NCT03126760

CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double Blind, Placebo Controlled Parallel Group, Pilot Study to Assess the Efficacy and Safety of Acthar® in Subjects With Relapsing-remitting Multiple Sclerosis

Protocol Number: MNK14274069

Date of Original Protocol:	27 July 2016
Date of Protocol Revision:	21 September 2016
Date of Protocol Amendment 1:	30 January 2017
Date of Protocol Amendment 2:	07 November 2017
Date of Protocol Amendment 3:	15 August 2019

Mallinckrodt ARD, LLC
1425 US Route 206
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PROTOCOL AMENDMENT 3

SUMMARY OF CHANGES

Protocol Amendment 3 was created to enhance enrollment.

The major changes are to:

1. Expand the screening period from 14 days to 28 days
2. Allow for Acthar use up to 6 months prior to study entry
3. Provide an exception to allow a 2 day window after the initiation of high dose corticosteroids to obtain certain screening assessments (FSS and EDSS, MSIS-29).
4. Allow prior and concomitant use of ocrelizumab
5. Add a primary efficacy outcome measure

A summary of changes provides the rationale and actual text.

PROTOCOL AMENDMENT 2

SUMMARY OF CHANGES

Protocol Amendment 2 was developed to update the Mallinckrodt ARD, Inc. address; remove outdated contact information; increase the screening period; increase the window from onset of relapse symptoms to first dose of intravenous methylprednisolone (IVMP), oral prednisone, or oral methylprednisolone; expand the Expanded Disability Index Scale (EDSS) range at entry; correct Interactive Phone/Web Response System (IXRS) contact requirements; and allow concomitant treatment with alemtuzumab and natalizumab.

Additional minor changes that do not impact study conduct or subject safety were also made.

The major protocol changes are summarized below:

The address of the sponsor, Mallinckrodt ARD, Inc. has been updated on the title page.

Contact information for the Medical Monitor, Clinical Technical Lead, and Clinical Trial Manager have been removed and will now be made available in a separate document.

The screening period has been increased from 24 days to 29 days and the approximate duration of subject participation has been increased from 10 to 11 weeks.

The allowable window between the onset of relapse symptoms and the first dose of IVMP, oral prednisone, or oral methylprednisolone has been increased from 10 to 14 days.

The EDSS range acceptable at entry (Inclusion Criterion 9) has been increased to 2.0 to 6.5 (formerly 3.5 to 6.5).

The Schedule of Study Events and Section 14 has been corrected to require IXRS contact at the Screening, and Baseline Visits only

Subjects treated with alemtuzumab are no longer excluded from the study (Exclusion Criterion 8) and alemtuzumab has been removed from the list of prohibited concomitant medications.

Subjects treated with natalizumab are no longer excluded from the study as long as those subjects are currently negative for the John Cunningham (JC) virus based on a negative test result within the 6 months prior to the first dose of study drug.

PROTOCOL AMENDMENT 1

SUMMARY OF CHANGES

Protocol Amendment 1 was developed to remove the requirement for male contraception, add ocrelizumab and daclizumab to the medications prohibited during the study, add microscopic examination to the urinalysis, and clarify the measurement of improvement prior to randomization.

Additional minor changes that do not impact study conduct or subject safety were also made.

The major protocol changes are summarized below:

- Inclusion criterion 4 that required male subjects to use contraception during the study was removed. The numbering of the list of inclusion criteria was not changed and inclusion criterion 4 is now left intentionally blank.
- Use of ocrelizumab or daclizumab for 6 months prior to the study was added to the exclusion criteria and ocrelizumab or daclizumab were added to the list of medication prohibited during the study.
- Microscopic examination (including specific tests) was added to the list of analyses required for urinalysis.
- The improvement in Functional Systems Score (FSS) required for randomization was clarified to allow subjects who failed to improve by at least 1 point in 1 or more functions (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral) to be randomized.
- The address of the sponsor has been updated on the title page.

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1. DISCLOSURE STATEMENT

1.1. Restricted Distribution of Documents

This document contains information that is confidential and proprietary to the sponsor. This information is being provided to the investigator solely for the purpose of evaluating and/or conducting a clinical study for the sponsor. The investigator may disclose the contents of this document only to study personnel under his/her supervision, institutional review boards (IRBs)/independent ethics committees (IECs), or duly authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity, or published without the prior written permission of the sponsor. The foregoing shall not apply to disclosure required by any regulations; however, the investigator will give prompt notice to the sponsor of any such disclosure. All other nonpublic information provided by the sponsor, as well as any information that may be added to this document, also is confidential and proprietary to the sponsor and must be kept in confidence in the same manner as the contents of this document.

2. CONTACTS

Current medical monitor and sponsor contacts will be provided in a separate document.

Please see Section 20.4 for detailed information regarding the Serious Adverse Event (SAE) Reporting Requirements for this study. Specific contact information for SAE reporting will be provided in a separate document.

3. SPONSOR SIGNATURE

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) (where applicable), all applicable national and local regulations, protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

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

[redacted] Digitally signed by [redacted]
Reason: I am approving this document
Date: 2019.08.15 13:46:19 -04'00'

Sponsor Signature

Date of Signature
(DD Month YYYY)

[redacted] PhD

Sponsor Name (print)

4. INVESTIGATOR SIGNATURE

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) (where appropriate), all applicable national and local regulations, 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.

Investigator's Signature	Date of Signature (DD Month YYYY)
Investigator's Name and Title (print)	

5. ABBREVIATIONS

Abbreviation	Term
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
[redacted]	[redacted]
CGI-I	Clinical Global Impression of Improvement Scale
CI	Confidence interval
eCRF	Electronic case report form
ECG	Electrocardiogram
EDSS	Expanded Disability Index Scale
FSS	Functional Systems Score
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCV	Hepatitis C virus antibody
HCV PCR	Hepatitis C virus polymerase chain reaction
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	[redacted]
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IGRA	Interferon gamma release assay
IMP	Investigational medicinal product
IVIg	Intravenous immunoglobulin
IVMP	Intravenous methylprednisolone
IXRS	Interactive Phone/Web Response System
JC virus	John Cunningham virus
LOCF	Last observation carried forward
MCR	Melanocortin receptor
mITT	Modified intent-to-treat
MM	Medical monitor
MS	Multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale Version 1
QD	Per day, daily
QOL	Quality of life
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event
SC	Subcutaneous
TB	Tuberculosis
TEAE	Treatment-emergent adverse event

Abbreviation	Term
U	Unit(s)
ULN	Upper limit of normal
[redacted]	[redacted]

6. SYNOPSIS

Study Title: A Multicenter, Randomized, Double Blind, Placebo Controlled Parallel Group, Pilot Study to Assess the Efficacy and Safety of Acthar® in Subjects With Relapsing-remitting Multiple Sclerosis	
Protocol Number: MNK14274069	Type: Phase 4
Condition/Disease:	Relapsing-remitting Multiple Sclerosis
Approximate Number of Subjects: 66	**Approximate Duration of Subject Participation:** 13 weeks
Approximate Number of Study Centers: 20	**Approximate Duration of Study:** 22 months

Design:

This is a multicenter, multiple dose study to estimate the response rate, and examine the safety of, Acthar in subjects with relapsing-remitting multiple sclerosis (RRMS) who have not responded to high dose intravenous methylprednisolone (IVMP), oral prednisone, or oral methylprednisolone. Approximately 66 subjects will be randomized.

Subjects with RRMS who have experienced a relapse and who will receive 3 to 5 days (given over a period of up to 7 days) of treatment with high dose IVMP (1g/day), oral prednisone (1,250 mg per day [QD]), or oral methylprednisolone (1,000 mg QD) within 28 days of the onset of relapse symptoms are candidates for the current study. The Screening Visit will take place during the initial 28 days of the 42-day screening period and subjects will be assessed with the Expanded Disability Index Scale (EDSS)/ Function Systems Score (FSS) prior to treatment with IVMP, oral prednisone, or oral methylprednisolone. At 14 (± 1) days following the initiation of high dose IVMP, oral prednisone, or oral methylprednisolone, subjects will be re-assessed with the EDSS/FSS and subjects who do not improve by at least 1 point in 1 or more functions of the FSS will be randomized on a 1:1 basis to receive subcutaneous (SC) Acthar 1 mL (80 units [U]) QD or SC matching placebo 1 mL QD for 14 days. The improvement on an FSS subscale will be relevant to the symptoms associated with the relapse based on the judgement of the treating physician. Subjects will be evaluated for treatment response using the EDSS and other standard measures up to 42 days after the start of study drug dosing.

