ACTHAR® GEL

A MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED EXPLORATORY STUDY TO ASSESS THE EFFICACY AND SAFETY OF ACTHAR® GEL IN SUBJECTS WITH PULMONARY SARCOIDOSIS

SPONSOR: MALLINCKRODT ARD LLC

1425 US-206

Bedminster, NJ 07921

United States of America

Protocol Number: MNK14344100

Clintrials.gov Registry Number: NCT03320070

Date of Protocol Version 2 Amendment 1: 15 May 2020

SPONSOR SIGNATURE PAGE

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable guidance documents and regulations including, but not limited to:

- International Council for Harmonisation (ICH) E6(R2): Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, which has its ethical foundation in the Declaration of Helsinki
- the US CFR (as appropriate, including 42 CFR 11: Final Rule for Clinical Trials Registration and Results Information Submission)
- NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information
- all applicable national and local regulations (as appropriate, including the EU Clinical Trials Regulation)
- protections for privacy (as appropriate, including the EU General Data Protection Regulation (GDPR)
- provisions of all local ethics committees

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Refer to e-signature page

Sponsor Signature

[redacted], BSN, MD

[redacted]

ACKNOWLEDGEMENT OF RECEIPT AND UNDERSTANDING OF SPONSOR STUDY MATERIALS

My signature confirms that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles such as the Declaration of Helsinki.
Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

I confirm that I have received, read, and understood the following document(s) for:

PRODUCT:

Acthar® Gel (Repository Corticotropin Injection)

STUDY:

Protocol MNK14344100

Protocol Version 2 Amendment 1

PRINCIPAL/COORDINATING INVESTIGATOR(S)

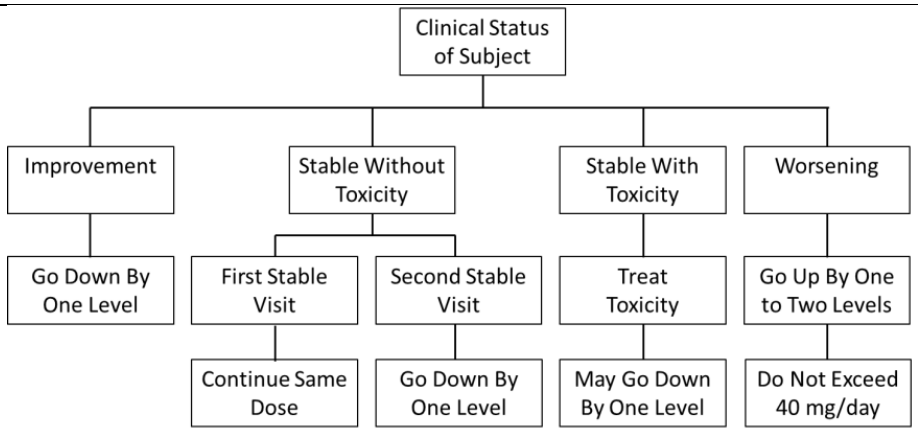
Name:

Title:

SIGNATURE_____DATE: _____

2. SYNOPSIS

<table>
<tr><td colspan="2">Study Title: A Multicenter, Randomized, Double Blind, Placebo Controlled Exploratory Study to Assess the Efficacy and Safety of Acthar® Gel in Subjects With Pulmonary Sarcoidosis</td></tr>
<tr><td>Protocol Number: MNK14344100</td><td>Type: Phase 4 (US) / Phase 2 (all other countries)</td></tr>
<tr><td>Condition/Disease:</td><td>Pulmonary Sarcoidosis</td></tr>
<tr><td>Approximate Number of Subjects: 100</td><td>Approximate Duration of Subject Participation: Up to 14 months.</td></tr>
<tr><td>Approximate Number of Study Centers: Approximately 75 sites globally</td><td>Approximate Duration of Study: The estimated study period is approximately 4 years from first subject enrolled to last subject last visit (completed open-label extension and follow up visit). Expected enrollment period is approximately 3 years (first subject enrolled to last subject enrolled).</td></tr>
<tr><td colspan="2">Objective: The objective of the study is to evaluate the efficacy and safety of Acthar® Gel in the treatment of pulmonary sarcoidosis.</td></tr>
<tr><td colspan="2">Design:
This is a multicenter, randomized, double-blind, placebo-controlled exploratory study evaluating the efficacy and safety of Acthar Gel in the treatment of pulmonary sarcoidosis. The study will have 3 phases: Screening (up to 28 days); double-blind treatment (24 weeks); and an optional open-label, 24 weeks extension. A follow-up visit will be conducted 4 weeks (± 2 days) after the last dose of IMP is administered. Following signature of the ICF and a screening period of up to 28 days, subjects who meet all eligibility criteria will be randomly assigned to receive:
• Double-blind treatment: Acthar Gel, 1 mL (80 U) or matching placebo (1 mL) administered twice weekly SC for up to 24 weeks.
• Optional open-label treatment: Acthar Gel, 1 mL (80 U) administered twice weekly SC for up to 24 weeks.
Subjects will be assigned to treatment in a 1:1 ratio with up to 50 subjects per arm for a total of approximately 100 subjects.
Dose reduction of 50% may be implemented once during the study if a subject meets one of the following pre-specified safety criteria based on clinical judgment:
• Uncontrolled hypertension (newly developed or worsening of existing hypertension) before/or in conjunction with addition/adjustment of antihypertensive therapy.
• Uncontrolled diabetic signs/symptoms (newly developed of worsening of existing diabetes) before/or in conjunction with addition/adjustment of antihyperglycemic therapy.
• Unacceptable toxicity defined as any adverse event (AE) of at least moderate intensity not adequately controlled by concomitant medication use or other nonstudy drug-related measure.
The justification for dose reduction will be captured in the eCRF. Subjects will remain on the 40 U or matching placebo 2×/week for the remainder of the study. Subjects, who despite dose reduction continue to experience from any of the above mentioned AEs, they will be withdrawn from the study due to AE.
Subjects will be followed every 4 weeks (± 5 days) for 24 weeks (Visit 2 to Visit 8). During each visit following randomization, steroid tapering evaluation will occur based on the following algorithm.</td></tr>
</table>



Incremental doses of prednisone for the study are 40, 30, 20, 10, 7.5, 5, 2.5, and 0 mg.

A justification for any deviation will be captured in the eCRF. In addition, subjects and physicians will complete patient reported outcomes, and safety will be evaluated based on targeted physical examination per organ involved, vital signs, imaging, and laboratory test results. 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 extra-pulmonary manifestations) will also be captured in the eCRF.

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). Subjects who decline participation in the Open-label Extension Phase, or those ineligible, will have their End-of-Treatment visit during Visit 8.

All subjects will have a follow-up visit 4 weeks (± 2 days) after the last dose of IMP, regardless of treatment group, and/or participation in the optional Open-label Extension Phase.

During the optional Open-label Extension Phase, subjects will be treated with Acthar Gel 80 U 2×/week for up to 24 weeks. Subjects who had their dose reduced once by half will be treated with Acthar Gel 40 U 2×/week. There will be 3 scheduled visits during this phase: Visit 9, 4 weeks (± 5 days) into the extension phase (Week 28), Visit 10 (Week 36) and Visit 11 (Week 48). During these visits corticosteroid taper will follow the same procedures and algorithm as in the double blind phase. Subjects and physicians will complete patient reported outcomes, and safety will be evaluated based on targeted physical examination per organ involved, vital signs, imaging, and laboratory test results. 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 extra-pulmonary manifestations) will also be captured in the eCRF.

During Visit 11, End-of-Treatment procedures will be completed.

Responder rate analysis (efficacy endpoints) will be determined by the investigator and an independent adjudication. Adjudication will serve to address inter-rater variability. In case of discrepancies, the adjudication determination will be utilized for purposes of efficacy endpoint analyses. Likewise, central HRCT and CXR readings will be used for the purpose of the imaging efficacy analyses.

Entry Criteria:

Inclusion Criteria

The subjects must meet all of the following criteria for inclusion in the study:

1. Subjects must be adequately informed and understand the nature and risks of the study and must be able to provide a signature and date on the ICF.
2. Subjects must be ≥ 18 and ≤ 90 years of age at Screening (Visit 1) and can be male or female.
3. Female subjects must be of non-childbearing potential (history of hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; or postmenopausal with no history of menstrual flow in the 12 months prior to Screening (Visit 1); or if of childbearing potential must be non-pregnant, non-lactating and agree to use effective contraception when with a male partner throughout study participation (through the Follow-up Visit). Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), and abstinence.
4. Subjects must be able to communicate effectively with study personnel.
5. Subjects must be able and willing to follow all protocol requirements and study restrictions including able and willing to inject SC Acthar Gel on their own or by caregiver.
6. Subjects must be able and willing to return for all study visits.
7. Subject with biopsy confirmed sarcoidosis meeting ATS criteria with onset of sarcoidosis ≥ 1 year prior to Screening.
8. Symptomatic pulmonary disease defined as any one of the following criteria for PFT; imaging; steroid dose; or symptoms:
   - Decrease ≥ 5% absolute change of % predicted in the best available FVC within the past 2 years.
   - Decrease ≥ 5% absolute change of % predicted in the best available diffusing capacity of the DLCO within the past 2 years.
   - Radiographic progression in chest imaging on side by side comparison within the past 2 years.
   - Progression of pulmonary sarcoidosis necessitating increase in antisarcoidosis therapy in the past 2 years.
   - Dyspnea with Medical Research Council Scale of ≥ 1 at Screening (Visit 1).
9. Subject receiving ≥ 5 mg and ≤ 40 mg daily prednisone (or equivalent) for pulmonary sarcoidosis.
10. Stable prednisone dose ≥ 4 weeks prior to Screening (Visit 1).
11. Subjects treated with any disease modifying antisarcoidosis drugs (eg, methotrexate) must be on stable dose for ≥ 3 months prior to Screening (Visit 1).
12. FVC ≥ 45% predicted. If FVC at Screening is more than 95% predicted, a documented decrease ≥ 5% absolute change of % predicted in the best available FVC is required after diagnosis of Sarcoidosis.
13. DLCO ≥ 30%.

Exclusion Criteria

Subjects are ineligible for the study if they meet any of the following criteria:

1. Subject is from a vulnerable population, as defined by the US CFR Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the clinical research organization, or of the IRB/IEC.

2. Subject is unwilling to receive, or is intolerant of, SC injections.
3. Subject has a history of sensitivity to ACTH preparations or sensitivity to porcine protein products.
4. Any difference >10% in FVC on spirometry between the determination at Screening (Visit 1) and the determination at Visit 2.
5. Pulmonary arterial hypertension requiring or receiving treatment.
6. Extra pulmonary involvement that per the Investigator's evaluation requires treatment that would impede corticosteroid tapering for pulmonary involvement.
7. Treatment with antitumor necrosis factor-α antibody (eg, infliximab, adalimumab) in prior 3 months.
8. Subject has any known contraindication(s) to Acthar Gel including, but not limited to:
   - Any known history of:
     - Scleroderma
     - Osteoporosis (evidence of vertebral or long bone fracture, or a lumbar T-score of more than -2.5 SD below the mean of the reference population). Subjects previously diagnosed as having osteoporosis and successfully treated will not be excluded solely on the basis of a historical diagnosis of osteoporosis as long as the lumbar T-score obtained per routine follow up within the 12 months prior to Screening (Visit1) is ≥ -2.5 SD.
     - Ocular herpes simplex
   - Any primary adrenocortical insufficiency or adrenal cortical hyperfunction.
   - Any current congestive heart failure (defined as New York Heart Association Functional Class III to IV).
   - Peptic ulcer requiring treatment or history of upper gastrointestinal bleeding within 24 weeks prior to Screening (Visit 1).
   - Recent major surgery (ie, major fluid or blood shift) within 24 weeks prior to Screening (Visit 1).
9. Subject has uncontrolled diabetes, hypertension, or other contra-indication to increased dosage of glucocorticoids.
10. Subject has chronic active hepatitis including active or chronic hepatitis B, or acute or chronic hepatitis C.
11. Subject has a history of TB infection, any signs/symptoms of TB, or any close contact with an individual with an active TB infection.
12. Subject has a clinically significant infection requiring administration of intravenous antibiotics or hospitalization in the 4 weeks prior to Screening (Visit 1) or between Screening and the first dose of IMP.
13. Subject has known immune compromised status (not related to disease/condition under study), including but not limited to, individuals who have undergone organ transplantation or who are known to be positive for the human immunodeficiency virus.
14. Subject has any solid tumor malignancy currently diagnosed or undergoing therapy, or has received therapy for any solid tumor malignancy in the 5 years prior to Screening (Visit 1); with the exception of treated and cured basal cell carcinoma, treated and cured squamous cell carcinoma of the skin, and treated and cured carcinoma in situ of the cervix.
15. Subject has a diagnosis of, is undergoing therapy for, or has received therapy for a hematologic malignancy in the 5 years prior to Screening (Visit 1).

16. Subject has current or recent (within 24 weeks prior to Screening (Visit 1) drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Diagnostic Criteria for Drug and Alcohol Abuse.
17. Subject has any of the following laboratory abnormalities at Screening (Visit 1):
    - Hemoglobin ≤ 8.0 g/dL.
    - Platelet count ≤ 50,000 cells/μL.
    - Absolute neutrophil count ≤ 1,000 cells/μL.
    - Aspartate aminotransferase, alanine aminotransferase, or total bilirubin > 2 times upper limit of normal.
    - Positive hepatitis B surface antigen or hepatitis B core antibody, or positive hepatitis C virus (HCV) antibody. (If HCV antibody is positive at Screening, HCV polymerase chain reaction will be automatically analyzed. Subjects with a positive HCV must have HCV polymerase chain reaction < 25 IU/mL at the Screening Visit to be eligible).
    - Positive or indeterminate IGRA for TB.
18. Subject has any other clinically significant disease, disorder or laboratory abnormality (including those listed on the Prescribing Information Section 5: Warnings and Precautions) which, in the opinion of the investigator (by its nature or by being inadequately controlled), might put the patient at risk due to participation in the study, or may influence the results of the study or the subject's ability to complete the study.
19. Subject is: 1) currently participating in another interventional clinical study or 2) has participated in another interventional clinical study within 30 days or five half-lives, whichever is longer, prior to Screening (Visit 1) or 3) plans to participate in another interventional clinical study prior to 90 days following the completion of current study.
20. Subject has any history of use of ACTH preparations for treatment of sarcoidosis.

Concomitant Medications and Treatments:

Subjects enrolled into the study must have been on stable prednisone dose for at least 4 weeks prior to Screening (Visit 1). Subjects who are treated with any disease modifying antisarcoidosis drug (eg, methotrexate) must have been on a stable dose for at least 3 months prior to Screening (Visit 1). Corticosteroid tapering will be initiated as of Week 4 (Visit 3) according to the tapering algorithm. All other antisarcoidosis medications should remain stable for the duration of the study. The dose may be reduced or discontinued only for toxicity but must not be increased. Treatment with antitumor necrosis factor-α antibody (eg, infliximab, adalimumab) in the 3 months prior to Screening (Visit 1) and any new antisarcoidosis medications are not permitted.

Subjects are not permitted to receive live or live-attenuated vaccines during the study.

All medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, herbal remedies, vitamin supplements) taken from 30 days prior to Screening (Visit 1) and throughout the study will be recorded.

Investigational medicinal product and Treatment Administration:

Acthar Gel, 1 mL (80 U) or matching placebo (1 mL) administered twice weekly SC for up to 24 weeks.

Optional open-label extension: Acthar Gel, 1 mL (80 U) administered twice weekly SC for up to 24 weeks.

Efficacy Evaluation:

The following efficacy assessments will be evaluated:

1. STS, a newly developed composite endpoint.

Sarcoidosis Treatment Score (STS) is a composite combining the results of PFT, chest imaging, quality of life, and changes in corticosteroid dosing.

	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 percentage.

Subject tolerating Acthar Gel (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 a reduction in corticosteroid dose (ie, a total score of +1 due to ≥ 50% reduction in corticosteroid dose).
- Nonresponse is defined as scores of ≤ 1/6 points without significant corticosteroid taper (stable or deterioration in corticosteroid response).

2. PFT.
3. Imaging: HRCT; CXR (including Scadding Score).
4. Corticosteroid tapering.

5. Physician Global Assessment.
6. Patient reported outcomes (King's Sarcoidosis Questionnaire, Fatigue Assessment Scale, and Patient's Global Assessment).
7. Symptom Assessment (Medical Research Council Dyspnea Scale, Leicester Cough Questionnaire, and steroid toxicity questionnaire).
8. Functional testing: 6MWT (including Borg Scale)
9. Extra pulmonary response (ePOST score).
10. Biomarkers, (eg, for genetic testing; optional).
11. WPAI.

Endpoints:

The endpoints for this study are:

- 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 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.
  - PFT (at applicable time points).
  - Extrapulmonary response (ePOST).
  - Supportive efficacy endpoints per applicable time points.
    - Six-minute walk test.
    - Symptom relief (Leicester Cough Questionnaire, Medical Research Council Dyspnea Scale, steroid toxicity questionnaire).
    - CXR (including Scadding score).
- Percentage change in overall DLCO.
- Percentage of subjects with improvement in DLCO of ≥ 5%; ≥10%; and ≥ 15%.
- Percentage change in overall FVC.
- Percentage of subjects with improvement in FVC of ≥ 5%; ≥10%; and ≥ 15%.
- Percentage of improved/stable/deteriorate - side by side comparison of HRCT based on a 5-point Likert score: much worse; worse; unchanged; better; much better (central reader).
- Percentage of improved/stable/deteriorated side by side comparison of CXRs based 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 WPAI over time.

Biomarkers:

- Biomarker levels will be compared between Screening, 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 point. 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.

Outcome Measures

Outcome measures are identified to facilitate trial registration and patient access to basic results disclosed on public registries. The primary outcome measures are:

- Number of participants in each category of assessment based on FVC, Weeks 24 and 48
- Number of participants in each category of assessment based on the DLCO, Weeks 24 and 48
- Number of participants in each category of assessment based on HRCT, Weeks 24 and 48
- Number of participants in each category of assessment based on the King's Sarcoidosis Questionnaire (General Health), Weeks 24 and 48
- Number of participants in each category of assessment based on the FAS, Weeks 24 and 48
- Number of participants receiving each dose of prednisone, Weeks 24 and 48

Safety Evaluation:

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

Statistical Methods:

Summary statistics will be provided for all study variables with descriptive statistics (number of observations, mean, SD, median, minimum, and maximum) for numerical (or continuous) variables. Frequency and percentages will be calculated for categorical variables. All data will be summarized by treatment groups as appropriate.

Pearson’s chi-squared test will be used to evaluate the treatment difference between treatment groups for the categorical response endpoints. The continuous response endpoints will be analyzed using the 2-sample t-test. The time-to-event endpoints will be analyzed using the log-rank test. Kaplan-Meier curves will also be presented.

Additional exploratory analyses will be performed as appropriate. Such analyses may include logistic regression model, analysis of variance model, and/or mixed-effects model. Subgroup analyses based on demographics, baseline characteristics, study compliance, etc, will also be performed.

Sample Size Justification:

Formal sample size calculations were not performed. The sample size is based on recent literature of comparative studies in sarcoidosis.

Date of Issue: 13 May 2020

SUMMARY OF CHANGES

The summary of changes presented below reflects the changes made in Version 2 Amendment 1. Formatting, consistency, and minor editorial changes are not included.

