CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double Blind, Placebo Controlled Study to Assess the Efficacy and Safety of [redacted] Acthar® Gel in Subjects With Persistently Active Systemic Lupus Erythematosus Despite Moderate Dose Corticosteroids

Protocol Number: MNK14304067

Date of Original Protocol: 02 June 2016

Date of Protocol Revision: 04 August 2016

Date of Protocol Revision: 26 August 2016

Date of Protocol Revision: 01 June 2017

Mallinckrodt ARD, Inc.
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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

2.1 Emergency Contacts

Role in Study	Name	Contact Information
Primary Contact:		
Medical Monitor	[redacted] MD	Toll Free Number: [redacted] Toll Number [redacted] Email: [redacted] FAX: [redacted]
Secondary Cintact:		
Medical Monitor	[redacted] MD	Toll Free Number: [redacted] Toll Number [redacted] Email: [redacted] FAX: [redacted]

Please see next page for additional telephone contact numbers in Section 2.2.

Please see Section 22.4 for detailed information regarding the Serious Adverse Event (SAE) Reporting Requirements for this study.

SAE reporting fax: [redacted]

SAE confirmation email: [redacted]

2.2 Additional Contacts

Role in Study	Name	Contact Information
Clinical Trial Manager	[redacted]	Telephone: [redacted] E-mail: [redacted]
Clinical Technical Lead	[redacted] PhD	Telephone: [redacted] E-mail: [redacted]

3 SPONSOR SIGNATURE

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR) (where applicable), all applicable national and local regulations, protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

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

Sponsor Signature	Date of Signature (DD Month YYYY)
[redacted] PhD	
Sponsor Name (print)	

4 INVESTIGATOR SIGNATURE

My signature confirms that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR) (where appropriate), all applicable national and local regulations, protections for privacy, and generally accepted ethical principles such as the Declaration of Helsinki.

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

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

5 SUMMARY OF CHANGES

1. Updated the pharmacovigilance email address.
2. Updated the approximate number of study centers from 45 to 60.
3. Updated the Schedule of Events to include: a) footnote “e” (positive urine test after randomization confirmed by serum pregnancy test) and b) footnote “f”(autoantibody testing at screening).
4. Added new inclusion criterion #8, and removed original inclusion criteria # 8 and # 9 in Section 13.1.
5. Updated the reporting of adverse events for physical examinations done between screening and randomization in Section 19.4.
6. Updated clinical laboratory tests in Section 19.7.
7. Updated subject withdrawal criteria in Section 23.1.

6 ABBREVIATIONS

Abbreviation	Term
2x/week	Twice a week
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BAFF	B cell activity factor
BILAG-2004	British Isles Lupus Assessment Group-2004
CFR	Code of Federal Regulations
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Score
CNS	Central nervous system
CTX-I	C-terminal crosslinking telopeptide of Type I collagen
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCV	Hepatitis C virus antibody
HCV PCR	Hepatitis C virus polymerase chain reaction
HIPAA	Health Insurance Portability and Accountability Act
hSLEDAI	Hybrid Systemic Lupus Erythematosus Disease Activity Index
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IFN-alpha	Interferon alpha
Ig	Immunoglobulin
IGRA	Interferon gamma release assay
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional Review Board
IV	Intravenous, intravenously
IXRS	Interactive Phone/Web Response System
MCR	Melanocortin receptor
mITT	Modified intent-to-treat
MM	Medical monitor
NSAID	Nonsteroidal anti-inflammatory drugs
PGA	Physician's Global Assessment
PINP	N-terminal propeptide of Type I collagen

Abbreviation	Term
QOL	Quality of life
SAE	Serious adverse event
SC	Subcutaneous, subcutaneously
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SFI	SELENA Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index-2000
SRI	Systemic Lupus Erythematosus Responder Index
sVCAM-1	Soluble vascular cell adhesion molecule-1
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
U	Unit(s)
US	United States
ULN	Upper limit of normal
WPAI	Work Productivity and Activity Impairment Questionnaire

7 SYNOPSIS

Study Title: A Multicenter, Randomized, Double Blind, Placebo Controlled Study to Assess the Efficacy and Safety of [redacted]Acthar® Gel in Subjects With Persistently Active Systemic Lupus Erythematosus Despite Moderate Dose Corticosteroids	
Protocol Number: MNK14304067	Type: Phase 4 (US)/ Phase 2 (Outside the US)
Condition/Disease:	Systemic Lupus Erythematosus
Approximate Number of Subjects: 162	Approximate Duration of Subject Participation: 32 weeks
Approximate Number of Study Centers: 60 globally	Approximate Duration of Study: 3 years