Objectives:

Primary Objectives

- To generate an estimate of the response rate for Acthar in subjects with RRMS who have not responded to high dose IVMP, oral prednisone, or oral methylprednisolone.
- To assess the safety and tolerability of Acthar in subjects with RRMS who have not responded to high dose IVMP, oral prednisone, or oral methylprednisolone.

Secondary Objective

- To assess the effect of Acthar on quality of life (QOL) in subjects with RRMS who have not responded to high dose IVMP, oral prednisone, or oral methylprednisolone.

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Condition/Disease:	Relapsing-remitting Multiple Sclerosis

Exploratory Objective

- To explore [redacted]

Entry Criteria:

Adult male or female subjects with a diagnosis of clinically RRMS who have experienced a relapse with onset ≤ 42 days prior to the Baseline Visit. Subject must have started treatment with 3 to 5 days (inclusive, over a period of up to 7 days) of 1 g per day of IVMP, 1,250 mg per day of oral prednisone, or 1,000 mg per day of oral methylprednisolone within 28 days of the onset of the first relapse symptom. Subjects must have failed to obtain an improvement of at least 1 point in 1 or more functions on the FSS 14 days following the first dose of high dose IVMP (1g/day for 3 to 5 days), oral prednisone (1,250 mg per day for 3 to 5 days), or oral methylprednisolone (1,000 mg per day for 3 to 5 days). Subjects must have an EDSS score of 2.0 to 6.5 (inclusive) at the Baseline Visit. Subjects must have a mean systolic blood pressure ≤ 140 mm Hg and a mean diastolic blood pressure of ≤ 90 mm Hg at the Screening and Baseline Visits. Subject may not have been treated with daclizumab, or any immunosuppressants (including but not limited to cyclophosphamide, mitoxantrone, or rituximab) in the 6 months prior to the Screening Visit or throughout the study. If subjects are receiving any nonexcluded disease modifying treatments, they must have been on a stable dose(s) for 30 days prior to the Baseline Visit and plan to remain on that dose(s) throughout the study. Subjects may not have any known contraindication(s) to Acthar, history of chronic active hepatitis including active or chronic hepatitis B, or acute or chronic hepatitis C, history of tuberculosis (TB) infection or positive TB test, or type 1 or type 2 diabetes mellitus.

Concomitant Medications/Nondrug Therapies:
The following medications/nondrug therapies are not permitted during the study from the Screening Visit through Day 42:

- Oral corticosteroids (prednisone/prednisone equivalent) in excess of the 3 to 5 days (given over a period of up to 7 days) of high dose treatment that is allowed during the screening period.
- Parenteral corticosteroids.
- Daclizumab, or any immunosuppressant (including but not limited to cyclophosphamide, mitoxantrone, or rituximab).
- Natalizumab, as long as the subject is currently negative for the John Cunningham (JC) virus based on a negative test result within the 6 months prior to the first dose of study drug.
- Live or live-attenuated vaccines.
- Intravenous immunoglobulin (IVIg).
- Any investigational drug, device, or procedure administered as part of a research study.

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All medications and nondrug therapies (eg, blood transfusions, oxygen supplementation) received by subjects from the Screening Visit through the Follow-up Visit will be recorded.

Investigational Medicinal Product and Treatment Administration:

Acthar is a porcine adrenocorticotropic hormone (ACTH) analogue currently approved by the FDA for the treatment of MS exacerbations. Acthar and its matching placebo will be supplied by the sponsor and administered SC as follows in this study:

Treatment A: Acthar 1 mL (80 U) administered QD for 14 days,

OR

Treatment B: Placebo 1 mL administered QD for 14 days.

Efficacy Evaluations:

The following efficacy assessments will be evaluated: Multiple Sclerosis Impact Scale Version 1 (MSIS-29), EDSS/FSS, and Clinical Global Impression of Improvement Scale (CGI-I).

Safety Evaluations:

The following safety assessments will be evaluated: adverse events, physical examinations, clinical laboratory tests, pregnancy testing, medical history, weight, and vital signs.

Quality of Life/Health Outcome Evaluations:

The following QOL and health outcome assessment will be evaluated: [redacted]

Statistical Methods:

Analysis Populations

- The Safety Population will include all randomized subjects who receive 1 or more doses of study drug.
- The Modified Intent-to-Treat (mITT) Population will include all enrolled subjects who receive 1 or more doses of study drug and who have at least 1 postbaseline EDSS score.
- The Per-Protocol Population will include the subset of the mITT population who complete the study as per protocol.

Sample Size

It is expected that 66 subjects will be randomized into 1 of 2 treatment groups: 80 U (1 mL) of Acthar per day for 14 consecutive days or placebo (1 mL) per day for 14 consecutive days in a 1:1 ratio (33 per group). The primary analysis is to generate point estimates and associated 90% confidence intervals (CI) for the response rates on EDSS in the Acthar group and the placebo group at Day 42, respectively using a mITT analysis population. Assuming 3 subjects will not qualify for the mITT analysis population after randomization in each treatment group, there will be 30 mITT subjects in each group. Based on an expected 60% response rate in the Acthar group, the study can build a 90% Wilson CI of (45.1%, 73.3%) with approximate precision of 14.1%. Based on an expected 25% response rate in the placebo group, the study can build an approximate 90% Wilson CI of (15.7%, 41.5%) with approximate precision of 12.9%.

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Endpoint Analyses

A responder on EDSS is defined as a subject who achieves the following:

- ≥ 1.0 point improvement on EDSS score compared to baseline if baseline EDSS score was ≤ 5.5.
- ≥ 0.5 point improvement on EDSS score if the baseline EDSS score was > 5.5.

A responder on MSIS-29 is defined as a patient who achieves a ≥ 8 point improvement on the physical subscale score of MSIS-29 compared to baseline.

Baseline is defined as the value observed prior to first dose of the study drug (Day 1).

The primary efficacy endpoint, the response rate on EDSS at Day 42, will be calculated by treatment group. Response rates and 90% Wilson CIs will be reported for each treatment group. These analyses will be performed for the mITT and Per-Protocol populations.

Summary statistics (n, mean, SD, median, minimum, and maximum) of the baseline value, the value at each scheduled postbaseline evaluation and the corresponding change from baseline for EDSS score will be presented by treatment group for all subjects in the mITT population and the Per-Protocol population.

A subject-by-subject data listing sorted by treatment group and subsequently by subject will be generated for all subjects in the mITT population.

For the secondary endpoints, the response rate endpoints will be analyzed and presented with the same approach as described above for the primary efficacy endpoint. The mean score endpoint will be calculated by treatment group. Mean, SD, and 90% CI will be presented by treatment group. All secondary efficacy analyses will use the mITT population.

For the exploratory endpoints, [redacted]

For all efficacy endpoints, the normality assumption of the data will be examined using appropriate normality test. If the test result shows the data is not normally distributed, then median, 10% and 90% percentiles will be presented instead of mean, SD and 90% CI.

Quality of Life/ Health Outcomes

[redacted]