The primary reason for Version 2 Amendment 1 is to extend this product's and this study's treatment to countries other than the US, as currently Acthar Gel is only approved in the US. Additionally, updates or revisions are established for: study design that is revised to exploratory, changing enrollment and study duration timelines, adding WPAI questionnaire for collection of data for health economics and outcomes research, adding provisions for remote collection of data for those extenuating occasions when visits cannot be made in person, adding diary training and reviews, adding monitoring for possible allergic reactions to the first dose of Acthar Gel in the Open-label Extension Phase, removing an additional definition for SAEs that are not part of the standard definitions, and adding corticosteroid tapering for subjects entering the open label study period. Further detail is presented in Appendix 1.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. ABBREVIATIONS

Abbreviation	Term
6MWT	Six-Minute Walk Test
AE	adverse event
ACTH	adrenocorticotropic hormone
ATS	American Thoracic Society
CFR	Code of Federal Regulations
CXR	chest x-ray
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
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
Hb	hemoglobin
HbA1C	hemoglobin (glycosylated)
HCV	hepatitis C virus
HEOR	Health Economics and Outcomes Research
HIPAA	Health Insurance Portability and Accountability Act
HRCT	high-resolution computed tomography
ICF	informed consent form
ICH	International Council For Harmonisation
ID	identification number
IEC	Independent Ethics Committee
IGRA	interferon gamma release assay
IMP	investigational medicinal product

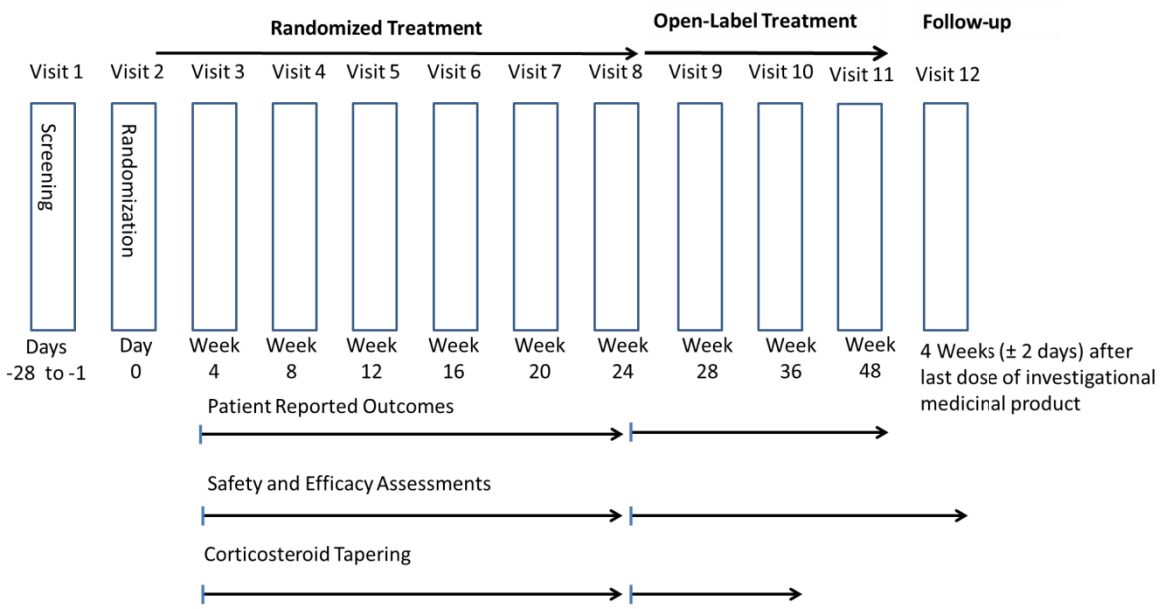
Abbreviation	Term
IRB	Institutional Review Board
IXRS	Interactive Telephone/Web Response System
LCQ	Leicester Cough Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention to treat
MM	medical monitor
MRC	medical research chronic
NHANES	National Health and Nutrition Examination Survey
PCR	polymerase chain reaction
PD	pharmacodynamics
PEFR	peak expiratory flow rate
PFT	pulmonary function test(ing)
RCI	repository corticotropin injection
RV	residual volume
SAE	serious adverse event
SC	subcutaneous
STS	Sarcoidosis Treatment Score
TB	tuberculosis
TEAE	treatment emergent adverse event
TLC	total lung capacity
WASOG	World Association of Sarcoidosis and Other Granulomatous
WPAI	Work Productivity and Activity Impairment

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS

4.1. Study Schematic

An overview of the study is presented in Figure 1.

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).

4.2. Schedule of Study Events

The schedule of study events is presented in Table 1.

Table 1: 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	

Table 1: Schedule of Study Events (Continued)

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	

Table 1: Schedule of Study Events (Continued)

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 no dose should be administered on study visit days (see Section 12.3).
[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.

5. ETHICAL CONSIDERATIONS

This clinical study is designed to comply with International Council for Harmonisation (ICH) Guidance on General Considerations for Clinical Trials (62 FR 66113, 17 Dec 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authority for Pharmaceuticals (75 FR 3471, 21 Jan 2010), and Good Clinical Practice: Consolidated Guidance (62 FR 25692, 09 May 1997).

5.1. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to obtain the approval of the IRB/IEC before the start of the study. The IRB must be registered and active with the Office for Human Research Protections of the US Department of Health and Human Services. A copy of the approval letter along with a roster of IRB members and/or the US Department of Health and Human Services general assurance number will be retained as part of the study records. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study at appropriate intervals (not to exceed 1 year) and at the completion of the study. The investigator will notify the IRB/IEC of SAEs or other significant safety findings per IRB/IEC guidelines. The study protocol, ICF, advertisements (if any), and amendments (if any) will be approved by the IRB/IEC in conformance with international, national and local regulatory requirements; and the 21 CFR §56.101-114 (where applicable).

5.2. Ethical Conduct of the Study

The study will be conducted in full compliance with applicable international, national and local regulatory requirements; US FDA regulations including 21 CFR §314.106 and §312.120, and ICH guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

5.3. Subject Information and Consent

The ICF must be approved by the sponsor and the IRB/IEC before any subject provides consent. The investigator will provide Mallinckrodt with a copy of the IRB/IEC-approved ICF and a copy of the IRB/IEC's written approval before the start of the study.

At the screening visit, subjects will read the ICF and a HIPAA authorization form (if applicable) after being given an explanation of the study. Before signing the ICF and the HIPAA authorization form (if applicable), subjects will have an opportunity to discuss the contents of these forms with study site personnel.

Subjects must assent understanding of and voluntarily sign these forms in compliance with ICH GCP guidelines and 21 CFR, Parts 50 and 312 (where applicable), before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined by national and local regulations including confidentiality. All versions of each subject's signed ICF must be kept on file by the site for possible inspection by

regulatory authorities and/or authorized Mallinckrodt personnel. Signed copies of the ICF and the HIPAA authorization form, if applicable, will be given to the subject.

The subjects will be made aware of their right to see and copy their records related to the study for as long as the investigator has possession of this information. If the subject withdraws consent and/or HIPAA authorization, the investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

6. BACKGROUND INFORMATION AND RATIONALE

6.1. Sarcoidosis Overview

Sarcoidosis is a chronic multisystem granulomatous disease, with a heterogeneous clinical presentation and disease course, characterized by the presence of noncaseating granulomas. Although sarcoidosis has been identified as a specific disease entity for more than a century, the specific cause of sarcoidosis is unknown. Current understanding is that the pathogenesis likely includes exposure to one or more, possibly airborne-transmitted antigens (bacterial, organic, anorganic), which then trigger an abnormal immune response in a genetically predisposed host (Ahmadzai et al., 2014; Chopra et al., 2016; Iannuzzi et al., 2007; Judson, 2012; Korsten et al., 2016). The disease may affect any organ system. Pulmonary is the most prevalent and is present in over 90% of patients. Ocular, lymph-node, and cutaneous manifestations are next in frequency (Al-Kofahi et al., 2016).

To date, there is no gold standard for diagnosis. Presently, the diagnosis is a clinical one as no reliable diagnostic test exists ATS criteria described in Hunninghake et al., 1999). Several biomarkers have been explored, including amyloid A, lysozyme, calcium, angiotensin converting enzyme, vitamin D, tumor necrosis factor-α, and various interleukins (eg, sIL-2R), to name a few. Despite many potential biomarkers being identified for monitoring and diagnosis, there is still a lack of adequately specific and sensitive disease markers for clinical usage, necessitating further research on these fronts. Accordingly, the diagnosis is based on the combination of clinical, radiological and histological (noncaseating epithelioid cell granuloma) parameters. In lieu of diagnostic test(s), diagnostic criteria have been developed, and while vetted by experts, these are arbitrary and inexact (Chopra et al., 2016; Judson, 2014; Ahmadzai et al., 2014).

Sarcoidosis does not mandate treatment because the disease may never cause symptoms, or organ dysfunction may remit spontaneously, in about 2/3 of patients (Iannuzzi et al., 2007), and therapy (particularly corticosteroids) is associated with a myriad of significant side effects. While the indications for treatment and the optimal treatment approach have not been standardized, the general consensus is that treatment should only be administered to avoid danger (eg, cardiac or neurologic manifestations) or to improve quality of life. (Judson, 2014; Baughman et al., 2012)

Various expert driven treatment recommendations exist for pulmonary and extra-pulmonary manifestations of sarcoidosis, however, the available evidence to guide treatment is limited. Corticosteroids are typically the first-line when treatment is required. Several off label alternative agents may be used, usually as corticosteroid sparing agents, because of the development or concerns of significant corticosteroid toxicity. Although often a small amount of corticosteroid may be continued for adequate efficacy. Second-line disease-modifying anti-sarcoid drugs may include antimetabolites (eg, methotrexate; azathioprine; leflunomide). Third-line typically includes anti-tumor necrosis factor-α biological agents (eg, infliximab; rituximab; adalimumab). Use of these agents should be individualized based on the patient's potential for toxicity and the organ that is being treated. In the future, there are goals to develop "personalized" or "precision" medical care where therapy will be individualized based on the patient's specific clinical features or genetics (Korsten et al., 2016; Judson, 2014; Judson, 2012; Baughman et al., 2012; Jamilloux et al., 2017).

Acthar® Gel has been included as third- or fourth-line therapy in several treatment algorithms (Korsten et al., 2016; Baughman et al, 2015). Three studies describing safety and efficacy of Acthar Gel in pulmonary sarcoidosis were recently published and described as follows.

The first study was a retrospective chart review of 47 patients with advanced sarcoidosis seen at 2 clinical centers who received at least 1 dose of Acthar Gel with at least 6 months of posttreatment follow-up. All patients initially received Acthar Gel 80 U intramuscular or SC administration twice a week (2×/week). Eighteen patients (37%) discontinued drug within 6 months due to study participation cost (4 patients), death (2 patients), or drug toxicity (11 patients), or noncompliance (1 patient). Of the remaining 29 patients, 11 experienced objective improvement in 1 or more affected organs. All but 2 patients noted disease improvement or oral glucocorticoid reduction. Twenty-one patients were treated for more than 6 months (median 274 days). Nineteen patients were taking prednisone at time of starting Acthar Gel: 17 had their prednisone dosage reduced by more than 50%, and 1 patient discontinued cyclophosphamide therapy. Acthar Gel treatment for at least 3 months was associated with objective improvement in a third of the patients. A third of the patients were unable to take treatment for at least 3 months (Baughman et al., 2016).

The second study was a prospective study of 16 patients with chronic pulmonary sarcoidosis receiving prednisone therapy with deterioration by at least 5% in FVC in the previous year. Acthar Gel was administered at a loading dose of 80 U SC for 10 days. Patients were randomized at Day 14 to receive either 40 U or 80 U Acthar Gel 2×/week for 24 weeks. The dose of prednisone was modified by the clinician who was blinded to the patient's dosage of Acthar Gel. At Week 24, there was a decrease in the dose of prednisone and improvements in DLCO, the King's Sarcoidosis Questionnaire (general health status), and the Fatigue Scale. There was no significant change in FVC % predicted. For the positron emission tomography scan, there was a significant fall in the standard uptake value of the lung lesions. Only 3/8 patients remained on 80 U repository corticotropin for full 24 weeks. There was no significant difference in the response to therapy for those treated with 40 U vs 80 U Acthar Gel. The authors concluded that Acthar Gel treatment was prednisone-sparing and associated with significant improvement in DLCO, positron emission tomography scan, and patient-reported outcome measures. A dose of 40 U repository corticotropin 2×/week was as effective as 80 U Acthar Gel and was better tolerated (Baughman et al., 2017).

[redacted]

The third study was large case series of patients with advanced symptomatic sarcoidosis treated with repository corticotropin injection (RCI). This large case series study describes patient characteristics, RCI utilization patterns, concomitant therapies, and physicians' assessments of treatment response. The study included 302 patients (mean age = 51 years; 52% women) with a mean of 4.8 years since initial diagnosis of sarcoidosis. Most patients (76%) had extrapulmonary involvement, primarily in the skin (28%), joints (25%), heart (22%), and eyes (22%); 34% had multiple (≥2) organ involvement. The mean duration of RCI treatment was 32.5 weeks, with 61.6% of patients continuing RCI therapy for ≥6 months. The RCI utilization pattern indicated an individualized approach to therapy, with a higher starting dose associated with a shorter duration of therapy compared with a lower starting dose. The

percentage of patients who used corticosteroids decreased from 61.3% during the 3 months before initiation of RCI to 12.9% at 3 months after RCI therapy; the mean daily dose of corticosteroid decreased from 18.2 mg to 9.9 mg. The proportion of patients given <10 mg/day of prednisone increased from 21% before RCI use to 47% at 3 months after RCI use. According to physicians' assessments of change in patients' health status after RCI therapy, overall status improved in 95% of patients, overall symptoms in 73%, lung function in 38%, and inflammation in 33%. The findings suggest that RCI is a viable treatment option for patients with advanced symptomatic sarcoidosis and provide insights on patient characteristics and practice patterns to help clinicians determine appropriate use (Chopra et al., 2019).

Several studies of various agents (eg, infliximab, ustekinumab, golimumab; Baughman et al., 2006; Judson, 2014b; Gibson et al., 1996) have highlighted important issues that may confound trial results, including selecting patients with active disease, identifying IMP effects in patients receiving concomitant corticosteroids, and establishing proper study endpoints. Establishment of an appropriate endpoint is probably the single most challenging issue in the design of a clinical sarcoidosis trial (Judson, 2014). The appropriate endpoint in sarcoidosis is dependent upon whether one wishes to measure the degree of granulomatous inflammation, the physiologic impact of that inflammation, or the effect of physiologic impairment on the patient's quality of life. This is a particularly important distinction in sarcoidosis, where active granulomatous inflammation may not significantly impair physiology or cause significant symptoms. Ideally, a clinically useful intervention in sarcoidosis should demonstrate a reduction in granulomatous inflammation that results in improved physiology and quality of life. Thus, multiple endpoints are likely needed to demonstrate clinical benefit (Baughman et al., 2012; Baughman et al, 2015).

The WASOG Diseases Task Force suggested that clinical endpoints for pulmonary sarcoidosis should be based on 4 broad categories: PFT, chest imaging, quality of life, and steroid-sparing. A composite score that include 2 or more of these categories was proposed as more effective than individual scores; however, these have not been rigorously tested (Baughman et al, 2015).

Clinical endpoints to measure disease activity in other systems affected by sarcoidosis such as skin, cardiac, ocular, and neurological endpoints are also planned for much needed attention by WASOG Disorders Task Force (Baughman et al, 2015).

6.2. Acthar Gel Overview

Acthar Gel is a naturally sourced complex mixture of ACTH analogs and other pituitary peptides. It is approved by the FDA for the treatment of symptomatic sarcoidosis (Mallinckrodt ARD LLC, 2019). ACTH is a member of the family of structurally related peptides known as melanocortin peptides. Melanocortin peptides, which in addition to ACTH include α-, β-, and γ-melanocyte stimulating hormones, are derived from the natural protein pro-opiomelanocortin and exert their physiologic effects by binding to cell surface G-protein coupled receptors known as melanocortin receptors (MCR) (Mountjoy et al, 1992). Five subtypes of MCRs have been identified to date (MC1R to MC5R), each with different tissue distributions, binding affinity characteristics, and physiological roles (Getting, 2006). MCRs play a key role in regulating inflammation and other cellular function (Catania, 2010). Acthar engages MCRs expressed on immune cells and other tissues throughout the body and is

thought to produce both an indirect anti-inflammatory effect and a direct cell effect (Catania, 2010; Wright et al., 2019; Olsen et al., 2015; Healy, 2017a; Wright et al., 2019b). Production of cortisol is mediated by activation of MC2Rs primarily expressed on the adrenal cortex. In i*n vitro* studies in cultured cells lines expressing MCR1-MCR5, the relative functional potency of MCRs was measured. It was shown that 6% of Acthar's relative functional potency occurred at MC2R. The remaining 94% occurred at the other MCRs (Wright et al., 2019). These data suggest that Acthar acts directly on cells involved in the pathogenesis of disease in addition to its indirect action via corticosteroid stimulation.

The effects of Acthar on human B-lymphocyte function *in vitro* were evaluated using highly purified B-cell populations cultured in the absence of glucocorticoids and stimulated by recombinant interleukin-4 and cluster of differentiation 40 ligand as specific B-cell activating signals. Immunoglobulin G was measured in supernatants from healthy human peripheral B cells that had been cultured for 6 days. The percentage of cells that divided and immunoglobulin G production were assessed under basal conditions (unstimulated) or stimulated with interleukin-4/cluster of differentiation 40 ligand plus vehicle. Acthar reduced B cell proliferation and immunoglobulin G production independent of cortisol release ($p<0.05$, compared to vehicle-treated group) (Olsen et al., 2015; Healy, 2017aHealy_2017, Healy, 2017b). In further experiments to explore the direct effects of Acthar on human macrophages and focusing on induction of pro-inflammatory mediators following lipopolysaccharide stimulation, Acthar inhibited the production of the pro-inflammatory cytokines interleukin-6 and tumor necrosis factor ($p<0.0001$, compared to vehicle-treated group; (Healy, 2017aHealy_2017, Healy, 2017b). These data further demonstrate a direct effect of Acthar on immune cell modulation independent of cortisol release.

[redacted]

While the exact mechanism of action of Acthar Gel is still unknown, further investigation is being conducted. This information is based on nonclinical data and pharmacodynamic data and the relationship to clinical benefit is unknown.

6.3. Rationale

This study will provide additional data to support the efficacy and safety of Acthar Gel in pulmonary sarcoidosis.

The Acthar Gel dose and dosing regimen for this study, namely 80 U 2×/week, are informed by patterns of clinical use in sarcoidosis, 2 recently published studies (Baughman et al., 2016; Baughman et al., 2017) and the package insert.

The prescribing information for Acthar Gel recommends the use of 40 U to 80 U administered intramuscularly or SC every 24- to 72 hours in adults and children over 2 years of age; the specific dose is individualized according to the medical condition (Mallinckrodt ARD LLC, 2019).

6.4. Risk and Benefits

The most common adverse reactions for Acthar Gel are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation of blood pressure, behavioral and mood changes, increased appetite, and weight gain. Acthar Gel may also be associated with increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infections. For a complete reference of known potential risks please refer to the Acthar Gel product labeling (Mallinckrodt ARD LLC, 2019).

