Official Title:	**A Multicenter, Double Blind, Placebo Controlled Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in the Treatment of Subjects With Amyotrophic Lateral Sclerosis**
NCT Number:	NCT03068754
Document Date:	Protocol Amendment 2: 11 Aug 2017

CLINICAL STUDY PROTOCOL

A Multicenter, Double Blind, Placebo Controlled Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in the Treatment of Subjects With Amyotrophic Lateral Sclerosis

Protocol Number: MNK14042068

Date of Original Protocol: 29 November 2016

Date of Amendment 1: 06 February 2017

Date of Amendment 2: 11 August 2017

Mallinckrodt ARD, Inc.
675 McDonnell Boulevard
Hazelwood MO 03042
United States of America

PROTOCOL AMENDMENT 2

SUMMARY OF CHANGES

Protocol Amendment 2 was developed to expand the study to sites outside the United States (US), revise analysis of the primary endpoint and increase sample size, make the concomitant use of riluzole optional, add an open label extension, simplify pulmonary function test requirements, reduce the number of required Investigator Administered Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) assessments, remove the positron emission tomography substudy, add and modify the entry criteria, update disallowed concomitant medications to include newly approved treatments, remove disease progression as a mandatory reason for withdrawal from the study, and update the statistics section to include endpoints and analysis for the open label extension. Additional minor changes that do not impact study conduct or subject safety were also made.

The major protocol changes are summarized below:

- All appropriate sections of the protocol have been updated to reflect that study may be conducted inside and outside the US, including the addition of the risk benefits section (Section 9.5).
- The analysis of the primary endpoint has been expanded to include a mixed model with repeat measures (MMRM).
- The samples size has been increased from 195 to 213 enrolled and from 126 to 140 in the modified intent to treat population to accommodate the MMRM analysis.
- The concomitant use of riluzole has been made optional.
- An open label extension has been added to the study with appropriate changes to the Schematic and Schedule of Events.
- The positron emission tomography substudy has been removed.
- The requirement to collect negative inspiratory force has been removed from the spirometry assessments and those assessments can be done at the study site (a separate pulmonary function test laboratory is not required). In addition, slow vital capacity (SVC) will be collected at the Baseline Visit only.

- The investigator administered ALSFRS-R will be completed at Baseline, Week 12, Week 24 and Week 36/Early Termination only.
- The use of edaravone 1 week prior to the Screening Visit and 2 weeks prior to randomization and throughout the study is excluded.
- Any previous use of stem cell replacement therapy is excluded.
- Exclusion criteria have been updated to reduce the restriction period for any dose of oral corticosteroids from 24 weeks to 8 weeks and parenteral corticosteroids from 8 weeks to 4 weeks prior to the Screening Visit and add the restriction of intrathecal/epidural corticosteroids in the 4 weeks prior to the Screening Visit. It is also noted that the use of intra-articular steroids is allowed during the study.
- Disease progression and its definition have been removed from the protocol as a requirement for study discontinuation.
- The statistical analysis section has been updated with endpoints and analysis for the open label extension.
- Specific contact information has been removed from Section 2. Contact information will now be provided in a separate document.
- Sponsor's legal address was corrected.

PROTOCOL AMENDMENT 1

SUMMARY OF CHANGES

Protocol Amendment 1 was developed to remove the updated wording for reporting of adverse events that are known consequences of the underlying disease or condition, add slow vital capacity (SVC) to the spirometry measures to be collected, clarify data to be collected for subjects who early terminate, define permanently assisted ventilation, [redacted], clarify prohibited concomitant medications, allow study visits to be conducted over 2 to 3 days, clarify and update the prediction algorithm, and update the sponsor address.

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

The major protocol changes are summarized below:

- The following text was added to Section 14 and the Schedule of Study Events (Table 7-1): "*If required, a visit can be completed over 2 to 3 days provided all assessments will be completed within the allowed ± 5 day visit window.*"
- The wording in Sections 15.3.1 and 22.1 was clarified as follows: "*Subjects who early terminate for any reason other than withdrawal of consent should be encouraged to continue minimal study participation via telephone contact. In this circumstance, the ALSFRS-R should be administered over the telephone by the site, and any status update should be collected.*"
- Permanent assisted ventilation was defined as bilevel positive airway pressure or invasive ventilation for >22 hours in a 24 hour period, for 7 consecutive days in Section 15.3.1.
- SVC was added to the spirometry measurements listed in Section 16.5 and to the appropriate places in the results analysis
- [redacted]
- [redacted]
- The following language was added to Section 21.2: Adverse experiences (serious or non-serious) that commonly occur in the study population or background regimen will be considered anticipated events. "*Such events include known consequences of the underlying disease (disease-related) or condition under investigation (eg, symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy. Anticipated events, when reported, to be associated with the use of the investigational product, are a subset of unexpected adverse events (events not listed in the Investigator's brochure). However, these events do not warrant expedited reporting as individual cases when serious criteria have been met because it is not possible to determine that there is a reasonable possibility that the drug caused the event. As a result, they do not meet the definition of a suspected adverse reaction.*"
- Section 32.2 Attachment 2 Stratification Algorithm Variables, and references to it, has been removed from the protocol because of errors. The corrected list of variables will be provided in a separate document. Section 15.1.1 was updated accordingly.

- The address of the sponsor was 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

Contact information will be provided in separate document.

Please see Section 21.4 for detailed information regarding the Serious Adverse Event (SAE) Reporting Requirements for this study. 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 United States 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]

15 Aug 2017
Date of Signature

(DD Month YYYY)

[redacted] MD

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 United States 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
1x/week	1 time per week, once a week
2x/week	2 times per week, twice a week
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ALS	Amyotrophic lateral sclerosis
[redacted]	[redacted]
ALSFRS	Amyotrophic Lateral Sclerosis Functional Rating Scale
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
[redacted]	[redacted]
BID	Twice a day
BLQ	below the lower limit of quantification
[redacted]	[redacted]
CDC	Centers for Disease Control and Prevention
[redacted]	[redacted]
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	Electronic case report form
DSMB	Data and Safety Monitoring Board
[redacted]	[redacted]
fALS	Familial ALS
FEV1	Forced volume expired in 1 second
FVC	Forced vital capacity
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
HDL	High density lipoprotein
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	[redacted]
ICF	Informed consent form
ICH	International Council for Harmonisation

Abbreviation	Term
ID	Identification
IEC	Independent Ethics Committee
IGRA	Interferon gamma release assay
IMP	Investigational medicinal product, also referred to as study drug
IRB	Institutional Review Board
IXRS	Interactive Phone/Web Response System
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LSmean	Least squares mean
MCR	Melanocortin receptor
mITT	Modified intent-to-treat
MM	Medical monitor
MMRM	Mixed model with repeat measures
OLE	Open Label Extension
[redacted]	[redacted]
PRO-ACT	Pooled Resource Open-Access ALS Clinical Trials
QD	Per day, daily
SAE	Serious adverse event
SC	Subcutaneous
SOD1	Copper/zinc superoxide dismutase
SVC	Slow vital capacity
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
U	Unit(s)
ULN	Upper limit of normal
[redacted]	[redacted]

6 SYNOPSIS

Study Title: A Multicenter, Double Blind, Placebo Controlled Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in the Treatment of Subjects With Amyotrophic Lateral Sclerosis	
Protocol Number: MNK14042068	Type: Phase 2b
Condition/Disease:	Amyotrophic Lateral Sclerosis
Approximate Number of Subjects: 213	**Approximate Duration of Subject Participation:** up to 95 weeks
Approximate Number of Study Centers: 45	**Approximate Duration of Study:** 44 months

Design:

This is a multicenter, multiple dose study to examine the effect of Acthar on functional decline in adult subjects with Amyotrophic Lateral Sclerosis (ALS). Approximately 213 subjects will be enrolled.

Following a screening period of up to 28 days, subjects with ALS and symptom onset (defined as first muscle weakness or dysarthria) ≤ 2 years prior to the Screening Visit, will be randomized on a 2:1 basis to receive subcutaneous (SC) Acthar 0.2 mL (16 Units [U]) once a day (QD) or SC matching placebo 0.2 mL QD for 36 weeks. At the end of 36 weeks subjects will either taper to SC Acthar 0.2 mL (16 U) QD or SC matching placebo 0.2 mL 2x/week for 2 weeks followed by 1 time per week (1x/week) for 1 week, or enter an open label extension where they will receive SC Acthar 0.2 mL (16 U) QD for an additional 48 weeks followed by a 3 week taper as described above.

Although riluzole is not a required concomitant medication, any subject taking riluzole must be on a stable dose (defined as 50 mg twice a day [BID] for at least 4 weeks prior to the Screening Visit) and remain on that dose throughout the study (if possible).

The randomization will be stratified for the predicted values of the 9-month decline rate of Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS) score from baseline (≤ 1 point change/month vs > 1 point change/month) using the prediction algorithm evaluated in the post hoc analysis of a previous study. Riluzole use will be a second stratification variable. Subjects will be evaluated for treatment response using the ALSFRS-R and other standard measures. All subjects will have a Follow-up Visit 28 (± 2) days after the last dose of study drug.

Objectives:

Primary Objective

- To assess the effect of Acthar given as a 0.2 mL (16 U) dose QD for 36 weeks on functional decline in subjects with ALS using the ALSFRS-R.

Secondary Objectives

- To assess the safety and tolerability of Acthar in subjects with ALS.
- To assess the effect of Acthar on survival in subjects with ALS.
- To assess the longitudinal effect of Acthar on functional decline in subject with ALS.
- To assess the longitudinal effect of Acthar on survival in subjects with ALS.