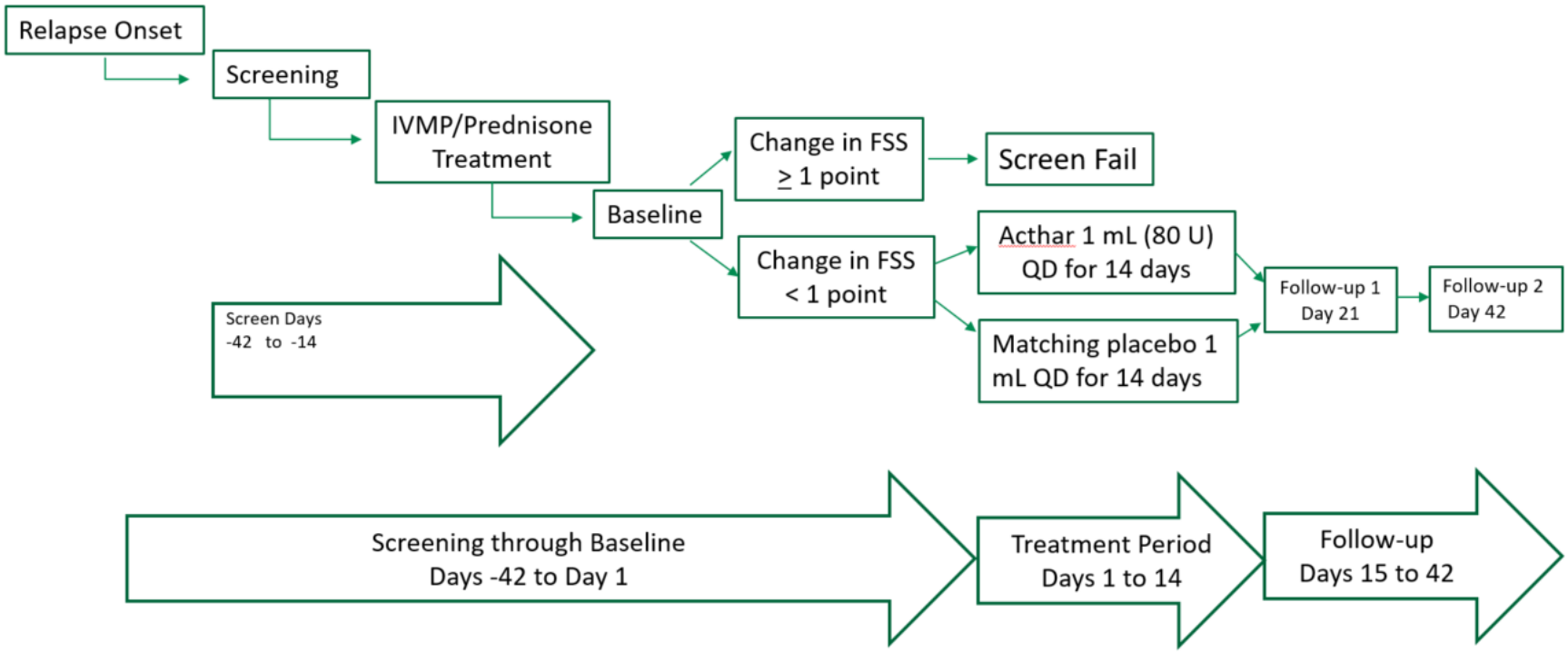
Safety

Treatment-emergent adverse events and serious adverse events will be summarized using the MedDRA by preferred term within system organ class. Other safety data will be listed and summarized descriptively or graphically, as appropriate.

7. STUDY SCHEMATIC AND SCHEDULE OF EVENTS

7.1. Study Schematic

Figure 1: Study Overview



7.2. Schedule of Study Events

Table 1: Schedule of Study Events

Assessment/Procedure	Screening (Day −42 to Day −1)	Baseline [a]	Treatment Period		Follow-up Visit 1	End of Study/ Follow-up Visit 2/
		Day 1	Day 7 (± 1 day)	Day 14 (± 2 days) [b]	Day 21 (± 2 days)	Day 42 (± 2 days)
Informed Consent	X					
Inclusion/Exclusion Criteria Review	X	X				
Medical/Surgical History	X					
Current Medical Condition Review		X	X		X	X
Demographics	X					
Complete Physical Examination		X				X
Limited Physical Examination	X		X		X	
Height and Weight [c]	X	X				X
Vital Signs [d]	X	X	X		X	X
12-lead ECG		X				X
Clinical Laboratory Tests [e]	X	X	X		X	X
HbA1c	X					
Serum Pregnancy Test	X					X
Urine Pregnancy Test		X	X		X	
Hepatitis Serology	X					
IGRA for TB	X					
EDSS/FSS	X	X	X		X	X

Assessment/Procedure	Screening (Day −42 to Day −1)	Baseline [a]	Treatment Period		Follow-up Visit 1	End of Study/ Follow-up Visit 2/
		Day 1	Day 7 (± 1 day)	Day 14 (± 2 days) [b]	Day 21 (± 2 days)	Day 42 (± 2 days)
MSIS-29	X	X	X	X	X	X
CGI-I			X		X	X
[redacted]		X			X	X
[redacted]		X			X	X
[redacted]		X			X	X
Study Drug and Diary Training		X				
IXRS Contact	X	X				
Dispense Study Drug		X				
Administer First Dose [f]		X				
Study Drug Accountability and Diary Review			X		X	
Adverse Events and Concomitant Treatments	X					

[a] The Baseline visit will occur 14 (± 1) days after the first dose of IVMP, oral prednisone or oral methylprednisolone.
[b] All Day 14 assessments will be done via telephone.
[c] Height will be collected at the Screening Visit only.
[d] Blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure will be measured in triplicate at the Screening and Baseline Visits.
[e] Chemistry, hematology, and urinalysis.
[f] The first dose will be administered clinic and the subject will be observed for at least 1 hour after dosing.

8. ETHICAL CONSIDERATIONS

This clinical study is designed to comply with International Council for Harmonisation (ICH) Guidance on General Considerations for Clinical Trials and applicable national and local regulations.

8.1. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to obtain the approval of the IRB before the start of the study. The investigator will provide Mallinckrodt Inc. with a statement of compliance from the IRB and/or the US Department of Health and Human Services general assurance number. A copy of the approval letter along with a roster of IRB/Independent Ethics Committee (IEC) members and compliance letter 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 serious adverse events (SAE) or other significant safety findings per IRB/IEC guidelines. The study protocol, informed consent form (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 Code of Federal Regulations (CFR), Title 21, Part 56 (where applicable).

8.2. Ethical Conduct of the Study

The study will be conducted in full compliance with applicable international, national and local regulatory requirements; 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.

8.3. Subject Information and Consent

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

At the Screening Visit, subjects will read the ICF and a Health Insurance Portability and Accountability Act (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. Subjects unable to give written informed consent must orally assent to the procedures, and written informed consent must be obtained from a legally authorized representative in accordance with national and local laws, as applicable.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined in 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.

9. BACKGROUND INFORMATION AND RATIONALE

9.1. Overview

Multiple sclerosis (MS) is a chronic neurodegenerative disease characterized by the demyelination of the central nervous system (Fox et al, 2012; Mayo Clinic). The incidence of MS in the US is estimated to be 4 cases per 100,000 per year with approximately 2,000 new cases diagnosed annually (MS International Federation). MS is more likely to occur in women than men (2:1 ratio) and mean age of onset in the US is approximately 33 years (MS International Federation). The most common form of MS is relapsing-remitting MS (RRMS) where patients experience acute relapses, also referred to as exacerbations, which are defined as episodes of worsening neurological function followed by partial or complete recovery periods (National MS Society; Nickerson et al, 2015; Ross et al, 2013b). Relapses in MS patients are associated with impaired daily abilities, residual disability, and reduced quality of life (QOL) (Nickerson et al, 2015; Ross et al, 2013b).

The goal of treating an MS relapse is to alleviate the symptoms as quickly as possible and to promote a complete recovery of the episode. Mild relapses, such as sensory changes or bouts of fatigue, can be left to recover over time without treatment. However, more severe relapses such as optic neuritis or loss of equilibrium, are primarily treated with corticosteroids or adrenocorticotrophic hormone (ACTH) (Ontaneda and Rae-Grant, 2009; Ross et al, 2013a; Ross et al, 2013b). ACTH is an alternative treatment for acute relapses in patients who do not respond to, or do not tolerate, high dose corticosteroids.

As described in the Package Insert, Acthar® (repository corticotropin injection, hereafter referred to as Acthar) is a porcine ACTH analogue (Mallinckrodt, 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), activation of the JAK-signal transducer and inhibition of nuclear factor-κB (Buggy, 1998; Mountjoy et al, 1992). Five subtypes of MCRs have been identified to date (MC1R-MC5R), each with different tissue distributions, binding affinity characteristics, and physiological roles (Getting, 2006). ACTH binds to all 5 subtypes of MCR (Schioth et al, 1995) and recent experiments demonstrate that Acthar also has agonist activity for all 5 MCRs (Mallinckrodt, Unpublished Data).

There are several potential mechanisms by which Acthar may impact the pathophysiologic processes involved in MS. The MC1R, MC3R, MC4R, and the MC5R are expressed on cell types that are relevant to MS, including neurons, microglia, astrocytes, lymphocytes, and monocytes/macrophages (Catania et al, 2004; Brzoska et al, 2008; Arnason et al, 2012). The therapeutic benefits of Acthar in MS are often ascribed to corticosteroid pathways; however, recent evidence suggests that the immune-modulating and anti-inflammatory effects of Acthar may also be mediated via corticosteroid-independent melanocortin signaling pathways (Ross et al, 2013a; Arnason et al, 2012; Delgado et al, 1998). Melanocortin peptides exert numerous anti-inflammatory effects, including attenuation of NF-κB activity, downregulation of pro-inflammatory cytokines and chemokines, inhibition of inflammatory cell migration, and upregulation of anti-inflammatory cytokines. Melanocortins also suppress the activation of

Th1 effector cells and promote the development of regulatory T lymphocytes (Catania et al, 2004; Getting, 2002; Ross et al, 2013a; Taylor et al, 1994; Taylor and Lee, 2011). Thus, Acthar may benefit patients with MS through both its effects on melanocortin receptors as well as through steroidogenic effects.