Design:

This is a randomized, placebo controlled, double blind study. Following a screening period of up to 28 days, subjects with persistently active systemic lupus erythematosus (SLE) and moderate to severe rash and/or arthritis despite receiving corticosteroids (7.5 mg to 30 mg per day of prednisone or equivalent) for ≥ 4 weeks prior to screening, will be randomized in a 1:1 ratio to receive 1 mL (80 Units [U]) of Acthar or matching placebo. At randomization, subjects will be stratified by prednisone equivalent dose (≤ 20 mg/day vs > 20 mg/day) and by location (United States [US] or outside the US). During Weeks 1 to 4, 1 mL (80 U) of Acthar or volume matched placebo will be administered subcutaneously (SC) every other day. For the remainder of the study (Weeks 5 to 24), Acthar 1 mL (80 U) or volume matched placebo will be administered SC 2x/week. The primary efficacy endpoint is the SLE Responder Index (SRI) at Week 16. Corticosteroid taper will be encouraged between Weeks 16 and 24. All subjects will have a follow-up visit 28 (± 5) days after the last dose of study drug.

Objectives:

Primary Objective

- To determine the ability of Acthar to reduce disease activity as measured by SRI, in subjects with SLE requiring moderate dose corticosteroids for persistently active disease.

Secondary Objectives

- To assess the impact of Acthar on disease activity, measured by the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K), British Isles Lupus Assessment Group-2004 (BILAG-2004), and Physician's Global Assessment (PGA), in subjects with SLE requiring moderate dose corticosteroids for persistently active disease.
- To assess the time to response to Acthar in subjects with SLE requiring moderate dose corticosteroids for persistently active disease.
- To further assess the safety and tolerability of Acthar in subjects with SLE requiring moderate dose corticosteroids for persistently active disease.

Exploratory Objectives

- [redacted]
- [redacted]

Entry Criteria:

Male or nonpregnant, nonlactating female subjects 18 years of age or older with a diagnosis of SLE according to the American College of Rheumatology revised criteria (fulfilled ≥ 4 criteria) and active disease defined as total SLEDAI-2K score ≥ 6 and clinical SLEDAI-2K (excluding laboratory domains) score of ≥ 4 at the time of screening and randomization (points for arthritis and/or rash must be present at both screening

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and randomization), and a BILAG-2004 score of A or B in the in the mucocutaneous and/or musculoskeletal body systems at screening and randomization. Subjects must have a documented history of a positive antinuclear antibody (ANA) or a screening result of a positive ANA test by immunofluorescent assay (IFA) with a titer ≥ 1:80 or an equivalent assay; or a documented history or positive screening result of elevated anti-dsDNA or ENA antibodies (e.g., anti-Smith, SSA, SSB, RNP).. Subjects with Type 1 or Type 2 diabetes, active central nervous system manifestations of SLE or active lupus nephritis, tuberculosis, history of hepatitis, peptic ulcer, active infection, or any contraindication for Acthar will be excluded. Subjects must exhibit disease activity despite being on a stable daily dose of a corticosteroid (7.5 mg to 30 mg per day [inclusive] of prednisone or prednisone equivalent) for at least 4 weeks prior to the Screening Visit.

Subjects may be taking antimalarials and nonsteroidal anti-inflammatory drugs if they are on a stable dose for at least 4 weeks prior to the Screening Visit and will remain on that dose throughout the study. Subjects may be taking methotrexate, azathioprine, and/or mycophenolate mofetil if they are on a stable dose for at least 8 weeks prior to the Screening Visit and will remain on that dose throughout the study. Subjects must not have received any steroid injection (intramuscular, intraarticular, or intravenous) within the 4 weeks prior to the Screening Visit. Subjects must not have received cyclosporine, oral corticosteroid doses > 30 mg per day of prednisone or equivalent, or any non-biologic investigational drug within the 3 months prior to the Screening Visit. Subjects must not have received intravenous immunoglobulin or plasmapheresis within the 4 months prior to the Screening Visit. Subjects must not have received cyclophosphamide, abatacept, B cell targeted therapies (anti-CD-22 agents [epratuzumab] or belimumab), B cell depleting therapy (rituximab or other anti-CD20 agents, or anti-CD52 agents [alemtuzumab]), or any biologic investigational agent within the 6 months prior screening.

Concomitant Medications and Treatments:

Subjects must remain on stable daily dose of prednisone or prednisone equivalent through Week 16 of the study. Taper of corticosteroid is encouraged between Weeks 16 and 24 as clinically indicated.