[redacted]

Study Title: A Multicenter, Double Blind, Placebo Controlled Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in the Treatment of Subjects With Amyotrophic Lateral Sclerosis	
Protocol Number: MNK14042068	Type: Phase 2b
Condition/Disease:	Amyotrophic Lateral Sclerosis
[redacted]	

Entry Criteria:

Male or nonpregnant, nonlactating female subjects 18 to 75 years of age (inclusive) with a diagnosis of clinically definite, clinically probable-laboratory supported, or clinically probable ALS based on the El Escorial criteria and onset of symptoms (defined as date of first muscle weakness or dysarthria) ≤ 2 years prior to the Screening Visit. Subjects must have a systolic blood pressure of ≤ 140 mm Hg, a diastolic blood pressure ≤ 90 mm Hg, and a percent predicted forced vital capacity ≥ 60%. Subjects may not have tracheostomy, diaphragm pacing, or the ongoing need for assisted ventilation of any type. Subjects who have been on a stable dose of 50 mg of riluzole BID ≥ 4 weeks prior to the Screening Visit and will remain on that dose throughout the study (unless taper or discontinuation is required for tolerability issues after the Baseline Visit) may be enrolled. Subjects may not have taken oral corticosteroids ≥ 10 mg prednisone/prednisone equivalent for more than 4 consecutive weeks, in the 8 weeks prior to, or any parenteral corticosteroids in the 8 weeks prior to, or any intrathecal/epidural corticosteroids in the 4 weeks prior to, the Screening Visit. Subjects may not have any contraindication as per the United States of America Prescribing Information for Acthar. Subjects cannot have any history of Type 1 or Type 2 diabetes mellitus, or have any clinically significant infection.

Subjects who have completed the 36 week Randomized Treatment Period and are willing and able to continue in the open label extension may do so if , in the opinion of the Investigator, the subject willbenefit from additional treatment with study drug.

Concomitant Medications/Nondrug Therapies:

The following medications/nondrug therapies are not permitted during the study (from the time of informed consent through the Follow-up Visit):

- Oral corticosteroids ≥ 10 mg of prednisone/prednisone or any parenteral, intrathecal or epidural corticosteroids. Intra-articular, topical, and inhaled corticosteroids are allowed during the study.
- Edaravone.
- Stem cell replacement therapy.
- Live or live-attenuated vaccines.
- Any investigational drug, device, or procedure administered as part of a research study.
- Any investigational treatment (drug, device, or procedure) for the treatment of ALS used for the sole purpose of impacting ALS functional decline and/or survival. This includes prescription and over-the-counter medicinal products.

The following medications are allowed during the study.

- Subjects on riluzole may enter the study provided they have been on a stable dose of 50 mg BID for at least 4 weeks prior to the Screening Visit and will remain on that dose throughout the study, if possible. Taper and/or discontinuation of riluzole is allowed for tolerability reasons after the Baseline Visit.
- Symptomatic treatment for sialorrhea, spasticity, depression, fatigue, and pseudobulbar palsy as per local clinical practice is allowed during the study.

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

Study Title: A Multicenter, Double Blind, Placebo Controlled Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in the Treatment of Subjects With Amyotrophic Lateral Sclerosis	
Protocol Number: MNK14042068	Type: Phase 2b
Condition/Disease:	Amyotrophic Lateral Sclerosis

Investigational Medicinal Product and Treatment Administration:

Acthar contains a highly purified porcine adrenocorticotropin hormone (ACTH) analogue and is currently approved by the FDA in multiple indications; Acthar is not approved for the treatment of ALS. Acthar and its matching placebo will be supplied by the sponsor and administered SC as follows in this study:

Randomized Treatment Period:

Treatment A: Acthar 0.2 mL (16 U) administered QD for 36 weeks. Subjects who do not enter the Open Label Extension will then taper with Acthar 0.2 mL (16 U) administered 2 times per week (2x/week) for 2 weeks, then once a week (1x/week) for 1 week,

OR

Treatment B: Placebo 0.2 mL administered QD for 36 weeks. Subjects who do not enter the Open Label Extension will then taper with placebo 0.2 mL administered 2x/week for 2 weeks, then 1x/week for 1 week.

Open Label Extension:

Acthar 0.2 mL (16 U) administered QD for 48 weeks, followed by Acthar 0.2 mL (16 U) administered 2x/week for 2 weeks, then 1x/week for 1 week.

Efficacy Evaluations:

The following efficacy assessments will be evaluated: Telephone and investigator administered ALSFRS-R, [redacted] and spirometry.

[redacted]

Safety Evaluations:

The following safety assessments will be evaluated: adverse events, physical examinations, clinical laboratory tests results, pregnancy testing, vital signs, and the Columbia-Suicide Severity Rating Scale.

Statistical Methods:

Analysis Populations

- The Safety Population will include all enrolled 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 one postbaseline telephone administered ALSFRS-R.
- The Per-Protocol Population will include the subset of the mITT population who complete the study as per protocol.

Study Title: A Multicenter, Double Blind, Placebo Controlled Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in the Treatment of Subjects With Amyotrophic Lateral Sclerosis	
Protocol Number: MNK14042068	Type: Phase 2b
Condition/Disease:	Amyotrophic Lateral Sclerosis

Sample Size

The primary efficacy analysis will compare the mean telephone administered ALSFRS-R total score change from baseline at Week 36 in the group treated with Acthar to that in the placebo group using mITT analysis population. With 140 mITT subjects in the group treated with Acthar and 70 mITT subjects in the placebo group (210 subjects total), assuming the expected ALSFRS-R total score change from baseline of 6.3 and 9 in Acthar and placebo groups, respectively, the common SD of the ALSFRS-R total score change from baseline at Week 36 of 5.83 (estimated from PRO-ACT database), and dropout rate of 20% prior to Week 36, the study will have at least 80% power to detect the treatment difference at the 0.05 level of significance. Assuming a few subjects might not qualify for the mITT analysis population after randomization, approximately 213 subjects will be enrolled and randomized into Acthar treated group and placebo group in a 2:1 ratio.

Efficacy

Randomized Treatment Period

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 ALSFRS-R score will be presented by treatment group for all subjects in the mITT population and the Per-Protocol population.

ALSFRS-R change from baseline at postbaseline visits will be computed as:

Change = baseline value - postbaseline value

Baseline is defined as the value observed at randomization (Week 0).

The primary efficacy endpoint, change from baseline in the telephone administered ALSFRS-R total score at Week 36 in the Acthar treated group vs the placebo group, will be compared using a mixed model with repeated measures (MMRM) analysis method. ALSFRS-R total score change from baseline will be used as a dependent variable, and the model will include the fixed effects of treatment, visit (categorical covariate), treatment-by-visit interaction, and baseline ALSFRS-R score as continuous covariates. The null hypothesis is that the least squared mean contrast between Acthar and placebo groups at Week 36 equals zero. Significance tests will be based on least-squares means using a two-sided test at $\alpha = 0.05$ (two-sided 95% confidence intervals). An unstructured covariance matrix will be used to model the within-subject variance-covariance. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, and compound symmetry covariance structure. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Least squares mean for each treatment group, least squares mean difference, and 95% confidence intervals between the treatment groups and the corresponding p-value will be reported.

All "mean slope decline" type of secondary endpoints will be analyzed using random coefficient model. Change from baseline will be the dependent variable, and treatment time (in month, continuous) and treatment-by-time interaction will be fixed effects and intercept will be random effect. Baseline values will be adjusted. Estimates of slope for each treatment group, estimates of slope difference, 95% confidence interval and the corresponding p-value will be reported.

For all "change from baseline" type of secondary [redacted] endpoints, the same approach as for the primary efficacy endpoint described above will be used.

The primary and secondary endpoints analyses will be performed for the mITT and Per-Protocol populations.

[redacted]

Study Title: A Multicenter, Double Blind, Placebo Controlled Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in the Treatment of Subjects With Amyotrophic Lateral Sclerosis	
Protocol Number: MNK14042068	Type: Phase 2b
Condition/Disease:	Amyotrophic Lateral Sclerosis

[redacted]

Open Label Extension

All efficacy endpoints for the Open Label Extension will be summarized by descriptive statistics only, no inferential statistical analysis will be performed.

All "change from baseline" and "mean slope decline" types of endpoints will be summarized with descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) for numerical (or continuous) variables and with frequencies and percentages for categorical variables at each visit. Box Whisker and trend plots maybe used to present the data if necessary.

All "time to event" type endpoint will be summarized descriptively (n, mean, standard deviation, minimum, Q1, median, Q3, maximum, and 95% CI) for each treatment group. Kaplan-Meier curve will be plotted to present the data.