Early placebo controlled studies of Acthar for MS relapses demonstrated faster recovery when compared to placebo (Rose et al, 1970). Trials comparing Acthar to corticosteroids in the treatment of MS relapses demonstrated similar marked improvement outcomes (Miller et al, 1961; Thompson et al, 1989). Acthar has been shown to provide positive outcomes and lower numbers of adverse events (AE) compared to intravenous methylprednisolone (IVMP) in MS patients who failed treatment with methylprednisolone (Berkovich et al, 2012).

Although IVMP 1 g per day, high dose oral prednisone (1,250 mg per day), or high dose oral methylprednisolone (1,000 mg per day) for 3 to 5 days has become the standard of care for patients who have experienced MS relapses, many patients do not recover to their baseline level of neurological function. In a retrospective study, (Lublin, 2003) showed that MS relapses result in sustained accumulation of disability over time. In this study, a total of 224 patients who had participated in the placebo groups of large clinical trials and who had experienced MS relapses were evaluated. Forty-two percent of patients were left with a residual deficit of at least 0.5 points on the Expanded Disability Status Scale (EDSS) and 28% with a deficit of at least 1.0 EDSS points at a mean of 64 days following the relapse.

Randomized clinical trials that have examined the response rate of patients who have been treated for MS relapse with either IVMP or oral methylprednisolone suggest that between 65% and 85% experienced significant improvement (Le Page et al, 2015; Sellebjerg et al, 1998). This indicates that 20% to 35% of patients do not experience significant improvement.

There are very limited treatment alternatives for patients who have experienced a relapse of MS and do not respond to corticosteroids. In a randomized, controlled, double blind trial of plasma exchange vs sham treatment in patients with acute demyelinating episodes (including some MS patients) who had failed to respond to treatment with IVMP, 42.1% responded to plasma exchange as compared to only 5.9% who responded to a sham treatment (Weinshenker et al, 1999).

Because a significant number of MS patients with relapse do not respond to corticosteroids, and plasma exchange is invasive and often involves a lengthy hospital stay, there remains a large unmet need for these patients. The current placebo controlled, pilot study is designed to generate response rates in this patient population following treatment with Acthar in order to facilitate a sample size calculation for a larger, more definitive study in the future.

9.2. Product Description

Acthar is a sterile preparation of a purified ACTH analogue formulated in 16% gelatin to provide prolonged release after intramuscular or subcutaneous (SC) injection. Acthar 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 is obtained from processing porcine pituitary using an FDA approved process.

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 except that it contains no active medication.

9.3. Dosage and Administration

Investigational medicinal product (IMP), also referred to as study drug, will be used to denote active drug (Acthar) and/or matching placebo.

Following a screening period of up to 42 days during which subjects will receive either IVMP 1g per day, oral prednisone 1,250 mg per day, or oral methylprednisolone 1,000 mg/day for 3 to 5 days, subjects with RRMS unresponsive to corticosteroid therapy with relapse onset ≤ 42 days prior to the Baseline Visit, will be randomized on a 1:1 basis to receive SC Acthar 1 mL (80 Units [U]) daily (QD) or SC matching placebo 1 mL QD for 14 days.

9.4. Dose Rationale

Acthar is currently approved in the US for treatment of acute exacerbations of MS with daily intramuscular or SC doses of 80 to 120 U for up to 2 to 3 weeks (Mallinckrodt, 2019). The 14 day regimen of 1 mL (80 U) was chosen for this study based on feasibility, safety, and current prescribing practices. The 1 mL (80 U) dose is lower than the maximum approved dose of 120 U.

9.5. Adverse Events

The most common adverse reactions for Acthar [redacted] include fluid retention, alteration in glucose tolerance, elevation of blood pressure, behavioral and mood changes, and increased appetite and weight gain. See the current Acthar package insert for more specific information on adverse events associated with Acthar (Mallinckrodt, [redacted]).

10. OBJECTIVES

10.1. Primary Objectives

The primary objectives of this study are:

- To generate an estimate of the response rate for Acthar in subjects with RRMS who have not responded to high dose IVMP, oral prednisone, or oral methylprednisolone.
- To assess the safety and tolerability of Acthar in subjects with RRMS who have not responded to high dose IVMP, oral prednisone, or oral methylprednisolone.

10.2. Secondary Objective

The secondary objective of this study is:

- To assess the effect of Acthar on QOL in subjects with RRMS who have not responded to high dose IVMP, oral prednisone, or oral methylprednisolone.

10.3. Exploratory Objective

The exploratory objective of this study is:

- [redacted]

10.4. Outcome Measures

The primary efficacy outcome measure is: Score on the Expanded Disability Status Scale (EDSS) at Baseline and Day 42.

The EDSS is a method to score the steps of progressive disability in MS patients. The scale ranges from 0 (no disability) to 10 (death) in ½ point increments (0, 0.5, 1.0, 1.5, 2.0, etc).

It is used by neurologists to track MS disability. Higher scores indicate more disability. Steps 0-4.5 mean the patient is progressively disabled in eight functions, but still able to walk without aid. By Step 6, the patient needs a pair of canes or crutches to walk. By Step 9, the patient is unable to get out of bed, but can still talk and eat.

11. STUDY DESIGN

11.1. Description

This is a multicenter, multiple dose study to estimate the response rate, and examine the safety of, Acthar in subjects with RRMS who have not responded to high dose intravenous methylprednisolone (IVMP), oral prednisone, or oral methylprednisolone. Approximately 66 subjects will be randomized.

Subjects with RRMS who have experienced a relapse and who will receive 3 to 5 days (given over a period of up to 7 days) of treatment with high dose IVMP (1g/day for 3 to 5 days), oral prednisone (1,250 mg per day [QD]), or oral methylprednisolone (1,000 mg QD) within 28 days of the onset of relapse symptoms are candidates for the current study. The Screening Visit will take place during the initial 28 days of the 42-day screening period and subjects will be assessed with the EDSS/ Function Systems Score (FSS) prior to treatment with IVMP, oral prednisone, or oral methylprednisolone. At 14 (± 1) days following the initiation of high dose IVMP, oral prednisone, or oral methylprednisolone, subjects will be re-assessed with the EDSS/FSS and subjects who do not improve by at least 1 point in 1 or more functions of the FSS will be randomized on a 1:1 basis to receive SC Acthar 1 mL (80 U) QD or SC matching placebo 1 mL QD for 14 days. The 1 point improvement on an FSS subscale will be relevant to the symptoms associated with the relapse based on the judgement of the treating physician. Subjects will be evaluated for treatment response using the EDSS and other standard measures up to 42 days after the start of study drug dosing.

11.2. Approximate Duration of Subject Participation

Subjects will participate in the study for a total of up to approximately 13 weeks, including a screening period of up to 42 days, and active treatment period of 14 days, and Follow-up Visits at 21 (± 2) and 42 (± 2) days after the start of study drug administration.

11.3. 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 sites to identify and enroll eligible subjects. The entire study is expected to require approximately 22 months to complete.

11.4. Approximate Number of Subjects

It is expected that approximately 320 subjects will be screened and 66 subjects will be randomized at approximately 20 sites in the US.

12. SELECTION OF SUBJECTS

12.1. Inclusion Criteria

Subjects must meet all of the following criteria for inclusion in the study at the Screening Visit and the Baseline Visit.

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 years of age at the Screening Visit and can be male or female.
3. Female subjects must be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit), or if of childbearing potential must be nonpregnant, nonlactating and agree to use effective contraception with a male partner throughout study participation (through the final Follow-up Visit). Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections), intrauterine devices, double barrier methods (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), and abstinence.
4. This number left intentionally blank.
5. Subjects must have a diagnosis of RRMS according to the revised McDonald criteria (Polman et al, 2011).
6. Subjects must have had a relapse with onset ≤ 42 days prior to the Baseline Visit. Relapse is defined as new neurological symptom(s) persisting for ≥ 24 hours and accompanied by an objective change in neurological examination.
7. Subject must have started treatment with 3 to 5 days (inclusive, given over a period of up to 7 days) of 1 g per day of IVMP, 1,250 mg per day of oral prednisone, or 1,000 mg per day of oral methylprednisolone within 28 days of the onset of the first relapse symptom.
8. Subjects must have failed to obtain an improvement of at least 1 point in 1 or more functions (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral) on the FSS 14 days following the first dose of high dose IVMP (1g/day for 3 to 5 days), oral prednisone (1,250 mg per day for 3 to 5 days), or oral methylprednisolone (1,000 mg per day for 3 to 5 days). The 1 point improvement in 1 or more symptoms on the FSS subscale will be relevant to the symptoms associated with the relapse based on the judgement of the treating physician.
9. Subjects must have an EDSS score of 2.0 to 6.5 (inclusive) at the Baseline Visit.
10. Subjects must have a mean systolic blood pressure ≤ 140 mm Hg and a mean diastolic blood pressure of ≤ 90 mm Hg determined by the average of 3 seated readings taken at least 5 minutes apart at the Screening and Baseline Visits.
11. Subjects must be able to communicate effectively with study personnel.
12. Subjects must be able and willing to follow all protocol requirements and study restrictions.

