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Mallinckrodt ARD, Inc.

MNK14344100

A Multicenter, Randomized, Double Blind, Placebo Controlled Exploratory Study to Assess the Efficacy and Safety of Acthar® Gel in Subjects with Pulmonary Sarcoidosis

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Draft Statistical Analysis Plan

Version 3.0

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List of Abbreviations

6MWT	Six-Minute Walk Test
AE	adverse event
ANOVA	analysis of variance
AR1	first-order autoregressive
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CXR	chest x-ray
CS	Compound Symmetry
DLCO	Diffusing capacity of the lungs for carbon monoxide
ECG	electrocardiogram
eCRF	electronic case report form
ePOST	extrapulmonary Physician Organ Severity Tool
FAS	Fatigue Assessment Scale
FEF	forced expiratory flow
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
Hb	hemoglobin
HbA1c	hemoglobin (glycosylated)
HRCT	high-resolution computed tomography
IMP	investigational medicinal product
KSQ	King's Sarcoidosis Questionnaire
LCQ	Leicester Cough Questionnaire
LLoQ	lower limit of quantitation
LOCF	last observation carried forward
LS	least square
MMRM	mixed model with repeated measures
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
PEFR	peak expiratory flow rate
PFT	pulmonary function test

PT	preferred term
RV	residual volume
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SE	standard error
SI	International System of Units
SOC	system organ class
STS	sarcoidosis treatment score
TEAE	treatment-emergent adverse events
TLC	total lung capacity
TTR	time to response
ULoQ	upper limit of quantitation
UN	unstructured
VA	alveolar volume
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

1. Introduction

The purpose of the Statistical Analysis Plan (SAP) is to describe the analyses and data presentations for the Sponsor's protocol MNK14344100. This SAP outlines the types of analyses that will address the study objectives and explains in detail how the data will be handled and analyzed. It contains the definitions of analysis populations and statistical methods for the analysis of safety and efficacy.

2. Study Objectives

The objective of the study is to evaluate the efficacy and safety of Acthar® Gel (Acthar) in the treatment of pulmonary sarcoidosis.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 4, multicenter, randomized, double-blind, placebo-controlled exploratory study evaluating the efficacy and safety of Acthar in the treatment of pulmonary sarcoidosis. The study will have 3 phases: screening (up to 28 days); double-blind treatment (Visit 2 to Visit 8, 24 weeks); and an optional open-label extension (Visit 9 to Visit 11, 24 weeks). A follow-up visit will be conducted at 4 weeks (± 2 days) after the last dose of investigational medicinal product (IMP) is administered.

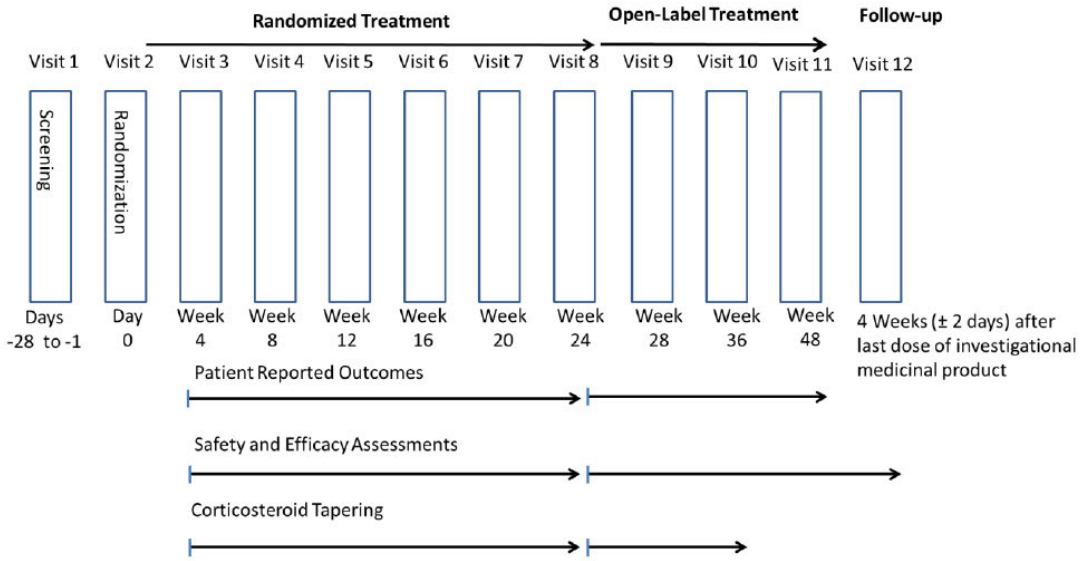
An overview of the study is presented in Figure 1.

Subjects who meet all eligibility criteria will be randomly assigned to receive either 1 mL (80 U) of Acthar or 1 mL of a matching placebo subcutaneously (SC) twice weekly. Following the completion of the double-blind phase, subjects will be invited to continue participation in an optional Open-label Extension Phase (Visit 9 to Visit 11, 24 weeks). Subjects who decline participation in the open-label extension phase, or those ineligible, will have their End-of-Treatment visit during Visit 8.

Dose reduction of 50% may be implemented once during the study if a subject meets one of the prespecified safety criteria (refer to protocol Section 9.1). Once dose reduction is implemented, subjects will remain on the 40 U or matching placebo twice weekly for the remainder of the study.

The schedule of study events is presented in Appendix 15.3.

Figure 1: Study Overview



Note: Visit 8 is the primary efficacy evaluation time point. Additional analyses of long term efficacy and safety of subjects participating in the Open-label Extension Phase will be conducted at the completion of Visit 12. PFT and sample collection for assessment of biomarkers will be performed every 12 weeks. HRCT will be performed at Screening (Visit 1) and every 24 weeks thereafter (Visits 8 and 11).

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

The endpoints for the efficacy objective are:

- Sarcoidosis treatment score (STS) response rate at 24 weeks (Visit 8).
- STS response rate at 48 weeks (Visit 11).
- Physician and subject independent responses to the question "Would you choose to continue current treatment?" at 24 and 48 weeks.
- Time to response (TTR) as evaluated at earlier time points (Weeks 4 to 20) as determined by the investigator based on clinical judgment and the following parameters:
    - Patient reported outcomes.
    - Corticosteroid tapering.
    - Patient Global Assessment.
    - Physician Global Assessment

  - Pulmonary function test (PFT) at applicable time points.
  - Extrapulmonary response by extrapulmonary Physician Organ Severity Tool (ePOST).
  - Supportive efficacy endpoints per applicable time points.
    - Six-minute walk test (6MWT).
    - Symptom relief (Leicester Cough Questionnaire, Medical Research Council Dyspnea Scale, steroid toxicity questionnaire).
    - Chest x-ray (CXR) (including Scadding score).

- Percentage change in overall diffusion capacity of the lung for carbon monoxide (DLCO).
- Percentage of subjects with improvement in DLCO of ≥ 5%; ≥10%; and ≥ 15%.
- Percentage change in overall forced vital capacity (FVC).
- Percentage of subjects with improvement in FVC of ≥ 5%, ≥10%, and ≥ 15%.
- Percentage of subjects with improved/stable/deteriorate side-by-side comparison of high-resolution computed tomography (HRCT) on a 5-point Likert score: much worse; worse; unchanged; better; much better (central reader).
- Percentage of subjects with improved/stable/deteriorated side-by-side comparison of CXRs on a 5-point Likert score: much worse; worse; unchanged; better; much better (central reader).
- Percentage change in Scadding score (side-by-side comparison of CXRs by a central reader).
- Percentage change in patient-reported outcomes and symptom questionnaires.
- Percentage failed corticosteroid taper.
- Time to failed corticosteroid taper (for subjects failing taper).
- Change from baseline in Work Productivity and Activity Impairment (WPAI) over time

3.2.2. Biomarker and Genetic Endpoints

Biomarkers levels will be compared between baseline, and every 12 weeks (up to 48 weeks for those subjects participating in the optional open-label extension phase). Serum aliquots will be kept for each of these time points. Possible biomarkers include angiotensinogen, sIL-2R and vitamin D 1, 25. The final selection of biomarkers will be made based on the scientific knowledge and emerging guidance closer to the completion of the study.

Genomic profile (optional) will be assessed based on the understanding of genetic factors at the time of study completion.

3.2.3. Safety Endpoints

Overall safety will be determined by the incidence, severity and relationship of AEs, physical examinations, vital signs, clinical laboratory abnormalities, and imaging.

4. General Statistical Considerations

4.1. Sample Size

Formal sample size calculations were not performed. The sample size is based on recent literature of comparative studies (Gibson et al., 1996; Baughman et al., 2006; Judson, 2014) in sarcoidosis. There are 55 subjects randomized to this study.

4.2. Randomization, Stratification, and Blinding

An interactive telephone/web response system will be used to allocate eligible subjects to each treatment group. Subjects will be randomized according to computer-generated allocation scheme to receive either Acthar Gel 1 mL (80 U) or placebo 1 mL administered twice a week in a 1:1 ratio. Both investigators and the subjects will be blinded to the treatment assignment. A block randomization will be performed.

4.3. Reporting Conventions

The following reporting conventions apply generally to tables, listings, and figures:

- All by-visit summaries and analyses will be provided separately for the double-blind treatment phase and the open-label extension phase, unless otherwise specified. Only subjects who continued to the open-label extension phase will be included in the summaries of open-label extension phase based on the open-label safety populations.

