-macrophage colony-stimulating factor
GM-CSFR	granulocyte-macrophage colony-stimulating factor receptor
HbA_{1C}	glycosylated hemoglobin
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HDL-C	high-density lipoprotein cholesterol
Hep	hepatitis
HIV	human immunodeficiency virus
HIVAb	Human immunodeficiency virus antibody
HPLC	High-performance liquid chromatography
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
ICD	implantable cardioverter defibrillator
ICF	informed consent form
ICH	International Conference on Harmonisation
ICSRs	Individual Case Safety Reports
Ig	immunoglobulin
IgG1κ	immunoglobulin G1 kappa
IGRA	interferon gamma release assay
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio

IRB	Institutional Review Board
IRT	Interactive Response Technology
IST(s)	immunosuppressive therapy(ies)
ITT	Intent-to-Treat
IV	intravenous
JAK	Janus kinase
KSQ	King's Sarcoidosis Questionnaire
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAP	modeling analysis plan
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MGC(s)	multinucleated giant cell(s)
mGTI	modified glucocorticoid toxicity index
mITT	modified Intent-to-Treat
mRNA	messenger ribonucleic acid
NT-proBNP	N-terminal (NT)-pro hormone brain natriuretic peptide
NYHA	New York Heart Association
OCS	oral corticosteroid(s)
OLE	open-label extension
PAP	pulmonary alveolar proteinosis
PE	physical examination
PET	positron emission tomography
PK	Pharmacokinetic(s)
PP	Per-Protocol
PPK	population pharmacokinetics
PRO(s)	patient-reported outcome(s)
PTCA	percutaneous transluminal coronary angioplasty
PV	pharmacovigilance
Q4W	every 4 weeks

QTcF	Fridericia corrected QT interval
RA	rheumatoid arthritis
RBC(s)	red blood cell(s)
RT-PCR	real time-polymerase chain reaction
SAA	serum amyloid A
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SGA	Subject Global Assessment
SOA	Schedule of Assessments
SOC	system organ class
SP	Safety Population
SP-D	serum surfactant protein D
TARC	thymus and activation-regulated chemokine
TB	tuberculosis
TC	total cholesterol
TEAE(s)	treatment-emergent adverse event(s)
TG(s)	triglyceride(s)
TNF	tumor necrosis factor
TTCW	time-to-clinical worsening
TTE	transthoracic echocardiography
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WBC(s)	white blood cell(s)
WCBP	woman of childbearing potential

1. INTRODUCTION

Namilumab (KIN-1902, IZN-101, MT203, or AMG203) is a human immunoglobulin G1kappa (IgG1κ) monoclonal antibody (mAb) targeting granulocyte-macrophage colony-stimulating factor (GM-CSF), with a molecular weight of approximately 146 kDa, which potently and specifically neutralizes human and macaque GM-CSF. GM-CSF is thought to be a key activator of the innate arm of the immune system and as such is involved in the chronic stages of inflammatory and autoimmune diseases. GM-CSF acts as a pro-inflammatory cytokine and is aberrantly overproduced in a multitude of inflammatory and autoimmune human diseases.

Sarcoidosis is highly heterogeneous condition, with effects ranging from chest radiograph abnormalities during routine screening of asymptomatic subjects to severe chronic disease with pulmonary fibrosis. In a large portion of subjects, granulomas resolve with or without therapy, and half of them experience remission within 2 years of diagnosis (Valeyre, 2014). Respiratory failure is the most common cause of death in sarcoidosis, and pulmonary hypertension, which occurs in at least 5% of subjects, and is a serious complication. Oral corticosteroids (OCS) are the mainstay of therapy, but chronic subjects require long-term dosing, which carries significant toxicities (Baughman, 2015; Khan, 2017; Spagnolo, 2018). Second-line antimetabolite and cytotoxic drugs including methotrexate, azathioprine, and mycophenolate mofetil (commonly termed DMARDs, or disease-modifying anti-rheumatic drugs) are commonly used as -steroid sparing immunosuppressive therapies (ISTs). Only about two-thirds of subjects are responsive to these therapies, and only 25% of subjects achieve full weaning off OCS (Crommelin, 2016; Beegle, 2013). For subjects who are unresponsive or intolerant to DMARDs, third-line therapy consists of anti-tumor necrosis factor (TNF)-α biologic therapy such as infliximab or adalimumab. While widely utilized in rheumatoid arthritis (RA) and other autoimmune conditions, these therapies are not approved by the Food and Drug Administration (FDA) for use to treat sarcoidosis and some subjects may become intolerant or are unresponsive due to formation of anti-treatment neutralizing antibodies, supporting the need for new therapies approved for use in this condition.

1.1. Study Rationale

The purpose of this study is to establish the safety and preliminary evidence of efficacy of namilumab in subjects who have active cardiac sarcoidosis (CS). If successful, the results will inform the design of a further clinical trials and registration of namilumab as the first novel therapy for sarcoidosis in decades and the first biologic option for this disease.

1.2. Background

Sarcoidosis is a multi-organ autoimmune disease characterized by the presence of non-necrotizing granulomas believed to be formed from an exaggerated immune response to as of yet unidentified antigens. Granulomas are tightly clustered formations of monocytes/macrophages and multinucleated giant cells (MGCs; fused activated macrophages) interspersed with CD4+ T cells. Normal granulomas contain central necrosis and form in response to foreign pathogens that cannot be eliminated. In contrast, sarcoid granulomas do not contain necrosis, and the cause of their formation is unknown.

The clinical course of sarcoidosis is highly heterogeneous, ranging from chest radiograph abnormalities discovered during routine screening of asymptomatic individuals to severe disease in patients with pulmonary fibrosis. Approximately 200,000 individuals are affected with sarcoidosis in the US (Baughman, 2016). About 25% to 33% of these patients have persistent granulomas and develop a chronic progressive disease that significantly impacts quality of life and causes increased morbidity and mortality (Broos, 2018; Spagnolo, 2018). Nearly all (~90%) patients experience pulmonary involvement, and respiratory failure is the most common cause of death for these patients (Spagnolo, 2018). Oral corticosteroids are the mainstay of therapy, and although patients with chronic disease may receive second-line immunosuppressive steroid-sparing agents, only 25% of patients achieve full weaning off OCS. Both OCS and ISTs often cause significant toxicities, including weight gain, osteoporosis, diabetes, hypertension, and opportunistic infections (Hu, 2017; Soto-Gomez, 2016; Khan, 2017). Given that no new therapy has been approved for sarcoidosis in decades, development of a new safe and effective steroid-sparing agent for this disease represents an area of significant unmet medical need.

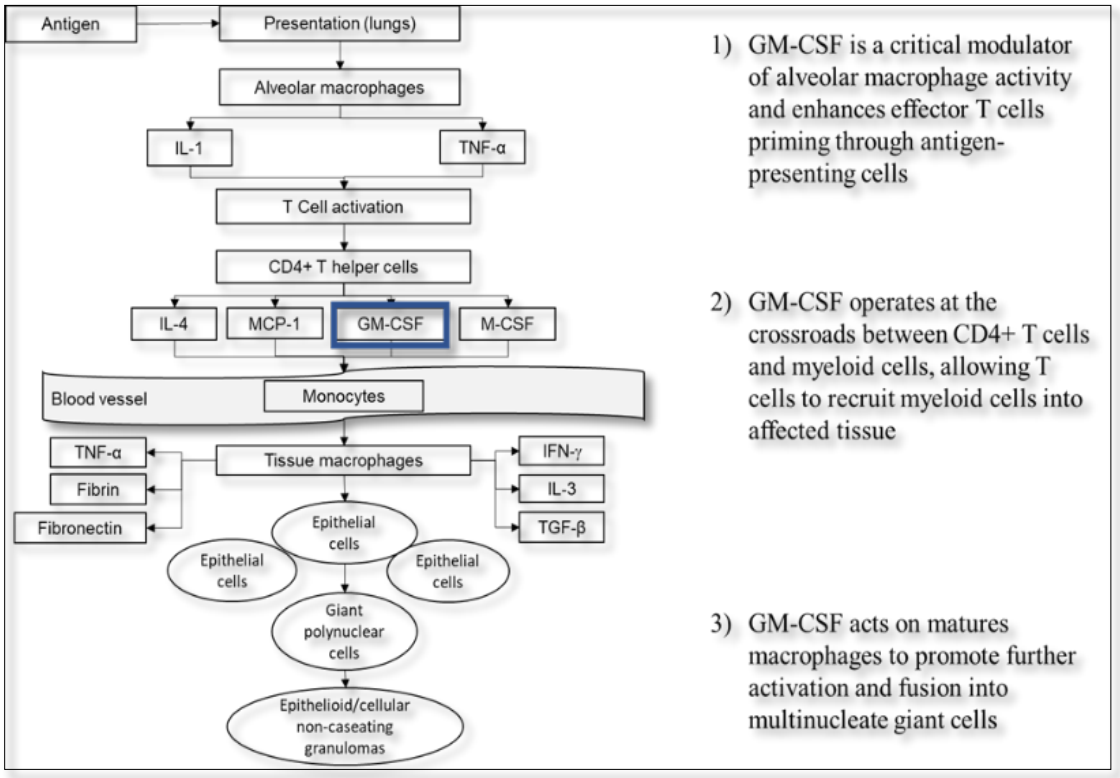
Patients with CS have non-necrotizing granulomas affecting the heart and represent 5% of the total sarcoidosis population (approximately 10,000 people in the US). The clinical manifestations include conduction abnormalities, arrhythmias (ventricular tachycardia/ventricular fibrillation), congestive heart failure, and sudden death (Hulten, 2016). Sarcoid granulomas may involve any part of the heart, although the left ventricle is the most commonly affected chamber. Prognosis of CS is related to extent and site(s) of involvement. Most deaths are due to arrhythmia or conduction defects; progressive heart failure due to massive granulomatous infiltration of the myocardium accounts for at least 25% of deaths (Lynch, 2014).

In addition to immunosuppressive and steroid-sparing therapies, patients with CS are treated with guideline-directed medical therapies for electrophysiological and heart failure manifestations (Gilotra, 2020). Data on immunosuppressive management is largely extrapolated from non-CS literature and from limited retrospective cohorts of CS patients and the role of these agents needs to be further defined in efforts to decrease the morbidity associated with corticosteroids. (Gilotra, 2020). Many CS patients are already being treated for arrythmia with a pacemaker or implantable cardioverter defibrillator (ICD).

Treatment with an anti-GM-CSF agent to impact the development of CS granulomas would aim to suppress inflammation, minimize recurrences, and decrease incidence of arrhythmias and the need for pacemakers. All second- and third-line therapies are not FDA approved for use in sarcoidosis, supporting the need for new therapies for use in this condition. GM-CSF, a pro-inflammatory cytokine and myeloid cell growth factor, is thought to play a key role in granuloma formation by stimulating activation of tissue-resident macrophages and mobilization of monocytes/macrophages from bone marrow to tissue (Iannuzzi, 2007). GM-CSF has been shown to be upregulated in lesioned tissues of subjects with many different autoimmune diseases, including sarcoidosis granulomas. Inhibition of the GM-CSF pathway via neutralizing antibodies has shown beneficial effects in animal models of multiple autoimmune conditions (Hamilton, 2020; Lang, 2020; Mehta, 2020). A Phase 2, randomized, placebo-controlled trial of an anti-GM-CSF mAb therapy in subjects with asthma demonstrated evidence of benefit in pre-specified subgroups, suggesting a role for GM-CSF in lung hyperinflammation (Molfino, 2016). More recently, treatment with mAbs against GM-CSF or GM-CSF receptor (GM-CSFR) yielded positive results in randomized, placebo-controlled trials of subjects with RA

(Hamilton, 2020), giant cell arteritis (Cid, 2020), and severe coronavirus disease 2019 (COVID-19) (Temesgen, 2021; Patel, 2021), solidifying the role of GM-CSF in aberrant immune responses. Given the importance of GM-CSF in autoimmunity and macrophage function, it is unsurprising that over the past 30 years, a multitude of human tissue and mouse model studies have shown that GM-CSF plays a key role in the formation of granulomas, including sarcoid granulomas.

GM-CSF is an important cytokine during multiple parts of the granulomatous response, including the fusion of macrophages into MGCs (Lemaire, 1996; Okamoto, 2003; Rangel, 2014), as well as the cross-talk between CD4+ T cells and myeloid cells (Zhang, 2013; Becher, 2016; Dougan, 2019). When overexpressed in rat lungs via adenovirus, GM-CSF caused aberrant granuloma development and pulmonary fibrosis (Xing, 1996a; Xing, 1996b). In mice, GM-CSF was required for normal granulomatous responses against tuberculosis (TB) as GM-CSF-/- mice quickly succumbed to infection (Gonzalez-Juarrero, 2005). Specific GM-CSF expression in either lung epithelial cells or T cells alone partially restored control of *Mycobacterium tuberculosis* infection in GM-CSF-/- mice (Gonzalez-Juarrero, 2005; Rothchild, 2017). Administration of anti-GM-CSF neutralizing antibody to mice after TB infection worsened granuloma integrity, promoted an anti-inflammatory cytokine and macrophage milieu, and impaired host bacterial control, leading to weight loss and deterioration (Benmerzoug, 2018). Corroborating these findings, Bryson et al., 2019, demonstrated that GM-CSF is a critical regulator of macrophage state during TB infection, whereby GM-CSF blockade made macrophages more permissive to TB growth and GM-CSF addition improved mycobacterial control (Bryson, 2019).



Tchernev, 2006

Multiple different groups have reported increased levels of GM-CSF in bronchoalveolar lavage fluid, lung tissue, eye fluid, and serum of sarcoidosis subjects, when compared to healthy controls (Hoshino, 1995; Ishioka, 1996; Prior, 1996; Crouser, 2009; Patterson, 2013; Abu El-Asrar, 2020). Inconsistent with these data, one study demonstrated no difference between serum GM-CSF in sarcoidosis subjects vs controls, whereas serum GM-CSF was elevated in idiopathic pulmonary fibrosis subjects (Ziora, 2015). Nevertheless, GM-CSF messenger ribonucleic acid (mRNA) levels in alveolar fluid of sarcoidosis subjects correlated with clinical severity (Itoh, 1990; Itoh, 1993), and alveolar macrophages within lesions of sarcoid subjects were shown to have increased GM-CSF secretion (Enthammer, 1993; Itoh, 1998; Oltmanns, 2003). In an in vitro model derived from peripheral blood mononuclear cells of sarcoidosis subjects, GM-CSF was upregulated during the formation of pathogenic granulomas (Crouser, 2017). Importantly, given that GM-CSF deficiency leads to pulmonary alveolar proteinosis (PAP), GM-CSF plays a particularly critical role in the maintenance and action of alveolar macrophages, which are known effector cells in sarcoid granuloma formation (Silva, 2013).

Taken together, GM-CSF is a key regulator of granulomatous responses, and significant evidence suggests that GM-CSF may drive sarcoid granuloma formation. Namilumab, an mAb that neutralizes GM-CSF, has the potential to improve organ function in CS by downregulating the granulomatous response that drives the disease.

1.3. Benefit-risk Assessment

The benefit-risk profile of namilumab is considered favorable for the evaluation of its potential to improve signs, symptoms, and health-related quality of life (HRQoL) in subjects with CS in this Phase 2 trial.

GM-CSF is required for the maintenance of alveolar macrophages which clear pulmonary surfactant. High levels of autoantibodies against GM-CSF may cause PAP, a rare lung disease characterized by accumulation of surfactant causing impaired gas exchange (Tazawa, 2019). A potential risk of GM-CSF inhibition with namilumab is the development of PAP. To date, no patient has developed PAP in any anti-GM-CSF or anti-GM-CSFR mAb published trial (Hamilton, 2020), including a long-term open-label extension (OLE) study with a median treatment duration of 2.5 years (Burmester, 2018). It has been hypothesized that PAP can develop only from profound and sustained GM-CSF neutralization by polyclonal autoantibodies (Lang, 2020). This hypothesis was based on experiments by Piccoli et al., 2015, who demonstrated in vivo and in vitro that individual antibodies only partially neutralized GM-CSF, while complete neutralization of GM-CSF could only be achieved with multiple non-cross-competing antibodies (Piccoli, 2015). Encouragingly, Campbell et al., 2016, showed that, while therapeutic-level intravenous (IV) doses of anti-GM-CSFR mAb affected systemic GM-CSF signaling, this dose level had no effect on cellular responses to GM-CSF in the lung, providing an alternative explanation for the lack of PAP observed in trials (Campbell, 2016). To date, no events pertaining to PAP have been reported in clinical trials with namilumab.