[redacted]

Safety

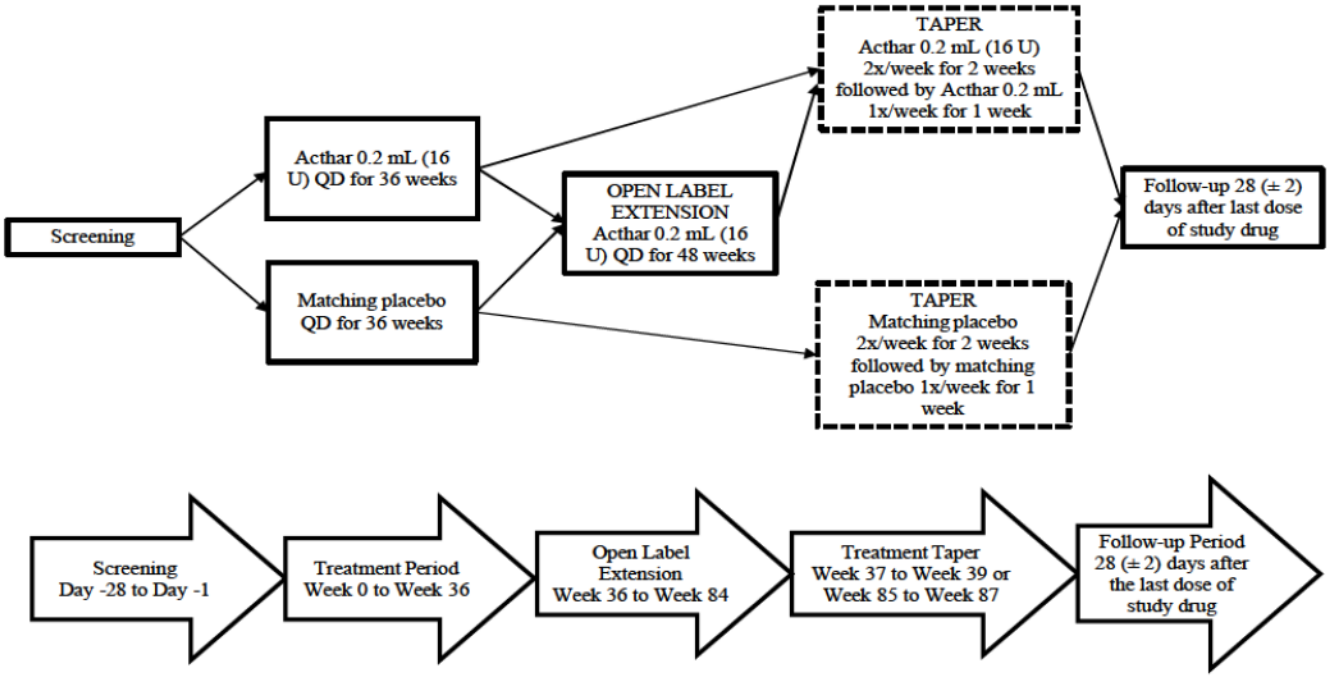
Treatment-emergent adverse events and serious adverse events will be summarized using the appropriate version of MedDRA by preferred term within system organ class. Other safety data will be listed and summarized descriptively or graphically, as appropriate.

[redacted]

7 STUDY SCHEMATIC AND SCHEDULE OF EVENTS

7.1 Study Schematic

Figure 7-1: Study Overview



7.2 Schedule of Study Events

Table 7–1: Schedule of Study Events

Assessment/Procedure	Screening (Day −28 to Day− 1)	Randomized Treatment Period (Weeks) After the Baseline Visit, the window for all visits is ± 5 days. If required, a visit can be completed over 2 to 3 days as long as all assessments will be completed within the allowed ± 5 day window.										Unscheduled Visit (if needed)[d]	Follow-up Visit 28 (± 2) days after the final dose of study drug[c]
		0/Baseline	4	8	12	16	20	24	28	32	36/ Early Termination[a]	39/End of Taper[b,c]	
Visit Number	1	2	3	4	5	6	7	8	9	10	11			
Informed Consent	X												
Inclusion/Exclusion Criteria Review	X	X									X[m]		
Family ALS/Neurologic Disease History	X												
Medical/Surgical History	X												
Current Medical Condition Review		X	X	X	X	X	X	X	X	X	X		X	X
Demographics	X												
Complete Physical Examination	X										X		
Limited Physical Examination		X	X	X	X	X	X	X	X	X			X	X
Height and Weight[e]	X	X	X	X	X	X	X	X	X	X	X		X	X
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X		X	X
Spirometry[g]	X	X	X	X	X	X	X	X	X	X	X			X
Clinical Laboratory Tests[h]	X	X	X	X	X	X	X	X	X	X	X			X
Lipid Panel[i]		X			X			X			X			
HbA1c	X				X			X			X			
Serum Pregnancy	X										X			
Urine Pregnancy		X	X	X	X	X	X	X	X	X				X

Assessment/Procedure	Screening (Day −28 to Day− 1)	Randomized Treatment Period (Weeks) After the Baseline Visit, the window for all visits is ± 5 days. If required, a visit can be completed over 2 to 3 days as long as all assessments will be completed within the allowed ± 5 day window.										Unscheduled Visit (if needed)[d]	Follow-up Visit 28 (± 2) days after the final dose of study drug[c]
		0/Baseline	4	8	12	16	20	24	28	32	36/ Early Termination[a]	39/End of Taper[b,c]	
Visit Number	1	2	3	4	5	6	7	8	9	10	11			
Hepatitis Serology	X													
IGRA for TB	X													
[redacted]														
C-SSRS		X	X	X	X	X	X	X	X	X	X			
Telephone Administered ALSFRS-R	X	X	X	X	X	X	X	X	X	X	X		X[k]	X[k]
Investigator Administered ALSFRS-R		X			X			X			X		X	X
[redacted]														
Study Drug and Diary Training		X									X[m]			
IXRS Contact	X	X	X	X	X	X	X	X	X	X	X			
Dispense Study Drug		X	X	X	X	X	X	X	X	X	X			
Administer Study Drug Dose in Clinic		X[n]									X[m,n]			
Study Drug Accountability and Diary Review			X	X	X	X	X	X	X	X	X			X
Adverse Events and Concomitant Treatments	X													

[a]Subjects who early terminate for any reason must undergo the taper (2x/week for 2 weeks followed by 1x/week for 1 week).
[b]End of Taper Visit will be conducted by telephone.

[c]For subjects **not** entering the open-label extension period only.
[d]Checked assessments are required at any unscheduled visit. Additional assessments may be done at the investigator's discretion.
[e]Height will be collected at the Screening Visit only.
[f]Blood pressure, pulse rate, respiratory rate and body temperature.
[g]FVC and FEV1. SVC will also be collected at the Baseline Visit only.
[h]Chemistry, hematology, and urinalysis.
[i]Total cholesterol, LDL, HDL, and triglycerides.
[redacted]
[k]Telephone administered ALSFRS-R is not required for unscheduled visits during the Open Label Extension or for the Follow-up Visit at the end of the Open Label Extension
[redacted]
[m]For subjects entering the open label extension only.
[n]The first dose of study drug for all subjects will be administered in the clinic and the subject will be observed for at least 1 hour after dosing. For subjects entering the Open Label Extension, the first dose given at Week 36 will be administered in the clinic and the subject will be observed for at least 1 hour after dosing.

Table 7-2: Open Label Extension Schedule of Events

	Open Label Extension Period (Weeks) The window for all visits is ± 5 days. If required, a visit can be completed over 2 to 3 days as long as all assessments will be completed within the allowed ± 5 day window.							Follow-up Visit 28 (± 2) days after the final dose of study drug
Assessment/Procedure	40	44	48	60	72	84/Early Termination	87/ End of Taper[a]	
Visit Number	OLE 2	OLE 3	OLE 4	OLE 5	OLE 6	OLE 7		
Current Medical Condition Review								
Complete Physical Examination						X		
Limited Physical Examination	X	X	X	X	X			X
Weight	X	X	X	X	X	X		X
Vital Signs[b]	X	X	X	X	X	X		X
Spirometry (FVC and FEV1)			X	X	X	X		X
Clinical Laboratory Tests[c]	X	X	X	X	X	X		X
Lipid Panel[d]			X	X	X	X		
HbA1c			X	X	X	X		
Serum Pregnancy						X		
Urine Pregnancy	X	X	X	X	X			X
C-SSRS	X	X	X	X	X	X		
Investigator Administered ALSFRS-R	X	X	X	X	X	X		X
[redacted]								
IXRS Contact	X	X	X	X	X	X		
Dispense Study Drug	X	X	X	X	X	X		
Study Drug Accountability and Diary Review	X	X	X	X	X	X		X
Adverse Events and Concomitant Treatments	X							

[a]The end of taper assessments may be done via telephone.
[b]Blood pressure, pulse rate, respiratory rate and body temperature.
[c]Chemistry, hematology, and urinalysis.
[d]Total cholesterol, LDL, HDL, and triglycerides.

[redacted]

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/IEC before the start of the study. The investigator will provide Mallinckrodt ARD, Inc. (Mallinckrodt) with a statement of compliance from the IRB/IEC and/or the United States of America (US) Department of Health and Human Services general assurance number. A copy of the approval letter along with a roster of IRB/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 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; US FDA regulations including 21 CFR 314.106 and 312.120, (where applicable); 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/IEC before any subject provides consent. The investigator will provide Mallinckrodt with a copy of the IRB/IEC-approved ICF and a copy of the IRB/IEC's written approval before the start of the study.

At the Screening Visit, subjects will read the ICF and a 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

First described by Jean-Martin Charcot, amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that affects the upper and lower motor neurons in the central nervous system (Goetz, 2000; Mitchell and Borasio, 2007). As upper motor neurons die, there is a loss of communication from the cerebral cortex with symptoms including spasticity and hyper-reflexia. As lower motor neurons die, there is a loss of communication between the brainstem and spinal cord and the muscles, resulting in weakness, muscle atrophy, and fasciculations (Bedlack et al, 2007; Mitchell and Borasio, 2007; Ravits and La Spada, 2009). Symptom expression is dependent on the site of motor neuron loss, with bulbar involvement manifesting as facial weakness, palatal weakness, weakness and fasciculations of the tongue, as well as pseudobulbar symptoms and dysarthria. Limb involvement can start at any spinal level, with spread of motor neuron death typically to the contralateral limb and then through different spinal cord levels (Mitchell and Borasio, 2007; Ravits and La Spada, 2009).