- For subjects who continued into the open-label extension phase, the first dose of IMP at the open-label extension phase will be used as the cutoff date. Since the first dose administration date at the open-label extension phase is not collected electronically, and the dosing schedule is twice/week, either the first IMP kits and equipment dispense date or the next date after completion date of double-blind phase, whichever is the later date, has been used as the best estimate of the first dose of IMP in the open label extension phase. The assessments collected before the cutoff date will be summarized in the double-blind treatment phase and the assessments collected on or after the cutoff date will be summarized in the open-label extension phase, unless specified otherwise. Subjects who did not continue into the open-label extension phase will be summarized in the double-blind treatment phase only.
- Summaries for the double-blind treatment phase will be based on the treatments that the subjects actually received at the double-blind treatment phase. Summaries for the open-label extension phase will also be based on the treatment sequences that the subjects actually received during overall study phase, e.g. Acthar/Acthar and Placebo/Acthar.
- Study Day 1 is defined as the date of the first dose of IMP at the double-blind treatment phase. Study days are calculated as the difference between the date of interest and Study Day 1 plus 1 day. For events before Study Day 1, study days will be calculated as the difference in days between Study Day 1 and the date of interest. The day before the date of the first dose at the double-blind treatment phase will be defined as Day -1. This means there will be no study Day 0.
- Two baselines, baseline of overall study and baseline of active treatment, have been defined. Baseline of overall study is defined as the last assessment prior to the first dose of IMP at the double-blind treatment phase. Baseline of active treatment is defined as the last assessment prior to the first dose of active treatment in either the double-blind treatment phase or the open-label extension phase. All the analysis in the open-label extension phase that involves presenting change and/or percent change from baseline will present change/percent change from both baselines.
- Summary statistics will be provided for all study variables with descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum,

and maximum) for numerical (or continuous) variables. Frequency and percentages will be calculated for categorical variables.

- Unless specified otherwise for a given analysis, all statistical tests, when applicable, will be 2-sided with a significance level of 0.05.
- All data collected will be presented in listings, sorted by treatment group, subject identifier and date/time of procedure or event, if applicable.

All analyses will be conducted using SAS® Version 9.4 or higher. The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 will be used for coding adverse events (AEs), and medical and surgical histories. Prior or concomitant medication data will be coded according to the Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) Drug Dictionary (Enhanced B2 dated March 2018 version, or higher) level 2 term.

4.4. Analysis Populations

4.4.1. Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) Population includes all randomized subjects who receive at least 1 dose of IMP and who contribute any efficacy data to the study. The mITT Population will be used for the efficacy analyses based on the treatment they actually received during double-blind treatment phase.

4.4.2. Safety Population

The Safety Population includes all randomized subjects who receive at least 1 dose of IMP and will be used for all the safety analyses which will be based on the actual treatment received at the double-blind treatment phase.

4.4.3. Open-label Safety Population

The Open-label Safety Population includes subjects who continue into open-label extension phase and receive at least one dose of IMP during the open-label extension phase. The Open-label Safety Population will be used for all the safety and efficacy analyses for open-label extension phase and will be based on the actual treatment sequences received during the overall study phase (Acthar/Acthar or Placebo/Acthar) and total.

5. Subject Disposition

A summary of analysis populations will be presented by treatment group and total for all randomized subjects, the mITT population, the safety population, and open-label safety population. Summary of subject disposition will be presented for double-blind treatment phase and open-label extension phase separately.

Disposition of all randomized subjects in double-blind treatment phase will be summarized by treatment group and total descriptively, including summaries of the number and percentage of subjects who completed the double-blind treatment phase, subjects who continued into the open-label extension phase, subjects who early terminated from the double-blind treatment phase and the reasons for early termination from the double-blind treatment.

In addition, disposition of subjects participating in the optional open-label extension phase will be summarized by actual treatment sequences and total descriptively, including summaries of the number and percentage of subjects who completed the double-blind treatment phase, subjects who continued into the open-label extension phase, subjects who completed the open-label extension phase, and subjects who early terminated from the open-label extension phase. The reasons for early termination from the open-label extension will also be summarized.

The reasons for early termination from the double-blind treatment and the reasons for early termination from the open label extension will be summarized based on the following categories:

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Met withdrawal criteria
- Non-compliance with study drug
- Physician decision
- Protocol violation
- Study terminated by sponsor

- Withdrawal by subject
- Other

Subject disposition for all randomized subjects and subject disposition for open-label safety population will be provided in by-subject listing, respectively.

6. Protocol Deviations

The significant protocol deviations will be summarized by category using frequency tabulations based on the safety population in the double-blind treatment phase and on open-label safety population in the open-label extension phase separately. The cut off of two study phases has been defined in reporting conventions section 4.3. Listings of significant protocol deviations will be provided to support the summary tables.

7. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and total using the mITT population and safety population in the double-blind treatment phase and open-label safety population in the open-label extension phase. Individual subject listings will be provided to support the summary tables for all randomized subjects in the double-blind phase.

7.1. Demographics

Descriptive statistics will be provided for the following continuous variables collected at baseline:

- Age (year)
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2) as recorded on the electronic case report form (eCRF)

The number and percentage of subjects will be provided for the following categorical variables:

- Sex (Male, Female)

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Unreported)
- Female Fertility Status (Surgically Sterile, Post-Menopausal, Childbearing potential)

A female fertility status listing will be provided for all randomized subjects.

7.2. Baseline Disease Characteristics

The following baseline disease characteristics and disease history will be summarized:

- Smoking history (Current Smoker; Ever Smoked, and Never Smoked)
- Current Employment Status (Full Time, Part Time, Retired, Home Maker, and Not Employed)
- Ever Employed/Worked (Yes, No)
- Organs involved in sarcoidosis (A subject may have more than one organ involved in sarcoidosis. The subject will be counted for each organ.)
- Occupational History (Exposure to Mold, Bacteria or Other Microbial Contaminants, Fumes, Asbestos, Wood Burning Smoke, Insecticide, Silicates, Metal Dust or Inorganic Dust, Aerosols, Inorganic Particulate, and Other) and duration of exposure to each type in years
- Time from sarcoidosis diagnosis (months)

Time from sarcoidosis diagnosis in months will be calculated as:

(date of screening - date of sarcoidosis diagnosis + 1)/30.4375.

Sarcoidosis history, smoking history and occupational history data for all randomized subjects will be provided in listings.

Disease characteristics for the subjects who enrolled in the open-label extension phase may be summarized using open-label safety population.

7.3. Medical and Surgical History

Medical and surgical history will be summarized by system organ class (SOC) and preferred term (PT) for the safety population. A subject will be counted only once within

each level of SOC and PT. Percentages are based on the number of subjects within each treatment group. SOC will be presented alphabetically and PTs within each SOC will be presented in decreasing order of frequency calculated based on the Acthar treatment group.

Medical and surgical history data for all randomized subjects will be presented in a listing.

8. Treatments and Medications

Study treatments, medications and sarcoidosis specific medications will be summarized by treatment group and total based on the safety population in double-blind treatment phase and then open-label safety population in the open-label extension phase, respectively. Descriptive statistics will be provided for continuous variables and frequency counts and percentages will be applied to categorical variables. Missing or partially missing start/stop dates for prior/concomitant medications will be imputed in order to justify prior/concomitant status, refer to Appendix 15.1.2 for imputation details.

8.1. Prior and Concomitant Medications

All prior and concomitant medications will be coded using the WHO Drug dictionary. Prior medications are defined as all non-study medications that were started before the start of the study treatment and either ended before the start of the study treatment or continued into the study treatment period.

Concomitant medications in the double-blind treatment phase are non-study medications that are ongoing during the double-blind treatment phase or with a start date occurring before the first dose of IMP in the open label extension phase.

Concomitant medications in the open-label extension phase are non-study medications that are ongoing during the open-label extension phase or with a start date occurring on or after the first dose of IMP at the open label extension phase.

Medications initiated prior to the first dose of IMP at the open-label extension phase and were continued into the open-label phase will be counted into both phases.

Prior and concomitant medications will be summarized separately. Concomitant medications will be summarized by the double-blind and the open-label phase separately. The tables will present the number and percentage of subjects by WHO ATC level 2 and preferred drug name for each treatment group and total. ATC level 2 will be presented alphabetically, while preferred drug name within each ATC level 2 will be presented in decreasing order of frequency calculated based on the Acthar treatment group. In addition,

the number and percentage of subjects receiving at least one prior or concomitant medication will be presented. A subject with multiple occurrences of a drug class or drug is counted only once in the ATC 2 level or preferred drug name, respectively.

All prior and concomitant medications for safety population will be presented in listings by study phases.

8.2. Prior and Concomitant Sarcoidosis Medications

The prior and concomitant sarcoidosis meditations will be summarized by preferred drug name for each treatment group and total. Concomitant sarcoidosis medications will be summarized by the double-blind and the open-label phase, respectively.

8.3. Study Treatments

Study treatments and extent of exposure summaries will be provided based on the safety population in the double-blind treatment phase and the open-label extension phase, respectively. Descriptive statistics will be provided for treatment duration, number of injections, dose reduction and justifications for dose reduction by study phases.

A listing for each study phase will be provided for drug accountability and treatment compliance, respectively.

8.3.1. Extent of Exposure

Treatment duration of double-blind treatment phase (weeks) is defined as:

[(date of last dose at double-blind treatment phase) – (date of first dose at double-blind treatment phase) + 1]/7.