7. OBJECTIVE AND EFFICACY

7.1. Objective

The objective of this study is to evaluate the efficacy and safety of Acthar Gel in the treatment for pulmonary sarcoidosis.

7.2. Assessments of Efficacy

The following assessments will be performed during this study:

- STS, a newly developed composite endpoint.
- PFT.
- Imaging: HRCT; CXR (including Scadding Score).
- Corticosteroid tapering.
- Physician Global Assessment.
- Patient-reported outcomes: King's Sarcoidosis Questionnaire; Fatigue Assessment Scale; Patient's Global Assessment.
- Symptom Assessments: Medical Research Council Dyspnea Scale; Leicester Cough Questionnaire; steroid toxicity questionnaire.
- Functional testing: 6MWT (including the Borg Scale).
- ePOST.
- Biomarkers (including RNA and DNA samples (screening only), if genetic ICF is signed).
- WPAI.

7.2.1. Sarcoidosis Treatment Score

This is a newly developed composite score that combines the results of PFT, chest imaging, quality of life, and changes in corticosteroid dosing as recommended by the WASOG task force (Baughman et al., 2015) and based on the results of the Acthar Gel prospective study; (Baughman et al., 2017). Individuals may score from -6 to +6. Higher scores indicate improvement.

Assessments and treatment scores categories are presented in Table 2.

Table 2: 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 Gel (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).

7.2.2. Pulmonary Function Tests

PFTs are routinely used in the evaluation of pulmonary sarcoidosis patients. However, there is no diagnostic pattern in PFTs. The most prevalent pattern of PFTs is restrictive lung disease, although obstruction can nevertheless also be present, either in isolation or concomitantly. FVC is most commonly used to measure response to therapy. Nonetheless, the volume of FVC does not correlate clinically with symptoms of dyspnea, and there is no definite consensus on how to follow changes in FVC in response to treatment. Based on intrapulmonary fibrosis, in the absence of better data, a decline of ≥ 5% (absolute change of predicted) FVC is consistent with refractoriness in sarcoidosis patients (Korsten et al., 2016; Baughman et al., 2015).

Diffuse lung capacity of carbon monoxide has also been used. However, there is a higher intra-subject variability than FVC. Significant reduction in DLCO may indicate refractory pulmonary disease in the absence of pulmonary arterial hypertension as a cause of drop in DLCO (Korsten et al., 2016; Baughman et al., 2015).

PFT will follow ATS/European Respiratory Society task force for standardization of lung function testing (Miller et al., 2005) and the revisions provided for DLCO (Graham et al., 2017).

PFT results will include FEV1, FVC, FVC % predicted (NHANES III reference values), FEV1/FVC ratio, PEFR or FEF_{max}, TLC, RV, DLCO (uncorrected for Hb), DLCO % predicted and DLCO/VA at screening visit, Visits 5, 8, 10, and 11 (every 12 weeks).

At the randomization visit, spirometry results will include FEV1, FVC, FVC % predicted (NHANES III reference values), FEV_1/FVC ratio and PEFR or FEF_{max}.

Patients should be instructed to avoid smoking within at least 1 hour of testing, consuming alcohol within 4 hours of testing, performing vigorous exercise within 30 minutes of testing, wearing clothing that substantially restricts full chest and abdominal expansion, and eating a large meal within 2 hours of testing. Ideally, when patients return for repeat testing, the equipment and the operator should be the same, and the time of day should be within 2 hours of previous test times. The order of the tests should be kept constant for each subject on each subsequent PFT.

7.2.3. Imaging (HRCT; CXR)

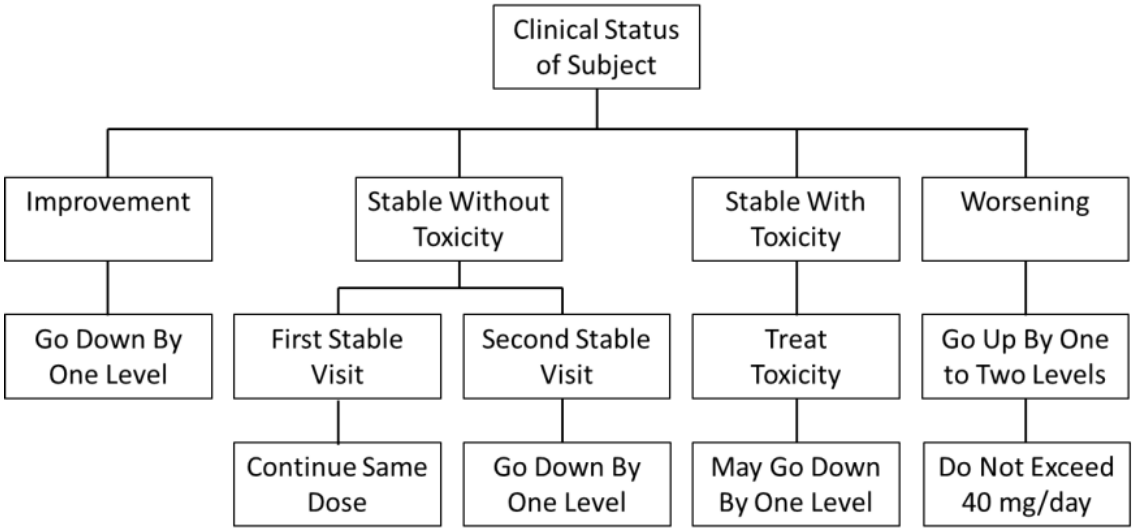
Although granulomas are microscopic structures, sarcoidosis granulomas have a proclivity to coalesce into macroscopic nodular conglomerations that are capable of being detected with plain radiographic or HRCT radiographic techniques. HRCT reveals more sarcoidosis lung involvement than the CXR including, identifying more parenchymal and mediastinal/hilar disease as well as parenchymal details to reliably differentiate from other diffuse lung diseases. HRCT findings have been correlated with lung pathology and have been proposed as a biomarker of disease activity.

The intriguing observations of chest radiographs in sarcoidosis published by Scadding in 1961 (Scadding, 1961; Attachment 11) are still considered the gold standard because of the limited use of radiation and its association with resolution or progression of the disease although these stages do not necessarily progress or regress from one to another. However, interobserver variability and lack of association with functional clinical parameters (eg, PFT, 6MWT) are limiting factors (Korsten et al., 2016; Chopra et al., 2016).

Imaging 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.

7.2.4. Corticosteroid Tapering

Corticosteroids are typically the first- line when treatment of sarcoidosis is required. Concerns of significant corticosteroid toxicity results in efforts to taper as early as possible. There is little consensus regarding the optimal algorithm for tapering corticosteroids (Judson, 2014). Subjects will be evaluated at each visit (following randomization) and the following algorithm will be used to taper the corticosteroid dosage:



Incremental doses of prednisone for the study are 40, 30, 20, 10, 7.5, 5, 2.5, and 0 mg (Baughman et al., 2002).

7.2.5. Steroid Toxicity Questionnaire

This directed questionnaire (Attachment 2) provides a Likert scale for the subject to score several specific potential symptoms which could be attributed to steroid toxicity (Baughman et al., 2002).

7.2.6. King's Sarcoidosis Questionnaire

The King's Sarcoidosis Questionnaire (Attachment 4) is a 28 item questionnaire for subjects to indicate the status of their sarcoidosis and treatment (Patel et al., 2013). Higher scores indicate improvement. A change of 4 points is considered clinically meaningful.

7.2.7. Fatigue Assessment Scale (FAS)

The Fatigue Assessment Scale (Attachment 5) is a 10 item checklist for subjects to indicate their level of fatigue (De Vries et al., 2004). Lower scores indicate improvement (less fatigue). A change of 4 points is considered clinically meaningful.

7.2.8. Patient's Global Assessment

The Patient's Global Assessment (Attachment 6) is a numerical rating scale typically used for patient reported outcomes. Patients report on improvement/worsening of their overall disease compared to the condition at baseline and at every visit (Nikiphorou et al., 2016).

7.2.9. Physician Global Assessment

The Physician Global Assessment (Attachment 7) is a physician's assessment of improvement/worsening of the patient's overall disease compared to the condition at baseline and at every visit as ranked on a numerical rating scale.

7.2.10. Medical Research Council Dyspnea Scale (MRC)

The Medical Research Council Dyspnea scale (Attachment 8) is a 5 score for subjects to indicate their degree of breathlessness related to activity (Fletcher, 1952).

7.2.11. Leicester Cough Questionnaire (LCQ)

The Leicester Cough Questionnaire (Attachment 9) is a 19 item questionnaire for subjects to indicate the impact of cough on various aspects of their life (Birring et al, 2003).

7.2.12. Six Minute Walk Test (6MWT)

The 6MWT (Attachment 12) is objective evaluation of functional exercise capacity. It is a practical test that requires a 100-ft hallway but no exercise equipment or advanced training. It measures the distance walked on a flat, hard surface during the period of 6 minutes (treadmill are not recommended). The 6MWT evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. Changes in 6MWT after therapeutic interventions correlate with subjective improvement in dyspnea.

The 6MWT will be performed according to ATS guidelines with an improvement of $\geq$ 30 meters being considered as meaningful. Repeat testing should be performed about the same time of day to minimize intraday variability. The Borg Scale is used to compare shortness of breath and fatigue between baseline prior to the 6MWT test and upon completion of the 6MWT test (ATS, 2002).

7.2.13. Extrapulmonary Physician Organ Severity Tool (ePOST)

The ePOST examines 18 extrapulmonary organs and assigns a score to each one (0 = not affected to 6 = very severely affected). The state of sarcoidosis is evaluated at each visit, by the investigator. Investigators use all clinical information available to them, including laboratory analyses, and assessments by subspecialists to assess each organ system. Scores are calculated by the ePOST score divided by the number of extrapulmonary organs involved at any time during the study (Judson et al., 2008).

7.2.14. Biomarkers/genomics

As stated in Section 6.1, despite many potential biomarkers being identified for monitoring and diagnosis, there is still a lack of adequately specific and sensitive disease markers for clinical usage, necessitating further research on these fronts. Accordingly, biomarkers levels will be collected as an exploratory assessment and compared between Screening, and every 12 weeks (up to 48 weeks for those subjects participating in the optional Open-label

Extension Phase). These 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.

Genomic profile (optional) will be assessed based on the evolution of science at the time of study completion.

7.2.15. Work Productivity and Activity Impairment

The WPAI is a validated assessment of work and activity impairment associated with health problems (Zhang et al., 2010). This questionnaire is to be completed by subjects. When this assessment is required, it should be the first assessment done at any visit (with the subject completed efficacy questionnaires) and must be completed prior to any study drug dosing.

Subjects will be provided a quiet, private place to complete the assessment. Subjects will be instructed to answer all questions to the best of their ability and without help from others (including study staff, relatives, or friends). Subjects may refrain from answering any question.

The study staff should review the questionnaire after it is completed and encourage the subjects to complete any missing information. Study staff will record the refusal of subjects to answer any questions in the source documents.

7.3. Efficacy Endpoints

The endpoints for the efficacy objective are:

- 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 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
  - PFT (at applicable time points).
  - ePOST.
  - Supportive efficacy endpoints per applicable time points.
    - 6MWT.
    - Symptom relief (Leicester Cough Questionnaire, Medical Research Council Dyspnea Scale, steroid toxicity questionnaire).
    - CXR - change in Scadding score.

- Percentage change in overall 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 improved/stable/deteriorate side-by-side comparison of HRCT on a 5-point Likert score: much worse; worse; unchanged; better; much better (central reader).
- Percentage of 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, (Scadding, 1961).
- 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 WPAI over time.

Biomarkers

Biomarker levels will be compared between Screening, 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.

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

7.4. Primary Outcome Measures

Outcome measures are identified to facilitate trial registration and patient access to basic results disclosed on public registries.

The primary outcome measures are:

- Number of participants in each category of assessment based on forced vital capacity, Weeks 24 and 48
- Number of participants in each category of assessment based on the diffusing capacity of the lungs for carbon monoxide (DLCO), Weeks 24 and 48
- Number of participants in each category of assessment based on high resolution computer tomography, Weeks 24 and 48
- Number of participants in each category of assessment based on the King's Sarcoidosis Questionnaire (General Health), Weeks 24 and 48

- Number of participants in each category of assessment based on the Fatigue Assessment Score, Weeks 24 and 48
- Number of participants receiving each dose of prednisone, Weeks 24 and 48

8. STUDY DESIGN

8.1. Description

This is a multicenter, randomized, double-blind, placebo-controlled exploratory study evaluating the efficacy and safety of Acthar Gel in the treatment of pulmonary sarcoidosis.

The study will have 3 phases: Screening (up to 28 days); double blind treatment (24 weeks); and an optional open-label, 24 weeks extension. A follow-up visit will be conducted 4 weeks (± 2 days) after the last dose of IMP is administered.

Following signature of the ICF and a screening period of up to 28 days, subjects who meet all eligibility criteria will be randomly assigned to receive either 1 mL (80 U) of Acthar Gel or 1 mL of a matching placebo SC 2×/week. Subjects will be assigned to treatment in a 1:1 ratio with up to 50 subjects per arm for a total of approximately 100 subjects.

Dose reduction of 50% may be implemented once during the study, if a subject meets one of the following prespecified safety criteria based on clinical judgment:

- Uncontrolled hypertension (newly developed or worsening of existing hypertension) before/or in conjunction with addition/adjustment of antihypertensive therapy.
- Uncontrolled diabetic signs/symptoms (newly developed of worsening of existing diabetes) before/or in conjunction with addition/adjustment of antihyperglycemic therapy.
- Unacceptable toxicity defined as any AE of at least moderate intensity not adequately controlled by concomitant medication use or other non IMP-related measure

The justification for dose reduction will be captured in the eCRF. Subjects will remain on the 40 U or matching placebo 2×/week for the remainder of the study. Subjects who, despite dose reduction, continue to experience any of the above mentioned AEs, (meet a criteria as above) or experience another event will be withdrawn from the study due to AE (Section 12.3).

Subjects will be followed every 4 weeks (± 5 days) for 24 weeks (Visit 2 to Visit 8). During each visit following Visit 2, steroid tapering evaluation will occur based on the corticosteroid tapering algorithm (Section 7.2.4). A justification for any deviation will be captured in the eCRF.

In addition, subjects and physicians will complete patient reported outcomes, and safety will be evaluated based on targeted physical examination per organ involved, vital signs, imaging, and laboratory test results. 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 extra-pulmonary manifestations) will also be captured in the eCRF. 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).

Subjects who decline participation in the Open-label Extension Phase, or those ineligible, will have their End-of-Treatment visit during Visit 8.

All subjects will have a follow-up visit 4 weeks (± 2 days) after the last dose of IMP, regardless of treatment group and/or participation in the optional Open-Label Extension Phase.

During the optional Open-label Extension Phase, subjects will be treated with Acthar Gel 80 U 2×/week for an additional 24 weeks. Subjects who had their dose reduced once by half will be treated with Acthar Gel 40 U 2×/week. There will be 3 scheduled visits during this phase. Visit 9, 4 weeks into the extension phase (Week 28), Visit 10 (Week 36) and Visit 11 (Week 48). During these visits corticosteroid tapering will follow the same procedures and algorithm as in the double blind phase. Subjects and physicians will complete patient reported outcomes, and safety will be evaluated based on targeted physical examination per organ involved, vital signs, imaging, and laboratory test results. 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.

During Visit 11 End-of-Treatment procedures will be completed. Responder rate analysis (efficacy endpoints) will be determined by the investigator and an independent adjudication. Adjudication will serve to address inter-rater variability. In case of discrepancies, the adjudication determination will be utilized for purposes of efficacy endpoint analyses. Likewise, central HRCT readings and CXR will be used for the purpose of the imaging efficacy analyses.

8.2. Approximate Duration of Subject Participation

Subjects will participate in the study for a total of approximately 14 months, including a screening period of up to 28 days, a double blind treatment period of 24 weeks, and an optional open-label extension period of an additional 24 weeks, and a follow up visit 4 weeks (± 2 days) after final dose of IMP.

8.3. Approximate Duration of Study

The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the site(s) to identify and enroll eligible subjects. The entire study is expected to require approximately 4 years to complete.

8.4. Approximate Number of Subjects

Approximately 100 subjects will be globally enrolled at approximately 75 sites.

9. SELECTION OF SUBJECTS

9.1. Inclusion Criteria

The subjects must meet all of the following criteria for inclusion in the study:

1. Subjects must be adequately informed and understand the nature and risks of the study and must be able to provide a signature and date on the ICF.
2. Subjects must be ≥ 18 and ≤ 90 years of age at Screening (Visit 1) and can be male or female.
3. Female subjects must be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; or postmenopausal with no history of menstrual flow in the 12 months prior to Screening (Visit 1); or if of childbearing potential must be nonpregnant, nonlactating and agree to use effective contraception when with a male partner throughout study participation (through the follow-up visit). Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), and abstinence.
4. Subjects must be able to communicate effectively with study personnel.
5. Subjects must be able and willing to follow all protocol requirements and study restrictions including able and willing to inject SC Acthar Gel on their own or by caregiver.
6. Subjects must be able and willing to return for all study visits.
7. Subject with biopsy confirmed sarcoidosis meeting ATS criteria with onset of sarcoidosis ≥ 1 year prior to Screening (Hunninghake et al., 1999).
8. Symptomatic pulmonary disease defined as any one of the following criteria for PFT; imaging; steroid dose; or symptoms:
    - Decrease ≥ 5% absolute change of % predicted in the best available FVC within the past 2 years.
    - Decrease ≥ 5% absolute change of % predicted in the best available DLCO within the past 2 years.
    - Radiographic progression in chest imaging on side by side comparison within the past 2 years.
    - Progression of pulmonary sarcoidosis necessitating increase in antisarcoidosis therapy in the past 2 years.
    - Dyspnea with Medical Research Council Scale of ≥ 1 at Screening (Visit 1).
9. Subject receiving ≥ 5 mg and ≤ 40 mg daily prednisone (or equivalent) for pulmonary sarcoidosis.
10. Stable prednisone dose ≥ 4 weeks prior to Screening (Visit 1).

11. Subjects treated with any disease modifying antisarcoidosis drugs (eg, methotrexate) must be on stable dose for ≥ 3 months prior to Screening (Visit 1).
12. Forced vital capacity (FVC) ≥ 45% predicted. If FVC at Screening is more than 95% predicted, a documented decrease ≥ 5% absolute change of % predicted in the best available FVC is required after diagnosis of Sarcoidosis.
13. Diffusing capacity of the lung for carbon monoxide (DLCO) ≥ 30%.