13. Subjects must be able and willing to return for all study visits.

12.2. Exclusion Criteria

Subjects are ineligible for study participation if they meet any of the following criteria at the Screening Visit and/or the Baseline Visit:

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 has used Acthar for the treatment of MS within the last 6 months.
3. Subject has only sensory, bowel/bladder, and/or cognitive symptoms of MS associated with the most recent relapse.
4. Subject is unwilling to receive, or is intolerant of, SC injections.
5. Subject has a history of sensitivity to ACTH preparations or to porcine protein products.
6. Subject has cognitive or behavioral impairment that in the opinion of the investigator would impair the ability of the subject to comply with study procedures.
7. Subject has received < 3 or > 5 days of dosing of IVMP, oral prednisone, or oral methylprednisolone during the screening period or who received their doses over a period of > 7 days. Divided doses of oral prednisone or oral methylprednisolone are acceptable as long as the total daily dose is 1,250 mg or 1,000 mg, respectively.
8. Subject has been treated with daclizumab, or any immunosuppressants (including but not limited to cyclophosphamide, mitoxantrone, or rituximab), in the 6 months prior to the Screening Visit or throughout the study. Subjects treated with natalizumab will be excluded if they are not currently negative for JC virus based on a negative John Cunningham (JC) virus test result in the 6 months prior to the first dose of Acthar.
9. Subjects receiving any nonexcluded disease modifying treatments (including beta-interferons, glatiramer acetate, fingolimod, teriflunomide, and dimethyl fumarate) must have been on a stable dose(s) for 30 days prior to the Baseline Visit and plan to remain on that dose(s) throughout the study.
10. Subject has any known contraindication(s) to Acthar (Mallinckrodt, 2019) including, but not limited to:
    - Any known history of scleroderma, osteoporosis, or ocular herpes simplex.
    - Any current uncontrolled hypertension, primary adrenocortical insufficiency, or adrenal cortical hyperfunction.
    - Any current psychoses, infectious disease, or Cushing's syndrome.
    - Any current congestive heart failure (defined as New York Heart Association Functional Class III to IV).

- Peptic ulcer (within 24 weeks prior to the Screening Visit).
- Recent major surgery (within 24 weeks prior to the Screening Visit).

11. Subject has a history of chronic active hepatitis including active or chronic hepatitis B, or acute or chronic hepatitis C.
12. Subject has a history of tuberculosis (TB) infection, any signs/symptoms of TB, or any close contact with an individual with an active TB infection.
13. Subject has a clinically significant infection requiring intravenous administration of antibiotics and hospitalization in the 4 weeks prior to the Screening Visit.
14. Subject has known immune compromised status, including but not limited to, individuals who have undergone organ transplantation or who are known to be positive for the human immunodeficiency virus.
15. Subject has type 1 or type 2 diabetes mellitus (prior diagnosis of gestational diabetes mellitus is not exclusionary).
16. 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 the Screening Visit, 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.
17. Subject has a diagnosis of, is undergoing therapy for, or has received therapy for a hematologic malignancy in the 5 years prior to the Screening Visit.
18. Subject has current or recent (within 24 weeks prior to the Screening Visit) 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).
19. Subject has any of the following laboratory abnormalities at the Screening Visit:
    - Hemoglobin ≤ 8.0 g/dL.
    - Platelets ≤ 50,000 cells/µL.
    - Absolute neutrophil count (ANC) ≤ 1,000 cells/µL.
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin > 2 times upper limit of normal (ULN).
    - Glycosylated hemoglobin (HbA1c) > 6.5%.
    - Positive Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb).
    - Positive Hepatitis C virus antibody (HCV) and HCV polymerase chain reaction (PCR) ≥ 25 IU/mL (HCV PCR will be automatically analyzed if HCV is positive).
    - Positive or indeterminate interferon gamma release assay (IGRA).
20. Subject has any other clinically significant disease, disorder or laboratory abnormality 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.

12.3. 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 starting screening related procedures at the Screening Visit to the Baseline Visit must not exceed 42 days, inclusive of any repeat screening procedures.

Subjects who do not meet all of the eligibility criteria at the Screening or Baseline Visits will be deemed a screen failure and the reason for the screen failure will be documented.

13. PRIOR AND CONCOMITANT MEDICATION/NONDRUG THERAPIES

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 42 days prior to the first dose of study drug) and concomitant medications and nondrug therapies (eg, blood transfusions, oxygen supplementation) received will be recorded.

In addition, all prior treatments for MS during the past 2 years will be recorded with start and stop date, dose, unit, frequency and route of administration.

13.1. Prohibited Concomitant Medications/Nondrug Therapies

The following medications/nondrug therapies are not permitted during the study from the Screening Visit through Day 42:

- Oral corticosteroids (prednisone/prednisone equivalent) in excess of the 3 to 5 days (given over a period of up to 7 days) of high dose treatment that is allowed during the screening period.
- Parenteral corticosteroids.
- Daclizumab, or any immunosuppressant (including but not limited to cyclophosphamide, mitoxantrone, or rituximab).
- Natalizumab (unless the subject is currently negative for JC virus based on a negative JC virus test in the 6 months prior to the first dose of Acthar).
- Live or live-attenuated vaccines.
- Intravenous immunoglobulin (IVIg).
- 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 electronic case report form (eCRF). The designated study medical monitor (MM) must be informed immediately so the sponsor may determine whether to continue the subject in the study.

13.2. Required and Allowed Concomitant Medications/Nondrug Therapies

Subject must have started treatment with 3 to 5 days (inclusive, given over a period of up to 7 days) of IVMP (1 g per day), oral prednisone (1,250 mg/day), or oral methylprednisolone (1,000 mg per day) within 28 days of the onset of the first relapse symptom.

Subjects receiving nonexcluded disease modifying treatment(s) (including beta-interferons, glatiramer acetate, fingolimod, teriflunomide, and dimethyl fumarate) must have been in a stable dose(s) for ≥ 30 days prior to the Baseline Visit and plan to remain on that dose(s) throughout the study.

14. PROCEDURES/ASSESSMENTS

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

14.1. Screening Visit (Study Days −42 to −14) Procedures/Assessments

Screening assessments must be performed within 42 and 14 days prior to the Baseline Visit. The following procedures will be performed at the Screening Visit:

- Informed consent.
- Inclusion/exclusion criteria.
- Medical and surgical history.
- Demographics.
- Limited physical examination.
- FSS and EDSS. (Exception: these assessments may be performed within a 2 day window after the initiation of high dose corticosteroids.)
- Multiple Sclerosis Impact Scale, Version 1 (MSIS-29). (Exception: this assessment may be performed within a 2 day window after the initiation of high dose corticosteroids.)
- Height and Weight.
- Vital signs.
- Clinical laboratory tests.
- HbA1c.
- Serum pregnancy test.
- Hepatitis serology.
- IGRA test for TB (to be performed locally).
- Contact the Interactive Phone/Web Response System (IXRS).
- Treat with IVMP (1g QD), oral prednisone (1,250 mg QD), or oral methylprednisolone (1,000 mg QD) for 3 to 5 days (given over a period of up to 7 days).
- Adverse events and concomitant medications.

Subjects will be allowed to repeat any screening procedure once, if necessary, if it is within the screening window.

14.2. Baseline Visit (Day 1) and First Dose Procedures/Assessments

Predose evaluations will occur prior to the first dose of study drug and 14 (± 1) days after the first dose of IVMP, oral prednisone, or oral methylprednisolone. The investigator or designee will complete the following procedures prior to the first study drug dose:

- Inclusion/exclusion criteria review; subject must meet all eligibility criteria at screening and baseline.
- MSIS-29, [redacted]
- Current medical condition review.
- Complete physical examination.
- FSS and EDSS.
- Weight.
- Vital signs.
- 12-lead electrocardiogram (ECG).
- Clinical laboratory tests.
- Urine pregnancy test.
- Contact IXRS and dispense study drug kits.
- Study drug administration under supervision of study staff and observation for at least 1 hour thereafter.
- Adverse events and concomitant medications.

