Statistical Analysis Plan

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

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Summary of Changes:

A summary and rationales of the changes within this SAP amendment is provided in the table below, with sections to be affected. The reader is referred to the redlined version of SAP amendment for the detailed changes, including original language and changed language.

Description of Change	Rationale	Affected Sections	Date of change
Added sensitivity analysis using random slope for pulmonary functions and KSQ Lung Score.	Added the sensitivity analysis to utilize all data collected, including data collected at rescue visits and unscheduled visits.	Section 5.4.2.1 Section 5.4.2.4 Section 5.4.3.1	29AUG2024
Clarified using the unstratified Chan and Zhang method as sensitivity analysis for primary efficacy endpoint.	Clarified using the unstratified Chan and Zhang method due to the limitation that Chan and Zhang method cannot provide stratified confidence interval.	Section 5.4.1.2	29AUG2024
Updated sample codes for primary analysis.	Updated sample codes to report pooled confidence interval instead of reporting confidence interval by strata.	Section 5.4.1.1	29AUG2024
Clarified the rules establishing the date for censoring the efficacy assessment data.	Detailed the rules establishing the data for censoring scheduled efficacy assessments and the algorithm to censor the data.	Appendix 5 Global	29AUG2024
Added by region subgroup analysis.	Added by region subgroup analysis to assess potential region differences.	Section 5.4.1.3	29AUG2024
Clarified the KSQ and mKSQ algorithm and analysis	Further clarified the 2-step calculation of the KSQ domain logit scores and the planned summary statistics for KSQ and mKSQ scores.	Section 5.4.3.2 Appendix 5	29AUG2024
Clarification and minor edits throughout the document.	Minor wording edits for clarity and accuracy.	Global	29AUG2024

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List of Abbreviations

Abbreviation	Term
6MWD	6-minute walking distance
ADA	Anti-Drug Activity
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
Biomarker-OL	Biomarker open-label
BSGIC	Bothersomeness and Subject Global Impression of Change
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
COVID-19	Coronavirus Disease of 2019
CPS	Chronic pulmonary sarcoidosis
CRF	Case Report Form
CS	Corticosteroids
COVID-19	Coronavirus Disease of 2019
CXCL	C-X-C motif chemokine ligand
DB	Double-Blind
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EOS	End-of-study
ET	Early termination
ePOST	Extrapulmonary Physician Organ Severity Tool
E-R	Exposure Response
FDG	Fluorodeoxyglucose
FEV1	forced expiratory volume in 1 second
FEV1/FVC	FEV1/FVC ratio
FVC	forced vital capacity
GGT	Gamma-Glutamy1 Transferase
GHS	General Health Status
GM-CSF	granulocyte-macrophage colony-stimulating factor
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography
hsCRP	high-sensitivity C-reactive protein
IL	Interleukin
IFNγ	Interferon-gamma
IST(s)	immunosuppressive therapy(ies)
IQR	Interquartile range
ITT	Intent-to-Treat
KSQ	King’s Sarcoidosis Questionnaire
LCQ	Leicester Cough Questionnaire

Abbreviation	Term
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mITT-OL	Modified Intent-to-Treat Open-Label
mKSQ	Modified King's Sarcoidosis Questionnaire
MMP	matrix metalloproteinase
MMRM	mixed model for repeated measures
MNAR	missing not at random
MRC	Medical research council breathlessness scale
PE	Physical Examination
PET	positron emission tomography
PK	Pharmacokinetic
PP	Per-Protocol
ppDLco	Percentage predicted Diffusing Capacity of Lung for Carbon Monoxide
ppFEV1	Percentage predicted forced expiratory volume in 1 second
ppFVC	Percent Predicted Forced Vital Capacity
PPK	Population pharmacokinetics
PRO	Patient Reported Outcome
PT	Preferred Term
OCS	Oral Corticosteroids
OLE	Open-label Extension
Q4W	Every 4 weeks
QTcF	Fridericia corrected QT interval
RBC	Red blood cells
SAA	serum amyloid A
SAE	Serious adverse event
Safety-OL	Safety open-label
Safety-ON	Safety on-namilumab
SAP	Statistical Analysis Plan
SC	Subcutaneously
SD	Standard Deviation
SE	Standard Error
SGA	Subject Global Assessment
SGRQ	St. George's Respiratory Questionnaire
SI	International System of Units
sIL-2R	soluble Interleukin-2 Receptor
SOC	System Organ Class
SP-D	surfactant protein D
SUV	standardized uptake value
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TFLs	Tables, Figures, and Listings
TNFα	Tumor necrosis factor alpha
ULN	Upper Limit of Normal

Abbreviation	Term
UN	unstructured
VEGFA	vascular endothelial growth factor A
WBC	White blood cells
WHODD	World Health Organization Drug Dictionary

1. OVERVIEW

This statistical analysis plan (SAP) details the statistical methods to be used in the analyses and presentation of the data collected in Study KIN-1902-2001. This document is prepared based on the study Protocol Amendment 2 (version 3.0, dated 13MAY2024). The reader is referred to the study protocol, the electronic case report from (eCRF), eCRF completion guidelines, and various data collection instruments employed in the study for details of study design, conduct, and data collection.

There will be two data analyses for this study. The first data analysis will occur when all subjects have completed the 26-week double-blind (DB) treatment period, hereafter referred to as DB period. The second data analysis will occur when all subjects have completed both the 28-week open-label extension (OLE) treatment period (hereafter referred to as OLE period) and the 14-week Follow-up period.

This SAP will be finalized by the sponsor prior to the first data analysis and unblinding of the database.

2. PROTOCOL DETAILS

2.1. OVERALL STUDY DESIGN

This is a phase 2, randomized, double-blind, placebo-controlled study with an optional open-label extension. Approximately 100 subjects (50 subjects in each of the 2 treatment arms) will be randomized 1:1 to receive namilumab or placebo in the DB period of the study. The randomization will be stratified by immunosuppressive therapy (IST) use at baseline, categorized as "yes" versus "no".

Double-blind Treatment Period:

- 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.

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

For subjects who only participate in the DB period, the duration will be approximately 46 weeks as follows:

- Up to 6-week Screening period
- 26-week DB period
- 14-week off-drug Follow-up period (see below).

Open-label Extension Treatment Period:

All subjects, regardless of treatment assignment in the DB period, who agree to participate in the OLE period will receive namilumab administered SC: 150 mg at Week 26 and then Q4W through Week 50.

For subjects who participate in both DB and OLE periods, the duration will be approximately 74 weeks as follows:

- Up to 6-week Screening period
- 26-week DB period
- 28-week OLE period
- 14-week off-drug Follow-up period (see below)

Follow-up Period:

Follow-up period (14 weeks): Safety follow-up will be from 4 weeks after the last dose of study treatment to approximately 18 weeks after the last dose of study treatment.

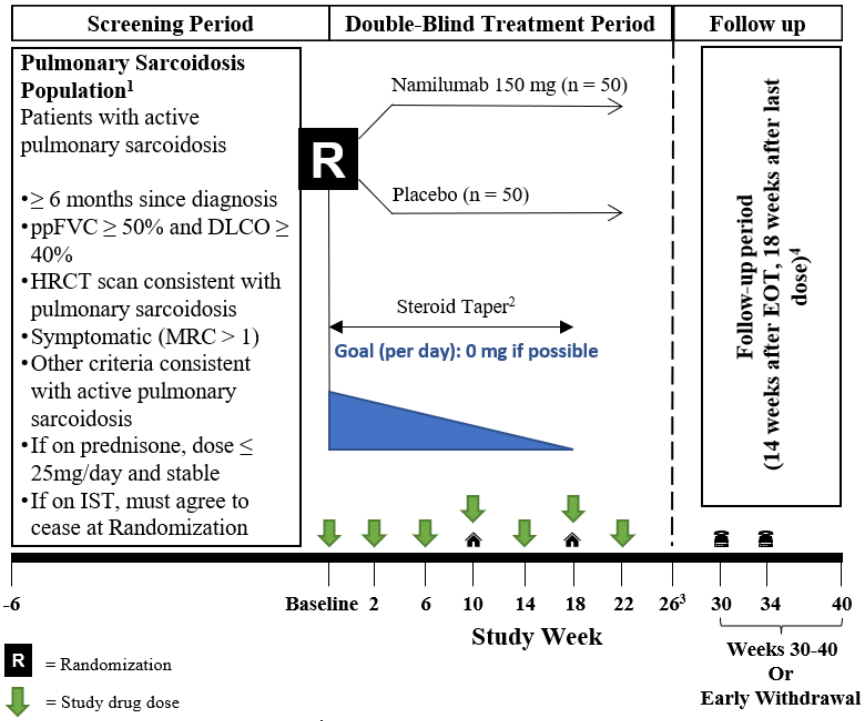
The visit at 18 weeks following the last dose of study treatment will be considered the End-of-Study (EOS) Visit.

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.

The study design is presented in Figure 1a for subjects who participate in only the DB period and Figure1b for subjects who participate in both DB and OLE periods.

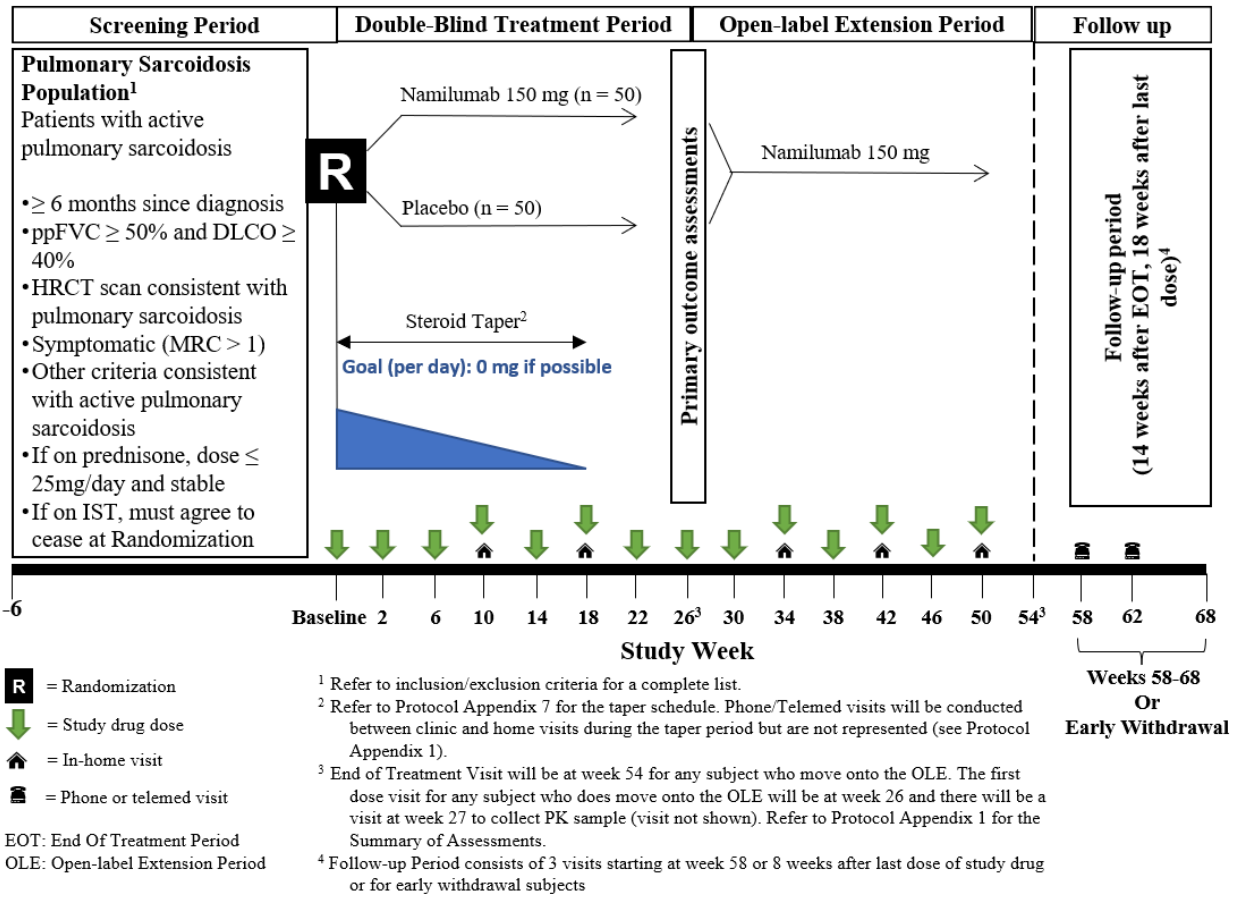
Figure 1. Study Design

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



[1] Refer to inclusion/exclusion criteria for a complete list.
[2] Refer to Protocol 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 Protocol Appendix 1).
[3] End of Treatment Visit will be at week 26 for any subject who does not move onto the OLE. Refer to Protocol 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



2.2. STUDY OBJECTIVES

2.2.1. Primary Objective

The primary objective is to evaluate the effect of namilumab on the need for rescue treatment for worsening of sarcoidosis.