9.2. Exclusion Criteria

Subjects are ineligible for the study if they meet any of the following criteria:

1. Subject is from a vulnerable population, as defined by the US CFR Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the clinical research organization, or of the IRB/IEC.
2. Subject is unwilling to receive, or is intolerant of, SC injections.
3. Subject has a history of sensitivity to ACTH preparations or sensitivity to porcine protein products.
4. Any difference >10% in FVC on spirometry between the determination at Screening (Visit 1) and the determination at Visit 2.
5. Pulmonary arterial hypertension requiring or receiving treatment.
6. Extra pulmonary involvement that per the Investigator's evaluation requires treatment that would impede corticosteroid tapering for pulmonary involvement.
7. Treatment with antitumor necrosis factor-α antibody (eg, infliximab, adalimumab) in prior 3 months.
8. Subject has any known contraindication(s) to Acthar Gel (Mallinckrodt ARD LLC, 2019) including, but not limited to:
    - Any known history of:
        - Scleroderma
        - Osteoporosis (evidence of vertebral or long bone fracture, or a lumbar T-score of more than -2.5 SD below the mean of the reference population). Subjects previously diagnosed as having osteoporosis and successfully treated will not be excluded solely on the basis of a historical diagnosis of osteoporosis as long as the lumbar T-score obtained per routine follow up within the 12 months prior to Screening (Visit 1) is ≥ -2.5 SD.
        - Ocular herpes simplex.
    - Any primary adrenocortical insufficiency, or adrenal cortical hyperfunction.
    - Any current congestive heart failure (defined as New York Heart Association Functional Class III to IV).

- Peptic ulcer requiring treatment or history of upper gastrointestinal bleeding within 24 weeks prior to Screening (Visit 1).
- Recent major surgery (ie, major fluid or blood shift) within 24 weeks prior to Screening (Visit 1).

9. Subject has uncontrolled diabetes, hypertension, or other contra-indication to increased dosage of glucocorticoids.
10. Subject has chronic active hepatitis including active or chronic hepatitis B, or acute or chronic hepatitis C.
11. Subject has a history of TB infection, any signs/symptoms of TB, or any close contact with an individual with an active TB infection.
12. Subject has a clinically significant infection requiring administration of intravenous antibiotics or hospitalization in the 4 weeks prior to Screening (Visit 1) or between Screening and the first dose of IMP.
13. Subject has known immune compromised status (not related to disease/condition under study), including but not limited to, individuals who have undergone organ transplantation or who are known to be positive for the human immunodeficiency virus.
14. Subject has any solid tumor malignancy currently diagnosed or undergoing therapy, or has received therapy for any solid tumor malignancy in the 5 years prior to Screening (Visit 1); with the exception of treated and cured basal cell carcinoma, treated and cured squamous cell carcinoma of the skin, and treated and cured carcinoma in situ of the cervix.
15. Subject has a diagnosis of, is undergoing therapy for, or has received therapy for a hematologic malignancy in the 5 years prior to Screening (Visit 1).
16. Subject has current or recent (within 24 weeks prior to Screening (Visit 1) drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Diagnostic Criteria for Drug and Alcohol Abuse (American Psychiatric Association, 2013).
17. Subject has any of the following laboratory abnormalities at Screening (Visit 1):
    - Hemoglobin ≤ 8.0 g/dL.
    - Platelet count ≤ 50,000 cells/µL.
    - Absolute neutrophil count ≤ 1,000 cells/µL.
    - Aspartate aminotransferase, alanine aminotransferase, or total bilirubin > 2 times upper limit of normal.
    - Positive hepatitis B surface antigen or hepatitis B core antibody, or positive HCV antibody. Note: If HCV antibody is positive at Screening, HCV polymerase chain reaction will be automatically analyzed. Subjects with a positive HCV must have HCV polymerase chain reaction < 25 IU/mL at the screening visit to be eligible.

- Positive or indeterminate IGRA for TB.

18. Subject has any other clinically significant disease, disorder or laboratory abnormality (including those listed on the Prescribing Information, Section 5: Warnings and Precautions [Mallinckrodt ARD LLC, 2019]) which, in the opinion of the investigator (by its nature or by being inadequately controlled), might put the patient at risk due to participation in the study, or may influence the results of the study or the subject's ability to complete the study.
19. Subject is: 1) currently participating in another interventional clinical study or 2) has participated in another interventional clinical study within 30 days or five half-lives, whichever is longer, prior to Screening (Visit 1) or 3) plans to participate in another interventional clinical study prior to 90 days following the completion of current study.
20. Subject has any history of use of ACTH preparations for treatment of Sarcoidosis.

9.3. Screen Failure

Subjects will be allowed to repeat any single screening assessment/procedure once, if necessary, if it is within the screening window. The subject will not be considered a screen failure unless the repeat assessment/procedure results do not meet eligibility criteria. The period from the beginning of screening-related procedures at Screening (Visit 1) to the Randomization (Visit 2) must not exceed 28 days, inclusive of any repeat screening procedures.

Subjects who do not meet all of the eligibility criteria at screening or randomization visits (Visits 1 and 2) will be deemed a screen failure and the reason for the screen failure will be documented. A subject who is a screen failure at the screening or randomization visits may be rescreened. The subject must repeat all screening procedures (except HRCT as long as it is performed within 28 days of Day -1). The period from the start of rescreening-related procedures to the first dose of IMP must not exceed 28 days. Subjects may be rescreened only once.

10. PRIOR AND CONCOMITANT MEDICATION

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 30 days prior to the screening visit) and concomitant (taken from the screening visit through the Follow-up Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation) received will be recorded.

In addition, all prior treatments for sarcoidosis administered since diagnosis will be recorded with start and stop date, dose, unit, frequency and route of administration to the extent of data availability.

10.1. Permitted Concomitant Medications

Subjects enrolled into the study must have been on stable prednisone dose for at least 4 weeks prior to Screening (Visit 1). Subjects who are treated with any disease modifying antisarcoidosis drugs (eg, methotrexate) must have been on a stable dose for at least 3 months prior to Screening (Visit 1). Corticosteroid tapering will be initiated as of Week 4 (Visit 3) according to the tapering algorithm described in Section 7.2.4. The dose of all other antisarcoidosis medications should remain stable for the duration of the study. The dose may be reduced or discontinued only for toxicity but must not be increased.

10.2. Prohibited Concomitant Medications/Treatments

The following treatments will not be permitted during the study:

- No new antisarcoidosis medication is permitted.
- Treatment with antitumor necrosis factor-α (eg, infliximab, adalimumab) in the 3 months prior to Screening (Visit 1) and throughout the study.
- Administration of live or live-attenuated vaccines.
- Long acting corticotropins.
- Any investigational drug, device, or procedure administered as part of a research study.

If any prohibited medication is taken during the study, all pertinent information will be recorded in source documents and the eCRF. The designated study MM must be informed immediately so the sponsor may determine whether to continue the subject in the study.

11. PROCEDURES

The schedule of study procedures is summarized in the Schedule of Events (Table 1).

If the subject is unable to come to the study site for any visit after the Baseline visit, all procedures that can be completed remotely (eg, by telephone) will be conducted as scheduled.

Collect as much information as possible, including but not limited to, AE information, new concomitant medications and changes in existing therapy, corticosteroid use, compliance with investigational therapy. Complete applicable physician assessments, PFT tests, subject-reported outcomes and assessments, 6MWT, ECG, imaging and laboratory tests at the next planned study visit as unscheduled procedures, if not already scheduled for that particular study visit.

Changes in study visit schedule, missed visits, and procedures will be captured in the eCRF.

11.1. Study Days -28 to -1 (Screening Visit 1)

Screening assessments must be performed within 28 days prior to Visit 2.

The following procedures will be performed at the screening visit:

- Informed consent. Neutral language should be used in describing the study to neutralized placebo effect.
- Injection and diary training. Subjects (or caregivers) will be trained on SC injections and diary completion using the training tools provided separately. The injection training may be foregone if either the subject or caregiver is a medically trained professional.
- Inclusion/exclusion criteria.
- Medical, surgical, and medication history. Medical history will include smoking history (classified into 1 the following categories: current smoker; ever smoked [more than 1 cigarette/day for more than 1 year]; never smoked), length of sarcoidosis diagnosis, organ involvement, and prior and current medication. Occupational history should also be collected.
- Demographics.
- Concomitant medications.
- Height.
- Vital signs. Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, and respiratory rate.
- Weight measured. Every effort should be made for weight to be measured by the same calibrated scale at every visit.
- Physical examination (see Section 14.3). The full physical examination will include a targeted examination of the organ(s) involved. All efforts must be undertaken for the same physician to perform the physical examination per subject, per organ involved, at each visit.

- Physician Global Assessment (Attachment 7)
- ePOST.
- 12-Lead ECG (see Section 14.6).
- Patient-reported outcomes and assessments. Patient-reported outcomes include: Steroid toxicity questionnaire; 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), 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.
- 6MWT: The 6MWT would be performed according to the ATS protocol (Attachment 12). Reasons for not performing the 6MWT will be captured in the eCRF.
- Clinical laboratory tests. Samples will be collected from subjects who have been fasted for at least 12 hours (drinking water is allowed). The following tests will be conducted:
  - Complete blood count.
  - Clinical chemistry (including liver function tests).
  - HbA1C.
  - Lipid profile.
  - 25-Hydroxy vitamin D and 1, 25-dihydroxy vitamin D, and parathyroid hormone.
  - C-reactive protein.
  - Thyroid stimulating hormone, thyroxine T3 and T4.
  - Hepatitis serology- Hepatitis B surface antigen, Hepatitis B core antibody, hepatitis C virus antibody, hepatitis C polymerase chain reaction for subjects positive for hepatitis C antibody only.
  - Biomarkers (including RNA and DNA, if genetic ICF signed).
  - Serum human chorionic gonadotropin hormone (females of child bearing potential only).
  - Urine analysis (local laboratory).
- Tuberculosis testing (tested by IGRA).
- PFT.
- CXR and HRCT should be performed within 28 days of Day -1. The CXR reading will also include Scadding scoring (Attachment 11).
- AEs (collected from the time of signature of the ICF).

- Contact IXRS to register subject.
- Schedule next visit and remind subjects to arrive in fasting condition for Visit 2 (drinking water is permitted).

11.2. Visit 2 Procedures

The investigator or designee will complete the following procedures at Visit 2:

- Inclusion/exclusion criteria review.
- Spirometry (ascertain any difference in FVC < 10% compared with FVC performed at Visit 1 before continuing).
- Vital sign determinations Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, and respiratory rate (see Section 14.4).
- Weight measured. Every effort should be made for weight to be measured by the same calibrated scale at every visit.
- Physical examination (see Section 14.3). The full physical examination will include a targeted examination of the organ involved. All efforts must be undertaken for the same physician to perform the physical examination (per organ involved) at each visit.
- ePOST: All efforts must be undertaken for the same physician to perform the ePOST (Attachment 3) side-by-side with prior evaluations.
- Physician Global Assessment (Attachment 7).
- Patient reported outcomes and assessments. Patient-reported outcomes include: Steroid toxicity questionnaire; 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), WPAI (Attachment 10).
- Clinical laboratory tests:
  - Complete blood count.
  - Clinical chemistry including liver function tests (samples will be collected from subjects who have been fasted for at least 12 hours. Drinking water is allowed).
  - HbA1C.
  - Human chorionic hormone (urine pregnancy testing, females of child bearing potential only [performed at a local laboratory]).
- Injection and diary training (if additional training is required).
- Contact IXRS to randomize subject and dispense study drug kits.
- Dosing will begin after Visit 2 procedures are completed and subject is randomized. Subjects (and/or caregivers) will be trained on SC injections and diary

completion using the training tools provided separately. Additional training may be provided during Visit 2 before randomization occurs. The injection training may be foregone if either the subject or caregiver is a medically trained professional. The subject or subject's caregiver will administer the first dose of IMP in the clinic under the supervision of study staff. The subject will remain in the clinic for at least 1 hour postinjection to monitor for allergic or anaphylactic reactions. Instruct the subject as to appropriate scheduling of weekly injections and the importance of compliance.

- AEs and concomitant medications.
- Remind the subject to return in fasting condition (drinking water is allowed) for the next visit and to bring all used and unused vials in a cooler. Subsequent visits should not be scheduled for the day of injection so as not to influence patient reported outcomes.

11.3. Visits 3, 4, 6, and 7, Procedures

The investigator or designee will complete the following procedures at Visit 3, 4, 6, and 7:

- Patient reported outcomes. Patient-reported outcomes include: Steroid toxicity questionnaire; 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), WPAI (Attachment 10).
- Vital sign determinations. Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, and respiratory rate (see Section 14.4).
- Weight determination. Every effort should be made for weight to be measured by the same calibrated scale at every visit.
- Physical examination (see Section 14.3). Full physical examination will include targeted examination per organ involved. All efforts must be undertaken for the same physician to perform the physical examination per subject, per organ involved at each visit.
- ePOST: All efforts must be undertaken for the same physician to perform the ePOST (Attachment 3) side-by-side with prior evaluations.
- Physician Global Assessment (Attachment 7).
- Clinical laboratory tests:
  - Complete blood count.
  - Clinical chemistry, including liver function tests. Samples will be collected from subjects who have been fasted for at least 12 hours.
  - HbA1C.
  - Human chorionic hormone (urine pregnancy testing, females of child bearing potential only – local laboratory).

- Subject diary review.
- Study drug accountability.
- Corticosteroid tapering. (At Visit 3, if the subject improved or was stable at both Visit 2 and Visit 3, tapering can be applied).
- AEs and concomitant medications.
- Contact IXRS and dispense IMP kits and encourage compliance.
- Remind the subjects to arrive in fasting condition (drinking water is permitted) for Visits 4, 5, 6, and 7 and to bring all IMP kits including used and unused vials to each visit in a cooler.

11.4. Visit 5 Procedures

In addition to all procedures described in Section 11.3 the following will also be performed at Visit 5 by the investigator or designee:

- C-reactive protein.
- 25-Hydroxy vitamin D, 1, 25-dihydroxy vitamin D, parathyroid hormone (Visit 5 only).
- Urinary analysis (local laboratory).
- Subject diary review.
- Study drug accountability.
- Biomarkers sample collection (including RNA, if genetic ICF signed).
- PFT.

11.5. Visit 8 Procedures

The investigator or designee will complete the following procedures at Visit 8:

- Patient reported outcomes. Patient-reported outcomes include: Steroid toxicity questionnaire; 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), WPAI (Attachment 10).
- Vital sign determinations Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, and respiratory rate (see Section 14.4).
- Weight measured. Every effort should be made for weight to be measured by the same calibrated scale at every visit.
- Physical examination (see Section 14.3). The full physical examination will include a targeted examination of the organ involved. All efforts must be undertaken for the same physician to perform the physical examination, per subject, per organ involved, at each visit.

- Physician Global Assessment (Attachment 7).
- ePOST: All efforts must be undertaken for the same physician to perform the ePOST (Attachment 3) side-by-side with prior evaluations.
- 12-Lead ECG (see Section 14.6).
- PFT (Section 7.2.2).
- CXR and HRCT. Both CXR and HRCT should be evaluated side by side by investigator/radiologist for determining if the condition is improving, stable, or deteriorating based on a 5-point Likert score (Section 7.2.3).
- 6MWT: The 6MWT (Section 7.2.12) would be performed according to the ATS protocol (Attachment 12). Reasons for not performing the 6MWT will be captured in eCRF.
- Clinical laboratory tests:
  - Complete blood count.
  - Clinical chemistry (including liver function tests, samples will be collected from subjects who have been fasted for at least 12 hours, drinking water is permitted).
  - HbA1C.
  - Lipid profile.
  - C-reactive protein.
  - 25-Hydroxy vitamin D and 1, 25-dihydroxy vitamin D, and parathyroid hormone.
  - Biomarkers (including RNA, if genetic ICF signed).
  - Human chorionic hormone (urine pregnancy testing, females of child bearing potential only- local laboratory).
  - Urine analysis (local laboratory).
- Subject diary review.
- Study drug accountability.
- AEs and concomitant medications.
- Both the investigator and the subjects will independently be asked if they would choose to continue treatment. The investigator must respond before seeing the subject's response. Subjects may continue to the optional Open-label Extension Phase irrespective of their response (eg, placebo treated) at the discretion of the principal investigator.
- Subjects declining participation or ineligible (at the discretion of the principal investigator) for the Open-label Extension Phase will have end-of-treatment procedures completed (eg, return or study drug and equipment).
- Contact IXRS.

- For subjects entering the Open-Label Extension Period:
  - Remind the subjects to arrive in fasting condition for Visit 9 (drinking water is permitted) and to bring all IMP kits including used and unused vials to each visit in a cooler.
  - Dispense IMP kits and equipment.
  - Administer Acthar Gel under supervision of study staff and observation for at least 1 hour thereafter.
  - Instruct the subject to inject Acthar Gel 80 U (1 mL) 2×/week unless the subject had a single reduction of dose, in which case only 40 U (0.5 mL) 2×/week will be injected for the remainder of the study.
  - Corticosteroid tapering.

11.6. Visit 9 Procedures, Open-Label Extension Period

The investigator or designee will complete the following procedures at Visit 9:

- Patient reported outcomes. Patient-reported outcomes include: Steroid toxicity questionnaire; 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), WPAI (Attachment 10).
- Vital sign determinations Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, and respiratory rate (see Section 14.4).
- Weight determination. Every effort should be made for weight to be measured by the same calibrated scale at every visit.
- Physical examination (see Section 14.3). Full physical examination will include targeted examination per organ involved. All efforts must be undertaken for the same physician to perform the physical examination per subject, per organ involved at each visit.
- Physician Global Assessment (Attachment 7).
- ePOST: All efforts must be undertaken for the same physician to perform the ePOST (Attachment 3) side-by-side with prior evaluations.
- Clinical laboratory tests:
  - Complete blood count.
  - Clinical chemistry, including liver function tests. Samples will be collected from subjects who have been fasted for at least 12 hours.
  - HbA1C.
  - Human chorionic hormone (urine pregnancy testing, females of child bearing potential only- Local laboratory).

- Subject diary review.
- Study drug accountability.
- Corticosteroid tapering.
- AEs and concomitant medications.
- Contact IXRS, dispense IMP kits, and encourage compliance.
- Remind the subjects to arrive in fasting condition for Visit 10 (drinking water is permitted) and to bring all IMP kits including used and unused vials to each visit in a cooler.

11.7. Visit 10 Procedures, Open-Label Extension Period

The investigator or designee will complete the following procedures at Visit 10:

- Patient reported outcomes and assessments. Patient-reported outcomes include: Steroid toxicity questionnaire; 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), WPAI (Attachment 10).
- Vital sign determinations (see Section 14.4).
- Weight measured. Every effort should be made for weight to be measured by the same calibrated scale at every visit.
- Physical examination (see Section 14.3). The physical examination will include a targeted examination of the organ involved. All efforts must be undertaken for the same physician to perform the physical examination (per organ involved) at each visit.
- Physician Global Assessment (Attachment 7).
- ePost: All efforts must be undertaken for the same physician to perform the ePOST (Attachment 3) side-by-side with prior evaluations.
- Clinical laboratory tests:
  - Complete blood count.
  - Clinical chemistry (including liver function tests, samples will be collected from subjects who have been fasted for at least 12 hours, drinking water is permitted).
  - HbA1C.
  - 25-Hydroxy vitamin D and 1, 25-dihydroxy vitamin D, and parathyroid hormone.
  - C-reactive protein.
  - Biomarkers (including RNA, if genetic ICF signed).

  - Human chorionic hormone (urine pregnancy testing, females of child bearing potential only- Local laboratory).
  - Urine analysis (local laboratory).
- Subject diary review.
- Study drug accountability.
- PFT (Section 7.2.2).
- Corticosteroid tapering.
- AEs and concomitant medications.
- Contact IXRS, dispense IMP kits, and encourage compliance.
- Remind the subjects to arrive in fasting condition (drinking water is permitted) for Visit 11 and to bring all IMP kits including used and unused vials to each visit in a cooler.