Because GM-CSF plays an important role in activating the immune system, another risk of namilumab administration is the increased chance for opportunistic infection. Indeed, high titers of autoantibodies against GM-CSF have been associated with infection (Rosen, 2013). Nevertheless, no anti-GM-CSF or anti-GM-CSFR trials have reported an increased infection risk

(Hamilton, 2020). Unlike trials of TNF-targeting agents, no increase in TB has been observed, despite GM-CSF's role in granuloma formation and TB protection in mice (Bryson, 2019; Hamilton, 2020). This benign safety profile has been corroborated in recently reported (not yet peer reviewed) trials of anti-GM-CSF mAbs for severe hospitalized COVID-19 subjects who were expected to be particularly susceptible to opportunistic infection (Patel, 2021; Temesgen, 2020). One suspected unexpected serious adverse reaction of bacterial pneumonia was reported in the COVID-19 Investigator-initiated study (CATALYST).

Another potential risk is the possibility of decreased neutrophil count/mild neutropenia. In the first-in-human (FIH) (M1-1188-001-EM) single dose escalation study of namilumab in healthy subjects (0.2 mg/kg to 8 mg/kg IV), a spontaneously reversible trend in decreased white blood cell (WBC) and absolute neutrophil count was observed in some subjects dosed with namilumab. The decrease in WBC was not clinically significant, and there was no dose-dependent pattern. Two subjects had clinically significant low neutrophil values during the trial: 1 subject on 0.5 mg/kg namilumab had a neutrophil count of 1.0×10^9/L on Day 8 and recovered without treatment by Day 15, and another subject on 3 mg/kg namilumab had a neutrophil count of 1.1×10^9/L on Day 29 and recovered spontaneously 4 days later. Both subjects recovered spontaneously without medical intervention. In the NEXUS study, neutrophil count, and WBC count decrease were recorded as drug related for 1 subject in the namilumab 80 mg treatment group and 1 subject in the namilumab 150 mg treatment group.

Neutralization of GM-CSF potentially may cause infection by depression of neutrophil and macrophage functions. The incidence of any severe and/or serious infection (with or without neutropenia) will be subject to ongoing pharmacovigilance (PV) monitoring in the clinical trial. To date, no serious adverse events (SAEs) of decreased neutrophil count and neutropenia have been reported with namilumab.

In the FIH study of namilumab, aspartate aminotransferase/alanine aminotransferase (AST/ALT) elevations were seen in isolated subjects. In a small trial in RA (PRIORA), ALT and/or AST values above the upper limit of normal (ULN) range were observed in all treatment groups, including 4/9 subjects in the placebo group, 1/8 subjects in the low-dose 150 mg group, and 3/7 subjects in the high-dose 300 mg dose group. The one patient in the low-dose group had measured ALT values >3 × ULN, meeting the alert threshold value; this was reported as an adverse event (AE). In a Phase 2 study in RA (NEXUS), ALT and AST increases were considered drug-related in 1 subject in the namilumab 150 mg treatment group. In a Phase 2 clinical study in psoriasis (NEPTUNE), 3 subjects in the Double-blind Treatment Period and 1 subject in the Follow-up Period experienced elevated AST or ALT, but these were not considered clinically significant. There were no clinically significant changes in liver enzyme parameters throughout the study. In the NAMASTE study, 3 non-serious reports of elevated ALT and/or AST were reported in the Double-blind Treatment Period, one of which was considered related to the study medication. Cumulatively, there were no SAEs of increased AST or ALT reported in the clinical studies with namilumab. Nevertheless, AST and ALT levels will continue to be monitored in all studies.

In the FIH study, 1 subject experienced a wide-complex tachycardia with a frequency of approximately 168 beats-per-minute on 3 occasions, each lasting for approximately 6 seconds, occurring 2 hours and 14 minutes after the end of the 1-hour IV infusion of 3 mg/kg namilumab. The subject only sensed a fast heartbeat when he was sitting up from a supine position. There

was no faintness or dizziness or any other AE during the event or at any later time. 12-lead electrocardiogram (ECG) showed no clinically significant abnormalities and no repeat of arrhythmia. The QT interval and the corrected QT interval according to Bazett's formula values were normal. This event was recorded and reported as a wide-complex tachycardia SAE of mild intensity, likely related to infusion of investigational medicinal product (IMP). The arrhythmia was evaluated by 2 independent cardiologists; both judged the event as tachycardia supraventricular with aberrant conduction but not as a life-threatening or medically serious event. One cardiologist suggested that the arrhythmia could indicate a vagal response, possibly due to a change in body position. However, a relation with the infusion of namilumab could not be excluded. The subject recovered fully and immediately with no sequelae. Subsequent cardiology follow-up examinations did not reveal any particular finding; no therapeutic actions were needed. In further clinical development, no further events of cardiac arrhythmia have been reported. Currently, the 1 reported event is not considered evidence of increased arrhythmia risk with namilumab; however, subjects with active CS may be at increased risk of arrhythmia and hence all subjects in the clinical trial will be carefully monitored for such events.

As with any biologic therapy, hypersensitivity reactions are considered a potential risk. Infusion reactions may be either type I hypersensitivity reactions (i.e., IgE-mediated allergic reactions) or non-IgE-mediated reactions. To date, there has been no evidence of allergic or hypersensitivity reactions to namilumab in any prior clinical trial.

The subcutaneous (SC) injection may cause administration site pain or inflammation; however, no such reactions have been recorded to date.

Namilumab has been studied in humans in doses ranging from 0.2 mg/kg to 8 mg/kg in Study M1 1188 001 EM; at 150 mg and 300 mg doses in Study M1 1188 002 EM (PRIORA) and Study MT 203 2004 (TELLUS); at 80 mg, 150 mg, and 300 mg in Study MT 203/CPH 001; at 20 mg, 80 mg, and 150 mg in Study M1 1188 202 (NEXUS); at 20 mg, 50 mg, 80 mg, 150 mg, and 300 mg in Study M1 1188 203 (NEPTUNE); at 150 mg in Study IZN 101 (NAMASTE); and at 150 mg in an Investigator-initiated trial (CATALYST). To date, 403 subjects or healthy volunteers have been enrolled into the clinical development program for namilumab, with 332 subjects estimated to have received namilumab. In addition, 57 subjects with COVID-19 were treated with a single dose of 150 mg namilumab in an Investigator-initiated trial in the UK known as the CATALYST study (n=55) or Investigator-sponsored compassionate use study (n=2). Overall, namilumab has been well tolerated with an acceptable safety profile for further development.

Based on the known data, the potential benefits of namilumab treatment outweigh the potential risks. Preclinical and human tissue studies have suggested that GM-CSF plays a key role in the formation of granulomas, including sarcoid granulomas. Positive clinical trials of anti-GM-CSF agents in RA, giant-cell arthritis, and COVID-19 have demonstrated a key role of GM-CSF as a driver of autoimmunity and hyperinflammation. The sarcoidosis subjects in this study will have relatively severe disease and may be receiving high doses of OCS or will have failed several agents. Current treatment strategies, including long-term use of OCS are associated with significant toxicities (Khan, 2017), and other treatment options for these subjects (cytotoxic agents and anti-TNF agents) have toxicity concerns of their own (Callejas-Rubio et al, 2018). Given that no new therapy has been approved for sarcoidosis in decades, namilumab may prove to be a useful treatment for these patients with limited options.

In summary, the anticipated potential risks include the occurrence of adverse reactions i.e., decreased neutrophil count/mild neutropenia, PAP, infection, and/or hypersensitivity reactions. No AEs suggestive of PAP, severe hypersensitivity, or severe neutropenia have been reported in the namilumab clinical program to date.

The following have been delineated as important identified risks:

- AST and/or ALT elevation.

The following have been delineated as important potential risks:

- Decreased neutrophil count/mild neutropenia;
- PAP;
- Hypersensitivity/allergic reactions (IgE-mediated; non-IgE-mediated);
- Infection.

Based on nonclinical studies and the available data from 8 completed clinical studies, the risks associated with exposure to namilumab are justified by the anticipated benefits that may be afforded. The benefit-risk ratio for namilumab is considered positive for the further study of namilumab in subjects with CS.

Identified potential risks and the planned mitigation strategies are described in Table 1. More detailed information about the known and expected benefits and risks, reasonably expected AEs associated with namilumab, and mitigation strategies may be found in the Investigator's Brochure.

Table 1. Identified and Potential Risks

Risk	Source	Key Details	Actions
AST/ALT elevation	Nonclinical studies (single-dose and repeat-dose toxicity studies); clinical studies (FIH, PRIORA, NEXUS, NEPTUNE, and NAMASTE studies)	Important identified risk	Exclusion criteria; routine PV monitoring: evaluation of Individual Case Safety Reports (ICSRs); AEs, signal detection, and aggregate reports
Decreased neutrophil count/mild neutropenia	FIH study and NEXUS study	Important potential risk	Exclusion criteria; routine PV monitoring
PAP	26-week monkey toxicity study; foamy macrophages were observed	Important potential risk	Exclusion criteria; targeted/close monitoring; Investigator Guidance for early detection and management

Table 1. Identified and Potential Risks

Risk	Source	Key Details	Actions
Hypersensitivity reactions/allergic reactions (IgE-mediated; non-IgE-mediated)	Biological nature of molecule	Important potential risk	Exclusion criteria; routine PV monitoring: evaluation of ICSRs, AEs, signal detection, and aggregate reports
Infection	Biological nature of molecule; clinical study (CATALYST)	Important potential risk	TB Screening, chest imaging at Baseline, exclusion criteria, routine PV monitoring: evaluation of ICSRs, AEs, signal detection, and aggregate reports

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of this study is:

- To determine the safety and tolerability of namilumab in subjects with CS based on treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations.

Secondary Objectives:

The secondary objectives of this study include the following:

- To evaluate other measures of safety and tolerability of namilumab;
- To evaluate the efficacy of namilumab on cardiac inflammation determined by [18-F] fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) (FDG-PET/CT);
- To assess the effect of namilumab on cardiac arrhythmia burden;
- To assess the effect of namilumab on cardiac function;
- To assess the effect of namilumab on cumulative oral corticosteroid (OCS) use and OCS toxicity;
- To assess the effect of namilumab on use of rescue therapy;
- To assess the effect of namilumab on patient-reported outcomes (PROs):
    - King's Sarcoidosis Questionnaire (KSQ);
    - Fatigue Assessment Scale (FAS);
    - Subject Global Assessment (SGA);
- To assess the population pharmacokinetics (PPK) and exposure-response (E-R) relationships for efficacy and safety of namilumab.

2.2. Endpoints

Primary Endpoints:

The primary endpoint of this study includes the following:

- Incidence and severity of TEAEs, SAEs, and adverse events (AEs) leading to discontinuation.

Secondary Endpoints:

- Other safety endpoints including:
    - Incidence and magnitude of treatment-emergent laboratory abnormalities;
    - Change from baseline in vital signs;
    - Change from baseline in ECG parameters.

- Mean change from baseline in PET maximum standardized update value (SUVmax), SUVmean, and total glycosylation;
- Cumulative arrhythmia burden and hospitalization for cardiac events;
- Mean change from baseline in left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) on transthoracic echocardiogram (TTE);
- Cumulative oral steroid use, modified glucocorticoid toxicity index (mGTI), and mean change from Baseline in glycosylated hemoglobin (HbA_{1C});
- Proportion of subjects requiring rescue therapy (either cohort) and proportion of subjects successfully achieving steroid taper without requiring rescue therapy (Cohort A);
- Mean change from baseline in KSQ (General and sub-domains), Fatigue Assessment Scale (FAS), and Subject Global Assessment (SGA);
- Assessments of PPK and E-R relationships for safety and efficacy if data permit.

Note: For endpoints defined as mean change from baseline, the primary assessment will be at Week 34.

3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

This is a Phase 2a, 2-cohort study including a randomized, double-blind, placebo-controlled cohort (Cohort A), and an open-label cohort (Cohort B) assessing the safety and tolerability of namilumab in subjects with active CS.

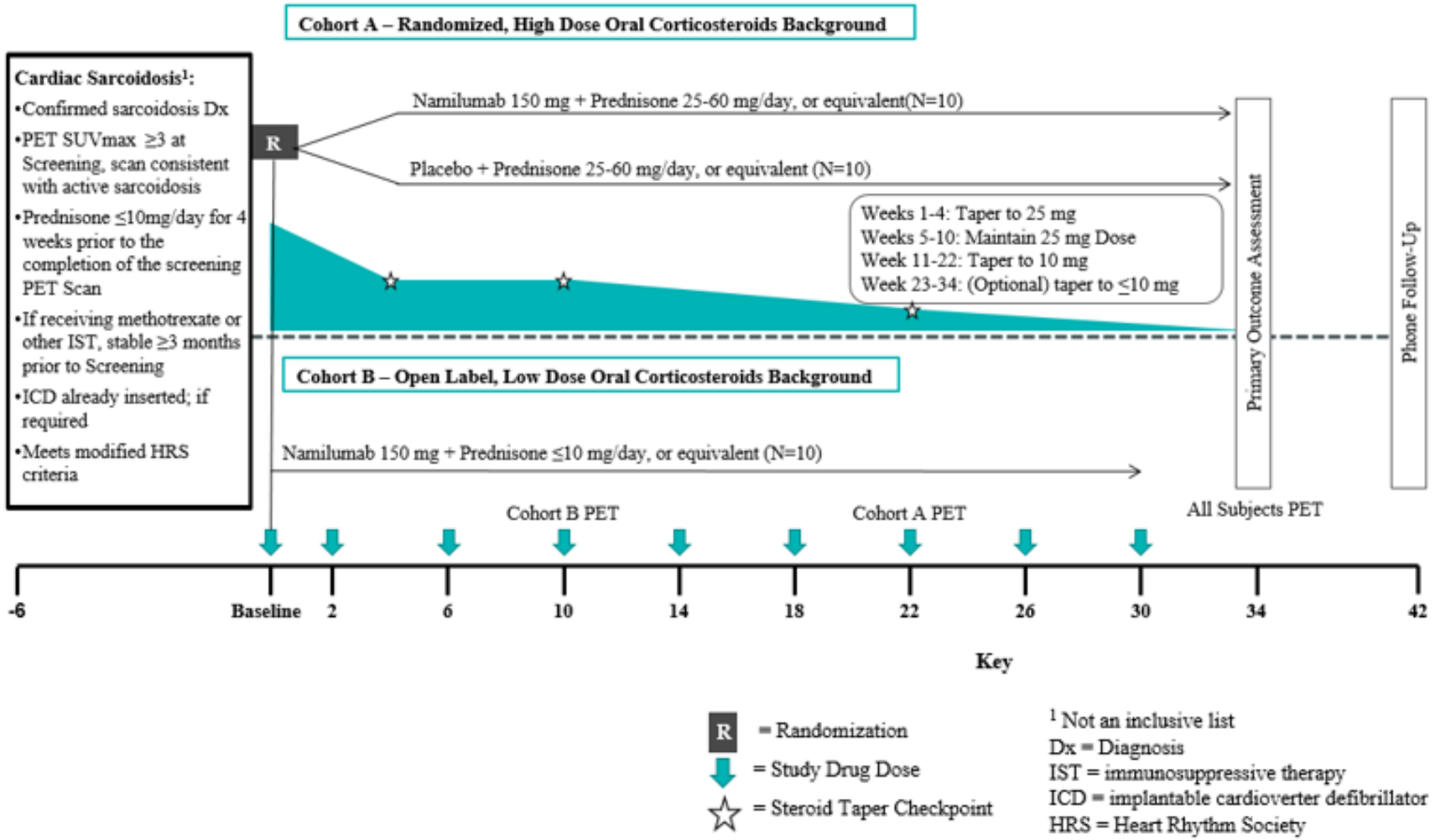
Approximately 30 total subjects are planned for this study. Cohort A will include 20 subjects. Cohort B is open-label and will include 10 subjects.

