CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-blind, Placebo-controlled Phase 2 Study with Open-label Extension to Assess the Efficacy and Safety of Namilumab in Subjects with Chronic Pulmonary Sarcoidosis		
Protocol Number:	KIN-1902-2001		
Study Name:	RESOLVE-Lung		
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EudraCT#:	2021-004794-31		
EUCT #	2024-511115-25-00		
Universal Trial Number:	U1111-1302-2991		
Compound Name and/or Number:	Namilumab		
Sponsor:	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.		
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Development Phase:	2		
Indication:	For the treatment of chronic pulmonary sarcoidosis		
Current Version and Effective Date:	Version: 3.0	Amendment 2	13-May-2024
Study Director:	PPD Phone: PPD Email: PPD		

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SPONSOR SIGNATURE PAGE

Study Title: A Randomized, Double-blind, Placebo-controlled Phase 2 Study with Open-label Extension to Assess the Efficacy and Safety of Namilumab in Subjects with Chronic Pulmonary Sarcoidosis

Protocol Number: KIN-1902-2001

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

PPD

Date

INVESTIGATOR SIGNATURE PAGE

Study Title: A Randomized, Double-blind, Placebo-controlled Phase 2 Study with Open-label Extension to Assess the Efficacy and Safety of Namilumab in Subjects with Chronic Pulmonary Sarcoidosis

Protocol Number: KIN-1902-2001

- I confirm agreement to conduct the study in compliance with the protocol.
- 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 2 Study with Open-label Extension to Assess the Efficacy and Safety of Namilumab in Subjects with Chronic Pulmonary Sarcoidosis
Indication	Treatment of chronic pulmonary sarcoidosis (CPS)
Study Centers	Approximately 50 sites globally
Study Objective(s)	**Primary Objective:** The primary objective of this study is: • To evaluate the effect of namilumab on the need for rescue treatment for worsening of sarcoidosis. The secondary objectives of this study are: • To evaluate the effect of namilumab on percent predicted forced vital capacity (ppFVC); • To evaluate the effect of namilumab on the time to the first rescue event; • To evaluate the effect of namilumab on proportion of subjects achieving OCS taper without rescue event; • To assess the effect of namilumab on respiratory symptoms based on the King's Sarcoidosis Questionnaire (KSQ) Lung domain; • To assess the safety and tolerability of namilumab. The exploratory objectives of this study are: • To assess the effect of namilumab on other measures of pulmonary function; • To assess the effect of namilumab on the following Patient Reported Outcomes (PROs): o St. George's Respiratory Questionnaire (SGRQ); o KSQ domains (including ad-hoc subscales); o Modified King's Sarcoidosis Questionnaire (mKSQ) Lung domain; o Subject Global Assessment (SGA); o Leicester Cough Questionnaire (LCQ); o Bothersomeness and Subject Global Impression of Change (BSGIC). • To assess the effect of namilumab on cumulative OCS use and other OCS use-related endpoints; • To evaluate clinical benefit of namilumab

	• To assess the effect of namilumab on the severity of extrapulmonary organ involvement; • To assess the population pharmacokinetics (PPK) and exposure-response (E-R) relationships for efficacy and safety of namilumab; • To assess the presence of anti-drug antibody (ADA); • To assess the effect of namilumab on circulating biomarkers, and the correlations between biomarker and clinical endpoint changes.
Study Rationale	Sarcoidosis is a multi-organ inflammatory 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. About 90% of the total sarcoidosis population exhibits pulmonary involvement. Granulocyte-macrophage colony-stimulating factor (GM-CSF), a proinflammatory 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 macrophage precursors into tissues, and supporting the crosstalk between CD4+ T cells and myeloid cells. Successful late-phase clinical trials of anti-GM-CSF monoclonal antibodies in rheumatoid arthritis, giant cell arteritis, and severe coronavirus disease 2019 (COVID-19) have provided evidence for the pathogenic role of GM-CSF in aberrant immune responses. Over the past 30 years, human tissue and mouse model studies have shown that GM-CSF plays a key role in the formation of granulomas, including sarcoid granulomas. Namilumab, a monoclonal antibody (mAb) that neutralizes GM-CSF, has the potential to improve outcomes in CPS by downregulating the granulomatous response that drives the disease.
Study Population	This study will include subjects with CPS who are not well controlled on OCS and/or immunosuppressive therapy (IST). The study population will include subjects who have been treated with, but are no longer receiving, OCS and/or IST.
Number of Planned Subjects	Approximately 100 subjects (50 subjects in each of 2 treatment arms, randomized 1:1 namilumab: placebo) are planned for this study. **Note:** Randomization will be stratified by IST use at baseline.
Study Design	Randomized, double-blind, placebo-controlled, with an optional open-label extension (OLE).
Study Treatments	**<u>Double-blind Treatment Period:</u>** • 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 22.

	• Treatment Arm 2: Placebo administered to match namilumab dosing. **<u>Open-label Extension (OLE) Treatment Period:</u>** All subjects, regardless of treatment assignment in the Double-blind Treatment Period, who agree and are eligible to participate in the OLE will receive namilumab administered SC: 150 mg at Week 26, and then Q4W through Week 50.
Treatment and Study Duration	For subjects who only participate in the Double-blind Treatment Period the duration will be approximately 46 weeks as follows: • Up to 6-week Screening Period; • 26-week Double-blind Treatment Period; • 14-week off-drug Follow-up Period. **Note:** Beginning at the Randomization Visit, each subject taking OCS will perform an OCS tapering protocol. Each subject will also stop all ISTs at randomization. For subjects who complete the Double-blind Treatment Period and continue in the OLE, participation will be approximately 74 weeks as follows: • Up to 6-week Screening Period; • 26-week Double-blind Treatment Period; • 28-week OLE Treatment Period; • 14-week off-drug Follow-up Period.
Study Endpoint(s)	**The primary endpoint of this study is:** • Proportion of subjects with a rescue event during the DB period **The secondary endpoints of this study are:** • Change from baseline in percent predicted forced vital capacity (ppFVC) at Week 26; • Time to the first rescue event during DB period; • Proportion of subjects successfully achieving OCS taper without rescue event during DB period; • Change from baseline in the KSQ Lung domain score at Week 26; • Safety and tolerability, including assessment of physical examinations (PEs), vital signs, electrocardiograms (ECGs), clinical laboratory measurements, and AEs during DB period. **The exploratory endpoints of this study are:** • Change from baseline and categorical assessments in pulmonary function in ppFVC (%),FVC (mL), FEV1 (mL), ppFEV1 (%), FEV1/FVC (mL/mL), and percent predicted diffusing capacity of lung for carbon monoxide hemoglobin corrected value (ppDLco) at Week 26;

	• Change from baseline in the following PRO scores at Week 26: o SGRQ; o KSQ domains (including ad-hoc subscales); o mKSQ Lung domain; o SGA; o LCQ; o BSGIC. • Cumulative OCS (expressed as prednisone equivalent) use and other OCS use related endpoints in the Double-blind Treatment and OLE Periods, separately and combined; • Rate of clinical benefit, defined as achieving at least two of the four following criteria (without clinically relevant decline in any of these parameters or rescue event) at end of the corresponding period: a) an improvement of ≥ 5% points from baseline in ppFVC; b) an improvement of ≥ 5% points from baseline in ppDLco; c) KSQ Lung domain score improvement of ≥ 4 points, d) successfully achieving OCS dose ≤ 5 mg/day and at least 5 mg decreased from baseline OCS dosing during the corresponding period for subjects who had OCS > 5 mg/day at baseline, or achieving OCS free at the end of the corresponding period for subjects who had OCS ≤ 5 mg/day at baseline during DB period • Change in extrapulmonary Physician Organ Severity Tool (ePOST) score at Week 26; • PPK and E-R relationship assessments for efficacy and safety, where data permit; • Number of subjects positive for ADA to namilumab during DB period; • Change and percent change from baseline in pre-specified exploratory biomarkers and the correlations between biomarker and clinical endpoint changes at Week 26. To assess the durability of efficacy and safety, all the endpoints will also be analyzed for the OLE period for all subjects.
Inclusion Criteria	**An individual will be eligible for participation in this study only if all of the following inclusion criteria are met:** 1. Male or female subjects age ≥ 18 years. 2. Able and willing to provide written informed consent, which includes compliance with study requirements, study procedures (including performing acceptable spirometry according to ATS criteria), and restrictions listed in the consent form. 3. ≥ 6-month history of documented sarcoidosis (must include histological report, from any organ, in the subject's medical records).

4. Have HRCT scan at screening consistent with pulmonary sarcoidosis of the lung parenchyma by central read.

   Note: An HRCT performed as part of clinical care may be used as the screening HRCT as long as the HRCT is performed within 4 weeks of the Screening Visit and is uploaded and deemed of acceptable quality by the imaging vendor/central reader. If not of acceptable quality for study inclusion, it needs to be obtained again as part of the study inclusion procedures.

5. ppFVC ≥ 50% and ppDLco (hemoglobin corrected value) ≥ 40% predicted at screening.
6. If receiving prednisone (or equivalent), dose must be ≤ 25 mg, and dose must have been stable for at least 4 weeks prior to screening. In addition, subject must agree to taper their steroids beginning at the time of randomization.
7. If receiving methotrexate and/or other IST, subject must agree to cessation of their IST therapy at randomization.
8. Have additional evidence of active pulmonary sarcoidosis as defined by:

   a. Medical Research Council Dyspnea scale > 1 (i.e., Grade 2 or more) at screening; AND

   b. Currently on a treatment regimen for pulmonary sarcoidosis that includes OCS, IST, or the combination of OCS and IST. If not currently being treated with either OCS or IST, subjects can still be eligible if there is documentation in the medical records that they have taken OCS and/or IST in the past 2 years for their pulmonary sarcoidosis and have been unable to tolerate them, treatment was not effective, or they subsequently refused to continue taking these medications; AND

   c. One or more of the following is present:

      i. Screening FDG-PET scan showing pulmonary parenchymal uptake consistent with active pulmonary sarcoidosis AND with pulmonary parenchymal SUVmax ≥ 3 on central read;

      Note: A PET/CT performed as part of clinical care may be used as the screening PET/CT as long as the PET/CT is performed within 4 weeks of the Screening Visit and is uploaded and deemed of acceptable quality by the imaging vendor/central reader. If not of acceptable quality for study inclusion, it needs to be obtained again as part of the study inclusion procedures.

      ii. Documentation in the subject's medical record of worsening sarcoidosis (i.e., a clinically meaningful worsening in pulmonary function parameters (e.g., ≥ 5 percent decline in ppFVC) or clinically relevant worsening of radiographic findings (e.g., HRCT, chest x-ray) in the past 12 months);

	iii. Documentation in the subject's medical record that tapering OCS (≥ 5 mg change) and/or tapering ISTs during the past 12 months resulted in an increase of pulmonary disease symptoms, signs, or activity necessitating maintenance or increase in dose of OCS and/or IST. 9. Female subjects must agree to use an approved highly effective birth control (BC) method (< 1% failure rate per year) for at least 4 weeks prior to randomization, throughout the study, and for 18 weeks following the last dose of study drug, unless documented to have a reproductive status of non-childbearing potential or is postmenopausal as defined below: a. Non-childbearing potential defined as pre-menopausal female with medical history of total hysterectomy, bilateral oophorectomy (removal of ovaries), bilateral salpingectomy, bilateral tubal ligation, or bilateral hysteroscopic sterilization at least 3 months prior to screening; b. Postmenopausal defined as 12 months of spontaneous amenorrhea without an alternative medical cause. 10. Male subjects must agree to use condoms when having sexual intercourse with female partners of childbearing potential and attest that female partners of childbearing potential will use a highly effective method of contraception as described above for at least 4 weeks prior to randomization/enrollment, throughout the study and for 18 weeks following the last dose of study drug. Male subjects must also agree to not donate sperm from the time of signing consent until 18 weeks 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	**An individual will not be eligible for participation in this study if any of the following exclusion criteria are met prior to randomization:** 1. Hospitalized for any respiratory illness ≤ 30 days prior to or during screening. 2. ≥ 20% fibrosis as indicated on HRCT-scan assessed by central read prior to randomization. 3. Estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD] equation) or requiring chronic renal replacement therapy. 4. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) > 2 × upper limit of normal range (ULN), or serum total bilirubin > 1.5 × ULN. **Note:** Subjects with documented history of Gilbert's syndrome may remain eligible if they have a direct bilirubin ≤ ULN).

	5. Platelet count < 100,000 per mm^3. 6. Hemoglobin ≤ 9.5 g/dL. 7. Absolute neutrophil count < 1,500 per mm^3. 8. Corrected serum calcium > 3.0 mmol/L (> 12 mg/dL). 9. History of pulmonary alveolar proteinosis (PAP). 10. Use of any prohibited immunomodulator agent, immunoglobulin or FcRn inhibitor (approved or investigational) within the 6 months prior to or during screening. **Note:** Allergens for hypersensitivity desensitization or vaccines are not excluded. EVUSHELD administration for COVID-19 prophylaxis is allowed up to within 2 weeks prior to baseline (V2). 11. Treatment with any Janus kinase (JAK) inhibitor within 6 months prior to or during screening. 12. Participation in another interventional clinical trial within 6 months prior to or during screening and throughout the duration of participation in this study. 13. History of left ventricular ejection fraction (LVEF) ≤ 40% or New York Heart Association (NYHA) class III or IV heart failure. 14. ECG abnormalities that warrant further clinical investigation or management at screening or 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. 15. Pulmonary hypertension requiring therapy. 16. Systolic blood pressure (SBP) < 90 or > 180 mm Hg; Diastolic blood pressure (DBP) < 60 or > 110 mm Hg at screening. 17. Documented laboratory-confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection with pulmonary involvement or signs/symptoms of long COVID as determined by approved testing ≤ 6 months prior to randomization. 18. Administration of any fully live virus or bacterial vaccinations within 3 months prior to or during 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. 19. Systemic (oral or parenteral) antibiotic or pulse OCS treatment for any indication within 6 weeks prior to randomization. **Note:** A systemic (oral or parenteral) antibiotic prescribed for infection prophylaxis (i.e., not for treatment of an infection) is

	allowed as long as it was started at least 6 weeks prior to the Baseline Visit AND is not a prohibited medication per protocol. 20. Three or more lower-respiratory tract infections requiring antimicrobial therapy within 12 months prior to screening. 21. Any history of mycetoma or fungal respiratory infection. 22. Requirement for supplemental oxygen at rest. 23. History of or planned solid organ or hematopoietic cell transplantation. 24. Prior or planned pneumonectomy and/or planned lobectomy. **Note:** Lobectomy performed ≥ 12 months prior to randomization is allowed. 25. Smoking or using any form of inhaled tobacco, inhaled nicotine (including vaping), or inhaled cannabis preparations within 6 months of screening. Subjects are also excluded if they are not likely to refrain from these activities throughout the Study Treatment Period and 18 weeks following the last dose of study drug. 26. A diagnosis of, or presentation consistent with, Lofgren's syndrome. 27. Other significant pulmonary disease, or conditions that prevent subject from performing acceptable spirometry. 28. Autoimmune disease other than sarcoidosis likely to require treatment during the subject's participation in this study. 29. Symptoms and/or signs of extra-pulmonary sarcoidosis (e.g., cardiac or neurologic sarcoidosis) that require ongoing treatment that would interfere with the protocol-specified treatment regimen or confound the interpretation of the study data (e.g., tapering of IST and/or OCS). **Note:** Subjects who require topical or intra-ocular therapies for skin or ophthalmic sarcoid disease are not excluded. 30. History of cardiac disease such as: a. Cardiac sarcoidosis with history of clinically significant cardiac rhythm disturbance such as complete heart block and ventricular tachycardia; history of cardiac device (e.g., pacemaker, defibrillator) implantation; or planned cardiac device implantation; or history of Class III/IV heart failure or an ejection fraction ≤ 40%; OR b. Significant ischemic heart disease, including myocardial infarction within 6 months, unstable angina, or percutaneous transluminal coronary angioplasty (PTCA)/stent within 3 months 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. 31. Known or suspected active, and untreated/inadequately treated or latent TB, human immunodeficiency virus (HIV), hepatitis B or C infection. 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. 32. Females who are pregnant or breastfeeding or intend to be during the study. 33. Prior history of any malignancy (not including fully resected squamous and basal 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. 34. History of severe allergic or anaphylactic reactions to therapeutic proteins or known sensitivity to study drug or to its inactive components. 35. History of alcohol or drug abuse, in the Investigator's opinion, unless in full remission for greater than 12 months prior to screening. 36. Any other acute or chronic medical condition, psychiatric condition, or laboratory abnormality 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 subject inappropriate for entry into this study. 37. Subjects who are treatment naïve (no history of exposure to a therapeutic agent used specifically for the treatment of their pulmonary sarcoidosis).
Database Lock	The database for the Double-blind period will be frozen and an unblinded analysis of efficacy and safety will be performed after all subjects have completed the Week 26 visit. A final database lock will be performed after the last subject, last visit and final data will be provided for all analyses.
Statistical Analyses	**<u>Sample Size Determination</u>** It is planned to randomize approximately 100 subjects in this study (50 subjects per arm, 45 evaluable subjects per arm assuming a 10% dropout). Assuming a placebo rate of 40%, 90 evaluable subjects (45 subjects per arm) will provide a power of approximately 80% to detect the 25% treatment difference at a 2-sided significance level of 0.10 based on Fisher's exact test. **<u>Populations for Analysis</u>** • The Intent-to-Treat (ITT) Population will include all randomized subjects. ITT subjects will be analyzed according to their randomized treatment. • The modified ITT (mITT) Population will include all randomized subjects who receive any amount of double-blind study treatment. The mITT will be analyzed according to the treatment assigned. This population will be used for efficacy analyses.