Amyotrophic lateral sclerosis is a relentlessly progressive disease, with mounting disability related to muscle paralysis and eventual death. Although some patients can survive for many years with ALS, up to 70% to 80% die within 5 years of symptoms onset, most commonly due to respiratory failure (Andersen et al, 2005; Beghi et al, 2006; Miller et al, 2009; Mitchell and Borasio, 2007). The incidence of ALS is about 2 in 100,000, and slightly higher in males than

females (Beghi et al, 2006; Berry and Cudkowicz, 2011; Mitchell and Borasio, 2007; Rothstein, 2009). The onset of symptoms in ALS is typically in 5th or 6th decade of life, and onset before 30 years of age is rare (Beghi et al, 2006; Berry and Cudkowicz, 2011; Rothstein, 2009).

In 5% to 10% of patients there is a positive family history for ALS, with a predominant autosomal dominant pattern of inheritance (Berry and Cudkowicz, 2011; Mitchell and Borasio, 2007; Rothstein, 2009). The first genetic mutation linked to familial ALS (fALS) involved the copper/zinc superoxide dismutase (SOD1) gene on chromosome 21, with mutations involving other genes being identified subsequently (Berry and Cudkowicz, 2011; Mitchell and Borasio, 2007; Rothstein, 2009). However, in up to 95% of cases there is no apparent genetic component, a group referred to sporadic ALS (Berry and Cudkowicz, 2011; Mitchell and Borasio, 2007; Rothstein, 2009). The clinical manifestations of fALS and sporadic ALS are similar (Rothstein, 2009), pointing to a potential common mechanism leading to the neurodegeneration.

Clinically, ALS is diagnosed based on patient history, physical examination, and disease course. Ancillary tests such as electrophysiologic studies and neuroimaging can help eliminate other potential etiologies (Berry and Cudkowicz, 2011; Brooks et al, 2000). The El Escorial diagnostic criteria for ALS were developed in the 1990's, subsequently revised to increase sensitivity, and are consensus diagnostic criteria that are typically used in clinical trials (Berry and Cudkowicz, 2011; Brooks et al, 2000; Mitchell and Borasio, 2007; World Federation of Neurology, 1994). The diagnosis of ALS requires the presence of upper and lower motor neuron degeneration as well as the progressive spread of signs or symptoms within a region or to other regions, and importantly the lack of evidence of another disease process that could explain the symptoms. By definition, sensory symptoms must be absent (Brooks et al, 2000; Mitchell and Borasio, 2007).

Clinical research in ALS was relatively sparse until the 1990's. The increase in clinical trials has been spurred by many factors including insights into the potential pathophysiology, development of preclinical and in vitro models and the approval by FDA of a disease modifying treatment (Aggarwal and Cudkowicz, 2008; Berry and Cudkowicz, 2011; Leigh et al, 2004). The pathophysiology of ALS is complex and not well understood. Current theories include abnormal protein aggregation, abnormal RNA processing, abnormal mitochondrial functioning, glutamate excitotoxicity, apoptosis, oxidative stress, and neuroinflammation with microglial activation and T cell infiltration (Bedlack et al, 2007; Berry and Cudkowicz, 2011; Henkel et al, 2009; Lanka and Cudkowicz, 2008; Leigh et al, 2004; Mitchell and Borasio, 2007; Rothstein, 2009).

The discovery of the SOD1 mutations in fALS led to the development of transgenic rodent models that overexpress a specific SOD1 mutation. Subsequent rodent models involving other genetic mutations have also been developed (Lanka and Cudkowicz, 2008; Rothstein, 2009). In vitro models

have also explored the SOD1 mutations, as well as other potential pathophysiologic pathways (Lanka and Cudkowicz, 2008).

Riluzole, approved by FDA in 1995, was shown to have a modest impact on survival in patients with ALS, delaying time to death on average by 2 to 3 months with no change in functional outcomes (Miller et al, 2012; Mitchell and Borasio, 2007; US Department of Health and Human Services, 1995). Riluzole inhibits presynaptic release of glutamate and modulates sodium, potassium, and calcium channels which target neuronal excitation (Bedlack et al, 2007; Bellingham, 2011; Miller et al, 2012). Edaravone was approved by FDA in May 2017, and prior to that it was approved in Japan as a treatment for ALS (FDA, 2017). Edaravone is a free radical scavenger (Kikuchi et al, 2011), and has been shown in 1 controlled 24-week study to delay functional decline in patients with "early ALS" defined by fairly well preserved respiratory function (forced vital capacity [FVC] ≥ 80%) and minimal functional decline (Tanaka et al, 2016).

Although some drug development for ALS has been targeted as symptomatic treatment, such as dextromethorphan/quinidine to treat pseudobulbar affect, the majority has been geared towards disease modification with a goal of slowing disease progression. In the 20 years since riluzole was approved, despite advances in elucidating potential pathophysiologic pathways and development of preclinical and in vitro models, only one drug, edaravone, has been shown to impact function and no other drug has been shown to change survival in ALS (Aggarwal and Cudkowicz, 2008; Berry and Cudkowicz, 2011; Gordon and Meininger, 2011; Tanaka et al, 2016). Over 30 agents that target specific potential pathophysiologic pathways implicated in ALS and that had shown promise in preclinical and in vitro models have failed to demonstrate any disease modification (Aggarwal and Cudkowicz, 2008; Berry and Cudkowicz, 2011; Gordon and Meininger, 2011). The reasons for the lack of progress are multifactorial. The discrepancy between improvement in preclinical models and ability to demonstrate benefit in clinical studies suggest possible mechanistic differences between the mouse model and the human disease expression, perhaps due to the relative rarity of fALS, difficulties transitioning from animal models to human studies, or potentially flawed clinical studies (Aggarwal and Cudkowicz, 2008; Lanka and Cudkowicz, 2008). It is clear, however, that there is significant unmet need given the very modest effects of riluzole and lack of any other available treatment option.

As described in the Package Insert, [redacted]Acthar® Gel (repository corticotropin injection, hereafter referred to as Acthar) contains a highly purified porcine adrenocorticotropic hormone (ACTH) analogue (Mallinckrodt, 2015). 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) (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 ALS. The MC1R, MC3R, MC4R, and the MC5R are expressed on tissues relevant to ALS, including the cerebral cortex, spinal cord and muscles (Cooray and Clark, 2011; Starowicz and Przewlocka, 2003). Additionally, ACTH has been shown to have neuroprotective and neuroregenerative activities that may also slow the progression of motor neuron death (Starowicz and Przewlocka, 2003; Strand and Kung, 1980). Anti-inflammatory effects are mediated by several mechanisms: the MC1R affects the Nuclear Factor- kappa B pathway leading to downregulation of pro-inflammatory cytokines and chemokines (Ahmed et al, 2013); activation of MC3R and MC4R attenuate pro-inflammatory cytokines, including nitric oxide synthase and nitric oxide (Caruso et al, 2013); and in the microglia, ACTH inhibits production of pro-inflammatory markers such as tumor necrosis factor-alpha, interleukin-6 and nitrous oxide (Delgado et al, 1998).

A pilot study (QSC01-ALS-01; Questcor Pharmaceuticals, 2015) evaluating 4 doses of Acthar (80 Units [U] 2 times per week [2x/week], 24 U daily [QD], 56 U 2x/week, 16 U QD) was completed. This open label study in 43 subjects with ALS demonstrated that Acthar was generally well tolerated, with treatment-emergent adverse events (TEAE) related to either the disease itself or known adverse effects of Acthar. A post hoc case-match control analysis using the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database was conducted. Cases were matched on variables known to predict disease course in ALS, including the ALS Functional Rating Scale (ALSFRS) baseline total score, time from symptom onset to study enrollment, gender, age at symptom onset, site of symptom onset, body mass index, and serum creatinine at baseline (Chiò et al, 2009; Ikeda et al, 2012; Küffner et al, 2015; Stambler et al, 1998; Tysnes et al, 1994). The ALSFRS differs from the ALS Functional Rating Scale-Revised (ALSFRS-R) in that questions assessing respiration (orthopnea, dyspnea, respiratory insufficiency) are not included (Cedarbaum et al, 1999); in accessing the PRO-ACT database, Mallinckrodt discovered that the majority of subjects in the database had ALSFRS assessments as opposed to ALSFRS-R assessments (Mallinckrodt, 2016a). Given this, ALSFRS scores for subjects in QSC01-ALS-01 were generated by excluding Questions 11 and 12 on the ALSFRS-R. In this post hoc analysis, the pooled Acthar treated subjects showed significant separation from the case matched control group on slope of ALSFRS total score change from baseline, suggesting that Acthar may be influencing disease progression.

A second post hoc analysis was conducted to explore the effect of Acthar on functional disease progression as measured by the ALSFRS/ALSFRS-R in patients with ALS. The DREAM Phil Bowen ALS Prize4Life Challenge was issued to promulgate development of algorithms that could predict disease progression in ALS. The algorithm developers were provided with a small subset of data from the PRO-ACT database that included 3 months of individual patient level clinical trial information that was to be used to predict disease progression over the subsequent 9 months (Küffner et al, 2015). There were 37 algorithm submissions each of which was then evaluated on a separate data set from the PRO-ACT database. The 2 winning algorithms both predicted disease progression better than a baseline model and clinicians using the same data (Küffner et al, 2015). Mallinckrodt contacted the developers of 1 of the prize winning algorithms, in order to apply the algorithm to the ALSFRS data generated in Study QSC01-ALS-01. As previously noted, ALSFRS-R scores were converted to an ALSFRS score. Baseline features used as predictors in the algorithm and available in the dataset for QSC01-ALS-01 were selected, and a slope estimate was generated for each subject at Week 36. A comparison of the actual observed slope vs the predicted slope using the algorithm was conducted. The predicted rate of decline was greater than the observed rate of decline in the ALSFRS, again suggesting a potential effect of Acthar on disease progression (Mallinckrodt, 2016a).