Treatment duration of open-label extension phase (weeks) is defined as:

[(date of last dose at open-label extension phase) – (date of first dose at open-label extension phase) + 1]/7,

Descriptive statistics will be provided for treatment durations by treatment group and total.

8.3.2. Treatment Compliance

During each visit, the number of injections that a subject was expected to take and the number of injections that a subject actually took since previous visit until prior to the current visit will be recorded on the eCRF.

Treatment compliance (%) of double-blind treatment phase is defined as:

$$\frac{(\text{Number of injections taken during double-blind treatment phase}) \times 100}{\text{Number of injections expected to be taken during double-blind treatment phase}}$$

Treatment compliance (%) of open-label extension phase is defined as:

$$\frac{(\text{Number of injections taken during the duration open-label extension phase}) \times 100}{\text{Number of injections expected to be taken during open-label extension phase}}$$

The study drug compliance rate in the double-blind treatment phase, and compliance rate in the open-label extension phase will be summarized by treatment group using the descriptive statistics. The compliance rates will also be summarized by categories (<80, 80 to <=120, and >120).

9. Efficacy Analysis

All efficacy evaluations will be conducted using the mITT population unless otherwise specified and will be provided by treatment group for the double-blind treatment phase. Efficacy evaluations will only be summarized descriptively using the open-label safety population by treatment group and total for the open-label extension phase. All summaries and analyses will be conducted on the observed values unless otherwise specified. All efficacy data will be presented in listings based on the mITT population in the double-blind treatment phase and based on the open-label safety population in the open-label extension phase. The derived efficacy variables will be displayed in data listings as well.

Additional subgroup analyses by sex, race and ethnicity will be performed on missing imputed data as specified. Other exploratory analyses may be performed as appropriate.

9.1. Sarcoidosis Treatment Score (STS)

STS is a newly developed composite score that combines the results of PFT, chest imaging, quality of life, and changes in corticosteroid dosing. Individuals may score from -6 to + 6. Higher scores indicate improvement. Subjects tolerating Acthar Gel (or placebo) will be categorized as Response, Partial Response, and Non Response. STS can be determined by using the assessments categories as presented in table below.

Table 1: Determining the Sarcoidosis Treatment Score

	Parameter	Improved	Unchanged	Deteriorate
Category of Assessment		+1	0	-1
PFT[a]	FVC	≥ 5%	> -5% to < 5%	≤ -5%
	DLCO	≥ 5%	> -5% to < 5%	≤ -5%
Imaging	HRCT	Improved	Unchanged	Worse
Quality of Life	King's Sarcoidosis Questionnaire (General Health)	≥ 4	> -4 to < 4	≤ -4
	Fatigue Assessment Score	≤ -4	> -4 to < 4	≥ 4
	Corticosteroid taper (dosage)	≥ 50% reduction	< 50% reduction or ≥ 5 mg increase for less than 2 weeks	≥ 5 mg increase for more than 2 weeks

[a]Absolute change of % predicted.

Subject tolerating Acthar (or placebo) will be categorized according the following scoring:

- Response is defined as scores of ≥ 3/6 points.
- Partial Response is defined as scores of 2/6 points or stable with corticosteroid reduction (ie, a total score of +1 due to ≥ 50% reduction in corticosteroid dosage).
- Non Response is defined as scores of ≤ 1/6 points without significant corticosteroid taper (stable or deterioration).

An STS responder is defined as a subject who has an assessed STS category of Response or Partial Response at 24 weeks (Visit 8) during double-blind treatment phase and at 48 weeks (Visit 11) during open-label phase.

The descriptive statistics for developed STS scores, number and percentage of subjects in each STS response category (response, partial response and non response) will be provided at both 24 weeks (Visit 8) and 48 weeks (Visit 11). At 24 weeks (Visit 8) during double-blind treatment phase, the proportions of STS responder (defined as response or partial response) and non-responder, and corresponding odds ratio will be calculated. The 95% confidence interval (CI) of the odds ratio will be calculated as well based on asymptotic method. Pearson's chi-square test (or Fisher's exact test if any expected count is less than 5) will be used to assess the comparability between treatment groups for the STS responder

vs. non-responder rate. At 48 weeks (Visit 11) during open-label phase, the proportions of STS responder and non-responder along with 95% CI will be provided. The 95% CI will be calculated by using the exact (Clopper-Pearson) method.

Missing STS scores will be imputed at 24 weeks (Visit 8) during double-blind treatment phase. Last observation carried forward (LOCF) method will be employed to impute missing component(s) if any component of STS is missing at the post-baseline visit during double-blind treatment phase. If there is still missing component(s) after applying LOCF imputation method, STS score will remain as missing. Subjects who do not provide data (after component level LOCF imputation) to allow classification as responders will be considered non-responders, that is, missing data will be imputed as non-responder. The same missing data imputation method will be applied to other similar efficacy endpoints in double-blind treatment phase. No imputation will be applied to the open-label extension phase. A bar plot of STS category will be provided at 24 weeks (Visit 8) during double-blind treatment phase and at 48 weeks (Visit 11) during open-label phase, respectively.

Sensitivity analyses with using only the observed data will be performed for the above analysis at 24 Weeks (visit 8) only.

Subgroup analyses by sex, race and ethnicity will be performed in similar manner as specified above on the imputed data only.

STS component scores including FVC % Predicted Score, DLCO % predicted Score, HRCT Score, King's Sarcoidosis Questionnaire (KSQ) General Health Score, Fatigue Assessment Score and Corticosteroid Taper Score will be summarized. Number and percentage of subjects in each category (Improved, Unchanged and Deteriorate) of each STS component score presented in Table 1 will be provided at 24 weeks (Visit 8) and at 48 weeks (Visit 11). Pearson's chi-square test (or Fisher's exact test if any expected count is less than 5) will be used to assess the comparability between treatment groups for each STS component at 24 Weeks (visit 8) only.

Listings of STS components and STS scores will be provided by study phases. Subjects with any missing component of STS will be indicated.

In addition, correlation analysis between STS score and each of its components and/or other assessments (e.g. Six-Minute Walk Test, Physician Global Assessment, ect.) may be performed based on the data from both study phases. Pearson or Spearman correlation coefficients and the corresponding p-values will be generated depending on the distribution

of the data. The data may also be presented in scatter plots with regression line, correlation coefficient and p-value annotated.

9.2. Physician and Subject Independent Response to Continue to Current Treatment

The number and percentage of physician and subject independent response (Yes, No) to the question "Would you choose to continue current treatment?" at week 24 (Visit 8) and at week 48 (Visit 11) will be summarized by treatment group. The response rate of "Yes" between treatment groups will be tested using Pearson's chi-square test (or Fisher's exact test if any expected count is less than 5), for both physician and subject at week 24 (Visit 8) only. In the double-blind phase only, missing response will be imputed as "No".

Physician and subject independent response to continue current treatment will be provided in a listing by study phase.

9.3. Pulmonary Function Tests

Descriptive statistics of observed and change from baseline will be presented for PFT results including DLCO % predicted and FVC % predicted at each scheduled visit during double-blind treatment phase and open-label extension phase, respectively. In addition, change from baseline of active treatment will be presented for open-label extension phase.

The treatment difference between Acthar and placebo for change from baseline to each visit in the double-blind treatment phase in DLCO % predicted and FVC % predicted will be evaluated using a two-sample T-test. Change in DLCO % predicted and FVC % predicted will be plotted in line graph over time showing the means and SEs by visit across both study phases.

Also, the treatment effect for the change from baseline to each scheduled visit in the double-blind treatment phase in DLCO % predicted and FVC % predicted will be estimated using a mixed effect model with repeated measures (MMRM) model. The MMRM model will use change from baseline as the response variable, and include visit, treatment group, and visit-by-treatment group interaction as covariates. Additionally, visit (categorical) will be specified as a repeated effect and unstructured (UN) correlation matrix will be used to model intra-subject correlation. In case a convergence issue will arise using the UN correlation matrix, (1) first-order autoregressive (AR1) or (2) Compound Symmetry (CS) will be used to enable model convergence (in this order). The least square (LS) mean difference with 95% CI and p-value will be presented.

In addition, improvement in DLCO % predicted and FVC % predicted will be explored by using criteria (≥ 5%, ≥ 10% and ≥ 15%, respectively). Number and percentage of subjects with improvement will be provided at each scheduled visit by double-blind treatment phase and open-label extension phase. Pearson's chi-square test (or Fisher's exact test if any expected count is less than 5) will be used to compare the treatment difference between treatment groups in the double-blind treatment phase. The following endpoints will be included:

- Percentage of subjects with improvement in DLCO % predicted of ≥ 5%
- Percentage of subjects with improvement in DLCO % predicted of ≥10%
- Percentage of subjects with improvement in DLCO % predicted of ≥ 15%
- Percentage of subjects with improvement in FVC % predicted of ≥ 5%
- Percentage of subjects with improvement in FVC % predicted of ≥10%
- Percentage of subjects with improvement in FVC % predicted of ≥ 15%

Percentage of subjects in each treatment group meeting each improvement criterion will be analyzed using both imputation and data as observed methods in double-blind treatment phase, and using data as observed method only in the open-label extension phase. For the analysis using imputation, mITT subjects without an evaluable assessment for the criterion will be considered as no improvement for that criterion. For the analysis of data as observed, mITT subjects without an evaluable assessment for the criterion will be excluded from the analysis for that criterion.