- The Per-Protocol (PP) Population will include all subjects in the mITT Population who have no major protocol violations which may impact effectiveness of the treatment. The PP Population will be used for supplementary analyses of the efficacy measurements.
- The Safety Population (SP) will include all randomized subjects who receive any amount of study drug. The SP will be analyzed according to the treatment received. This population will be used for safety analyses.

Statistical Methods in General

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 SD will be summarized. Categorical variables will be described by the count and proportion in each category.

Efficacy Analyses

The primary efficacy endpoint is the proportion of subjects with a rescue event during the Double-blind Treatment Period. The primary efficacy analysis will be performed using the mITT population. A Cohcran-Mantel-Haenszel (CMH) test stratified by use of IST at baseline will be used to compare the treatment difference. The difference in proportions between treatment groups and the confidence interval based on stratified Miettinen-Nurminen method will be provided.

The analysis will also be performed using the PP population. Supplementary analyses based on multiple imputation and tipping point analysis for subjects who prematurely discontinue the study treatment will also be performed. Details will be pre-specified in the SAP.

For secondary efficacy endpoints, binary endpoints will be summarized using numbers and frequency. The CMH test, stratified by baseline IST usage, will be used for treatment comparison. Difference in proportions between treatment groups as well as the confidence interval based on stratified Miettinen-Nurminen method will be provided if needed. Continuous endpoints will be summarized using descriptive statistics and compared using a mixed model for repeated measures analysis with the treatment, visit, IST usage at baseline, and the interaction between treatment and visit as factors, and the baseline score as a covariate. Time to event endpoints will be summarized using Kaplan-Meier estimates. The treatment effects of the time to event endpoints will be evaluated using a log rank test stratified by use of IST usage at baseline.

Adjustment of Multiple Comparisons

There is only one primary hypothesis, and it will be tested at a 2-sided alpha of 0.10.

No adjustments will be made to account for multiplicity for secondary and exploratory endpoints. P-values presented for these endpoints will be nominal p-values.

	Analysis at the nd of the Double-blind Treatment Period After all subjects have completed the Week 26 visit, the database will be frozen and an unblinded analysis of efficacy and safety will be performed. **Analysis at the End of the Open-label Treatment Period** Unless otherwise specified, descriptive summaries will be provided for data collected during the Open-label Period after all subjects complete the Open-label Period. The details will be described in the statistical analysis plan (SAP). **Handling of Missing Data** Analysis of the primary endpoint will be performed using a CMH test based on collected data. The reasons for premature discontinuation will be identified. Sensitivity analysis based on multiple imputation and assumptions of missing not at random, including tipping point analysis, for subjects who prematurely discontinue study treatment will be performed. Details on missing data sensitivity analyses will be pre-specified in the SAP. **Safety Analyses** Safety will be assessed based on the SP for AEs, ECGs, laboratory parameters, PEs, vital signs, clinical laboratory tests, and the other safety assessments. Full details will be described in the SAP. **Population Pharmacokinetic Analyses** The PPK and E-R analyses will be performed based on the modeling analysis plan (MAP) and reported separately from the final clinical study report. **Biomarkers:** The effect of namilumab on circulating biomarkers, and the correlations between biomarker and clinical endpoint changes will be performed and reported separately from the final clinical study report. **Statistical Analysis Plan** A detailed SAP will be submitted as necessary to regulatory agencies prior to unblinding for the Week 26 analysis.

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
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the concentration-time curve
BC	birth control
BMI	body mass index
BP	blood pressure
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CBC	complete blood count
C_{avg}	average serum concentration over the dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
cLDA	constrained longitudinal data analysis
C_{max}	maximum observed concentration
CMH	Cochran–Mantel–Haenszel
C_{min}	minimum serum concentration
COVID-19	Coronavirus disease 2019
CRO	clinical research organization
CRP	C-reactive protein
CT	computed tomography
CYP	cytochrome P450
DAS	Disease Activity Score

Abbreviation	Definition
DBP	diastolic blood pressure
DLco	diffusing capacity of lung for carbon monoxide
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
EMA	European Medicines Agency
EOS	End-of-Study
EOT	End-of-Treatment
ePOST	extrapulmonary Physician Organ Severity Tool
E-R	exposure-response
ERS	European Respiratory Society
ET	Early Termination
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FEV1	forced expiratory volume in 1 second
FEV1/FVC	FEV1/FVC ratio
FIH	first-in-human
FVC	forced vital capacity
GCA	giant cell arthritis
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
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

Abbreviation	Definition
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
hsCRP	high-sensitivity C-reactive protein
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Reports
IgE	immunoglobulin E
IgG1κ	human immunoglobulin G1 kappa
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IST(s)	immunosuppressive therapy(ies)
ITT	Intent-to-Treat
IVIG	intravenous immunoglobulin
JAK	Janus kinase
KSQ	King’s Sarcoidosis Questionnaire
MAH	Marketing Authorization Holder
mKSQ	modified King’s Sarcoidosis Questionnaire
mRNA	messenger ribonucleic acid
LABA(s)	long-acting beta agonist(s)
LAMA(s)	long-acting muscarinic agonist(s)
LCQ	Leicester Cough Questionnaire

Abbreviation	Definition
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
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MGC(s)	multinucleated-giant cell(s)
MHP	mobile health professional
mITT	modified Intent-to-Treat
MMRM	mixed-effect model for repeated measures
MRC	Medical Research Council
NRP2	neuropilin 2
NYHA	New York Heart Association
OCS	oral corticosteroids
OLE	open-label extension
PAP	pulmonary alveolar proteinosis
PE	physical examination
PET	positron emission tomography
PFT(s)	pulmonary function test(s)
PK	pharmacokinetic
PP	per-protocol
ppFVC	percent predicted forced vital capacity
ppDLco	percent predicted diffusing capacity of lung for carbon monoxide
PPK	population pharmacokinetics
PRO(s)	patient-reported outcome(s)
PTCA	percutaneous transluminal coronary angioplasty

Abbreviation	Definition
PV	pharmacovigilance
Q4W	every 4 weeks
QTcF	Fridericia corrected QT interval
RA	rheumatoid arthritis
RBC	red blood count
RT-PCR	real time - polymerase chain reaction
SAA	serum amyloid A
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SARS-CoV-2	serious acute respiratory syndrome Coronavirus-2
SBP	systolic blood pressure
SC	subcutaneous(ly)
SD	standard deviation
SE	standard error
SGA	Subject Global Assessment of overall disease burden
SGRQ	St. George's Respiratory Questionnaire
sIL-2R	soluble interleukin-2 receptor
SOC	system organ class
SP	safety population
SP-D	serum surfactant protein D
SUSAR	suspected unexpected serious adverse reaction
TARC	thymus activation regulated chemokine
TB	tuberculosis
TC	total cholesterol
TEAE(s)	treatment-emergent adverse event(s)
T_{max}	time of maximum observed concentration
TNF	tumor necrosis factor
TG(s)	total triglyceride(s)
TTCW	time-to-clinical worsening
ULN	upper limit of normal

Abbreviation	Definition
UN	unstructured
VEGF	vascular endothelial growth factor
WBC	white blood count
WCBP	woman of childbearing potential

1. INTRODUCTION

Namilumab (KIN-1902, IZN-101, MT203, or AMG203) is a human immunoglobulin G1 kappa (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 several inflammatory and autoimmune human diseases.

Sarcoidosis is a highly heterogeneous condition, with effects ranging from chest radiograph abnormalities during routine screening of asymptomatic patients to severe chronic disease with pulmonary fibrosis. In a large portion of patients, 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 patients with sarcoidosis, and pulmonary hypertension, which occurs in at least 5% of patients, is a serious complication. Oral corticosteroids (OCS) are the mainstay of therapy, but chronic patients require long-term dosing, which carries significant toxicities (Baughman, 2015; Khan, 2017; Bargagli, 2018; 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 immunosuppressive steroid-sparing therapies (ISTs). Only about two-thirds of patients are responsive to these therapies, and only 25% of patients achieve full weaning off OCS (Crommelin, 2016; Beegle, 2013). For patients who are unresponsive or intolerant to DMARDs, third-line therapy consists of anti-tumor necrosis (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 the treatment of sarcoidosis and some patients 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 efficacy and safety of namilumab in subjects who have chronic pulmonary sarcoidosis (CPS) who are not well controlled on OCS and/or ISTs. The study population includes subjects on treatment, or who have been treated but are no longer receiving OCS and/or IST so long as all inclusion and exclusion criteria are otherwise met (see Section 4). If successful, the results will inform the design of further clinical trials and registration of namilumab.

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.

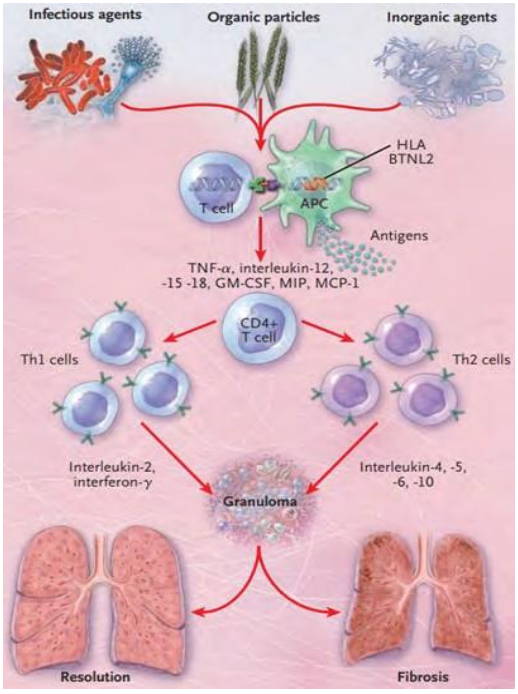
During chronic infections like tuberculosis, caseating granulomas develop that wall off necrosis from the surrounding tissue. In contrast, sarcoidosis granulomas are typically non-caseating and do not contain a necrotic center (Rosen, 2022). The cause of granuloma formation in sarcoidosis is unknown but is believed to be driven by a dysregulated response to an unknown antigen that triggers both innate and adaptive immune responses. These responses are coordinated through the expression of multiple cytokines (e.g., GM-CSF, IFNγ, IL-6, TNFα) and chemokines (e.g., CCL3, CCL5, CCL17) (Iannuzzi, 2007; Drent, 2021).

The clinical course of sarcoidosis is highly heterogeneous, ranging from chest radiograph abnormalities during routine screening of asymptomatic patients to severe disease with pulmonary fibrosis. Approximately 200,000 individuals are affected with sarcoidosis in the United States (Baughman, 2016). About 25% to 33% of patients have persistent granulomas and develop chronic progressive disease that significantly impacts their 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 ISTs, only 25% of patients achieve full weaning off OCS. Both OCS and ISTs are known to 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.

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 COVID-19 (Temesgen, 2022; 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, several 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 multinucleated giant cells (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 an 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 TB infection in GM-CSF-/- mice (Gonzalez-Juarrero, 2005; Rothchild, 2017).



From Iannuzzi, 2007

Administration of anti-GM-CSF neutralizing antibodies 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 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).

Multiple 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 versus 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 up-regulated 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. The mAb namilumab neutralizes GM-CSF and has the potential to improve organ function in patients with pulmonary sarcoidosis 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 CPS 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; however, no subject 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., 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. 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. High titers of autoantibodies against GM-CSF have been associated with infection (Rosen, 2013). Nevertheless, no anti-GM-CSF or anti-GM-CSFR trial has reported an increased infection risk (Hamilton, 2020). Unlike trials of TNF-targeting agents, no increase in TB has been observed despite the role of GM-CSF in granuloma formation and TB protection in mice (Bryson, 2019; Hamilton, 2020). This safety profile has been corroborated in recently reported trials of anti-GM-CSF mAbs for severe hospitalized COVID-19 subjects who were expected to be particularly susceptible to opportunistic infection (not yet peer reviewed: Patel, 2021; and peer reviewed: Temesgen, 2020; Temesgen, 2022; Criner, 2022). One suspected unexpected serious adverse reaction (SUSAR) of bacterial pneumonia was reported in the COVID-19 Investigator-initiated study (CATALYST, data not published). In this study additional unrelated cases were reported as 2 COVID pneumonitis, 1 pneumonitis and 1 progression of COVID-19 pneumonia. In a Phase 2b clinical trial with an anti-GM-CSF mAb (GSK 3196165), low rates of serious infections and cytopenias were noted, and the adverse event (AE) profile was similar across treatment groups (Buckley, 2020). Over 1,000 patients have been administered anti-GM-CSF(R) antibodies in clinical trials, with acceptable safety profiles seen to date (Hamilton, 2020).

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 decreasing but spontaneously reversible trend of the white blood count (WBC) and absolute neutrophil count (ANC) was noticed in some subjects in namilumab Groups 4 (3 mg/kg dose level) and 5 (6 mg/kg dose level). The values of WBC and ANC were not of clinical concern, and there was no dose-dependent pattern. Two subjects had clinically significant low neutrophil values during the study: 1 subject receiving 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 receiving 3 mg/kg namilumab had a neutrophil count of 1.1×10^9/L on Day 29 and recovered spontaneously 4 days later.

In the NEXUS study, ANC and WBC decreases were recorded as drug-related for one subject in the namilumab 80 mg treatment group and one subject in the namilumab 150 mg treatment group; there were no clinically severe or serious events.

Neutralization of GM-CSF may potentially 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 or neutropenia have been reported with namilumab.

In the FIH clinical 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 the 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 AE.

In a Phase 2 clinical study in RA (NEXUS), ALT and AST increases were considered drug-related in one 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 Phase 2 clinical study in axial spondyloarthritis (NAMASTE), 3 non-serious AEs 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.

As with any biologic therapy, hypersensitivity reactions are considered a potential risk. Infusion reactions may be either type I hypersensitivity reactions (i.e., immunoglobulin 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. Also, the subcutaneous (SC) injection may cause administration site pain or inflammation.

Namilumab has been studied in humans in doses ranging from 0.2 mg/kg to 8 mg/kg in Study M1-1188-001-EM (FIM); 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); and at 150 mg in Study IZN-101 (NAMASTE) and Study KIN-1902-2002 (RESOLVE-Heart). Across 9 completed studies, a total of 404 subjects or healthy volunteers have been enrolled into the clinical development program for namilumab, with 333 subjects estimated to have received namilumab. In addition, subjects with COVID-19 were treated with a single dose of 150 mg namilumab in an Investigator-initiated trial in the United Kingdom 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 chronic and 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, 2008).

Given that no new therapy has been approved for sarcoidosis in decades, namilumab may prove to be a useful treatment for these chronic progressive subjects 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 identified risks:

- AST and/or ALT elevation.

The following have been delineated as potential risks:

- PAP;
- Immune and immunomodulatory reactions;
- Decreased white cell count/neutropenia;
- Infection;
- Injection site findings.

Based on nonclinical studies and the available data from 9 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 CPS.

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 & repeat dose toxicity studies); Clinical Studies (FIH, PRIORA, NEXUS, NEPTUNE, and NAMASTE studies)	Important identified risk	Exclusion criteria; routine pharmacovigilance (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 & management
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

AEs = adverse events; AST = aspartate aminotransferase; ALT = alanine aminotransferase; FIH = first-in-human; ICSR = Individual Case Safety Reports; PAP = pulmonary alveolar proteinosis; PV = pharmacovigilance; TB = tuberculosis.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of this study is:

- To evaluate the effect of namilumab on the need for rescue treatment for worsening of sarcoidosis.

The secondary objectives of this study are:

- To evaluate the effect of namilumab on percent predicted forced vital capacity (ppFVC);
- To evaluate the effect of namilumab on the time to the first rescue event;
- To evaluate the effect of namilumab on proportion of subjects achieving OCS taper without rescue event;
- To assess the effect of namilumab on respiratory symptoms based on the King's Sarcoidosis Questionnaire (KSQ) Lung domain;
- To assess the safety and tolerability of namilumab.

The exploratory objectives of this study are:

- To assess the effect of namilumab on other measures of pulmonary function;
- To assess the effect of namilumab on the following Patient Reported Outcomes (PROs):
  - St. George's Respiratory Questionnaire (SGRQ);
  - KSQ domains (including ad-hoc subscales);
  - Modified King's Sarcoidosis Questionnaire (mKSQ) Lung domain
  - Subject Global Assessment (SGA);
  - Leicester Cough Questionnaire (LCQ);
  - Bothersomeness and Subject Global Impression of Change (BSGIC).
- To assess the effect of namilumab on cumulative OCS use and other OCS use-related endpoints;
- To evaluate clinical benefit of namilumab;
- To assess the effect of namilumab on the severity of extrapulmonary organ involvement;
- To assess the population pharmacokinetics (PPK) and exposure-response (E-R) relationships for efficacy and safety of namilumab;
- To assess the presence of anti-drug antibody (ADA);
- To assess the effect of namilumab on circulating biomarkers, and the correlations between biomarker and clinical endpoint changes.

2.2. Endpoints

The primary endpoint of this study is:

- Proportion of subjects with a rescue event during the DB period

The secondary endpoints of this study are:

- Change from baseline in percent predicted forced vital capacity (ppFVC) at Week 26;
- Time to first rescue event during DB period;
- Proportion of subjects successfully achieving OCS taper without rescue event during DB period;
- Change from baseline in the KSQ Lung domain score at Week 26;
- Safety and tolerability, including assessment of physical examinations (PEs), vital signs, electrocardiograms (ECGs), clinical laboratory measurements, and AEs during DB period.