14.3. Day 7 (± 1 Day) Procedures/Assessments

- MSIS-29.
- Current medical condition review.
- Limited physical examination.
- FSS and EDSS.
- Global Clinical Impressions Scale (CGI-I).
- Vital signs.
- Clinical laboratory tests.
- Urine pregnancy test.
- Subject diary review.
- Study drug accountability.
- Adverse events and concomitant medications.

14.4. Day 14 (± 2 Days) Procedures/Assessments

- MSIS-29 (to be administered via telephone).
- Adverse events and concomitant medications.

14.5. Day 21 (± 2 Days)/Follow-up Visit 1

- MSIS-29, [redacted]
- Current medical condition review.
- Limited physical examination.
- FSS and EDSS.
- CGI-I.
- Vital signs.
- Clinical laboratory tests.
- Urine pregnancy test.
- Subject diary review.
- Study drug accountability.
- Adverse events and concomitant medications.

14.6. Day 42 (± 2 Days) Follow-up Visit 2/Early Termination Procedures/Assessments

The following procedures will be completed at Study Day 42 (± 2 days) or whenever a subject terminates early from the study:

- MSIS-29, [redacted]
- Current medical condition review.
- Complete physical examination.
- FSS and EDSS.
- CGI-I.
- Weight.
- Vital signs.
- 12-lead ECG.
- Clinical laboratory tests.
- Serum pregnancy test.
- Diary review and study drug accountability (if appropriate, for early termination only).
- Adverse events and concomitant medications.

15. INVESTIGATIONAL MEDICINAL PRODUCT (STUDY DRUG)

15.1. Methods of Assigning Subjects to Treatment Groups

15.1.1. Randomization

Subjects will be randomized according to a computer-generated allocation scheme to receive either Acthar 1 mL (80 U) or placebo 1 mL administered QD for 14 consecutive days. 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.

15.1.2. IXRS

The investigator or designee will contact IXRS to register subjects at screening. The subject's identification (ID) number 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 Baseline, qualified subjects who meet all of the eligibility criteria will be enrolled into the study.

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

The investigator or designee must contact IXRS to register the subject at screening, to receive the study drug kit 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.

15.2. Emergency Identification of Investigational Medicinal Product

In case of an emergency during the study, when knowledge of the investigational product assignment is required for the medical management of an individual subject, the investigator may obtain the treatment assignment of the subject experiencing the emergency. The treatment blind for that subject may be broken by accessing the IXRS using instructions provided. The investigator must notify the sponsor's MM or physician designee immediately after determining that it is necessary to unblind the treatment assignment. The investigator and sponsor should make every effort to document and limit the people who are unblinded to the subject's treatment assignment. The investigator must also indicate in source documents and in the eCRF that the blind was broken and provide the date, time, and reason for breaking the blind.

15.3. Dosing Procedures

Both Acthar and the placebo are supplied as 5 mL multidose vials. Acthar vials contain 80 U of ACTH per mL. The vials should not be over pressurized prior to withdrawing the product. The vials should be warmed to room temperature before using and will be labeled according to all applicable national and local regulations.

The following treatments will be administered:

- Treatment A: Acthar 1 mL (80 U) SC QD for 14 days, **OR**
- Treatment B: Placebo 1 mL SC QD for 14 days.

The subject or subject's caregiver will administer the first dose of Acthar 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. Thereafter, all doses will be administered by the subject or the subject's caregiver at home.

15.3.1. Treatment Discontinuation

Treatment with study drug should be discontinued if any of the following occur:

- Development of accelerated hypertension (defined as systolic blood pressure ≥ 180 *and* 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 that cannot be managed by the adjustment of concomitant medications such as diuretics and antihypertensive medications.
- Development of diabetic signs/symptoms (ie, HbA1c > 6.5%, or fasting plasma glucose > 126 mg/dL, or classic symptoms of hyperglycemia with random plasma glucose > 200 mg/dL).
- Subjects who undergo plasma exchange or IVIg due to lack of efficacy will be considered treatment failures and will be withdrawn from the study.
- Development of any other AE of at least moderate intensity and possibly, probably or definitely related to study drug that cannot be managed by the adjustment of concomitant medications.

15.4. Storage of Clinical Supplies

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

Study drug will be supplied in kits containing the appropriate amount of vials according to the treatment group to which the subject is assigned. Study drug 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 study drug.

15.5. Drug Accountability

In accordance with ICH requirements, the investigator will, at all times, be able to account for all study drug 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 study drug received, to whom it was dispensed (subject-by-subject accounting) and accounts of any study drug accidentally or deliberately destroyed. All unused study drug not involved in immediate subject dosing will be maintained under locked, temperature-controlled storage at the study site.

15.6. Compliance Monitoring

Prior to beginning the administration of study drug, subjects and/or their caregiver will be trained on dosing administration and must exhibit proper technique. 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. 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.

16. EFFICACY ASSESSMENTS

Efficacy assessments will be evaluated at times specified in the Schedule of Study Events (Table 1). Below are general instructions for the administration of these assessments. Specific instructions and questionnaires will be provided in a separate document.

16.1. Subject Completed Assessments

The MSIS-29 is a subject reported outcome measure. When this assessment is required, it should be the first assessment done at any visit 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). The study staff should review the questionnaire after it completed and encourage the subjects to complete any missing information. Subjects may refrain from answering any question. Study staff will record the refusal of subjects to answer any questions in the source documents.

16.1.1. MS Impact Scale (Version 1)

The MSIS-29 measures the physical (20 items) and psychological (9 items) impact of MS from the subjects perspective (Hobart et al, 2001). This validated questionnaire will result in a total score between 29 and 145 and can provide separate scores for physical and psychological impact. The MSIS-29 will be completed by the subject at all required times points during the study except on Study Day 14 when the MSIS-29 will be administered via telephone by a call center trained in the administration of the MSIS-29 or captured via a web portal.

16.2. Investigator (or Designee) and Blinded Rater Completed Assessments

The EDSS and FSS are to be completed by an appropriately trained blinded rater. The CGI-I assessment will be completed by an appropriately trained investigator or designee. When these assessments are required, they should be the done immediately after subject reported outcome/questionnaire completion (if applicable) and must be completed prior to any study drug dosing. The same trained rater should complete these assessments at all required time points for a subject.

16.2.1. Expanded Disability Status Score/Functional Systems Score

The EDSS is a 10 step assessment of neurological impairment/disability in MS ranging from 0 (normal neurological examination) to 10 (death due to MS) (Kurtzke, 1983) that is completed by a blinded rater.

The FSS is a component of the EDSS that requires the rater to score function in 7 functions (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral) on a scale from 0 (normal) to 5 or 6 (severe impairment) (Kurtzke, 1983).

Each site will designate 1 primary rater (neurologist or advanced practitioner experienced in performing EDSS/FSS) for each subject who will be responsible for performing all EDSS and FSS evaluations and who will be blinded to all other study aspects. The blinded rater should remain constant for each subject whenever possible. Subjects will be instructed not to discuss

MS therapy, any skin reactions, or other therapy side effects they have experienced with the blinded rater. The blinded rater will not be involved in any aspects of subject care and management other than performing the EDSS/FSS evaluations in subjects in the study.

16.3. Clinical Global Impression of Improvement

The CGI-I was developed for use in clinical research to provide a brief overview of the change in a subject's global function compared to baseline and regardless of study drug treatment (Guy, 1976; Busner and Targum, 2007). It requires a rating from 1 (very much improved) to 7 (very much worse).

17. SAFETY ASSESSMENTS AND PROCEDURES

The following safety assessments will be evaluated: AEs, physical examinations, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs, medical history, current medical condition, and weight. All safety assessments will be performed at times outlined in the Schedule of Study Events (Table 1Table71). Additional (unscheduled) safety assessments may be performed as needed.

17.1. Adverse Events

Adverse events will be recorded from signing of the ICF and followed by the investigator until the AE is resolved or stabilized. 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 20 for additional details on the handling of AEs and SAEs.

17.2. Medical and Surgical History

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

17.3. Current Medical Conditions

At each visit after screening, subjects will be asked about any changes in medical conditions, specifically new medical conditions and worsening of existing medical conditions. Any changes since the Screening Visit will be recorded as AEs, as appropriate.

17.4. Physical Examination

A complete physical examination will be performed at the Baseline Visit and the Day 42/Early Termination Visit. The complete physical examination includes 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.

A limited physical examination, including evaluation of lungs, heart, abdomen, and extremities will be done at all other clinic visits.

The findings of the physical examinations will be recorded. Any change from the Screening Visit physical examination that is considered clinically significant by the investigator will be recorded as an AE.