Participation will be approximately 44 weeks (308 days) as follows:

- Up to 6-week (42 days) Screening Period;
- 34-week (238 days) Treatment Period (with steroid tapering during the first 22 weeks for subjects participating in Cohort A);
- Follow-up phone call approximately 4 weeks (28 days) after the End-of Treatment (EOT) Visit (approximately 8 weeks [56 days] after the last dose of study drug at Week 30).

The study design is presented in Figure 1.

Figure 1. Study Design



3.1.1. Screening Period

Written informed consent will be obtained from all subjects prior to beginning any study-related procedures. The collection of SAEs will begin after the subject has signed the informed consent form (ICF). The Screening Period is up to 42 days; however, subjects may be randomized/enrolled as soon as they are deemed eligible.

For Cohort A, all subjects will also be treated with prednisone 25-60 mg/day, or equivalent, in addition to any other background IST they are already receiving. The starting dose of OCS will be determined by the Investigator. Subjects will be treated with prednisone 25-60 mg/day, or equivalent, no sooner than after completion of the Screening PET/CT scan, or by the Baseline Visit at the latest. Note the timing requirement for the OCS and PET/CT scan pertains to the intended study dose of OCS (25-60 mg/day of prednisone or equivalent) and not to any pre-existing treatment of ≤10 mg/day of prednisone or equivalent. In addition, subjects must agree to taper OCS over 22 weeks after randomization.

For the purpose of the study, the screening PET/CT scan is considered to be either the scan performed after informed consent or a scan performed as part of usual care of the subject (e.g. for clinical diagnosis of suspected CS) that meets eligibility criteria as further defined in Section 7.1.2.1.

For Cohort B, subjects who, in the opinion of the Investigator, are not eligible for, or prefer not to receive, high dose OCS as required in Cohort A, will be enrolled in this cohort. The reason for not providing high dose OCS should be documented in subject's chart. All subjects will receive open-label namilumab in addition to their background therapy without change to their prior OCS dose (≤10 mg/day of prednisone or equivalent) or ISTs.

3.1.2. 34-week Treatment Period

All subjects will begin the 34-week Treatment Period after confirmation that all protocol eligibility criteria have been met. The Treatment Period includes up to 11 clinic visits and 16 phone or telemed visits as described in the Schedule of Assessments (SOA; Appendix 1).

Subjects in Cohort A will begin tapering their OCS at the time of randomization as described in Appendix 8. During the steroid taper period, Investigators will contact subjects weekly via phone or telemed visits as outlined in Appendix 1.

If a subject needs to discontinue study drug (temporarily or permanently) or terminate study participation before completion of the Treatment Period, please refer to Section 4.4.2 for detailed instructions regarding recommended follow-up.

3.1.3. Follow-up Period

All subjects will have a contact (telephone call) approximately 8 weeks (56 days) after the last dose of study drug to obtain information on concomitant medication use and SAEs or any AEs that were ongoing at the time of the EOT/Early Termination (ET) Visit. See the SOA (Appendix 1) for details on what assessments are required.

3.1.4. Unscheduled Visits

During the course of the study, additional contact by telephone call(s), or unscheduled site visit(s) (or both), may be considered, based on the Investigator's discretion. Assessments completed during these visits (in clinic or by telephone call), may include evaluation of any AEs or SAEs the subject is experiencing. The unscheduled visit electronic case report form (eCRF) will be completed for each unscheduled telephone contact or site visit. If an unscheduled visit occurs due to the need for rescue therapy the Investigator should follow the instructions in Section 3.1.4.1 prior to commencing rescue.

3.1.4.1. Rescue Visit

During the study, if a subject requires rescue therapy outside of a required study visit, the Investigator should schedule a Rescue Visit to confirm the need for rescue therapy. Prior to providing rescue therapy, and dependent on the subject's clinical condition, the Investigator should attempt to complete all efficacy assessments that would be required during a Week 10 (Cohort B), or Week 22 (Cohort A) in-clinic visit as outlined in Appendix 1. The Rescue Visit should be documented on the appropriate eCRF page.

3.2. Discussion of Study Design, Including the Choice of Control Group

This study is an exploratory trial evaluating safety and tolerability of namilumab compared to placebo and in an open-label cohort in subjects with active CS. A robust, double-blind, randomized, placebo-controlled design has been selected for Cohort A. Such a design will provide strong evidence concerning the use of GM-CSF inhibition for the treatment of CS in addition to standard of care high dose OCS. It has been designed to closely match the standard of care for many CS subjects who would be typically treated with high dose OCS, then followed using [18-F] FDG-PET/CT scanning for response. Cohort B is designed to assess subjects who only receive open label namilumab in addition to their background OCS and/or IST. It has been designed to closely match the standard of care for those who are ineligible for, or who prefer not to receive high dose OCS. Although not placebo controlled, this cohort will provide evidence of the activity of namilumab in CS when used alone in addition to stable background therapy.

The trial is designed overall to provide strong evidence of safety and tolerability and preliminary evidence of the efficacy of namilumab in CS subjects and provide the evidence to support the further development of namilumab in this disease.

3.3. End of Study Definition

Study completion for each subject is defined as having completed the End-of-Study (EOS) Follow-up Phone Visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

3.4. Selection of Doses in the Study

Namilumab 150 mg SC on Days 1 and 15 followed by every 4 weeks (Q4W) through Week 30 is considered likely to be efficacious for subjects with sarcoidosis based on previous experience. With comparable dosing regimens in other indications such as RA, a dose-related improvement

in the Disease Activity Score (DAS) 28-joint count (DAS-28) C-reactive protein (CRP) was observed reaching significance with the 150 mg dose, but not with lower doses. Efficacy with the 150 mg dose was like that observed with other biologics approved in RA. At this dosing regimen, the PPK model-projected $AUC_{0\text{-}672h}$ at steady state is 415 µg•day/mL, which is under the FDA-capped $AUC_{0\text{-}672h}$ of 690 µg•day/mL, as per discussions with the FDA. Thirty weeks of treatment is considered the minimum duration to fully understand the kinetics of the efficacy response to namilumab in the CS population. There are currently no known biomarkers for sarcoidosis and a lower dose may be sub-optimal for efficacy.

4. SELECTION OF STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Inclusion Criteria

An individual will be eligible for participation in this study only if all the following inclusion criteria are met:

1. Male or female age ≥18 years.
2. Able and willing to provide written informed consent, which includes compliance with study requirements and restrictions listed in the consent form.
3. History of documented sarcoidosis (must include histological confirmation, from any organ, in the subject's medical history or records).
4. Meet Heart Rhythm Society Cardiac Sarcoid Diagnostic Criteria (modified).
5. PET SUVmax ≥3 at Screening and scan consistent with active CS on central over-read.
6. If receiving OCS, dose must have been ≤10 mg of prednisone or equivalent, and dose must have been stable for at least 4 weeks prior to completion of the screening PET scan.
7. For subjects in Cohort A: subjects must agree to be treated with high-dose OCS and agree to taper their OCS over 22 weeks starting after the time of randomization.
8. If receiving methotrexate and/or other IST, dose must have been stable for ≥3 months prior to completion of the screening PET scan.
9. Female subjects must agree to use an approved highly effective birth control (BC) method (<1% failure rate per year) for at least 28 days prior to randomization, throughout enrollment, and for at least 8 weeks (56 days) post last dose of study drug, unless documented to have a reproductive status of nonchildbearing potential or is postmenopausal:
    - Non-childbearing potential defined as pre-menopausal female with medical history of bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries), bilateral salpingectomy, bilateral tubal ligation, bilateral hysteroscopic sterilization, or total hysterectomy at least 3 months prior to Screening.
    - Postmenopausal defined as 12 months of spontaneous amenorrhea; otherwise, a follicle-stimulating hormone (FSH) confirmation will be required. For females with questionable menopausal history (e.g., irregular menstrual periods and age >40 years), a documented serum FSH level must be ≥30 mIU/mL.

- Woman of childbearing potential (WCBP) who is already using an established method of highly effective contraception or agrees to use one of the allowed BC methods, for at least 28 days prior to randomization, throughout the study, and for 8 weeks (56 days) following the last dose of study drug.

10. Male subjects must agree to, and attest that, female partners of childbearing potential are using one of the allowed highly effective methods of contraception as described above for at least 28 days prior to randomization/enrollment, throughout the study, and for 8 weeks (56 days) following the last dose of study drug.
11. Body Mass Index (BMI) ≤40 kg/m^2 at Screening.
12. Vaccination for COVID-19 with completion of the primary series at least 2 weeks prior to randomization.

4.2. Exclusion Criteria

An individual will not be eligible for participation in this study if any of the following exclusion criteria are met:

1. Hospitalized for any respiratory or cardiac illness ≤30 days prior to Screening.
2. Known pulmonary hypertension requiring therapy.
3. Systemic (oral or parenteral) antibiotic or pulse OCS treatment for any indication within 42 days prior to randomization.
4. Autoimmune disease other than sarcoidosis likely to require treatment during the subject's participation in this study.
5. Symptoms and/or signs of extracardiac sarcoidosis that are likely to warrant treatment in addition to that required for the subject's cardiac disease.
6. Estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD] equation) or requiring renal replacement therapy.
7. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >2 × upper limit of normal (ULN).
8. Platelet count <100,000 per mm^3.
9. Hemoglobin ≤9.5 g/dL.
10. Absolute neutrophil count <1,000 per mm^3.
11. Serum albumin-corrected calcium >3.5 mmol/L (14 mg/dL).
12. Positive anti-GM-CSF autoantibody, or history of pulmonary alveolar proteinosis (PAP).
13. Use of any biologic immunomodulator (approved or investigational) within the 6 months prior to Screening. Allergens for hypersensitivity desensitization or vaccines are not excluded per this criterion. Treatment with immunoglobulin within 6 months prior to Screening. Treatment with any investigational immunomodulator (e.g., Neuropilin 2 [NRP2] modulator) within 6 months prior to Screening.
14. Treatment with any Janus kinase (JAK) inhibitor within 3 months prior to Screening.
15. Participation in another interventional clinical trial within 6 months prior to Screening and throughout the duration of participation in this study.

16. History of left ventricular ejection fraction (LVEF) ≤30% or NYHA class III or IV heart failure.
17. Fridericia corrected QT interval (QTcF) >480 msec on the 12-lead ECG at Screening; if QTcF exceeds 480 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF measures should be used to determine eligibility.
    Note: If a subject has a pre-existing bundle branch block (BBB), the QTcF exclusion cutoff will be >500 msec.
18. Systolic blood pressure (SBP) <90 or >180 mm Hg; diastolic blood pressure (DBP) <60 or >110 mm Hg at Screening.
19. Has documented laboratory-confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as determined by polymerase chain reaction (PCR) or other approved clinical testing ≤3 months prior to randomization.
20. Administration of any fully live virus or bacterial vaccinations within 3 months prior to Screening or administration of non-live or live-attenuated vaccine within 2 weeks of randomization. Note: COVID-19 booster and influenza vaccinations are allowed to be completed during the study.
21. History of mycetoma or fungal respiratory infection.
22. History of or planned solid organ or hematopoietic cell transplantation.
23. A diagnosis of, or presentation consistent with, Lofgren's syndrome.
24. Significant ischemic heart disease, including myocardial infarction within 6 months, unstable angina, or percutaneous transluminal coronary angioplasty (PTCA)/stent within 1 month prior to Screening; or planned coronary intervention (e.g., coronary artery bypass graft [CABG] or PTCA/stent) during the subject's participation in this study.
25. Significant valvular heart disease known or anticipated to require surgical repair or replacement during the subjects' participation in this study.
26. Subject is indicated for a permanent implantable cardioverter defibrillator (ICD) or permanent pacemaker (per Investigator's opinion) but not yet implanted for any reason, or not planned to be implanted, at least 1 week before initiating treatment with study drug. Subjects with temporary pacing devices or external defibrillator devices are excluded under this criterion even if planned for conversion to a permanent device if that cannot occur at least 1 week prior to treatment with study drug.
27. Known or suspected active and untreated/inadequately treated tuberculosis (TB), human immunodeficiency virus (HIV), hepatitis B or C infection. Subjects with latent TB may be enrolled if anti-TB therapy is commenced prior to randomization. Subjects with positive serology for HIV, hepatitis B or C must have an undetectable viral load by real-time polymerase chain reaction (RT-PCR) prior to randomization.
28. Female subjects who are pregnant or breastfeeding or intend to be, during the study.
29. Prior history of any malignancy (not including fully resected squamous cell carcinoma of the skin, fully resected intra-epithelial neoplasia, or carcinoma in situ of the cervix) or lymphoproliferative disorder within the past 5 years.
30. History of severe allergic or anaphylactic reactions to therapeutic proteins or known sensitivity to namilumab or to its inactive components.

31. History of alcohol or drug abuse, in the Investigator's opinion, unless in full remission for greater than 12 months prior to Screening.
32. Abnormal chest radiographic findings that are inconsistent with a diagnosis of sarcoidosis, or are inconsistent with the subjects past medical history, and that warrant further evaluation in the opinion of the Investigator.
33. Any other acute or chronic medical condition that, in the judgment of the Investigator or Sponsor, may increase the risk associated with study participation or investigational product administration, or may interfere with the interpretation of study results, and would make the participant inappropriate for entry into this study.

4.3. Disease Diagnostic Criteria

Subjects will require a diagnosis of CS, with histological confirmation of sarcoidosis (any site; any organ) in their medical record. A repeat diagnostic workup is not required. Sufficient documentation of histology includes a histopathological report in the medical record, or written confirmation (letter, email, or fax) from another provider that such a report exists.

4.4. Discontinuation Criteria

4.4.1. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but do not meet all eligibility criteria and therefore are unable to be randomized/enrolled into the study. Subjects not meeting eligibility criteria because of laboratory result(s), borderline vital sign assessments, or time requirements for infection (including COVID-19), smoking, vaccination, or prior therapy use may have the test(s) repeated once during the Screening Period at the discretion of the Investigator to determine eligibility or may be rescreened after the appropriate time has elapsed to meet entry criteria. If the 6 weeks of the initial Screening Period has elapsed before eligibility can be ascertained, subjects may repeat all screening requirements after re-consenting. No subject may be screened more than twice for inclusion into the trial.

Note: If the reason for screen failure is related to the central read of [18-F] FDG-PET/CT scans, the subject cannot be rescreened. If an eligible [18-F] FDG-PET/CT scan has been completed, however, and the subject failed Screening for other reasons and is re-screened successfully, the [18-F] FDG-PET/CT scans do not need to be repeated so long as all other inclusion/exclusion criteria are satisfied on rescreening and the subject can be randomized/enrolled within 8 weeks of the original [18-F] FDG-PET/CT scan.

Demographics, screen-fail details, eligibility criteria, assessments completed during the Screening Visit, and any SAEs must be completed and entered into the eCRF for all subjects who screen-fail.

4.4.2. Discontinuation of Study Treatment

4.4.2.1. Permanent Cessation of Study Drug

Study drug administration may be halted for any of the following reasons, but are not limited to:

- A life-threatening or serious adverse event;

- Noncompliance, including refusal of the drug and/or failure to adhere to the study requirements as specified in the study protocol;
- The Investigator decides that, in the interest of the subject, it is not medically acceptable to continue participation in the study;
- The Sponsor decides to terminate the study.

Temporary or permanent cessation of study drug administration is NOT considered to be withdrawal of consent from study participation unless the subject explicitly withdraws informed consent.

4.4.2.2. Temporary Cessation of Study Drug

Study drug may temporarily be stopped for safety reasons at the discretion of the Investigator; however, not more than one dose may be missed. If more than one dose is missed, the subject will be withdrawn from study drug and followed for safety.

If the Investigator unblinds subject data for safety purposes, study drug will be permanently withdrawn.

4.4.2.3. Participant Discontinuation/Withdrawal of Consent

Subjects may withdraw from the study at any time, for any reason, and may leave the study without specifying a reason at his/her own request. Additionally, subjects may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

The Investigator should make all efforts to obtain information about possible underlying AEs leading to the decision to withdraw from study participation. Any AE or SAE information elicited must be documented in the subject's source documents and the eCRF. Refer to the SOA (Appendix 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Unless the subject who prematurely discontinues trial participation, specifically withdraws consent for any follow-up contact, all subjects will continue to be contacted at the same visit interval through the end of the study to obtain their health status. Investigators and site staff should encourage subjects to allow as much follow-up as possible and will need to clearly identify and document in writing as to which of the following options the subject has chosen.