Other PFT assessments including FEV1, FVC, FEV1/FVC ratio, PEFR or FEF_{max}, TLC, RV, DLCO (uncorrected for Hb) and DLCO/VA if available will be summarized by using descriptive statistics for observed and change from baseline at the scheduled visits during double-blind treatment phase and open-label extension phase. The treatment difference between Acthar and placebo for change from baseline to each visit in the double-blind treatment phase will be evaluated using a two-sample T-test.

A listing will be provided for the PFT data by subject and visit.

9.4. Imaging

9.4.1. HRCT and CXR

Imaging (HRCT and CXR) will be evaluated by the investigator/radiologist and the central reader to determine if the condition is improving, stable, or deteriorating based on a 5-point Likert score: much worse; worse; unchanged; better; much better at week 24 (Visit 8) and week 48 (Visit 11). Data from central reader will be analyzed and listed. Data from investigator/radiologist will only be listed.

Response (improved, stable, and deteriorate) based on the side-by-side comparison of HRCT and CXR is defined as:

Response	**Likert Score**
Improved	Better; Much Better
Stable	Unchanged
Deteriorate	Much Worse; Worse

The number and percentage of subjects for each Likert score will be summarized for each treatment group by visits, along with number and percentage of subjects with each response of improved, stable, and deteriorate for HRCT and CXR, respectively. The percentage will be calculated based on number of subjects in each treatment group. A bar plot of responses will also be provided.

Pearson's chi-square test (or Fisher's exact test if any expected count is less than 5) will be used to compare the treatment difference between treatment groups for the proportion of subjects with response of improved vs. not improved, and the proportion of subjects with response of not deteriorate vs. deteriorate at week 24 (Visit 8) for HRCT and CXR separately. Subjects who have missing assessments at the visit will be imputed as opposite outcome for the given categorization, i.e. missing response will be imputed as not improved or deteriorate, as applicable.

A secondary analysis will then be performed by only including subjects with assessments evaluated. The percentage of subjects in each category will be calculated based on number of subjects with assessments in each treatment group at each scheduled visit (Visit 8 and Visit 11).

9.4.2. Scadding Score

The number and percentage of subjects for each Scadding score (Stage 0, Stage I; Stage II; Stage III; and Stage IV) will be summarized at week 24 (Visit 8) and week 48 (Visit 11) by treatment group. Pearson's chi-square test (or Fisher's exact test if any expected count is less than 5) will be used to compare the treatment difference between treatment groups.

The Scadding score will be converted to numeric score in the following manner:

0 - Stage 0

1 - Stage I

2 - Stage II

3 - Stage III

4 - Stage IV

Descriptive statistics of observed, change from baseline and percentage change from baseline values will be presented by treatment group at week 24 (Visit 8) and week 48 (Visit 11) for the Scadding score. Baseline of active treatment, change from baseline and percentage change from baseline values will be presented as well for week 48 (Visit 11). Note that the percentage change will not be calculated for subjects with Scadding score stage 0 at baseline.

The treatment difference between Acthar and placebo for both change from baseline and percentage change from baseline to week 24 (Visit 8) in Scadding score will be evaluated using a Wilcoxon rank sum test.

A listing will be provided for the imaging data and Scadding score by subject and visit.

9.5. Patient-Reported Outcomes and Symptom Questionnaires

Descriptive statistics of observed, change from baseline and percentage change from baseline values will be provided at scheduled visits during double-blind treatment phase and open-label extension phase, respectively. Descriptive statistics of baseline of active treatment, change and percentage change from baseline of active treatment values at visits in open-label extension phase will be provided additionally. The change from baseline and percentage change from baseline values to each visit will be analyzed using similar statistical methodology for all patient-reported outcomes and symptom questionnaires unless specified otherwise at visits during double-blind treatment phase.

The patient-reported outcomes and symptom questionnaires will include the following:

- Total score of Steroid Toxicity Questionnaire where lower scores indicate better status.
- Scores of each of the 5 King's Sarcoidosis Questionnaire Modules (General Health Status, Lung, Medication, Skin, and Eyes) where higher scores indicate improvement.
- Total scores of each of the 4 King's Sarcoidosis Questionnaire overall scales (Lung Health Status [General Health Status module and Lung module], Skin Health Status [General Health Status module and Skin module], Eye Health Status [General Health Status module and Eye module], Lung-Skin Health Status [General Health Status module, Lung module and Skin module]) where higher scores indicate improvement and a change of 4 points is considered clinically meaningful.
- Total score of Fatigue Assessment Scale where lower scores indicate improvement and a change of 4 points is considered clinically meaningful.
- Patient's Global Assessment where higher scores indicate better status.
- Physician Global Assessment where higher scores indicate better status.
- Medical Research Council Dyspnea Scale where lower scores indicate better status.
- Total score and each score of the 3 domains (Physical, Psychological and Social) of Leicester Cough Questionnaire where higher scores indicate better health status.
- Work Productivity and Activity Impairment (WPAI)

Calculation for above scores are provided in Appendix 15.2.

The treatment difference between Acthar and placebo for both change from baseline and percentage change from baseline to visits in the double-blind treatment phase in each outcome or questionnaire score will be evaluated using a two-sample T-test. Wilcoxon rank sum test may be used if the data are not normally distributed. Percentage change in King's Sarcoidosis Questionnaire and Fatigue Assessment Scale will plotted in line graph over time showing the means and SEs. For WPAI data, only a listing will be provided.

If result is missing at a post-baseline visit, the missing result will be imputed using the LOCF method. No imputation will be applied to the open-label extension phase. All

summaries and analyses will be conducted on both the observed values and the LOCF values.

Listings will be provided for each patient-reported outcome and symptom questionnaire by subject and visit.

9.6. Six-Minute Walk Test (6MWT)

Descriptive statistics of observed and change from baseline values at week 24 (Visit 8) and descriptive statistics of observed, change from baseline values, change from baseline of active treatment at week 48 (Visit 11) will be summarized by treatment group for the following measurements:

- Total Distance Walked
- Number of Laps
- Number of Rests

The number and percentage of subjects will be provided at scheduled visits by treatment group for the following categorical measurements:

- Supplemental Oxygen Used (Yes, No) prior to the 6MWT, upon completion of the 6MWT and 1 Minute after walk
- Limiting Factors to Walk (SOB, LOW Sp02, Heart Disease, Desaturation <80%, Other)

The treatment difference between Acthar and placebo for change from baseline in each assessment will be evaluated using a two-sample t-test for week 24 (Visit 8) only. A listing will be provided for the 6MWT data by subject and visit.

9.7. Extrapulmonary Physician Organ Severity Tool (ePOST)

The ePOST examines 17 extrapulmonary organs (Lung excluded) and assigns a score to each one (0 = not affected to 6 = very severely affected). The adjusted overall score will be derived as the sum of the ePOST score for each extrapulmonary organ divided by the number of extrapulmonary organs involved at any time by visit during the study.

The ePOST score assigned for each individual extrapulmonary organ will be summarized categorically using number of subjects and percentage with score from 0 (not affected) to 6 (very severe) for each treatment group by visits.

The adjusted overall score, changes from baseline and percent change from baseline, and changes and percent change from baseline of active treatment (open-label extension phase only) to each scheduled visit will be summarized by treatment group using descriptive statistics.

A listing will be provided for the ePOST data by subject and visit.

9.8. Corticosteroid Tapering

The number and percentage of subjects who have dose adjustment and justifications for dose change will be summarized at each scheduled visit by treatment group and study phase. Descriptive statistics will be provided for doses and doses change from baseline at each scheduled visit. All corticosteroid dose will be converted to prednisone equivalent dose. Additionally, weekly average prednisone or equivalent daily dose (mg/day) will be calculated from prior and concomitant medication data for prednisone collected prior to week 4 (Visit 3) and post week 48 (Visit 11) and corticosteroid use data collected between week 4 (Visit 3) and week 48 (Visit 11). The average weekly daily dose change and percent change from baseline, and change and percent change from baseline of active treatment to week (from week 25 to week 48 in open-label phase only) will be summarized descriptively by weeks from week 1 to week 24 in double-blind phase and from 25 to week 48 in open-label phase. The line plots of mean (+/- standard error) percent change of average weekly daily dose from baseline by weeks will be provided for double-blind treatment phase and overall study phase.

Subjects whose corticosteroid dosage increased for more than 2 weeks will be considered as failing to corticosteroid taper. Pearson's chi-square test (or Fisher's exact test if any expected count is less than 5) will be used to compare the treatment difference between treatment groups for the percentage of subjects who fail corticosteroid taper in double-blind treatment phase only.

Time to failing corticosteroid taper is defined as:

Time to failing corticosteroid taper (day) = date of failing corticosteroid taper - date of first dose + 1.

Time to failing corticosteroid taper will be summarized by descriptive statistics by treatment group for subjects who fail corticosteroid taper.

A listing will be provided for the corticosteroid use by subject and visit.

10. Safety Analysis

All safety analyses will be conducted using safety population for the double-blind treatment phase and open-label safety population for the open-label extension phase separately. No imputation will be applied for missing data on any safety results. Missing or partially missing adverse event start dates will be imputed for treatment-emergent AE (TEAE) justification, refer to Appendix 15.1.1 for imputation details. All safety data will be presented in listings based on the safety population in the double-blind treatment phase and in the open-label extension phase, respectively.