9.2 Product Description

Acthar has been approved by FDA for commercial sale and distribution in the US since 1952, and is currently approved for numerous indications including monotherapy for the treatment of infantile spasms in infants and children under 2 years of age; treatment of acute exacerbations of multiple sclerosis in adults; adjunctive therapy for short-term administration in psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), and ankylosing spondylitis; during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus or systemic dermatomyositis (polymyositis); severe erythema multiforme; Stevens-Johnson syndrome; serum sickness; severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation; symptomatic sarcoidosis; and to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus (Mallinckrodt, 2015). Acthar is not approved for the treatment of ALS.

Acthar is a highly purified sterile preparation of prolonged-release porcine ACTH analogue in 16% gelatin for intramuscular or subcutaneous (SC) injection. Acthar also 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. Placebo formulation is identical to Acthar except that it contains no active medication.

9.3 Dosage and Administration

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

Following a screening period of up to 28 days, subjects with ALS and symptom onset (defined as first muscle weakness or dysarthria) ≤ 2 years prior to the Screening will be randomized on a 2:1 basis to receive SC Acthar 0.2 mL (16 U) QD or SC matching placebo 0.2 mL QD for 36 weeks. At the end of 36 weeks subjects will either taper to SC Acthar 0.2 mL (16 U) QD or SC matching placebo 0.2 mL 2x/week for 2 weeks followed by 1 time per week (1x/week) for 1 week or enter an open label extension study where they will receive SC Acthar 0.2 mL (16 U) QD for an additional 48 weeks, followed by a 3 week taper as described above.

9.4 Dose Rationale

A potential design flaw in some clinical studies in ALS has been dose selection, with the maximum tolerated dose proving either more detrimental or to be associated with more treatment-limiting adverse events (AE) (Aggarwal and Cudkowicz, 2008; Lanka and Cudkowicz, 2008), which suggests that careful consideration of dose selection is merited.

ALS is not an approved indication for Acthar. For the approved indications, the prescribing information for Acthar recommends the use of 40 to 80 U administered intramuscularly or SC every 24 to 72 hours in adults and children over 2 years of age. The specific dose is individualized according to the medical condition (Mallinckrodt, 2015). The maximal dose is 80 to 120 U SC daily, which has been used safely for the treatment of acute multiple sclerosis exacerbations over a period of 2 to 3 weeks.

For many of the approved indications, Acthar is intended for short-term use. In ALS, it is anticipated that use will be chronic. Given this, a potential off-target effect specific to ALS is skeletal myopathy associated with chronic use. Muscle weakness is a known potential effect of Acthar (Mallinckrodt, 2015), and, it is a well described effect of systemically administered

corticosteroids, an effect that may be related to total exposure (Dekhuijzen and Decramer, 1992).

Although Study QSC01-ALS-01 was not a formal dose-ranging study, it did provide useful information to guide dose selection for this Phase 2b study. In Study QSC01-ALS-01, the 4 treatment arms included a high dose group with 2 different dosing regimens (80 U 2x/week or 24 U QD) and a low dose group with 2 different dosing regimens (56 U 2x/week, 16 U QD). The dosing regimens in both the high dose group and the low dose group were selected to provide the same approximately weekly exposure to Acthar. More subjects in the low-dose group than the high dose group completed through Week 36 (13 and 7, respectively). Additionally, fewer subjects in the low-dose group were withdrawn from the study due to an AE (3 and 7, respectively) (Questcor Pharmaceuticals, 2015).

Considering all available information, including theoretical risk and data generated in Study QSC01-ALS-01, this study will evaluate a dose of Acthar of 16 U.

9.5 Risk/Benefit Assessment

The most common known adverse reactions for Acthar are similar to those of corticosteroids and 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 AEs associated with Acthar (Mallinckrodt, 2015).

ALS is a progressive fatal neurologic disorder with limited treatment options (Miller et al, 2009; FDA, 2017), and considerable unmet need. An uncontrolled pilot study evaluating safety and tolerability of Acthar in 43 subjects showed that AEs that were consistent with the established safety profile of Acthar. A posthoc analyses case-match control analysis showed potential benefit for Acthar in slowing disease progression (Mallinckrodt, 2016a).

10 OBJECTIVES

10.1 Primary Objective

The primary objective of this study is:

- To assess the effect of Acthar given as a 0.2 mL (16 U) dose QD for 36 weeks on functional decline in subjects with ALS using the ALSFRS-R.

10.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the safety and tolerability of Acthar in subjects with ALS.
- To assess the effect of Acthar on survival in subjects with ALS.
- To assess longitudinal effect of Acthar on functional decline in subjects with ALS
- To assess the longitudinal effect of Acthar on survival in subjects with ALS

[redacted]

11 STUDY DESIGN

11.1 Description

This is a multicenter, multiple dose study to examine the effect of Acthar on functional decline in adult subjects with ALS. Approximately 213 subjects will be enrolled.

Following a screening period of up to 28 days, subjects with ALS and symptom onset (defined as first muscle weakness or dysarthria) ≤ 2 years prior to the Screening Visit, will be randomized on a 2:1 basis to receive SC Acthar 0.2 mL (16 U) QD or SC matching placebo 0.2 mL QD for 36 weeks. At the end of 36 weeks subjects will either taper to SC Acthar 0.2 mL (16 U) QD or SC matching placebo 0.2 mL 2x/week for 2 weeks followed by 1 time per

week (1x/week) for 1 week, or enter an open label extension where they will receive SC Acthar 0.2 mL (16 U) QD for an additional 48 weeks followed by a 3 week taper as described above.

Although riluzole is not a required concomitant medication, any subject taking riluzole must be on a stable dose (defined as 50 mg BID for at least 4 weeks prior to the Screening Visit) and remain on that dose throughout the study (if possible).

The randomization will be stratified for the predicted values of the 9-month decline rate of ALSFRS score from baseline (≤ 1 point change/month vs > 1 point change/month) using the prediction algorithm evaluated in the post hoc analysis of Study QSC01-ALS-01 (Kuffner et al, 2015). Riluzole use will be a second stratification variable. Subjects will be evaluated for treatment response using the ALSFRS-R and other standard measures. All subjects will have a Follow-up Visit 28 (± 2) days after the last dose of study drug.

11.2 Approximate Duration of Subject Participation

For subjects in the Randomized Treatment Period , participation will be approximately 47 weeks (approximately 12 months), including a screening period of up to 28 days, and active treatment period of 36 weeks, a 3 week taper, and follow-up visit of 28 (± 2) days after discontinuation of study drug.

For subjects who also participate in the Open Label Extension, study duration will be approximately 95 weeks (approximately 24 months), including a screening period of up to 28 days, and active treatment period of 36 weeks, an open label extension of 48 weeks, a 3 week taper follow-up visit of 28 (± 2) days after discontinuation of study drug. Subjects who do not chose to enter the open label extension will participate in the study for a total of up to approximately 47 weeks (approximately 12 months).

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 44 months to complete.

11.4 Approximate Number of Subjects

It is expected that approximately 300 subjects will be screened and 213 subjects will be enrolled at approximately 45 sites globally.

11.5 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be convened in order to ensure that the safety of subjects is adequately protected. The DSMB will be chartered, with the charter defining the frequency of meetings as well as the unblinded datasets to be reviewed. The interim analysis will be conducted under the auspices of the DSMB.

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. 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.
2. Subjects must be 18 to 75 years of age (inclusive) at Screening Visit and can be male or female.
3. Female subjects must be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, 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 Follow-up Visit). Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), and abstinence.
4. Subjects must have a diagnosis of clinically definite ALS, clinically probable- laboratory supported ALS, or clinically probable ALS based on revised El Escorial criteria (Brooks et al, 2000; World Federation of Neurological Research, 1994).
5. Subjects must have had ALS symptom onset ≤ 2 years prior to the Screening Visit. Symptom onset is defined as date of first muscle weakness or dysarthria. If exact date is unknown, default to the first day of the month of symptom onset.

6. Subjects who have been on riluzole may enter the study if they have been on a stable dose of 50 mg BID for ≥ 4 weeks prior to the Screening Visit and, if possible, should remain on that dose throughout the study. Taper and/or discontinuation of riluzole is allowed for tolerability reasons after the Baseline Visit.
7. Subjects must have a percent predicted FVC of ≥ 60% at the Screening Visit.
8. 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.
9. Subjects must be able to communicate effectively with study personnel.
10. Subjects must be able and willing to follow all protocol requirements and study restrictions.
11. Subjects must be able and willing to return for all study visits.

12.1.1 Open Label Extension Inclusion Criteria

Subjects may enter an open label extension of up to 48 weeks if they meet the following criteria:

1. Subject has completed the 36 week Randomized Treatment Period.
2. Subject will, in the opinion of the Investigator, benefit from additional treatment with study drug.
3. Subject is willing and able to continue in the open label extension.

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 as outlined below:

4. 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.
5. Subject has participated in any previous ALS therapeutic drug study unless at least 5 half lifes have passed between the last dose of study drug in the previous trial and the Screening Visit in this study.