- The subject has withdrawn from further treatment with study drug but will agree to continue with study visits and study assessments through the end of the Double-blind Treatment Period.
- The subject has withdrawn from further treatment with study drug, will not agree to continue with study visits and study assessments, but will agree to phone call assessments in accordance with the visit schedule.
- The subject is not willing to be contacted in accordance with the visit schedule but will allow the Investigator access to their medical records and EOS contact.

- The subject is not willing to allow any direct contact, access to medical records, or contact with care provider. In this case, public records may be used to confirm vital status at the end of the study.

For the purpose of this protocol, only subjects who are not willing to allow any direct contact, access to medical records, or contact with care provider will be deemed as subjects who have withdrawn consent.

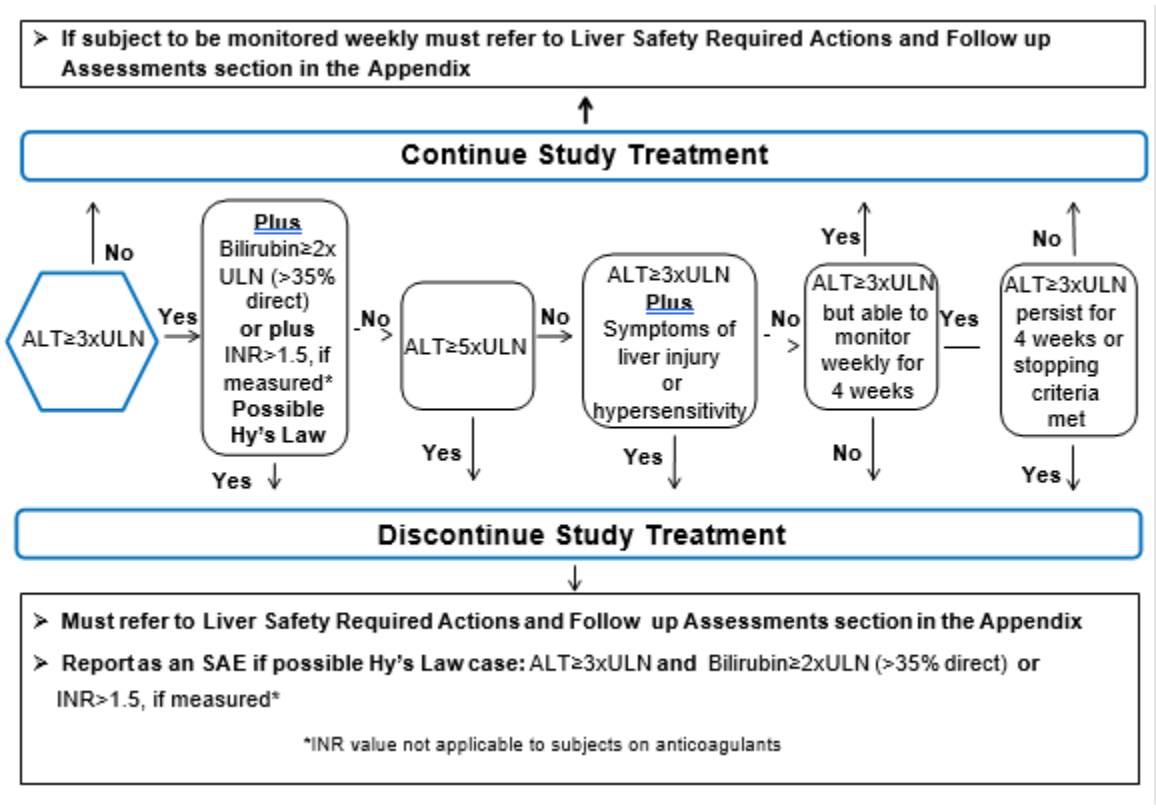
If a subject decides to withdraw consent from study participation, it is necessary to ensure that relevant safeguards are put in place to maintain the individual's safety in the case of any future safety issues that are discovered. In this case, the decision to withdraw informed consent should be put in writing and, if possible, signed by the subject or subject's representative. A copy of this document should be maintained at the study site (with key data items recorded in the eCRF). This written information should specify which aspect(s) of the study consent is being withdrawn as described above. In accordance with International Conference on Harmonisation (ICH) guidelines, FDA guidance, and other international ethical directives, data that have already been collected and incorporated into the study database, including the results of laboratory assays, will continue to be processed. In addition, every effort should be made to have the subject return to the clinic for the final EOT visit as described in the SOA (Appendix 1).

If the subject or the subject's representative refuses to withdraw consent in writing, the site must document and the Investigator must attest by signature, the reason for the subject's failure to withdraw the consent in writing. The Sponsor or designee should be immediately notified.

4.4.2.4. Liver Injury

Discontinuation of study treatment for abnormal liver tests should be considered by the Investigator when a subject meets one of the conditions outlined in the algorithm in Figure 2 or if the Investigator believes that it is in the best interest of the subject. In all cases of suspected liver injury, a discussion with Sponsor or Sponsor designee is required prior to withdrawing the subject.

Figure 2. Suggested Liver Injury Stopping Criteria



Suggested actions and follow-up assessments can be found in Appendix 7.

4.4.2.5. Cardiac Changes

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcF after enrollment), the Investigator or qualified designee will determine if the subject can continue in the study and if any change in subject management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A subject who meets the following criterion based on the average of triplicate ECG readings will be withdrawn from the study.

- QTcF >500 msec OR uncorrected QT >600 msec.

For subjects with underlying bundle branch block, follow the discontinuation criteria listed in Table 2.

Table 2. Discontinuation Criteria for Subjects with Underlying Bundle Branch Block

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF Threshold with Bundle Branch Block
<450 msec	>500 msec
450 to 500 msec	≥530 msec

4.4.2.6. Pregnancy

For all female subjects of childbearing potential, a pregnancy test will be performed at the times indicated in the SOA (Appendix 1). Subjects testing positive for pregnancy at Screening or prior to dosing will be ineligible for study participation. Subjects testing positive for pregnancy during the study will be withdrawn from the study. Refer to Section 7.3.3 for follow-up procedures for subjects who become pregnant during the study.

4.4.3. Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record. This level of diligence is necessary to obtain (at minimum) vital status (whether the subject is alive), and thus avoid being lost to follow-up for efficacy and safety assessment.
- Should the subject continue to be unreachable, he/she will be considered lost to follow-up. In this case, every attempt should be made to search public health records for the subject's vital status and document findings in the eCRF.

4.4.4. Subject Replacement

Subjects who are withdrawn from the study may not re-enter the study but may be replaced at the Sponsor's discretion.

4.5. Study Termination

4.5.1. Early Termination of the Study

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. If the Steering Committee, Data Monitoring Committee (DMC), Sponsor, or regulatory officials discover conditions arising during the study that indicate that the study should be halted or terminated, this action may be taken after appropriate consultation between the Steering Committee, Sponsor, and the DMC. Full details on the roles of the Steering committee and DMC will be provided in each committee's respective charter. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study;
- AEs unknown to date (i.e., not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration);
- Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as Baseline signs and symptoms);
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in the recruitment of subjects;
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

4.5.2. Early Termination of a Study Center

Conduct of the study at a particular center may be terminated by the Sponsor or Investigator for the following reasons, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the Institutional Review Board (IRB)/Ethics Committee (EC) or local regulatory and/or health authorities' regulations, the Sponsor's procedures, or ICH/GCP guidelines;
- Inadequate recruitment of participants by the Investigator;
- Submission of knowingly false information from the research facility to the Sponsor, Sponsor-designated contract research organization (CRO) or vendors, study monitor, the FDA, and/or other applicable regulatory authorities.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

If a study center or Investigator is terminated, the Sponsor will make all efforts possible to have another investigative site assume responsibility for continuing trial activities.

Study termination and follow-up will be performed in compliance with the conditions set forth in the following sections of the Code of Federal Regulations (CFR): 21 CFR 312.50 and 21 CFR 312.56, and other local regulatory authorities.

5. STUDY TREATMENTS

For Cohort A after randomization, subjects will be administered namilumab 150 mg or placebo via SC injection on Day 1 (Baseline) and then at Weeks 2, 6, 10, 14, 18, 22, 26, and 30. In addition, these subjects will begin tapering their prednisone or equivalent per the guidelines in Appendix 8.

Subjects in Cohort B will be administered namilumab 150 mg via SC injection on Day 1 (Baseline) and then at Weeks 2, 6, 10, 14, 18, 22, 26, and 30, in addition to their prior low-dose prednisone or equivalent.

The study drug eCRF will be completed each time study drug is dispensed.

5.1. Treatments Administered

The identity, potency/strength, and appearance of the study drug used are presented in Table 3. It should be noted that the vials for both placebo and study drug will be masked to maintain the blind in Cohort A.

Table 3. Description of Study Treatments

Study Treatment Name	Namilumab	Placebo
Dosage Formulation:	Solution for injection	Solution for injection
Unit Dose Strength(s)/Dosage Level(s):	150 mg Each vial contains 1.2 mL	Each vial contains 1.2 mL
Route of Administration:	SC injection, which may be administered in the thigh, abdomen, or upper arm	SC injection, which may be administered in the thigh, abdomen, or upper arm
Dosing Instructions:	1 mL administered	1 mL administered
Packaging and Labeling:	Study treatment will be provided in a sterile, single-use glass vial containing 1.2 mL of solution. Each vial will be labeled as required per country requirement.	Study treatment will be provided in a vial containing 1.2 mL of solution. Each vial will be labeled as required per country requirement.

5.2. Preparation, Storage, Handling, and Accountability

Study drug will be provided in sterile, single-use, masked glass vials. Each vial contains 1.2 mL drug product or placebo solution to ensure a withdrawal volume of 1 mL for SC injection.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

Namilumab and placebo must be stored at 2°C to 8°C (36°F to 46°F).

All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

Only subjects enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug.

5.2.1. Return of Study Drug

Vials of used, partially used, and unused study drug products should be retained until the clinical research associate (CRA) has been able to complete drug accountability and reconciliation. If retention of used vials is not allowed per site standard operating procedure(s) then approval for immediate destruction must be approved by the Sponsor.

Upon completion or termination of the study, all unused and/or partially used study drug must be returned to the Sponsor or designee, if not authorized by the Sponsor to be destroyed at the site.

All study drug returned to the Sponsor or designee, or other authorized party must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original vials (e.g., vials that have clinical labels attached). Empty vials should not be returned to the Sponsor or designee. It is the Investigator's responsibility to arrange for disposal and destruction of all empty vials, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused study drug should be arranged by the assigned CRA.

5.2.2. Destruction of Study Drug

If study drug is to be destroyed at the site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by the Sponsor, procedures for proper disposal have been established according to applicable regulations and guidelines and institutional procedures, and appropriate records of the disposal have been documented and provided to the Sponsor or designee. Unused study drug can only be destroyed after being inspected, reconciled by the responsible CRA and Sponsor approval has been obtained in writing.

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

5.3. Treatment Assignment and Administration

Once a subject is confirmed as eligible for study participation, the subject will be randomized (if in Cohort A) using the Interactive Response Technology (IRT) system. The IRT system will also be used for subjects in Cohort B in order to assign the appropriate vial/kit number at each clinic visit. Study drug will be dispensed at the study visits summarized in the SOA (Appendix 1). Study drug will be administered via SC injection, which may be administered in the thigh, abdomen, or upper arm.

Returned study drug should not be re-dispensed to the subjects.

5.3.1. Dose Modification

Dose reductions will not be allowed. If a dose reduction is needed, the subject should be discontinued from study drug and all EOT assessments completed. See Section 4.4.2.2 for missed doses.

5.4. Blinding

Namilumab and placebo are not visually identical. Study drug will be provided in a blinded fashion and packaged and labeled to protect the blind. Sites will be provided with masked syringes to administer the study drug.

Subjects in Cohort A will be randomized 1:1 to namilumab or placebo using the IRT. At the time of randomization, subjects will be assigned a randomization number by the IRT. Subjects in Cohort B will receive unblinded study drug.

The Investigator will have the ability to unblind a subject using the IRT system. The study blind may be broken by the Investigator using the IRT if, in the opinion of the Investigator, it is in the subject's best interest to know the study drug assignment. The Sponsor must be notified before the blind is broken unless identification of the study drug is required for a medical emergency in which the knowledge of the specific blinded study drug will affect the immediate management of the subject's condition.

5.5. Treatment Compliance

5.5.1. Study Drug Compliance

The Investigator must maintain accurate records of study drug receipt, dispensing information and disposition. Sponsor will provide forms to facilitate inventory control, if the staff at the investigational site does not have an established system that meets these requirements.

Treatment compliance will be calculated based on number of used vials returned for each subject.

5.5.2. Corticosteroid Use and Taper Compliance

Corticosteroids (OCS) will be self-administered by the subjects during the study. At each study visit, Investigators must review and document a subject's compliance with OCS use and taper during the corticosteroid tapering period and throughout the study until the subject completes their EOT/ET Visit. In order to verify corticosteroid dose on a daily basis, subjects will be required to complete an eDiary to document their steroid intake.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use;
- dates of administration, including start and end dates;
- dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.2. Prohibited Medications/Therapies

The following medications are prohibited during the study:

- Recombinant GM-CSF (e.g., sargramostim, molgramostim);
- Recombinant granulocyte colony-stimulating factor (e.g., filgrastim, lenograstim, pegfilgrastim, lipegfilgrastim);
- Kinase inhibitors, including JAK inhibitors (e.g., baricitinib, tofacitinib, ruxolitinib, upadacitinib) and Bruton's tyrosine kinase inhibitors (e.g., ibrutinib, acalabrutinib, zanubrutinib);
- Biologic agents targeting one or more specific cytokines or cytokine receptors, including but not limited to mAbs inhibiting TNF (e.g., adalimumab, etanercept, infliximab, golimumab, certolizumab), interleukin (IL)-1 (e.g., anakinra, canakinumab), IL-6 (e.g., tocilizumab, sarilumab, siltuximab), IL-17 (e.g., secukinumab, ixekizumab, brodalumab), IL-12/23 (e.g., ustekinumab), selective inhibitors of IL-23p19 (e.g., guselkumab, tildrakizumab, risankizumab);
- Biologic agents targeting one or more specific molecules expressed on immune cells, including but not limited to mAbs against CD20 (e.g., rituximab) and CD3 (e.g., otelixizumab, teplizumab, visilizumab);
- Agents targeting the complement pathway (e.g., eculizumab, berinert, cinryze);
- IV (or SC) Ig;
- Any other investigational agent not approved by the FDA;
- Vaccines in general are not permitted with the exception of COVID-19 booster shots and routine Flu shots.

The Medical Monitor should be contacted if there are any questions regarding whether a medication is prohibited. If a prohibited medication must be used due to clinical decline of a subject, the medication will be counted as a rescue medication.
New use of ISTs, including methotrexate, azathioprine, or mycophenolate mofetil, is subject to the rescue requirements discussed in Section 6.4.

6.3. Contraception

Females of childbearing potential who participate in this study must use highly effective contraceptive methods from at least 28 days prior to randomization, throughout the study, and for at least 8 weeks (56 days) post last dose of study drug. For this study, females are of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include total hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal ligation, or bilateral hysteroscopic sterilization at least 3 months prior to Screening. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high serum FSH level in the postmenopausal range

(FSH ≥30 mIU/mL) may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. Any use of hormonal contraception must be documented in the subject's chart as a concomitant medication.

For this study, the following methods of contraception are considered to be acceptable effective contraceptive measures (based on annual failure rate of <1% when used consistently and correctly):

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable;
    - Implantable.
- Intrauterine device;
- Intrauterine hormone-releasing system;
- Vasectomized male partner provided that partner is the sole sexual partner of the female study subject.
- Sexual abstinence: Note: sexual abstinence is considered a highly effective method only if defined as a refraining from heterosexual intercourse during the entire study period of risk associated with the study treatments; for this study that includes 28 days prior to randomization/enrollment, throughout the study and, for 8 weeks (56 days) following the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. The Investigator must confirm at every clinic visit that subject is still practicing sexual abstinence and document the discussion in the subject's source documents.

Male subjects must agree to, and attest that, female partners of childbearing potential are using one of the allowed highly effective methods of contraception as described above for at least 28 days prior to randomization/enrollment, throughout the study, and for 8 weeks (56 days) following the last dose of study drug.