10.1. Adverse Events

An AE is any untoward or undesirable medical occurrence in a subject who is administered an IMP, which does not necessarily have to have a causal relationship with this treatment.

A TEAE is defined as an event that begin or worsen on or after the start of study drug through 30 days after the date of the last dose. The first dose of IMP at the open-label extension phase will be used as cutoff date, the TEAEs started before the cutoff date will be summarized in the double-blind treatment phase and the TEAES started on or after the cutoff date will be summarized in the open-label extension phase; Subjects who did not continue into the open-label extension phase will be summarized in the double-blind treatment phase only.

If a subject experience the same AE more than once with different severity, then the event with the highest severity level will be tabulated in “by severity” tables. If a subject experience the same AE more than once with different relationship to study drug, then the event with the most related level will be tabulated in “by relationship” tables. Note that AEs with a missing severity will be considered as severe, and AEs with missing relationship will be considered as related to study drug. Adverse events are considered treatment-related if the relationship to study drug is possibly related, related or missing.

The incidence of AEs will be summarized in tables with the number and percentage of subjects with AEs by SOC and PT. At each level of SOC or PT, a subject with multiple events will only be counted once per SOC or PT. Percentages of subjects with AEs will be calculated out of the number of subjects in the safety population. SOC will be presented alphabetically and PTs within each SOC will be presented in decreasing order of frequency based on the total number of subjects with each AE in the Acthar group. The following categories of TEAE will be summarized by SOC and PT by treatment group and total for the double-blind treatment phase and the open-label extension phase separately:

- TEAEs
- TEAEs by severity (Mild, Moderate, and Severe)
- TEAEs by relationship (Not Related, Unlikely Related, Possibly Related, and Related)
- Treatment related TEAEs
- Serious TEAEs
- Serious TEAEs by relationship (Not Related, Unlikely Related, Possibly Related, and Related)
- TEAEs leading to study drug discontinuation
- TEAEs leading to death

Overview tables of the above categories will also be provided.

All AEs will be presented in a data listing by study phase and TEAEs will be flagged in the listing.

10.2. Clinical Laboratory Evaluations

Clinical laboratory tests (including serum chemistry, hematology, urinalysis, lipid panel, hormones, and hepatitis serology) will be collected per the timing presented according to the protocol. All summaries will be based on the International System of Units (SI) and the central lab results. Laboratory values that are below the limit of quantitation (LLoQ) or above the upper limit of quantitation (ULoQ) will be assigned the numerical part of the results.

10.2.1. Hematology

Descriptive statistics of observed and change from baseline values will be presented by treatment group and total at the scheduled visits for white blood cell count including differential, red blood cell count, hemoglobin, hematocrit, and platelet count. A shift table representing the change from baseline to the worst post-baseline values in normal, low, or high will also be provided by treatment group and total. A subject could be counted in both low and high categories if the subject experiences both low and high in the post-baseline visits.

A listing will be provided for all hematology tests by study phase and local lab data will be flagged in the listing. In addition, a listing of hematology tests will be provided for subjects with any clinically significant abnormality.

10.2.2. Serum Chemistry

Descriptive statistics of observed and change from baseline values will be presented by treatment group and total at the scheduled visits for alanine aminotransferase, albumin (total), alkaline phosphatase, aspartate aminotransferase, bilirubin (total), blood urea nitrogen, calcium, chloride, creatinine level, creatine phosphokinase, c-reactive protein, gamma-glutamyl transferase, glucose, HbA1C, phosphorus, potassium, protein (total), sodium and urate. A shift table representing the change from baseline the worst post-baseline values in normal, low, or high will also be provided by treatment group and total. A subject could be counted in both low and high categories if the subject experiences both low and high in the post-baseline visits.

A listing will be provided for all chemistry tests and local lab data will be flagged in the listing. In addition, a listing of chemistry tests will be provided for subjects with any clinically significant abnormality.

10.2.3. Hormone

Descriptive statistics of observed and change from baseline values will be presented by treatment group and total at the scheduled visits for parathyroid hormone, 25-Hydroxy vitamin D, and 1, 25-Dihydroxy vitamin D.

A listing will be provided for all hormone tests by subject and visit.

10.2.4. Lipid Panel

Descriptive statistics of observed and change from baseline values will be presented by treatment group and total at the scheduled visits for cholesterol (total), high density lipoprotein, low density lipoprotein and triglyceride.

A listing will be provided for all lipid panel tests by subject and visit.

10.2.5. Urinalysis, Hepatitis serology, Tuberculosis Testing and Pregnancy Testing

Listings will be provided for urinalysis, hepatitis serology tests, tuberculosis testing, and pregnancy testing by subject and visit.

10.3. Vital Sign Measurements

Vital sign measurements include pulse rate (beats per minute), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths per minute), weight (kg), and BMI (kg/m^2) as collected on the eCRF. Descriptive statistics will be provided for observed and change from baseline values by treatment group and total at the scheduled visits.

All vital signs will be presented in a listing by study phase.

10.4. Physical Examination

The number and percentage of subjects with different response (Normal, Abnormal Not Clinically Significant, and Abnormal Clinically Significant) will be summarized for each physical assessment by treatment group and total at scheduled visits.

All physical examination results will be presented in a listing by study phase.

10.5. Electrocardiogram

The 12-lead electrocardiogram (ECG) assessments include heart rate (beats per minute), PR interval (milliseconds), RR interval (milliseconds), QRS duration (milliseconds), QT interval (milliseconds), and QTcB (milliseconds). Descriptive statistics will be provided for observed and change from baseline values by treatment group and total at the scheduled visits.

The number and percentage of subjects with each ECG overall interpretation (Normal, Abnormal Not Clinically Significant, and Abnormal Clinically Significant) and the number and percentage of subjects with normal sinus rhythm (Yes, No) will be summarized by treatment group and total at scheduled visits.

All ECG assessments will be presented in a by-subject listing by study phase.

11. Biomarker Analysis

11.1. Biomarkers

Descriptive summary will be provided to describe the selected biomarker endpoints using the safety population by treatment group, if data is available. The selected biomarker endpoints may include angiotensin-converting enzyme, sIL-2R and vitamin D 1,25. The final determination as to the selection of biomarkers will be made based on the evolution of the science and emerging guidance closer to the completion of the study. Descriptive

statistics will be provided for observed and change from baseline values for each selected biomarker at scheduled visits.

All biomarker data will be presented in a listing by subject and visit.

11.2. Genetic Profile

Genetic sample obtained for subjects who has signed the genetic inform consent form at study entry may be explored and presented in tables. Descriptive statistics will be provided if data is available.

All genetic data will be presented in a listing.

12. Interim Analysis

No formal interim analysis is planned.

13. Changes in the Planned Analysis

The summary of changes presented below reflects the changes in the planned analysis described in protocol:

- The protocol planned endpoint analysis for "Change from baseline in WPAI over time" will not be performed given very few subjects have taken WPAI questionnaire. WPAI data will be only presented in listings.
- The protocol planned endpoint analysis for "Time to response (TTR) as evaluated at earlier time points (Weeks 4 to 20) as determined by the investigator based on clinical judgment" will not be performed.
- The protocol planned analysis for biomarker and genetic endpoints may not be performed depending on the availability of the data.

14. References

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15.Appendices

15.1. Date Imputation Guideline

15.1.1. Adverse Events

Missing start dates for AE data will be handled as follows:

- Missing day only:
    - If the month and year are the same as the first dose month and year, then it will be imputed as the date of the first dose.
    - If either the year is the same as the first dose year, but the month is prior to the first dose month or the year is prior to the first dose year, then it will be imputed as the last day of the collected month.
    - If either the year is the same as the first dose year, but the month is after the first dose month or the year is after the first dose year, then it will be imputed as the first day of the collected month.
- Missing day and month:
    - If the year is the same as the first dose year, then it will be imputed as the date of the first dose.
    - If the year is prior to the first dose year, then it will be imputed as December 31st of the collected year.
    - If the year is after the first dose year, then it will be imputed as January 1st of the collected year.
- Missing day, month and year:
    - It will be imputed as the date of the first dose.

No imputation will be applied to the missing or partial stop dates for AEs. If the AE end date is complete and the partial AE start date imputed by the rules above is after the AE end date, then the start date will be imputed by the AE end date.

15.1.2. Prior/Concomitant Medications

Missing start dates for concomitant medications data will be handled as follows:

- Missing day only:

  - If the month and year are the same as the first dose month and year, then it will be imputed as the date of first dose.
  - If either the year is the same as the first dose year but the month is prior to the first dose month or the year is prior to the first dose year, then it will be imputed as the last day of the collected month.
  - If either the year is the same as the first dose year but the month is after the first dose month or the year is after the first dose year, then it will be imputed as the first day of the collected month.

- Missing month:
  - If the year is the same as the first dose year, then it will be imputed as the date of first dose.
  - If the year is prior to the first dose year, then it will be imputed as December.
  - If the year is after the first dose year, then it will be imputed as January.
- Missing day and month:
  - If the year is the same as the first dose year, then it will be imputed as the date of first dose.
  - If the year is prior to the first dose year, then it will be imputed as December 31st of the collected year.
  - If the year is after the first dose year, then it will be imputed as January 1st of the collected year.
- Missing day, month and year:
  - It will be imputed as the date of first dose.