All other background medications for SLE must remain stable throughout the study.

No new immunosuppressant therapies or other new treatments for SLE may be initiated during the study.

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

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

Study Drug and Treatment Administration:

Acthar is a sterile preparation of purified adrenocorticotropic hormone (ACTH) analogue formulated in a gel for repository administration. Acthar and its matching placebo will be supplied by the sponsor and administered SC as follows in this study:

Treatment A: Acthar 1 mL (80 U) administered SC every other day from Week 0 to 4 and 2x/week from Weeks 5 to 24.

Treatment B: Placebo 1 mL administered SC every other day from Week 0 to 4 and 2x/week from Weeks 5 to 24.

Efficacy Evaluations:

The following efficacy assessments will be evaluated: SRI, SLEDAI-2K, BILAG-2004, PGA, Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) Flare Index (SFI), Cutaneous Lupus Erythematosus Disease Area and Severity Score (CLASI), 28 Joint Count, and prednisone usage after Week 16.

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[redacted]

Safety Evaluations:

The following safety assessments will be evaluated: adverse events, physical examination, clinical laboratory tests, pregnancy testing, vital signs, [redacted] and hospital admissions.

[redacted]

Statistical Methods:

Analysis Populations

- The Modified Intent-to-Treat (mITT) Population will include all randomized subjects who receive at least 1 dose of study drug and who contribute any postbaseline efficacy data to the study.
- The Per-Protocol Population will include the subset of the mITT population who complete the study as per protocol, have no missing primary endpoint data, and do not have any major protocol deviations.
- The Safety Population will include all subjects who receive 1 or more doses of study drug.

Sample Size

It is expected that approximately 270 subjects will be screened to randomize a total of 162 subjects into 1 of the 2 treatment groups: 1 mL (80 U) of Acthar every other day for 4 weeks followed by 1 mL (80 U) of Acthar 2 times per week for 20 weeks or 1 mL of placebo every other day for 4 weeks followed by 1 mL of placebo 2 times per week for 20 weeks in a 1:1 ratio (81 per group). The primary efficacy analysis will compare the SRI response rate in the Acthar group to the SRI response rate in the placebo group. Assuming 2 subjects might not qualify for the mITT analysis population after randomization, with 80 mITT subjects in each treatment group (160 total) and a response rate of 30% in the placebo group and 55% in the Acthar group, the study will have a 90% power to detect a treatment difference at the 0.05 level of significance.

Statistical Analysis

The safety analyses will be performed using the safety population. The efficacy [redacted] analyses will be performed using the mITT and per protocol populations. Analyses performed on the mITT population will be considered primary.

Summaries for continuous variables will include standard statistics (n, mean, SD, median, relevant percentiles, minimum, and maximum). Categorical data will be summarized using frequency tables that will present the subject counts and the percent of subjects falling into that category. All statistical tests will be 2-sided with a significance level of 0.05. The statistical analysis plan will describe in further detail the analyses for primary, secondary, [redacted] efficacy endpoints.

Efficacy Analysis

Subjects will be included in the efficacy analyses based on their treatment assignment. The primary endpoint is the proportion of SRI responders at Week 16. The proportions of SRI responders for the 2 treatment groups will be summarized descriptively by visit and treatment group in tabular format and compared using a 2-sided Pearson's chi-square test at a significance level of 0.05. If the responder or nonresponder count falls to equal or below 5 in either treatment group, 2-sided Fisher's exact test will be used instead. All quantitative secondary and exploratory endpoints will be analyzed using analysis of covariance models with treatment

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Condition/Disease:	Systemic Lupus Erythematosus

group as a factor and the baseline value of the corresponding endpoint as a covariate. Mixed model with repeated measurements will be performed as deemed necessary. Secondary and exploratory endpoints that are proportions will be analyzed using Pearson's chi-square test or Fisher's exact tests.

[redacted]

Safety Analysis

Treatment-emergent adverse events and serious adverse events will be summarized using the MedDRA by preferred term within system organ class.

Hospital admissions and the reason for each admission will be listed and summarized descriptively by visit and treatment. The cumulative number of hospital admissions will be compared between treatment groups at Week 24 with a 2-sided Pearson's chi-square test or Fisher's exact test at a significance level of 0.05.