6. Subject has participated in any non-ALS therapeutic (drug or device) trial in the 4 weeks prior to the Screening Visit.
7. Subject is unwilling to receive, or is intolerant of, SC injections.
8. Subject has any history of use of ACTH preparations for treatment of ALS.
9. Subject has a history of sensitivity to ACTH preparations or to porcine protein products.
10. Subject has any medical condition known to have an association with motor neuron dysfunction (other than ALS) which might confound or obscure the diagnosis of ALS.
11. Subject has tracheostomy, diaphragm pacing, or ongoing (used for greater than 7 consecutive days in the 4 weeks prior to the Screening Visit) need for assisted ventilation of any type.
12. 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.
13. Subject has used edaravone in the 1 week prior to the Screening Visit or in the 2 weeks prior to the Randomization Visit.
14. Subject has received any stem cell replacement therapy.
15. Subject has used chronic oral corticosteroids in the 8 weeks prior to the Screening Visit. Chronic oral corticosteroid use is defined as ≥ 10 mg of prednisone/prednisone equivalent for > 4 consecutive weeks.
16. Subject has had any dose of parenteral any intrathecal/epidural corticosteroids in the 4 weeks prior to the Screening Visit. Intra-articular, topical and/or inhaled corticosteroid use is allowed during the study.
17. Subject has any known contraindication(s) to Acthar (Mallinckrodt, 2015) 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 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).
18. Subject has a history of chronic active hepatitis including acute or chronic hepatitis B, or acute or chronic hepatitis C.

19. Subject has a history of tuberculosis (TB) infection or any signs/symptoms of TB.
20. Subject has a clinically significant infection requiring intravenous administration of antibiotics and hospitalization in the 4 weeks prior to the Screening Visit.
21. 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.
22. Subject has Type 1 or Type 2 diabetes mellitus (prior diagnosis of gestational diabetes mellitus is not exclusionary).
23. 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.
24. 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.
25. 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).
26. 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) ≤ 1000 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).

27. Subject has any other clinically significant disease, disorder or laboratory abnormality (including those listed on the Prescribing Information Section 5: Warnings and Precautions [Mallinckrodt, 2015]) which, in the opinion of the investigator (by its nature or by being inadequately controlled), might put the subject 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 28 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. A subject who is a screen failure at the Screening or Baseline Visit may be rescreened. The subject must repeat all screening procedures. The period from the start of rescreening related procedures to the first dose of study drug must not exceed 28 days. Subjects may be rescreened only once.

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 30 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 ALS 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 time of informed consent through the Follow-up Visit):

- Edaravone.
- Stem cell replacement therapy.
- Oral corticosteroids ≥ 10 mg of prednisone/prednisone or any parenteral, intrathecal, or epidural corticosteroids. Intra-articular, topical, and inhaled corticosteroids are allowed during the study.

- Live or live-attenuated vaccines.
- Any investigational drug, device, or procedure administered as part of a research study.
- Any investigational treatment (drug, device, or procedure) for the treatment of ALS used for the sole purpose of impacting ALS functional decline and/or survival. This includes prescription and over-the-counter medicinal products.

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 Allowed Concomitant Medications/Nondrug Therapies

The following medications/nondrug therapies are permitted during the study (from the time of informed consent through the Follow-up Visit):

- Subjects taking riluzole must be on a stable dose for at least 4 weeks prior to the Screening Visit and, if possible, should remain on that dose throughout the study. Taper and/or discontinuation of riluzole is allowed for tolerability reasons after the Baseline Visit.
- Symptomatic treatment for sialorrhea, spasticity, depression, fatigue, and pseudobulbar palsy as per local clinical practice is allowed during the study.

14 PROCEDURES/ASSESSMENTS

The schedule of study procedures is summarized in the Schedule of Study Events (Table 7-1). Except where noted, in person visits with the subject at the study site are preferred. If the subject is unable to come to the study site for any visit after the Baseline Visit, all procedures that can be completed by telephone will be done as scheduled.

If required, a visit can be completed over 2 to 3 days provided all assessments will be completed within the allowed ± 5 day visit window.

14.1 Screening Visit (Study Days -28 to -1) Procedures/Assessments

Screening assessments must be performed within 1 to 28 days prior to the Baseline Visit. The following procedures will be performed at the Screening Visit:

- Informed consent.
- Inclusion/exclusion criteria.
- Telephone administered ALSFRS-R.

- Family history of ALS and family neurologic history.
- Medical and surgical history.
- Demographics.
- Complete physical examination.
- Height and Weight.
- Vital signs.
- Spirometry.
- Clinical laboratory tests.
- HbA1c.
- Serum pregnancy test.
- Hepatitis serology.
- IGRA test for TB.
- Contact the Interactive Phone/Web Response System (IXRS).
- AEs 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 (Week 0) and First Dose Procedures/Assessments

Predose evaluations will occur prior to the first dose of study drug. The Baseline Visit can be completed over a period of 2 to 3 days provided it is completed within 28 days of the Screening Visit. The investigator or designee will complete the following procedures predose:

- Inclusion/exclusion criteria review; subject must meet all eligibility criteria at screening and baseline.
- [redacted]
- [redacted]
- [redacted]
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Telephone administered ALSFRS-R.
- Investigator administered ALSFRS-R.

- [redacted]
- Current medical condition review.
- Limited physical examination.
- Weight.
- Vital signs.
- Spirometry.
- [redacted]
- Clinical laboratory tests.
- Lipid Panel.
- Urine pregnancy test.
- [redacted]
- [redacted]
- Contact IXRS and dispense study drug kits.
- Study drug and diary training.
- AEs and concomitant medications.

The investigator will complete the following at dosing and postdose:

- Study drug administration under supervision of study staff and observation for at least 1 hour thereafter.
- AEs and concomitant medications.

14.3 Weeks 4, 8, 16, 20, 28, and 32 (± 5 days) Procedures/Assessments

- [redacted]
- [redacted]
- [redacted]
- C-SSRS.
- Telephone administered ALSFRS-R.
- Current medical condition review.
- Limited physical examination.

- Weight.
- Vital signs.
- Spirometry.
- Clinical laboratory tests.
- Urine pregnancy test.
- [redacted]
- Subject diary review.
- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- AEs and concomitant medications.

14.4 Week 12 and 24 (± 5 days) Procedures/Assessments

- [redacted]
- [redacted]
- [redacted]
- C-SSRS.
- Telephone administered ALSFRS-R.
- Investigator administered ALSFRS-R.
- [redacted]
- Current medical condition review.
- Limited physical examination.
- Weight.
- Vital signs.
- Spirometry.
- [redacted]
- Clinical laboratory tests.
- Lipid Panel.
- HbA1c.

- Urine pregnancy test.
- [redacted]
- [redacted]
- Subject diary review.
- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- AEs and concomitant medications.

14.5 Week 36 (± 5 days)/Early Termination Procedures/Assessments

- [redacted]
- [redacted]
- [redacted]
- C-SSRS.
- Telephone administered ALSFRS-R.
- Investigator administered ALSFRS-R.
- [redacted]
- Current medical condition review.
- Complete physical examination.
- Weight.
- Vital signs.
- Spirometry.
- [redacted]
- Clinical laboratory tests.
- Lipid Panel.
- HbA1c.
- Serum pregnancy test.
- [redacted]
- Subject diary review.
- Study drug accountability.

- Contact IXRS and dispense study drug kits (for taper for subjects **not** entering the open label extension).
- AEs and concomitant medications.

Subjects who early terminate from the Randomized Treatment Period for any reason must undergo the taper of study drug (2x/week for 2 weeks followed by 1x/week for 1 week) and should complete the End of Taper and Follow-up Visits.

14.6 Week 36 (± 5 days) Additional Procedures/Assessments for Subjects Entering the Open Label Extension Only

- Open Label Extension entry criteria review.
- Contact IXRS and dispense active study drug kits.
- Study drug and diary training.
- Study drug administration under supervision of study staff and observation for at least 1 hour thereafter.
- AEs and concomitant medications.

14.7 Open Label Extension Weeks 40 and 44 Procedures/Assessments

- Investigator administered ALSFRS-R.
- C-SSRS.
- Limited physical examination.
- Weight.
- Vital signs.
- Clinical laboratory tests.
- Urine pregnancy.
- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- AEs and concomitant medications.

14.8 Open Label Extension Weeks 48 and 72 Procedures/Assessments

- [redacted]
- [redacted]
- [redacted]

- C-SSRS.
- Investigator administered ALSFRS-R.
- [redacted]
- Limited physical examination.
- Weight.
- Vital signs.
- Spirometry.
- Clinical laboratory tests.
- Lipid panel.
- HbA1c.
- Urine pregnancy.
- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- AEs and concomitant medications.

14.9 Open Label Extension Week 60 Procedures/Assessments

- [redacted]
- [redacted]
- [redacted]
- C-SSRS.
- Investigator administered ALSFRS-R.
- [redacted]
- Limited physical examination.
- Weight.
- Vital signs.
- Spirometry.
- [redacted]
- Clinical laboratory tests.
- Lipid panel.

- HbA1c.
- Urine pregnancy.
- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- AEs and concomitant medications.

14.10 Open Label Extension Week 84/ Early Termination Procedures/Assessments

- [redacted]
- [redacted]
- [redacted]
- C-SSRS.
- Investigator administered ALSFRS-R.
- [redacted]
- Complete physical examination.
- Weight.
- Vital signs.
- Spirometry.
- [redacted]
- Clinical laboratory tests.
- Lipid panel.
- HbA1c.
- Serum pregnancy.
- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- AEs and concomitant medications.

Subjects who early terminate from the Open Label Extension for any reason must undergo the taper of study drug (2x/week for 2 weeks followed by 1x/week for 1 week) and should complete the End of Taper and Follow-up Visits.

14.11 Week 39 or Week 87/End of Taper Procedures/Assessments

At Week 39 (+ 5 days) or Week 87 (+ 5 days) the subject will be contacted via telephone and the following assessments will be made:

- AEs and concomitant medications.