17.5. Height and Weight

Height will be collected at screening only. Weight will be collected at specified times during the study.

17.6. 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, respiratory rate, and body temperature. Additionally, at the Screening and Baseline Visits, blood pressure will be measured at least 3 times, with 5 minutes between assessments after the subject has been seated for a minimum of 5 minutes prior to the initial blood pressure assessment. The date and time for all vital sign assessments will be recorded.

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.

Screening/Baseline Assessments

A subject with systolic blood pressure > 140 mm Hg and diastolic blood pressure > 90 mm Hg (average of 3 assessments) at the Screening or Baseline Visits does not qualify for the study.

On Study Assessments

If an on study vital sign is not in the site's standard reference range, an AE will be recorded if the investigator determines the change is clinically significant or requires a change in the subject's clinical management.

17.7. Clinical Laboratory Tests (Chemistry, Hematology, Urinalysis, HbA1c, Hepatitis Serology, IGRA, and Pregnancy Tests)

The clinical laboratory tests are listed in Section 31.1. All clinical laboratory tests will be done at a central laboratory facility except urine pregnancy (at the site) and IGRA (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 laboratory testing at all visits may be collected under fasted or nonfasted conditions. Fasting early morning samples are preferred, but a random daytime sample is acceptable. 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.

Hematology with differential, serum chemistry, and urinalysis samples will be collected at the specific times starting at screening and throughout the study.

In addition:

- All female subjects of child-bearing potential will have a serum pregnancy test at the Screening and Day 42/Early Termination Visits. Urine pregnancy tests will be

done at all other visits throughout the study. Results must be available prior to dosing with protocol mandated study drug. Subjects with positive results will be ineligible for study entry (Screening Visit or Predose) or withdrawn from the study if the positive result is obtained before the end of the treatment period. Any female subject that becomes pregnant before the end of the treatment period will be immediately withdrawn. All subjects who became pregnant after the last dose of the treatment will be continued in the study for follow-up visits. All pregnancies will be reported as per Section 20.6.

If applicable, the subject's agreement to use contraception throughout their study participation (through the Follow-up Visit) will be documented.

- HBsAg and HBcAb will be performed at the Screening Visit. Results of these tests must be negative or nonreactive for subjects to qualify for the study.
- HCV will be performed at the Screening Visit. 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 the Screening Visit. Results of this test must be negative for subjects to qualify for the study.
- HbA1c will be performed at the Screening Visit. HbA1c must be ≤ 6.5% for subjects to qualify for the study.

Out-of-Range Laboratory Values

Laboratory values from samples collected at the Screening Visit 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 that fall outside the reference range from samples collected during the study or at study exit or early termination 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.

18. QUALITY OF LIFE/ HEALTH OUTCOME ASSESSMENTS

The following QOL/Health Outcome questionnaires are to be completed by the subject. When these assessments are required, they should be the second assessment done at any visit (after MSIS-29) and must be completed prior to any study drug dosing. Subjects will be provided a quiet, private place to complete the assessments. 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). The study staff should review the questionnaires after they are completed and encourage the subjects to complete any missing information. Subjects may refrain from answering any question. Study staff will record the refusal of subjects to answer any questions in the source documents.

18.1. [redacted]

[redacted]

18.2. [redacted]

[redacted]

[redacted]

19. STATISTICAL METHODS AND PLANNED ANALYSIS

19.1. 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. A more detailed statistical analysis plan will be provided in a separate document that will be finalized prior to database lock.

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. Data summary and analyses will be performed with SAS 9.2 or higher.

19.2. Analysis Populations

- The Safety Population will include all randomized subjects who receive 1 or more doses of study drug.
- The Modified Intent-to-Treat (mITT) Population will include all enrolled subjects who receive 1 or more doses of study drug and who have at least 1 postbaseline EDSS score.
- The Per-Protocol Population will include the subset of the mITT population who complete the study as per protocol.

19.3. Endpoints

19.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be the response rate on EDSS and 90% confidence interval (CI) on Day 42 for each treatment group.

19.3.2. Primary Safety Endpoint

The primary safety endpoint will be a summary of general safety profile, including adverse events (serious and nonserious), vital signs and laboratory assessments by study period and over the entire study.

19.3.3. Secondary Efficacy Endpoints

- The response rates on MSIS-29 and 90% CIs on Day 7, Day 14, Day 21 and Day 42 for each treatment group.
- The response rates on EDSS and 90% CIs on Day 7 and Day 21 for each treatment group.
- CGI-I mean scores and 90% CIs on Day 7, Day 21 and Day 42 for each treatment group.

19.3.4. Exploratory Endpoints

[redacted]

19.4. Subject Characteristics

19.4.1. Demographics

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

19.4.2. Medical and Surgical History

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

19.4.3. 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.

19.4.4. Subject Disposition and Exposure to Study Drug

Subject disposition will be summarized for all randomized subjects. 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.

19.5. Efficacy Analysis

A responder on EDSS is defined as a subject who achieves the following:

- ≥ 1.0 point improvement on EDSS score compared to baseline if baseline EDSS score was ≤ 5.5.
- ≥ 0.5 point improvement on EDSS score if the baseline EDSS score was > 5.5.

A responder on MSIS-29 is defined as a patient who achieves ≥ 8 point improvement on the physical subscale score of MSIS-29 compared to baseline.

Baseline is defined as the value observed prior to first dose of the study drug (Day 1).

The primary efficacy endpoint, the response rate on EDSS at Day 42, will be calculated by treatment group. Response rates and 90% Wilson CIs will be reported for each treatment group. These analyses will be performed for the mITT and Per-Protocol populations.

Summary statistics (n, mean, SD, median, minimum, and maximum) of the baseline value, the value at each scheduled postbaseline evaluation and the corresponding change from baseline for EDSS score will be presented by treatment group for all subjects in the mITT population and the Per-Protocol population.

A subject-by-subject data listing sorted by treatment group and subsequently by subject will be generated for all subjects in the mITT population.

For the secondary endpoints, the response rate endpoints will be analyzed and presented with the same approach as described above for the primary efficacy endpoint. The mean score endpoint will be calculated by treatment group. Mean, SD, and 90% CI will be presented by treatment group. All secondary efficacy analyses will use the mITT population.

For the exploratory endpoints, scores change from baseline will be calculated by treatment group. Mean, SD, and 90% CI will be presented by treatment group. All exploratory efficacy analyses will use the mITT population.

For all efficacy endpoints, the normality assumption of the data will be examined using appropriate normality test. If the test result shows the data is not normally distributed, then median, 10% and 90% percentiles will be presented instead of mean, SD and 90% CI.

The statistical analysis plan will describe in further detail the analyses for primary, secondary, and exploratory efficacy endpoints.

19.6. Safety Analysis

All subjects who receive at least 1 dose of study drug will be included in the safety analyses. Safety data will be summarized descriptively or graphically, as appropriate.

19.6.1. Adverse Events

Adverse events will be coded using the appropriate version of MedDRA. All AEs will be presented in a data listing. Only treatment-emergent adverse events (TEAEs) (events that are new in onset or aggravated in severity following treatment) will be included in all summaries. TEAEs will be summarized for each treatment group, by system organ class and preferred term. Serious adverse events (including death) will be summarized. In addition, adverse events will be summarized by severity and relation to study drug.

19.6.2. Clinical Laboratory Tests

Hematology, blood chemistry, and urinalysis results will be summarized at baseline and at each visit by treatment group. Change from baseline to each visit will also be summarized. Abnormal laboratory values will be identified and analyzed.

19.6.3. Vital Signs

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

19.6.4. Other Safety Analysis

Other safety assessments including physical examinations, weight, and pregnancy testing, will be analyzed with appropriate summary statistics.

19.7. Quality of Life/ Health Outcomes Analysis

The change from baseline in [redacted] will be summarized with mean change, SD, and 90% CI.

19.8. Interim Analysis

No interim analyses are planned for this study.

19.9. Statistical Power and Sample Size Considerations

It is expected that 66 subjects will be randomized into 1 of 2 treatment groups: 80 U (1 mL) of Acthar per day for 14 consecutive days or placebo (1 mL) per day for 14 consecutive days in a 1:1 ratio (33 per group). The primary analysis is to generate point estimates and associated 90% CIs for the response rates on EDSS in the Acthar group and the placebo group at Day 42, respectively using a mITT analysis population. Assuming 3 subjects will not qualify for the mITT analysis population after randomization in each treatment group, there will be 30 mITT subjects in each group. Based on an expected 60% response rate in the Acthar group, the study can build a 90% Wilson CI of (45.1%, 73.3%) with approximate precision of 14.1%. Based on an expected 25% response rate in the placebo group, the study can build an approximate 90% Wilson CI of (15.7%, 41.5%) with approximate precision of 12.9%.