2.2.2. Secondary Objectives

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

2.2.3. Exploratory Objectives

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 KSQ (mKSQ) Lung domain
  - Subject Global Assessment (SGA)
  - Leicester Cough Questionnaire (LCQ, including ad-hoc subscales)
  - 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

2.3. EFFICACY AND SAFETY ENDPOINTS

2.3.1. Primary Endpoint

The primary efficacy endpoint of this study is the proportion of subjects with a rescue event during the DB period.

2.3.2. Secondary Endpoints

The secondary efficacy endpoints of this study are:

- Change from baseline in 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, electrocardiogram (ECG), clinical laboratory measurements, and adverse events (AEs) during DB period

2.3.3. Exploratory Endpoints

The exploratory efficacy endpoints of this study are:

- Change from baseline and categorical assessments in pulmonary function in ppFVC (%), forced vital capacity (FVC, mL), forced expiratory volume in the first second (FEV1, mL), percentage predicted FEV1 (ppFEV1, %), FEV1/FVC (mL/mL), and percentage predicted Diffusing Capacity of Lung for Carbon Monoxide hemoglobin corrected (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 (including ad-hoc subscales)
  - BSGIC
- Cumulative OCS (expressed as prednisone equivalent) use and other OCS use-related endpoints in 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 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 the endpoints will also be analyzed for the OLE period for all subjects.

2.4. SAMPLE SIZE AND POWER

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 1 lists the sample size (number of evaluable subjects per arm) for a range of possible rates of subjects with a rescue event 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 a difference of 25 percentage points at a two-sided significance level of 0.10 based on Fisher's exact test.

Table 1. Sample Size Per Arm to Achieve 80% Power Under Different Scenarios

Rate in Placebo	Rescue Event 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

3. ANALYSIS POPULATIONS

In accordance with ICH E3 and E9(R1), the following analysis sets will be used for the analyses.

3.1. INTENT-TO-TREAT (ITT) POPULATION

The Intent-to-Treat (ITT) Population will include all randomized subjects. ITT subjects will be analyzed according to their randomized treatment.

3.2. MODIFIED INTENT-TO-TREAT (MITT) POPULATION

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 randomized treatment assigned. This population will be used for efficacy analyses.

In addition, subjects who had a study quality event may be excluded from mITT Popluation as described in Section 4.9. The list of subjects to be excluded from mITT Population will be finalized prior to unblinding.

3.3. PER-PROTOCOL POPULATION

The Per-Protocol (PP) Population is a subset of mITT Population. Subjects who meet the following protocol violations which may impact effectiveness of the treatment will be excluded from the PP Population.

- Received at least one dose of study treatment different from the randomized treatment or missed at least one dose of study treatment during the DB period for subject without rescue event, and prior to the first rescue event for the subject with a rescue event during the DB period.
- Premature study treatment discontinuation in the DB period without any rescue event
- Had inclusion or exclusion criteria violations which may impact effectiveness of the treatment
- Had other protocol deviations which may impact effectiveness of treatment or integrity of the data

The PP Population will be used for primary efficacy endpoint and selected secondary endpoints as supportive analysis. The list of subjects excluded from PP Population and the criteria will be finalized prior to treatment unblinding.

3.4. SAFETY POPULATION

The Safety Population will include all randomized subjects who receive any amount of study treatment. The Safety Population will be analyzed according to the treatment received. If a subject receives both treatments by error, then the subject will be analyzed according to the randomized treatment.

3.5. MODIFIED INTENT-TO-TREAT OPEN-LABEL (MITT-OL) POPULATION

The Modified ITT Open-Label (mITT-OL) Population will include all subjects who receive any amount of study treatment during the OLE period. This population will be used for efficacy analyses during the OLE period.

In addition, subjects who had a study quality event may be excluded from mITT-OL Population as described in Section 4.9. The list of subjects to be excluded from mITT-OL Population will be finalized prior to unblinding.

3.6. SAFETY ON-NAMILUMAB (SAFETY-ON) POPULATION

The Safety On-Namilumab (Safety-ON) Population will include all randomized subjects who receive any amount of namilumab during the study regardless of double-blind or open-label study treatment. This population will be used for safety analyses during the On-Namilumab period.

3.7. SAFETY OPEN-LABEL (SAFETY-OL) POPULATION

The Safety Open-Label (Safety-OL) Population will include all randomized subjects who receive any amount of study treatment during the OLE period. This population will be used for AE summaries during the OLE period.

3.8. PHARMACOKINETIC (PK) POPULATION

The Pharmacokinetic (PK) Population will include all randomized subjects who receive any amount of namilumab during the study and have at least one valid post-treatment concentration value. This population will be used for PK summaries.

3.9. IMMUNOGENICITY POPULATION

The Immunogenicity Population will include all randomized subjects who receive any amount of namilumab during the study and have at least one valid post-treatment anti-drug antibody determination. This population will be used for immunogenicity summaries.

3.10. BIOMARKER POPULATION

The Biomarker Population will include all randomized subjects who receive any amount of study treatment during the study and have at least one valid biomarker assessment. This population will be used for biomarker summaries.

3.11. BIOMARKER OPEN-LABEL (BIOMARKER-OL) POPULATION

The Biomarker Open-Label (Biomarker-OL) Population will include all randomized subjects who receive any amount of study treatment during the OLE period and have at least one valid

biomarker assessment during the OLE period. This population will be used for biomarker summaries.

4. GENERAL CONSIDERATIONS

4.1. ESTIMAND FOR THE PRIMARY OBJECTIVE

The primary objective is to evaluate the effect of namilumab on the need for rescue treatment for worsening of sarcoidosis. The primary efficacy endpoint of this study is proportion of subjects with a rescue event during the DB period. The estimand for primary objective is defined as a population average treatment difference between namilumab and placebo in the proportion of subjects with a rescue event during the DB period.

4.1.1. Population of Subjects Targeted by the Clinical Question

The treatment effect is to be estimated for the population of subjects ≥ 18 years of age in subjects with chronic pulmonary sarcoidosis (CPS) as described in Section 4 of the Protocol.

4.1.2. Treatment Condition of Interest

The primary treatment condition of interest is namilumab 150 mg administered via SC on Day 1 (Baseline, Week 0) and then at Weeks 2, 6, 10, 14, 18, and 22 and is compared against the alternative treatment condition of placebo administered according to the same schedule.

4.1.3. Variable of Interest

Efficacy is to be measured using the proportion of subjects with a rescue event during the 26 weeks DB period.

For subjects who completed the DB period but did not participate in the OLE period, a rescue event within 8 weeks after the last dose of double-blind study treatment will be included in the analysis. For subjects who participated in the OLE period, a rescue event up to the first dose of open-label treatment will be considered. For subjects who missed multiple doses in the DB period, and had a treatment gap longer than 8 weeks, only a rescue event up to 8 weeks after the last dose of the study treatment prior to the gap will be considered as a rescue event for the analysis. Using the 8-week window after the last dose of study treatment to identify rescue events is to be consistent with the protocol allowed one missing dose, i.e., 8 weeks of no study treatment.

There are several paths through which the protocol defined rescue events (e.g., the need for rescue treatment due to worsening sarcoidosis and the failure to achieve protocol defined tapering of corticosteroids) can be achieved. Appendix 5 defines all rescue events and describes the review process by which rescue events are identified. The review process will be completed in a manner blind to treatment allocation by an internal Kinevant committee. This review will be completed before the unblinding of the database for the week 26 analysis. This list of confirmed rescue events (hereafter referred as Final Rescue Event Summary) for the DB period will serve as the basis for the primary analysis. This event summary will be considered the final listing for

the DB period even after the completion of the extension period. A similar identification process will occur for the OLE period before final database lock. Appendix 5

4.1.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Premature treatment discontinuation

The intercurrent events will be handled using composite variable strategies as below for the primary analysis:

- If a subject discontinued the treatment prior to Week 22 and had a rescue event during the DB period or within 8 weeks after the last dose of double-blind study treatment and prior to the first dose of the open-label study treatment, the subject will be considered as having a rescue event during the DB period.
- If a subject discontinued the double-blind study treatment, the reason and status of the subject will be reviewed and adjudicated, if needed, to determine if the subject will be considered as having a rescue event during the DB period as described in Section 4.1.3.
- If a subject discontinued the treatment due to reasons not deemed having a rescue event per adjudication during the DB period, or within 8 weeks after the last dose of double-blind study treatment, the subject will be considered as having missing information for rescue event status, i.e., this missing information will be considered as missing at random (MAR) and will not be included in the primary analysis.

All subjects who prematurely discontinued during the DB period will be reviewed and the rescue event status will be finalized prior to the treatment unblinding as described in Section 4.1.3.

Additional sensitivity analysis using different imputation methods will be performed as described in Section 5.4.1.2 of this SAP.

4.1.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the difference in proportion of subjects with a rescue event between namilumab and in placebo treatment arms during the DB period. The difference in proportions and corresponding confidence intervals (CIs) will be estimated based on the stratified Miettienn-Nurminen method. The two-sided p-value will be computed using the Cochran-Mantel-Haenszel (CMH) test stratified by IST use at baseline (yes, no) as described in Section 5.4.1.1.

4.2. ANALYSIS PERIODS

The analysis periods used for the analysis are defined as below, unless specified otherwise.

Double-blind Treatment Period:

The DB period is defined as from the date of the reference date as described in Section 4.11 to the date of the 1st dose of open-label study treatment or 8 weeks after the last dose of double blind study treatment, whichever is earlier, for subjects who enrolled into OLE period, and to the last known date on study or 8 weeks after the last dose of double-blind study treatment, whichever is earlier, for subjects who did not enroll into OLE period. The assessments carried out at Week 26 visit will be considered as the DB period assessments if it cannot be determined whether the assessments occurred prior to the first open-label study treatment.

The DB period will be used for efficacy analysis and safety analysis.

Open-label Extension Treatment Period:

For subjects who continue to the OLE period, the OLE period is defined as from the date of the first dose of open-label study treatment to the last known date on study or 8 weeks after the last dose of open-label study treatment, whichever is earlier. The assessments carried out at Week 26 visit will not be considered as OLE period assessment if the corresponding times of the assessments have not been recorded.

The OLE period will be used for efficacy analysis and safety analysis.

On-Namilumab Period:

On-Namilumab period is the period where subjects were on namilumab during the study, regardless of double-blind or open-label study treatment. This period is defined as from the date of the first dose of namilumab treatment to the last known date on study or 8 weeks after the last dose of namilumab (regardless double-blind or open-label) study treatment, whichever is earlier. For subjects who did not enroll into the OLE period and were randomized to placebo group, this period is not defined.

This period will be used to summarize safety parameters.

Overall Treatment Period:

The Overall Treatment period is defined as from the date of the randomization to the last known date on study or 8 weeks after the last dose study treatment, whichever is earlier.

The Overall Treatment period will be used for summaries of efficacy endpoints.

4.3. BASELINE AND CHANGE FROM BASELINE

The baseline is defined as below if not specified otherwise:

- For the DB period and Overall Treatment period, baseline for efficacy endpoints and biomarkers is the last assessment on or prior to the randomization, and baseline for safety endpoints is the last assessment on or prior to the first dose of double-blind study treatment.

- For the OLE period, the baseline is the last assessment between Week 22 and 26 and prior to the first dose of the open-label study treatment on Week 26.
- For On-Namilumab period, the baseline is the last assessment on or prior to the first dose of namilumab, i.e., the first dose of double-blind study treatment for subjects who were randomized to namilumab treatment group, and the first dose of open-label study treatment for subjects who were randomized to placebo group.

Assessments carried out on the day of randomization are considered to have taken place before randomization if the corresponding times have not been recorded. Similarly, the assessments carried out on the day of first dose of double-blind or open-label study treatment are considered to have taken place before the dose of the double-blind or open-label study treatment, respectively, if the corresponding times have not been recorded. For randomized but not treated subjects, the baseline is the last assessment prior to or on randomization date.

Change from baseline and percentage change from baseline will be calculated as:

- Change from baseline = (post-baseline value – baseline value). Unless specified otherwise, the change from baseline for ppFVC and ppDLco refers to the simple difference between post-baseline and baseline values (e.g., 5% improvement in ppFVC from baseline is the 5% points increase from baseline).
- Percentage change from baseline = [(post-baseline value – baseline value) / baseline value] × 100

4.4. DATA MONITORING COMMITTEE

A Data Monitoring Committee (DMC) has been set up for this study. The primary responsibility of the DMC is to safeguard the interests of study subjects and assess the safety of the interventions during the trial. Unblinded outputs on subject disposition, demographic and baseline characteristic, and safety will be periodically provided to the DMC members. The details of DMC are provided in the DMC charter.

4.5. INTERIM ANALYSIS

No formal interim analyses are planned to stop the study early for either success or futility due to the efficacy.

4.6. TIMING OF THE ANALYSES

There will be two data analyses for this study.

The first data analysis, referred to as Week 26 analysis hereafter, will be performed after the Week 26 visit of the last subject. The analysis will include all the efficacy and safety assessments collected during the DB period, and for AE up to the date of the last subject's Week 26 visit, including available safety information during the OLE period.