11.8. Visit 11 Procedures, Open-Label Extension Period

The investigator or designee will complete the following procedures at Visit 11:

- Patient reported outcomes and assessments. Patient-reported outcomes include: Steroid toxicity questionnaire; 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), WPAI (Attachment 10).
- Vital sign determinations (see Section 14.4).
- Weight measured. Every effort should be made for weight to be measured by the same calibrated scale at every visit.
- Physical examination (see Section 14.3). The physical examination will include a targeted examination of the organ involved. All efforts must be undertaken for the same physician to perform the physical examination (per organ involved) at each visit.
- Physician Global Assessment (Attachment 7).
- ePOST: All efforts must be undertaken for the same physician to perform the ePOST (Attachment 3) side-by-side with prior evaluations.
- 12-Lead ECG (see Section 14.6).
- PFT (Section 7.2.2).
- CXR and HRCT. Both CXR and HRCT should be evaluated side by side by investigator/radiologist for determining if the condition is improving, stable, or deteriorating based on a 5-point Likert score (Section 7.2.3).
- 6MWT. The 6MWT (Section 7.2.12) would be performed according to the ATS protocol (Attachment 12). Reasons for not performing the 6MWT will be captured in eCRF.

- Clinical laboratory tests:
  - Complete blood count.
  - Clinical chemistry (including liver function tests, samples will be collected from subjects who have been fasted for at least 12 hours).
  - HbA1C.
  - Lipid profile.
  - C-reactive protein.
  - 25-Hydroxy vitamin D and 1, 25-dihydroxy vitamin D, and parathyroid hormone.
  - Biomarkers (including RNA, if genetic ICF signed).
  - Human chorionic hormone (urine pregnancy testing, females of child bearing potential only, local laboratory).
  - Urine analysis (local laboratory).
- Subject diary review.
- Study drug accountability.
- AEs and concomitant medications.
- Both the investigator and the subjects will be independently asked if they would choose to continue treatment.

Used and unused medication and study supplies will be collected from the subjects and all other end-of-treatment procedures will be performed.

11.9. Visit 12 Procedures, Follow-up Visit

The following procedures will be completed at the follow-up visit 4 weeks (± 2) days after the final dose of IMP has been administered, regardless of treatment group, and/or participation in the optional open label extension:

- Physical examination (see Section 14.3). The physical examination will include a targeted examination of the organ involved. All efforts must be undertaken for the same physician to perform the physical examination (per organ involved) at each visit.
- Vital sign determinations (see Section 14.4).
- Weight measured. Every effort should be made for weight to be measured by the same calibrated scale at every visit.
- Clinical laboratory tests:
  - Complete blood count.
  - Clinical chemistry (including liver function tests, samples will be collected from subjects who have been fasted for at least 12 hours).

- Human chorionic hormone (urine pregnancy testing, females of child bearing potential only, local laboratory).
- Urine analysis (local laboratory).

- AEs and concomitant medications.

11.10. Early Termination Procedures

Subjects who discontinue participation for any reason prior to Visit 8 or Visit 11 will have the procedures listed for Visit 8 completed as soon as possible. The reason for discontinuation should be documented in eCRF. Unused medication and study supplies will be collected from the subjects. Subjects should also return to complete the follow-up procedures during Visit 12.

12. INVESTIGATIONAL MEDICINAL PRODUCT

Acthar Gel is a naturally sourced complex mixture of ACTH analogs and other pituitary peptides in 16% gelatin for intramuscular or SC injection. Acthar Gel contains 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH, and water for injection. Acthar Gel is obtained from processing porcine pituitary using an FDA approved process. Sarcoidosis is an approved indication for Acthar Gel (Mallinckrodt ARD LLC, 2019).

Placebo is a sterile preparation of 16% gelatin for intramuscular or SC injection. Placebo contains 0.5% phenol, not more than 0.1% cysteine, sodium hydroxide and/or acetic acid to adjust pH, and water for injection. The placebo formulation is identical to Acthar Gel except that it contains no active medication.

12.1. Methods of Assigning Subjects to Treatment Groups

12.1.1. Randomization

Subjects will be randomized according to computer-generated allocation scheme to receive either Acthar Gel 1 mL (80 U) or placebo 1 mL administered 2×/week. Both investigators and the subjects will be blinded to the treatment assignment. A block randomization will be performed. The biostatistician will decide on the details at the time of the creation of the randomization scheme.

12.1.2. Interactive Telephone/Web Response System

The investigator or designee will contact IXRS to register subjects at Screening (Visit 1). The subject's identification number (ID) will be determined by the IXRS and will be used to identify the subjects for the duration of the study within all systems and documentation. Subject identification numbers will consist of 7 digits: the first 4 digits reflect the site number assigned to the Investigator and the last 3 digits are the subject number.

A subject ID number will not be assigned to more than 1 subject. If a subject is not eligible to receive treatment, or should a subject discontinue from the study, the subject ID number cannot be reassigned to another subject.

In the event that a subject is rescreened within the screening window, they do not need a new subject ID number. At the Randomization Visit, qualified subjects who meet all of the eligibility criteria will be randomized into the study.

The investigator or designee must contact the IXRS to report a subject as a screen failure if the subject does not meet eligibility criteria prior to randomization.

The investigator or designee must contact IXRS to record each subject visit, to receive the IMP assignments, and to report any subject status changes.

The investigator must maintain a subject master log linking the subject ID to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject will be masked on material received by the sponsor.

12.2. Identification of Investigational medicinal product

When knowledge of the IMP assignment is required for the medical management of an individual subject, the investigator may obtain the treatment assignment of the subject experiencing the AE or SAE. The treatment blind for that subject may be broken by accessing the IXRS using instructions provided in the Study Operations Manual. The investigator must notify the sponsor's MM or physician designee before unblinding, if at all possible, or immediately after unblinding the treatment assignment. The investigator and sponsor should make every effort to document and limit the subjects who are unblinded to the treatment assignment. The investigator must also indicate in source documents that the blind was broken and provide the date and reason for breaking the blind.

12.3. Dosing Procedures

Both Acthar Gel and placebo are supplied as 5 mL multidose vials. Acthar Gel vials contain 80 U of ACTH per mL. Vials will be labeled according to all applicable national and local regulations.

The vials should be warmed to room temperature before using. The vials should not be over pressurized; assure that no excess air (beyond the volume of product to be withdrawn) is inserted into the vial prior to withdrawing the product. After use the vial should be returned to refrigeration.

Subjects or their caregivers will administer SC injections of Acthar Gel or placebo after randomly assigned to treatment at Visit 2. The subject or subject's caregiver will administer the first dose of study drug and the first dose of Acthar Gel in the Open-Label at Week 24 in the clinic under the supervision of study staff. The subject will remain in the clinic for at least 1 hour postdose to monitor for allergic or anaphylactic reactions. All other doses will be administered by the subject or the subject's caregiver at home, but no dose should be administered on study visit days.

IMP cannot be taken on 2 consecutive days and cannot be taken more than 3 days apart. Therefore the following dosing schedule should be recommended to subjects at Visit 2, dose administration on either Monday and Thursday, Tuesday and Friday, or Wednesday and Saturday, and would be determined by the day of the week Visit 2 occurred.

In the double-blind treatment period Acthar Gel, 1 mL (80 U) or matching placebo (1 mL) will be administered twice weekly SC for up to 24 weeks. In the optional open-label extension, Acthar Gel 1 mL (80 U) will be administered SC twice weekly for up to 24 weeks. If a dose reduction of IMP is deemed necessary, a reduction of 50% (40 U) may be implemented once during the study based on safety criteria previously defined (see Section 8.1). The justification for dose reduction will be captured in the eCRF.

Subjects who, despite dose reduction, continue to experience any of the AE defined in Section 8.1, will be withdrawn from the study due to AE.

Subject who required dose reduction (50%) will inject 40 U (0.5mL) throughout the study, including during the optional Open-label Extension Phase, if applicable.

12.3.1. Treatment Discontinuation

Should any of the following occur, treatment with IMP may be reduced once by 50% (Section 8) or should be discontinued:

- Development of accelerated hypertension (defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg) that cannot be managed by the adjustment of concomitant medications such as antihypertensive medications.
- Development of congestive heart failure (Class III or IV) that cannot be managed by the adjustment of concomitant medications such as diuretics and antihypertensive medications.
- Development of uncontrolled diabetic signs/symptoms that cannot be managed by the adjustment of concomitant medications such as insulin and oral hypoglycemic agents.
- Development of any other AE of at least moderate intensity and possibly, probably or definitely related to IMP that cannot be managed by the adjustment of concomitant medications.

If the subject is withdrawn due to an AE, all efforts should be made to complete end-of-treatment procedures (Visit 8, Section 11.5) as soon as deemed possible and follow-up procedures (Visit 12, Section 11.9). If applicable, the suitability of subject continuing into the optional Open-label Extension Phase will be determined by the investigator.

12.4. Storage of Clinical Supplies

Acthar Gel and placebo will be maintained in a temperature controlled, secure locked area with restricted access at the study site.

Both Acthar Gel and Placebo will be supplied in kits containing the appropriate amount of vials. Both Acthar Gel and placebo will be stored under refrigeration between 2°to 8°C (36°to 46°F). Please refer to the Pharmacy Manual for complete information regarding storage and accountability of IMP.

12.5. Drug Accountability

In accordance with US FDA and ICH requirements, the investigator will, at all times, be able to account for all IMP furnished to the study site. A drug accountability record will be maintained for this purpose. The investigator must maintain accurate records indicating dates and quantity of IMP received, to whom it was dispensed (subject-by-subject accounting) and accounts of any IMP accidentally or deliberately destroyed. All unused IMP not involved in immediate subject dosing will be maintained under locked, temperature-controlled storage at the study site.

12.6. Compliance Monitoring

Prior to beginning the administration of IMP, subjects and/or their caregiver will be trained on dosing and SC injection, and must exhibit proper technique of SC administration during initial IMP administration at Visit 2. Subjects and/or their caregiver will be trained on the

completion of the study diary and will complete study diary entries to record all study drug administration and will bring it, along with all study drug kits including used vials to each visit. Used and unused vials will be inspected. Number of expected, administered doses and reason for discrepancies will be documented. Each time study drug is dispensed compliance will be encouraged. Subject diary training is an ongoing process as the diary will be reviewed with the subject at each visit to monitor compliance with study drug administration.

13. EFFICACY ASSESSMENTS

Efficacy will be evaluated using a combination of measures including: patient reported outcomes, imaging, PFT, and corticosteroid tapering. Detailed description of efficacy assessments is provided in Section 7.2.

14. SAFETY ASSESSMENTS AND PROCEDURES

Overall safety will be determined by the incidence, severity and relationship of AEs, physical examinations, vital signs, clinical laboratory abnormalities, and imaging. All safety assessments will be performed at times outlined in the Schedule of Study Events (Table 1). Additional (unscheduled) safety assessments may be performed as needed.

14.1. Adverse Events

AEs will be recorded from signing of the ICF and followed by the investigator until the AE is resolved or stabilized or at such time as the investigator refers the subject to a nonstudy physician for follow-up treatment. Any and all safety measures (which includes standard of care activities) should be provided by the study site to the subject. Any study site follow-up should be documented.

Refer to Section 16 for additional details on the handling of AEs and SAEs.

14.2. Medical and Surgical History

Medical and surgical history will be obtained at Screening (Visit 1). Medical history will include a review of the following systems: general, dermatological, respiratory, cardiovascular, gastrointestinal, genitourinary, gynecological (when applicable), endocrine, musculoskeletal, hematological, neuropsychological, immune (allergies), and head, eyes, ears, nose, and throat. Historical and current medical conditions including and date of last menstrual period for female subjects will be recorded. Occupational history will also be collected.

14.3. Physical Examination

A complete physical examination will be performed at all visits and will include evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart, peripheral pulses, presence or absence of edema), lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles) neurological system (including cranial nerves, reflexes, sensation, strength), skin, extremities and other conditions of note. Special emphasis will be made to sarcoidosis manifestations per organ involvement.

The findings of the physical examinations will be recorded. Any changes in medical conditions, specifically new medical conditions and worsening of existing medical conditions will be recorded as AE, as appropriate.

14.4. Vital Signs

Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, and respiratory rate.

The investigator may perform additional unscheduled vital sign measurements to evaluate or manage a suspected AE. These unscheduled vital sign measurements should be obtained after the subject has been seated for at least 5 minutes, if possible. Unscheduled vital signs will be recorded.

The date and time for all vital sign assessments will be recorded.

14.5. Clinical Laboratory Tests

The clinical laboratory tests are listed in Attachment 1. Tests should be conducted as described in the Schedule of Study Events (Table 1). All clinical laboratory tests will be done at a central laboratory facility except for urine analysis, and urine pregnancy test which will be performed at the local laboratory. Specific instructions for collection, processing, storage, and shipment of clinical laboratory samples will be provided in a separate laboratory manual, where appropriate.

Samples for serum chemistry testing for all visits will be collected under fasting conditions (at least 12 hours, drinking water is permitted). The date and time of the sample collection must be documented on the laboratory report. Investigators must review and sign laboratory reports. The clinical significance of each laboratory abnormality will be documented. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs, as appropriate.

In addition:

All female subjects of child bearing potential will have a serum pregnancy test at Screening (Visit 1). Urine pregnancy tests will be done at all other visits throughout the study. Results must be available prior to dosing with IMP. Subjects with positive results will be ineligible for study entry (Visit 1 or Visit 2) or immediately withdrawn from the study (Visit 3 through Visit 11) and the pregnancy reported as per Section 16.5.

HBsAg and HBcAb will be performed at Screening (Visit 1). Results of these tests must be negative or nonreactive for subjects to qualify for the study.

HCV will be performed at Screening (Visit 1). A positive HCV will automatically trigger a HCV PCR analysis. HCV PCR must be < 25 IU/mL to qualify for the study.

IGRA for TB will be performed at Screening (Visit 1). Results of this test must be negative for subjects to qualify for the study.

Out-of-Range Laboratory Values

Laboratory values from samples collected at Screening (Visit 1) will be evaluated by the investigator for eligibility of the subject in the study. Clinical laboratory tests may be repeated once to determine subject eligibility.

Laboratory values from scheduled or unscheduled laboratory assessments that fall outside the reference range from samples collected during the study or at study exit or early discontinuation will be assessed by the investigator for clinical significance. If the out of range value for samples is deemed clinically significant by the investigator, an AE will be recorded.

14.6. 12-Lead Electrocardiogram

Electrocardiogram will include assessment of sinus rhythm, heart rate, PR Interval, RR Interval, QRS Duration, Q-T Interval and QTcB.

A 12-lead ECG will be obtained for all subjects at Screening (Visit 1) and Visits 8 and 11. The date of the ECG must be documented on the ECG tracing. An appropriately trained and experienced physician must interpret this ECG. Date, time, and clinical parameters from the

all ECGs will be entered in the eCRF. At the discretion of the investigator a repeat ECG may be collected at the screening visit to confirm findings.

Additional ECGs may be performed any time throughout the study if deemed clinically necessary and entered into eCRF.

15. STATISTICAL METHODS AND PLANNED ANALYSIS

15.1. General Considerations

This section provides a general description of the statistical methods to be used in analyzing both safety and efficacy data. The key statistical issues or considerations will be addressed in more detail in a statistical analysis plan to be provided as a separate document that will be finalized prior to database lock. The analyses for the double-blind phase data will be performed after the database lock for the double-blind phase.

Unless otherwise specified, all statistical tests, when applicable, will be 2-sided with a significance level of 0.05. Summary statistics will be provided for all study variables with descriptive statistics (number of observations, mean, SD, median, minimum, and maximum) for numerical (or continuous) variables. Frequency and percentages will be calculated for categorical variables. All data will be summarized by treatment groups as appropriate. Data summary and analyses will be performed with SAS 9.4 or higher.

15.2. Analysis Populations

The following populations will be identified and analyzed in this study:

A Modified Intent-to -Treat (mITT) Population that includes all randomized subjects who receive at least 1 dose of IMP and who contribute any efficacy data to the study will be used for the efficacy analyses. A Safety Population that includes all randomized subjects who receive at least 1 dose of IMP will be used for all the safety analyses.

15.3. Subject Characteristics

15.3.1. Demographics

The demographic information will be summarized for each analysis population by treatment group.

15.3.2. Medical and Surgical History

Prior medical conditions or procedures will be summarized by body system and treatment group.

15.3.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the WHO Drug Dictionary. The incidence (number and percent) of prior and concomitant medication use will be summarized by treatment group.

15.3.4. Subject Disposition and Exposure to Investigational Medicinal Product

Subject disposition and treatment exposure will be summarized. The number of subjects who complete the study and who do not complete the study along with the reasons for discontinuation from the study will be summarized.

15.4. Safety Analysis

All subjects who receive at least 1 dose of IMP will be included in the safety analyses.

15.4.1. Adverse Events

The MedDRA coding terms will be used for coding AEs. The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by body system, preferred term, severity, and causality for each treatment group. Only TEAEs (events that are new in onset or aggravated in severity following treatment), will be included in all summaries. SAEs and deaths will be summarized.

15.4.2. Clinical Laboratory Tests

Clinical laboratory test results will be summarized descriptively and presented in data listings.

15.4.3. Physical Examination Findings

All physical examination results will be summarized descriptively and presented in a data listing.

15.4.4. Electrocardiogram Findings

Electrocardiogram measured changes from baseline for sinus rhythm, heart rate, PR interval, RR interval, QRS duration, Q-T Interval, and QTcB will be summarized.

15.4.5. Vital Signs

Vital sign results (heart rate, diastolic/systolic blood pressures, respiratory rate and weight) and corresponding changes from baseline values will be summarized at each visit with descriptive statistics by treatment group.

15.5. Efficacy Analysis

Efficacy analyses will be performed on the mITT Population. All efficacy endpoints will be summarized and analyzed. Pearson's chi-squared test will be used to evaluate the treatment difference between treatment groups for the categorical response endpoints. The continuous response endpoints will be analyzed using 2-sample t-test. The time-to-event endpoints will be analyzed using log-rank test. Kaplan-Meier curves will also be presented.

Additional exploratory analyses will be performed as appropriate. Such analyses may include logistic regression model, analysis of variance model, and/or mixed-effects model. Subgroup analyses based on demographics, baseline characteristics, study compliance, etc, will also be performed.

Missing data imputations will be performed as appropriate. In general, the last-observation-carried-forward method will be used to impute missing data. Additional missing data imputation may be performed as needed.

15.6. Interim Analysis

No interim analysis of the data is planned.

15.7. Statistical Power and Sample Size Considerations

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.

15.8. Deviations from Statistical Analysis Plan

Any deviations from the planned statistical analysis will be described and justified in the final clinical study report as appropriate.

16. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

16.1. Safety

For safety information about Acthar Gel, refer to the most recent version of the Package Insert (Mallinckrodt ARD LLC, 2019).

16.2. Definitions

AE

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. Examples of AEs include but are not limited to:

- Clinically significant laboratory findings.
- Clinically significant changes in physical examination findings.
- An AE occurring due to IMP overdose whether accidental or intentional.
- An AE occurring from investigational medicinal abuse.
- An AE associated with investigational medicinal withdrawal.
- Unexpected AE.

An unexpected AE is defined as an AE, the nature and severity of which is not consistent with the applicable product information in the most recent version of the package insert (Mallinckrodt ARD LLC, 2019).