The exploratory endpoints of this study are:

- Change from baseline and categorical assessments in pulmonary function in ppFVC (%), FVC (mL), FEV1 (mL), ppFEV1 (%), FEV1/FVC (mL/mL), and ppDLco at Week 26;
- Change from baseline in the following PRO scores at Week 26:
  - SGRQ;
  - KSQ domains (including ad-hoc subscales);
  - mKSQ Lung domain;
  - SGA;
  - LCQ;
  - BSGIC.
- Cumulative OCS (expressed as prednisone equivalent) use and other OCS use related endpoints in the DB and OLE Periods, separately and combined;
- Rate of clinical benefit, defined as achieving at least two of the four following criteria (without clinically relevant decline in any of these parameters or rescue event) at end of the corresponding period: a) an improvement of ≥ 5% points from baseline in ppFVC; b) an improvement of ≥ 5% points from baseline in ppDLco; c) KSQ Lung domain score improvement of ≥ 4 points, d) successfully achieving OCS dose ≤ 5 mg/day and at least 5 mg decreased from baseline OCS dosing during the corresponding period for subjects who had OCS > 5 mg/day at baseline, or achieving OCS free at the end of the corresponding period for subjects who had OCS ≤ 5 mg/day at baseline during DB period
- Change in extrapulmonary Physician Organ Severity Tool (ePOST) score at Week 26;
- PPK and E-R relationship assessments for efficacy and safety during the DB period, where data permit;

- Number of subjects positive for ADA to namilumab during DB period;
- Change and percent change from baseline in pre-specified exploratory biomarkers and the correlations between biomarker and clinical endpoint changes at Week 26.

To assess the durability of efficacy and safety, all endpoints will also be analyzed for the OLE period.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan Description

This is a Phase 2, randomized, double-blind, placebo-controlled study with an optional open-label extension (OLE).

Approximately 100 subjects (50 subjects in each of 2 treatment arms) will be randomized 1:1 to receive study drug or placebo in the Double-blind Treatment Period of the study. The randomization will be stratified by IST use at baseline.

Double-blind Treatment Period:

- Treatment Arm 1: Study drug administered subcutaneously (SC): 150 mg on Day 1, Day 15 (Week 2), and then every 4 weeks (Q4W) thereafter through Week 22;
- Treatment Arm 2: Placebo administered to match study drug dosing.

Beginning at the Randomization Visit, each subject taking OCS will perform an OCS tapering protocol as outlined in Appendix 7. Each subject will also stop all ISTs at randomization.

For subjects who only participate in the Double-blind Treatment Period, the duration will be approximately 46 weeks as follows:

- Up to 6-week Screening Period;
- 26-week Double-blind Treatment Period;
- 14-week off-drug Follow-up Period (see below).

Open-label Extension (OLE) Treatment Period:

All subjects, regardless of treatment assignment in the Double-blind Treatment Period, who agree to participate in the OLE will receive study drug administered SC: 150 mg at Week 26 and then Q4W through Week 50.

For subjects who participate in the OLE, the duration will be approximately 42 weeks as follows:

- Up to 28 weeks OLE Treatment Period
- 14 weeks off-drug Follow-up Period (see below)

For subjects who participate in both the Double-blind and OLE Treatment Periods, the duration will be approximately 74 weeks as follows:

- Up to 6-week Screening Period;
- 26-week Double-blind Treatment Period;

- 28-week OLE Treatment Period
- 14-week off-drug Follow-up Period (see below)

Follow-up Period:

Safety follow-up phone call or telemedicine visits will occur approximately 4 weeks and 8 weeks following the EOT; a follow-up clinic visit will occur at approximately 14 weeks following the EOT.

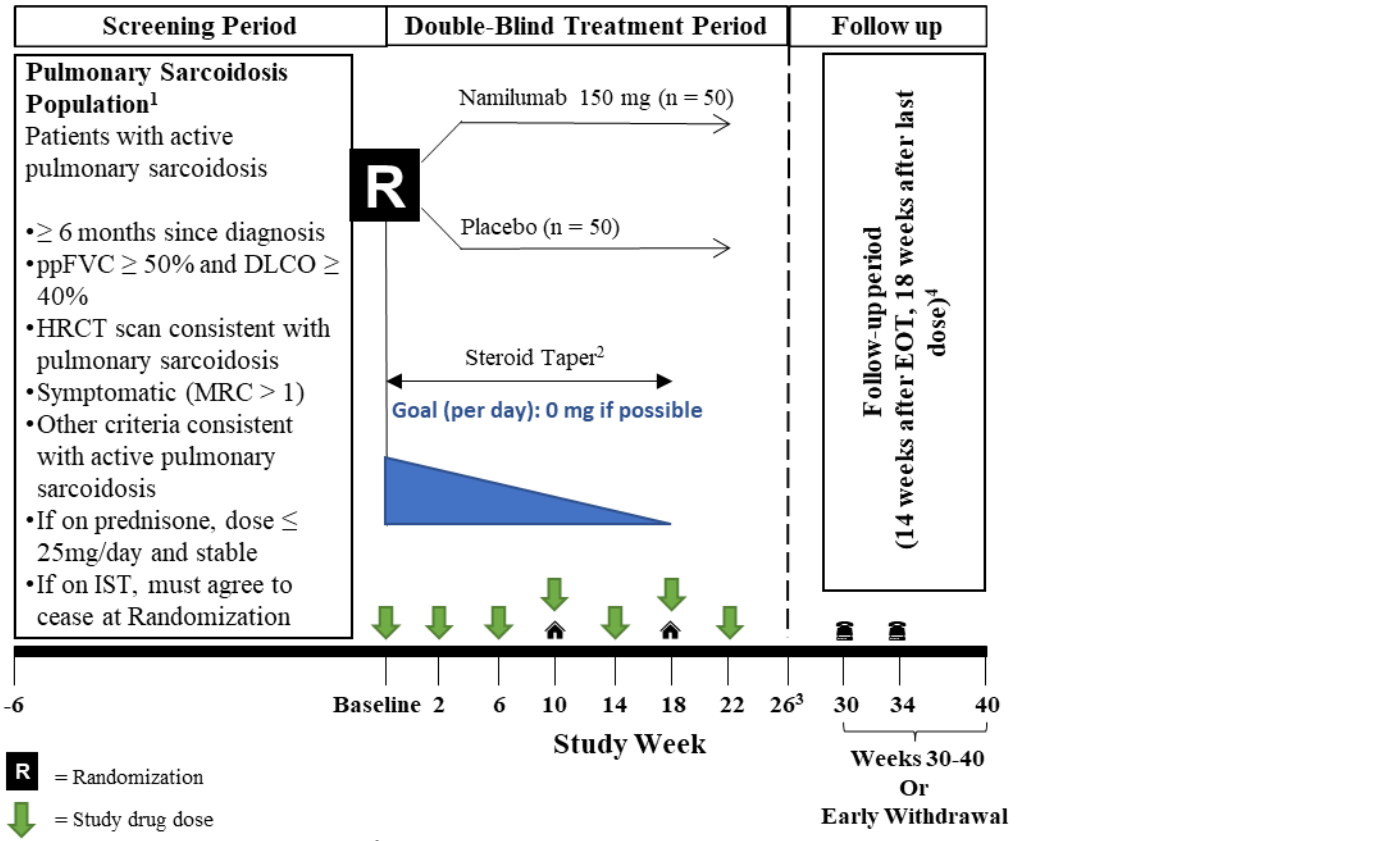
The visit at 18 weeks following the last dose of study drug will be considered the End-of-Study (EOS) Visit.

Note: If in the opinion of the Investigator there is a clinically relevant safety concern during the Follow-up Period, the Investigator will bring the subject into the clinic for an unscheduled visit.

After End-of-Study (EOS) Visit, subjects may resume Standard of Care (SOC) treatment. The study design is presented in Figure 1a for subjects who participate in only the Double-blind Treatment Period and Figure 1b for subjects who participate in both the Double Blind and OLE Treatment Periods.

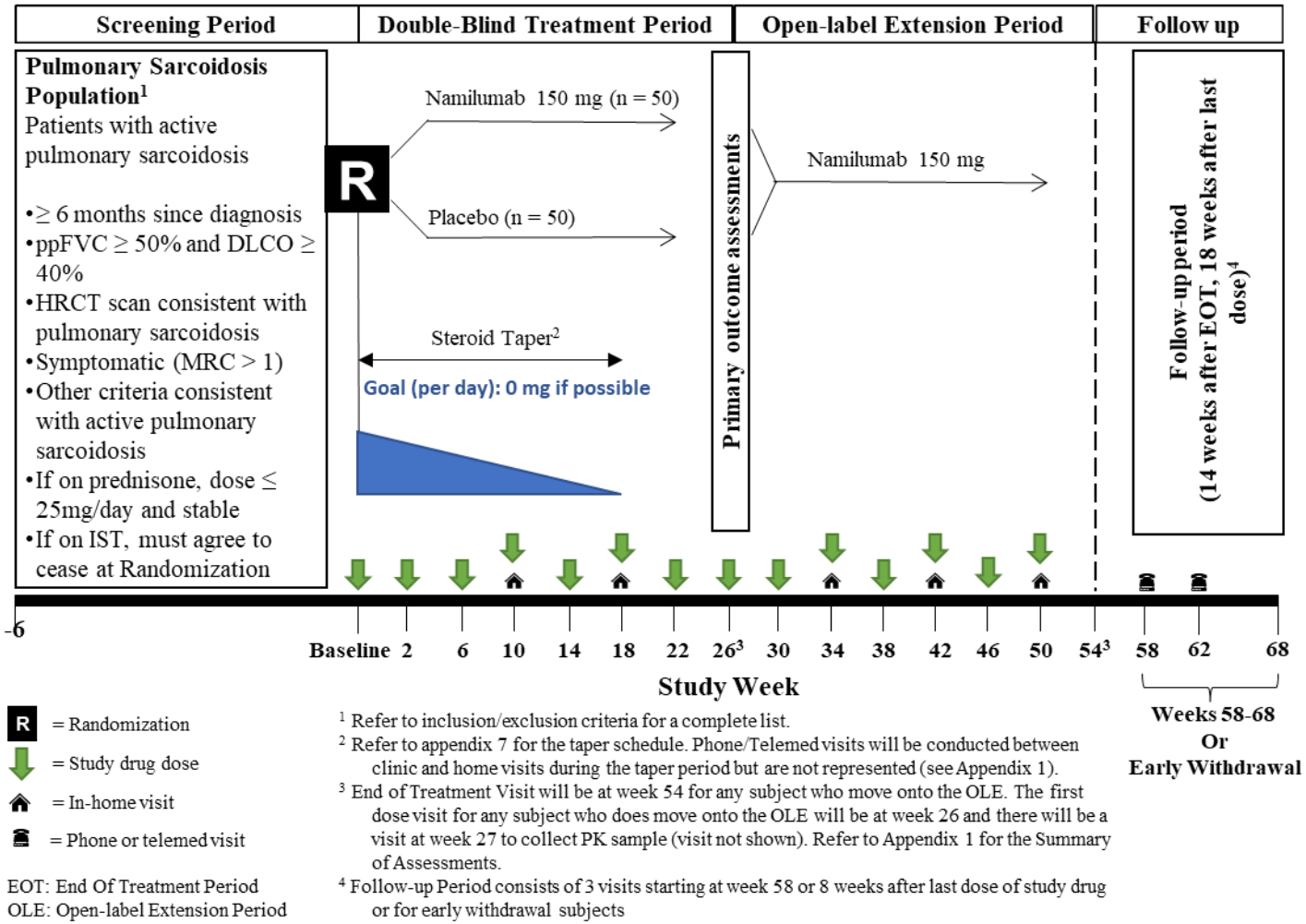
Figure 1. Study Design

a. Subjects who Participate in Only the Double-blind Treatment Period



[1] Refer to inclusion/exclusion criteria for a complete list.
[2] Refer to Appendix 7 for the taper schedule. Phone/Telemed visits will be conducted between clinic and home visits during the taper period but are not represented (see Appendix 1).
[3] End of Treatment Visit will be at week 26 for any subject who does not move onto the OLE. Refer to Appendix 1 for the Summary of Assessments.
[4] Follow-up Period consists of 3 visits starting at week 30 or 8 weeks after last dose of study drug or for early withdrawal subjects

b. Subjects who Participate in Both the Double-blind and Open-label Extension Treatment Periods



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 6 weeks; however, subjects may be randomized as soon as they are deemed eligible as long as they continue to meet eligibility criteria. During the Screening Period, doses of OCS should remain unchanged. If there is a change in OCS, the subject should be screen failed.

3.1.2. 26-Week Double-blind Treatment Period

Subjects will begin the 26-week Double-blind Treatment Period after confirmation that all protocol eligibility criteria have been met.

Some visits in the Double-blind Treatment Period will be required to be conducted in the clinic, some may be conducted either at the clinic or at the subject's home (in applicable countries) with a Sponsor-approved home healthcare professional, and some will be conducted via phone or telemedicine, per the Schedule of Assessments (SOA) (Appendix 1).

Subjects receiving OCS at the time of randomization will begin tapering their OCS as described in Appendix 7. During the steroid taper period, Investigators will contact subjects weekly via phone or telemedicine visits as outlined in Appendix 1. In addition, subjects must cease any IST at the time of randomization prior to the first dose of study drug.

Prior to completing the Week 26 End-of-Treatment/Early Termination (EOT/ET) visit, Investigators should confirm whether the subject is eligible and willing to participate in the OLE Period. If the subject is eligible and willing to participate in the OLE Period, they will complete the Week 26 visit on the Schedule of Assessments for the OLE Period and will not move into the Follow-up Period until they have completed the OLE or have discontinued study drug permanently. See the SOA for all assessments required for each visit (Appendix 1).

If a subject needs to discontinue study drug (temporarily or permanently) or terminate study participation before completion of the Double-blind Treatment Period, please refer to Section 4.4.2.3 for detailed instructions regarding recommended follow-up.

3.1.3. Open-label Extension Period

The purpose of the 28-week OLE Period is to provide additional data on the benefit-risk of study drug over a treatment period of up to 54 weeks, and to assess the durability of efficacy in subjects treated with study drug. Further, the OLE will allow for an assessment of the efficacy of study drug in subjects who initially received placebo.

The OLE Period is optional; subjects will be eligible for the OLE if: a) they have completed their treatment through Week 22 of the Double-blind Treatment Period, and b) sign the informed consent addendum for the OLE. All subjects who choose to participate in the OLE Period will receive study drug regardless of treatment assignment during the Double-blind Treatment Period.

As with the Double-blind Treatment Period, some visits of the OLE will be required to be conducted in the clinic, some visits may be conducted either at the clinic or at the subject's home

(in applicable countries) with a Sponsor-approved home healthcare professional, and some visits will be conducted via phone or telemedicine, per the SOA (Appendix 1).

All subjects in the OLE Period will be treated with open-label study drug and should also continue to take any OCS or allowed ISTs that they are taking which may have been added as rescue treatment during the Double-blind Treatment Period. Starting at Week 30, efforts should be made to taper/remove OCS and ISTs as described in Appendix 7. If a subject discontinues study drug (temporarily or permanently) or terminates study participation before completion of the OLE Period, please refer to Section 4.4.2.3 for detailed instructions regarding recommended follow-up.

3.1.4. Follow-up Period

All subjects, regardless of when they complete their last dose of study drug, will have 3 follow-up visits following the End-of-Treatment Visit to obtain information on safety laboratories, concomitant medication use, SAEs, and any AEs that were ongoing at the time of the EOT/ET Visit.

End of Treatment (EOT)/Early termination (ET) will occur approximately 4 weeks following last dose of study drug.

Phone call or telemedicine visits will occur approximately 8 weeks and 12 weeks following the last dose of study drug; a follow-up clinic visit will occur approximately 18 weeks following the last dose of study drug. See the SOA (Appendix 1) for details on what assessments are required.

For phone or telemedicine visits, female subjects will be required to complete a home urine pregnancy test and report the result to the Investigator at the time of the phone call/telemedicine visit. If a positive result is obtained, the Investigator will schedule an on-site visit at the clinic for a confirmatory serum pregnancy test. In addition, if any other clinically relevant safety concern is identified during one of these visits, the Investigator will schedule an unscheduled clinic visit to complete any necessary safety assessments.

3.1.5. Unscheduled Visits

During the study, additional contact by phone 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 phone 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 phone contact or site visit. If an unscheduled visit occurs due to the need for rescue treatment the Investigator should follow the instructions in Section 3.1.5.1 prior to commencing rescue treatment.

3.1.5.1. Rescue Visit

A Rescue Visit is an unscheduled visit that must be conducted the first time a subject requires a rescue treatment. During the Double-blind and OLE Treatment Periods, if a subject requires, or have received, rescue treatment outside of a required study visit the Investigator must schedule a

Rescue Visit to confirm the need for rescue treatment for worsening sarcoidosis (see Section 6.4).

A Rescue Visit may only be scheduled one time during the Double-blind and one time in the OLE Period of the study, even though unscheduled visits and/or changes in medicines may occur after a Rescue Visit.

Prior to providing rescue treatment (Section 6.4), every effort should be made to complete all assessments specified for the week 26 clinic visit as outlined in Appendix 1. Thereafter the subject should complete the visits per protocol (Appendix 1).

The Rescue Visit should be documented on the appropriate eCRF page, including the medical reason for rescue treatment. If subject requires rescue treatment for the signs/symptoms of worsening sarcoidosis, investigators must document worsening sarcoidosis on the AE eCRF. Changes in medications should be recorded on the concomitant medication page of the eCRF.

At the Rescue Visit, the Investigator should adjust medications to achieve clinical stability. An unscheduled visit may be added for subsequent alterations of medications for worsening sarcoidosis in the Double-blind and OLE Treatment Periods.