14.12 Follow-up Visit Procedures/Assessments

The following procedures will be completed at the follow-up visit 28 (± 2) days after the final dose of study drug:

- Telephone administered ALSFRS-R (not required for the Open Label Extension Follow-up Visit).
- Investigator administered ALSFRS-R.
- Current medical condition review.
- Limited physical examination.
- Weight.
- Vital signs.
- Spirometry.
- Clinical laboratory tests.
- Urine pregnancy test.
- Subject diary review.
- Study drug accountability.
- AEs and concomitant medications.

14.13 Unscheduled Visit Procedures/Assessments

Any time that an unscheduled visit is needed during the Randomized Treatment Period to assess the subject for the study (for example, for an AE), the following minimum evaluations must be completed:

- Telephone administered ALSFRS-R.
- Current medical condition review.
- Limited physical examination.
- Weight.

- Vital signs.
- AEs and concomitant medications.

15 INVESTIGATIONAL MEDICINAL PRODUCT (Study Drug)

15.1 Methods of Assigning Subjects to Treatment Groups

15.1.1 Randomization and Stratification

Subjects will be randomized according to a computer-generated allocation scheme to receive either Acthar 0.2 mL (16 U) or placebo 0.2 mL. Both investigators and the subjects will be blinded to the treatment assignment. The randomization will be stratified for riluzole use (yes/no) and the predicted values of the 9-month decline rate of ALSFRS score from baseline (≤ 1 point change/month vs > 1 point change/month) generated from the prize winning algorithm of the DREAM Phil Bowen ALS Prediction Prize4Life Challenge (Küffner et al, 2015).

In the Randomized Treatment Period, for each stratum, a separate randomization scheme will be produced. A block randomization will be performed. Subjects will not be randomized in the Open Label Extension Period. The biostatistician will decide on the details at the time of the creation of the randomization scheme.

The DREAM Phil Bowen ALS Prize4Life Challenge was issued to promulgate development of algorithms that could predict disease progression in ALS. The algorithm developers were provided with a small subset of data from the PRO-ACT database that included 3 months of individual patient level clinical trial information that was to be used to predict disease progression over the subsequent 9 months. There were 37 algorithm submissions, and each algorithm was then evaluated on a separate data set from the PRO-ACT database. The 2 winning algorithms both predicted disease progression better than a baseline model and clinicians using the same data.

Mallinckrodt contacted the developers of 1 of the prize winning algorithms in order to apply the algorithm to stratify the subjects in a previous trial (QSC01-ALS-01, Mallinckrodt, 2016a). The algorithm was modified to only use the available variables as predictors, which were collected from subjects' Screening Visit. The algorithm was validated with a subset of PRO-ACT data, and the root mean square error of the validation is 0.517, which is very close to the original algorithm. In this study, the ALSFRS-R score collected at the Baseline Visit will be converted to ALSFRS score by dropping the last 2 questions (Questions 11 and 12) since most of the records in PRO-ACT database use ALSFRS scoring system.

The algorithm will be implemented after the Screening Visit, and a 9-month decline rate in ALSFRS score will be generated based on the screening and baseline data, which will be used to stratify the subjects when they return for the Baseline Visit.

15.2 Interactive Phone/Web Response System

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 record each subject visit, 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.

15.3 Emergency Identification of Investigational Medicinal Product

In case of an emergency during the Randomized Treatment Period, 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 that the blind was broken and provide the date and reason for breaking the blind.

15.4 Dosing Procedures

Both Acthar (80 U/mL) and the placebo are supplied as 5 mL multidose vials. 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:

Randomized Treatment Period

- Treatment A: Acthar 0.2 mL (16 U) SC QD for 36 weeks. Subjects who do not enter the open label extension will then taper with Acthar 0.2 mL (16 U) administered 2x/week for 2 weeks, then 1x/week for 1 week.

  OR

- Treatment B: Placebo 0.2 mL SC QD for 36 weeks. Subjects who do not enter the open label extension will then taper with placebo 0.2 mL administered 2x/week for 2 weeks, then 1x/week for 1 week.

Open Label Extension:

- Acthar 0.2 mL (16 U) SC QD for 48 weeks, followed by Acthar 0.2 mL (16 U) administered 2x/week for 2 weeks, then 1x/week for 1 week.

The subject or subject's caregiver will administer the first dose of study drug and the first dose of Acthar in the Open Label Extension in the clinic under the supervision of study staff. The subject will remain in the clinic for at least 1 hour postdose to monitor for allergic or anaphylactic reactions. All other doses will be administered by the subject or the subject's caregiver at home.

15.4.1 Treatment Discontinuation

Subjects who early terminate for any reason must undergo the taper (2x/week for 2 weeks followed by 1x/week for 1 week) and should complete the End of Taper and Follow-up Visits.

Subjects who early terminate from the Randomized Treatment Period for any reason other than withdrawal of consent should be encouraged to continue minimal study participation via

telephone contact on a monthly basis if possible. In this circumstance, the ALSFRS-R should be administered over the telephone by the site, and any status update should be collected.

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) that cannot be managed by the adjustment of concomitant medications such as insulin and oral hypoglycemic agents.
- MedDRA System Organ Class infection/infestation 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).

15.5 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.

15.6 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.

15.7 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 7-1). Below are general instructions for the administration of these assessments. Specific instructions and questionnaires will be provided in a separate document.

16.1 Telephone Administered Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised

The ALSFRS-R is a validated questionnaire-based scale used extensively as a primary outcome measure in ALS clinical trials and is considered a predictor of survival (Castrillo-Viguera et al, 2010; Cedarbaum and Stambler, 1997; Cedarbaum et al, 1999; Kollewe et al, 2008; Traynor et al, 2004). Subjects are rated on a scale of 0 to 4 for each of 10 aspects of daily function. The ALSFRS-R has been shown to have good inter- and intra-rater reliability when administered by face-to-face and via telephone (Kasarskis et al, 2005; Kaufmann et al, 2007). In this study, a trained independent rater(s) will administer the questionnaire to each subject/subject's caregiver by telephone at specified times.

16.2 Investigator Administered Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised

The ALSFRS-R trained investigator or designee will administer the ALSFRS-R questionnaire in person with the subject or subject's caregiver at specified times during the study.

[redacted]

[redacted]

16.5 Spirometry

Spirometry will be administered after the subject has rested for at least 5 minutes using the study site's standard equipment and processes (Fallat et al, 1979; Lechtzin, et al, 2002). Spirometry results must include FVC and forced expiratory volume in 1 second (FEV1). In addition slow vital capacity (SVC) will be collected at the Baseline Visit only.

Subjects with FVC < 60% of predicted at the Screening or Baseline Visit are not eligible for the study.

[redacted]

[redacted]

18 SAFETY ASSESSMENTS AND PROCEDURES

The following safety assessments will be evaluated: AEs, physical examinations, clinical laboratory test results (chemistry, hematology, HbA1c, urinalysis, hepatitis serology, IGRA for TB test), vital signs, and C-SSRS. All safety assessments will be performed at times outlined in the Schedule of Study Events (Table 7-1). Additional (unscheduled) safety assessments may be performed as needed.

18.1 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 21 for additional details on the handling of AEs and SAEs.

18.2 Family History of ALS and Neurologic Disease

Family history of ALS and family history of neurologic disease will be collected at the screening visit. Subjects will be asked to identify any family members with a confirmed diagnosis of ALS or a history of neurologic disease including mother, father, son, daughter, sister, brother, maternal and paternal grandmother, maternal and paternal grandfather, maternal and paternal aunt(s), maternal and paternal uncle(s), maternal and paternal cousin(s),

maternal and paternal nephew(s), maternal and paternal niece(s), and any other family members.

18.3 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. Subjects will specifically be asked for history of stroke (ischemic, hemorrhagic, other/unknown), dementia (dementia of the Alzheimer's type or other), Parkinson's disease, and/or brain tumor.

In addition, the date of onset and the site (limb, bulbar, or limb and bulbar) of first symptom of ALS will be collected.

18.4 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.

18.5 Physical Examination

A complete physical examination will be performed at the Screening Visit and the Week 36/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 visits.

The findings of the physical examinations will be recorded.

18.6 Height and Weight

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

18.7 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. The date for all vital sign assessments will be recorded, additionally time will be recorded for blood pressure assessments.

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.

18.8 Clinical Laboratory Tests (Chemistry, Hematology, Urinalysis, Lipid Panel, HbA1c, Hepatitis Serology, IGRA, Pregnancy Tests, [redacted])

The clinical laboratory tests are listed in Section 32.1. All clinical laboratory tests will be done at a central laboratory facility except urine pregnancy (at the site). 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. 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, other specific tests, and urinalysis samples will be collected at the specific times starting at screening and throughout the study. Fasting early morning samples are preferred, but a random daytime sample is acceptable.

In addition:

- All female subjects of child-bearing potential will have a serum pregnancy test at the Screening and Week 36/End of Study 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. Any female subject that becomes pregnant during the study will be immediately withdrawn and the pregnancy report as per Section 21.5.

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

- Lipid panels will be done at specified times during the study. The lipid panel will include total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides.

- 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. Additional HbA1c tests will be done at specified times during the study.

- [redacted]

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.

18.9 Columbia -Suicide Severity Rating Scale

The C-SSRS is designed to quantify the severity of suicide ideation and behavior (Posner et al, 2011). The C-SSRS will be administered by the investigator or designee.

When this assessment is required, they should be the first assessment done at any visit (with other investigator completed assessments) and must be completed prior to any study drug dosing.

[redacted]

[redacted]

[redacted]

20 STATISTICAL METHODS AND PLANNED ANALYSIS

20.1 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 interim analysis.