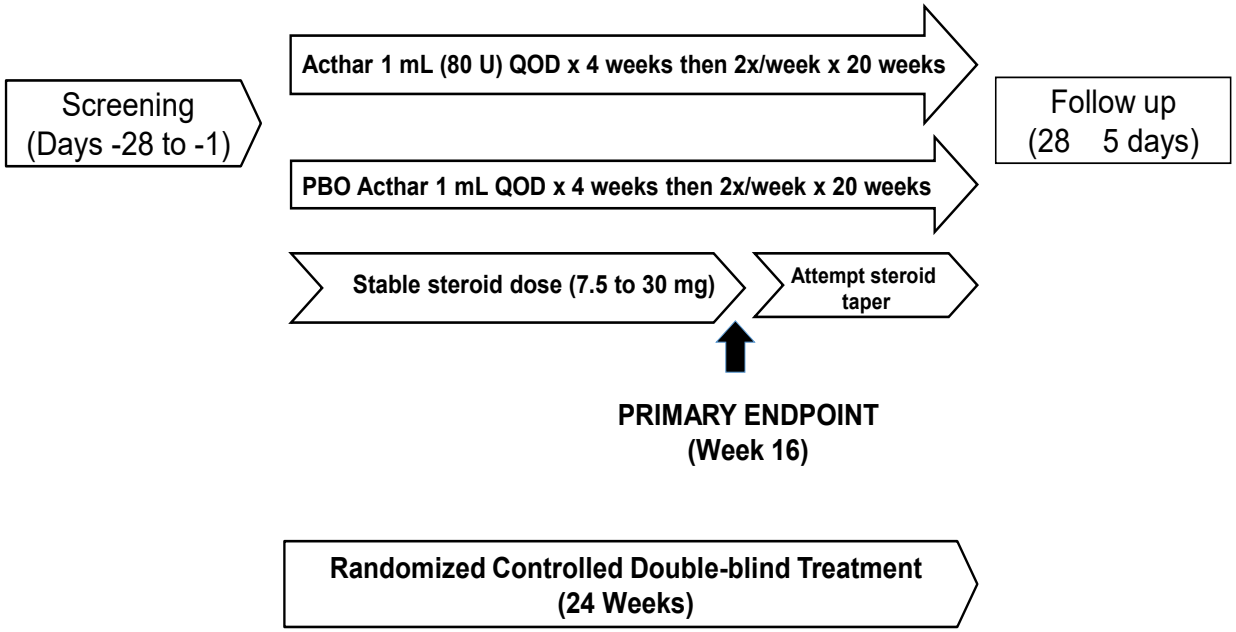
Other safety data will be listed and summarized descriptively or graphically, as appropriate.

[redacted]

8 STUDY SCHEMATIC AND SCHEDULE OF EVENTS

8.1 Study Schematic

Figure 8-1: Study Overview



8.2 Schedule of Study Events

Table 8-1: Schedule of Study Events

Assessment/Procedure	Screening (Day -28 to Day -1)	Randomization	Dosing	Treatment Period								Follow-up
Week		0	0	2 (± 3 days)	4 (± 3 days)	6 (± 3 days)	8 (± 3 days)	12 (± 5 days)	16 (± 5 days)	20 (± 5 days)	24 (± 5 days)/Early Termination	28 (± 5 days)
Informed Consent	X											
Inclusion/Exclusion Criteria Review	X	X										
Demographics	X											
Medical/Surgical History	X											
Current Medical Condition Review		X		X	X	X	X	X	X	X	X	X
Complete Physical Examination	X										X	
Limited Physical Examination		X		X	X	X	X	X	X	X		X
Height and Weight[a]	X	X		X	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X		X	X	X	X	X	X	X	X	X
12-lead ECG	X										X	
Clinical Laboratory Tests[c]	X	X		X	X	X	X	X	X	X	X	X
Lipid Panel	X	X						X			X	
HbA1c	X							X			X	
Serum Pregnancy Test	X										X	
Urine Pregnancy Test[d]		X					X		X			X
IGRA for TB	X											
Hepatitis Serology[e]	X											
[redacted]		X						X			X	
C3, C4 and anti-ds DNA antibodies	X	X		X	X	X	X	X	X	X	X	
Serology (ANA, ENA)[f]	X											