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

A robust, double-blind, randomized, placebo-controlled design has been selected. Such a design will provide evidence concerning the use of GM-CSF inhibition for the treatment of pulmonary sarcoidosis. Subjects in the study will have a relatively severe and chronic phenotype, having been not well controlled or failed on first line and second-line therapies. Given the limited natural history data on these subjects and the highly heterogeneous nature of sarcoidosis, a blinded placebo control is critical to ensure that the study is as generalizable and as unbiased as possible. It is not known how study drug or placebo, along with tapering of OCS and/or removal of IST, will affect outcomes and quality of life for these subjects.

3.3. End of Study Definition

The visit 18 weeks following the last dose of study drug will be considered the End-of-Study (EOS) 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

Study drug 150 mg SC on Days 1 and 15 followed by every 4 weeks (Q4W) through Week 22 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 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. A 26-week Treatment

Period is considered the minimum duration to fully understand the kinetics of the efficacy response to study drug in the CPS sarcoidosis population. Furthermore, the OLE with a treatment period up to Week 54 will provide additional safety and efficacy information and will provide the opportunity for study subjects to receive study drug for an extended duration (and placebo subjects to cross over). There are currently no known biomarkers for sarcoidosis and a lower dose may be sub-optimal for efficacy.

4. SELECTION OF SUBJECT 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 of the following inclusion criteria are met:

1. Male or female subjects age ≥ 18 years.
2. Able and willing to provide written informed consent, which includes compliance with study requirements, study procedures (including performing acceptable spirometry according to ATS criteria), and restrictions listed in the consent form.
3. ≥ 6-month history of documented sarcoidosis (must include histological report, from any organ, in the subject's medical records).
4. Have HRCT scan at screening consistent with pulmonary sarcoidosis of the lung parenchyma by central read.

   Note: An HRCT performed as part of clinical care may be used as the screening HRCT as long as the HRCT is performed within 4 weeks of the Screening Visit and is uploaded and deemed of acceptable quality by the imaging vendor/central reader. If not of acceptable quality for study inclusion, it needs to be obtained again as part of the study inclusion procedures.
5. ppFVC ≥ 50% and ppDLco (hemoglobin corrected value) ≥ 40% predicted at screening.
6. If receiving prednisone (or equivalent), dose must be ≤ 25 mg, and dose must have been stable for at least 4 weeks prior to screening. In addition, subject must agree to taper their steroids beginning at the time of randomization.
7. If receiving methotrexate and/or other IST, subject must agree to cessation of their IST therapy at randomization.
8. Have additional evidence of active pulmonary sarcoidosis as defined by:
   a. Medical Research Council Dyspnea scale > 1 (i.e., Grade 2 or more) at screening (Appendix 10); AND
   b. Currently on a treatment regimen for pulmonary sarcoidosis that includes OCS, IST, or the combination of OCS and IST. If not currently being treated with either OCS or IST, subjects can still be eligible if there is documentation in the medical records that

they have taken OCS and/or IST in the past 2 years for their pulmonary sarcoidosis and have been unable to tolerate them, treatment was not effective, or they subsequently refused to continue taking these medications; AND

c. One or more of the following is present:

   i. Screening FDG-PET scan showing pulmonary parenchymal uptake consistent with active pulmonary sarcoidosis AND with pulmonary parenchymal SUVmax ≥ 3 on central read;

      Note: A PET/CT performed as part of clinical care may be used as the screening PET/CT as long as the PET/CT is performed within 4 weeks of the Screening Visit and is uploaded and deemed of acceptable quality by the imaging vendor/central reader. If not of acceptable quality for study inclusion, it needs to be obtained again as part of the study inclusion procedures.

   ii. Documentation in the subject's medical record of worsening sarcoidosis (i.e., a clinically meaningful worsening in pulmonary function parameters (e.g., ≥ 5 percent decline in ppFVC) or clinically relevant worsening of radiographic findings (e.g., HRCT, chest x-ray) in the past 12 months);

   iii. Documentation in the subject's medical record that tapering OCS (≥ 5 mg change) and/or tapering ISTs during the past 12 months resulted in an increase of pulmonary disease symptoms, signs, or activity necessitating maintenance or increase in dose of OCS and/or IST.

9. Female subjects must agree to use an approved highly effective birth control (BC) method (< 1% failure rate per year) for at least 4 weeks prior to randomization, throughout the study, and for 18 weeks following the last dose of study drug (Section 6.3), unless documented to have a reproductive status of non-childbearing potential or is postmenopausal as defined below:

   a. Non-childbearing potential defined as pre-menopausal female with medical history of total hysterectomy, bilateral oophorectomy (removal of ovaries), bilateral salpingectomy, bilateral tubal ligation, or bilateral hysteroscopic sterilization at least 3 months prior to screening;

   b. Postmenopausal defined as 12 months of spontaneous amenorrhea without an alternative medical cause.

10. Male subjects must agree to use condoms when having sexual intercourse with female partners of childbearing potential and attest that female partners of childbearing potential will use a highly effective method of contraception as described above for at least 4 weeks prior to randomization/enrollment, throughout the study and for 18 weeks following the last dose of study drug. Male subjects must also agree to not donate sperm from the time of signing consent until 18 weeks 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 prior to randomization:

1. Hospitalized for any respiratory illness ≤ 30 days prior to or during screening.
2. ≥ 20% fibrosis as indicated on HRCT-scan assessed by central read prior to randomization.
3. Estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD] equation) or requiring chronic renal replacement therapy.
4. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) > 2 × upper limit of normal range (ULN), or serum total bilirubin > 1.5 × ULN.

   Note: Subjects with documented history of Gilbert's syndrome may remain eligible if they have a direct bilirubin ≤ ULN).
5. Platelet count < 100,000 per mm^3.
6. Hemoglobin ≤ 9.5 g/dL.
7. Absolute neutrophil count < 1,500 per mm^3.
8. Corrected serum calcium > 3.0 mmol/L (> 12 mg/dL).
9. History of pulmonary alveolar proteinosis (PAP).
10. Use of any prohibited immunomodulator agent, immunoglobulin or FcRn inhibitor (approved or investigational) (Section 6.2) within the 6 months prior to or during screening.

    Note: Allergens for hypersensitivity desensitization or vaccines are not excluded. EVUSHELD administration for COVID-19 prophylaxis is allowed up to within 2 weeks prior to baseline (V2).
11. Treatment with any Janus kinase (JAK) inhibitor within 6 months prior to or during screening.
12. Participation in another interventional clinical trial within 6 months prior to or during screening and throughout the duration of participation in this study.
13. History of left ventricular ejection fraction (LVEF) ≤ 40% or New York Heart Association (NYHA) class III or IV heart failure.
14. ECG abnormalities that warrant further clinical investigation or management at screening or 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.
15. Pulmonary hypertension requiring therapy.

16. Systolic blood pressure (SBP) < 90 or > 180 mm Hg; Diastolic blood pressure (DBP) < 60 or > 110 mm Hg at screening.
17. Documented laboratory-confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection with pulmonary involvement or signs/symptoms of long COVID as determined by approved testing ≤ 6 months prior to randomization.
18. Administration of any fully live virus or bacterial vaccinations within 3 months prior to or during 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.
19. Systemic (oral or parenteral) antibiotic or pulse OCS treatment for any indication within 6 weeks prior to randomization.

    Note: A systemic (oral or parenteral) antibiotic prescribed for infection prophylaxis (i.e., not for treatment of an infection) is allowed as long as it was started at least 6 weeks prior to the Baseline Visit AND is not a prohibited medication per protocol.
20. Three or more lower-respiratory tract infections requiring antimicrobial therapy within 12 months prior to screening.
21. Any history of mycetoma or fungal respiratory infection.
22. Requirement for supplemental oxygen at rest.
23. History of or planned solid organ or hematopoietic cell transplantation.
24. Prior or planned pneumonectomy and/or planned lobectomy.

    Note: Lobectomy performed ≥ 12 months prior to randomization is allowed.
25. Smoking or using any form of inhaled tobacco, inhaled nicotine (including vaping), or inhaled cannabis preparations within 6 months of screening. Subjects are also excluded if they are not likely to refrain from these activities throughout the Study Treatment Period and 18 weeks following the last dose of study drug.
26. A diagnosis of, or presentation consistent with, Lofgren's syndrome.
27. Other significant pulmonary disease, or conditions that prevent subject from performing acceptable spirometry.
28. Autoimmune disease other than sarcoidosis likely to require treatment during the subject's participation in this study.
29. Symptoms and/or signs of extra-pulmonary sarcoidosis (e.g., cardiac or neurologic sarcoidosis) that require ongoing treatment that would interfere with the protocol-specified treatment regimen or confound the interpretation of the study data (e.g., tapering of IST and/or OCS).

    Note: Subjects who require topical or intra-ocular therapies for skin or ophthalmic sarcoid disease are not excluded.

30. History of cardiac disease such as:
    a. Cardiac sarcoidosis with history of clinically significant cardiac rhythm disturbance such as complete heart block and ventricular tachycardia; history of cardiac device (e.g., pacemaker, defibrillator) implantation; or planned cardiac device implantation; or history of Class III/IV heart failure or an ejection fraction ≤ 40%; OR
    b. Significant ischemic heart disease, including myocardial infarction within 6 months, unstable angina, or percutaneous transluminal coronary angioplasty (PTCA)/stent within 3 months 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.
31. Known or suspected active, and untreated/inadequately treated or latent TB, human immunodeficiency virus (HIV), hepatitis B or C infection. 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.
32. Females who are pregnant or breastfeeding or intend to be during the study.
33. Prior history of any malignancy (not including fully resected squamous and basal 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.
34. History of severe allergic or anaphylactic reactions to therapeutic proteins or known sensitivity to study drug or to its inactive components.
35. History of alcohol or drug abuse, in the Investigator's opinion, unless in full remission for greater than 12 months prior to screening.
36. Any other acute or chronic medical condition, psychiatric condition, or laboratory abnormality 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 subject inappropriate for entry into this study.
37. Subjects who are treatment naïve (no history of exposure to a therapeutic agent used specifically for the treatment of their pulmonary sarcoidosis).

4.3. Disease Diagnostic Criteria

Subjects will require at least a 6-month diagnosis of pulmonary sarcoidosis, with histological confirmation of the diagnosis in their medical record. A repeat diagnostic work-up is not required. Sufficient documentation of histology includes a histopathological report in the medical record. A histopathological report on fine needle aspirate can also serve as sufficient documentation.

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 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 reconsenting. No one subject may be screened more than twice for inclusion in the trial.

If the reason for screen failure is related to the central read of the HRCT scan not being consistent with the eligibility criteria, the subject cannot be rescreened. If an eligible HRCT or PET scan has been completed, however, and if the subject failed screening for other reasons and is re-screened successfully, the HRCT and PET scan do not need to be repeated so long as all other Inclusion/Exclusion criteria are satisfied on re-screening and the HRCT and PET scan were performed within 3 months of re-screening.

Note: An HRCT and/or PET/CT as part of clinical care may be used as screening scans as long as the scans are performed within 4 weeks of the Screening Visit and are uploaded and deemed of acceptable quality by the imaging vendor/central reader. If not of acceptable quality for study inclusion, it needs to be obtained again as part of the study inclusion procedures.

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 effect;
- Noncompliance, including refusal of the drug and/or failure to adhere to the study requirements (e.g., OCS taper, discontinuation of ISTs) 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;
- Pregnancy;
- Subject withdraws consent;
- Use of prohibited medication;
- 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.

Refer to Section 4.4.2.3 for follow-up of subjects who permanently discontinue study drug.

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, no more than 1 total doses during the Double-blind Treatment Period may be missed. If 2 total doses during the Double-Blind Treatment Period are missed, or if the Investigator unblinds subject data for safety purposes, study drug will be permanently withdrawn and follow-up procedures as described in Section 4.4.2.3 will apply.

4.4.2.3. Follow-up for Subjects Who Are Withdrawn from Study Drug

If a subject permanently discontinues study drug prior to the last study drug administration during the Double-blind Treatment Period, the subject should attend an Early Termination (ET) Visit as described in the SOA in Appendix 1. Thereafter, the subject should subsequently attend visits in the Follow-up Period as specified in the SOA.

If a subject will not agree to continue with study visits and study assessments, but will agree to phone call assessments, the subject should complete the phone/telemedicine visits in the Follow-up Period as specified in the SOA in Appendix 1.

4.4.2.4. Subject 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 blood/plasma 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 as described in Section 4.4.2.3;

- 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 Section 4.4.2.3;
- The subject is not willing to be contacted in accordance with the visit schedule but will allow the Investigator access to their medical records;
- The subject is not willing to allow any direct contact, access to medical records, or contact with a care provider. In this case, public records may be used to confirm vital status at the end of the study.

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).

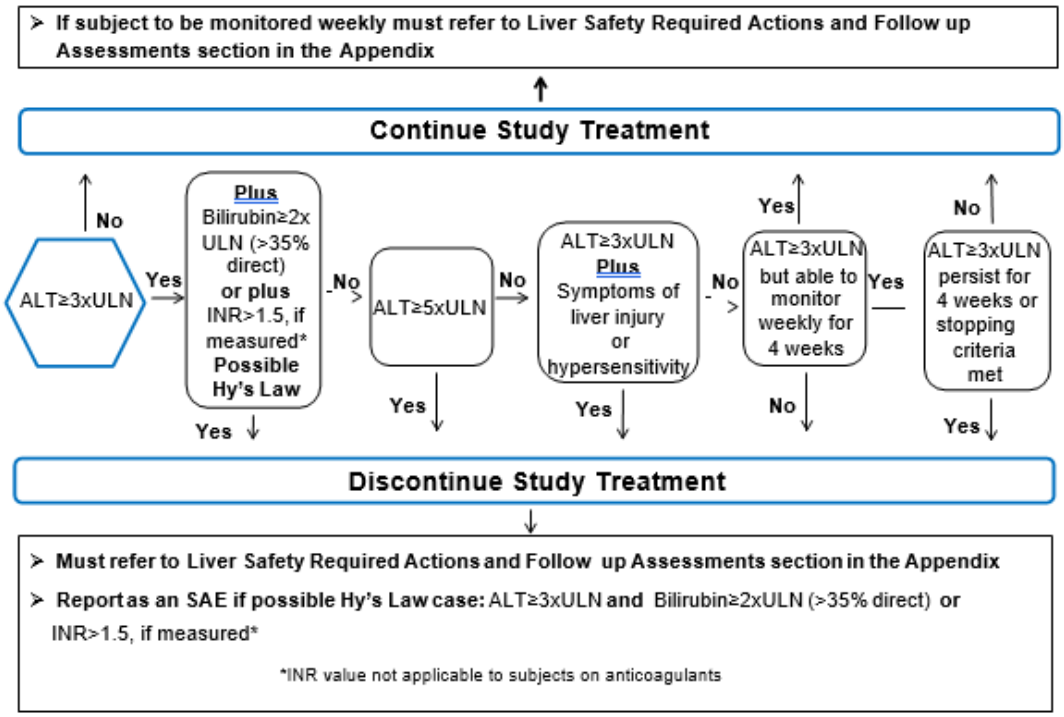
This written information should specify which aspect(s) of the study consent is being withdrawn as described below. In accordance with International Conference for Harmonisation (ICH) guidelines, FDA guidance, and other international ethical directives, data that have already been collected and incorporated 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 and complete the Follow-up Period as described in the SOA (Appendix 1).

If the subject 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.

4.4.2.5. 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. Liver Injury Stopping Criteria



Suggested actions and follow-up assessments can be found in Appendix 6.

4.4.2.6. 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. Also refer to section 7.3.3 Electrocardiograms. 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 QTc with Bundle Branch Block	Discontinuation QTc Threshold with Bundle Branch Block
< 450 msec	≥ 500 msec
450 to 480 msec	≥ 530 msec

4.4.2.7. 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 7.4.3 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 phone 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 assessments;
- 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 or Source Document

4.4.4. Subject Replacement

Subjects who are withdrawn from the study may not re-enter the study and will not be replaced.

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 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 Sponsor and the DMC. Full details on the roles of the DMC will be provided in the DMC 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. In the event of premature termination of the trial for safety reasons, the Sponsor will inform the regulatory authorities consistent with local reporting requirements.

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/Good Clinical Practice (GCP) guidelines;
- Inadequate recruitment of subjects 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, European Medicines Agency, 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 requirements. In the event of premature termination of the trial for safety reasons, the Sponsor will inform the regulatory authorities consistent with local reporting requirements.

5. STUDY TREATMENT

After randomization, subjects will be administered study drug 150 mg or placebo via SC injection on Day 1 (Baseline Visit - Week 0) and then at Weeks 2, 6, 10, 14, 18 and 22. If the subject is eligible and willing to continue onto the OLE Period, subjects will receive study drug 150 mg via SC injection at Weeks 26, 30, 34, 38, 42, 46, and 50 regardless of treatment in the Double-blind Treatment Period.

The study drug eCRF will be completed each time study drug is dispensed (See SOA, Appendix 1).

5.1. Treatments Administered

Namilumab is an investigational medicinal product that is not currently authorized for use in any country.

The identity, potency/strength, and appearance of the study drugs 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.

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:	Subcutaneous (SC) injection, which may be administered in the thigh, abdomen, or upper arm. Subjects will be observed for approximately 30 minutes (± 5 minutes) following the SC injection for adverse reactions. Vital signs should also be assessed at approximately 30 minutes (± 5 minutes)	SC injection, which may be administered in the thigh, abdomen, or upper arm. Subjects will be observed for approximately 30 minutes (± 5 minutes) following the SC injection for adverse reactions. Vital signs should also be assessed at approximately 30 minutes (± 5 minutes)
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.