The second data analysis, referred to as Week 68 analysis hereafter, will occur when all subjects have completed the 28-week OLE period and Follow-up period. The analysis will include all data collected during the whole study.

4.7. MULTIPLICITY ADJUSTMENT

There is only one primary hypothesis, and it will be tested at two-sided alpha of 0.10. If the two-sided p-value < 0.10, then the primary endpoint will be considered statistically significant, and the study will be declared positive.

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

4.8. MISSING DATA HANDLING

4.8.1. Handling of Missing Efficacy Data

For the primary endpoint, inference will be done using a CMH test. The missing data will be imputed as described in Section 4.1.4, which imputes the rescue event status based on available information, and assuming MAR for the missing information without informative evidence as described in Section 4.1.4.

Sensitivity analysis based on multiple imputation and assumptions of missing not at random (MNAR), including tipping point analysis, for subjects who prematurely discontinued study treatment will be performed. Further details on missing data sensitivity analyses are specified in Section 5.4.1.

4.8.2. Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. AE imputations for missing severity or relationship are given in Section 5.5.3. Unknown or partial medication and AE date imputations are given in Appendix 2 and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

4.9. STUDY QUALITY EVENT

If there are study quality events, e.g., accidental unblinding of study treatment assignment, the impact will be evaluated prior to the unblinding of the study. If deemed necessary, for all efficacy endpoints, the primary analyses will be performed by excluding the subjects who are impacted. A sensitivity analysis for all efficacy endpoints will be performed by including the subjects who are impacted. The list of the subjects and the reasons to exclude subjects will be finalized prior to the unblinding of the study.

4.10. STRATIFICATION FACTOR

The randomization of this study is stratified by IST use at baseline. The analysis plan is to adjust for IST use at baseline in the analyses of efficacy endpoints in this study. However, during the study, the patients were not consistently assigned to the corrected strata. To improve the efficiency of the analysis, the actual IST use at baseline will be used for all related analysis described in this SAP.

The actual IST use at baseline will be determined by searching records in prior and concomitant medication Case Report Form (CRF) page with ATC2="IMMUNOSUPPRESSANTS". Any subject who had at least one dose of IST use within 14 days prior to Randomization, or on the date of Randomization (i.e., at least one dose of IST use from Date of Randomization – 14 days to Date of Randomization, inclusive), will be considered as having IST use at baseline. Subjects may have more than one ISTs use at baseline.

4.11. STUDY DAY DEFINITIONS

For efficacy analysis for DB period and Overall Treatment period, the assessment days will be calculated corresponding to the date of randomization (reference date for efficacy analysis for DB period and Overall Treatment period). Day 1 for efficacy analysis is the day of randomization. For safety analysis for DB period, the assessment days will be calculated corresponding to the date of the first dose of double-blind study treatment (reference date for safety analysis for DB period). Day 1 for safety analysis is the day of the first dose of double-blind study treatment. For efficacy and safety analysis for OLE period, the assessment days will be calculated corresponding to the date of the first dose of open-label study treatment (reference date for OLE period).

i.e., Assessment day = Assessment date – Reference date + 1.

For all assessments done prior to the reference date, the assessment day will be calculated as:

Assessment day= Assessment date – Reference date.

The day prior to Day 1 is Day -1. Day 0 is not defined.

4.12. ANALYSIS PERIODS AND VISIT WINDOWS

For the purpose of statistical analysis, time windows will need defining for presentations that summarize values by visit. The windows for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the 2 visits (the lower limit of the first post-baseline visit will be Day 2). The assignment of data to visit windows will use the relative day defined in Section 4.11.

Table 2. Analysis Windows for Double-Blind Treatment Period

Week	Scheduled Day	Visit Window for Analysis (Days)
DB Baseline	1	Last assessment prior to randomization or the first dose of the double-blind study treatment*
DB Week 2	15	[2, 29]
DB Week 6	43	[30, 57]
DB Week 10	71	[58, 85]
DB Week 14	99	[86, 113]
DB Week 18	127	[114, 141]
DB Week 22	155	[142, 169]
DB Week 26	183	[170, 211] for subjects who did not participate open-label extension period [170, days to the first dose of open-label study medication] for subjects who participated open-label extension period

Abbreviations: DB = double-blind

*: An assessment carried out on the same day of reference day (randomization for efficacy endpoints, and the day of the first dose of double-blind study treatment for safety endpoints) will be considered as baseline if the corresponding time has not been recorded.

Table 3. Analysis Windows for Open-label Extension Treatment Period

Week	Scheduled Day	Visit Window for Analysis (Days)
OLE Baseline	183	Last assessment on or after Day 142 and prior to the first dose of open-label study treatment*
OLE Week 30	211	[Days to the first dose of open-label study medication + 1, 225]
OLE Week 34	239	[226, 253]
OLE Week 38	267	[254, 281]
OLE Week 42	295	[282, 309]
OLE Week 46	323	[310, 337]
OLE Week 50	351	[338, 365]
OLE Week 54	379	[366, 435]
Follow-up		As collected on eCRF

Abbreviations: eCRF = electronic Case Report Form; OLE = open-label extension

*: If a subject had a rescue event between the last assessment in the window and the first dose of open-label study treatment, the baseline for open-label extension treatment period will be set as missing for the subject. An assessment carried out on the same day as the date of the first open-label study treatment will be considered as baseline if the corresponding time has not been recorded.

Table 4. Analysis Windows for Overall Treatment Period

Week	Scheduled Day	Visit Window for Analysis (Days)
OA Baseline	1	Same as the baseline in DB period
OA Week 2	15	[2, 29]
OA Week 6	43	[30, 57]
OA Week 10	71	[58, 85]
OA Week 14	99	[86, 113]

Week	Scheduled Day	Visit Window for Analysis (Days)
OA Week 18	127	[114, 141]
OA Week 22	155	[142, 169]
OA Week 26	183	[170, 197]
OA Week 30	211	[198, 225]
OA Week 34	239	[226, 253]
OA Week 38	267	[254, 281]
OA Week 42	295	[282, 309]
OA Week 46	323	[310, 337]
OA Week 50	351	[338, 365]
OA Week 54	379	[366, 435]
Follow-up		As collected on eCRF

Abbreviations: DB = double-blind; eCRF = electronic Case Report Form; OA = Overall

Table 5. Analysis Windows for On-Namilumab Treatment Period

Analysis Week	Namilumab/Namilumab Group		Placebo/Namilumab Group	
	Scheduled Day	Visit Window for Analysis (Days)	Scheduled Day	Visit Window for Analysis (Days)
ON Baseline	1	Same as the baseline for DB period	183	Same as the baseline for OLE period
ON Week 2	15	[2, 29]		
ON Week 4			211	[Days to the first dose of open-label study medication + 1, 225]
ON Week 6	43	[30, 57]		
ON Week 8			239	[226, 253]
ON Week 10	71	[58, 85]		
ON Week 12			267	[254, 281]
ON Week 14	99	[86, 113]		
ON Week 16			295	[282, 309]
ON Week 18	127	[114, 141]		
ON Week 20			323	[310, 337]
ON Week 22	155	[142, 169]		
ON Week 24			351	[338, 365]
ON Week 26	183	[170, 197]		
ON Week 28			379	[366, 435]
ON Week 30	211	[198, 225]		
ON Week 34	239	[226, 253]		
ON Week 38	267	[254, 281]		
ON Week 42	295	[282, 309]		
ON Week 46	323	[310, 337]		
ON Week 50	351	[338, 365]		
ON Week 54	379	[366, 435]		

Analysis Week	Namilumab/Namilumab Group		Placebo/Namilumab Group	
Follow-up		As collected on eCRF		As collected on eCRF

Abbreviations: DB = double-blind; eCRF = electronic Case Report Form; OLE = open-label extension; ON = On-Namilumab

If a subject has more than 1 assessment occurring in the same visit window, the data from the assessment closest to the scheduled day will be used. If 2 assessments have the same distance from the scheduled day, the data of the assessment after the scheduled day will be used. If a subject has more than 1 assessment occurring on the same day, the latest assessment will be used, unless specified otherwise.

4.13. GENERAL PRINCIPLES

All data processing, summarization, and analyses described in this SAP will be performed using Version 9.4 (or later) of the SAS® statistical software package.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max), for those subjects with data. For qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of subjects in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in Tables, Figures, and Listings (TFLs) mock shells.

Unless specified otherwise, the demographics and baseline characteristics will be summarized by treatment group and overall for both Safety and mITT populations.

The efficacy assessments will be summarized for by treatment and overall for the DB period in mITT Population, by treatment sequence and overall for the OLE period in mITT-OL Population, and by treatment sequence and overall for Overall Treatment period in mITT Population. The difference of change from baseline between the two treatment groups and corresponding 90% CI based on t-test will also be presented for DB period. Unless specified otherwise, for efficacy endpoints, including PROs, the assessments on or after censoring date as in Final Rescue Event Summary will be set as missing for all analyses and summaries, where applicable. The assessments performed on the same day as the rescue visit will not be censored. Two-sided p-value and 90% CI will be presented for all analyses, where applicable.

The safety assessments will be summarized for the DB period and On-Namilumab period, for Safety Population and Safety-ON Population, respectively, by treatment group/sequence and overall, where applicable. For binary efficacy endpoint, corresponding bar plot will be presented. For continuous efficacy endpoints, line plot of mean values by visit and treatment group/sequence will be presented.

By-subject listing will be created for each eCRF domain and external data transfer sorted by treatment group/sequence, subject ID, and associated dates, where applicable.

Assessments performed per earlier version of the protocol(s) but removed from later protocol amendments, e.g., 6-minute walking distance (6MWD), pain visual analog scale, and general sleep disturbance scale, will only be listed.

5. STATISTICAL METHODS

5.1. SUBJECT DISPOSITION AND DATA SETS ANALYZED

Subject disposition will be summarized by treatment group for the DB period, and by treatment sequence and overall for the OLE period for the All Screened Subjects. The following information will be reported:

- Number of subjects for the following categories:
    - Screened
    - Reasons for Screen Failures
- Number and percentage of subjects for the following categories for the DB period:
    - Randomized
    - Received at least one dose of double-blind study treatment
    - Did not receive any double-blind study treatment
    - Completed the DB period
    - Discontinued study treatment during the DB period
    - Reasons for study treatment discontinuation
    - Discontinued study during the DB period
    - Reasons for study discontinuation
- Number and percentage of subjects for the following categories for the OLE period:
    - Consented in the OLE period
    - Received at least one dose of open-label study treatment
    - Did not receive any open-label study treatment
    - Completed the OLE period
    - Discontinued study treatment during the OLE period
    - Reasons for study treatment discontinuation
    - Discontinued during the OLE period
    - Reasons for study discontinuation
- Number and percentage of subjects included in, and excluded from, each study population together with the reasons for exclusion from the analysis population
- Number and percentage of subjects who completed / discontinued treatment, including the reasons for treatment discontinuation
- Number and percentage of subjects at each region / site

A subject will be regarded as having completed the study if the status recorded on the End of Study eCRF form is complete. A subject will be considered as having discontinued the study if they have an eCRF status of premature study discontinuation.

A listing of all subjects with their treatment and study completion status, including the respective reasons for treatment and study discontinuation will be presented for the ITT Population.

A listing of all randomized subjects with their randomization details (randomization date, randomization number, and randomized stratification), including first dose date and actual treatment received will be presented for the ITT Population.

A listing of all subjects excluded from at least one analysis set will be presented for the ITT Population.

A listing of the subjects who had a study quality event and were excluded from mITT Population, such as accidental unblinding, will also be listed.

5.2. PROTOCOL DEVIATIONS

All important protocol deviations will be summarized for the mITT and Safety populations for both DB and OLE periods by treatment group, treatment sequence, and overall, where appropriate, as described below:

- The number of unique subjects with at least one important protocol deviation as well as the number of subjects in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all subjects with one or more important / non-important protocol deviations will be presented for the ITT Population.

5.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

5.3.1. Demographic Characteristics

Demographic characteristics will be summarized for the mITT and Safety populations for the DB period, and for the mITT-OL and Safety-OL populations for the OLE period as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Height (cm) at baseline
- Weight (kg) at baseline
- Body mass index (kg/m^2) at baseline

Total counts and percentages of subjects will be presented for the categorical variables of:

- Age (≥ 18 to < 65 years, ≥ 65 years)
- Sex (female, male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)

Demographic characteristics will be listed for the ITT Population.

5.3.2. Baseline Characteristics

Baseline characteristics will be summarized for the mITT for the DB period and mITT-OL for the OLE period as described below.

The number of subjects and percentage for following parameters will be summarized by categories. All missing data will be presented as part of a missing category, if appropriate.