Missing stop dates for concomitant medications data will be handled as follows:

- Missing day only:
  - It will be imputed as the last day of the collected month or the death date, whichever is earlier.
- Missing day and month:

- It will be imputed as December 31st of the collected year or the death date, whichever is earlier.

- Missing day, month and year:
  - No imputation is needed.

If the imputed start date is after the stop date, then the start date will be imputed as the stop date.

15.2. Calculation of Patient-Reported Outcomes and Symptom Questionnaires

15.2.1. Steroid Toxicity Questionnaire

- Total score of Steroid Toxicity Questionnaire which is defined as the sum of 11 item scores. Each item is graded in the following manner:

  0 - None of the Time

  1 - A Little

  2 - Some of the Time

  3 - Most of the Time

  4 - All of the Time

15.2.2. King's Sarcoidosis Questionnaire

- KSQ – General Health Score

  This score is determined using the total score of answers recorded from the KSQ questionnaire general health module. The General Health module of the KSQ questionnaire includes questions 1-10 which can be completed using a scale of 1-7. The table below shows the rescore values that are added to calculate the total score:

Item	Max Score	Rescored	1	2	3	4	5	6	7
I0001	4	Y	0	1	2	3	3	4	4
I0002	6		0	1	2	3	4	5	6
I0003	3	Y	0	1	1	2	2	3	3
I0004	6		0	1	2	3	4	5	6
I0005	3	Y	0	1	2	2	3	3	3
I0006	2	Y	0	0	1	1	1	2	2
I0007	3	Y	0	0	0	1	2	2	3
I0008	2	Y	0	0	1	1	1	2	2

I0009	2	Y	0	0	1	1	1	2	2
I0010	2	Y	0	0	1	1	1	2	2

The total score can range from 0-33; this number is used to identify the KSQ General Health Score using the table below. For example, if the total score from the KSQ questionnaire is 22, the KSQ General Health score will be 59.9.

Total Score	KSQ General Health Score
0	0.0
1	9.3
2	15.7
3	20.2
4	23.8
5	26.7
6	29.4
7	31.7
8	33.9
9	36.0
10	38.0
11	39.9
12	41.7
13	43.5
14	45.3
15	47.1
16	48.9
17	50.7
18	52.5
19	54.3
20	56.2
21	58.0
22	59.9
23	61.9
24	63.9
25	66.1
26	68.4
27	70.9
28	73.6
29	76.7
30	80.3
31	84.7

32	91.0
33	100.0

- KSQ – Lung Score

  This score is determined using the total score of the answers recorded from the KSQ questionnaire lung module. The lung module of the KSQ questionnaire includes questions 11-16 which can be completed using a scale of 1-7. The table below shows the rescore values that are added to calculate the total score:

Item	Max Score	Rescored	1	2	3	4	5	6	7
I0011	5	Y	0	1	2	3	4	4	5
I0012	6	Y	0	1	2	3	4	5	6
I0013	6	Y	0	1	2	3	4	5	6
I0014	6	Y	0	1	2	3	4	5	6
I0015	6	Y	0	1	2	3	4	5	6
I0016	5	Y	0	1	2	3	4	4	5

  The total score can range from 0-34; this number is used to identify the Lung score using the table below. For example, if the total score from the KSQ questionnaire is 19, the lung score will be 50.2.

Total Score	Lung Score
0	0.0
1	10.4
2	17.5
3	22.3
4	26.0
5	29.0
6	31.4
7	33.6
8	35.5
9	37.2
10	38.8
11	40.2
12	41.6
13	42.9
14	44.2
15	45.5
16	46.7
17	47.9

18	49.1
19	50.2
20	51.4
21	52.6
22	53.8
23	55.1
24	56.4
25	57.8
26	59.3
27	61.0
28	62.9
29	65.2
30	68.0
31	71.7
32	77.1
33	85.8
34	100.0

- KSQ – Medication Score

  This score is determined using the answers recorded from the KSQ questionnaire medication module. The medication module of the KSQ questionnaire includes questions 17-19 which can be completed using a scale of 1-7. The table below shows the rescore values that are added to calculate the total score:

Item	Max Score	Rescored	1	2	3	4	5	6	7
I0017	3	Y	0	1	2	2	2	3	3
I0018	3	Y	0	1	2	2	2	3	3
I0019	2	Y	0	0	1	1	1	1	2

  The total score can range from 0-8; this number is used to identify the Medication Score using the table below. For example, if the total score from the KSQ questionnaire is 7, the Medication score will be 80.9.

Total Score	Medication Score
0	0.0
1	14.5
2	26.8
3	37.2
4	47.0
5	56.5

6	66.9
7	80.9
8	100.0

- KSQ – Skin Score

  This score is determined using the answers recorded from the KSQ questionnaire skin module. The skin module of the KSQ questionnaire includes questions 20-22 which can be completed using a scale of 1-7. The table below shows the rescore values that are added to calculate the total score:

Item	Max Score	Rescored	1	2	3	4	5	6	7
I0020	4	Y	0	1	2	2	2	3	4
I0021	3	Y	0	1	1	2	2	2	3
I0022	2	Y	0	0	1	1	1	2	2

  The total score can range from 0-9; this number is used to identify the Skin Score using the table below. For example, if the total score from the KSQ questionnaire is 4, the Skin score will be 35.4.

Total Score	Skin Score
0	0.0
1	13.7
2	25.4
3	35.4
4	44.7
5	53.8
6	63.3
7	73.7
8	86.1
9	100.0

- KSQ – Eye Score

  This score is determined using the answers recorded from the KSQ questionnaire eyes module. The eyes module of the KSQ questionnaire includes questions 23-29 which can be completed using a scale of 1-7. The table below shows the rescore values that are added to calculate the total score:

Item	Max Score	Rescored	1	2	3	4	5	6	7
I0023	2	Y	0	0	1	1	1	2	2

I0024	3	Y	0	1	2	2	2	2	3
I0025	3	Y	0	1	2	2	2	3	3
I0026	2	Y	0	0	1	1	1	2	2
I0027	2	Y	0	0	1	1	1	2	2
I0028	3	Y	0	0	0	1	1	2	3
I0029	2	Y	0	0	1	1	1	1	2

The total score can range from 0-17; this number is used to identify the Eye Score using the table below. For example, if the total score from the KSQ questionnaire is 12, the Eyes score will be 61.1.

Total Score	Eye Score
0	0.0
1	11.3
2	19.6
3	25.8
4	31.0
5	35.5
6	39.7
7	43.5
8	47.2
9	50.6
10	54.0
11	57.5
12	61.1
13	65.2
14	70.1
15	76.4
16	85.8
17	100.0

- KSQ – General Health & Lung Score

  This score is determined using the answers recorded from the KSQ questionnaire general health module and lung module combined. The General Health module of the KSQ questionnaire includes questions 1-10 and the lung module of the KSQ questionnaire includes questions 11-16 which can be completed using a scale of 1-7 The table below shows the rescore values that are added to calculate the total score:

Item	Max Score	Rescored	1	2	3	4	5	6	7
I0001	4	Y	0	1	2	3	3	4	4

I0002	6		0	1	2	3	4	5	6
I0003	3	Y	0	1	1	2	2	3	3
I0004	6		0	1	2	3	4	5	6
I0005	3	Y	0	1	2	2	3	3	3
I0006	2	Y	0	0	1	1	1	2	2
I0007	3	Y	0	0	0	1	2	2	3
I0008	2	Y	0	0	1	1	1	2	2
I0009	2	Y	0	0	1	1	1	2	2
I0010	2	Y	0	0	1	1	1	2	2
I0011	5	Y	0	1	2	3	4	4	5
I0012	6	Y	0	1	2	3	4	5	6
I0013	6	Y	0	1	2	3	4	5	6
I0014	6	Y	0	1	2	3	4	5	6
I0015	6	Y	0	1	2	3	4	5	6
I0016	5	Y	0	1	2	3	4	4	5

The total score can range from 0-67; this number is used to identify the General Health & Lung Score using the table below. For example, if the total score from the KSQ questionnaire is 40, the General Health & Lung score will be 58.1.

Total Score	General Health & Lung Score
0	0.0
1	11.6
2	19.0
3	23.8
4	27.2
5	29.9
6	32.0
7	33.8
8	35.4
9	36.7
10	38.0
11	39.1
12	40.1
13	41.0
14	41.9
15	42.8
16	43.5
17	44.3
18	45.0

19	45.7
20	46.4
21	47.0
22	47.7
23	48.3
24	48.9
25	49.5
26	50.1
27	50.7
28	51.2
29	51.8
30	52.4
31	52.9
32	53.5
33	54.1
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
63	80.0
64	82.6
65	86.1
66	91.5
67	100.0

- KSQ – General Health & Skin Score

  This score is determined the answers recorded from the KSQ questionnaire general health module and skin module combined. The General Health module of the KSQ questionnaire includes questions 1-10 and the skin module of the KSQ questionnaire includes questions 20-22, which can be completed using a scale of 1-7 The table below shows the rescore values that are added to calculate the total score:

Item	Max Score	Rescored	1	2	3	4	5	6	7
I0001	4	Y	0	1	2	3	3	4	4
I0002	6		0	1	2	3	4	5	6
I0003	3	Y	0	1	1	2	2	3	3
I0004	6		0	1	2	3	4	5	6
I0005	3	Y	0	1	2	2	3	3	3
I0006	2	Y	0	0	1	1	1	2	2
I0007	3	Y	0	0	0	1	2	2	3
I0008	2	Y	0	0	1	1	1	2	2
I0009	2	Y	0	0	1	1	1	2	2
I0010	2	Y	0	0	1	1	1	2	2
I0020	4	Y	0	1	2	2	2	3	4
I0021	3	Y	0	1	1	2	2	2	3
I0022	2	Y	0	0	1	1	1	2	2

  The total score can range from 0-42; this number is used to identify the General Health & Skin Score using the table below. For example, if the total score from the KSQ questionnaire is 25, the General Health & Skin score will be 51.2.