Masked syringes will be used for administration of the study drug to maintain the blind. Refer to the Pharmacy Manual for further details.

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.

Study drug and placebo must be stored at 2°C -8°C (36°F -46°F).

Study drug 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.

Traceability is accounted for and overseen using Interactive Response Technology (IRT) for receipt, dispensing, return by patient, and destruction or return to depot.

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 request 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 the 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 eligible for study participation, the subject will be randomized 1:1 at the Baseline Visit to study drug or placebo using the IRT system. Randomization will be stratified by IST use at baseline. Study drug will be dispensed at the study visits summarized in the SOA (Appendix 1). Study drug will be administered by SC injection, which may be administered in the thigh, abdomen, or upper arm. Subjects will be observed for approximately 30 minutes (± 5 minutes) following study drug administration.

At the Investigator's discretion a Mobile Health Professional (MHP) service may be utilized to administer study drug at home (in applicable countries) on the in-home visit days per the SOA (Appendix 1). The MHP service will follow the same requirements for storage and accountability for study drug as the study site personnel as documented in the MHP written guidance materials.

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

5.3.1. Dose Modification

Study drug dose reductions and escalations will not be allowed. If a dose reduction is needed, a single dose may be omitted, or the subject should be discontinued from study drug. If 2 total doses are missed, or if study drug is permanently discontinued, follow-up procedures as described in Section 4.4.2.3 will apply.

5.3.2. Mobile Health Professional

At applicable sites, certain study procedures may be performed by a MHP service or (at sites with established teams) by appropriately qualified site personnel at the subject's home or another suitable location, to improve access and convenience for subjects participating in the study. The Investigator at a participating site will determine if the MHP services are appropriate for a subject, MHP services will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MHP.

The schedules of assessments (Appendix 1) will specify the assessments that may be performed by an MHP.

For participating sites without an established MHP team, the Sponsor may select a health care company that will be responsible for providing MHP services for participating sites (the MHP vendor). The MHP vendor is responsible for ensuring that all MHPs are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. All MHP requirements, procedures and documentation requirements are contained within the MHP guidance materials.

5.4. Blinding

Study drug 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 will be randomized 1:1 to study drug or placebo using the IRT. At the time of randomization, subjects will be assigned a randomization number by the IRT.

Computer-generated randomization lists will be prepared by the study sponsor or delegate. The randomization lists will be provided to an IRT vendor, who will maintain the codes. Sponsor personnel responsible for bioanalytics and unblinded statistician responsible for DMC output will have access to the randomization list as will pharmacovigiliance and the 24-hour emergency medical cover physician. Investigators, participants, and study personnel will remain blinded before the unblinded analysis at Week 26.

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.

Instructions for the return of used vials for visits that occur at home by a MHP will be provided in the MHP guidance materials.

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

5.5.2. Oral Corticosteroid Use and Taper Compliance

Oral Corticosteroids (OCS) will be self-administered by the subjects during the study. On a daily basis, subjects will be required to complete an eDiary to document their steroid intake. The site must review and document a Subject's compliance with OCS use and taper at each study visit. The site must also enter all doses and start and end dates in the concomitant medication pages in the eCRFs and source, during the oral corticosteroid tapering period and weekly throughout the study until the subject completes their EOS Visit.

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 beginning 6 months prior to screening, during screening, and during the study:

- Recombinant GM-CSF (e.g., sargramostim, molgramostim, filgrastim, lenograstim, pegfilgrastim, lipefilgrastim);
- 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., 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 monoclonal antibodies against CD20 (e.g., rituximab) and CD3 (e.g., otelixizumab, teplizumab, visilizumab);
- Agents targeting the complement pathway (e.g., eculizumab, berinert, cinryze);
- Intravenous or SC immunoglobulin;
- FcRn inhibitors (e.g., efgartigimod);
- Agents consisting of ILs or interferons (e.g., IL-2 [e.g., aldesleukin], interferon alpha-2b or beta-1a, IL-1 receptor antagonist [e.g., anakinra]);
- EVUSHELD administration is not allowed during the Double-blind Treatment Period of the study; **Note:** EVUSHELD administration is allowed during the OLE Period of the study (consistent with provisions of any local regulatory authorization) at the clinical

discretion of the Investigator. If used in the OLE Period, administration of EVUSHELD should occur approximately 14 days (± 2 days) prior to or following administration of study investigational product.

- Any other investigational/unapproved agent;
- Vaccines in general are not permitted with the exception of COVID-19 booster shots and routine influenza 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 due to pulmonary sarcoidosis, the medication will be counted as a rescue medication and subject will be discontinued from study drug. If a prohibited medication must be used for other reasons, the subject will be discontinued from study drug.

ISTs (all routes of administration other than topical or ophthalmic) including methotrexate, azathioprine, mycophenolate mofetil, (hydroxy)chloroquine, leflunomide, and sulfasalazine, must be stopped at randomization and prohibited throughout the study unless part of rescue treatment. ISTs given as rescue treatment are subject to the rescue requirements discussed in Section 6.4.

The following scenarios are allowed, if necessary:

- Use of short-course OCS (≤ 14 days) for the purpose of treating a non-sarcoidosis-related event (e.g., an acute allergic reaction, acute contact dermatitis); the patient must return to their pre-treatment baseline by Day 15
- Use of inhaled corticosteroids or bronchodilators (e.g., long-acting beta agonists or long-acting muscarinic agonists), topical or ophthalmic therapy for skin or eye sarcoid disease

6.3. Contraception

Females of childbearing potential who participate in this study must use a highly effective contraceptive method from at least 4 weeks prior to randomization, throughout the study, and for at least 18 weeks post last dose of study drug. For this study, females are of childbearing potential following menarche and until becoming post-menopausal 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. 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 acceptable highly 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 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 from the time the subject has been randomized through 18 weeks after 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 the subject is still practicing sexual abstinence and document the discussion in the subject's source documents.

Male subjects must agree to condom use when having sexual intercourse with female partners of childbearing potential and attest that female partners of childbearing potential are using a form of birth control as described above for at least 4 weeks prior to randomization/enrollment, throughout the study, and for 18 weeks following the last dose of study drug.

Urine pregnancy testing for all female subjects of childbearing potential will be performed as specified in 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

At randomization, subjects taking OCS will be required to taper their OCS (as described in Appendix 7). In addition, any subject taking ISTs (for example methotrexate, hydroxychloroquine; see also Section 6.2) will be required to stop these medications. Subjects may experience a worsening of their sarcoidosis symptoms and/or signs at any time during the study. The Investigator should instruct subjects to contact study staff immediately if they experience symptoms and feel that they may need therapy. If a subject has clinically significant worsening of sarcoidosis symptoms and/or signs "rescue" treatment may be instituted by the Investigator at any point in the study (see Section 3.1.5.1); however, administering this treatment is not encouraged until after pulmonary function testing at Week 6 during the Double-blind Period.

If the subject does have worsening symptoms and/or signs, especially of the respiratory system, the Investigators should ascertain whether these new findings are due to acute co-morbid illnesses (bronchitis/pneumonia, asthma exacerbation, etc.) or due to worsening of sarcoidosis

disease activity. Treatment of an acute co-morbid illness with a short course of OCS (≤ 14 days) is allowed, but the patient should taper to their pre-illness dose by Day 14.

To maintain study integrity, it is highly encouraged that Investigators do not rescue subjects unless absolutely necessary, i.e., only if the subject's symptoms warrant intervention or there is clinically significant worsening where it would be unethical to withhold treatment.

If an Investigator deems that rescue treatment is medically necessary, OCS is the preferred rescue medication and the lowest effective dose with the shortest duration should be used. Prior to providing rescue treatment (Section 6.4, every effort should be made to complete the rescue form and all assessment as specified under the Week 26 visit as outlined in Appendix 1.

During the Double-blind Treatment Period, only the first episode of rescue treatment requires a rescue eCRF page to be completed and all assessments as specified under the Week 26 visit (Appendix 1). Similarly, in the OLE Treatment Period only the first episode of rescue treatment requires a rescue page and assessments as specified under the Week 26 visit (Appendix 1).

If rescue treatment is initiated by the Investigator, study visits and study drug administration should continue as described in the SOA (Appendix 1); however, additional unscheduled clinic visits may be conducted at the Investigator's discretion. If study drug is missed or discontinued (temporarily or permanently), procedures will be followed as outlined in Section 4.4.2.3. Once a subject's status has stabilized, the Investigator may adjust the steroid and IST doses as clinically indicated.

The definition of a rescue event is clinically significant worsening of pulmonary or extra-pulmonary sarcoidosis that requires rescue treatment with prednisone or equivalent, start of an IST, or use of a prohibited medication.

Clinically significant worsening of pulmonary sarcoidosis should include one or more of the following: new or worsening of pulmonary symptoms and/or signs related to sarcoidosis for ≥ 1 week in duration including clinical testing (ppFVC or ppDLco reduction, worsening infiltrates on chest x-ray or on HRCT), indicating a worsening of pulmonary sarcoidosis disease activity and for which other causes have been ruled out based upon the judgment of the investigator (e.g., COVID, pneumonia, pulmonary embolism).

The following will also constitute a rescue event, but will not require a rescue visit form or additional assessment to be performed:

- A premature discontinuation associated with the lack of benefit;
- Failure of the OCS taper i.e., the subject does not reach the goal pre-specified in the protocol (Appendix 7).
- Prolonged use of increased OCS, other than as allowed for treatment of an acute co-morbid illness, or restarting ISTs or prohibited immunomodulators for any reason (Section 6.2).

OCS administered as rescue treatment should be used in accordance with the terms of its marketing authorization. IST used as rescue treatment for worsening sarcoidosis is considered use outside its marketing authorization; however, IST is widely accepted as second line treatment for both acute and chronic sarcoidosis and recommended according to clinical practice guidelines (Baughman, 2021).

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SOA (Appendix 1). Adherence to the study design requirements, including those specified in the SOA (Appendix 1), is essential and required for study conduct. All study endpoints must be conducted with attention to the quality of the measurement, ensuring the greatest precision and accuracy of the endpoint measurement.

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 Informed Consent Form (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 (Appendix 1).

7.1. Radiographic Assessments

Details for the HRCT and [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 HRCT & PET scans for eligibility. In all cases the lowest radiation dose approach for imaging should be used.

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

- HRCT and [18-F] FDG-PET/CT scans should only be performed after subjects have completed other screening requirements successfully;
- If possible combined HRCT/PET can be performed, if this is not possible, low resolution CT scanning for [18-F] FDG-PET/CT should be performed in addition to the HRCT;
- The lowest dose of injectable radioisotope should be used per the guidance in the Participant Scanning Guide.

Scans must be of sufficient quality to allow assessment of inclusion criteria. If insufficient, they must either be repeated, or the subject not randomized.

Subjects will undergo up to one HRCT scan and one [18-F] FDG-PET/CT scans; cumulative radiation exposure from these scans will range from 8.4 mSv to 21.4 mSv, depending primarily on CT technique used.

The central reader of HRCT and PET/CT will not document or report incidental findings on these radiographic assessments. Investigators are responsible for assuring local review of these assessments for incidental findings. The local review must be documented in source records, signed and dated by the Investigator. If no incidental finding is detected, it is sufficient to note this on the source document. If incidental findings are detected, they should be detailed with a statement whether "not clinically significant" or "clinically significant", the latter defined when any clinical management, e.g., follow-up or treatment, is ordered. All clinically significant

findings should be captured in EDC, either as an entry in Medical History if detected prior to first dose of Double-blind study drug or as an entry in Adverse Events if detected after first dose of Double-blind study drug. The Principal Investigator is also responsible for clinical follow-up of incidental findings including communication to the subject's treating physician.

7.1.1. High-Resolution Computed Tomography

HRCT will be utilized in this study for assessing study eligibility (Appendix 1). The HRCT scan of the lung without contrast agent will be acquired at full inspiration according to parameters as listed in the separate Participant Scanning Guide. The scan will be interpreted locally to confirm evidence of parenchymal infiltrates consistent with pulmonary sarcoidosis and whether there are any incidental findings (see above).

The scan is subject to central reading as described in the Independent Review Charter. The central read will determine final study eligibility compared to local interpretation.

An HRCT performed as part of clinical care may be used as the Screening HRCT as long as the HRCT is performed within 4 weeks of the Screening Visit and is uploaded and deemed of acceptable quality by the imaging vendor/central reader. If not of acceptable quality for study inclusion, it needs to be obtained again as part of the study inclusion procedures.

Interpretation criteria will be described in the Independent Review Charter.

7.1.2. [18-F] Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET)/ Computed Tomography (CT)

All subjects will undergo [18-F] FDG-PET/CT imaging from head to mid-thigh with a reconstructed resolution of ≤ 5 mm during screening for assessing study eligibility (Appendix 1).Details of the scan requirements and procedures are contained in the Participant Scanning Guide. [18-F] FDG-PET/CT will be utilized in this study for assessing study eligibility. The scan will be interpreted locally to determine whether there are any incidental findings (see above).

The scan is subject to central reading as described in the Independent Review Charter. The central read will determine final study eligibility compared to local interpretation.

A PET/CT performed as part of clinical care may be used as the screening PET/CT as long as the PET/CT is performed within 4 weeks prior to the Screening Visit and is uploaded and deemed of acceptable quality by the imaging vendor/central reader. If not of acceptable quality for study inclusion, it needs to be obtained again as part of the study inclusion procedures.

The scan will be acquired according to the parameters as listed in the separate Participant Scanning Guide.

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.

7.2. 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, ECG, spirometry, and DLCo are performed in that sequence, and study drug administration is performed last. The study visits should follow the schedule as much as possible. 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.

7.2.1. Pulmonary Function Tests

Standardized spirometry equipment and procedure guidelines will be provided to all study sites for spirometry assessments. On visits at which spirometry and DLCO are to be performed spirometry should be performed first, followed by DLCO.

7.2.1.1. Spirometry

Spirometry will be performed to determine the subject's FEV1 (L), ppFEV1, FVC (L), ppFVC, and FEV1/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 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.

7.2.1.2. DLco Testing

DLco is a measure of the quantity of carbon monoxide (CO) transferred per minute from alveolar gas to red blood cells (specifically hemoglobin) in pulmonary capillaries. DLco is expressed as mmol/min/kPa, that is, the millimoles of CO transferred per minute for each kilopascal of pressure difference across the total available functioning lung gas exchange surface. DLco maneuvers will be performed on the sites' own testing equipment. The same calibrated equipment must be utilized throughout the study. The assessments shall be obtained at the visits

designated in the SOA (Appendix 1). Subjects should avoid wearing restrictive clothing, vigorous exercise 30 minutes prior, eating a substantial meal 2 hours prior, and consuming alcohol 4 hours prior to testing. Subjects should be seated throughout the procedure and should be allowed several minutes of quiet breathing prior to testing to become accustomed to the mouthpiece and nose clip. A minimum of 2 acceptable maneuvers should be completed, with values within 0.67 mmol/min/kPa or 2mL.min-1mmHg-1 of each other. Subjects should be given a 4-minute window between maneuvers to allow for adequate elimination of the test gas from the lungs. Not more than 5 maneuvers should be attempted. Predicted DLco value will be produced using the 2017 Global Lung Function Initiative reference values. The DLco predicted value will be corrected for hemoglobin. The DLco results and reports will be entered into and electronically transmitted through the spirometry software. The details of this procedure will be described in the study pulmonary testing manual provided by the spirometry vendor.

7.2.2. Patient Reported Outcomes

The effect of study drug on selected PROs will be evaluated. Representative examples of the PROs used in this study are provided in Appendix 8 and include:

- SGRQ;
- mKSQ;
- SGA;
- LCQ;
- BSGIC.

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, the 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.

7.2.2.1. Saint George's Respiratory Questionnaire

The SGRQ (Appendix 8.1) is a self-administered questionnaire that contains 50 items distributed over three scales. The symptom scale assesses the severity of respiratory symptoms; the activity scale examines impairment in subject activity as a result of respiratory symptoms; and the impact scale evaluates effects of respiratory symptoms on overall function and wellbeing. Each scale can be scored from 0 to 100 and a total score represents the weighted average of the three sub-scores (Jones, 1992).

7.2.2.2. Modified King's Sarcoidosis Questionnaire

The KSQ is a self-administered questionnaire that contains 29 questions. The KSQ quickly assesses the impact sarcoidosis is having on a person's life. The KSQ is a modular, multi-organ health status measure for subjects with sarcoidosis for use in the clinic and the evaluation of therapies. The mKSQ consists of five modules: General health status (10 items), expanded Lung (15 items), Medication (3 items), Skin (3 items) and Eye (7 items) (Patel, 2013). For the purposes of this trial additional questions removed during the original validation of the KSQ have been added to the Lung module, hence that part of the instrument is termed "expanded Lung", and the overall KSQ is termed "modified" (Appendix 8.2).

Scoring will be done for the KSQ domains of the mKSQ and separately for the expanded Lung domain of the mKSQ. Higher numbers indicate better health.

7.2.2.3. Subject Global Assessment

The Subject Global Assessment (SGA) (Appendix 8.3), 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 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).

7.2.2.4. Leicester Cough Questionnaire

Chronic cough is a common condition which has a significant impact on quality of life. The LCQ (Appendix 8.4) a self-completed health related quality of life measure of chronic cough, the LCQ is a valid, repeatable 19 item self-completed quality of life measure of chronic cough which is responsive to change. It is a useful tool in clinical trials and longitudinal studies (Baughman, 2017). Higher scores indicate better health-related quality of life.