Urine pregnancy testing for all females of childbearing potential will be performed as specified in the SOA (Appendix 1). Any positive urine test result must be confirmed based on a serum pregnancy test. The Investigator may perform additional pregnancy tests at their discretion or as required by local regulations.

6.4. Rescue Therapy

The clinical status of a subject in either Cohort may deteriorate. The Investigator should instruct subjects to contact study staff immediately if they feel their symptoms or signs of sarcoidosis, particularly of their cardiac disease, are worsening.

The Investigator may assess that the clinical deterioration is due to progression of CS and may wish to provide rescue therapy. In this circumstance, increased OCS dosing at the lowest effective increment with the shortest duration is the preferred option so that integrity of the study may be preserved. Alternatively, the change in regimen may be increased dosing of a current IST or the addition of a new one.

In this protocol rescue therapy is defined as any of the following:

- (Cohort A) Failure of the OCS taper, i.e., the subject requires an increase in OCS dose during the protocol-specified taper (Appendix 8);
- (Cohort A) Protocol-specified dose levels cannot be reached by the pre-specified timepoints (Appendix 8);
- (Cohort A) Increase in OCS dose above 10 mg/day prednisone, or equivalent, after the taper is complete;
- (Cohort B) Increase in OCS dose above 10 mg/day prednisone, or equivalent, at any time;
- (Either Cohort) Start of a new IST or change in dose or frequency of a current IST;
- (Either Cohort) Use of a prohibited medication to treat sarcoidosis-related signs or symptoms.

The following do not constitute rescue therapy:

- Use of OCS for up to 14 days or less for treatment of an event not related to sarcoidosis, e.g., an acute allergic reaction, acute contact dermatitis;
- Use of inhaled OCS or bronchodilators, e.g., long-acting beta agonists or long-acting muscarinic agonists.

Prior to initiating rescue therapy in a subject who is not hospitalized, an unscheduled visit should be performed; see Sections 3.1.4 and 3.1.4.1 for details.

If it would not adversely affect a subject's safety or wellbeing, PET/CT and TTE should be performed before initiation of rescue therapy.

Cohort A subjects should resume the protocol-specified steroid taper (Appendix 8) at the earliest opportunity based on the Investigator's clinical judgement.

The Medical Monitor must be contacted if rescue therapy is initiated, and the reason(s) should be captured in source records and in the CRF.

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SOA (Appendix 1). As protocol waivers or exemptions are not allowed, except for immediate safety concerns, these should be

discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue the study drug. Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure (Section 4.4.1), as applicable. Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing the ICF may be utilized for Screening or Baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SOA.

7.1. Efficacy Assessments

Efficacy assessments and procedures should be performed in the sequence that is most practical for the site, as long as PROs are performed first, and study drug administration is performed last. The study visits should follow the schedule as much as possible and should occur on the same day of the week. Study drug is also to be administered on the same day. All procedures must occur no more than ±3 days from the scheduled date for the study visit.

7.1.1. Cardiac Testing

7.1.1.1. Transthoracic Echocardiography

Transthoracic echocardiography (TTE) will be performed at the sites by qualified echocardiographic personnel (technicians or physicians) in accordance with standard echocardiographic clinical practice and with the Mitchell et al, 2019 Guidelines on TTE in adults from the American Society of Echocardiography. The baseline echocardiogram should be performed before administration of study medication. The TTE required will be a standard echocardiographic examination and will include the majority of standard echocardiographic views normally obtained for clinical practice (Table 4).

Echocardiograms will be recorded to digital media. All digital images should be stored in a DICOM format and sent to the core laboratory for analysis. Detailed image acquisition and transmission will be provided in Echocardiography Participant Scanning Guide and forwarded to all sites.

All echocardiographic measurements will be made at the core laboratory, with initial evaluation performed by experienced ECHO technician, and the overread performed by experienced ECHO cardiologist. Detailed echocardiographic parameters, and their definitions will be provided in Imaging Review Charter (IRC) and reviewed and approved by the sponsor.

Table 4. Summary of Standard Echocardiographic Views

Echocardiographic view	Images
Parasternal long axis view	2-D image for septal and posterior wall thickness, volume, and ejection fraction measures, LA size/volume M-mode images

Table 4. Summary of Standard Echocardiographic Views

Echocardiographic view	Images
	Color flow Doppler
Parasternal short axis view, papillary muscle	2-D image for septal and posterior wall thickness
Apical 4-chamber view	2-D images for volume and ejection fraction measures, LA size/volume, and RV function Color flow Doppler for assessment of mitral regurgitation Global longitudinal strain Doppler Tissue Imaging of mitral annular velocities Mitral inflow pulsed Doppler

Additional images may be acquired if the anatomy is not well visualized on the required views (Table 5).

Table 5. Additional Imaging Parameters

Echo Views	Parameters
Parasternal Long Axis View	● 2D at normal depth ● Color Doppler of MR and AR
Parasternal Short Axis View	● 2D of the LV at Mid-Papillary Muscle level
Apical 4 Chamber View	● 2D Standard 4 Chamber view ● 2D optimize view of the LV ● 2D with optimize view of the RV, Reduce the depth and focus only on the RV ● Color Doppler of MR ● Color Doppler of TR ● CW Doppler of TR jet ● M-Mode of Tricuspid Annular Motion or TAPSE ● Tissue Doppler of Tricuspid lateral annulus
Apical Long Axis View	● 2D of LA and LV, LVOT ● Color Doppler for MR
Apical 2 Chamber View	● 2D with LV and LA optimized ● Color Doppler of MR

7.1.1.2. Wearable Device for Arrhythmia Assessment

An ambulatory ECG monitor (ePatch) will be placed on the subject at each visit (from Screening through Week 30). The device is made up of a sensor which is placed in an electrode patch. Together, they are placed on the subject. The ePatch will continuously record a 1-channel ECG. Subjects will be monitored via ePatch for 10 consecutive days; one patch will be worn for 5 days, then the patch will be replaced by the subject, and the second patch will be worn for an additional 5 days. After 10 days of wearing the device, the Subject should remove it and return it to the investigational site at their next clinic visit. The site will upload the data as described in the ePatch acquisition guide and give the subject a new device. The initial recording period during screening provides an opportunity for the software system that will be used to interpret the data during treatment to learn the Subjects usual physiology prior to commencing study drug. A detailed manual (ePatch Acquisition Guide) describing affixation and removal of the device, and requirements for upload of recorded data will be provided and all site staff will be trained on the use of the ePatch device.

7.1.2. Radiographic Assessments

Details for the [18-F] FDG-PET/CT imaging requirements, scanner validation, procedures for phantom image capture, and data transfer requirements are described in the Participant Scanning Guide provided to all Investigators and collaborating radiology units.

To avoid unnecessary radiation, it is recommended all other Screening activities need to be completed prior to PET scans for eligibility. In all cases, the lowest radiation dose approach for imaging should be used. Subjects will undergo up to 3 [18-F] FDG-PET/CT scans; cumulative radiation exposure from these scans will range from 22.2 mSv to 41.7 mSv, depending primarily on CT technique used.

7.1.2.1. [18-F] Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography

All subjects will undergo whole-body head to mid-thigh [18-F] FDG-PET/CT imaging with a reconstructed resolution of ≤5mm during Screening and at Week 34. Subjects in Cohort A will receive an additional scan at Week 22, and subjects in Cohort B will receive an additional scan at Week 10. Timepoints for imaging are specified in the SOA (Appendix 1). All subjects must adhere to a low carbohydrate/low calorie diet 24 hours prior to the PET scan; the treating Investigator should discuss the appropriate diet options with subjects, see Appendix 11 for diet recommendations. Details of the scan requirements and procedures are contained in the Participant Scanning Guide. At Screening, the scan may be interpreted locally to confirm evidence of disease activity consistent with active CS; however, all scans are subject to central read for the purposes of eligibility. Only central imaging interpretation will be accepted for eligibility determination.

A PET/CT scan conducted as part of the usual clinical management of the subject (e.g. assessment for suspected CS) within 2 weeks prior to informed consent may be considered/assessed for use in place of the Screening PET/CT exam if the scan can be uploaded to the central imaging vendor for central read and the OCS dose has not changed in the 4 weeks prior to the scan. If this PET/CT scan is deemed unable to be assessed, is of insufficient quality on central read, or was performed more than 2 weeks prior to informed consent, the PET/ CT scan must be repeated and performed as part of screening, per protocol. The central read will determine final study eligibility compared to local interpretation. For subjects considered for inclusion into Cohort A, high-dose OCS may be commenced at any time after a potentially eligible PET/ CT scan has been performed including before informed consent (e.g. after diagnosis of CS, it may be likely to start high dose OCS as part of the usual care of CS, before entering into Screening and signing informed consent); however, if the OCS dose is changed to >10 mg/ day of prednisone (or equivalent), and the PET/CT scan needs to be repeated (i.e. performed as part of usual management and unable to be assessed or insufficient quality on central read) then the subject will be ineligible for inclusion. If the OCS dose commenced as part of usual care, before informed consent, is not within the protocol-defined range of 25-60 mg/ day prednisone (or equivalent), it should be adjusted to be within the protocol-defined range as soon as is practical after the subject has signed informed consent and no later than the time the subject is randomized/enrolled.

Subjects with glucose levels above 11 mmol/L (200 mg/dL) should have their scan delayed or be rescheduled as appropriate. The blood glucose level measured prior to the radiotracer administration should be recorded in the image transmittal form. Subjects will have the radiotracer administered through an IV line, after which they will be positioned comfortably in a supine position as stated in the Participant Scanning Guide.

Screening, Week 10 (Cohort B only), Week 22 (Cohort A only), and Week 34 scans will be assessed as follows.

- Change in the SUVmax – mean change from Baseline;
- Mean change in SUVmean from Baseline;
- Mean change in Total Glycosylation vs Baseline;
- Mean change in SUVmax in extracardiac regions of interest;
- Percentage lesion resolution rate in the cardiac and extracardiac regions of interest, to an SUV of 1.2 or less. For exploratory purposes, different sensitivity thresholds will be applied to define resolution.

Total radiation exposure for study subjects will be minimized as far as possible as follows:

- [18-F] FDG-PET/CT scans should ideally be performed after subjects have completed other Screening requirement successfully;
- Lowest dose of injectable radioisotope should be used per the guidance in the Participant Scanning Guide;
- Poor quality scans will not be repeated for study purposes, unless indeterminate for study inclusion.

Subjects will undergo up to 3 [18-F] FDG-PET/CT scans; cumulative radiation exposure from these scans will range from 22.2 mSv to 41.7 mSv, depending primarily on CT technique used.

7.1.3. Patient-reported Outcomes

The effect of namilumab on select PROs will be evaluated, see Appendix 9 for examples. The PROs used in this study include:

- KSQ General Score and Sub-scores;
- FAS;
- SGA.

Subjects will complete these assessments via electronic tablet as per the times specified in the SOA (Appendix 1).

During the administration of the instruments, the subjects should be allowed to sit alone in a quiet environment to answer the survey questions. All specific PRO assessments during a visit should be conducted before any tests, procedures, or other consultations to prevent influencing the subject's perception. Site staff and subjects will be given information on the rationale for including PROs in the study and clear instructions on how to complete the instruments.

The staff at the study site/clinic should never help the subject choose an answer and must be neutral in their responses to the subject's questions. The clinic staff are not allowed to interpret or rephrase the questions to the subjects. After the subject has completed the instruments, study staff will collect the data and check for completeness only.

The procedures for administration of the PRO instruments will be highlighted at the site training at each Investigator meeting. Study-specific PRO training will be given to all site Investigators and staff to ensure consistent oversight and management of the PRO administration process to ensure the highest possible quality of data. It is critical that all site Investigators and staff understand the rationale for including PROs in the protocol and the manner in which PRO instruments should be collected.

7.1.3.1. King's Sarcoidosis Questionnaire

The King's Sarcoidosis Questionnaire (KSQ) is a modular, multi-organ health status measure for subjects with sarcoidosis for use in the clinic and the evaluation of therapies. The KSQ consists of 5 modules: General health status (10 items), Lung (6 items), Medication (3 items), Skin (3 items), and Eye (7 items). The General health status module is intended to be administered to all subjects with sarcoidosis. In addition to this, all subjects will also complete organ-specific modules if relevant to their condition. All subjects will complete General health, and Medication modules and self-select the Lung, Skin and Eye modules if they have relevant symptoms for these assessments (Patel, 2013).

7.1.3.2. Fatigue Assessment Scale

The Fatigue Assessment Scale (FAS) is a 10-item self-reported fatigue questionnaire. The reliability and validity of the FAS have been demonstrated in sarcoidosis subjects. Subjects indicate their responses on a 5-point scale (from 1 never to 5 always). Total scores on the FAS can therefore range from 10 to 50, with high scores indicating more fatigue. Changes from baseline can range therefore from -40 to +40 on follow-up (Michielsen, 2004).

7.1.3.3. Subject Global Assessment

The Subject Global Assessment (SGA) is a subject reported outcome instrument used to assess their overall perception of the frequency and severity of sarcoid symptoms. The SGA- also sometimes termed Patient Global Assessment or PGA, is a 5-point scale which can be completed in less than a minute. It is similar to the pain VAS scale, which has been widely adapted to clinical practice. Using a Likert scale; the Subject rates how he/she feels regarding their sarcoidosis in the previous 2 weeks prior to the Study visit based on the frequency and severity of their symptoms. The SGA is based on the PGA published by Baughman et al but has been modified to be in line with FDA's recommendations on collection of patient global assessments (Baughman, 2016).

7.1.4. Other Reported Outcomes

The effect of namilumab on other physician-reported outcomes (Appendix 10) will be evaluated. These physician-reported assessments will include:

- Modified Glucocorticoid Toxicity Index (mGTI).

A representative example of this assessment is included in Appendix 10. Subjects will complete these assessments via electronic tablet as per the times specified in the SOA (Appendix 1).

7.1.4.1. Modified Glucocorticoid Toxicity Index

The mGTI is a composite measure of the changes in OCS toxicity measured at 3-month intervals across 11 domains and 23 items. For the purposes of this study, radiographic assessment of bone mineral density is not being performed; therefore, this item is not being assessed in the tool and the tool is termed "modified" for this study. The change in the total score is from −35 to +410 with the exclusion of bone mineral density.

The mGTI measures changes in OCS toxicity rather than the absolute GC toxicity in order to account for the effects of prior OCS therapy and the background rate of AEs. The mGTI will be completed at the timepoints specified in the SOA (Appendix 1) (Miloslavsky, 2017).

7.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SOA (Appendix 1). Assessments for safety include vital signs, height, and weight, PEs, ECGs, clinical laboratory assessments, and AEs.

7.2.1. Vital Signs, Height, and Body Weight

7.2.1.1. Vital Signs

Vital signs (BP, heart rate, respirations, and temperature) will be measured after 5 minutes of rest, with the participant in a quiet setting without distractions (e.g., television, cell phones). Vital sign measurements should be taken prior to any blood collections taken during the visit.

BP and heart rate measurements should be assessed in a seated position with a completely automated device; however, manual techniques may be used if an automated device is not available.

For the Screening Visit only, BP may be repeated 2 additional times at least 5 minutes apart if the subject does not meet inclusion/exclusion criteria. An average of the three systolic and diastolic readings may then be used for inclusion determination and should be entered into the eCRF.

The same method (oral temperature preferred) for assessing temperature should be used at all visits for a particular participant.

7.2.1.2. Height

Standing height will be measured without shoes.

7.2.1.3. Body Weight

Body weight will be measured in kilograms using a scale with appropriate range and resolution, and it must be placed on a stable, flat surface. Subjects should remove their shoes and bulky layers of clothing (jacket/coat), so that only light street clothing remains. Subjects should also remove the contents of their pockets and remain still during the weight measurement.

7.2.2. Physical Examinations

A complete PE will include, at a minimum, assessments of the head, ears, eyes, nose, mouth, skin, lymph nodes, and abdomen (liver and spleen), as well as the cardiovascular, respiratory, gastrointestinal, and neurological systems.

A brief (targeted) PE will include, at a minimum, assessments of general appearance, the skin, and the cardiovascular and respiratory systems, and assessment of any subject-reported symptoms.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

PEs may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulations.