Adverse experiences (serious or non-serious) that commonly occur in the study population or background regimen will be considered anticipated events. Such events include known consequences of the underlying disease (disease-related) or condition under investigation (eg, symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy. Anticipated events, when reported, to be associated with the use of the investigational product, are a subset of unexpected AEs (events not listed in the package insert [Mallinckrodt ARD LLC, 2019]). However, these events do not warrant expedited reporting as individual cases when serious criteria have been met because it is not possible to determine that there is a reasonable possibility that the drug caused the event. As a result, they do not meet the definition of a suspected adverse reaction.

SAE

An SAE is defined as any untoward medical occurrence that at any dose results in any of the following outcomes:

- Death.
- A life-threatening AE.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- Results in a congenital anomaly/birth defect.

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

Death

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the SAE Form. All causes of death must be reported as SAEs. The investigator should make every effort to obtain and send death certificates and autopsy reports (if applicable) to Mallinckrodt.

Life-Threatening Event

A life-threatening event refers to immediate risk of death as the event occurred per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death but, as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization

Hospitalization is defined as an official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported by the investigator as an SAE. Such situations include, but are not limited to, the following:

- A hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- A hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.
- A hospitalization for a preexisting condition that has not worsened.
- Note that the following hospitalizations are not considered SAEs in Mallinckrodt clinical studies:
    - A visit to the emergency department or other hospital department of less than 24 hours that does not result in admission (unless considered "important medical event" or life-threatening event).

16.3. Adverse Event and Serious Adverse Event Classifications

Investigational Medicinal Product Relatedness

The following classifications should be used when evaluating the relationship of AEs or SAEs to study treatment (Table 3).

Table 3: AE Relationships

Relationship	Definition
Not Related	No relationship between the experience and the administration of study treatment; related to other etiologies such as concomitant medications or subject's clinical state.
Unlikely Related	The current state of knowledge indicates that a relationship is unlikely.
Possibly Related	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Related	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment and can be confirmed with a positive re-challenge test or supporting laboratory data.

Severity Assessment

For purposes of consistency, if required, the investigator may use the intensity grades presented in Table 4.

Table 4: AE Severity Grades

Grade	Definition
Mild	Does not interfere with subject's usual function and activities
Moderate	Interferes to some extent with subject's usual function and activities
Severe	Interferes significantly with subject's usual function and activities

If an AE increases in severity (eg, from moderate to severe); decreases in severity (eg, changes from moderate to mild); or there is a change in seriousness, a new AE will be opened and the original AE will be closed. If an AE is still ongoing at the time of a subject's completion of the final visit, the resolution/stop date and time is left blank.

To ensure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical importance (such as a severe headache). This is not the same as "serious,"

which is based on the subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

16.4. Adverse Event and Serious Adverse Event Recording and Reporting

AEs and SAEs will be recorded from signing of the ICF through completion of the follow-up visit, which will take place 4 weeks (± 2 days) after the subject has received the last administration of IMP. The investigator is required to record the AE or SAE regardless of the severity of the event or its relationship to study treatment. The investigator must follow up on all AEs and SAEs until the event has resolved or stabilized or at such time the investigator refers the subject to a nonstudy physician. The investigator will document the further follow-up information in the subject's source document.

During the period specified above, the investigator will:

Record all AEs and SAEs in the source documents from the signing of the ICF through the completion of the follow-up telephone call.

Record all AEs and SAEs in the eCRF from the initial IMP dose through the completion of the follow-up telephone call.

Report all SAEs on an SAE Report Form to Mallinckrodt Pharmacovigilance.

Report all pregnancies to Mallinckrodt Pharmacovigilance on the Pregnancy Surveillance Form.

Submit the Safety Alert from Mallinckrodt to the IRB/IEC. (Submit any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction from Global Pharmacovigilance to the IRB/IEC.)

The reporting requirements for AEs are summarized in Table 5.

Table 5: Reporting Requirements for Adverse Events

Seriousness	Reporting Time	Type of Report
All Serious	Within 24 hours of first knowledge of event	Initial report on the SAE Form, appropriate eCRF, and source document
	Within 24 hours of receipt of follow-up information	Follow up report on the SAE Form, appropriate eCRF, and source document
Nonserious	Per case report form submission procedure	Appropriate eCRF and source document

AEs

AEs can be reported spontaneously or elicited during open-ended questioning (ie, "How have you been feeling since your last visit?"), examination, or evaluation of a subject. Signs and symptoms must be recorded using standard medical terminology.

All fields on the AE CRF page should be completed for each event with a full description of the event and date and time of onset/start and resolution/stop. A medical diagnosis if known, should be recorded in lieu of each individual sign and symptom associated with the diagnosis and experienced by the subject. If no medical diagnosis is known, the term used by the subject to describe the event or signs noted by the site personnel should be recorded.

SAEs

Initial Reporting

SAEs (based on US FDA/ICH definition of an SAE) require immediate reporting to Mallinckrodt Global Pharmacovigilance or designated representative.

- For all fatal or life-threatening events, the investigator, or designee, must report information to the MM.
- For all SAEs, the investigator, or designee, must complete the SAE Report Form with the minimum information required by US FDA and ICH and fax it to Mallinckrodt Global Pharmacovigilance or designee within 24 hours of first knowledge of the event even if the experience does not appear to be related to the IMP.
- The investigator, or designee, will receive acknowledgement of receipt of the SAE Report Form from Mallinckrodt.
- If there is any doubt about whether the information constitutes an SAE, the information is to be treated as an SAE.

The investigator(s) or designee is required to submit the Safety Alert to the responsible IRB/IEC.

The sponsor will submit safety reports to the US FDA and other regulatory agencies, as appropriate.

Follow Up Reporting

The investigator or designee must complete an SAE Report Form for all follow-up information received and fax or e-mail it to Mallinckrodt Global Pharmacovigilance or designee within 24 hours of receipt (eg, detailed written descriptions that include copies of relevant subject records, autopsy reports and other supporting documents). The investigator(s) or designee will receive acknowledgement of receipt for each SAE Report Form from Mallinckrodt.

- The investigator or designee is required to provide all related information/supporting documentation of an SAE until the SAE is resolved or stabilized or the subject has been referred to a nonstudy physician for follow-up treatment.
- The investigator(s) or designee is required to submit the Safety Alert to the responsible IRB/IEC.
- The sponsor will submit safety reports to the US FDA. (The sponsor will ensure that any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction are submitted to the FDA and other regulatory agencies as appropriate).

16.5. Pregnancy Reporting

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated. This includes the following:

Pregnancy exposure to an IMP, except for exposure to prenatal vitamins. Subjects should not become pregnant during the study. If the subject becomes pregnant, study treatment must be discontinued immediately. The investigator must report the pregnancy by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance within 24 hours of confirmation of a pregnancy (ie, positive serum or urine pregnancy test result). The outcome of pregnancy (eg, spontaneous abortion, live birth, still birth, congenital anomalies, birth defects) must be reported by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance within 24 hours of the pregnancy outcome being submitted to the study site. If the pregnancy results in a live birth, a post-delivery follow-up will be performed at least 28 days after the baby is born and must be reported to Mallinckrodt Pharmacovigilance within 24 hours of the study site becoming aware of the follow-up information. Both maternal and paternal IMP exposures are collected.

If the female partner of a male subject becomes pregnant during the study, the site will forward the appropriate forms to Mallinckrodt Global Pharmacovigilance or designee, within 24 hours of being notified. The outcome of pregnancy (eg, spontaneous abortion, live birth, still birth, congenital anomalies, birth defects) must be reported by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance or designee within 24 hours of the pregnancy outcome being submitted to the study site. If the pregnancy results in a live birth, a postdelivery follow-up will be performed at least 28 days after the baby is born and must be reported to Mallinckrodt Global Pharmacovigilance or designee within 24 hours of the study site becoming aware of the follow-up information.

17. SUBJECT DISCONTINUATION OR WITHDRAWAL

17.1. Subject Withdrawal

Subjects who discontinue, or are withdrawn from the study for any reason, will be required to have the early termination safety and efficacy assessment procedures (Visit 8, see Section 11.5) as well as follow up procedures (Visit 12, see Section 11.9).

The reason for discontinuation will be recorded. A subject may be discontinued from the study for the following medical or administrative reasons:

Withdrawal by Subject

Subjects will be free to discontinue from the study at any time. Subjects who have received at least 1 dose of IMP but do not complete the study will not be replaced.

AE

If a dosed subject experiences an AE that, in the judgment of the investigator, sponsor or MM, presents an unacceptable consequence or risk to the subject, the subject will be discontinued from IMP. In addition, subjects who experience any of the AEs described in Section 12.3.1 may have their dose reduced by 50% once or discontinued (Section 17).

Death

In the event that a subject dies during the study, death will be the reason for discontinuation.

Lost to Follow-up

Every effort should be made to maintain contact with subjects during their participation in the study. A subject may be considered lost to follow-up if there is no response to 3 attempts to reach the subject by telephone or electronically and no response to a certified letter sent to the last known address of the subject. Efforts to contact the subject should be noted in source documentation.

Met Withdrawal Criteria

Discontinuation from IMP is mandated if the subject becomes pregnant or receives live or live-attenuated vaccines.

Worsening of Disease Activity

Subjects may be withdrawn if, in the opinion of the investigator, there is a lack of efficacy during the study.

Other

If the above reasons are not applicable, please use the “Other” option and provide the appropriate reason for subject withdrawal.

18. STUDY SUSPENSION, TERMINATION, AND COMPLETION

The sponsor may suspend or terminate the study or part of the study at any time for any reason. If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor and the IRB/IEC and provide them with a detailed written explanation. Upon study completion, the investigator will provide the sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations. Study termination and follow-up will be performed in compliance with Mallinckrodt standard operating procedures.

19. PROTOCOL AMENDMENTS

Any change in the study plan requires a protocol amendment or an administrative letter. An investigator must not make any changes to the study without IRB/IEC and sponsor approval except when necessary to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame, if appropriate.

20. QUALITY CONTROL AND ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study.

Study and Study Site Discontinuation Criteria

The sponsor, investigator, MM or local and national regulatory authorities may discover conditions during the study that indicate that the study or study site should be terminated. This action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study/study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- The decision on the part of the sponsor to suspend or discontinue testing, evaluation or development of the IMP.
- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulations.
- Submission of knowingly false information from the study site to the sponsor, study monitor, or local and national regulatory authorities.
- Insufficient adherence to protocol requirements
- Study/study site termination and follow-up will be performed in compliance with Mallinckrodt standard operating procedures.

21. DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

21.1. Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to original source data and documents.

All subject information recorded in the eCRF will be attributable to source data from the investigational site. Each subject's eCRF should be fully completed and submitted to the Sponsor in a timely fashion. If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

Any significant changes in study personnel will require an updated Statement of Investigator (ie, US FDA form 1572) to be filed with the sponsor.

The investigator must notify their IRB/IEC of protocol violations in accordance with local regulatory and IRB/IEC requirements.

21.2. Sponsor

The eCRF data are stored in a database and processed electronically. The sponsor's MM reviews the data for safety information. The data are reviewed for completeness, and logical consistency. Automated validation programs will identify missing data, out-of-range data, and other data inconsistencies. Clinical laboratory data will be processed electronically. Requests for data clarification are forwarded to the study site for resolution.

22. SUBJECT INJURY

In general, subject to specific provisions in the clinical trial agreement, if a subject is injured as a direct result of an IMP, the sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor shall comply with such laws or regulations. Where applicable, the sponsor has taken specific national insurance.

23. RECORDS RETENTION

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

24. BIOLOGICAL SAMPLES

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. After the study ends, the clinical laboratory samples will be destroyed, with the exception of samples for biomarker and genomic analysis. Samples for biomarker analysis and optional genetic testing will be retained at a biologic storage facility for future testing for no more than 5 years following the completion of the study. The subject may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from that sample will still be used for this research.

25. PUBLICATION POLICY

25.1. Sponsor's Publication Policy

The sponsor's policy is to publish or otherwise communicate the results of its hypothesis-testing clinical studies, regardless of outcome, for marketed products, compound(s) or product(s) being investigated that are later approved for marketing. Hypothesis-testing clinical studies are those studies intended to provide meaningful results by examining prestated questions using predefined statistically valid plans for data analysis, thereby providing firm evidence of safety and/or efficacy to support product claims.

The sponsor's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and sponsor policies regarding publication and communication of clinical study results.

25.2. Investigator's Ability to Publish

Terms and provisions of publication rights are governed by the publication section in the clinical trial agreement.

26. REFERENCES

Ahmadzai H, Loke WSJ, Huang S, Herbert C, Wakefield D. Biomarkers in sarcoidosis: a review. *Current Biomarker Findings* 2014: 4: 93-104.

Al-Kofahi K, Korsten P, Ascoli C, Virupannavar S, Mirsaeidi M. Management of extrapulmonary sarcoidosis: challenges and solutions. *Therap Clinical Risk Manag* 2016; 12: 1623-1634.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (5th Edition) 2013. Washington, DC.

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: Guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med.* 2002;166: 111–117.

Baughman RP, Barney JB, O'Hare L, Lower EE. A retrospective pilot study examining the use of Acthar gel in sarcoidosis patients. *Respiratory Medicine* 2016; 110: 66-72.

Baughman RP, Drent M, Culver DA, Grutters JC, Handa T. Endpoints for clinical trials of sarcoidosis. *Sarcoidosis Vasculitis and Diffuse Lung Diseases* 2012; 29: 90-98.

Baughman RP, Grutters JC. New treatment strategies for pulmonary sarcoidosis: antimetabolites, biological drugs, and other treatment approaches. *Lancet Respir Med* 2015; 3: 813-822.

Baughman RP, Iannuzzi MC, Lower EE, Moller DR, Balkissoon RC. Use of Fluticasone in Acute Symptomatic Pulmonary Sarcoidosis. *Sarcoidosis Vasculitis Diffuse Lung Diseases* 2002; 19: 198-204.

Baughman RP, Lowera EE, Saketkoo LA. Clinical trials in pulmonary sarcoidosis. *Curr Opin Pulm Med* 2015; 21, 525–531.

Baughman RP, Kavuru M, Judson MA, Costabel U, du Bois R. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med* 2006; 174: 795–802.

Baughman RP, Nunes H. Therapy for sarcoidosis: evidence-based recommendations. *Expert Rev Clin Immunol* 2012; 8(1): 95–103.

Baughman RP, Sweiss N, Keijsers R, Birring SS, Shipley R et al. Repository corticotropin for Chronic Pulmonary Sarcoidosis. *Lung* 2017; 195(3): 313-322.

Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MDL, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003; 58: 339–343.

Catania A, Lonati C, Sordi A, Carlin A, Leonardi P, Gatti S. The melanocortin system in control of inflammation. TheScientificWorldJournal 2010; 10:1840-1853.

Chopra A, Kalkanis A, Judson MA. Biomarkers in sarcoidosis. *Expert Rev Clin Immunology*. 2016; 12(11): 1191-1208.

Chopra I, Qin Y, Kranyak J, Gallagher JR, Heap K, Carroll S, Wan G. Repository corticotropin injection in patients with advanced symptomatic sarcoidosis: retrospective analysis of medical records. Ther Adv Respir Dis 2019; Vol. 13: 1–11.

De Vries MH, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). *Br J Health Psychol* 2004; 9: 279-291.

Fletcher CM. The clinical diagnosis of pulmonary emphysema-an experimental study. *Proc R Soc Med* 1952; 45: 577-584.

Gibson GJ, Prescott RJ, Muers MF, Middleton WG, Mitchell DN et al. British Thoracic Society Sarcoidosis study: effects of long term corticosteroid treatment. *Thorax* 1996; 51: 238-247.

Getting SJ. Targeting Melanocortin Receptors as Potential Novel Therapeutics. *Pharmacol. Ther*. 2006; 111: 1-15.

Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. 2017; 49: 1-31

Healy LM, Jang JH, Lin YH, Rao V, Antel JP, Wright D. Melanocortin receptor mediated anti-inflammatory effect of repository corticotropin injection on human monocyte-derived macrophages [ECTRIMS-ACTRIMS abstract EP1481]. Mult Scler J. 2017a; 23(suppl 3):777.

Healy LM, Lin YH, Jang JH,Rao V, Antel JP, Wright D. Melanocortin receptor mediated anti-inflammatory effect of repository corticotropin injection on human monocyte-derived macrophages. Poster presented at: 7th Joint ECTRIMS-ACTRIMS Meeting; October 25-28, 2017b; Paris, France. Poster EP1481.

Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF et al. ATS/ERS/WASOG Statement on Sarcoidosis. *Sarcoidosis Vasculitis and Diffuse Lung Diseases* 1999; 16: 149-173.

Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med*. 2007; 22: 357, 2153-2165.

Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, Maucort-Boulch D, Marquet A et al. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: A multicenter study of 132 patients. *Seminars in Arthritis and Rheumatism* 2017; 47(2):288-294.

Judson MA. The treatment of pulmonary sarcoidosis. *Respiratory Medicine* 2012; 106: 1351-1361.

Judson MA. Advances in the diagnosis and treatment of sarcoidosis. *F1000Prime Reports* 2014; 6: 89.

Judson MA, Baughman RP, Costabel U, Drent M, Gibson KF et al. Safety and efficacy of ustekinumab or golimumab in patients with chronic sarcoidosis. *Eur Respir J* 2014b; 44: 1296–1307.

Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH et al. Sarcoidosis Investigators. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J*. 2008; 31: 1189-1196.

Korsten P, Strohmayer K, Baughman RP, Sweiss NJ. Refractory pulmonary sarcoidosis: proposal of a definition and recommendations for the diagnostic and therapeutic approaches. *Clin. Pulm. Med.* 2016; 23(2): 67–75.

Mallinckrodt ARD LLC; *Acthar® Gel*; Package Insert: Mallinckrodt Pharmaceuticals, Bedminster, NJ, 2019. Accessed April 2020.

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi, R. et al. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.

Mountjoy KG, Robbins LS, Mortrud MT, Cone RD. The cloning of a family of genes that encode the melanocortin receptors. *Science*. 1992;257(5074): 1248-1251.

Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. *Arthritis Res Ther* 2016; 18(1): 251.

Olsen NJ, Decker DA, Higgins P et al. Direct effects of HP Acthar Gel on human B lymphocyte activation in vitro. Arthritis Res Ther. 2015; 17:300.

Patel AS, Siegert RJ, Creamer D, Larkin G, Maher TM et al. The development and validation of the King's Sarcoidosis Questionnaire for the assessment of health status. *Thorax* 2013; 68: 57-65.

Scadding JG. Prognosis of intrathoracic sarcoidosis in England: Review of 136 cases after five years observation. *Br Med J* 1961; 2(5261): 1165-1172.

Unpublished Sponsor data: REF-MNK14314065. Mallinckrodt ARD LLC.

Unpublished Sponsor data: REF-MNK03003. Mallinckrodt ARD LLC.

Wright D, Fitch R. Repository corticotropin injection (H.P. Acthar Gel) enhances remyelination after cuprizone-induced demyelination [CMSC abstract NDM04]. Int J MS Care. 2019; 21(suppl 1): 61-62.

Wright D, Zweifel B, Prabha S, Galen K, Fitch R. Reduced steriodogenic activity of repository corticotropin injection (RCI) induces a distinct cytokine response following T cell activation [EULAR abstract AB0082]. Ann Rheum Dis 2019b; 78(supp1 2): 1504.

Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire - general health version in patients with rheumatoid arthritis. Arthritis Res Ther. 2010; 12(5): R177.

Zoorob RJ, Cender D. A different look at corticosteroids. Am Fam Physician. 1998; 58(2):443-450.

APPENDIX 1. PROTOCOL AMENDMENT CHANGES

The Summary of Changes presented below reflects the major changes made in Protocol Version 2 Amendment 1. Formatting, consistency, and minor editorial changes are not included. Refer to the Section Summary of Changes for a high level summary of the reasons for this amendment.

Rationale	Location	Original	Revisions/Additions in Bold
H.P. (highly purified) should be removed	Globally	H.P. Acthar® Gel	Acthar® Gel
To update Acthar package insert reference to the most current one.	Globally	(Mallinckrodt, 2015)	(Mallinckrodt ARD LLC, **2019**)
Clarification	Title Page and Synopsis Section 9.1 Description	A Phase 4 Multicenter, Randomized, Double Blind, Placebo Controlled Pilot Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in Subjects with Pulmonary Sarcoidosis This is a Phase 4, multicenter, randomized, double-blind, placebo-controlled pilot study evaluating the efficacy and safety of Acthar in the treatment of pulmonary sarcoidosis.	A Multicenter, Randomized, Double Blind, Placebo Controlled **Exploratory** Study to Assess the Efficacy and Safety of Acthar® Gel in Subjects with Pulmonary Sarcoidosis This is a multicenter, randomized, double-blind, placebo-controlled **exploratory** study evaluating the efficacy and safety of Acthar in the treatment of pulmonary sarcoidosis.
Company name & address change	Title page	Mallinckrodt ARD, Inc. 675 McDonnell Boulevard Hazelwood, MO 63042 United States of America	Mallinckrodt ARD **LLC** **1425 US Route 206** **Bedminster, New Jersey 07921** **United States of America**

Rationale	Location	Original	Revisions/Additions in Bold
Addition of Clintrials.gov Registry Number	Title page	NA	**Clintrials.gov Registry Number: NCT03320070**
Updated header to remove H.P.	All page headers	H.P. Acthar® Gel (Repository Corticotrophin Injection)	Protocol MNK14344100 Acthar® Gel (Repository Corticotropin Injection)
Update of sponsor's signature page for more detail about applicable laws and other regulations related to study conduct.	Sponsor's Signature Page	My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.	• International Council for Harmonisation (ICH) **E6(R2): Integrated Addendum to ICH E6(R1):** Guideline for Good Clinical Practice, which has its **ethical** foundation in the Declaration of Helsinki • **the US CFR (as appropriate, including 42 CFR 11: Final Rule for Clinical Trials Registration and Results Information Submission)** • **NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information** • **all applicable national and local regulations (as appropriate, including the EU Clinical Trials Regulation)** • **protections for privacy (as appropriate, including the EU General Data Protection Regulation (GDPR)** • **provisions of all local ethics committees**

Rationale	Location	Original	Revisions/Additions in Bold
Expand site regions	Section 2 Synopsis, Type:	Type: Phase 4 (US)/Phase 2 (Canada)	Type: Phase 4 (US)/Phase 2 **(all other countries)**
Adjust the number of sites and their potential location	Section 2 Synopsis, Approximate Number of Study Centers:	Up to 45 in the US and/or Canada	**Approximately 75 sites globally**
	Section 9.4 Approximate Number of Subjects	Up to 100 subjects will be enrolled at up to 45 sites in the US and/or Canada.	**Approximately** 100 subjects will be **globally** enrolled at **approximately 75** sites.
Revise study duration.	Section 2 Synopsis	Approximate Duration of Study: The estimated study period is approximately 3 years from first subject enrolled to last subject last visit (completed open-label extension and follow up visit). Expected enrollment period is approximately 2 years (first subject enrolled to last subject enrolled).	Approximate Duration of Study: The estimated study period is approximately **4** years from first subject enrolled to last subject last visit (completed open-label extension and follow up visit). Expected enrollment period is approximately **3** years (first subject enrolled to last subject enrolled).
	Section 9.3	The entire study is expected to require approximately 3 years to complete.	The entire study is expected to require approximately **4** years to complete.

Rationale	Location	Original	Revisions/Additions in Bold
Clarification of dosing	Section 2 Synopsis, Design	1 mL (80 U) of Acthar or 1 mL of a matching placebo subcutaneously (SC) 2 x/week	**Double-blind treatment: Acthar, 1 mL (80 U) or matching placebo (1 mL) administered SC twice weekly for up to 24 weeks.** **Optional open-label extension: Acthar Gel, 1 mL (80 U) administered twice weekly SC for up to 24 weeks.** **Subjects will be assigned to treatment in a 1:1 ratio with up to 50 subjects per arm for a total of approximately 100 subjects.**
	Section 2 Synopsis, Investigational medicinal product and Treatment Administration	Acthar, 1 mL (80 U) or matching placebo (1 mL) administered twice weekly SC for up to 12 months.	Acthar **Gel,** 1 mL (80 U) or matching placebo (1 mL) administered twice weekly SC for up **to 24 weeks.** **Optional open-label extension: Acthar Gel, 1 mL (80 U) administered twice weekly SC for up to 24 weeks.**
	Section 13.3 Dosing Procedures	Subjects or their caregivers will administer SC injections of Acthar or placebo after randomly assigned to treatment at Visit 2. The subject or subject's caregiver will administer the first dose of IMP in the clinic under the supervision of study staff. The subject will remain in the clinic for at least 1 hour post	Subjects or their caregivers will administer SC injections of Acthar **Gel** or placebo after randomly assigned to treatment at Visit 2. The subject or subject's caregiver will administer the first dose **of study drug and the first dose of Acthar in the Open-Label at Week 24 in the clinic under the supervision of study staff. The subject will remain in the clinic for at least 1 hour postdose to monitor for allergic or anaphylactic reactions. All other doses**

Rationale	Location	Original	Revisions/Additions in Bold
		injection to monitor for allergic or anaphylactic reactions.	**will be administered by the subject or the subject's caregiver at home, except for doses administered on the days of the study visits**
	Section 13.3 Dosing Procedures	Injections of 1 mL Acthar (80 U) or matching placebo will be administered SC 2x/week throughout the study.	**In the double-blind treatment period Acthar Gel, 1 mL (80 U) or matching placebo (1 mL) will be administered twice weekly SC for up to 24 weeks. In the optional open-label extension Acthar Gel, 1 mL (80 U) will administered SC twice weekly for up to 24 weeks.**
Combining optional genomics assessment with biomarkers assessment	Section 2 Synopsis, Efficacy Evaluation	12. Genomics (optional).	Removed
Added high level Summary of Changes	Summary of Changes	Not applicable.	See Section Summary of Changes.
Combining optional genomics assessment with biomarkers assessment	Table 1: Schedule of Study Events	Genetic Sampling (Optional)	Removed assessment.
	Table 1: Schedule of Study Events original footnote k	[k] Genetic profile (optional) will be assessed based on the understanding of genetic factors at the time of study completion.	Removed.

Rationale	Location	Original	Revisions/Additions in Bold
Clarification for biomarkers assessments	Synopsis, Biomarkers	• Genetic profile (optional) will be assessed based on the understanding of genetic factors at the time of study completion.	• **Genomic** profile (optional) will be assessed based on the understanding of genetic factors at the time of study completion.
	Table 1: Schedule of Study Events footnote j	[j] 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). Aliquots will be kept for each of these time points. The final determination as to the selection of biomarkers will be made based on the scientific knowledge and emerging guidance closer to the completion of the study.	[j] **Biomarkers sampling must include RNA and DNA samples (screening only), if genetic Informed Consent Form (ICF) is signed**

Rationale	Location	Original	Revisions/Additions in Bold
	Sections 12.1 Study Days -28 to -1 (Screening Visit 1), Section 12.4 Visit 5 Procedures, 12.5 Visit 8 Procedures, 12.7 Visit 10 Procedures, Open-Label Extension Period, 12.8 Visit 11 Procedures, Open-Label Extension Period	Biomarkers	For Screening Visit 1: Biomarkers **(including RNA and DNA, if genetic ICF signed).** For all other visits listed: Screening Visit:1 Biomarkers **(including RNA, if genetic ICF signed).**
Clarification of ECG assessment	Table 1: Schedule of Study Events, footnote m	12 lead ECG[m]	**[m]ECG will include assessment of sinus rhythm, heart rate, PR Interval, RR Interval, QRS Duration, Q-T Interval and QTcB**
	Heading of Section 15.6 Screening 12-Lead Electrocardiogram	Screening 12-Lead Electrocardiogram	12-Lead Electrocardiogram
	Section 15.6 12-Lead Electrocardiogram	N/A	**Electrocardiogram will include assessment of sinus rhythm, heart rate, PR Interval, RR Interval, QRS Duration, Q-T Interval and QTcB**

Rationale	Location	Original	Revisions/Additions in Bold
Addition of a requirement to monitor 1st dose for allergic or anaphylactic reactions in open label treatment so that subjects in Placebo group who enter the Open Label treatment period and receive their first Acthar dose receive the same level of safety monitoring as those who receive Acthar treatment in the Double Blind period.	Table 1: Schedule of Study Events, footnote s	[s] Dosing will begin after Visit 2 procedures are completed and subject is randomized. Dosing will be performed 2×/week but not on visit days (see Section 15.3).	[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).**
Clarification for SC injections training	Table 1: Schedule of Study Events, footnote q	[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. The training may be forgone if either the subject or caregiver is a medically trained professional. The subject or subject's caregiver will administer the first dose of IMP in the clinic under the supervision of study staff.	[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.

Rationale	Location	Original	Revisions/Additions in Bold
		The subject will remain in the clinic for at least 1 hour postinjection to monitor for allergic or anaphylactic reactions.	
Typo and added description of study of subjects with advanced symptomatic sarcoidosis treated with repository corticotropin injection (Chopra et al., 2019).	Section 7.1 Sarcoidosis Overview	[redacted].	[redacted]. **The third study was large case series of patients with advanced symptomatic sarcoidosis treated with repository corticotropin injection (RCI). This large case series study describes patient characteristics, RCI utilization patterns, concomitant therapies, and physicians' assessments of treatment response. The study included 302 patients (mean age = 51 years; 52% women) with a mean of 4.8 years since initial diagnosis of sarcoidosis. Most patients (76%) had extrapulmonary involvement, primarily in the skin (28%), joints (25%), heart (22%), and eyes (22%); 34% had multiple (≥2) organ involvement. The mean duration of RCI treatment was 32.5 weeks, with 61.6% of patients continuing RCI therapy**

Rationale	Location	Original	Revisions/Additions in Bold
			for ≥6 months. The RCI utilization pattern indicated an individualized approach to therapy, with a higher starting dose associated with a shorter duration of therapy compared with a lower starting dose. The percentage of patients who used corticosteroids decreased from 61.3% during the 3 months before initiation of RCI to 12.9% at 3 months after RCI therapy; the mean daily dose of corticosteroid decreased from 18.2 mg to 9.9 mg. The proportion of patients given <10 mg/day of prednisone increased from 21% before RCI use to 47% at 3 months after RCI use. According to physicians' assessments of change in patients' health status after RCI therapy, overall status improved in 95% of patients, overall symptoms in 73%, lung function in 38%, and inflammation in 33%. The findings suggest that RCI is a viable treatment option for patients with advanced symptomatic sarcoidosis and provide insights on patient characteristics and practice patterns to help clinicians determine appropriate use (Chopra et al., 2019).
Update description and addition of supporting	Section 7.2, Acthar Gel Overview	NA	**Acthar Gel is a naturally sourced complex mixture of ACTH analogs and other**

Rationale	Location	Original	Revisions/Additions in Bold
publications related to MCRs			**pituitary peptides.** Further down in the same paragraph: **MCRs play a key role in regulating inflammation and other cellular function (Catania, 2010). Acthar engages MCRs expressed on immune cells and other tissues throughout the body and is thought to produce both an indirect anti-inflammatory effect and a direct cell effect (Catania, 2010; Wright et al., 2019; Olsen et al., 2015; Healy, 2017a; Wright et al., 2019b). Production of cortisol is mediated by activation of MC2Rs primarily expressed on the adrenal cortex. In in vitro studies in cultured cells lines expressing MCR1-MCR5, the relative functional potency of MCRs was measured. It was shown that 6% of Acthar's relative functional potency occurred at MC2R. The remaining 94% occurred at the other MCRs (Wright et al., 2019). These data suggest that Acthar acts directly on cells involved in the pathogenesis of disease in addition to its indirect action via corticosteroid stimulation.** **The effects of Acthar on human B-lymphocyte function in vitro were evaluated using highly purified B-cell populations cultured in the absence of**

Rationale	Location	Original	Revisions/Additions in Bold
			glucocorticoids and stimulated by recombinant interleukin-4 and cluster of differentiation 40 ligand as specific B-cell activating signals. Immunoglobulin G was measured in supernatants from healthy human peripheral B cells that had been cultured for 6 days. The percentage of cells that divided and immunoglobulin G production were assessed under basal conditions (unstimulated) or stimulated with interleukin-4/cluster of differentiation 40 ligand plus vehicle. Acthar reduced B cell proliferation and immunoglobulin G production independent of cortisol release ($p<0.05$, compared to vehicle-treated group) (Olsen et al., 2015; Healy, 2017a, Healy, 2017b). In further experiments to explore the direct effects of Acthar on human macrophages and focusing on induction of pro-inflammatory mediators following lipopolysaccharide stimulation, Acthar inhibited the production of the pro-inflammatory cytokines interleukin-6 and tumor necrosis factor ($p<0.0001$, compared to vehicle-treated group; (Healy, 2017a, Healy, 2017b). These data further demonstrate a direct effect of Acthar on immune cell modulation independent of cortisol release.

Rationale	Location	Original	Revisions/Additions in Bold
			[redacted]s

Rationale	Location	Original	Revisions/Additions in Bold
			[redacted]. **While the exact mechanism of action of Acthar Gel is still unknown, further investigation is being conducted. This information is based on nonclinical data and pharmacodynamic data and the relationship to clinical benefit is unknown.**
Update description	Section 13, Investigational Medicinal Product	Acthar contains a highly purified sterile preparation of prolonged-release porcine ACTH analogue in 16% gelatin for intramuscular or SC injection.	**Acthar Gel is a naturally sourced complex mixture of ACTH analogs and other pituitary peptides in 16% gelatin for intramuscular or SC injection.**
Defining outcome measures for clinicaltrials.gov reporting	Synopsis, Outcome Measures and Section 8.4 Primary Outcome Measures	Not available	**Outcome measures are identified to facilitate trial registration and patient access to basic results disclosed on public registries.** **The primary outcome measures are:** • **Number of participants in each category of assessment based on forced vital capacity, Weeks 24 and 48** • **Number of participants in each category of assessment based on the**

Rationale	Location	Original	Revisions/Additions in Bold
			diffusing capacity of the lungs for carbon monoxide (DLCO), Weeks 24 and 48 • **Number of participants in each category of assessment based on high resolution computer tomography, Weeks 24 and 48** • **Number of participants in each category of assessment based on the King's Sarcoidosis Questionnaire (General Health), Weeks 24 and 48** • **Number of participants in each category of assessment based on the Fatigue Assessment Score, Weeks 24 and 48** • **Number of participants receiving each dose of prednisone, Weeks 24 and 48**
Allowing subjects who had biopsy performed less than 1 year ago, but whose disease started for more than 1 year ago.	Section 10.1 Inclusion Criteria #7	7. Subject with biopsy confirmed sarcoidosis meeting ATS criteria ≥ 1 year at screening (Visit 1) (Hunninghake et al., 1999).	7. Subject with biopsy confirmed sarcoidosis meeting ATS criteria **with onset of sarcoidosis ≥ 1 year prior to screening** (Hunninghake et al., 1999).
Clarification for "daily" prednisone	Section 10.1 Inclusion Criteria #9	9. Subject receiving ≥ 5 mg and ≤ 40 mg prednisone (or equivalent) for pulmonary sarcoidosis.	9. Subject receiving ≥ 5 mg and ≤ 40 mg **daily** prednisone (or equivalent) for pulmonary sarcoidosis.

Rationale	Location	Original	Revisions/Additions in Bold
Allowing subjects whose FVC is higher than 95% predicted at screening and can potentially show improvement in FVC.	Section 10.1 Inclusion Criteria #12	12. Forced vital capacity (FVC) ≥ 45% ≤ 95% predicted.	12. Forced vital capacity (FVC) ≥ 45% predicted. **If FVC at Screening is more than 95% predicted, a documented decrease ≥ 5% absolute change of % predicted in the best available FVC is required after diagnosis of Sarcoidosis.**
Excluding subjects with prior history of Sarcoidosis treatment with Acthar	Section 10.2 Exclusion Criteria #8	Not available	**Subject has any history of use of ACTH preparations for treatment of Sarcoidosis.**
Address missed procedures and visits	Section 12 PROCEDURES	The schedule of study procedures is summarized in the Schedule of Events (Table 1).	The schedule of study procedures is summarized in the Schedule of Events (Table 1). **If the subject is unable to come to the study site for any visit after the Baseline visit, all procedures that can be completed remotely (eg, by telephone) will be conducted as scheduled.** **Collect as much information as possible, including but not limited to, AE information, new concomitant medications and changes in existing therapy, corticosteroid use, compliance with investigational therapy. Complete applicable physician assessments, PFT tests, subject reported outcomes and assessments, 6MWT, ECG, imaging and laboratory tests at the next planned study visit as unscheduled procedures, if not**

Rationale	Location	Original	Revisions/Additions in Bold
			already scheduled for that particular study visit. **Changes in study visit schedule, missed visits, and procedures will be captured in the eCRF.**
Addition of WPAI, a questionnaire to assess HEOR outcomes	Synopsis, Efficacy Evaluation	Not Available	**11. WPAI.**
	Table 1: Schedule of Study Events Footnote f	[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).	[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).**
	Section 8.2 Assessments of Efficacy	Not available	The following assessments will be performed during this study: - **WPAI**
	Section 8.2.15, Work Productivity and Activity Impairment	Not available	**8.2.15 Work Productivity and Activity Impairment**

Rationale	Location	Original	Revisions/Additions in Bold
			The WPAI is a validated assessment of work and activity impairment associated with health problems (Zhang et al, 2010). This questionnaire is to be completed by subjects. When this assessment is required, it should be the first assessment done at any visit (with the subject completed efficacy questionnaires) and must be completed prior to any study drug dosing. **Subjects will be provided a quiet, private place to complete the assessment. Subjects will be instructed to answer all questions to the best of their ability and without help from others (including study staff, relatives, or friends). Subjects may refrain from answering any question.** **The study staff should review the questionnaire after it is completed and encourage the subjects to complete any missing information. Study staff will record the refusal of subjects to answer any questions in the source documents.**
	Synopsis, Endpoints and Section 8.3 Efficacy Endpoints	Not available	• **Change from baseline in WPAI over time.**

Rationale	Location	Original	Revisions/Additions in Bold
	Section 12 PROCEDURES Visits 1 through 11	Patient reported outcomes. Patient-reported outcomes include: Steroid toxicity questionnaire; 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).	Patient reported outcomes. Patient-reported outcomes include: Steroid toxicity questionnaire; 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); **WPAI (Attachment 10).**
	Section 27 Attachments	Not available	**ATTACHMENT 10: WPAI**
	Section 12.5 Visit 8 Procedures	For subjects interested in participating in the Open-Label Extension Period: Contact IXRS, dispense IMP kits and equipment, and instruct the subject to inject Acthar 80 U (1 mL) 2x/week unless the subject had a single reduction of dose, in which case only	• **Contact IXRS.** • **For subjects entering the Open-Label Extension Period:** o Remind the subjects to arrive in fasting condition for Visit 9 (drinking water is permitted) and to bring all IMP kits including used and unused vials to each visit in a cooler.