0	0.0
1	9.0
2	15.0

3	19.2
4	22.3
5	25.0
6	27.3
7	29.3
8	31.1
9	32.8
10	34.3
11	35.8
12	37.1
13	38.4
14	39.6
15	40.8
16	41.9
17	43.0
18	44.1
19	45.1
20	46.1
21	47.2
22	48.2
23	49.2
24	50.2
25	51.2
26	52.2
27	53.2
28	54.3
29	55.4
30	56.5
31	57.7
32	59.0
33	60.4
34	62.0
35	63.7
36	65.6
37	67.9
38	70.6
39	74.2
40	79.1
41	87.1
42	100.0

- KSQ – General Health & Eye Score

  This score is determined by the answers recorded from the KSQ questionnaire general health module and eyes module combined. The General Health module of the KSQ questionnaire includes questions 1-10 and the eyes module of the KSQ questionnaire includes questions 23-29, which can be completed using a scale of 1-7 The table below shows the rescore values that are added to calculate the total score:

Item	Max Score	Rescored	1	2	3	4	5	6	7
I0001	4	Y	0	1	2	3	3	4	4
I0002	6		0	1	2	3	4	5	6
I0003	3	Y	0	1	1	2	2	3	3
I0004	6		0	1	2	3	4	5	6
I0005	3	Y	0	1	2	2	3	3	3
I0006	2	Y	0	0	1	1	1	2	2
I0007	3	Y	0	0	0	1	2	2	3
I0008	2	Y	0	0	1	1	1	2	2
I0009	2	Y	0	0	1	1	1	2	2
I0010	2	Y	0	0	1	1	1	2	2
I0023	2	Y	0	0	1	1	1	2	2
I0024	3	Y	0	1	2	2	2	2	3
I0025	3	Y	0	1	2	2	2	3	3
I0026	2	Y	0	0	1	1	1	2	2
I0027	2	Y	0	0	1	1	1	2	2
I0028	3	Y	0	0	0	1	1	2	3
I0029	2	Y	0	0	1	1	1	1	2

  The total score can range from 0-50; this number is used to identify the General Health & Eyes Score using the table below. For example, if the total score from the KSQ questionnaire is 30, the General Health & Eyes score will be 55.7.

Total Score	General Health & Eye Score
0	0.0
1	9.1
2	15.3
3	19.5
4	22.8
5	25.5
6	27.8

Total Score	General Health & Eye Score
7	29.8
8	31.7
9	33.4
10	34.9
11	36.4
12	37.7
13	39.0
14	40.2
15	41.4
16	42.5
17	43.5
18	44.5
19	45.5
20	46.5
21	47.5
22	48.4
23	49.3
24	50.2
25	51.1
26	52.0
27	52.9
28	53.8
29	54.8
30	55.7
31	56.6
32	57.6
33	58.6
34	59.6
35	60.7
36	61.8
37	62.9
38	64.1
39	65.3
40	66.7
41	68.1
42	69.6
43	71.2
44	73.0
45	75.1

Total Score	General Health & Eye Score
46	77.6
47	80.6
48	84.6
49	90.7
50	100.0

- KSQ – General Health & Lung & Skin Score

  This score is calculated with the following calculation below using the answers recorded from the KSQ questionnaire general health module, lung module and skin module combined. The General Health module of the KSQ questionnaire includes questions 1-10, the lung module of the KSQ questionnaire includes questions 11-16 and the skin module of the KSQ questionnaire includes questions 20-22, which can be completed using a scale of 1-7 The table below shows the rescore values that are added to calculate the total score:

Item	Max Score	Rescored	1	2	3	4	5	6	7
I0001	4	Y	0	1	2	3	3	4	4
I0002	6		0	1	2	3	4	5	6
I0003	3	Y	0	1	1	2	2	3	3
I0004	6		0	1	2	3	4	5	6
I0005	3	Y	0	1	2	2	3	3	3
I0006	2	Y	0	0	1	1	1	2	2
I0007	3	Y	0	0	0	1	2	2	3
I0008	2	Y	0	0	1	1	1	2	2
I0009	2	Y	0	0	1	1	1	2	2
I0010	2	Y	0	0	1	1	1	2	2
I0011	5	Y	0	1	2	3	4	4	5
I0012	6	Y	0	1	2	3	4	5	6
I0013	6	Y	0	1	2	3	4	5	6
I0014	6	Y	0	1	2	3	4	5	6
I0015	6	Y	0	1	2	3	4	5	6
I0016	5	Y	0	1	2	3	4	4	5
I0020	4	Y	0	1	2	2	2	3	4
I0021	3	Y	0	1	1	2	2	2	3
I0022	2	Y	0	0	1	1	1	2	2

  The total score can range from 0-76; this number is used to identify the General Health & Lung & Skin Score using the table below. For example, if the total score

from the KSQ questionnaire is 50, the General Health & Lung & Skin Score will be 49.5.

Total Score	General Health & Lung &Skin Score
0	0.0
1	8.5
2	14.1
3	17.9
4	20.6
5	22.8
6	24.6
7	26.2
8	27.5
9	28.7
10	29.8
11	30.7
12	31.6
13	32.4
14	33.1
15	33.8
16	34.5
17	35.1
18	35.6
19	36.2
20	36.7
21	37.2
22	37.7
23	38.2
24	38.7
25	39.1
26	39.5
27	40.0
28	40.4
29	40.8
30	41.2
31	41.6
32	42.0
33	42.4
34	42.8
35	43.2

Total Score	General Health & Lung &Skin Score
36	43.6
37	44.0
38	44.4
39	44.8
40	45.2
41	45.6
42	46.0
43	46.4
44	46.8
45	47.2
46	47.7
47	48.1
48	48.6
49	49.0
50	49.5
51	50.0
52	50.5
53	51.0
54	51.5
55	52.1
56	52.6
57	53.2
58	53.9
59	54.5
60	55.2
61	56.0
62	56.8
63	57.6
64	58.6
65	59.6
66	60.7
67	61.9
68	63.3
69	64.8
70	66.6
71	68.8
72	71.4
73	74.8
74	79.6

Total Score	General Health & Lung &Skin Score
75	87.3
76	100.0

15.2.3. Fatigue Assessment Scale (FAS)

- FAS Total Score is calculated by the total sum of all the answers recorded in the FAS questionnaire. The scores for questions 4 and 10 will be equal to the following when recorded.

  If the answer 1 is recorded this will equal 5.

  If the answer 2 is recorded this will equal 4.

  If the answer 3 is recorded this will equal 3.

  If the answer 4 is recorded this will equal 2.

  If the answer 5 is recorded this will equal 1.

15.2.4. Patient Global Assessment Score

- This score is the answer recorded by answering the patient global assessment question.

15.2.5. Physician Global Assessment Score

- This score is the answer recorded by answering the physician global assessment question.

15.2.6 Medical Research Council Dyspnea Scale

- This score is the answer recorded by answering the medical research council dyspnea scale.

15.2.7 Leicester Cough Questionnaire

- LCQ Total Score

  This score is calculated with the following calculation below.
  (LCQ Physical Score + LCQ Social Score +LCQ Psychological Score);

- LCQ Physical Score

  This score is calculated with the following calculation below using the answers recorded from the LCQ questionnaire physical module. The physical module of the LCQ questionnaire includes questions 1,2,3,9,10,11,14 and 15.

(Total score from questions in module / Number of questions in module).

- LCQ Social Score

  This score is calculated with the following calculation below using the answers recorded from the LCQ questionnaire social module. The social module of the LCQ questionnaire includes questions 7,8,18 and 19.
  (Total score from questions in module / Number of questions in module).

- LCQ Psychological Score

  This score is calculated with the following calculation below using the answers recorded from the LCQ questionnaire social module. The psychological module of the LCQ questionnaire includes questions 4,5,6,12,13,16 and 17.
  (Total score from questions in module / Number of questions in module).