7.2.2.5. Bothersomeness and Subject Global Impression of Change

The assessment of BSGIC (Appendix 8.5) is a tool to assess the qualitative impact to the subject of their sarcoidosis on their worst, or most bothersome symptom that they have, and the perceived overall impact of their randomized treatment allocation to their disease management.

At baseline, subjects will be asked to select from five symptom options, which one symptom is the most bothersome in their daily life:

- Breathlessness.
- Fatigue, tiredness, or lack of energy.
- Disturbed sleep.
- Cough.
- Pain (any location).

Subjects will then rate their most bothersome symptom on a 100 mm linear VAS from 0 mm – being not bothersome at all (no impact at all to activities of daily life), to 100 mm being the most bothersome imaginable (severely impacting all aspects of their daily life).

At the final assessment at Week 26 (or withdrawal/ET); subjects will be reminded of their most bothersome symptom selected at baseline (but not their baseline score); then they will re-rate their symptom based on their EOS symptoms.

Subjects will then also be asked to rate their global impression of treatment effectiveness, based on their perception of change from baseline on a 7-point scale. Subjects will answer the following question:

> Since you started your study medication, how have your sarcoidosis lung symptoms (coughing, breathlessness and/or chest pain/tightness) changed?

Much Improved	Moderately Improved	Minimally Improved	No Change	Minimally Worse	Moderately Worse	Much Worse
☐	☐	☐	☐	☐	☐	☐

7.2.3. Clinician Reported Outcomes

The effect of study drug on selected clinician-reported outcomes will be evaluated. Representative examples of the Clinician Reported Outcomes used in this study is provided in Appendix 9:

- ePOST;

Clinicians will complete this assessment via electronic tablet as per the times specified in the SOA (Appendix 1).

7.2.3.1. Extrapulmonary Physician Organ Severity Tool

The ePOST (Appendix 9.1) has been previously developed and assessed in a prior trial of a biologic intervention in sarcoidosis. ePOST assesses disease involvement in 17 extrapulmonary organs. At each assessment each of the 17 organs is evaluated by the Study Investigator. Each organ is scored on a scale from 0 (not affected) to 6 (very severely affected), with the total score ranging from 0 to 102.

Organ systems assessed are as follows: skin, peripheral lymph nodes, eyes, liver, spleen, central nervous system, peripheral nervous system, parotid/salivary glands, bone marrow, ear, nose, throat, cardiac, renal, bone/joint, muscle and gastrointestinal (Judson, 2008).

7.2.4. Cytokine, Chemokine, and Sarcoidosis Biomarker Analyses

Blood will be collected throughout the study according to the SOA (Appendix 1) to assess the effect of study drug on circulating proteins and to better understand sarcoidosis. Details for collection and sample handling can be found in the laboratory manual.

Serum samples may be tested for inflammatory proteins (e.g., GM-CSF, IL-1β, IL-6, TNFα) using protein ELISA-based or other comparable methodology.

Biomarkers related to the pathogenesis of sarcoidosis (e.g., soluble IL-2 receptor (sIL-2R), serum amyloid A, high-sensitivity CRP (hsCRP) will also be tested.

Samples may be stored to assess at a future timepoint for additional biomarkers related to study drug or sarcoidosis.

7.3. Safety Assessments

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

7.3.1. Vital Signs, Height, and Body Weight

7.3.1.1. Vital Signs

Vital signs (BP, heart rate, respirations, and temperature) will be measured after 5 minutes of rest, with the subject 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. Vital sign measurements should also be taken approximately 15 minutes (± 5 minutes) prior to study drug administration and approximately 30 minutes (± 5 minutes) after administration of study drug.

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 subject.

7.3.1.2. Height

Standing height will be measured without shoes.

7.3.1.3. 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.

7.3.2. 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.

7.3.3. Electrocardiograms

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position and prior to any blood collections.

Single 12-lead ECGs will be obtained using Sponsor-provided equipment at timepoints outlined in the SOA (Appendix 1). In case of issues with Sponsor-provided equipment, local equipment may be used to obtain ECGs, but use of local equipment must be approved by Sponsor. These ECGs must also be submitted for central review.

The initial review of the ECG for safety, printed at the time of collection and read locally using site procedures, must be documented in the source documents. The final assessment captured in EDC by Investigator or qualified designee should take into consideration the central cardiologist's analysis, once available. Any clinically significant findings from the central

cardiologist's analysis must be reviewed by the Investigator or designee, to determine if an AE has occurred

When triplicate ECGs are required (e.g., at screening if the initial QTcF is > 480 msec or as outlined in Section 4.4.2.6 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. When required, the QTcF times as reported by the central cardiologist's overread should be averaged to make a final determination.

7.3.4. 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.

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 if such a specialist) who determines that risk of infection is low (i.e., subject would be acceptable for immunosuppressant treatment without additional action or therapy). Such a determination should include discussion with the Study Medical Monitor and be documented in the subject's source record.

7.3.5. 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 a measurement of viral load by RT PCR that is undetectable 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.

7.3.6. Clinical Safety Laboratory Assessments

See Appendix 4 for the list of clinical laboratory tests to be performed for screening and safety monitoring, and also for 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.

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 subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within approximately 18 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 subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose interruption/discontinuation), then the results must be recorded.

All collected biological samples will be analyzed for the objectives of the trial. The collected biological samples will be managed and stored in accordance with all national and local regulations after the completion of the informed consent process. Remainders of biological samples may be stored for the sponsor for 25 years, and may be used for future research, in accordance with local requirements as described in the informed consent form.

7.3.7. Sample Requirements

The maximum amount of blood collected from each subject over the duration of the study, not including any extra assessments that may be required, will be approximately 133.5 mL for subjects who participate in the Double-blind Treatment Period only (Table 4) and approximately 191.5 mL for subjects who participate in both the Double-blind and OLE Treatment Periods (Table 5). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 4. Estimated Blood Sample Requirements Per Subject for Subjects who Participate in the Double-blind Treatment Period Only

	Approximate sample volume per collection	Number of collection time points	Approximate total volume collected (mL)
Clinical laboratory: chemistry panel	2.5	8	20
Clinical laboratory: hematology panel	2	8	16
Clinical laboratory: lipids	Included in Chemistry panel sample		0
hsCRP	Included in Chemistry panel sample		0
HbA_{1C}	Included in Hematology panel sample		0
QuantiFERON® Gold/ IGRA	4	1	4

	Approximate sample volume per collection	Number of collection time points	Approximate total volume collected (mL)
Virology labs and DNA/RNA (hep B, hep C)	9.5	1	9.5
Virology HIV	2.5	1	2.5
Anti-GM-CSF autoAb	3.5	1	3.5
PK	3.5	5	17.5
ADA	3.5	3	10.5
Cytokine & chemokine panel	3.5	4	14
SAA	2.5	4	10
SP-D	3.5	4	14
Other sarcoidosis biomarkers	3	4	12
		Total:	133.5

Table 5. Estimated Blood Sample Requirements Per Subject for Subjects who Participate in Both the Double-blind and OLE Treatment Periods

	Approximate sample volume per collection	Number of collection time points	Approximate total volume collected (mL)
Clinical laboratory: chemistry panel	2.5	13	32.5
Clinical laboratory: hematology panel	2	13	26
Clinical laboratory: lipids	Included in Chemistry panel sample		0
hsCRP	Included in Chemistry panel sample		0
HbA_{1C}	Included in Hematology panel sample		0
QuantiFERON® Gold/ IGRA	4	1	4
Virology labs and DNA/RNA (hep B, hep C)	9.5	1	9.5
Virology HIV	2.5	1	2.5
Anti-GM-CSF autoAb	3.5	1	3.5
PK	3.5	8	28
ADA	3.5	5	17.5
Cytokine & chemokine panel	3.5	6	21
SAA	2.5	6	15
SP-D	3.5	4	14
Other sarcoidosis biomarkers	3	6	18
		Total:	191.5

7.3.8. Pregnancy Testing

Women of childbearing potential 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 4.1 and Section 6.3, a negative pregnancy test result will be required prior to all radiation exposing procedures, and at Day 1 (baseline) prior to the subject receiving study drug and at subsequent visits where pregnancy testing is specified in the SOA (Appendix 1). Additionally, if the site staff become aware of a subject having a missed menstrual cycle between visits, the subject 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.

For site visits, urine pregnancy tests will be performed at the site. For phone or telemedicine visits, female subjects will be required to complete a home urine pregnancy test and report the result to the Investigator at the time of the phone call/telemedicine visit. If a positive result is obtained, the Investigator will schedule an on-site visit at the clinic for a confirmatory serum pregnancy test. The Investigator may provide home urine pregnancy test kits to the subject where required. 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 from the study. 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 subject must be discontinued from the study and followed if pregnancy is confirmed by a positive serum β-hCG.

7.4. Adverse and Serious Events

7.4.1. Adverse Events

Adverse event definitions and assignment of severity and causality are detailed in Appendix 2.

Nonserious AE reporting begins from the time the first dose of double-blind study drug has been taken and ends 18 weeks after the last dose of study drug.

Any sign, symptom, or illness occurring prior to first dose of double-blind study drug will be captured in the medical history. Treatment-emergent adverse events are defined as any AE reported after the first dose of double-blind study drug. Adverse event definitions and assignment of severity and causality are detailed in Appendix 2.

Adverse events will be elicited from the subject (or, when appropriate, from a caregiver, surrogate, 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 serious AE (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).

The Investigator, per routine practice, should report AEs with suspected causal relationship with OCS and IST used as rescue treatment to the marketing authorization holder (MAH) or manufacturer listed on the prescribing information. Reference the clinical trial number (EudraCT, EUCT, or NCT) in any rescue treatment safety report submitted to the MAH. A copy of the report should also be sent to the Sponsor using the email or fax numbers outlined in Section 7.4.2.

7.4.2. Reporting Serious Adverse Events

All SAEs, occurring after the signing of the ICF until 18 weeks after the last dose of study drug, and regardless of study drug relationship, must be reported immediately without exceeding 24 hours of becoming aware of the event to appropriate Sponsor/contract research organization (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. It is understood that SAEs occurring during the Screening Period, by definition, will not be assessed as related to the investigational drug because there is no investigational drug in the Screening Period.

Serious Adverse event definitions and assignment of severity and causality are detailed in Appendix 2.

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.

The Sponsor/CRO will report all SUSARs to the appropriate regulatory agencies, adhering to timelines for reporting outlined per the local regulatory requirements and ICH GCP Guidelines. SUSAR reports will also be submitted to EudraVigilance.

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@fortrea.com

If email access is not available, the SAE may be reported via fax using the below regional numbers or by phone hotline:

US Fax# 1-888 887 8097

EU Fax# 0800 633 5595

Safety Hotline: 1-888-724-4908

7.4.3. Pregnancy

Although not considered an SAE (unless the event occurs with a serious outcome), pregnancy (Section 4.4.2.7) 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) immediately without exceeding 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.

7.5. Pharmacokinetic Analysis

Pre-dose blood samples will be collected into appropriately labeled tubes for measurement of study drug serum concentrations as specified in the SOA (Appendix 1) from all subjects who receive at least one dose of study drug or placebo. 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 bioanalysis sample analysis plan) will be used to measure serum concentrations of study drug.

7.6. Immunogenicity Analysis

Blood samples will be collected as specified in the SOA (Appendix 1) from all subjects who receive at least one dose of study drug. A specific bioassay to determine development of ADA to study drug will be performed in serum using a tier approach, i.e., screening, confirmatory, and titer assessment. The impact of ADAs on the PK of study drug may be assessed.

8. SAMPLE SIZE AND DATA ANALYSES

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to the primary hypothesis, or the statistical methods related to the hypothesis, then the protocol will be amended (consistent with ICH Guideline E9). Changes to secondary or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in the Statistical Analysis Plan (SAP) and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. The PPK and E-R analyses will be performed based on modeling analysis plan (MAP) and reported separately from the final clinical study report.

8.1. Determination of Sample Size

It is planned to randomize approximately 100 subjects in this study (50 subjects per arm, 45 evaluable subjects per arm assuming a 10% dropout).

Table 6 lists the sample size (number of evaluable subjects per arm) for a range of possible rates of subjects requiring rescue treatment in the placebo group (from convenience sample, observational cohorts) and detectable differences between treatment groups (in the absence of data from randomized trials, the range has face validity as clinically relevant) at a power of approximately 80% and a two-sided significance level of 0.10 based on Fisher's exact test.

Assuming a placebo rate of 40%, 90 evaluable subjects (45 subjects per arm) will provide a power of approximately 80% to detect the 25% treatment difference at a 2-sided significance level of 0.10 based on Fisher's exact test.

Table 6. Sample Size Per Arm Under Different Scenarios

Rate in Placebo	Rescue Rate difference (Placebo - Namilumab)					
	20.0%	**22.5%**	**25.0%**	**27.5%**	**30.0%**	**32.5%**
50%	84	66	54	44	36	31
45%	78	61	49	41	34	28
40%	73	57	46	37	30	24
35%	65	51	39	32	25	21

8.2. Analysis Populations

The following analysis populations will be included for this study:

8.2.1. Intent-to-treat (ITT) Population

The ITT Population will include all randomized subjects. ITT subjects will be analyzed according to their randomized treatment.

8.2.2. Modified Intent-to-treat (mITT) Population

The mITT Population will include all randomized subjects who receive any amount of double-blind study treatment. The mITT will be analyzed according to the treatment assigned. This population will be used for efficacy analyses.

8.2.3. Per-protocol (PP) Population

The Per-Protocol (PP) Population will include all subjects in the mITT Population who have no major protocol violations which may impact effectiveness of the treatment. The PP Population will be used for supplementary analyses of the efficacy measurements.

8.2.4. Safety Population (SP)

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

8.3. General Considerations

All statistical analyses will be conducted using SAS, Version 9.4 or later. Demographic and baseline characteristics will be summarized by treatment group and overall for both Safety and mITT populations. For continuous measures the mean and SD will be summarized. Categorical variables will be described by the count and proportion in each category.

8.4. Handling of Missing Data

Analysis of the primary endpoint will be performed using a Cohcran-Mantel-Haenszel (CMH) test based on collected data. The reasons for premature discontinuation will be identified. Sensitivity analysis based on multiple imputation and assumptions of missing not at random, including tipping point analysis, for subjects who prematurely discontinue study treatment will be performed. Details on missing data sensitivity analyses will be pre-specified in the SAP.

8.5. Efficacy Analyses

8.5.1. Primary Efficacy Outcome Measure

The primary efficacy endpoint is the proportion of subjects with a rescue event , identified as described in Section 6.4, during the Double-blind Treatment Period. The primary efficacy analysis will be performed using the mITT population. A CMH test stratified by use of IST at baseline will be used to compare the treatment difference. The difference in proportions between treatment groups and the confidence interval based on stratified Miettinen-Nurminen method will be provided.

The analysis will also be performed using the PP population. Supplementary analyses based on multiple imputation and tipping point analysis to account for subjects who prematurely discontinue the study treatment will also be performed. Details will be pre-specified in the SAP.

8.5.2. Secondary Efficacy Outcomes Measures

Unless otherwise specified, binary endpoints will be summarized using numbers and frequency. The CMH test, stratified by baseline IST usage, will be used for treatment comparison. Difference in proportions between treatment groups as well as the confidence interval based on stratified Miettinen-Nurminen method will be provided if needed. Continuous endpoints will be summarized using descriptive statistics. The continuous endpoints between the 2 treatment groups will be compared using a mixed model for repeated measures analysis with the treatment, visit, IST usage at baseline, and the interaction between treatment and visit as factors, and the baseline score as a covariate. Time to event endpoints will be summarized using Kaplan-Meier estimates. The treatment effects of the time to event endpoints will be evaluated using a log rank test stratified by use of IST usage at baseline. More details about the analysis methods will be described separately in the SAP.

8.5.3. Adjustment of Multiple Comparisons

There is only one primary hypothesis, and it will be tested at a 2-sided alpha of 0.10.

No adjustments will be made to account for multiplicity for secondary and exploratory endpoints. P-values presented for these endpoints will be nominal p-values.

8.6. Safety Analyses

Safety variables include assessments of PEs, vital signs, electrocardiograms (ECGs), clinical laboratory measurements, and incidence of AEs or TEAEs. 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 testing of safety endpoints will be performed.

Summary tables will be provided for all AEs by treatment group. The incidence of AEs, study 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 one episode of a particular AE, the subject will be counted only once for that event. If a subject has more than one AE that is coded to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a 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, and mean change from baseline). 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 summarized as counts and frequencies. 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 the treatment groups. PE findings will be listed for each subject.

8.7. Population Pharmacokinetic Analyses

The PPK and E-R analyses will be performed based on the modeling analysis plan (MAP) and reported separately from the final clinical study report.

8.8. Biomarkers

The effect of namilumab on circulating biomarkers, and the correlations between biomarker and clinical endpoint changes will be performed and reported separately from the final clinical study report.

8.9. Statistical Analysis Plan

A detailed SAP will be finalized prior to unblinding and submitted as necessary to the regulatory agencies prior to unblinding.

8.10. Analysis at the End of the Double-blind Treatment Period

An unblinded analysis of efficacy and safety will be performed after all subjects have completed the Week 26 visit.

8.11. Analysis at the End of the Open-label Treatment Period

Unless otherwise specified, descriptive summaries will be provided for data collected during the Open-label Period after all subjects complete the Open-label Period. The details will be described in the SAP.

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10. APPENDICES

APPENDIX 1: SCHEDULE OF ASSESSMENTS

The Schedule of Assessments for the Double-blind Treatment Period and the Open-label Extension Period (OLE) are presented below.