- IST use at baseline (yes, no)
    - Subtype (preferred term, PT) of IST at baseline
- OCS Dose at baseline (≤ 5 mg/day, > 5 mg/day)
- Baseline positron emission tomography (PET) standardized uptake value (SUV) max (< 5, ≥ 5)
- Baseline ppFVC (< 80%, ≥ 80%)
- Baseline FEV1/FVC ratio (< 0.7, ≥ 0.7)
- Baseline ppDLco (< 80%, ≥ 80%)
- Medical research council breathlessness scale (MRC, 1 to 5)

The OCS dose at baseline is defined as daily dose based on the last dose within 7 days prior to Randomization, or on the date of Randomization (i.e., last dose from Date of Randomization – 7 days to Date of Randomization, inclusive). Dose will be converted to mg/day, such as multiplying dose with 2 if BID or dividing dose by 2 if every other day. The OCS use will be determined by corticosteroid (CS) use (defined as ATC2="CORTICOSTEROIDS FOR SYSTEMIC USE") with "ORAL" route in prior and concomitant medication CRF page.

The following parameters will be summarized as quantitative assessments.

- OCS Dose at baseline
- Baseline PET SUV max
- Baseline percentage pulmonary fibrosis by HRCT scan
- Baseline spirometry (ppFVC, and FEV1/FVC)

- Baseline biomarkers (high-sensitivity C-reactive protein [hsCRP], serum amyloid A [SAA], and soluble Interleukin-2 Receptor [sIL-2R])
- Baseline ppDLco
- Baseline KSQ Lung domain score
- Years of disease duration at Screening

Years of disease duration at Screening will be calculated based on imputed dates as described in Appendix 2 if the start date is not completed in Medical History CRF page.

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

A listing of baseline characteristics, including previously mentioned assessments, will be presented for the ITT Population.

5.3.3. Medical History

Medical history is defined as any condition that the subject may have had prior to enrollment in the study, including any chronic conditions diagnosed prior to entry in the study.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 24.1, or later] and will be presented by System Organ Class (SOC) and PT and total. The SOCs and PTs are to be sorted by Internationally Agreed order SOCs and descending PTs in the total column.

Medical history records will be summarized for the Safety Population by treatment group and overall for DB period as follows:

- The number and percentage of subjects with at least one medical history record will be presented.
- The number and percentage of subjects with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using the internationally agreed order for SOC and using descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

A listing will be prepared for all medical history with PT="Sarcoidosis".

Medical history records will be listed by-subject and within-subject by medical history start date for the ITT Population.

5.3.4. Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary (WHODD, version September 2021/B3 or later), Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows, unless specified otherwise:

- Prior medications are those taken at least one dose within 6 months prior to the date of randomization.
- Concomitant medications during the DB period are those taken at least one dose during DB period as defined in Section 4.2.
- Concomitant medications during the OLE period are those taken at least one dose during OLE period as defined in Section 4.2.

See Appendix 2 for imputation of missing or partial dates for medication.

Prior medication will be summarized for the Safety Population, concomitant medications during the DB period will be summarized for the Safety Population, concomitant medications during the OLE period will be summarized for the Safety-OL Population, as follows:

- The number and percentage of subjects with at least one prior / concomitant medication will be presented.
- The number and percentage of subjects with at least one prior / concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), and PT will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then descending order of PT in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications will be listed for the Safety Population. In the listings the relative start and stop day of prior /concomitant medication use will be calculated relative to the first dose date of study treatment for Safety Population. If the concomitant medication is “Ongoing” it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

Prior medication given for pulmonary sarcoidosis within 2 years prior to screening will also be summarized for the Safety Population.

Medications checked as rescue treatment on the eCRF will also be summarized separately in a table and listing in the same manner as prior and concomitant medications.

5.4. EFFICACY ANALYSIS

Unless otherwise specified, the by-visit summaries will be generated separately as described in Section 4.12 for the DB period in mITT Population, OLE period in mITT-OL Population, and Overall Treatment period in mITT Population.

5.4.1. Primary Efficacy Endpoint

5.4.1.1. Primary Analysis

The primary efficacy endpoint is the proportion of subjects with a rescue event during the DB period based on adjudication confirmed Final Rescue Event Summary as described in Section 4.1.3. The missing rescue event status due to intercurrent events will be handled as described in Section 4.1.4.

The null and alternative hypotheses for this endpoint are as follows:

H_0: $p_A = p_P$

H_A: $p_A \neq p_P$

Where H_0 and H_A refer to the null and alternative hypothesis to be tested, p_A and p_p refers to the proportion of subjects with rescue event during the DB period for subjects randomized to namilumab and placebo groups, respectively.

Primary analysis to compare the proportion of subjects with rescue event during the DB period will be a CMH test stratified by use of IST at baseline (yes, no) based on mITT Population. The frequency and percentage of the proportions for each group with 90% CI using Wilson (1927) method, and the difference in proportion between treatment groups and the CI based on stratified Miettinen-Nurminen method will be provided. The difference and 90% CI based on CMH method will also be provided for reference.

The example SAS code is listed below:

```
/* Code for CMH test */
  PROC FREQ data=datain;
    TABLE ISTUse*TRT*Resp / commonriskdiff(TEST=MH CL=MH) cmh;
  Run;

/* Code for proportions within treatment group */
  PROC FREQ data=datain;
    By TRT;
    TABLE Resp / binomial(Wilson) alpha=0.10;
  RUN;

/* Code for proportion difference and Miettinen-Nurminen treatment
difference */
  PROC FREQ data=datain;
    TABLE ISTUse*TRT*Resp / RiskDiff(CL=SCORE);
  RUN;
```

where

```
  ISTUse = IST use at baseline
  TRT = Randomized treatment group
  Resp = Rescue event status.
```

5.4.1.2. Sensitivity Analysis

As a sensitivity analysis, the primary analysis method will be repeated for PP Population.

The primary endpoint will also be analyzed using similar CMH test in the primary analysis but stratified by use of IST at baseline (yes, no) and OCS dose at baseline (≤ 5 mg/day, > 5 mg/day) based on mITT Population to assess the impact of OCS dose at baseline, and to adjust for potential imbalance of the baseline OCS use.

If there are less than 5 rescue events within one or more strata in one treatment arm, the unstratified CMH test will be conducted.

The primary endpoint will also be analyzed using the unstratified Chan and Zhang (1999) method. The corresponding treatment difference and 90% CI will be reported.

The primary analysis will also be repeated by including the subjects who prematurely discontinued during the DB period with missing rescue event information as having rescue event as a sensitivity analysis.

To assess the impact of coronavirus disease 2019 (COVID-19), an analysis similar to the primary analysis will be performed in mITT Population, excluding all subjects who had any visits affected by COVID-19 during the DB period. Any visits affected by COVID-19 will be captured as protocol deviation.

For the primary analysis, all subjects who prematurely discontinued during the DB period and were not considered as having rescue event per adjudication will be considered missing rescue event status assuming missing at random. To further assess the impact of missing data, missing data will be imputed using multiple imputation for analysis described below. The details are provided in Appendix 3 of this SAP.

- Under an assumption of MNAR, the imputation will be performed using the following variables to model the missing rescue event status: treatment group, IST use at baseline
- Impute all subjects with missing rescue event status, in both treatment group, following the distribution of control group
- To explore how extreme the difference between randomized treatments would have to be among subjects with missing data to overwhelm the treatment effect obtain in the primary, a tipping point analysis will be conducted by shifting the proportion of subjects having rescue event in both treatment arms

5.4.1.3. Subgroup Analysis

The frequency and percentage of the subjects requiring rescue treatment will be summarized for subgroups below:

- Age (≥ 18 to < 65 years, ≥ 65 years)
- Sex (female, male)
- Race (White, African American, others)
    - The subgroup "others" includes the subjects with race reported other than White and African American, and the subjects with race not reported.
- Region (North American, Europe Excluding Turkey, Turkey)
- Baseline PET SUV max (< median, ≥ median)
- IST usage at baseline (Yes, No)
- Baseline OCS dosage (≤ 5 mg/day, > 5 mg/day)
- Baseline ppFVC (< 80%, ≥ 80%)
- Baseline FEV1/FVC ratio (< 0.7, ≥ 0.7)
- Baseline ppDLco (< 80%, ≥ 80%)
- Baseline sIL-2R (< median, ≥ median)
- Baseline hsCRP (< median, ≥ median)
- Baseline KSQ Lung domain score (< median, ≥ median)

5.4.1.4. Other Supportive Analysis

The categories for the rescue events and the type of rescue treatments used during the DB period will be summarized based on Final Rescue Event Summary.

The frequency and percentage of the subjects with rescue event during the OLE period will be summarized by treatment sequence, with reason of the rescue event and type of rescue treatment using during the OLE period. The frequency and percentage of subjects with rescue event during the Overall Treatment period will also be summarized similarly.

5.4.2. Secondary Efficacy Endpoints

All secondary efficacy analysis will be presented based on the mITT Population, unless otherwise specified.

5.4.2.1. Percent predicted forced vital capacity (ppFVC)

The change from baseline in ppFVC(%) at Week 26 is a secondary efficacy endpoint. The treatment difference in the change from baseline in ppFVC will be evaluated based on a mixed model for repeated measures (MMRM) assuming MAR. The change from baseline at Week 26 will be compared between namilumab and placebo. The estimated treatment difference at Week 26 and the corresponding 90% CI will be presented. To assess the variability, the treatment difference at Week 22 will also be reported. The MMRM model will use the treatment,

visit, IST usage at baseline, and the interaction between treatment and visit as factors, and the baseline ppFVC as a covariate. An unstructured (UN) covariance structure will be used to model the within-patient errors. If this analysis fails to converge, the following covariance structures will be tested in order, and the first covariance structure that converges will be used: Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, and autoregressive. For this analysis, the assessments on or after censoring date as in Final Rescue Event Summary will be set as missing.

The example SAS code is listed below:

```
PROC MIXED data=datain method=reml;
  CLASS ISTUse TRT Visit Usubjid;
  MODEL CHGppFVC = TRT Visit ISTUse BLppFVC TRT*Visit;
  REPEATED Visit / Type=UN Subject=Usubjid;
  LSMEANS TRT*Visit / pdiff CL alpha=0.10;
Run;
```

where

```
ISTUse = IST use at baseline
TRT = Randomized treatment group
Visit = Analysis Visit
Usubjid = Unique Subject ID
CHGppFVC = Change from baseline in ppFVC at Week 6, 14, 22, and 26
BLppFVC = Baseline ppFVC
```

The same MMRM analysis will be performed on PP Population as a sensitivity analysis.

MI assuming MNAR will be performed to assess the assumption of MAR of the MMRM. The imputation will be performed using the following variables to model the missing ppFVC: treatment group, IST use at baseline, baseline ppFVC, and post-baseline ppFVC assessments. A tipping point analysis will be performed based upon this MNAR method analysis in order evaluate the robustness of the results.

In addition, the MMRM analysis will be performed as below to assess impact of rescue event.

- The assessments on or after censoring date as in Final Rescue Event Summary will be imputed using values of the 5th quantile of ppFVC distribution of all subjects at all visits, regardless of treatment group/sequence
- Use all observed assessments, including the assessments after rescue event

To assess the impact of baseline OCS use, a similar MMRM analysis will be performed with adding baseline OCS dose as a covariate.

As a sensitivity analysis using all observed data in DB period (including baseline assessments and all post-baseline assessments at scheduled, rescue, and unscheduled visit) prior to censoring date, a MMRM model will be employed using a random intercept and a random slope of change per week assuming missing assessment are MAR. The change from baseline at Week 26 will be compared. The MMRM model will include baseline IST use, baseline OCS dose (as a continuous

variable), treatment, week (actual week at the assessment as a continuous variable), and the interaction of week and treatment.

The frequency and percentage of subjects within the following categories will be summarized for the DB period:

- Observed ppFVC
  - <30%
  - <50%
  - <60%
  - <70%
  - <80%
- Change from baseline in ppFVC
  - < -5%
  - ≥ -5% to < 0%
  - ≥ 0% < 2.5%
  - ≥ 2.5% < 5%
  - ≥ 5%
  - ≥ 10%
  - ≥ 15%

The ppFVC during the DB period will also be summarized by treatment group for the subgroups used for primary efficacy endpoint as listed in Section 5.4.1.3.

The observed values and change from baseline in ppFVC at each post-baseline visit will be summarized by treatment for the DB period, by treatment sequence for the OLE period, and by treatment sequence for Overall Treatment period.

5.4.2.2. Time to the First Rescue Event

Time of first rescue event is defined as the time from randomization to the rescue event date as described in Appendix 5. The rescue event is defined the same as the primary efficacy endpoint.

Time to the first rescue event during the DB period will be evaluated using a log-rank test and Kaplan-Meier plot, as well as a Cox proportional hazards model with treatment and IST usage at baseline (Yes, No) as covariates. Number and percentage of subjects who had event and who are censored, quartiles of survival time with corresponding 90% CI from Kaplan-Meier analysis, p-value from log-rank test, hazard ratio with 90% CI from Cox proportional hazards model will be reported. Plots of the Kaplan-Meier curves will be provided for each treatment group.

Subjects who do not have a rescue event will be censored:

- at the day of the 1st dose of open-label study treatment or 8 weeks after the last dose of double-blind study treatment, whichever is the earlier, for subjects who participate in OLE period,
- at the last known date on study or 8 weeks after the last dose of double-blind study treatment, whichever is earlier, for subjects who do not participate in OLE period.