15.3. Schedule of Study Events

Assessments and Procedures	Screening	Randomization	Double-Blind Treatment Period[a]						Open-label Extension (Optional)[a]			Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Days/Week	Days -28 to -1	Day 0	4 (± 5 days)	8 (± 5 days)	12 (± 5 days)	16 (± 5 days)	20 (± 5 days)	24 (± 5 days)	28 (± 5 days)	36 (± 5 days)	48 (± 5 days)	4 weeks after final dose of IMP (± 2 days)
Informed consent[b]	X											
Inclusion/exclusion criteria	X	X										
Medical/surgical/medication history[c]	X											
Demographics	X											
Height	X											
Vital signs including weight[d]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[e]	X	X	X	X	X	X	X	X	X	X	X	X
Patient reported outcomes and assessments[f]	X	X	X	X	X	X	X	X	X	X	X	
ePOST[g]	X	X	X	X	X	X	X	X	X	X	X	
Physician Global Assessment	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Accountability and Diary Review			X	X	X	X	X	X	X	X	X	
Complete blood count	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry/liver function tests[h]	X	X	X	X	X	X	X	X	X	X	X	X
HbA1C	X	X	X	X	X	X	X	X	X	X	X	
Lipid profile[i]	X							X			X	
25-Hydroxy vitamin D, 1, 25-dihydroxy vitamin D, parathyroid hormone	X				X			X		X	X	
C-Reactive protein	X				X			X		X	X	
Biomarkers[j]	X				X			X		X	X	

Assessments and Procedures	Screening	Randomization	Double-Blind Treatment Period[a]						Open-label Extension (Optional)[a]			Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Days/Week	**Days -28 to -1**	**Day 0**	**4 (± 5 days)**	**8 (± 5 days)**	**12 (± 5 days)**	**16 (± 5 days)**	**20 (± 5 days)**	**24 (± 5 days)**	**28 (± 5 days)**	**36 (± 5 days)**	**48 (± 5 days)**	**4 weeks after final dose of IMP (± 2 days)**
Thyroid stimulating hormone; thyroxine T3 and T4	X											
Hepatitis serology[k]	X											
Urinary analysis	X				X			X		X	X	X
Pregnancy testing (serum)	X											
Pregnancy testing (urinary)		X	X	X	X	X	X	X	X	X	X	X
TB testing[l]	X											
12 lead ECG[m]	X							X			X	
PFT[n]	X				X			X		X	X	
Spirometry		X										
CXR and HRCT[o]	X							X			X	
6MWT[p]	X							X			X	
Injection and diary training[q]	X	X										
Randomization		X										
IXRS contact, dispense IMP and equipment[r]	X	X	X	X	X	X	X	X[r]	X	X		
Dosing 2×/week[s]		X	X	X	X	X	X	X	X	X	X	
Study drug accountability and diary review			X	X	X	X	X	X	X	X	X	

Assessments and Procedures	Screening	Randomization	Double-Blind Treatment Period[a]						Open-label Extension (Optional)[a]			Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Days/Week	**Days -28 to -1**	**Day 0**	**4 (± 5 days)**	**8 (± 5 days)**	**12 (± 5 days)**	**16 (± 5 days)**	**20 (± 5 days)**	**24 (± 5 days)**	**28 (± 5 days)**	**36 (± 5 days)**	**48 (± 5 days)**	**4 weeks after final dose of IMP (± 2 days)**
Corticosteroid tapering[t]			X	X	X	X	X	X	X	X		
Concomitant medications		X										X
Safety (AEs)[u]	X											

IMP = Investigational Medicinal Product; IXRS = Interactive Telephone/Web Response System

[a] Visits 2 through 11 should occur within ± 5 days of the indicated weeks and should not be scheduled for the day of injection so as not to influence patient reported outcomes. Any additional visits, hospitalization, or additional tests or imaging performed beyond those dictated by the protocol, at the discretion of the investigator (or other disciplines for extrapulmonary manifestations) will also be captured in the eCRF.

[b] Neutral language should be used in describing the study to neutralized placebo effect.

[c] Medical history will include smoking history (classified into one the following categories: current smoker; ever smoked [more than 1cigarette/day for more than1year]; never smoked), length of sarcoidosis diagnosis, organ involvement, and prior and current medication. Occupational history should also be collected.

[d] Every effort should be made for weight to be measured by the same calibrated scale at every visit.

[e] Physical examination will also include targeted examination per organ(s) involved. All efforts must be undertaken for the same physician to perform the physical examination for each subject (per subject, per organ involved) at each visit.

[f] Patient-reported outcomes include: Steroid toxicity questionnaire (Attachment 2); King's Sarcoidosis Questionnaire (Attachment 4); Fatigue Assessment Scale (Attachment 5); Patient's Global Assessment (Attachment 6); Medical Research Council Dyspnea Scale (Attachment 8); Leicester Cough Questionnaire (Attachment 9), Work Productivity and Activity Impairment (WPAI) (Attachment 10). Prior to filling out any patient-reported outcomes at Visit 1, training will be provided as to the nature, purpose, and best way of filling these out. For example, reading the last question of the Fatigue Assessment Scale carefully. PRO assessments should be completed at each visit before undertaking any activities or tests that can influence the reporting. At Visit 8 and Visit 11 both the investigator and the subjects will asked independently if they would choose to continue treatment.

[g] All efforts must be undertaken for the same physician to perform the Extrapulmonary Physician's Organ Severity Tool (ePOST), per subject, (Attachment 3) side-by-side with prior evaluations.

[h] Chemistry panel including liver function tests will include: alanine aminotransferase; albumin (total); alkaline phosphatase; aspartate aminotransferase; bicarbonate; bilirubin (total); blood urea nitrogen; calcium; chloride; creatinine; creatine phosphokinase; glucose; phosphorus; potassium; protein (total); sodium; uric acid. Samples will be collected from subjects who have been fasted for at least 12 hours (drinking water is permitted).

[i] Lipid profile will include: high density lipoprotein; low density lipoprotein; triglycerides; total cholesterol. Samples will be collected from subjects who have been fasted for at least 12 hours.
[j] Biomarkers sampling must include RNA and DNA samples (screening only), if genetic Informed Consent Form (ICF) is signed.
[k] Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus (HCV) antibody, HCV polymerase chain reaction (for subjects positive for HCV antibody only).
[l] Tuberculosis (TB) will be tested by interferon gamma release assay (IGRA). Central laboratory test results must be negative for subjects to qualify for the study.
[m] ECG will include assessment of sinus rhythm, heart rate, PR Interval, RR Interval, QRS Duration, Q-T Interval and QTcB.
[n] Full pulmonary function test (PFT) results will include forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FVC % predicted (NHANES III reference values), FEV1/FVC ratio, peak expiratory flow rate (PEFR) or forced exploratory flow at maximum effort (FEF_{max}), total lung capacity, residual volume, diffusing capacity of the lungs for carbon monoxide (DLCO; uncorrected for Hb), DLCO: % predicted and DLCO/alveolar volume.
[o] High-resolution computed tomography (HRCT) should be performed within 28 days of Day -1. Both CXR and HRCT should be evaluated side by side by investigator/radiologist/central reader for determining if the condition is improving, stable, or deteriorating based on a 5-point Likert score: much worse; worse; unchanged; better; much better. The CXR will also include Scadding scoring (Attachment 11).
[p] The Six Minute Walk Test (6MWT) would be performed according to the ATS protocol (Attachment 12). Reasons for not performing the 6MWT will be captured in eCRF.
[q] Subjects (and/or caregivers) will be trained on SC injections using the training tools provided separately. Additional training may be provided during Visit 2 before randomization occurs. SC injections training may be forgone if either the subject or caregiver is a medically trained professional.
[r] The importance of adhering to treatment will be encouraged at every visit. At Visit 8, IMP will only be dispensed for subjects participating in the optional Open-label Extension Phase.
[s] Dosing will begin after Visit 2 procedures are completed and subject is randomized. The first dose of study drug for all subjects will be administered in the clinic and the subject will be observed for at least 1 hour after dosing. For subjects entering the Open Label Extension, the first dose given at Week 24 will be administered in the clinic and the subject will be observed for at least 1 hour after dosing. All other doses will be administered by the subject or the subject's caregiver at home 2×/week but not on visit days (see Section 13.3).
[t] Corticosteroid taper will follow the specified algorithm. Corticosteroid tapering at Visit 8 is done for patients entering open label extension only. Reasons for determining worsening will be captured in the eCRF (FVC, DLCO, imaging, symptoms, other). Justification for any deviations will also be captured in the eCRF.
[u] At each visit following signature of the ICF, AE will be reported based on questioning subjects as to new medical conditions since last visit and as to experiencing worsening of existing medical conditions since last visit, physical exam, laboratory and imaging findings.

15.4. SAS Procedures

- T test

```
ods output ttests=ttest;
proc ttest data=xxx sides=2 alpha=0.05 h0=0;
  class TRT;
  var AnalVar;
run;
```

- Pearson's chi-square test

```
proc freq data=xxx;
  tables TRT*AnalVar /chisq;
  output out=chisq pchi;
run;
```

- Fisher's exact test

```
proc freq data=xxx;
  tables TRT*AnalVar / fisher;
  output out= fisher exact;
run;
```

- MMRM

```
ods output lsmeans=lsm diffs=diff;
proc mixed data=xxx;
  class TRT AVISITN USUBJID;
  model AnalVar = BASVAR TRT AVISITN TRT*AVISITN;
  repeated AVISITN / type=UN subject=USUBJID;
  lsmeans TRT*AVISITN / diff cl;
run;
```

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Mallinckrodt ARD, LLC**
Protocol Number:	**MNK14344100**

Document Description:	Final Statistical Analysis Plan
SAP Title:	A Multicenter, Randomized, Double Blind, Placebo Controlled Exploratory Study to Assess the Efficacy and Safety of Acthar® Gel in Subjects with Pulmonary Sarcoidosis
SAP Version Number:	3.0
Effective Date:	02FEB2022

Author(s):

For PPD: [redacted], [redacted] [redacted] I approve this document 02 Feb 2022 11:21:10 -05:00 [redacted]

Approved by:

[redacted]

02-Feb-2022
Date *(DD-MMM-YYYY)*

[redacted]
Mallinckrodt ARD, LLC

Date *(DD-MMM-YYYY)*

[redacted]
Mallinckrodt ARD, LLC