Schedule of Assessments – Double-blind Treatment Period

Study Period	**Screen**	**Treatment Period**												**Follow-up[d]**		
Visit # (V)	**V1**	**Baseline V2[a]**	**V3[a]**	**☎ V4-6[b]**	**V7[a]**	**☎ V8-10[b]**	**⌂ V11[a]**	**☎ V12-14[b]**	**V15[a]**	**☎ V16-18[b]**	**⌂ V19[a]**	**V20[a]**	**EOT/ ET[c] V21[a]**	**☎[b] V22**	**☎[b] V23**	**EOS V24[a]**
Week (W)	**W -6**	**W0**	**W2**	**W3-5**	**W6**	**W7- 9**	**W10**	**W11-13**	**W14**	**W15-17**	**W18**	**W22**	**W26**	**W30**	**W34**	**W40**
Study Day (D) [Window based on Day 1 visit]	**D -42 to 1 [+ 3]**	**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]**	**D155 [± 3]**	**D183 [± 3]**	**D211 [± 7]**	**D239 [± 7]**	**D281 [± 7]**
Informed consent	X															
Inclusion/Exclusion criteria	X															
Demographic information	X															
Medical history	X															
Prior medications[e]	X															
Physical examination[f]	X	X	X		X				X				X			X
Height and weight[g]	X	X							X				X			
Vital signs[h] (Blood pressure [sitting], heart rate, respirationrate, and body temperature)	X	X	X		X		X		X		X	X	X			X
12-lead ECG[i]	X												X			X
FDG-PET-High resolution CT (HRCT) scan [j]	X															
High resolution CT (HRCT) scan [j]	X															
MRC	X															
mKSQ		X							X				X			
SGA		X							X				X			
SGRQ and LCQ		X							X				X			
BSGIC		X											X			

Study Period	**Screen**	**Treatment Period**												**Follow-up**[d]		
Visit # (V)	**V1**	**Baseline V2**[a]	**V3**[a]	☎ **V4-6**[b]	**V7**[a]	☎ **V8-10**[b]	🏠 **V11**[a]	☎ **V12-14**[b]	**V15**[a]	☎ **V16-18**[b]	🏠 **V19**[a]	**V20**[a]	**EOT/ ET**[c] **V21**[a]	☎[b] **V22**	☎[b] **V23**	**EOS V24**[a]
Week (W)	**W -6**	**W0**	**W2**	**W3-5**	**W6**	**W7- 9**	**W10**	**W11-13**	**W14**	**W15-17**	**W18**	**W22**	**W26**	**W30**	**W34**	**W40**
Study Day (D) [Window based on Day 1 visit]	**D -42 to 1 [+ 3]**	**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]**	**D155 [± 3]**	**D183 [± 3]**	**D211 [± 7]**	**D239 [± 7]**	**D281 [± 7]**
ePOST		X							X				X			
Spirometry (FEV1, FEV1/FVC, and FVC)[k]	X	X			X				X			X	X			
DLco[k]	X	X											X			
Confirm and record steroid taper/use[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/concurrent procedures[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse event collection (SAE)[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-serious adverse event collection[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis (TB) test	X															
Viral Screen (Hep B, Hep C, HIV)	X															
Sample for anti-GM-CSF auto-antibody	X															
Sample for ADA (antibodies to study drug)[o]		X			X								X			
Sample for cytokine and chemokine analyses[p]		X			X				X				X			
Sample for SAA analyses[p]		X			X				X				X			
Sample for SP-D analysis[p]		X			X								X			
hsCRP[p]		X			X				X				X			

Study Period	**Screen**	**Treatment Period**												**Follow-up**[d]		
Visit # (V)	**V1**	**Baseline V2**[a]	**V3**[a]	☎ **V4-6**[b]	**V7**[a]	☎ **V8-10**[b]	🏠 **V11**[a]	☎ **V12-14**[b]	**V15**[a]	☎ **V16-18**[b]	🏠 **V19**[a]	**V20**[a]	**EOT/ ET**[c] **V21**[a]	☎[b] **V22**	☎[b] **V23**	**EOS V24**[a]
Week (W)	**W -6**	**W0**	**W2**	**W3-5**	**W6**	**W7- 9**	**W10**	**W11-13**	**W14**	**W15-17**	**W18**	**W22**	**W26**	**W30**	**W34**	**W40**
Study Day (D) [Window based on Day 1 visit]	**D -42 to 1 [+ 3]**	**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]**	**D155 [± 3]**	**D183 [± 3]**	**D211 [± 7]**	**D239 [± 7]**	**D281 [± 7]**
Sample for analysis of other sarcoidosis biomarkers[p]		X			X				X				X			
HbA_{1C}		X											X			
Clinical laboratory: hematology	X	X	X		X				X			X	X			X
Clinical laboratory: serum chemistry	X	X	X		X				X			X	X			X
Clinical laboratory: urinalysis	X	X	X		X				X			X	X			X
Clinical laboratory: lipids	X	X	X		X				X			X	X			X
Urine pregnancy test β hCG (WCBP only)[q]	X	X	X		X		X		X		X	X	X	X	X	X
PK sample[r]		X	X		X				X				X			
Randomization		X														
Administration of study drug[s]		X	X		X		X		X		X	X				

ADA = anti-drug antibodies, β-hCG = beta human chorionic gonadotropin, BSGIC = Bothersomeness and Subject Global Impression Change, CT = computed tomography, DLco = diffusing capacity of the lungs for carbon monoxide, ECG = electrocardiogram, EOS = End-of-Study, EOT = End-of-Treatment, ET = early termination, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, FU = Follow-up visit, GM-CSF autoAb = granulocyte macrophage colony- stimulating factor auto-antibody, Hep = hepatitis; HIV = human immunodeficiency virus, hsCRP = high-sensitivity C-reactive protein, HRCT = high-resolution CT scan, mKSQ = Modified King's Sarcoidosis Questionnaire, MRC = medical research council, FDG-PET = fluorodeoxyglucose-positron-emission tomography, PK = pharmacokinetics, PRO = Patient Reported Outcomes, SAA = serum amyloid A , SC = subcutaneous, SGA = subject global assessment, sIL-2R = soluble IL-2 receptor, SP-D = serum surfactant protein D, SGRQ = St George's Respiratory Questionnaire, TB = tuberculosis, 🏠 = home visit, ☎ = phone call or telemedicine visit.

a. Visits at Week 0, 2, 6, 14, 22, 26 (EOT/ET), and 40 (EOS) will be in the clinic. Visits at Week 10 and 18 can be completed in the clinic or at the subject's home (in applicable countries) with a Sponsor approved home healthcare professional;

b. Visits at Weeks 3-5, 7-9, 11-13, 15-17, 30, and 34 will be conducted via phone or telemedicine.

c. Subjects who withdraw or are withdrawn from the Double-blind Treatment Period of the study early will undergo all Week 26 ET/EOT visit procedures. Subjects who continue in the Open-label Extension (OLE) Period will undergo activities specified in the OLE Schedule of Events for the Week 26 visit.

d. For all subjects, regardless of when the subject completes their last dose of study drug, phone call or telemedicine visits will occur approximately 8 weeks and 12 weeks following the last dose of study drug; Follow-up visit at approximately 18 weeks following the last dose of study drug will take place in the clinic.

e. 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. In addition, record medication history of any treatments given for pulmonary sarcoidosis in the 2 years prior to screening.

f. A full physical examination (PE) will be performed at screening and the EOT/ET visit; an abbreviated targeted PE will be performed at all remaining clinic visits.

g. Height will be measured at screening only; weight will be measured at all indicated timepoints.

h. Vital signs will be assessed at all timepoints specified above. On study drug administration days, vital signs will be assessed pre-dose (approximately 15 minutes ± 5 minutes) and approximately 30 minutes (± 5 minutes) post-dose.

i. Single 12-lead standard ECGs will be obtained using Sponsor-provided equipment and read locally using site procedures at all timepoints specified above.

j. Only central imaging interpretation will be accepted for eligibility determination. A PET/HRCT performed as part of clinical care may be used as the screening PET/CT as long as the PET/CT is performed within 4 weeks of screening and is uploaded and deemed of acceptable quality by the imaging vendor/central reader. If not of acceptable quality for study inclusion, it needs to be obtained again as part of the study inclusion procedures. If the FDG-PET scan does not also have a HRCT included, then a separate HRCT must be completed. If HRCT is included as part of FDG-PET, the separate HRCT assessment is not required.

k. On visits at which spirometry and DLco are to be performed, spirometry should be performed first, followed by DLco.

l. Document whether and when the subject has completed taper or whether a dose increase/maintenance was needed. See Appendix 7: Corticosteroid Taper, and Section 6.4: Rescue Treatment, for more details. Patients should record OCS dose daily on provided e-diary and Investigator should verify and record OCS use on a weekly basis. If the steroid dose is altered from the protocol defined treatment regimen, site should contact the subject to determine if an unscheduled/rescue visit is necessary.

m. Collect information on concomitant medications and concurrent procedures from the time of randomization 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 subject's medical history.

n. All serious adverse events (SAEs) will be monitored and collected from the time of informed consent through to the 18-week post last dose of study drug Follow-up visit. All adverse events (AEs) will be monitored and collected from the time of first dose through the 18-week post last dose of study drug follow-up visit. Treatment-emergent adverse events (TEAEs) will be those that start or change in severity after the first dose of study drug.

o. The ADA samples will be collected at timepoints specified above. If study drug administration occurs at the same visit, the ADA sample will be collected prior to study drug administration. For subjects who terminate the study early, an ADA sample will be collected before discharging, when possible. Actual sampling time will be recorded.

p. The biomarker samples will be collected prior to study drug administration. See the Laboratory Manual for more details.

q. A negative urine pregnancy test result must be obtained prior to administration of study drug. A positive urine β-hCG test at any time during the study requires immediate interruption of study drug and must be followed by a confirmed positive serum β-hCG test. For site visits, urine pregnancy tests will be performed at the site. Urine pregnancy tests for phone Follow-up visits may be performed at home and results reported to the Investigator during the follow-up phone calls. The Investigator may provide home urine pregnancy kits to the subject where required.

r. The PK samples will be collected prior to study drug administration at the appropriate timepoints; actual sampling time will be recorded.

s. Study drug will be administered on Days as specified above. Subjects will be observed for approximately 30 minutes (± 5 minutes) following the SC injection for adverse reactions.

Schedule of Assessments – Open-label Extension (OLE) Period

Study Period	**Treatment Period**												**Follow-up[c]**		
Visit # (V)	**V21[a]**	**V22**	**V23[a]**	**☎ V24[t]**	**🏠 V25[a]**	**☎ V26[t]**	**V27[a]**	**☎ V28[t]**	**🏠 V29[a]**	**V30[a]**	**🏠 V31[a]**	**EOT/ ET[b] V32[a]**	**☎ V33[t]**	**☎ V34[t]**	**EOS V35**
Week (W)	**W26[d]**	**W27[e]**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W46**	**W50**	**W54**	**W58**	**W62**	**W68**
Study Day (D) [Window based on Day 1 visit]	**D183 [± 3]**	**D188 [± 1]**	**D211 [± 3]**	**D225 [± 3]**	**D239 [± 3]**	**D253 [± 3]**	**D267 [± 3]**	**D281 [± 3]**	**D295 [± 3]**	**D323 [± 3]**	**D351 [± 3]**	**D379 [± 3]**	**D407 [± 7]**	**D435 [± 7]**	**D477 [± 7]**
Confirm eligibility and sign informed consent addendum[f]	X														
Physical examination[g]	X						X			X		X			X
Height and weight[h]	X						X					X			
Vital signs[i] (blood pressure [sitting], heart rate, respiration rate, and body temperature)	X		X		X		X		X	X	X	X			X
12-lead ECG[j]	X											X			X
SGRQ, mKSQ, SGA, and LCQ	X											X			
BSGIC	X											X			
ePOST	X											X			
Spirometry (FEV1, FEV1/FVC, FVC)[k]	X						X					X			
DLco[k]	X											X			
Confirm and record steroid taper/use[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/concurrent procedures[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse event collection (SAE)[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-serious adverse event collection[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample for ADA (antibodies to study drug)[o]	X						X					X			
Sample for cytokine and chemokine analyses[p]	X						X					X			
Sample for SAA analyses[p]	X						X					X			

Study Period	**Treatment Period**												**Follow-up[c]**		
Visit # (V)	**V21[a]**	**V22**	**V23[a]**	**☎ V24[t]**	**🏠 V25[a]**	**☎ V26[t]**	**V27[a]**	**☎ V28[t]**	**🏠 V29[a]**	**V30[a]**	**🏠 V31[a]**	**EOT/ ET[b] V32[a]**	**☎ V33[t]**	**☎ V34[t]**	**EOS V35**
Week (W)	**W26[d]**	**W27[e]**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W46**	**W50**	**W54**	**W58**	**W62**	**W68**
Study Day (D) [Window based on Day 1 visit]	**D183 [± 3]**	**D188 [± 1]**	**D211 [± 3]**	**D225 [± 3]**	**D239 [± 3]**	**D253 [± 3]**	**D267 [± 3]**	**D281 [± 3]**	**D295 [± 3]**	**D323 [± 3]**	**D351 [± 3]**	**D379 [± 3]**	**D407 [± 7]**	**D435 [± 7]**	**D477 [± 7]**
Sample for SP-D analysis[p]	X											X			
hsCRP[p]	X						X					X			
Sample for analysis of other sarcoidosis biomarkers[p]	X						X					X			
HbA_{1C}	X											X			
Clinical laboratory: hematology	X		X				X			X		X			X
Clinical laboratory: serum chemistry	X		X				X			X		X			X
Clinical laboratory: urinalysis	X		X				X			X		X			X
Clinical Laboratory: lipids	X		X				X			X		X			X
Urine pregnancy test β-hCG (WCBP subjects only)[q]	X		X		X		X		X	X	X	X	X	X	X
PK sample[r]	X	X[e]					X					X			
Administration of study drug[s]	X		X		X		X		X	X	X				

ADA = anti-drug antibodies, β-hCG = beta human chorionic gonadotropin, BSGIC = Bothersomeness and Subject Global Impression Change, CT = computed tomography, DLco = diffusing capacity of the lungs for carbon monoxide, ECG = electrocardiogram, EOS = End-of-Study, EOT = End-of-Treatment, ET = early termination, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, FU = Follow-up visit, GM-CSF autoAb = granulocyte macrophage colony- stimulating factor auto-antibody, Hep = hepatitis; HIV = human immunodeficiency virus, hsCRP = high sensitivity C-reactive protein, HRCT = high-resolution CT scan, mKSQ = Modified King's Sarcoidosis Questionnaire, FDG-PET = fluorodeoxyglucose positron-emission tomography, PK = pharmacokinetics, PRO = Patient Reported Outcomes, SAA = serum amyloid A, SC = subcutaneous, SGA = subject global assessment, sIL-2R = soluble IL-2 receptor, SP-D = serum surfactant protein D, SGRQ = St George's Respiratory Questionnaire, TB = tuberculosis, 🏠 = home visit, ☎ = phone call or telemedicine visit.

a. Visits at Weeks 26, 27, 30, 38, 46, 54 (EOT/ET), and 68 (EOS) will be performed in the clinic. Visits at Weeks 34, 42, and 50 can be completed in the clinic or at the subject's home (in applicable countries) with a Sponsor approved home healthcare professional.

b. Subjects who withdraw or are withdrawn from OLE Period of the study early will undergo all Week 54 ET/EOT visit procedures whenever possible.

c. For all subjects, regardless of when the subject completes their last dose of study drug, phone call or telemedicine visits will occur approximately 8 weeks and 12 weeks following the last dose of study drug; Follow-up visit at approximately18 weeks following the last dose of study drug will take place in the clinic.

d. For subjects participating in the OLE Period, only the Week 26 assessments specified in the OLE Schedule of Assessments will be performed; Week 26 assessments will not be performed twice.

e. The site should make every effort to have subjects return to the site 5 days after the Week 26 visit for a PK sample.

f. Eligibility will be confirmed by ensuring subjects have completed Week 26 and remained on study drug in order to move forward in the OLE. An informed consent addendum should also be completed by all study subjects continuing into the OLE.

g. A full physical examination (PE) will be performed at Week 26 and the ET/EOT visit; an abbreviated targeted PE will be performed at all remaining clinic visits.

h. Height will be measured at screening only; weight will be measured at all indicated timepoints.

i. Vital signs will be assessed at all timepoints specified above. On study drug administration days, vital signs will be assessed pre-dose (approximately 15 minutes ± 5 minutes) and approximately 30 minutes ± 5 minutes post-dose.

j. Single 12-lead standard ECGs will be obtained using Sponsor-provided equipment and read locally using site procedures at all timepoints specified above.

k. On visits at which spirometry and DLco are to be performed, spirometry should be performed first, followed by DLco.

l. Document whether and when the subject has completed taper or whether a dose increase/maintenance was needed. See Appendix 7: Corticosteroid Taper, and Section 6.4: Rescue Treatment, for more details. Patients should record OCS dose daily on provided e-diary and Investigator should verify and record OCS use on a weekly basis. If the steroid dose is altered from the protocol defined treatment regimen, site should contact the subject to determine if an unscheduled/rescue visit is necessary.

m. 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.

n. All serious adverse events (SAEs) will be monitored and collected from the time of informed consent through to the 18-week post last dose of study drug Follow-up visit. All adverse events (AEs) will be monitored and collected from the time of first dose through 18 weeks post last dose of study drug. Treatment-emergent adverse events (TEAEs) will be those that start or change in severity after the first dose of study drug.

o. The ADA samples will be collected at the timepoints specified above. If study drug administration occurs at the same visit, the ADA sample will be collected prior to study drug administration. For subjects who terminate the study early, an ADA sample will be collected before discharging, when possible. Actual sampling time will be recorded.

p. The biomarker samples will be collected prior to study drug administration. See the Laboratory Manual for more details.

q. A negative urine pregnancy test result must be obtained prior to administration of study drug. A positive urine β-hCG test at any time during the study requires immediate interruption of study drug and must be followed by a confirmed positive serum β-hCG test. For site visits, urine pregnancy tests will be performed at the site. Urine pregnancy tests for phone Follow-up visits may be performed at home and results reported to the Investigator during the follow-up phone calls. The investigator may provide home urine pregnancy kits to the subject where required.

r. The PK samples will be collected prior to study drug administration at the appropriate timepoints (with the exception of the collection on Day 188 [visit 22]); actual sampling time will be recorded

s. A SC injection of study drug 150 mg will be administered on Days as specified above. Subjects will be observed for approximately 30 minutes ± 5 minutes following the SC injection for adverse reactions.

t. Visits at Weeks 32, 36, 40, 58 and 62 will be conducted via phone or telemedicine.