A similar analysis will also be performed for time to the first rescue event during Overall Treatment period.

This analysis will be based on the Final Rescue Event Summary of the subjects with a rescue event and time of rescue event as described in Section 4.1.3.

5.4.2.3. OCS Taper Without Rescue Event

The proportion of subjects successfully achieving OCS taper (achieving OCS dose ≤ 5 mg within protocol specified time period as in Protocol Appendix 7. i.e., achieving OCS dose ≤ 5 mg at end of Week 10 (Day 77) for subjects with baseline OCS >10 mg/day, achieving ≤ 5 mg at end of Week 6 (Day 49) for subjects with baseline OCS >5 to ≤ 10 mg/day) without rescue event during the DB period per treatment group over the total number of subjects with baseline OCS dose > 5 mg in the respective treatment group will be computed. A CMH test stratified by use of IST at baseline will be used for treatment comparison. Difference in proportions between treatment groups and the corresponding 90% CI for the difference based on stratified Miettinen-Nurminen method will also be computed. This analysis will be performed at Week 26.

The proportion of subjects successfully achieving OCS taper (achieving OCS dose ≤ 5 mg at Week 38 (Day 91 from the date of the 1st dose of open-label study treatment) without rescue event during the OLE period over the total number of subjects with OL baseline OCS dose > 5 mg in the respective treatment sequence will be summarized.

5.4.2.4. King's Sarcoidosis Questionnaire (KSQ) Lung Domain Score

The KSQ has 29 questions (items 1 to 16, and items 26-38 in Appendix 4). The KSQ Lung domain score will be calculated based on items 11 to 16. The raw item scores will be first converted into item re-scores using a first conversion step. as Then, the re-scores for the six items will be totaled and the total converted into the logit 1-100 score (Appendix 4). The change from baseline in logit score at Week 26 is the secondary endpoint for KSQ Lung domain score.

The treatment difference in the KSQ Lung domain logit 1-100 score will be evaluated based on the similar MMRM model for analyzing ppFVC. The change from baseline to Week 26 will be compared between namilumab and placebo. The estimated treatment difference at Week 26 and the corresponding 90% CI will be presented. In this analysis, the assessments on or after the censoring date as in the Final Rescue Event Summary will be set as missing.

To assess the impact of rescue events, a sensitivity analysis will be performed using the same MMRM model using all observed KSQ assessments, including the assessments after the first rescue event.

In addition, a similar MMRM model using random intercept and slope as described in Section 5.4.2.1 will be performed.

5.4.3. Exploratory Efficacy Endpoint

All exploratory efficacy analysis will be presented based on the mITT, mITT-OL, and mITT populations, for DB, OLE, and Overall Treatment periods, respectively, unless otherwise specified.

5.4.3.1. Pulmonary Function Tests

Pulmonary function tests related exploratory efficacy endpoints are FVC (mL), FEV1 (mL), ppFEV1 (%), FEV1/FVC (mL/mL), and ppDLco (%) at Week 26.

The observed values and change from baseline at each post-baseline visit will be summarized by treatment for DB period, by treatment sequence for OLE period, and by treatment sequence for Overall Treatment period.

The following will also be summarized at each analysis visit (Section 4.12) for DB period, OLE period, and Overall Treatment period separately:

- The frequency and percentage of subjects within the following categories for change from baseline in ppDLco:
  - $\geq 5\%$
  - $\geq 7.5\%$
  - $\geq 10\%$
  - $\geq 15\%$

In addition, the MMRM analysis will be performed for FVC, FEV1, ppFEV1, FEV1/FVC, and ppDLco, respectively, during the DB period, in a similar manner as for ppFVC. The MMRM analysis with random intercept and slope as described in Section 5.4.2.1 will also be performed for the listed parameters.

A listing of all pulmonary function tests will be provided for the ITT Population.

5.4.3.2. Patient Reported Outcomes (PROs)

The PROs related exploratory endpoints are SGRQ, KSQ domains other than Lung, mKSQ Lung, LCQ, SGA, and BSGIC at Week 26. The PROs will be summarized at each visit, when taken, by treatment group and overall for mITT population in DB period and in Overall Treatment period, by treatment sequence and overall for mITT-OL population in OLE period.

St. George's Respiratory Questionnaire (SGRQ)

SGRQ consists of 2 parts (Part 1: symptom, questions 1 to 8, and Part 2: activity and impact, questions 9 to 17). Three component scores (Symptoms, Activity, and Impacts) are calculated for the SGRQ. Each scale is scored from 0 to 100, with higher scores indicating more limitations. The total score will be calculated as weighted average of these three sub-scores.

Each domain score and the total score will be summarized by visit.

King's Sarcoidosis Questionnaire Domains other Than Lung Domain

The KSQ consists of five modules: General health status (10 items, items 1-10), , Medication (3 items, items 26-28), Skin (3 items, items 29-31) and Eye (7 items, items 32-38) will be scored following the same two-conversion process than for the KSQ Lung domain Section 5.4.2.4 and Appendix 4.

- General Health Status (GHS) domain logit 1-100 score
- Lung domain logit 1-100 score
- GHS Lung combined domain logit 1-100 score
- Medication domain logit 1-100 score
- Skin domain logit 1-100 score
- Eye domain logit 1-100 score

The logit scores and re-scores for each domain above will be summarized by visit.

Modified King's Sarcoidosis Questionnaire Lung Domain

The KSQ was modified by expanding the Lung domain with 9 items hereafter referred to as expanded Lung items (items 17 to 25). These items were tested and removed as part of the original KSQ validation work (Patel, 2013) and added back in this study for exploratory purpose. The questionnaire with the expanded Lung domain is referred to as the Modified KSQ or mKSQ. Scoring will be done separately for the expanded Lung domain of the mKSQ. Since there is no validated conversion scoring method for the expanded Lung domain item raw scores will be used and totaled into a mKSQ Lung domain raw score.

The raw scores for items below will be summarized by each item and combined scores:

- Expanded Lung–raw score: individual items from 11 to 25
- Lung–raw score: Items 11 to 16 combined
- Expanded Lung-raw score: Items 17 to 25 combined
- Lung and Expanded Lung-raw score: Items 11 to 25 combined

King's Sarcoidosis Questionnaire Derived Domains

The raw scores of the items in each group below will be converted into re-scores and totaled at the domain level.

- Fatigue-KSQ:
  - Item 2
  - Item 3
  - Item 4
  - Item 10
  - Item 4 and 10 combined
  - Item 2, 3, 4, and 10 combined
- Aches and Pains-KSQ:
  - Item 6

The raw scores and re-scores will be summarized for Fatigue-KSQ and Aches and Pains-KSQ items.

Subject Global Assessment (SGA)

The SGA consists of 2 questions. The frequency of outcome of each question will be summarized by visit. The shift table by visit will also be provided.

Leicester Cough Questionnaire (LCQ)

The LCQ consists of 19 questions for 3 domains: Physical (1,2,3,9,10,11,14, and 15), Psychological (4,5,6, 12,13,16, and 17), and Social (7,8,18, and 19), with scores ranging from 1 to 7 for each question and the higher score indicated better health status. The domain score will be calculated as the mean scores for all questions within the domain. If more than 20% of items are missing within one domain, the domain score will be set as missing. The total score will be the sum of the 3 domain scores. If at least one domain score is missing, the total score will not be calculated.

As an exploratory analysis, the raw score of items or the mean of the items in the groups below will be summarized:

- Fatigue-LCQ:
  - Q3
  - Q15
  - Q3 and Q15 combined

Bothersomeness and Subject Global Impression of Change (BSGIC)

The BSGIC consists of one lead question, two scales of bothersomeness, and one question for severity of symptoms. The scales and change from baseline will be summarized by the most

bothersome symptom at baseline. The frequency and percentage of severity of symptoms will be summarized for each visit.

5.4.3.3. OCS Use

Cumulative OCS use and other OCS use-related endpoints in DB and OLE periods, separately and combined, are exploratory endpoints.

All OCS dosing during the study, regardless of the indication of the OCS treatment, will be included in the summaries of OCS use. The days of corticosteroids use via other route (excluding inhaled and topical CS), such as subcutaneous, intravenous, will be considered as CS use when deriving CS free related endpoints (the 4th to 8th endpoints listed below), but the dose of corticosteroids use other than oral dose will not be used in the calculation. Prednisone equivalent dose will be used for the analysis of OCS use, where applicable. The endpoints will be summarized for the periods (as defined in Section 4.2) and population as described below:

- Cumulative OCS Dose (mg) = the sum of all administered OCS doses per subject during the corresponding period
- OCS Dose Intensity (mg/day) = Cumulative OCS dose (mg) / (Number of days of OCS dosing) during the corresponding period
    - Number of days of OCS dosing = ([date of last OCS dose – date of first OCS dose] + 1) – (number of OCS free days between the first and last OCS doses) during the corresponding period
- Number and percentage of subjects who successfully complete the taper during the corresponding period for subjects with baseline OCS dose > 5 mg
- Number and percentage of subjects who achieving CS free during the corresponding period for subjects with OCS dose use at baseline
- Number and percentage of subjects who starting/achieving CS free during the period and stay CS free until the end of the corresponding period for all subjects
- Number and percentage of subjects who starting/achieving CS free during the period and stay CS free without rescue event and clinical relevant decline (as defined in Section 5.4.3.4) for all subjects
- CS free days during the corresponding period for all subjects
- Proportion of CS free days = CS free days / Number of days during the corresponding period

Achieving OCS dose ≤ 5 mg will be considered as completion of taper.

The cumulative OCS dose and OCS dosing intensity will be summarized for:

- DB, OLE, and Overall Treatment periods for mITT, mITT-OL, and mITT populations, respectively

- DB period for subjects with baseline OCS dosing > 0 mg/day in mITT Population
- After starting/achieving OCS dosing ≤ 5 mg/day in DB period for subjects with baseline OCS dosing > 0 mg/day in mITT Population
- DB period for subjects with baseline OCS free in mITT Population

The number and percentage of subjects who successfully complete the taper will be summarized for:

- DB and Overall Treatment period for mITT Population
- OLE period for subjects who needs taper during OLE period for mITT-OL Population

The number and percentage of subjects who achieving CS free will be summarized for:

- DB, OLE, and Overall Treatment periods for subjects with baseline OCS dosing > 0 mg/day in mITT, mITT-OL, and mITT populations, respectively
- OLE period for subjects who needs taper during OLE period for mITT-OL Population

The number and percentage of subjects who starting/achieving CS free during the period and stay CS free will be summarized for:

- DB period for mITT Population
- DB period for the subjects with baseline OCS dosing > 0 mg/day in mITT Population
- DB period for the subjects with baseline OCS free in mITT Population

CS free days and proportion of CS free days will be summarized for:

- DB, OLE, and Overall Treatment periods for mITT, mITT-OL, and mITT populations, respectively
- DB, OLE, Overall Treatment periods for subjects with baseline OCS dosing > 0 mg/day in mITT, mITT-OL, and mITT populations, respectively
- after starting/achieving OCS dosing ≤ 5 mg/day in DB period for subjects with baseline OCS dosing > 0 mg/day in DB, OLE, and Overall Treatment periods for mITT, mITT-OL, and mITT populations, respectively
- DB, OLE, and Overall Treatment period for subjects with baseline OCS free in mITT, mITT-OL, and mITT populations, respectively

Above summaries will also be performed for the subgroups below for DB period:

- IST usage at baseline (Yes, No)
- Baseline OCS dosage (≤ 5 mg/day, > 5 mg/day)

This study is not stratified by OCS use at baseline. If unbalanced OCS use at baseline is observed between placebo and namilumab treatment group, additional ad hoc analysis for OCS use may be performed.

5.4.3.4. Clinical Benefit Rate (CBR)

The Clinical Benefit Rate (CBR) during DB period is an exploratory endpoint. CBR is defined the proportion of subjects achieving at least two of the 4 following at the end of corresponding period:

- an improvement from baseline of ≥ 5% points in ppFVC
- an improvement from baseline of ≥ 5% points in ppDLco
- KSQ Lung Score improvement of ≥ 4 points
- successfully achieving OCS dose ≤ 5 mg/day and at least 5 mg decreased from baseline OCS dosing during the DB period for subjects who had OCS > 5mg/day at baseline or achieving CS free at the end of the corresponding period for subjects who had OCS ≤ 5 mg/day at baseline

without clinically relevant decline in any of these parameters and without rescue event prior to the end of the period. Clinically relevant decline will be defined as:

- a deterioration from baseline of ≥ 5% points in ppFVC
- a deterioration from baseline of ≥ 5% points in ppDLco
- KSQ Lung Score deterioration of ≥ 4 points
- an increasing of at least 5 mg/day OCS dosing after successfully achieving OCS dose ≤ 5 mg/day and at least 5 mg decreased from baseline OCS dosing during the DB period for subjects who had OCS > 5 mg/day at baseline or after achieving CS free for subjects who had OCS ≤ 5 mg/day at baseline

CBR will be computed for the two treatment groups as a proportion of subjects achieving CBR over the total number of subjects for the corresponding population at each planned timepoint.