7.2.3. Electrocardiograms

A single 12-lead ECG(s) will be obtained as outlined in the SOA (Appendix 1) using the study-specific ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals, and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position and prior to any blood collections.

When triplicate ECGs are required (e.g., at Screening only if the initial QTcF is >480 msec or as outlined in Section 4.4.2.5 to assess changes in QTcF or QT that exceed thresholds), 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart, and averaged together to make a determination.

7.2.4. Chest Radiography

A standard posterior-anterior and lateral chest x-ray should be performed at Screening as outlined in the SOA (Appendix 1). No study specific requirements based on x-ray are required for inclusion; however, subjects with abnormal radiographic findings inconsistent with the diagnosis of sarcoidosis or the subject's past medical history and that warrant further investigation should be excluded.

7.2.5. Spirometry

Spirometry will be performed to determine the subject's FEV1, ppFEV1, FVC, ppFVC, FEV1/FVC, and pFEV1/FVC. The predicted spirometry values will be determined using the 2012 Global Lung Function Equations. Spirometry assessments shall be obtained at the visits designated in the SOA (Appendix 1). Spirometry will be conducted while the subject is in a seated position. Every attempt should be made to standardize the time of day that a subject undergoes lung function testing throughout the study, and it is preferable that the same trained individual performs the spirometry testing for a given subject. All Site Investigators performing spirometry testing must pass competency prior to subject testing.

Spirometry results will be captured on standardized spirometry software and equipment and will be electronically transmitted and reviewed by a central over-reading service. Spirometry tests will be performed on a centralized spirometry system (provided to all sites by a central spirometry vendor) configured to the requirements of the study and in accordance with American

Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. The quality of the tests will be reported back to the site Investigators. Within each spirometry session, it is required that subjects produce flow-volume loops of acceptable and repeatable quality, as per ATS/ERS recommendations. To obtain the highest FEV1 and the highest FVC a minimum of three acceptable FVC maneuvers must be performed (with a maximum of 8 efforts per session).

Spirometry sessions must be stopped if the subject becomes tired or breathless. The details of these procedures will be described in the study pulmonary testing manual provided by the spirometry vendor.

7.2.6. Tuberculosis Screening

Subjects will be screened for TB using an interferon gamma release assay (IGRA) as supplied by the central laboratory. IGRA will be tested during Screening. Site personnel should follow the processing and analyses steps as outlined by the central laboratory manual. Ensure incubation steps are followed as appropriate.

If results of the IGRA are indeterminant, the test may be repeated, and if a negative result is obtained, enrollment may proceed as normal if the subject is otherwise eligible. A positive test on repeat requires that a subject commence appropriate anti-TB therapy prior to randomization as noted in Section 4.2. Subjects with repeat indeterminate IGRA results should have a different IGRA test, if available, and may be enrolled without anti-TB therapy after consultation with an infectious disease and/or pulmonary specialist (the Investigator may qualify as such a specialist) who determines that risk of infection is low (i.e., participant would be acceptable for immunosuppressant treatment without additional action or therapy). Such determination should be documented in the subject's source record.

7.2.7. HIV and Hepatitis Screening

During the study Screening period, all subjects will be screened for HIV antibody (HIVAb), hepatitis B (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], and hepatitis B core antibody [HBcAb] with reflex testing as applicable), and hepatitis C (hepatitis C virus antibody [HCVAb] with reflex testing as applicable). Subjects with serologic evidence of infection with HIV, hepatitis B, or hepatitis C must have an undetectable viral load by RT-PCR prior to randomization to be eligible.

Subjects with hepatitis B serology suggestive of prior vaccination (i.e., negative HBsAg, negative HBcAb and positive HBsAb) and provide documentation of hepatitis B virus vaccination will not require RT-PCR evaluation prior to randomization.

7.2.8. Clinical Safety Laboratory Assessments

See Appendix 5 for the list of clinical laboratory tests to be performed for Screening and safety monitoring; see the SOA (Appendix 1) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. New York State investigators will be blinded to the screening anti-GM-CSF auto-antibody laboratory results due to New York State regulations. These results will be made available to the New York State sites at the end of the trial.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within approximately 4 weeks after the last dose of study drug should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If clinically significant values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the SOA (Appendix 1).

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose interruption/discontinuation), then the results must be recorded.

7.2.9. Cytokine and Chemokine Analyses

The following will be tested according to the SOA (Appendix 1) using a commercially available testing panel: GM-CSF; IL-1α; IL-5; IL-7; IL-12/IL-23p40; IL-15; IL-16; IL-17A; TNF-β; vascular endothelial growth factor; Interferon gamma (IFN-γ); IL-10; IL-12(p70); IL-13; IL-1β; IL-2; IL-4; IL-6; IL-8; TNF-α; Eotaxin, MIP-1β, Eotaxin-3, thymus activation regulated chemokine (TARC), MIP-1α, Monocyte Chemoattractant Protein (MCP)-1, Macrophage Derived Chemokine (MDC), MCP-4, and 2 CXC (homeostatic) chemokine assays (IP-10, IL-8) (see Appendix 5).

7.2.10. Sarcoidosis Biomarkers

The following will be tested according to the SOA (Appendix 1): soluble IL-2 receptor, and serum amyloid A with the inflammatory markers high-sensitivity CRP and erythrocyte sedimentation rate (ESR). A sample will be taken on the same sampling schedule for storage to assess at a future timepoint for additional biomarkers.

7.2.11. Sample Requirements

The maximum amount of blood (Table 6) collected from each subject over the duration of the study, including any extra assessments that may be required, will be approximately 250 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 6. Estimated Sample Requirements Per Subject

	Approximate sample volume per collection (mL)	Number of collection timepoints	Approximate total volume collected (mL)
Clinical laboratory tests	16.5	11	181.5
QuantiFERON® Gold/IGRA	11	1	11
Anti-GM-CSF autoantibody	2	1	2
PK	4	5	20
ADA	4	3	12
Cytokine and chemokine panel	8.5	5	42.5
SP-D, SAA, and biomarkers	5	5	25
FSH (if necessary)	3.5	1	3.5
Virology labs (hepatitis B, hepatitis C, and HIV)	5	1	5
		Total:	302.5

7.2.12. Pregnancy Testing

WCBP must have a urine beta human chorionic gonadotropin (β-hCG) pregnancy test at study visits indicated on the SOA (Appendix 1). Following a negative pregnancy test at Screening and verification of appropriate contraception as outlined in Section 4.4.2.6 and Section 6.3, a negative pregnancy test result will be required at Day 1 (Baseline) prior to the subject receiving study drug and at subsequent visits where pregnancy testing is specified. Additionally, if the site staff become aware of a participant having a missed menstrual cycle between visits, the participant should come to the site for a urine pregnancy test (as an unscheduled visit if necessary). The Investigator may perform additional pregnancy tests at their discretion or as required by local regulations.

Urine pregnancy tests (supplied by the central laboratory) will be performed at the site. A positive urine β-hCG test must be followed up with a serum β-hCG pregnancy test. A positive pregnancy test prior to randomization requires exclusion. A positive urine β-hCG test during the study after randomization requires immediate interruption of study drug until a serum β-hCG is

performed and found to be negative. The participant must be discontinued from the study and followed if pregnancy is confirmed by a positive serum β-hCG.

7.3. Adverse and Serious Events

7.3.1. Adverse Events

AE definitions and assignment of severity and causality are detailed in Appendix 3.

Non-serious AE collection will be initiated after the subject has been randomized/enrolled and continue to be collected through the follow up phone call visit.

Any sign, symptom, or illness occurring prior to first dose of double-blind study drug will be captured in the medical history. TEAEs are defined as any AE reported after the first dose of study drug and continue to be collected through the follow up phone call visit. AE definitions and assignment of severity and causality are detailed in Appendix 3.

AEs will be elicited from the subject (or, when appropriate, from a caregiver, delegate, or the subject's legally authorized representative) by the study site staff using a non-leading question such as "How are you feeling today?" or "Have you had any health concerns since your last visit?"

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or the study, or that caused the subject to discontinue the study drug (see Section 4.4.2).

7.3.2. Reporting Serious Adverse Events

All SAEs, occurring after the signing of the ICF until 56 days after the last dose of study drug, and regardless of study drug relationship, must be reported within 24 hours of becoming aware of the event to appropriate Sponsor/CRO Drug Safety representatives. The Investigator or study site personnel will provide the initial notification by completing the SAE page in the eCRF (which will trigger an automatic SAE alert email to safety contacts), which must include the Investigator's assessment of the relationship of the event to study drug and must be signed by the Investigator. There may be situations in which minimal information is available. However, it is very important that the Investigator always makes an assessment of causality. The Investigator may change his/her assessment of the causality based on follow-up information and should amend the SAE report form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements. SAE definitions and assignment of severity and causality are detailed in Appendix 3.

Sponsor/CRO Drug Safety will forward SAE queries directly to the Investigator via email or through electronic data capture (EDC), requesting additional information. It is the Investigator's responsibility to be diligent in providing this information to Sponsor/CRO as soon as it is available. SAEs will be followed until resolution, stabilization, or death.

If an event meets serious criteria and it is not possible to access the EDC, the SAE should be submitted by completing SAE form electronically using this email address:

SAEintake@labcorp.com. If email access is not available, the SAE may be reported via fax using the below regional numbers or by telephone hotline:

US Fax# 1-888 887 8097

Safety Hotline# 1-888-724-4908

7.3.3. Pregnancy

Although not considered an SAE (unless the event occurs with a serious outcome), pregnancy (Section 4.4.2.6) information on female subjects will be collected by the authorized safety designee.

If a female subject becomes pregnant during the study, study drug should be discontinued immediately. The Investigator must complete and submit a Pregnancy Report Form (or designated form) within 24 hours of awareness of the pregnancy. In addition, subjects who become pregnant will complete the EOS or ET evaluations according to the SOA (Appendix 1).

Female subjects who become pregnant will also be followed to determine the outcome of the pregnancy and the presence or absence of a congenital abnormality will be documented by completion of a Pregnancy Outcome Reporting Form (or designated form) and should be submitted to the Sponsor once the outcome is known.

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy (spontaneous or intended) must also be reported.

If a female partner of a male subject becomes pregnant during the study, the female partner must complete the female partner ICF and the same reporting and follow-up guidelines for female subjects must be followed.

7.4. Pharmacokinetic Analysis

Predose blood samples will be collected into appropriately labeled tubes for measurement of namilumab plasma concentrations as specified in the SOA (Appendix 1) from all subjects who receive at least 1 dose of namilumab. The actual date and time (24-hour clock time) of each sample will be recorded.

Instructions for the collection and handling of biological samples will be provided in the laboratory manual. All samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps and any actions taken must be documented and reported to the Sponsor.

A specific bioanalytical method (detailed in BA sample analysis plan) will be used to measure plasma concentrations of namilumab.

7.5. Immunogenicity Assessment

Blood samples will be collected based on the SOA (Appendix 1) from all subjects who receive at least 1 dose of namilumab. A specific bioassay to determine development of ADA will be performed using a tier approach, i.e., Screening, confirmatory, and titer assessment. The impact of ADA on the PK of namilumab will be assessed.

8. SAMPLE SIZE AND DATA ANALYSES

This section outlines the statistical analysis strategy and procedures for the study.

8.1. Determination of Sample Size

The sample size for this study is not based on formal statistical calculations of study power. The planned sample size is considered sufficient to meet the primary objective.

8.2. Analysis Populations

The following analysis populations will be included for this study:

8.2.1. Intent-to-treat Population

The Intent-to-Treat (ITT) Population will include all randomized/enrolled subjects.

8.2.2. Modified Intent-to-treat Population

The modified ITT (mITT) Population will include all randomized/enrolled subjects who receive any amount of study drug. For analysis of endpoints defined as changes from baseline, subjects must also have at least 1 Baseline or post-baseline assessment. The mITT will be analyzed according to the treatment assigned. All efficacy analyses will be performed using the mITT Population.

8.2.3. Per-Protocol Population

The Per-Protocol (PP) Population will include all subjects in the ITT Population who have no major protocol violations. The PP Population will be used for sensitivity analyses of the efficacy measurements.

8.2.4. Safety Population

The Safety Population (SP) will include all randomized/enrolled subjects who receive any amount of study drug. The SP will be analyzed according to the treatment received. This set will be used for safety analyses.

8.3. General Considerations

All statistical analyses will be conducted using SAS, Version 9.3 or later. Demographic and Baseline characteristics will be summarized by treatment arm. For continuous measures, the mean and standard deviation (SD) will be summarized. Categorical variables will be described by the count and proportion in each category.

8.4. Handling of Missing Data

Missing data will not be imputed for safety or efficacy assessment. The reasons of missing data, including lost to follow-up, SAEs/AEs, and any other causes, will be identified, and the percentage of these subjects will be summarized by treatment. Large proportions of missing data may introduce bias, particularly if they are imbalanced between treatment groups. Possible bias due to missing data will be explored with sensitivity analysis.

More details will be pre-specified in the statistical analysis plan (SAP).

8.5. Efficacy Analyses

Efficacy analysis will be performed separately for subjects in Cohort A and subjects in Cohort B.

No hypothesis testing is planned for efficacy endpoints analyses. Nominal p values for treatment comparisons in efficacy analysis (Cohort A) will be provided as descriptive measures and should not be interpreted as conclusive evidence.

8.5.1. Efficacy Analysis Approaches

For continuous efficacy endpoints, summary statistics such as means, medians, and SDs will be provided by treatment groups. Model-based LS means and confidence intervals (CIs) for within treatment estimates and between treatment differences (Cohort A) will also be provided.

Categorical efficacy endpoints will be summarized by treatment with counts and percentages of the subjects. CIs for within treatment estimate and between treatment differences (Cohort A) will also be provided.

Time to event endpoints will be summarized using the Kaplan-Meier method.

Details for efficacy analysis methodologies will be provided in the SAP.

8.5.2. Adjustment of Multiple Comparisons

No hypothesis testing is planned for the study; therefore, adjustment for multiple comparisons will not be needed.

8.6. Safety Analyses

Safety analysis will be performed separately for subjects in Cohort A and Cohort B, as well as pooled across Cohorts A and B.

Safety variables include incidence of AEs or TEAEs, laboratory test results, vital signs, ECG results, and PE findings. A TEAE is defined as any AE that newly appeared or worsened in severity on or after the initiation of active treatment. All safety analyses will be based on the SP. No formal statistical analysis of the safety data will be performed.

Summary tables will be provided for all AEs by treatment group. The incidence of AEs, drug-related AEs, SAEs, and AEs leading to discontinuation of the study drug will be presented by the Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term. In addition, the incidence of AEs by severity will be presented by SOC and preferred term.

The AE summary tables will include counts of subjects. Therefore, if a subject experiences more than 1 episode of a particular AE, the subject will be counted only once for that event. Similarly, if a subject has more than 1 AE within an SOC, the subject will be counted only once in that SOC.

Laboratory test variables will be summarized by treatment group and visit using descriptive statistics (number of subjects, mean, SD, minimum, maximum). Shift tables (low, normal, high) between Baseline and post-baseline timepoints will be presented by laboratory test and treatment

group. Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries but will be listed. Data obtained from laboratory tests not required by the protocol will not be summarized but will be listed.

Descriptive statistics of vital signs and ECG results at each visit will be presented by treatment groups. PE findings will be listed for each subject.

Full details will be described in the Statistical Analysis Plan (SAP.)

8.7. Population Pharmacokinetic Analysis

The PPK and E-R analyses will be performed based on modeling analysis plan (MAP) and reported separately from the final clinical study report. The MAP will be submitted to the Food and Drug Administration (FDA) prior to unblinding subject data for analysis.

8.8. Statistical Analysis Plan

A detailed SAP will be signed and submitted to the FDA prior to database lock.