Note: For subjects participating in the OLE Period, only the Week 26 assessments specified in the OLE Schedule of Assessments will be performed; Week 26 assessments will not be performed twice.

APPENDIX 2: ADVERSE EVENT DEFINITIONS AND REPORTING

Definitions

An adverse event (AE) is any untoward medical occurrence 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 Informed Consent Form 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

Non-serious AE reporting begins from the time the first dose of double-blind study drug has been taken and ends 18 weeks after the last dose of study drug.

Serious AE reporting begins from the time of informed consent and ends 18 weeks after the last dose of study drug.

At each visit the Investigator, or delegate, will determine whether 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

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 adverse event*** 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 four-category system according to the following guidelines:

- **Not related:** when the AE 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 actions taken for the AE in the eCRF. Actions taken will include the following with respect to study drug:

- **Dose not changed:** The medication schedule was not changed.
- **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.

Follow-up of Adverse Events

All SAEs that are ongoing at the time of discontinuation, or that develop prior to the final Follow-up visit, will be followed for 18 weeks from last study drug administration , 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 3: COMPARISON OF SYSTEMIC GLUCOCORTICOID PREPARATIONS

Glucocorticoids	Equivalent doses (mg)	Duration of action (hours)
Short Acting		
Cortisone acetate	25	8 to 12
Hydrocortisone (cortisol)	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, 2022)

APPENDIX 4: CLINICAL LABORATORY EVALUATIONS

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

<table>
<tr><th colspan="2">Serum Chemistry</th><th>Serology</th></tr>
<tr><td>- Albumin
- ALP
- ALT
- AST
- Urea nitrogen (BUN)
- Calcium (absolute, corrected)
- Creatinine
- eGFR
- GGT
- Glucose</td><td>- LDH
- Phosphorus
- Potassium
- Sodium
- Chloride
- Total Bilirubin (total and direct)
- Total CO2 (measured as bicarbonate)
- Total Protein
- Uric Acid</td><td>- Anti GM-CSF
- ADAs (to study drug)
- HBcAb
- HBsAb
- HBsAg
- HCVab
- Hep B (reflex testing if applicable)
- Hep C (reflex testing if applicable)
- HIV Ab
- RT-PCR (if applicable, based on serology results)</td></tr>
<tr><th colspan="2">Hematology</th><th>Urinalysis</th></tr>
<tr><td colspan="2">- Hematocrit
- Hemoglobin
- MCH
- MCHC
- MCV
- Platelet count
- RBC
- Reticulocytes (%, absolute)
- WBC
- WBC Differential (%, absolute), including:
o Basophils and Eosinophils,
o Monocytes,
o Neutrophils, Lymphocytes</td><td>- Bilirubin
- Color and appearance
- Urine pregnancy test (for WCBP only)
- Glucose
- Ketones
- Leukocyte esterase
- Microscopic (including RBC and WBC)
- Nitrate
- Occult blood
- pH and specific gravity
- Protein</td></tr>
<tr><th colspan="2">Lipid Profile</th><th>Other Assessments</th></tr>
<tr><td colspan="2">- Total cholesterol (TC)
- Triglycerides (TGs)
- High-density lipoprotein cholesterol (HDL-C)
- Low-density lipoprotein cholesterol (LDL-C)</td><td>- HbA_{1C}
- IGRA (QFT-G)</td></tr>
<tr><th colspan="3">Biomarker Assessments</th></tr>
<tr><td colspan="2">- Cytokine panel
- Chemokine panel</td><td>- SAA
- SP-D
- sIL-2R
- hsCRP</td></tr>
</table>

APPENDIX 5: 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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines;
- The regulation (EU) No. 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Ethics Committee (EC) by the Investigator and reviewed and approved by the IRB/EC before the study is initiated.

- Any substantial modifications to the protocol must be submitted and approved by the applicable Regulatory Authorities before implementation.
- Any amendments to the protocol will require IRB/EC 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/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of serious adverse events or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Recruitment and Informed Consent

Potential participants will be identified by clinical site staff though routine review of patient lists, review of patient records, or during patient visits to participating sites. Potential participants may also be identified outside of participating clinical sites and referred to study sites through study

advertising outreach The exact methods and frequency of study advertising may vary due to geography, site preference, and other considerations.

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 will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC 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 electronic Case Report Forms (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 and detailed in the informed consent. The subject must also be informed that his/her medical records may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities, while at the study site. No subject level specific identifiers will be sent outside of the study site.

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.

The Sponsor will submit a summary of the results of the clinical trial together with a summary that is understandable to a layperson, where applicable, within 1 year whether results are positive, negative, or inconclusive.

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/EC 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) or in the study site archive for at least 15 years after completion or discontinuation of the trial or at least 2 years after the granting of the last marketing authorization in the European Union (when there are no pending or contemplated marketing applications in the EU) or for at least 2 years after formal discontinuation of clinical development of the investigational product, whatever is the longest; unless local regulations or institutional policies require a longer retention period. 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, pharmacokinetics, pharmacodynamics, electrocardiogram, 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 (CSA). Unless otherwise specified in the CSA, 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 6: LIVER SAFETY SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

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

Appendix 6.1: Phase II 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 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 immediately without exceeding 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. o 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 pharmacokinetic (PK) analysis obtained after the most recent dose.[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • 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.

Actions and Follow-up Assessments Following ANY Liver Function Event that Requires Study Treatment Discontinuation	
Actions	**Follow-Up Assessments**
MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver function follow-up assessments within 24 hrs. • 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, alkaline phosphatase, 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 immunoglobulin G (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 computerized tomography) 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; hepatitis B surface antigen and hepatitis B Core Antibody (HBcAb); hepatitis C RNA; 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 aPK sample. Instructions for sample handling and shipping are in the laboratory manual.

Appendix 6.2: Phase II Liver Function Increased Monitoring Criteria with Continued Therapy

Liver Function Increased Monitoring Criterion and Follow-up	
Criteria	**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 immediately without exceeding 24 hours of learning of the abnormality to discuss subject safety.
	• Subject can continue study treatment
	  o Subject must return weekly for repeat liver function tests (ALT, AST, alkaline phosphatase, 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.
	  o 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 7: ORAL CORTICOSTEROID TAPER

Double-blind Period

If a subject begins with a baseline dose of > 10 mg/day prednisone or equivalent, this dose will be reduced to 10 mg/day or less by the end of Week 6. The dose will then be reduced further to 5 mg/day or less by the end of Week 10.

If a subject begins with a baseline dose of ≤ 10 mg/day prednisone or equivalent, this dose will be reduced to 5 mg/day or less by the end of Week 6, as indicated in Table 7.

Table 7. Corticosteroid Taper Schedule Double-Blind Period

Baseline Dose	Week 0-6	Week 7-10	Week 11-18
11-25 mg/day	Goal ≤ 10 mg/day by end of Week 6	Goal ≤ 5 mg/day by end of Week 10	Goal 0 mg/day by Week 18 if possible*
6-10 mg/day	Goal ≤ 5 mg/day by end of Week 6	Goal 0 mg/day by end of Week 10 if possible*	Maintain 0 mg/day if possible*

* A taper below 5 mg should be initiated, depending on the subject's status and the judgment of the Investigator. The taper may be stopped at any point between 5 and 0 mg/day in the judgment of the Investigator. If the taper is stopped between 5 and 0 mg/day, the Investigator must document the reason in the source documents.

Investigators will determine the specific incremental tapering schedule to achieve the above goals by the specified timepoints. The Investigator will conduct weekly follow-up visits (via phone, telemedicine or any site approved remote method) to ensure proper tapering of OCS and document in the eCRF. The subjects will record daily steroid usage in an eDiary and the Investigator should verify and record OCS use on a weekly basis. If the steroid dose is altered from the protocol defined treatment regimen, site should contact the subject to determine if an unscheduled visit/rescue visit is necessary.

If a subject tapers to a dose of 5 mg/day prednisone or equivalent in the timeframes given in Table 7, then the subject is considered to have successfully completed the taper. The Investigator will then determine whether to continue the taper below 5 mg/day, although this 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 6.4). 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 the rescue treatment.

After increasing the OCS doses for an intercurrent illness, the patient should have the dose of OCS returned to the pre-illness dose within 14 days.

Open-Label Extension Period

A subject enrolling in the OLE Period of the trial may be on OCS and/or ISTs that may have been added for rescue treatment in the Double-blind Treatment Period. In the OLE, starting at Week 30, efforts should be made to taper/remove OCS and ISTs. Taper of OCS to ≤ 5 mg/day

and removal of IST should be completed by Week 38 and if feasible, taper of OCS to 0 mg/day by Week 42 (Table 8).

Table 8. Corticosteroid Taper Schedule Open-Label Extension Period

Week 26-30	Week 30-38	Week 39-42
If on OCS, maintain current dose	Goal OCS ≤ 5 mg/day by end of Week 38 if possible*	Goal OCS 0 mg/day by Week 42 if possible*

* A taper below 5 mg should be initiated, depending on the subject's status and the judgment of the Investigator. The taper may be stopped at any point between 5 and 0 mg/day in the judgment of the Investigator. If the taper is stopped between 5 and 0 mg/day, the Investigator must document the reason in the source documents.

APPENDIX 8: PATIENT REPORTED OUTCOMES ASSESSMENTS

Appendix 8.1: St. George's Respiratory Questionnaire (SGRQ)

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:	Very good	Good	Fair	Poor	Very poor
	☐	☐	☐	☐	☐

St. George's Respiratory Questionnaire

PART 1

Please describe how often your respiratory problems have affected you over the past 3 months.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 3 months have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:

- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 3 months, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:

- No ☐
- Yes ☐

St. George's Respiratory Questionnaire

PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

The most important problem I have	☐
Causes me quite a lot of problems	☐
Causes me a few problems	☐
Causes no problems	☐

If you have ever held a job:

Please check (✓) *one*:

My respiratory problems made me stop working altogether	☐
My respiratory problems interfere with my job or made me change my job	☐
My respiratory problems do not affect my job	☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

For each statement please check (✓) ***the box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

St. George's Respiratory Questionnaire

PART 2 (continued)

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) ***the box*** that applies to you ***these days:*** True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

St. George's Respiratory Questionnaire

PART 2 (concluded)

Section 6

These are questions about how your activities might be affected by your respiratory problems.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

Appendix 8.2: Modified King's Sarcoidosis Questionnaire (mKSQ)

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 amount	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 hunger'	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
17	I have been breathless walking on level ground	1	2	3	4	5	6	7
18	I have had a wheeze or whistling sound from my chest	1	2	3	4	5	6	7
19	I have had trouble breathing	1	2	3	4	5	6	7
20	I have had to clear phlegm (sputum) from my chest	1	2	3	4	5	6	7
21	My cough has been intense	1	2	3	4	5	6	7
22	My cough has disturbed my sleep	1	2	3	4	5	6	7
23	My sleep has been disturbed by breathlessness	1	2	3	4	5	6	7
24	I have had coughing bouts during the night	1	2	3	4	5	6	7
25	I have had coughing bouts during the daytime (awake hours only)	1	2	3	4	5	6	7

MEDICATION

	In the last 2 weeks...	A huge amount	A considerable amount	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
26	I have worried about the side effects of my medication for sarcoidosis	1	2	3	4	5	6	7
27	I have felt worse because of my medication	1	2	3	4	5	6	7
28	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 amount	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
29	I have been bothered by my skin problems	1	2	3	4	5	6	7
30	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
31	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
32	I have had dry eyes	1	2	3	4	5	6	7
33	I have had difficulty with bright lights	1	2	3	4	5	6	7
34	My eyes have been red	1	2	3	4	5	6	7
35	I have had pain in/or around the eyes	1	2	3	4	5	6	7
36	I have had difficulty reading	1	2	3	4	5	6	7

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

Appendix 8.3: Subject Global Assessment (SGA)

Frequency

Over the last two weeks, please rate how frequently you experienced sarcoidosis lung symptoms (coughing, breathlessness, and chest pain/tightness):

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

Severity

Over the last two weeks, please rate how severe your sarcoidosis lung symptoms (coughing, breathlessness and chest pain/tightness) have been:

None	Mild	Moderate	Severe	Very Severe
☐	☐	☐	☐	☐

Appendix 8.4: Leicester Cough Questionnaire (LCQ)

LEICESTER COUGH QUESTIONNAIRE

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

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
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

2. In the last 2 weeks, have you been bothered by phlegm production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Sometimes	Occasionally	Rarely	Never

3. In the last 2 weeks, have you been tired because of your cough?

1	2	3	4	5	6	7
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

4. In the last 2 weeks, have you felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the	A little of the time	Some of the time	A lot of the time	Most of the time	All of the time

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
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

6. In the last 2 weeks, my cough has made me feel anxious

1	2	3	4	5	6	7
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

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
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

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

1	2	3	4	5	6	7
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

9. In the last 2 weeks, exposure to paints or fumes has made me cough

1	2	3	4	5	6	7
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

10. In the last 2 weeks, has your cough disturbed your sleep?

1	2	3	4	5	6	7
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. In the last 2 weeks, how many times a day have you had coughing fits?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Sometimes during the day	Occasionally through the day	Rarely	None

12. In the last 2 weeks, my cough has made me feel frustrated

1	2	3	4	5	6	7
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

13. In the last 2 weeks, my cough has made me feel fed up

1	2	3	4	5	6	7
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

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
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

15. In the last 2 weeks, have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A lot of the time	Most of the time	All of the time

16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?

1	2	3	4	5	6	7
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

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you because of your cough?

1	2	3	4	5	6	7
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

18. In the last 2 weeks, my cough has interrupted conversations or telephone calls

1	2	3	4	5	6	7
Every time	Most times	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Sometimes when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

Appendix 8.5: Bothersomeness and Subject Global Impression of Change (BSGIC)

The assessment of Bothersomeness and Subject Global Impression of Change is a tool to assess of the qualitative impact of your sarcoidosis on your worst, or most bothersome symptoms that you have, and the perceived overall impact of the randomized treatment allocation to your disease after 26 weeks of therapy.

At baseline, please identify which symptom is the most bothersome in your daily life:

1. Breathlessness.
2. Fatigue, tiredness, or lack of energy.
3. Disturbed Sleep.
4. Cough.
5. Pain (any location).

Please rate your worst symptom on a 100 mm linear VAS from 0 mm - not bothersome at all (no impact at all to activities of your daily life), to 100 mm being the most bothersome imaginable (severely impacting all aspects of your daily life).

PLACE A VERTICAL MARK (I) ON THE LINE TO INDICATE YOUR ANSWER

At the final assessment at Week 26 (or withdrawal/ early termination); you will be reminded of your most bothersome symptom (but not your Baseline score); please re-rate based on your end of study symptoms.

Your Baseline Most Bothersome Symptom was _____.

Please re-rate from 0 mm - not bothersome at all (no impact at all to activities of your daily life), to 100 mm being the most bothersome imaginable (severely impacting all aspects of your daily life).

PLACE A VERTICAL MARK (I) ON THE LINE TO INDICATE YOUR ANSWER

Please rate your overall impression based on the totality of the treatment you received (i.e., the total effect of the blinded study medication plus the effect of oral steroids and the steroid taper, stopping other immune therapies, and any rescue medication for sarcoidosis you received.

Since you started your study medication, how have your sarcoidosis lung symptoms (coughing, breathlessness and/or chest pain/tightness) changed?

Much Improved	Moderately Improved	Minimally Improved	No Change	Minimally Worse	Moderately Worse	Much Worse
☐	☐	☐	☐	☐	☐	☐

APPENDIX 9: CLINICIAN REPORTED OUTCOME

Appendix 9.1: Extrapulmonary Physician Organ Severity Tool (EPOST)

TABLE 1 Organs evaluated in the extrapulmonary physician organ severity tool score

Skin
Peripheral lymph nodes
Eyes
Liver
Spleen
Central nervous system
Peripheral nervous system
Parotid/salivary glands
Bone marrow
Ear
Nose
Throat
Cardiac
Renal
Bone/joint
Muscle
Gastrointestinal

TABLE 2 Severity assessment of each organ

Score	Description
0	Not affected
1	Slight
2	Mild
3	Moderate
4	Moderate to severe
5	Severe
6	Very severe

APPENDIX 10: THE MEDICAL RESEARCH COUNCIL BREATHLESSNESS SCALE

The MRC Breathlessness Scale is to be used to ensure at least minimal dyspnea in the subjects taking part in the study (see inclusion #8, Section 4.1). The scale consists of 5 levels of perceived breathlessness based on different physical activity: its categories range from 1-5 as shown below (Stenton, 2008).

Subjects must report 2 or above at screening to be eligible.

1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yards or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

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