CBR during the DB period will be compared between treatment groups using the CMH test, stratified by IST usage at baseline, and the corresponding 90% CI for the difference in CBRs between the two treatment groups will be calculated. The 90% CIs for the CBR for each of the treatment groups will be computed using Wilson (1927) method.

The frequency and percentage of CBR during OLE period and Overall Treatment period will be summarized.

5.4.3.5. Extrapulmonary Physician Organ Severity Tool (ePOST)

The change from baseline at Week 26 in ePOST is an exploratory endpoint.

At each assessment each of the 17 organs (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, and muscle and gastrointestinal) 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. If 3 or less scales are missing at a visit for a subject, the total score will be standardized by multiplying the sum of the scores in the x organs by17/x. If 4 or more scales are missing at a visit for a subject, the total score will not be calculated. The total score and change from baseline in total score will be summarized.

In addition, the following will be summarized by visit and by treatment group and overall for DB period and Overall Treatment period and by treatment sequence and overall for OLE period for the mITT and mITT-OL populations, respectively:

- Number of subjects with total score change from baseline ≤ -1 (at least one point improvement)
- Number of subjects with total score change from baseline = 0 (no change)
- Number of subjects with total score change from baseline ≥ 1 (at least one point worsening)
- Number of affected organs per subject

5.5. SAFETY ANALYSIS

The safety analysis will be summarized for Safety Population. Unless specified otherwise, the safety parameters will be summarized by DB period, and On-Namilumab period. The by visit summary will be provided for lab assessments, ECG, vital signs, and physical exams. In addition, treatment exposure, compliance, and TEAEs will be summarized for OLE period.

5.5.1. Extent of Exposure

The following will be calculated for treatment exposure by treatment group:

- Cumulative Dose (mg) = the sum of all administered doses per subject.
- Duration of Treatment (days) = (date of last dose – date of first dose) + 29, assuming the last dose covers 28 days of treatment.
- Dose Intensity (mg/day) = Cumulative dose (mg) / (Duration of treatment [days])
- Relative Dose Intensity = Dose intensity (mg/day) divided by the one-day equivalent dose (150 mg / 28 days = 5.35 mg/day) *100.

The number of doses, cumulative dose, duration of treatment, dose intensity, and relative dose intensity will be summarized using descriptive statistics for the Safety Population for DB period and Overall Treatment period, and for the Safety-OL Population for OLE period.

A listing of overall treatment exposure data, including the first and last dates of treatment will be presented together for the Safety Population. Further, study treatment administration data collected from the CRF will be listed for the Safety Population.

5.5.2. Study Treatment Compliance

The study treatment compliance during a period will be calculated as below:

- Study treatment compliance during a period = Actual doses administrated (in mg) during the period / (Number of planned doses during the period * 150 mg) * 100%

The study treatment compliance will be summarized using descriptive statistics for the Safety Population for DB and OLE periods, separately.

In addition, the study treatment compliance will be summarized categorically (<80%, >=80% to <= 125%, and >125%). Number and percentage of subjects who had missing dose (1 missing doses, >1 missing doses) during DB and OLE periods will also be summarized.

A listing of study treatment compliance will be presented for the Safety Population.

5.5.3. Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary (version 24.1, or later) and classified as either pre-treatment AEs or treatment–emergent AEs (TEAEs) as follows:

- Pre-treatment AEs are events that start prior to the start of treatment dosing.
- TEAEs are either events with start date on or after the start of the treatment dosing, or events with start date prior to the start of treatment dosing whose severity worsens on or after the start of treatment dosing. AEs that occur more than 18 weeks after the last study treatment will not be considered as TEAEs. AEs that occur on or after the date of the first dose of open-label study treatment will be considered AE for OLE period.
- Treatment-Emergent Serious AEs (TESAEs) will be defined as TEAEs regarded by the investigator as Serious = “Yes”.
- The relationship between a TEAE and treatment is assessed as definitely, possibly, unlikely, or not related. A treatment related TEAE will be defined as a TEAE considered by the investigator as definitely or possibly related to treatment. The unknown/missing relationship will be imputed as definitely related to treatment in the analysis.
- Assessment of AE severity / intensity will be based on investigator assessment of mild, moderate, or severe (including those events where severity/intensity is missing) in intensity.
- TEAEs leading to discontinuation of treatment are defined as TEAEs where “Primary Action Taken with Study Treatment” is indicated as “Drug Withdrawn”.

Adverse events will be summarized by default descriptive summary statistics for categorical variables for the Safety Population for DB period, Safety-ON Population for On-Namilumab period, and for the Safety-OL Population for OLE period as follows:

- An overview of TEAEs including the number and percentage of subjects with at least one of each mentioned TEAE type:

  - Any TEAE
    - Leading to discontinuation of study treatment
    - Mild
    - Moderate
    - Severe
  - Any study treatment related TEAE
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any TESAE
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any study treatment related TESAE
    - Leading to discontinuation of study treatment
    - Leading to death

In the above summaries, a subject will be counted only once in the three severity categories using the most severe TEAE among all TEAEs the subject experience.

- The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs for DB, OLE, and On-Namilumab periods separately:
  - All TEAEs
  - TEAEs Leading to Discontinuation of Study Treatment
  - TEAEs by Maximum Severity
  - TEAEs by Relationship to Treatment
  - Study Treatment Related TEAEs
  - Study Treatment Related TEAEs Leading to Discontinuation of Study Treatment
  - Study Treatment Related TEAEs Leading to Death
  - TESAEs
  - TESAEs Leading to Discontinuation of Study Treatment
  - TESAEs Leading to Death
  - Study Treatment Related TESAEs
  - Study Treatment Related TESAEs Leading to Discontinuation of Study Treatment
  - Study Treatment Related TESAEs Leading to Death
  - TEAEs with ≥ 5% Incidence Rate

    - Non-TESAEs

- The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by PT in descending frequency of number of subjects in total for DB, On-Namilumab, and OLE periods, respectively

In the above summaries, subjects with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one TEAE within a particular PT are counted only once for that PT, respectively.

For summaries by maximum severity, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. Similarly, for summaries by relationship to treatment, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of the most related TEAE with that SOC or PT.

Summaries by SOCs and PTs will be sorted by SOCs by their Internationally Agreed Order (MedDRA) and PTs within SOC by descending order of total incidence. Where preferred terms tie PTs will be sorted alphabetically.

No statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed and Pre-treatment AEs and TEAEs will be presented together. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment and will be presented for those subjects who received at least one dose of treatment. If the AE is “Ongoing” it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented:

- Listing of Deaths
- Listing of Serious TEAEs
- Listing of Related TEAEs
- Listing of AEs Leading to Interruption of Study Treatment
- Listing of AEs Leading to Discontinuation of Study Treatment
- Listing of AEs with PT=“Sarcoidosis”

5.5.4. Laboratory Evaluations

All laboratory test results will be received from the central laboratories. Data for the hematology, serum chemistry, lipid profile, and urinalysis analytes listed in the Table 6 are to be summarized.

Table 6. Safety Laboratory Tests and Exploratory Biomarker to Be Summarized

Category	Test
Hematology	Hematocrit, hemoglobin, platelet count, RBC, WBC with differentials (absolute and %), MCH, MCV, reticulocytes (absolute and %)
Chemistry	Albumin, ALP, ALT, AST, BUN, calcium, creatinine, eGFR, GGT, glucose, LDH, phosphorus, potassium, sodium, chloride, total bilirubin, bicarbonate, HbA1c, total protein, uric acid
Lipid Profile	Total cholesterol, triglycerides, HDL, LDL
Urinalysis	pH, specific gravity, glucose, occult blood, protein
Exploratory Biomarker	SP-D

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cells; SP-D = serum surfactant protein D; WBC = white blood cells.

All laboratory data will be reported in International System of Unit (SI) units. The laboratory test will be compared at each assessed timepoint with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For summaries which present worst value with respect to the reference range at the subject level, low and high are each chosen in preference to normal values. For parameters with both low and high reference ranges, subjects who have assessments within both low and high ranges will be counted within each category for worst value summary tables.

For glucose, occult blood, and protein from urinalysis, the frequency and percentage will be reported.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables for the Safety Population for DB period, and Safety-ON Population for On-Namilumab period, separately as follows:

- Observed values and change from baseline at each assessed visit for each standard continuous laboratory parameter
- Number and percentage of subjects with categorized shift (low, normal and high) values relative to the reference range at baseline compared to each post-baseline timepoint for hematology and serum chemistry
- Number and percentage of subjects with worst categorized (low, normal and high) values relative to the reference range
- Number and percentage of subjects at each assessed visit for each categorical laboratory parameter

In addition, the abnormal laboratory as defined in Table 7 will be summarized.

Table 7. Category for Abnormal Laboratory Assessments

Category	Criteria
Elevated Liver Function Test	• ALT > 3 × ULN • ALT > 5 × ULN • ALT > 10 × ULN • ALT > 20 × ULN • AST > 3 × ULN • AST > 5 × ULN • AST > 10 × ULN • AST > 20 × ULN • ALT or AST > 3 × ULN • ALT or AST > 5 × ULN • ALT or AST > 10 × ULN • ALT or AST > 20 × ULN • TBL > 2 × ULN • ALT or AST > 3 × ULN and TBL > 1.5 × ULN • ALT or AST > 3 × ULN and TBL > 2 × ULN • ALP > 1.5 × ULN • GGT > ULN • GGT > 2 × ULN • GGT > 3 × ULN
Neutropenia	• Absolute neutrophil count >= 1000 and < 1500 × 10^6 /L • Absolute neutrophil count >= 500 and < 1000 × 10^6 /L • Absolute neutrophil count < 500 × 10^6 /L

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transferase; TBL = total bilirubin; ULN = upper limit of normal.

Listings of all clinical laboratory data including change from baseline will be provided for the Safety Population. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low will be provided for applicable laboratory assessments.

5.5.5. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- systolic blood pressure (mmHg)
- diastolic blood pressure (mmHg)
- heart rate (bpm)
- respiration rate (breaths / min)
- body temperature (°C)

The following will be summarized for the Safety Population for DB period, and Safety-ON Population for On-Namilumab period, separately:

- Observed values and change from baseline at each assessed timepoint for each standard vital sign parameter using default summary statistics for continuous variables
- Observed values and change from pre-dose at each visit

A listing of all vital signs data including change from baseline will be provided for the Safety Population.

Vital signs assessed at Unscheduled visit and Early Termination (ET) visit will not be summarized because the multiple assessments (pre-dose and post-dose assessments) are expected at dosing visits.

5.5.6. Electrocardiograms

The following ECG assessments will be taken during the study:

- An overall investigator assessment classified as normal, abnormal, not clinically significant, and abnormal, clinically significant
- Heart rate (bpm)
- RR interval (msec)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- Fridericia corrected QT interval (QTcF) (msec)

The ECG findings will be summarized by treatment group and overall for the Safety Population as follows:

- Observed values and change from baseline at each assessed timepoint for each ECG parameter from external vendor data transfer using default summary statistics for

continuous variables. If multiple ECG assessments are performed on the same day, the average of all assessments in the same day will be used for summary.

- The ECG overall assessment as reported by the investigator on CRF will be summarized at each assessed timepoint by providing number and percentage of subjects within each assessment category. If multiple overall assessments are collected on the same day, the most severe overall assessment will be used for summary.

The ECG prolongation as described in Table 8 based on QTcF as in will also be summarized.

Table 8: Criteria for ECG prolongation

Category	Criteria
Absolute QTc interval prolongation	• QTcF > 450 msec • QTcF > 480 msec • QTcF > 500 msec
Change from baseline in QTc interval	• QTcF increases from baseline > 30 msec • QTcF increases from baseline > 60 msec

Note: QTcF = corrected QT interval by Fridericia.

A listing of all ECG data including change from baseline will be provided for the Safety Population.

5.5.7. Physical Examination

For each physical examination body system, the number and percentage of subjects with abnormalities at baseline and at each assessed timepoint will be summarized for the Safety Population.

Physical examination abnormalities at screening will be recorded on the Medical History CRF and post-baseline abnormalities will be recorded as AEs. Physical examination findings (normal/ abnormal) and details of abnormalities will be listed for each subject at each assessed timepoint for the Safety Population.

5.6. Analysis of Pharmacokinetic Assessments

Pharmacokinetic (PK) samples will be collected prior to the study treatment administration at Weeks 0, 2, 6, 14, 26, 38, and 54, and at Week 27 (about 5 days after the Week 26 dosing). PK concentration will be summarized by visit during the DB period, and by treatment sequence during On-Namilumab period for PK Population. Only the concentration collected while subjects taking namilumab will be summarized.

The PPK and E-R analyses will be performed and reported separately.

5.7. Analysis of Biomarker Data

The biomarker listed in Table 9 will be summarized.