Unless otherwise specified, all statistical tests will be two-sided with a significance level of 0.05. Summary statistics will be provided for all study variables with descriptive statistics (number of observations, mean, standard deviation, 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.

20.2 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 one postbaseline telephone administered ALSFRS-R.
- The Per-Protocol Population will include the subset of the mITT population who complete the study as per protocol.

20.3 Endpoints

20.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the change from baseline in the telephone administered ALSFRS-R total score at Week 36.

20.3.2 Secondary Efficacy Endpoints- Randomized Treatment Period

- Mean slope of the telephone administered ALSFRS-R total score decline from baseline in the group treated with Acthar vs the placebo group.
- Mean slope of investigator administered ALSFRS-R total score decline from baseline in the group treated with Acthar vs the placebo group.
- Change from baseline in telephone administered ALSFRS-R total score and investigator administered ALSFRS-R total score over time.
- Mean slope of pulmonary function tests (FVC and FEV1) decline from baseline in the group treated with Acthar vs the placebo group.

20.3.3 Secondary Efficacy Endpoints-Open Label Extension Period

- Change from baseline in telephone administered ALSFRS-R over time in the group treated with Acthar followed by Acthar (Acthar-Acthar) and the group treated with placebo followed by Acthar (placebo-Acthar).
- Mean slope of telephone administered ALSFRS-R total score decline from baseline in Acthar-Acthar and placebo-Acthar groups.
- Mean slope of pulmonary function test (FVC, FEV1, and SVC) decline in Acthar-Acthar and placebo-Acthar groups.
- Survival in Acthar-Acthar and placebo-Acthar groups.

20.3.4 Secondary Safety Endpoints

- Summary of C-SSRS.
- Summary of general safety profile, including AEs (serious and nonserious), vital signs and laboratory assessments by study period and over the entire study.

[redacted]

[redacted]

20.4 Subject Characteristics

20.4.1 Demographics

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

20.4.2 Medical and Surgical History

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

20.4.3 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.

20.4.4 Subject Disposition and Exposure to Study Drug

Subject disposition will be summarized for all enrolled 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.

20.5 Efficacy Analysis

20.5.1 Randomized Treatment Period

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

ALSFRS-R change from baseline at postbaseline visits will be computed as:

Change = baseline value - postbaseline value

Baseline is defined as the value observed at randomization (Week 0).

The primary efficacy endpoint, change from baseline in the telephone administered ALSFRS-R total score at Week 36 in the Acthar treated group vs the placebo group, will be compared using a mixed model with repeated measures (MMRM) analysis method. ALSFRS-R total score change from baseline will be used as a dependent variable, and the model will include the fixed effects of treatment, visit (categorical covariate), treatment-by-visit interaction, and baseline ALSFRS-R score as continuous covariates. The null hypothesis is that the least squared mean contrast between Acthar and placebo groups at Week 36 equals zero. Significance tests will be based on least-squares means using a two-sided test at $\alpha = 0.05$ (two-sided 95% confidence intervals). An unstructured covariance matrix will be used to model the within-subject variance-covariance. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, and compound symmetry covariance structure. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Least squares mean for each treatment group,

least squares mean difference, and 95% confidence intervals between the treatment groups and the corresponding p-value will be reported.

All "mean slope decline" type of secondary endpoints will be analyzed using random coefficient model. Change from baseline will be the dependent variable, and treatment time (in month, continuous) and treatment-by-time interaction will be fixed effects and intercept will be random effect. Baseline values will be adjusted. Estimates of slope for each treatment group, estimates of slope difference, 95% confidence interval and the corresponding p-value will be reported.

For all "change from baseline" type of secondary [redacted] endpoints, the same approach as for the primary efficacy endpoint described above will be used.

The primary and secondary endpoints analyses will be performed for the mITT and Per-Protocol populations.

[redacted]

[redacted]

[redacted]

20.5.2 Open-Label Extension Period

All efficacy endpoints for the Open Label Extension will be summarized by descriptive statistics, no inferential statistical analysis will be performed.

All "change from baseline" and "mean slope decline" types of endpoints will be summarized with descriptive statistics (number of observations, mean, standard deviation, median,

minimum, and maximum) for numerical (or continuous) variables and with frequencies and percentages for categorical variables at each visit. Box Whisker and trend plots maybe used to present the data if necessary.

All "time to event" type endpoint will be summarized descriptively (n, mean, standard deviation, minimum, Q1, median, Q3, maximum, and 95% CI) for each treatment group. Kaplan-Meier curve will be plotted to present the data.

The statistical analysis plan will describe in further detail the analyses for primary, secondary, [redacted] efficacy endpoints.

[redacted]

20.7 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.

20.7.1 Adverse Events

Adverse events will be coded using the appropriate version of MedDRA. All AEs will be presented in a data listing. Only 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, AEs will be summarized by severity and relation to study drug.

20.7.2 Clinical Laboratory Tests

Hematology, blood chemistry, lipid panel, urinalysis and HbA1c 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.

20.7.3 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.

20.7.4 Other Safety Analysis

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

[redacted]

20.9 Interim Analysis

An interim analysis will be done when 40% of subjects have completed the Week 24 visit. Details of the interim analysis will be provided in the statistical analysis plan.

20.10 Statistical Power and Sample Size Considerations

The primary efficacy analysis will compare the mean telephone administered ALSFRS-R total score change from baseline at Week 36 in the group treated with Acthar to that in the placebo group using mITT analysis population. With 140 mITT subjects in the group treated with Acthar and 70 mITT subjects in the placebo group (210 subjects total), assuming the expected ALSFRS-R total score change from baseline of 6.3 and 9 in Acthar and placebo groups, respectively, the common SD of the ALSFRS-R total score change from baseline at Week 36 of 5.83 (estimated from PRO-ACT database), and dropout rate of 20% prior to Week 36, the study will have at least 80% power to detect the treatment difference at the 0.05 level of significance. Assuming a few subjects might not qualify for the mITT analysis population after randomization, approximately 213 subjects will be enrolled and randomized into Acthar treated group and placebo group in a 2:1 ratio.

20.11 Missing Data

20.11.1 Imputation for Missing Data

Imputation procedures and key sensitivity analyses will be outlined in the statistical analysis plan.

20.11.2 Sensitivity Analysis

Sensitivity analyses of the primary endpoint will be performed by using different missing data imputation methodologies.

20.12 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.

21 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

21.1 Safety

For safety information about Acthar, refer to the most recent version of the Prescribing Information (Mallinckrodt, 2015) and the Investigator's Brochure (Mallinckrodt, 2016b).

21.2 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 the Investigator's Brochure.

Adverse experiences (serious or non-serious) that commonly occur in the study population or background regimen will be considered anticipated events. Such events include known consequences of the underlying disease (disease-related) or condition under investigation (eg,

symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy. Anticipated events, when reported, to be associated with the use of the investigational product, are a subset of unexpected adverse events (events not listed in the Investigator's brochure). However, these events do not warrant expedited reporting as individual cases when serious criteria have been met because it is not possible to determine that there is a reasonable possibility that the drug caused the event. As a result, they do not meet the definition of a suspected adverse reaction.

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).

Hospitalization for procedures that are electively performed for the management of ALS, such as percutaneous endoscopic gastrostomy tube placement or tracheostomy, in the absence of a true life-threatening situation will not be considered SAEs.

21.3 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 21-1).

Table 21–1: Adverse Event Relationships

Relationship	Definition
Related to ALS Disease Progression	A known consequence of the underlying disease related to disease progression with no plausible relationship to the administration of study treatments.
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 21-2.

Table 21–2: 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.

21.4 Adverse Event and Serious Adverse Event Recording and Reporting

AEs and SAEs will be recorded from signing of the ICF through completion of the follow-up visit. 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/Visit 2, only AEs and SAEs related to study procedures will be recorded. The investigator must follow up on all AEs and SAEs reported to have occurred 28 days after the last dose of study drug 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 Mallinckrodt Global Pharmacovigilance or designee.
- Report all pregnancies to Mallinckrodt Global Pharmacovigilance or designee on the Pregnancy Surveillance Form.
- Submit any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction from Mallinckrodt Global Pharmacovigilance or designee to the IRB/IEC.

The reporting requirements for AEs are summarized in Table 21-3.

Table 21–3: 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 Global Pharmacovigilance.

- For all SAEs, the investigator, or designee, must complete the SAE Report Form with the minimum information required by FDA and ICH and submit 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 submit 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.

21.5 Pregnancy Reporting

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

Pregnancy exposure to an 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. 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.

22 SUBJECT DISCONTINUATION OR WITHDRAWAL

22.1 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 to assess their continued well-being.

Subjects who early terminate for any reason other than withdrawal of consent should be encouraged to continue minimal study participation via telephone contact. In this circumstance, the ALSFRS-R should be administered over the telephone by the site, and any status update should be collected.

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.

Investigator Judgment

If, in the opinion of the Investigator, the benefit/risk balance no longer favors continued study participation for any reason, the subject should be withdrawn.

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 the 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 is noncompliant (eg, has a positive pregnancy or 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 15.4.1.

Other

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

23 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.

24 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.

25 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.

25.1 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.

26 DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

26.1 Investigator

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

All subject information recorded in the eCRF will be attributable to source data from the investigational site. Each subject's eCRF should be fully completed and submitted to the sponsor in a timely manner.

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.

26.2 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.

27 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.

28 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.

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30 PUBLICATION POLICY

30.1 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.

30.2 Investigator's Ability to Publish

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

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32 Attachments

32.1 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
Lipid Panel	
Total Cholesterol	LDL
Triglycerides	HDL
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	
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)	