8.9. Interim Analysis

No formal interim analysis is planned. The DMC will be responsible for closely reviewing the unblinded safety data and for providing their recommendations. The detailed objectives and procedures will be described in the DMC Charter.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Schedule of Assessments																	
Study Period	**Screen**	**Treatment Period**															**☎ FU[a]**
Visit # (V)	**V1**	**Baseline V2**	**V3**	**☎ V4-6 [a]**	**V7**	**☎ V8-10 [a]**	**V11**	**☎ V12-14 [a]**	**V15**	**☎ V16-18 [a]**	**V19**	**☎ V20-22 [a]**	**V23**	**V24**	**V25**	**EOT/ ET [b] V26**	**EOS FU [c] V27**
Week (W)	**W -6**	**W0**	**W2**	**W3-5**	**W6**	**W7-9**	**W10**	**W11-13**	**W14**	**W15-17**	**W18**	**W19-21**	**W22**	**W26**	**W30**	**W34**	**W38**
Study Day (D) [Window based on Day 1 Visit]	**D -42 to -1**	**D1**	**D15 [±3]**	**D22, D29, & D36 [±3]**	**D43 [±3]**	**D50, D57, & D64 [±3]**	**D71 [±3]**	**D78, D85, & D92 [±3]**	**D99 [±3]**	**D106, D113, & D120 [±3]**	**D127 [±3]**	**D134, D141, & D148 [±3]**	**D155 [±3]**	**D183 [±3]**	**D211 [±3]**	**D238 [±3]**	**295 [±7]**
Informed consent	**X**																
Inclusion/ exclusion criteria	**X**																
Demographic information	**X**																
Medical history	**X**																
Prior medications[d]	**X**																
Physical examination[e]	**X**	**X**	**X**		**X**		**X**		**X**		**X**		**X**	**X**	**X**	**X**	
Height and weight[f]	**X**	**X**														**X**	
Vital signs (blood pressure [sitting], heart rate, respiration rate, and body temperature)[g]	**X**	**X**	**X**		**X**		**X**		**X**		**X**		**X**	**X**	**X**	**X**	
Heart rhythm monitoring (wearable)[h]	**X**	**X**	**X**		**X**		**X**		**X**		**X**		**X**	**X**	**X**		

Schedule of Assessments																	
Study Period	**Screen**	**Treatment Period**															**☎ FU[a]**
Visit # (V)	**V1**	**Baseline V2**	**V3**	**☎ V4-6 [a]**	**V7**	**☎ V8-10 [a]**	**V11**	**☎ V12-14 [a]**	**V15**	**☎ V16-18 [a]**	**V19**	**☎ V20-22 [a]**	**V23**	**V24**	**V25**	**EOT/ ET [b] V26**	**EOS FU [c] V27**
Week (W)	**W -6**	**W0**	**W2**	**W3-5**	**W6**	**W7-9**	**W10**	**W11-13**	**W14**	**W15-17**	**W18**	**W19-21**	**W22**	**W26**	**W30**	**W34**	**W38**
Study Day (D) [Window based on Day 1 Visit]	**D -42 to -1**	**D1**	**D15 [±3]**	**D22, D29, & D36 [±3]**	**D43 [±3]**	**D50, D57, & D64 [±3]**	**D71 [±3]**	**D78, D85, & D92 [±3]**	**D99 [±3]**	**D106, D113, & D120 [±3]**	**D127 [±3]**	**D134, D141, & D148 [±3]**	**D155 [±3]**	**D183 [±3]**	**D211 [±3]**	**D238 [±3]**	**295 [±7]**
12-lead ECG[i]	X	X	X		X		X		X		X		X	X	X	X	
Chest X-ray	X																
FDG-PET CT scan[j]	X						X (Cohort B only)						X (Cohort A only)			X	
ECHO	X						X						X			X	
Pulmonary function tests (FEV1, FEV1/FVC, and FVC)		X					X						X			X	
PROs (KSQ, FAS, and SGA)		X					X						X			X	
mGTI		X					X						X			X	
Recording of steroid dose and rescue therapy use[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication/ concurrent procedures[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse event monitoring[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Assessments																	
Study Period	**Screen**	**Treatment Period**															**☎ FU[a]**
Visit # (V)	**V1**	**Baseline V2**	**V3**	**☎ V4-6 [a]**	**V7**	**☎ V8-10 [a]**	**V11**	**☎ V12-14 [a]**	**V15**	**☎ V16-18 [a]**	**V19**	**☎ V20-22 [a]**	**V23**	**V24**	**V25**	**EOT/ ET [b] V26**	**EOS FU [c] V27**
Week (W)	**W -6**	**W0**	**W2**	**W3-5**	**W6**	**W7-9**	**W10**	**W11-13**	**W14**	**W15-17**	**W18**	**W19-21**	**W22**	**W26**	**W30**	**W34**	**W38**
Study Day (D) [Window based on Day 1 Visit]	**D -42 to -1**	**D1**	**D15 [±3]**	**D22, D29, & D36 [±3]**	**D43 [±3]**	**D50, D57, & D64 [±3]**	**D71 [±3]**	**D78, D85, & D92 [±3]**	**D99 [±3]**	**D106, D113, & D120 [±3]**	**D127 [±3]**	**D134, D141, & D148 [±3]**	**D155 [±3]**	**D183 [±3]**	**D211 [±3]**	**D238 [±3]**	**295 [±7]**
Adverse event monitoring[m]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
TB test	**X**																
Viral screen (Hep B, Hep C, HIV)	**X**																
FSH (women only & if indicated)[n]	**X**																
Sample for anti GM-CSF autoAb[q]	**X**																
Sample for ADA (antibodies to namilumab)[o]		**X**							**X**							**X**	
Cytokine and chemokine samples		**X**					**X**		**X**					**X**		**X**	
Samples for hsCRP, SAA, sarcoid biomarkers, and SP-D measurement		**X**					**X**		**X**					**X**		**X**	

Schedule of Assessments																	
Study Period	**Screen**	**Treatment Period**															**☎ FU[a]**
Visit # (V)	**V1**	**Baseline V2**	**V3**	**☎ V4-6 [a]**	**V7**	**☎ V8-10 [a]**	**V11**	**☎ V12-14 [a]**	**V15**	**☎ V16-18 [a]**	**V19**	**☎ V20-22 [a]**	**V23**	**V24**	**V25**	**EOT/ ET [b] V26**	**EOS FU [c] V27**
Week (W)	**W -6**	**W0**	**W2**	**W3-5**	**W6**	**W7-9**	**W10**	**W11-13**	**W14**	**W15-17**	**W18**	**W19-21**	**W22**	**W26**	**W30**	**W34**	**W38**
Study Day (D) [Window based on Day 1 Visit]	**D -42 to -1**	**D1**	**D15 [±3]**	**D22, D29, & D36 [±3]**	**D43 [±3]**	**D50, D57, & D64 [±3]**	**D71 [±3]**	**D78, D85, & D92 [±3]**	**D99 [±3]**	**D106, D113, & D120 [±3]**	**D127 [±3]**	**D134, D141, & D148 [±3]**	**D155 [±3]**	**D183 [±3]**	**D211 [±3]**	**D238 [±3]**	**295 [±7]**
Clinical laboratory: hematology	X	X	X		X		X		X		X		X	X	X	X	
Clinical laboratory: blood chemistry	X	X	X		X		X		X		X		X	X	X	X	
Clinical laboratory: urinalysis	X	X	X		X		X		X		X		X	X	X	X	
HbA_{1C}		X					X						X			X	
Vitamin D		X					X						X			X	
NT-proBNP		X					X						X			X	
Troponin		X					X						X			X	
Urine pregnancy test β-hCG (WCBP only)	X	X					X							X		X	
PK sample[p]			X		X				X					X		X	
Randomization and/or treatment assignment		X															
Administration of study drug		X	X		X		X		X		X		X	X	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin, ADA = anti-drug antibodies, CT = computed tomography, ECG = electrocardiogram, ECHO = echocardiogram, EOS = End-of-Study, EOT = End-of-Treatment, ET = early termination, FAS = Fatigue Assessment Scale, FDG = fluorodeoxyglucose, FSH = follicle-stimulating hormone, FU = Follow-up Visit, GM-CSF autoAb = granulocyte macrophage colony-stimulating factor autoantibody, HbA_{1C} = glycosylated hemoglobin, Hep = hepatitis, HIV = human immunodeficiency virus, hsCRP = high-sensitivity C-reactive protein, KSQ = King's Sarcoidosis Questionnaire, mGTI = modified glucocorticoid toxicity index,

NT-proBNP = N-terminal (NT)-proB-type natriuretic peptide, PET = positron emission tomography, PK = pharmacokinetic, PRO = patient-reported outcome, SAA = serum amyloid A, SGA = Subject Global Assessment, SP-D = serum surfactant protein D, TB = tuberculosis, WCBP = woman of childbearing potential.

a. The Investigator will conduct weekly FU (via phone, telemed, or any site-approved remote method).
b. Subjects who withdraw or are withdrawn from the study early will undergo all Week 34 ET/EOT Visit procedures whenever possible.
c. The FU will be a phone call approximately 8 weeks (56 days) following the last dose of study drug.
d. Collect medication history from the 6 months leading up to, and including, the time of the Screening Visit, including prescription medications, over-the-counter medications, and herbal supplements/vitamins.
e. A full physical examination will be performed at Screening and the EOT/ET Visit; an abbreviated targeted physical examination will be performed at all other clinic Visits.
f. Height will be measured at Screening only; weight will be measured at all indicated timepoints.
g. Vital signs will be assessed at all timepoints specified above. On study drug administration days, vital signs will be assessed predose (within 15 minutes) and ±30 minutes post-dose.
h. Subjects will be monitored via ePatch for 10 consecutive days; one patch will be worn for 5 days, then the patch will be replaced by the subject, and the second patch will be worn for an additional 5 days.
i. A single 12-lead standard ECG will be recorded at all timepoints specified above.
j. Only central imaging interpretation will be accepted for eligibility determination. Scans conducted as part of the usual clinical management of the subject within 2 weeks prior to informed consent may be considered/assessed for use in place of the Screening PET/CT scan if the scans can be uploaded to central imaging vendor for central read and the OCS dose has not changed in the 4 weeks prior to the scan. Refer to Section 7.1.2.1 for details
k. Document whether the patient has completed taper by the specified timepoints described in Appendix 8 or whether a dose increase/maintenance was needed. See Section 6.4 for more details regarding rescue therapy. Patients should record OCS dose daily on provided eDiary.
l. Collect information on concomitant medications and concurrent procedures from the time of informed consent through the EOS Visit, including prescription medications, over-the-counter medications, and herbal supplements/vitamins. All medications and procedures prior to randomization should be listed in the subject's medical history.
m. All serious adverse events will be monitored and collected from the time of informed consent through the 8 weeks (56 day) post last dose of study drug FU. All adverse events will be monitored and collected from the time of randomization through the 8 weeks (56 day) post last dose of study drug FU. Treatment-emergent adverse events will be those that start or change in severity after the first dose of study drug.
n. If necessary, follicle-stimulating hormone will be measured at Screening to confirm postmenopausal status.
o. The ADA samples will be collected at Baseline (prior to the first dose) of Day 1 (Week 0), at Week 14, and at EOT. For subjects who terminate the study early, one ADA sample will be collected before discharging, when possible. Actual sampling time will be recorded.
p. The PK samples will be collected prior to study drug administration at the appropriate timepoints and actual sampling time will be recorded.
q. Investigators in the state of New York will remain blinded to the anti-GMCSF auto-antibody assay results until the end of the trial due to regulations within the state of New York.

APPENDIX 2. HEART RHYTHM SOCIETY DIAGNOSTIC CRITERIA BASED ON 2 DIAGNOSTIC PATHWAYS

1. Histological diagnosis from myocardial tissue - cardiac sarcoidosis (CS) 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). Note this criterion is not required for this trial.
2. Clinical diagnosis from invasive and/or non-invasive studies: it is probable that there is CS if (a) through (c) are satisfied:
    a) Histological diagnosis of extracardiac sarcoidosis
    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 CS (PET SUVmax ≥3, as required in the inclusion criteria)
        - Late gadolinium enhancement on cardiac magnetic resonance (in a pattern consistent with CS)
        - Positive gallium uptake (in a pattern consistent with CS)
    c) Other causes for the cardiac manifestation(s) have been reasonably excluded.

APPENDIX 3. ADVERSE EVENT DEFINITIONS AND REPORTING

Adverse event (AE) reporting begins from the time the first dose of study drug has been taken and ends 8 weeks (56 days) after the last dose of study drug.

Definitions:

An AE is any untoward medical occurrence temporally associated with the use of a drug in humans, whether or not considered drug related. This includes the following:

- Any clinically significant worsening of a pre-existing condition.
- **Note:** Emergence of a new pathogen associated with a clinical event during therapy at a site other than the initial site of infection will be considered an AE.
- Any recurrence of a pre-existing condition.
- An AE occurring from overdose of a Sponsor study drug whether accidental or intentional (i.e., a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a Sponsor study drug (i.e., use for nonclinical reasons).
- An AE that has been associated with the discontinuation of the use of a Sponsor study drug.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. A procedure is not an AE, but the reason for a procedure may be an AE.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the ICF and that is documented as part of the subject's medical history.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a TEAE. An AE is considered to be treatment emergent if:

(1) It is not present when the active phase of the study begins and is not a chronic condition that is part of the subject's medical history, or (2) It is present at the start of the active phase of the study or as part of the subject's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the follow-up visit.

Reporting of Adverse Events:

At each visit, the Investigator, or delegate, will determine whether or not any AEs have occurred. Non-leading questions such as "How are you feeling today?" or "Have you had any health concerns since your last visit?" should be used to elicit the subject to report any possible AEs. If any AEs have occurred, they will be recorded in the AE section of the eCRF and in the subject's source documents. If known, the diagnosis should be recorded, in preference to listing the individual signs and symptoms.

Serious Adverse Events:

SAE reporting begins from the time of informed consent and ends 8 weeks (56 days) after the last dose of study drug.

An SAE is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death;
- Is life threatening (see below);
- Requires subject hospitalization or prolongation of an existing hospitalization (see below);
- Results in a persistent or significant disability or incapacity (see below);
- Results in a congenital anomaly or birth defect;
- Results in an important medical event, also known as medically significant (see below).

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

A ***life-threatening AE*** is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis of a more severe nature can be fatal. Hospitalization is to be considered only as an overnight admission.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating Investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious;
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file;
- Hospitalization for survey visits or annual physicals fall in the same category.

In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions (i.e., the AE resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the subject's bodily function/structure, physical activities, or quality of life).

Medical and scientific judgment should be exercised in deciding whether a case is serious in those situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity. These include events that may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. Such events should usually be considered as serious.

Assessment of Severity:

The Investigator will be asked to provide an assessment of the severity for each AE and SAE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living;
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject;
- **Severe**: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

It is emphasized that the term severe is a measure of severity: thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe but may not be clinically serious.

Relationship to Study Treatment:

The Investigator will make a determination of the relationship of the AE/SAE to the study drug using a 4-category system according to the following guidelines:

- **Not Related**: when the AE/SAE is definitely caused by the subject's clinical state, or the study procedure/conditions, or the subject did not receive the drug;
- **Unlikely Related**: when the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE;
- **Possibly Related**: when the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions;
- **Definitely Related**: when the AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Action Taken for Adverse Events:

The Investigator or designee will record the action taken for the AE in the eCRF. Actions taken will include:

- **Dose increased**: The medication schedule was modified by addition, either by changing the frequency, strength, or amount;
- **Dose not changed**: The medication schedule was not changed;
- **Dose reduced**: The medication schedule was modified by subtraction, either by changing the frequency, strength, or amount;
- **Drug interrupted**: The medication schedule was modified by temporarily withholding the prescribed regimen of medication;
- **Drug withdrawn**: The medication schedule was modified through discontinuation of the prescribed regimen of medication;
- **Not applicable**;
- **Unknown**.

Follow-up of Adverse Events:

All (S)AEs that are ongoing at the time of discontinuation, or that develop prior to the final follow-up telephone call, will be followed for 56 days, or until resolution or stabilization.

Adverse Drug Reactions

All noxious and unintended responses to an investigational medicinal product (IMP; i.e., where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function, is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved IMP).

APPENDIX 4. COMPARISON OF SYSTEMIC GLUCOCORTICOID PREPARATIONS

Glucocorticoids	Equivalent doses (mg)	Duration of action (hours)
Short Acting		
• **Cortisone**	**25**	**8 to 12**
• **Hydrocortisone**	**20**	**8 to 12**
Intermediate Acting		
• **Methylprednisolone**	**4**	**12 to 36**
• **Prednisolone**	**5**	**12 to 36**
• **Prednisone**	**5**	**12 to 36**
• **Triamcinolone**	**4**	**12 to 36**
Long Acting		
• **Betamethasone**	**0.6**	**36 to 72**
• **Dexamethasone**	**0.75**	**36 to 72**

(UpToDate, 2021)

APPENDIX 5. CLINICAL LABORATORY EVALUATIONS

The following clinical laboratory analytes will be assessed as timepoints specified in the SOA (Appendix 1).