Table 9. Efficacy-Related Biomarker Parameters to Be Summarized

Category	Parameters
Disease specific biomarkers	GM-CSF, IFNγ, sIL-2R, IL-6, IL-15, CXCL10, SAA, TNFα
Pathway specific biomarkers	IL-1β, IL-4, IL-27, CXCL9
Other biomarkers	hsCRP, VEGFA, MMP1, MMP3

Note: CXCL = C-X-C motif chemokine ligand; GM-CSF = granulocyte-macrophage colony-stimulating factor; hsCRP = high-sensitivity C-reactive protein; IL = interleukin; MMP = matrix metalloproteinase; SAA = serum amyloid A; sIL-2R = soluble Interleukin-2 Receptor;

Note: hsCRP and SAA will be summarized using CLS data. The assessments for other parameters will be summarized using OLINK data.

Baseline, change from baseline for biomarkers listed in Table 9 will be summarized using descriptive statistics (mean, median, SD, standard error (SE), interquartile range (IQR), minimum, maximum) at each visit by treatment group and overall during the DB period, and by treatment sequence and overall during the OLE period and Overall Treatment period for Biomarker Population. In addition, percentage change from baseline will be summarized similarly for SAA and hsCRP. The difference of change from baseline between the two treatment groups and corresponding 90% CI based on t-test will also be presented for DB period.

The biomarkers will also be summarized by subgroups as follows:

- Rescue event status during the DB period (Yes, No)
- Achieving OCS free and stay OCS free during DB period (yes, no)

The hsCRP and SAA will also be summarized by subgroups as for primary efficacy endpoint for DB period.

The correlation will be calculated as described below between each of the biomarkers and each of the following efficacy endpoints: KSQ Lung domain score, KSQ General Health domain score, ppFVC, FEV1, and ppDLco. The corresponding scatter plots will also be generated.

- biomarker at baseline vs. efficacy endpoint at baseline
- biomarker at baseline vs. change from baseline in efficacy endpoint at each post baseline visit (Week 6, 14, 26)
- change from baseline in biomarker at Week 26 vs. change from baseline in efficacy endpoint at Week 26 (for subject who had rescue event during DB period, the last pair of biomarker and efficacy endpoint at the same visit prior to rescue censoring date will be used for the calculation)

Additional analysis for cytokine, chemokine, and other sarcoidosis biomarkers, correlation between biomarkers and additional baseline characteristics, correlation between biomarkers and other efficacy assessments, correlation between biomarkers and PK, and correlation between biomarkers and ADA, will be described in a separate document and will be reported separately

from the clinical study report (CSR). Proteomic analysis will be conducted by both targeted, pre-specified protein assessment for proteins known to be associated with either sarcoidosis or GM-CSF signaling, and by hypothesis free methodologies as described in the separate biomarker analysis plan.

5.8. ANALYSIS OF IMMUNOGENICITY DATA

ADA status will be determined using a tiered testing strategy. Samples that confirm positive for ADA will be titered. The number and percentage of of development of ADA (i.e., positive, negative, or not tested) will be summarized by visit and by treatment group during DB period, and by treatment sequence during On-Namilumab period for Immunogenicity Population. The number and percentage of subject overall ADA status (positive, negative, or not tested) during DB period, and On-Namilumab period will also be summarized by treatment and treatment sequence, respectively, for Immunogenicity Population. Overall ADA positive is defined as at least one positive ADA during the corresponding period. Only the ADA status assessed while subjects taking namilumab will be summarized. ADA titer may also be summarized if data allowed.

Additional immunogenicity analyses, if any, will be described in a separate report from the CSR.

6. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

No changes from the Protocol Amendment 2 (Version 3.0, dated 13MAY2024).

7. APPENDICES

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 1.0, Final, 06 June 2024	Not applicable; the first version
Version 2.0, Final, 29 August 2024	• Added sensitivity analysis using random slope for pulmonary functions and KSQ to utilize all collected assessments. • Clarified using the unstratified Chan and Zhang method as sensitivity analysis for primary efficacy endpoint. • Updated sample codes for primary analysis. • Clarified the rules establishing the date for censoring the efficacy assessment data. • Added by region subgroup analysis. • Clarified KSQ and mKSQ score calculation and planned summary. • Clarification and minor edits throughout the document.

Appendix 2: Handling of Partial and Missing Dates for Date of Birth, Adverse Events, Prior / Concomitant Medications

Missing or Partial Adverse Event and Prior / Concomitant Medication Start Dates

Missing and / or incomplete dates for medications and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the study up to the date of last study treatment, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication or AE is "Ongoing". Technically, this imputation will be done as follows:

For a missing / incomplete start date the earliest date of the following will be imputed:

- The later date of the earliest possible start date, and the date of first dose of treatment.
- The latest possible start date.
- The latest possible stop date.

For a missing / incomplete stop date the later date of the following will be imputed:

- The earlier date of the latest possible stop date and the date of last dose of treatment.
- The earliest possible stop date.
- The earliest possible start date.

Here, the earliest possible date is defined as:

- The date itself if available.
- The date of the first day of the month at 00:00 hrs, if month and year are available but the day is missing.
- The date of the first day of the year at 00:00 hrs, if year is available but day and month are missing.
- 00:00 hrs on the day of informed consent, if the date is completely missing.

The latest possible date / time is defined as:

- The date itself if available.
- The date of the last day of the month at 23:59 hrs, if month and year are available but the day is missing.
- The date of the last day of the year at 23:59 hrs, if year is available but day and month are missing.
- 23:59 hrs on the date of last known date on the study for the subject plus one year, if the date is completely missing.

Appendix 3: Steps to Perform Tipping Point Analysis

Proportion of subjects with rescue event for worsening of sarcoidosis

The steps to perform the tipping point analysis for the proportion of subjects with rescue event for worsening of sarcoidosis are as follows:

1. The MI imputation method will be performed to impute missing data as MNAR for the analysis.
2. All imputed rescue event status for each subject with missing outcome during the DB period will be penalized by adding a penalty of shift parameter, δ, e.g., 0.1%, in each complete dataset. One hundred complete datasets for each shift parameter will be simulated.
3. The primary analysis modelling approach will be performed using the same MNAR in each completed dataset.
4. Results will be combined across complete datasets using PROC MIANALYZE.

Change from baseline in ppFVC

The steps to perform the tipping point analysis for change from baseline ppFVC are as follows:

1. The MI imputation method will be performed to impute missing data as MNAR for the analysis.
2. All imputed ppFVC values at Week 22 and 26 will be penalized by adding a penalty of shift parameter, δ, e.g., 0.1, in each complete dataset.
3. The primary analysis modelling approach will be performed using the same MNAR in each completed dataset.
4. Results will be combined across complete datasets using PROC MIANALYZE.

Table 10: Seeds to Be Used for Multiple Imputation

Case	Seed
Rescue - MI	11565
Rescue - tipping point	95299
ppFVC - MI	4423
ppFVC - tipping point	80172

Sample code for multiple imputation:

```
proc MI data=midata out=midataout seed=12345 nimpute=100;
  class TRT01PN ISTuse Rescue;
  var ISTuse Rescue;
  FCS reg (ISTuse Rescue);
run;
```

For multiple imputation for ppFVC, use statement:

```
FCS reg (ISTuse WK00 WK06 WK14 WK22 WK26)
```

For control-based multiple imputation, use statement:

```
MNAR model (TRT01PN ISTuse Rescue / modelobs=(TRT01PN='0');
```

For tipping point analysis, use statement:

```
MNAR adjust (TRT01PN ISTuse Rescue / shift = # adjustobs=(TRT01PN='1'));
```

where # is the shift parameter, and will be determined based on the observed results.

Appendix 4: KSQ Scoring

The KSQ scoring (excluding items 17 to 25) was validated (Patel, 2013). The domain scores will be calculated using a two-conversion process as per King's scoring guide and described below.

First the raw score for each question is converted into a re-score (Table 11).

Table 11. Table for Converting Raw Scores to Re-scores

		Raw Scores						
Domain	**Items**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
GHS	**1**	0	1	2	3	3	4	4
	2	0	1	2	3	4	5	6
	3	0	1	1	2	2	3	3
	4	0	1	2	3	4	5	6
	5	0	1	2	2	3	3	3
	6	0	0	1	1	1	2	2
	7	0	0	0	1	2	2	3
	8	0	0	1	1	1	2	2
	9	0	0	1	1	1	2	2
	10	0	0	1	1	1	2	2
Lung	**11**	0	1	2	3	4	4	5
	12	0	1	2	3	4	5	6
	13	0	1	2	3	4	5	6
	14	0	1	2	3	4	5	6
	15	0	1	2	3	4	5	6
	16	0	1	2	3	4	4	5
Expanded Lung	**17**	**NA**						
	18							
	19							
	20							
	21							
	22							
	23							
	24							
	25							
Medication	**26**	0	1	2	2	2	3	3
	27	0	1	2	2	2	3	3
	28	0	0	1	1	1	1	2
Skin	**29**	0	1	2	2	2	3	4
	30	0	1	1	2	2	2	3
	31	0	0	1	1	1	2	2
Eyes	**32**	0	0	1	1	1	2	2
	33	0	1	2	2	2	2	3
	34	0	1	2	2	2	3	3
	35	0	0	1	1	1	2	2
	36	0	0	1	1	1	2	2

		Raw Scores						
Domain	**Items**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
	37	0	0	0	1	1	2	3
	38	0	0	1	1	1	1	2

Abbreviations: GHS = general health domain score; mKSQ = Modified King's Sarcoidosis Questionnaire; NA = Not Applicable

Then the re-scores are totaled for each domain (Lung, General Health, GH-Lung combined, Medication, Skin, and Eyes) and converted into domain level logit 1-100 scores (Table 12)

Table 12. Table for Converting Domain Re-score Totals to Domain Logit 1-100 Scores

Lung		GH		GH-Lung		Medication		Skin		Eyes	
Re-score Total	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**
0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
1	10.4	1	9.3	1	11.6	1	14.5	1	13.7	1	11.3
2	17.5	2	15.7	2	19.0	2	26.8	2	25.4	2	19.6
3	22.3	3	20.2	3	23.8	3	37.2	3	35.4	3	25.8
4	26.0	4	23.8	4	27.2	4	47.0	4	44.7	4	31.0
5	29.0	5	26.7	5	29.9	5	56.5	5	53.8	5	35.5
6	31.4	6	29.4	6	32.0	6	66.9	6	63.3	6	39.7
7	33.6	7	31.7	7	33.8	7	80.9	7	73.7	7	43.5
8	35.5	8	33.9	8	35.4	8	100.0	8	86.1	8	47.2
9	37.2	9	36.0	9	36.7			9	100.0	9	50.6
10	38.8	10	38.0	10	38.0					10	54.0
11	40.2	11	39.9	11	39.1					11	57.5
12	41.6	12	41.7	12	40.1					12	61.1
13	42.9	13	43.5	13	41.0					13	65.2
14	44.2	14	45.3	14	41.9					14	70.1
15	45.5	15	47.1	15	42.8					15	76.4
16	46.7	16	48.9	16	43.5					16	85.8
17	47.9	17	50.7	17	44.3					17	100.0
18	49.1	18	52.5	18	45.0						
19	50.2	19	54.3	19	45.7						
20	51.4	20	56.2	20	46.4						
21	52.6	21	58.0	21	47.0						
22	53.8	22	59.9	22	47.7						
23	55.1	23	61.9	23	48.3						
24	56.4	24	63.9	24	48.9						
25	57.8	25	66.1	25	49.5						
26	59.3	26	68.4	26	50.1						

Lung		GH		GH-Lung		Medication		Skin		Eyes	
Re-score Total	Logit 1-100 Score	Re-score Total	Logit 1-100 Score	Re-score Total	Logit 1-100 Score	Re-score Total	Logit 1-100 Score	Re-score Total	Logit 1-100 Score	Re-score Total	Logit 1-100 Score
27	61.0	27	70.9	27	50.7						
28	62.9	28	73.6	28	51.2						
29	65.2	29	76.7	29	51.8						
30	68.0	30	80.3	30	52.4						
31	71.7	31	84.7	31	52.9						
32	77.1	32	91.0	32	53.5						
33	85.8	33	100.0	33	54.1						
34	100.0			34	54.6						
				35	55.2						
				36	55.8						
				37	56.4						
				38	56.9						
				39	57.5						
				40	58.1						
				41	58.7						
				42	59.3						
				43	59.9						
				44	60.5						
				45	61.2						
				46	61.8						
				47	62.5						
				48	63.2						
				49	63.9						
				50	64.7						
				51	65.4						
				52	66.2						
				53	67.1						
				54	68.0						
				55	68.9						
				56	69.9						
				57	71.0						
				58	72.1						
				59	73.3						
				60	74.7						
				61	76.2						
				62	77.9						

Lung		GH		GH-Lung		Medication		Skin		Eyes	
Re-score Total	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**	**Re-score Total**	**Logit 1-100 Score**
				63	80.0						
				64	82.6						
				65	86.1						
				66	91.5						
				67	100.0						

Abbreviations: GH = general health; KSQ = King's Sarcoidosis Questionnaire

Appendix 5: Rescue Events Review Process

Purpose

This document outlines the process and rules for an internal review committee for the purpose of defining rescue events for this study. This study has two periods: a) a double-blind (DB), placebo-controlled period; b) a follow-on open-label extension (OLE), single arm, active treatment period.