19.10. Missing Data

Given the mITT design, an imputation or some other procedure for handling missing primary endpoints is required.

For the primary efficacy endpoint, subjects who do not provide data to allow classification as responders will be considered nonresponders, that is, missing data will be imputed as "nonresponder". A similar approach will be applied to secondary efficacy endpoints that are proportions.

For continuous secondary efficacy endpoints collected directly from the CRF, the method of last observation carried forward (LOCF) will be used to impute the missing values. For other continuous secondary efficacy endpoints that need to be derived based on patients' response to a questionnaire, if the responses to an entire questionnaire are missing, LOCF will be applied; otherwise, the method of handling missing response is described in each individual section for the secondary efficacy endpoint analysis.

A full description of missing data imputation method for all endpoints will be described in the statistical analysis plan.

19.11. Deviations From the Statistical Analysis Plan

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

20. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

20.1. Safety

For safety information about Acthar, refer to the most recent version of the Prescribing Information (Mallinckrodt, 20159).

20.2. Definitions

Adverse Event

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 IMP abuse.
- An AE associated with IMP withdrawal.
- Unexpected Adverse Event.

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 Acthar Package Insert (Mallinckrodt, 2019).

Serious Adverse Event

An SAE is defined as any untoward medical occurrence that 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 or 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 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).

20.3. Adverse Event and Serious Adverse Event Classifications

Study Drug Relatedness

The following classifications should be used when evaluating the relationship of AEs or SAEs to study treatment (Table 2).

Table 2: Adverse Event 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 3.

Table 3: Adverse Event 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 follow-up 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.

20.4. Adverse Event and Serious Adverse Event Recording and Reporting

AEs and SAEs will be recorded from signing of the ICF through completion of the final study visit. The investigator is required to record the AE or SAE regardless of the severity of the event or its relationship to study treatment. Prior to the Baseline Visit/Day 1, only AEs and SAEs related to study procedures will be recorded. The investigator must follow up on all AEs and SAEs reported 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 from the signing of the ICF through the completion of the End of Study/Early Termination visit.

Report all SAEs on an SAE Report Form to Global Pharmacovigilance or designee.

Report all pregnancies to the Global Pharmacovigilance or designee contact-on the Pregnancy Surveillance Form.

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

The reporting requirements for AEs are summarized in Table 4.

Table 4: 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

Adverse Events

Adverse events 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. For subjects incapable of giving consent, the legally acceptable representative may provide information regarding the subject's status.

All fields on the AE CRF page should be completed for each event with a full description of the event and date 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.

Serious Adverse Events

Initial Reporting

Serious adverse events (based on FDA/ICH definition of an SAE) require immediate reporting to Mallinckrodt Global Pharmacovigilance or designee.

For all SAEs, the investigator, or designee, must complete the SAE Report Form with the minimum information required by 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 Global Pharmacovigilance or designee.

Should the investigator or designee have any difficulty in sending the SAE Report, they may contact Mallinckrodt Global Pharmacovigilance or designee based on the information in the Study Operations Manual.

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 any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction to the responsible IRB/IEC.

The sponsor will ensure that any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction is submitted to the 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 it to Mallinckrodt Global Pharmacovigilance or designee within 24 hours of receipt. The investigator(s) or designee will receive acknowledgement of receipt for each SAE Report Form from Mallinckrodt Global Pharmacovigilance or designee.

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 ensure that any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction is submitted to the FDA and other regulatory agencies as appropriate.

20.5. Adverse Events of Special Interest

AEs of special interest for this study are outlined below. Adverse events of special interest will be followed until resolution or return to baseline.

- Elevated blood pressure (defined as systolic blood pressure ≥ 180 *and* diastolic blood pressure ≥ 100 mm Hg).
- Hyperglycemia (HbA1c > 6.5%, or fasting plasma glucose > 126 mg/dL, or classic symptoms of hyperglycemia with random plasma glucose > 200 mg/dL).
- MedDRA System Organ Class infection/infestation of ≥ moderate intensity.
- AEs considered possibly, probably, or definitely related to study drug treatment of ≥ moderate intensity.
- Hy's Law cases (ALT > 3 x ULN, with total bilirubin > 2 x ULN, no initial signs of cholestasis [alkaline phosphatase within the reference range]), and no other reason can be found to explain liver injury).

20.6. 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 investigational medicinal product, 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 (subjects may complete follow-up visits). The investigator must report the pregnancy by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance or designee within 24 hours of confirmation of a pregnancy (ie, positive serum 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 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. Both maternal and paternal investigational medicinal product exposures are collected.

If the female partner of a male subject becomes pregnant during the study, the site will forward the Pregnancy Notification form and the Pregnancy Report Fax cover page 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.

21. SUBJECT DISCONTINUATION OR WITHDRAWAL

21.1. Subject Withdrawal

Subjects who discontinue, or are withdrawn from the study for any reason, will be required to enter the follow-up period and have the Early Termination and Follow-up safety assessments (see Section 14.5 and Section 14.6) to assess their continued well-being.

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 study drug but do not complete the study will not be replaced.

Lack of Efficacy

Subjects who undergo plasma exchange or receive IVIg following treatment with Acthar due to lack of efficacy will be considered treatment failures and will be withdrawn from the study.

Adverse Event

If a dosed subject suffers 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 further participation in the study.

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 used 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 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

If a subject develops a condition that meets any of the exclusion criteria (Section 12.2) or fails to meet an inclusion criteria (Section 12.1) during the study that is not considered to be an AE or is noncompliant (eg, has a positive pregnancy during the screening or treatment periods or positive drug screening test), the subject will be discontinued from further participation in the study. Discontinuation is also mandated for safety and/or tolerability issues as outlined in Section 15.3.1.

Other

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

22. 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.

23. PROTOCOL AMENDMENTS

Any change in the study plan requires a protocol amendment. 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.

24. 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 Investigator's Brochure, 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. During these study site visits, information recorded in the eCRFs will be verified against source documents.

24.1. Study and Study Site Discontinuation Criteria

The sponsor, investigator, 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.

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

25.1. 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 will be recorded on source documents. The eCRFs must be fully completed and include all required data for all subjects enrolled. All eCRF data must be submitted to the sponsor throughout and at the end of the study.

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, FDA form 1572) to be filed with the sponsor.

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

25.2. 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.

26. SUBJECT INJURY

In general, subject to specific provisions in the clinical trial agreement, if a subject is injured as a direct result of an investigational medicinal product, 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.

27. 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 investigational medicinal product. 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.

28. 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 urine and serum samples for biomarker analysis (if applicable). Urine and serum samples for biomarker analysis will be retained at a biologic storage facility for future testing. 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.

29. PUBLICATION POLICY

29.1. 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.

Exploratory studies, in contrast, serve to set direction for possible future studies. They have significant statistical limitations, provide only preliminary information about a disease, condition, or product, and are not designed to provide final conclusions on product claims. The sponsor does not commit to publish or otherwise communicate the results of every exploratory study, because this information is of an exploratory nature and often highly proprietary. However, if information from an exploratory study is of significant medical importance, the sponsor will publish or otherwise communicate the results.

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.

29.2. Investigator's Ability to Publish

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

30. REFERENCES

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31. ATTACHMENTS

31.1. Attachment 1: Clinical Laboratory Tests

Serum Chemistry	
Alanine aminotransferase (ALT)	Chloride
Albumin (total)	Creatinine
Alkaline phosphatase	Glucose
Aspartate aminotransferase (AST)	Phosphorus
Bilirubin (total)	Potassium
Blood urea nitrogen	Protein, total
Calcium	Sodium
CO_2	Uric acid
Diabetes Screen	
Hemoglobin A1c	
Hormones	
Serum and urine beta-human chorionic gonadotropin (pregnancy test)	
Hematology Assays	
Hematocrit	Platelet count
Hemoglobin	Red blood cell count
White blood cell count, including differential	Absolute neutrophil count
Urinalysis	
Blood	Nitrite
Color, clarity	Protein
Glucose	pH
Leukocyte esterase	Specific gravity
Ketones	
Microscopy, including white blood cells, red blood cells, bacteria, yeasts, casts, and crystals.	
Hepatitis Serology	
Hepatitis B core antibody	Hepatitis C virus antibody (HCV)
Hepatitis B surface antigen	Hepatitis C virus PCR (only if HCV +)
TB Assay	
Interferon gamma release assay (IGRA)	