Blood Chemistry	
-Albumin	
-ALP	-LDH
-ALT	-Phosphorus
-AST	-Potassium
-BUN	-Sodium
-Calcium (absolute, corrected)	-SP-D (Surfactant Protein D)
-Creatinine	-Total Bilirubin (total and direct)
-eGFR	-Total CO_2 (measured as bicarbonate)
-GGT	-Total Protein
-Glucose	-Uric Acid
-High-sensitivity CRP	

Serology
-anti-GM-CSF
-ADAs (to namilumab)
-HBcAb
-HBsAb
-HBsAg
-HCVab
-Hep B (reflex testing if applicable)
-Hep C (reflex testing if applicable)
-HIVAb
-RT-PCR (if applicable, based on serology results)

Hematology	
-ESR	-White blood cell (WBC) count
-Hematocrit	-WBC Differential (%, absolute) including:
-Hemoglobin	-Basophils
-MCH	-Eosinophils
-MCHC	-Monocytes
-MCV	-Neutrophils
-Platelet count	-Lymphocytes
-Red blood cell (RBC) count	
-Reticulocytes (%, absolute)	

Urinalysis
-Bilirubin
-Color and appearance
-Urine pregnancy test (for WCBP only)
-Glucose
-Ketones
-Leukocyte esterase
-Microscopic (including RBCs and WBCs)
-Nitrate
-Occult blood
-pH and specific gravity
-Protein

Lipid Profile
-Total cholesterol (TC)
-Triglycerides (TGs)
-High-density lipoprotein cholesterol (HDL-C)
-Low-density lipoprotein cholesterol (LDL-C)

Other Assessments & Biomarkers
-FSH (as indicated to confirm postmenopausal status)
-HbA_{1c}
-IGRA (QFT-G)
-SAA
-Soluble IL2 Receptor (SIL2R)
-25-hydroxyvitamin D (serum)
-1,25-dihydroxyvitamin D (serum)
-NT-proBNP
-Troponin I

Cytokine and Chemokine Analyses		
-GM-CSF	-IL-12/IL-23p40	-TNF-β
-IL-1α	-IL-15	-VEGF
-IL-1β	-IL-16	-IFN-γ
-IL-2	-IL-17A	-Eotaxin, MIP-1β
-IL-4	-IL-10	-Eotaxin-3
-IL-5	-IL-12(p70)	-MCP-1
-IL-6	-IL-13	-MCP-4
-IL-7	-IP-10	-MDC
-IL-8	-TNF-α	-MIP-1α
	-TARC	-CXC (homeostatic)

APPENDIX 6. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines;
- Applicable ICH GCP Guidelines;
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB;
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary, and they are free to withdraw from the study at any time.

Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB or study center, where applicable. The subject will be given a copy of the signed ICF, and the original will be maintained with the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her medical records may be examined by Sponsor or CRO auditors or other authorized personnel appointed by the **S**ponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF;
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF;
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents;
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Pre-defined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan;
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements;

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) (US site). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will be entered into a 21 CFR Part 11-compliant EDC system on an eCRF in a timely fashion. All data generated from external sources (e.g., central laboratory, PK, pharmacodynamics, ECG central readers) and transmitted to the Sponsor or designee electronically will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each subject who signs an ICF and undergoes any pre-Screening or Screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement. Unless otherwise specified in the clinical study agreement, the following process shall occur:

The institution and Investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor shall have 60 days to respond with any requested revisions, including (without limitation) the deletion of confidential information. The Investigator shall act in good faith upon requested revisions, except the Investigator shall delete any confidential information from such proposed publications. The Investigator shall delay submission of such publication or presentation materials for up to an additional 90 days to have a patent application(s) filed.

APPENDIX 7. LIVER SAFETY SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Phase 2 liver function stopping criteria are designed to ensure subject safety and to evaluate liver event etiology.

Phase 2 Liver Function Stopping Criteria and Follow-up Assessments

Liver Function Stopping Criteria	
ALT-absolute	ALT ≥5×ULN
ALT Increase	ALT ≥3×ULN persists for ≥4 weeks
Bilirubin[1,2]	ALT ≥3×ULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3×ULN **and** international normalized ratio (INR) >1.5, if INR measured
Cannot Monitor	ALT ≥3×ULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3×ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Actions and Follow-up Assessments following ANY Liver Function Event that Requires Study Treatment Discontinuation	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study treatment. • Report the event to the Sponsor **within 24 hours**. • Complete the liver event eCRF and complete an SAE data collection tool if the event also met the criteria for an SAE.[2] • Perform liver function follow-up assessments. • Monitor the subject until liver function test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**). • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and Sponsor Medical Governance approval is granted. • If restart/rechallenge **not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments.	• Viral hepatitis serology.[4] • Blood sample for PK analysis obtained after the most recent dose.[5] • Serum creatine phosphokinase and lactate dehydrogenase. • Fractionate bilirubin if total bilirubin is ≥2×ULN. • Complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form. • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications report form. • Record alcohol use on the liver event alcohol intake eCRF.

MONITORING: **<u>For bilirubin or INR criteria:</u>** Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow-up assessments within 24 hours. Monitor subject twice weekly until liver function test abnormalities resolve, stabilize or return to Baseline. A specialist or hepatology consultation is recommended. **<u>For all other criteria:</u>** Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow-up assessments within 24 to 72 hours. Monitor subjects weekly until liver function abnormalities resolve, stabilize, or return to Baseline.	**<u>For bilirubin or INR criteria:</u>** Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. Serum acetaminophens adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week). Liver imaging (ultrasound, magnetic resonance, or CT) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRFs.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment if ALT ≥3×ULN **and** bilirubin ≥2×ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥3×ULN **and** bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR measurement is not required, and the stated threshold value will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).
4. Includes: Hepatitis A IgM antibody; HBsAg and HBcAb; hepatitis C ribonucleic acid; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5. PK sample may not be required for subjects known to be receiving placebo or non-comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the laboratory manual.

Phase II Liver Function Increased Monitoring Criteria with Continued Therapy

Liver Function Increased Monitoring Criterion and Follow-up	
Criterion	**Actions**
ALT ≥3×ULN and <5×ULN **and** bilirubin <2×ULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the Sponsor Medical Monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment. • Subject must return weekly for repeat liver function tests (ALT, AST, ALP, bilirubin) until the abnormalities resolve, stabilize or return to Baseline. • If at any time, the subject meets liver function stopping criteria, proceed as previously described. • If, after 4 weeks of monitoring, ALT <3×ULN and bilirubin <2×ULN, monitor subjects twice monthly until liver function tests normalize or return to Baseline.

APPENDIX 8. ORAL CORTICOSTEROID TAPERING PROTOCOL

Only Subjects enrolled in Cohort A will receive high dose OCS and undertake and follow the steroid taper. All subjects will be commenced at a dose of 25 to 60 mg of prednisone daily or its equivalent. The high dose steroid treatment may start as soon as the screening PET scan has been completed or up until the Baseline visit/ day of randomization. The investigator will determine the starting dose of OCS.

Prednisone or equivalent tapering schedule

Weeks 1-4

Maintain 25 mg/day or reduce from up to 60 mg/day to 25 mg/day by Week 4 (per Investigator's determination).

In all cases by the Week 4 Visit, the subject should be receiving 25 mg of prednisone or equivalent daily. For subjects receiving >25 mg daily of prednisone or its equivalent initially, the investigator must agree the doses to be received between commencing high-dose OCS treatment and the Week 4 visit and confirm via the planned phone visits (Appendix 1) that the subject is taking their OCS as intended. Irrespective of the dose of OCS received all subjects should have phone visits to ensure their adherence to the intended OCS dose and to assess for (S)AEs.

Weeks 5-10

Maintain 25 mg/day

Following the Week 4 Visit through the Week 10 Visit, all subjects should receive 25 mg per day of prednisone or its equivalent.

Weeks 11-22

Taper to 10 mg/day by Week 22

Following the Week 10 Visit, subjects should commence the steroid taper with the goal of receiving no more than 10 mg of prednisone daily (or equivalent) by the Week 22 Visit. The precise dose on a day by day and week by week basis will be determined by the Investigator and Subject compliance is to be assured at the phone follow up visits.

Weeks 22-34

Following the Week 22 Visit, subjects will receive 10 mg or less of prednisone daily (or its equivalent); based on the opinion of the Investigator. Further dose reduction below 10 mg of prednisone daily or its equivalent is encouraged if the clinical situation allows but is not required.

If a subject substantially deteriorates during the taper period in the opinion of the Investigator, then a "rescue" may be performed (see Section 3.1.4.1). In this scenario, the steroid dose may be maintained or increased back to a prior level, and the subject is considered to have failed the steroid taper. Steroid taper may be recommenced after assessing clinical response to rescue based on clinical judgement.

APPENDIX 9. PATIENT-REPORTED OUTCOMES ASSESSMENTS

Examples of the following patient-reported outcomes (PROs) are provided in this appendix:

- Kings Sarcoidosis Questionnaire
- Fatigue Assessment Scale
- Subject Global Assessment

King's Sarcoidosis Questionnaire

This questionnaire is designed to assess the impact of sarcoidosis on various aspects of your life. Read each question carefully and answer by SELECTING the response that best applies to you. Please answer ALL questions as honestly as you can. This questionnaire is confidential.

All questions relate to how SARCOIDOSIS has affected your health.

GENERAL HEALTH STATUS

	In the last 2 weeks...	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
1	I have felt frustrated	1	2	3	4	5	6	7
2	I have had trouble concentrating	1	2	3	4	5	6	7
3	I have lacked motivation	1	2	3	4	5	6	7
4	I have felt tired	1	2	3	4	5	6	7
5	I have felt anxious	1	2	3	4	5	6	7
6	I have felt aches and pains in my muscles/joints	1	2	3	4	5	6	7
7	I have felt embarrassed	1	2	3	4	5	6	7
8	I have worried about my weight	1	2	3	4	5	6	7
9	I have worried about my sarcoidosis	1	2	3	4	5	6	7

	In the last 2 weeks...	A huge amount	A considerable	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
10	Tiredness has interfered with my normal social activities such as going out with friends/family	1	2	3	4	5	6	7

Lungs

	In the last 2 weeks...	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
11	My cough has caused pain/discomfort	1	2	3	4	5	6	7
12	I have been breathless climbing stairs or walking up slight inclines	1	2	3	4	5	6	7
13	I have had to take deep breaths, also known as 'air	1	2	3	4	5	6	7
14	My chest has felt tight	1	2	3	4	5	6	7
15	I have had episodes of breathlessness	1	2	3	4	5	6	7
16	I have experienced chest pains	1	2	3	4	5	6	7

Medication

	In the last 2 weeks...	A huge amount	A considerable	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
17	I have worried about the side effects of my medication for sarcoidosis	1	2	3	4	5	6	7
18	I have felt worse because of my medication	1	2	3	4	5	6	7
19	I have gained weight because of my medication	1	2	3	4	5	6	7

Skin

	In the last 2 weeks...	A huge amount	A considerable	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
20	I have been bothered by my skin problems	1	2	3	4	5	6	7
21	I have been concerned about changes in the color of my skin lesions	1	2	3	4	5	6	7

	In the last 2 weeks...	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
22	I have been embarrassed about my skin	1	2	3	4	5	6	7

Eyes

	In the last 2 weeks...	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
23	I have had dry eyes	1	2	3	4	5	6	7
24	I have had difficulty with bright lights	1	2	3	4	5	6	7
25	My eyes have been red	1	2	3	4	5	6	7
26	I have had pain in/or around the eyes	1	2	3	4	5	6	7
27	I have had difficulty reading	1	2	3	4	5	6	7

	In the last 2 weeks...	A huge amount	A considerable	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
28	I have had blurred vision	1	2	3	4	5	6	7
29	I have been worried about my eyesight	1	2	3	4	5	6	7

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Fatigue Assessment Scale (FAS)

Fatigue Assessment Scale (FAS)

The following ten statements refer to how you usually feel. Per statement you can choose one out of five answer categories, varying from Never to Always.
Please circle the answer to each question that is applicable to you. Please give an answer to each question, even if you do not have any complaints at the moment.

1. **Never**
2. **Sometimes** (about monthly or less)
3. **Regularly** (about a few times a month)
4. **Often** (about weekly)
5. **Always** (about every day)

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue	○	○	○	○	○
2. I get tired very quickly	○	○	○	○	○
3. I don't do much during the day	○	○	○	○	○
4. I have enough energy for everyday life	○	○	○	○	○
5. Physically, I feel exhausted	○	○	○	○	○
6. I have problems to start things	○	○	○	○	○
7. I have problems to think clearly	○	○	○	○	○
8. I feel no desire to do anything	○	○	○	○	○
9. Mentally, I feel exhausted	○	○	○	○	○
10. When I am doing something, I can concentrate quite well	○	○	○	○	○

References:
1. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. Eur Respir J 2012; 40: 255–263. http://www.ncbi.nlm.nih.gov/pubmed/22441750
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3. De Vries, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol 2004; 9: 279-91. http://www.ncbi.nlm.nih.gov/pubmed/15296678
4. Hendriks C, Drent M, Elfferich M, De Vries J. The Fatigue Assessment Scale (FAS): quality and availability in sarcoidosis and other diseases. Curr Opin Pulm Med 2018; 24 (5): 495-503. https://pubmed.ncbi.nlm.nih.gov/29889115

Subject Global Assessment

Over the last two weeks, please rate how frequently you experienced sarcoidosis symptoms (coughing, breathlessness, dizziness, palpitations, chest pain/tightness or other ways your sarcoidosis affects you):

None of the time	A little of the time	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

Over the last two weeks, please rate how severe your sarcoidosis symptoms (coughing, breathlessness, dizziness, palpitations, chest pain/tightness or other ways your sarcoidosis affects you) have been:

None	Mild	Moderate	Severe	Very Severe
☐	☐	☐	☐	☐

APPENDIX 10. OTHER REPORTED OUTCOMES

Modified Glucocorticoid Toxicity Index

Table 1 The Glucocorticoid Toxicity Index

Composite GTI	Item weight	Specific List
BMI		
Improvement in BMI	–8	Major increase in BMI
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	36	
Glucose tolerance		
Improvement in glucose tolerance	–8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose tolerance	32	Diabetic neuropathy
Worsening of glucose tolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	–10	Hypertensive emergency
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	–9	
No change in lipids	0	
Worsening hyperlipidaemia	10	

APPENDIX 11. DIET PREPARATION RECOMMENDATIONS FOR SUBJECTS 24 HOURS PRIOR TO PET SCAN

PET/CT Preparation – For 24 hours before the scan

- Do not exercise
- If you are diabetic, get instructions from your physician
- Follow a low carbohydrate diet (no pasta, bread, rice, potatoes, beans, cereal, desserts, candy, fruits, jam/jelly, honey, shakes/smoothies, etc.)
- Do not consume dairy products (milk, yogurt, sour cream, soft cheeses)
- Do not consume sugar or artificial sweeteners
- Do not drink alcohol

Foods you CAN eat:

- Eggs
- Leafy-green vegetables
    - Oil and lemon or vinegar dressing (nothing sweet)
- Fried or broiled fish or meats seasoned with salt and pepper (nothing sweet)
- Hard cheeses
- Nuts, nut milk (e.g. almond milk), and UNSWEETENED nut butter

PET/CT Preparation – Day of the scan

- Medications
    - Take routine medications with PLAIN, UNFLAVORED WATER
    - If you need pain or anxiety medication, take it at least 1 hour before the scan
- If you are diabetic, let your doctor and the staff at the scanner know
    - Your blood sugar will be checked
- DO NOT EAT ANYTHING, including gum, breath mints, cough drops, or candy, FOR 6 HOURS BEFORE THE SCAN
    - Drink only water
- Do not wear metal zippers or jewelry of any kind

- When your scan is completed, you will be able to go home and resume normal activities and diet

Note: These are the minimum required recommendations, if the Investigator or site guidelines are more stringent or detailed, they supersede these recommendations.