The primary end point for the study has been defined as the proportion of subjects having a rescue event from randomization until the end of the DB period. A defined secondary endpoint will be the time to first rescue event during the DB period. Rescue events will also be collected and summarized in the OLE period.

The design of this study requires that subjects stop immunosuppressant therapies (ISTs) at randomization and oral corticosteroids (OCS) to be tapered according to a protocol-defined algorithm (Protocol Version 3.0 Appendix 7). A similar approach allows for continued withdrawal of these concomitant medications in the OLE period.

The purpose of the review committee is to identify and adjudicate, where needed, the presence of the rescue events in the ITT population. This document summarizes the role and responsibility of the review committee, the definitions used in identifying rescue events including the time to rescue and the date at which time the efficacy assessments data, including the PRO data, will be censored, consistent with the protocol, the SAP, and the process of rescue events review.

Definition of Rescue Events

Rescue events will fall into 2 broad categories:

A) Subjects with worsening sarcoidosis requiring rescue treatment.
B) Subjects failing to follow protocol defined concomitant sarcoidosis medication requirements (OCS taper/IST removal/prohibited medication).

Each subject with a rescue event (and a time to event) will be defined by one of the following sub-categories described in Table 13.

Censoring rules

The date at which point the efficacy assessment data will be censored will be defined for each rescue event according to the rules described in Table 13. This date will be referred to as the censoring date.

When there is multiple recue events in the study for any given subject, the earliest of the censoring dates will be used for censoring the efficacy assessments data, including the PRO data.

Table 13: Rescue Event Categories and Definitions

CATEGORY A	CATEGORY B
A. Worsening sarcoidosis (pulmonary or extra-pulmonary)	**B. Failure to follow protocol defined concomitant medications (OCS tapering/IST/prohibited medication use)**
A1 Defined as: A rescue visit form completed irrespective of rescue treatment given **Rescue event date:** Rescue visit date on the rescue form or start of treatment given, whichever occurs first **Censoring date[1]:** The rescue treatment start date + 1 day.	**B1 Defined as:** Not achieving taper goal ≤ 5 mg/day prednisolone (or equivalent) by: - end of Week 6 (= Day 49) for subjects on 6-10 mg/day at randomization - end of Week 10 (=Day 77) for subjects on dose 11-25 mg/day at randomization **Rescue event date:** a) Day 50 for subjects on 6-10 mg/day at randomization b) Day 78 for subjects on 11-25 mg/day at randomization **Censoring date[3]:** a) Day 57 for subjects on 6-10 mg/day at randomization who do not meet the taper goal by Day 56 b) Day 85 for subjects on 11-25 mg/day at randomization who do not meet the taper goal by Day 84
A2 Defined as: Treatment Discontinuation due to or perceived lack of efficacy **Rescue Event date:** Day of decision to discontinue treatment **Censoring date[2]:** The date of the last dose + 57 days.	**B2 Defined as:** Increased corticosteroid use (allowed up to 14 days) for treatment of non-sarcoidosis-related intercurrent event during the formal taper period, not achieving taper goal ≤ 5 mg/day prednisolone equivalent by: - end of Week 6 (= Day 49) + 14 days for subjects on 6-10 mg/day at randomization - end of Week 10 (= Day 77) + 14 days for subjects on dose 11-25 mg/day at randomization **Rescue event date:** a) Day 64 for subjects on 6-10 mg/day at randomization b) Day 92 for subjects on 11-25 mg/day at randomization **Censoring date[3]:** a) Day 71 for subjects on 6-10 mg/day at randomization who do not meet the taper goal by Day 70 b) Day 99 for subjects on 11-25 mg/day at randomization who do not meet the taper goal by Day 98
	B3 Defined as: Increased use of corticosteroid for > 14 days for treatment of non-sarcoidosis-related intercurrent

CATEGORY A	CATEGORY B
	event with a total daily dose > 5 mg/day prednisone equivalent and after 14 days, OCS dose is not back to the dose-level of the day prior to temporary OCS increase, regardless of that prior dose (including 0 mg). **Rescue event date:** 15th day of increased of OCS use **Censoring date[3]:** 22nd day of increased of OCS if OCS dosing is not back to dose prior to the increase at Day 21.
	B4 Defined as: IST continuation post- randomization for more than 7 days, or start of IST or prohibited anti-inflammatory medications for a non-sarcoidosis-related event or for a minor change in sarcoidosis associated symptoms. **Rescue event date:** a) Day 8 for subjects on IST at randomization and the IST was not stopped b) Day of start of IST/anti-inflammatory medication **Censoring date:** a) Rescue event date b) Day of start of IST/anti-inflammatory medication + 1 day[1].
	B5 Defined as: Increase of OCS to a level > 5 mg not otherwise identified with a rescue page or a specified intercurrent illness (e.g., subject lack of compliance) **Rescue event date:** Day of increase in OCS > 5 mg **Censoring date[1]:** Date of increase in OCS > 5 mg + 1 day

1: The censoring date is 1 day after the start or increase date of OCS as intended to treat sarcoidosis/inflammatory disease. This 1-day window allows for analysis of the efficacy assessments performed on the same day of the start of the rescue treatment.

2. The censoring date is 8 weeks +1 day after the last dose, equivalent to the period in which rescue events are analyzed

3: The censoring date is 7 days after the rescue visit date. This is a "grace" period to allow for unintended delay in meeting the taper goal or stopping the IST as per protocol.

Committee Members

The review committee will consist of the Kinevant Chief Medical Officer, Head of Clinical Development, Lead Clinical Scientist (or the interim or acting persons in those roles) and

identified consultants, and will work by consensus. Kinevant Data Management and/or Statistical Programing will provide the necessary blinded data for review to the committee.

Process

The committee will review on an ongoing basis all rescue events that occur in the DB and OLE periods for each subject. A tracker will be used, on a per subject basis, to collect all information necessary (as described above) to define the presence of a rescue event. Every attempt will be made to identify these by programing of the database.

Rescue events will be identified via the Rescue eCRF form and by reviewing relevant patient information (including, but not limited to discontinuations, concomitant medications and adverse events). However, it is understood that there will be situations where the presence or absence of a rescue event is indeterminant and clinical judgement will be needed. For these occurrences, a conservative approach will be used; if a subject is considered indeterminate for a rescue event, the subject will be considered to have had a rescue event. If the subject meets rescue event criteria in multiple categories, the earliest rescue event will be recorded.

The censoring date will be defined for each event as part of the adjudication process and recorded in the rescue tracker.

A subset of this information will be provided for the formal analysis as a 'Final Rescue Event Summary' for each study period before the corresponding database freeze/lock. Prior to unblinding for DB period and before completion of OLE period, the output of the adjudication process will be reviewed as "complete and valid" by the Kinevant Statistical Director (or acting) and signed off jointly by the Kinevant Statistical Director and Review Committee.

After approval of the SAP, any changes to this review process will be documented as an addendum. Additionally, after SAP approval, any critical issues discussed by the review committee will be documented and placed in the trial master file.

Appendix 6: SGRQ Score Calculations

The SGRQ consists of 17 questions (Symptoms: questions 1 – 8, Activity: questions 11 and 15, and Impacts: questions 9, 10, 12-14, 16, 17).

To calculate component score, the answer to each question will be converted to weighted score as in Table 14. For questions 11 to 16, a negative response will be assigned a weighted score of 0, and a positive response will be assigned a weighted score as in the table.

The symptoms raw score will be calculated as the sum of weighted scores for questions 1 to 8. If more than 2 items are missing, the symptoms score will be set as missing.

The activity raw score will be calculated as the sum of weighted scores for questions 11 and 15. If more than 4 items are missing, the activity score will be set as missing.

The impacts raw score will be calculated as the sum of weighted scores for questions 9, 10, 12 to 14, 16, and 17. If more than 6 items are missing, the impact score will be set as missing.

The final score for each component will be calculated as 100*(component raw score)/(sum of the highest possible weights for all items in the component). If the missing items are within tolerated range, the weight for missed item is subtracted from the total possible weight.

If all three component scores are not missing, the total score will be calculated as (sum of three component raw scores)/(sum of the highest possible weights for all items in the component).

Table 14: Weighted Score for SGRQ

Questions and Answers	Weighted Score
Part 1	
1) Over the past 3 months, I have coughed:	
Most	80.6
Several	63.2
A few	29.3
Only	28.1
Not	0
2) Over the past 3 months, I have brought up phlegm (sputum):	
Most	76.8
Several	60
A few	34
Only	30.2
Not	0
3) Over the past 3 months, I have had shortness of breath:	
Most	87.2
Several	71.4
A few	43.7

Only	35.7
Not	0
4) Over the past 3 months, I have had attacks of wheezing:	
Most	86.2
Several	71
A few	45.6
Only	36.4
Not	0
5) How many times during the past 3 months have you suffered from severe or very bad unpleasant attacks?	
More than three	86.7
3 attacks	73.5
2 attacks	60.3
1 attack	44.2
None	0
6) How long did the worst attack of chest trouble last?	
a week or more	89.7
3 or more days	73.5
1 or 2 days	58.8
less than a day	41.9
7) Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?	
None	93.3
1 or 2	76.6
3 or 4	61.5
nearly every day	15.4
every day	0
8) If you have a wheeze, is it worse in the morning?	
No	0
Yes	62
PART 2	
9) How would you describe your chest condition?	
The most important problem I have	83.2
Causes me quite a lot of problems	82.5
Causes me a few problems	34.6
Causes no problem	0
10) If you have ever had paid employment?	
My chest trouble made me stop work	88.9
My chest trouble interferes with my work or made me change my work	77.6

My chest trouble does not affect my work	0
11) Questions about what activities usually make you feel breathless.	
Sitting or lying still	90.6
Getting washed or dressed	82.8
Walking around the home	80.2
Walking outside on the level	81.4
Walking up a flight of stairs	76.1
Walking up hills	75.1
Playing sports or games	72.1
12) More questions about your cough and breathlessness.	
My cough hurts	81.1
My cough makes me tired	79.1
I get breathless when I talk	84.5
I get breathless when I bend over	76.8
My cough or breathing disturbs my sleep	87.9
I get exhausted easily	84
13) Questions about other effects your chest trouble may have on you.	
My cough or breathing is embarrassing in public	74.1
My chest trouble is a nuisance to my family, friends or neighbours	79.1
I get afraid or panic when I cannot get my breath	87.7
I feel that I am not in control of my chest problem	90.1
I do not expect my chest to get any better	82.3
I have become frail or an invalid because of my chest	89.9
Exercise is not safe for me	75.7
Everything seems too much of an effort	84.5
14) Questions about your medication.	
My medication does not help me very much	88.2
I get embarrassed using my medication in public	53.9
I have unpleasant side effects from my medication	81.1
My medication interferes with my life a lot	70.3
15) Questions about how activities may be affected by your breathing.	
I take a long time to get washed or dressed	74.2
I cannot take a bath or shower, or I take a long time	81
I walk more slowly than other people, or I stop for rests	71.7
Jobs such as housework take a long time, or I have to stop for rests	70.6
If I walk up one flight of stairs, I have to go slowly or stop	71.6
If I hurry or walk fast, I have to stop or slow down	72.3

My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf	74.5
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	71.4
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	63.5
16) We would like to know how your chest trouble usually affects your daily life.	
I cannot play sports or games	64.8
I cannot go out for entertainment or recreation	79.8
I cannot go out of the house to do the shopping	81
I cannot do housework	79.1
I cannot move far from my bed or chair	94
17) Tick the statement which you think best describes how your chest affects you.	
It does not stop me doing anything I would like to do	0
It stops me doing one or two things I would like to do	42
It stops me doing most of the things I would like to do	84.2
It stops me doing everything I would like to do	96.7

Appendix 7: Schedule of Assessments:

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**															

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]**
MRC	**X**															
mKSQ		**X**							**X**				**X**			
SGA		**X**							**X**				**X**			
SGRQ and LCQ		**X**							**X**				**X**			
BSGIC		**X**											**X**			
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	**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]**
auto-antibody																
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			
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			

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]
Randomization		X														
Administration of study drug[g]		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 Protocol 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

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 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			
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 Protocol 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.

8. REFERENCES

ICH. *Structure and Content of Clinical Study Reports*, Guideline E3, 1995. Available at https://database.ich.org/sites/default/files/E3_Guideline.pdf

ICH. *Statistical Principles for Clinical Trials – Scientific Guideline* E9, 1998.

ICH. *Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* E9(R1), 2021.

Patel AS, Siegert RJ, Creamer D, Larkin G, Maher TM, et al. 2013. The development and validation of the king's sarcoidosis questionnaire for the assessment of health status. Thorax. Jan;68(1):57-65.

Chan ISF & Zhang Z. 1999. Test based exact confidence intervals for the difference of two binomial proportions. Biometrics, 1999: 55(4):1202-9.

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