Rationale	Location	Original	Revisions/Additions in Bold
		40 U (0.5 mL) 2x/week will be injected for the remainder of the study.	○ **Dispense IMP kits and equipment.** ○ **Administer Acthar Gel under supervision of study staff and observation for at least 1 hour thereafter.** ○ **Instruct the subject to inject Acthar Gel 80 U (1 mL) 2×/week unless the subject had a single reduction of dose, in which case only 40 U (0.5 mL) 2×/week will be injected for the remainder of the study.** ○ **Corticosteroid tapering.**
Addition of corticosteroid tapering for subjects entering open label extension	Table 1: Schedule of Study Events Visit 8 procedures	Not available	Corticosteroid tapering for patients entering open label extension
	Section 12.5 Visit 8 Procedures	Not available	- Corticosteroid tapering.
Clarification for PFT assessment	Table 1: Schedule of Study Events Footnote n	[n] Full PFT (including DLCO) will be performed at Visits 1, 5, 8, 10, and 11 (every 12 weeks).	[n] Full PFT **results will include 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**

Rationale	Location	Original	Revisions/Additions in Bold
			flow at maximum effort (FEFmax), total lung capacity, residual volume, diffusing capacity of the lungs for carbon monoxide (DLCO; uncorrected for Hb), DLCO: % predicted and DLCO/alveolar volume.
	Section 8.2.2 Pulmonary Function Tests (PFT)	Not available	**PFT results will include FEV1, FVC, FVC % predicted (NHANES III reference values), FEV1/FVC ratio, PEFR or FEFmax, TLC, RV, DLCO (uncorrected for Hb), DLCO % predicted and DLCO/VA at screening visit, Visits 5, 8, 10, and 11 (every 12 weeks).** **At the randomization visit, spirometry results will include FEV1, FVC, FVC % predicted (NHANES III reference values), FEV1/FVC ratio and PEFR or FEF_{max}.**
Enforcement of IMP compliance	Table 1: Schedule of Study Events	Not available in Assessments and Procedure column	**Study Drug Accountability and Diary Review**
		Injection training	Injection **and Diary** Training
	Section 12, PROCEDURES Visits 3 through 11	Not available	**Study Drug Accountability and Diary Review**
	Sections 12.1 and 12.2 Study Days -28 to -1	• Injection training. Subjects (or caregivers) will be trained on SC injections using the training tools provided separately. The training	• Injection **and diary** training. Subjects (or caregivers) will be trained on SC injections **and diary completion** using the training tools provided separately. The injection

Rationale	Location	Original	Revisions/Additions in Bold
	(Screening Visit 1) and Visit 2 Procedures	may be forgone if either the subject or caregiver is a medically trained professional.	training may be **foregone** if either the subject or caregiver is a medically trained professional.
	Section 13.6 Compliance Monitoring	At each applicable visit, all IMP kits including used and unused vials will be inspected and compliance will be encouraged when IMP is dispensed.	**Subjects and/or their caregiver will be trained on the completion of the study diary and will complete study diary entries to record all study drug administration and will bring it, along with all study drug kits including used vials to each visit. Used and unused vials will be inspected. Number of expected, administered doses and reason for discrepancies will be documented. Each time study drug is dispensed compliance will be encouraged. Subject diary training is an ongoing process as the diary will be reviewed with the subject at each visit to monitor compliance with study drug administration.**
Typo to replace QTcF with QTcB	Section 16.4.4 Electrocardiogram Findings	Electrocardiogram measured changes from baseline for heart rate, PR interval, QRS interval, QTcF, and RR interval will be summarized.	Electrocardiogram measured changes from baseline for **sinus rhythm**, heart rate, PR interval, RR interval, **QRS duration, Q-T Interval, and QTcB** will be summarized.
Over reporting of SAEs	Section 17.2 Definitions	Additionally, any AE that does not meet at least one of the above criteria, but that codes to a	Additional AE definition was removed.

Rationale	Location	Original	Revisions/Additions in Bold
		preferred term of the European Medicines Agency Important Medical Event list will also be considered as a SAE.	
Clarification	Section 25	After the study ends, the clinical laboratory samples will be destroyed, with the exception of samples for biomarker and genetic analysis.	After the study ends, the clinical laboratory samples will be destroyed, with the exception of samples for biomarker and **genomic** analysis.
Clarification	ATTACHMENT 1: CLINICAL LABORATORY TESTS Hormones	beta-Human chorionic gonadotropin (urinary pregnancy test)	**Urine and serum** beta-human chorionic gonadotropin (pregnancy test)
Clarification	ATTACHMENT 1: CLINICAL LABORATORY TESTS Urinalysis	In the event that any of the above assays are abnormal, a microscopic examination will be performed.	In the event that any of the above assays are abnormal **and evaluated by an investigator as clinically significant**, a microscopic examination will be performed **at a central laboratory**.

ATTACHMENT 1: CLINICAL LABORATORY TESTS

Serum chemistry	
Alanine aminotransferase	Creatine phosphokinase
Albumin (total)	Gamma-glutamyl transferase
Alkaline phosphatase	Glucose
Aspartate aminotransferase	HbA1C
Bilirubin (total)	Phosphorus
Blood urea nitrogen	Potassium
Calcium	Protein (total)
Chloride	Sodium
Creatinine level	Urate
Lipid Panel	
Cholesterol (total)	Low density lipoprotein
High density lipoprotein	Triglyceride
Hormones	
Urine and serum beta-human chorionic gonadotropin (pregnancy test)	25-Hydroxy vitamin D
Parathyroid hormone	1, 25-Dihydroxy vitamin D
Thyroid stimulating hormone	Thyroxine T3 and T4
Hematology Assays	
Hematocrit	Platelet count
Hemoglobin	Red blood cell count
White blood cell count, including differential	
Urinalysis	
Blood	Nitrite
Clarity	Protein
Color	pH
Glucose	Specific gravity
Leukocyte esterase	
In the event that any of the above assays are abnormal and evaluated by an investigator as clinically significant, a microscopic examination will be performed at a central laboratory.	
Hepatitis Serology	
Hepatitis B core antibody	HCV antibody
Hepatitis B surface antigen	HCV PCR (only if positive for HCV antibody)

ATTACHMENT 2: STERIOD TOXICITY QUESTIONNAIRE

Steroid Toxicity Questionnaire

Please describe your experiences over the past four weeks regarding your experience using these rating numbers:

(0) - None of the Time (1) A Little (2) Some of the Time (3) Most of the Time (4) All of the Time

Experience	None of the Time	A Little	Some of the Time	Most of the Time	All of the Time
Increased appetite					
Mood swings					
Depression					
Difficulty sleeping					
Easy bruising					
Sore throat					
Coating of the tongue					
Hoarseness					
Wheezing					
Going to the bathroom at night					
Headaches					

Source: Baughman, 2002

ATTACHMENT 3: EXTRAPULMONARY PHYSICIAN ORGAN SEVERITY TOOL - ePOST

ePOST Score							
Organ System	**0 Not affected**	**1 Slight**	**2 Mild**	**3 Moderate**	**4 Mod to severe**	**5 Severe**	**6 Very Severe**
Lung							
Skin							
Peripheral Lymph Node							
Eyes							
Liver							
Spleen							
Central Nervous System							
Peripheral Nervous System							
Parotid/Salivary Glands							
Bone marrow							
Ear							
Nose							
Throat							
Cardiac							
Renal							
Bone/Joint							
Muscle							
Gastrointestinal							

Source: Judson et al. 2008

ATTACHMENT 4: KING'S SARCOIDOSIS QUESTIONNAIRE

General Health status

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

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

Lung

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

Medication

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

Skin

	In the last 2 weeks	A huge amount	Considerable amount	A moderate amount	A modest amount	A small amount	A tiny amount	None at all
20	I have been bothered by my skin problems	1	2	3	4	5	6	7
21	I have been concerned about changes in colour of my skin lesions	1	2	3	4	5	6	7
	In the last 2 weeks	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**Hardly any of the time**	**None of the time**
22	I have been embarrassed about my skin	1	2	3	4	5	6	7

Eyes

	In the last 2 weeks	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

23	I have had dry eyes	1	2	3	4	5	6	7
24	I have had difficulty with bright lights	1	2	3	4	5	6	7
25	My eyes have been red	1	2	3	4	5	6	7
26	I have had pain in/or around the eyes	1	2	3	4	5	6	7
27	I have had difficulty reading	1	2	3	4	5	6	7
	In the last 2 weeks	**A huge amount**	**Considerable amount**	**A moderate amount**	**A modest amount**	**A small amount**	**A tiny amount**	**None at all**
28	I have had blurred vision	1	2	3	4	5	6	7
29	I have been worried about my eyesight	1	2	3	4	5	6	7

Source: Patel et al. 2013

ATTACHMENT 5: FATIGUE ASSESSMENT SCALE

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

1 = Never, 2 = Sometimes; 3 = Regularly; 4 = Often and 5 = Always.

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

ATTACHMENT 6: PATIENT'S GLOBAL ASSESSMENT

Date ___ ___ / ___ ___ / ___ ___

Subject Study Number: _____

Sarcoidosis Activity Scale: **PATIENT COMPLETES**

Considering all the ways your sarcoidosis affects you, rate how well you were doing in the past week

_____l_____I_____l_____l_____l_____l_____l_____l_____l_____l_____

0 1 2 3 4 5 6 7 8 9 10

Doing very poorly Doing very well

ATTACHMENT 7: PHYSICIAN GLOBAL ASSESSMENT

Date ___ ___ / ___ ___ / ___ ___

Subject Study Number: _____

Sarcoidosis Activity Scale: **PHYSICIAN COMPLETES**

Indicate your assessment of the subject's sarcoidosis disease condition on the following scale.

_____l_____I_____l_____l_____l_____l_____l_____l_____l_____l_____l_____

0 1 2 3 4 5 6 7 8 9 10

Poor Excellent

ATTACHMENT 8: MEDICAL RESEARCH COUNCIL DYSPNEA SCALE

Rate your degree of breathlessness related to activity.

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

Adapted from Fletcher CM. The clinical diagnosis of pulmonary emphysema—an experimental study. Proc R Soc Med 1952;45:577–584.

ATTACHMENT 9: LEICESTER COUGH QUESTIONNAIRE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11. In the last 2 weeks, how many times a day have you had coughing bouts?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thank you for completing this questionnaire.

Source: Birring, et al, 2003

ATTACHMENT 10: WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT

Work Productivity and Activity Impairment Questionnaire:

Sarcoidosis V1.0 (WPAI: Sarcoidosis)

The following questions ask about the effect of your sarcoidosis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your sarcoidosis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your sarcoidosis. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your sarcoidosis affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If sarcoidosis affected your work only a little, choose a low number. Choose a high number if sarcoidosis affected your work a great deal.

   Consider only how much sarcoidosis affected productivity while you were working.

Sarcoidosis had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Sarcoidosis completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your sarcoidosis affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If sarcoidosis affected your activities only a little, choose a low number. Choose a high number if sarcoidosis affected your activities a great deal.

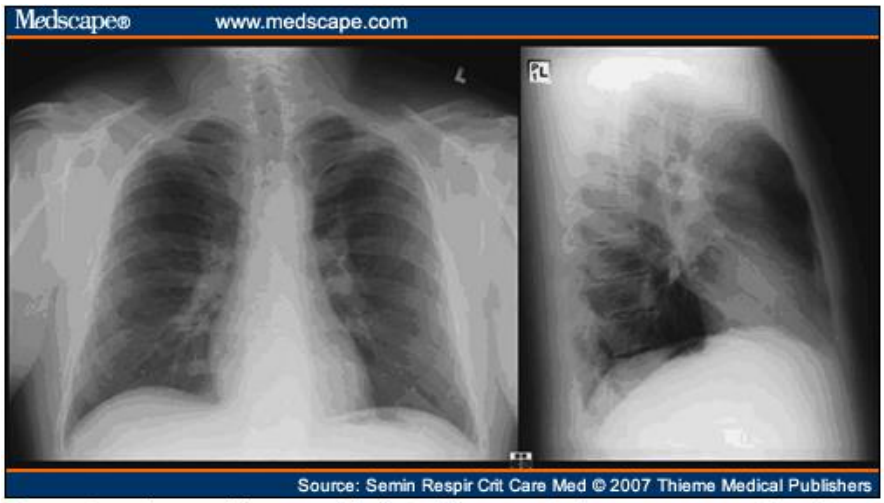
Consider only how much sarcoidosis affected your ability to do your regular daily activities, other than work at a job.

Sarcoidosis had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Sarcoidosis completely prevented me from doing my daily activities

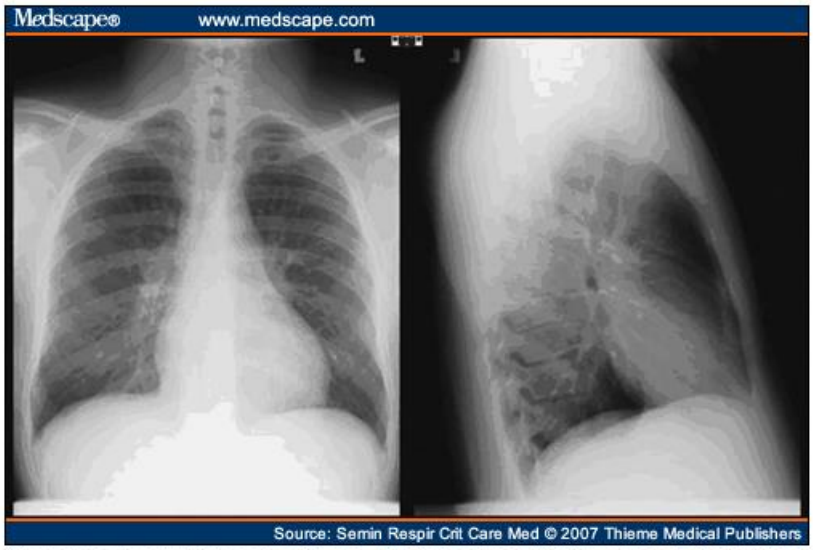
CIRCLE A NUMBER

WPAI: Sarcoidosis V1.0 (US English)

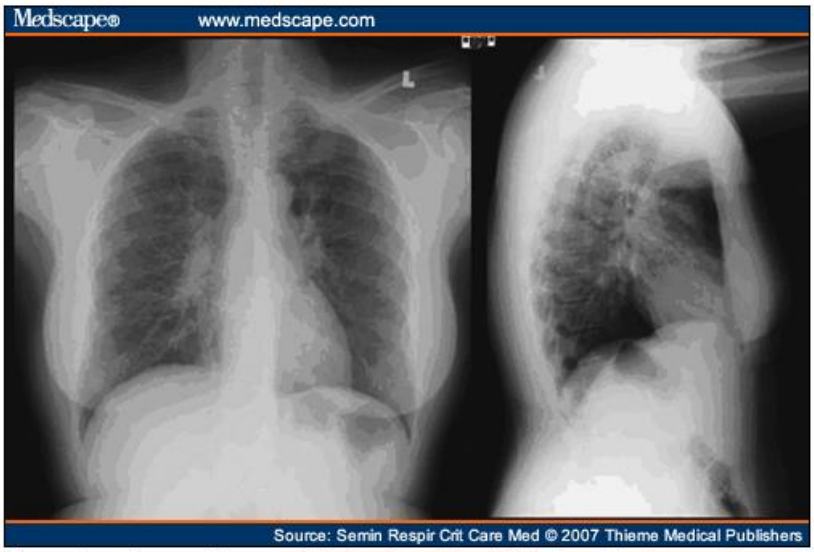
ATTACHMENT 11: SCADDING CXR SCORE



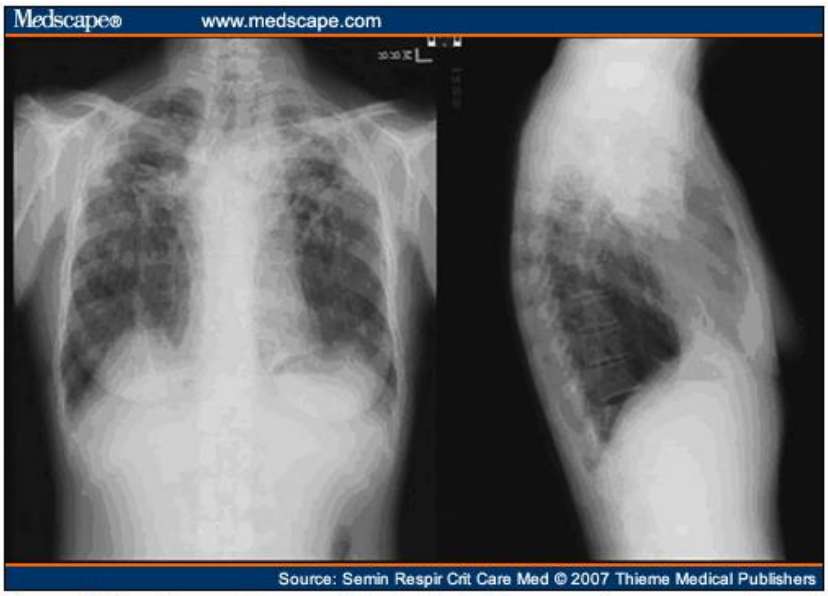
Stage 0 radiographic sarcoidosis. This normal chest x-ray may be observed in 5 to 15% of cases.



Stage I radiographic sarcoidosis. Bilateral hilar lymphadenopathy with clear lung fields.



Stage II radiographic sarcoidosis. Combined hilar lymphadenopathy and upper lung zone predominant interstitial infiltrates.



Stage III/IV radiographic sarcoidosis. Note the upper lung zone volume loss, upward retraction of the hilae, and tenting of the hemidiaphragms.

Source: Scadding, 1961

ATTACHMENT 12: SIX-MINUTE WALK TEST

Visit 1, 8, 11

Borg Scale

0	**Nothing at all**
0.5	**Very, Very Slight (just noticeable)**
1	**Very Slight**
2	**Slight**
3	**Moderate**
4	**Somewhat Severe**
5	**Severe (heavy)**
6	
7	**Very Severe**
8	
9	
10	**Very, Very Severe**
Maximal	

At the beginning of the 6-minute walk test, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale". Then ask this: "Please grade your level of fatigue using this scale."

After the posttest recovery period, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them their grade before the walk test.

Vital Signs	Baseline	Six minutes	1 Minute after walk
Heart Rate			
Oxygen Sat			
Lpm SA O_2			
Borg Score (Shortness of Breath)			
Borg Score (Level of Fatigue)			

Laps		**# of Rests**	

Limiting factors to test:
◯ **SOB** ◯ **LOW Sp02** ◯**Heart Disease** ◯**Desaturation <80%**
◯ **Other:_____**

Total distance walked _____Feet _____ Meters

Signature Page for VV-CLIN-023158 v2.0

Approval	[redacted] Clinical 18-May-2020 16:35:27 GMT+0000

Signature Page for VV-CLIN-023158 v2.0