Assessment/Procedure	Screening (Day-28 to Day -1)	Randomization	Dosing	Treatment Period								Follow-up
Week		0	0	2 (± 3 days)	4 (± 3 days)	6 (± 3 days)	8 (± 3 days)	12 (± 5 days)	16 (± 5 days)	20 (± 5 days)	24 (± 5 days)/Early Termination	28 (± 5 days)
[redacted]		X					X		X		X	
[redacted]		X					X		X		X	
[redacted]		X					X		X		X	
SLEDAI-2K	X	X		X	X	X	X	X	X	X	X	
BILAG-2004	X	X			X		X	X	X	X	X	
PGA		X			X		X	X	X	X	X	
SFI					X		X	X	X	X	X	
CLASI-Activity		X			X		X	X	X	X	X	
28 Joint Count		X			X		X	X	X	X	X	
[redacted]		X					X		X		X	
[redacted]		X					X		X		X	
Hospital Admissions				X	X	X	X	X	X	X	X	
IXRS Contact	X	X		X	X	X	X	X	X	X	X	
Study Drug and Diary Training		X										
Study Drug Accountability and Diary Review				X	X	X	X	X	X	X	X	
Dispense Study Drug and Diary		X		X	X	X	X	X	X	X		
Administer First Dose			X									
Adverse Events and Concomitant Treatments	X											

[a]Height at screening only.
[b]Blood pressure, respiratory rate, pulse rate and body temperature. For blood pressure, an average of 3 readings after the subject has been seated for ≥ 5 minutes at The Screening and Randomization Visits. Single readings after subject has been seated for ≥ 5 minutes at all other time points.
[c] Chemistry, hematology assays, and urinalysis (see Attachment 1). [redacted]
[d]Positive urine test after randomization will be confirmed by serum pregnancy test.
[e]Hepatitis B surface antigen, Hepatitis B core antibody (HBcAb), hepatitis C virus antibody (HCV Ab), hepatitis C polymerase chain reaction([(HCV PCR] for subjects positive for HCV Ab only).
[f]Autoantibody testing (ANA, ENA) may be performed if history is unavailable.

9 ETHICAL CONSIDERATIONS

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

9.1 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to obtain the approval of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before the start of the study. The investigator will provide Mallinckrodt with a statement of compliance from the IRB/IEC and/or the United States (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 (if applicable) will be retained as part of the study records. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study at appropriate intervals (not to exceed 1 year) and at the completion of the study. The investigator will notify the IRB/IEC of serious adverse events (SAE) or other significant safety findings per IRB/IEC guidelines. The study protocol, informed consent form (ICF), advertisements (if any), and amendments (if any) will be approved by the IRB/IEC in conformance with international, national and local regulatory requirements; and the Code of Federal Regulations (CFR), Title 21, Part 56 (where applicable).

9.2 Ethical Conduct of the Study

The study will be conducted in full compliance with applicable international, national and local regulatory requirements; US Food and Drug Administration (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.

9.3 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 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.

10 BACKGROUND INFORMATION AND RATIONALE

10.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease characterized by excess production of proinflammatory cytokines and formation of autoantibodies resulting in immune complex deposition, and tissue damage. A range of organ systems may be involved (Von Feldt, 1995). The frequency of SLE varies by race and ethnicity, with higher rates reported among black and Hispanics, particularly women aged 14 to 64 years (Helmick et al, 2008).

SLE currently carries an average 10 year survival rate that exceeds 90% (Kasitanon et al, 2006; Trager and Ward, 2001). Before 1955, the 5 year survival rate was less than 50%. Decreased mortality rates associated with SLE can be attributed to earlier diagnosis (including milder cases), improvement in disease-specific treatments, and advances in general medical care. According to the Centers for Disease Control and Prevention, one third of SLE-related deaths in the US occur in patients younger than 45 years, making this a serious issue despite declining overall mortality rates. In 1976, Urowitz first reported bimodal mortality in early vs late SLE, noting that SLE-related deaths usually occur within the first 5 to10 years of symptom onset (Urowitz, 1976).

A number of medications are used in the treatment of SLE including nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials, glucocorticoids, and immunosuppressive agents. In general, low dose glucocorticoids are used for nonorgan-threatening disease (cutaneous, musculoskeletal, serositis, arthritis, and constitutional symptoms) and high dose glucocorticoids are reserved for organ threatening disease (eg, cardiopulmonary, hepatic, renal, hemolytic anemia, immune thrombocytopenia). Immunosuppressive agents are generally reserved for patients with significant organ involvement or patients who have had an inadequate response to glucocorticoids. Although the use of glucocorticoids is common in SLE, response to treatment is variable, with some patients responding well to low dose therapy and others requiring high doses, although a minority of patients does not respond to even long courses of high dose therapy (Petri, 2011). While glucocorticoid treatment is effective in many cases, side effects are common.

The primary goal of lupus treatment is to control or halt the inflammatory disease process while minimizing side effects. Treatments that reduce or eliminate disease activity without adding significant toxicity are needed.

Belimumab (Benlysta®), a B lymphocyte stimulator inhibitor, is an SLE targeted therapy approved by the FDA in 2011. It was the first new SLE drug approved in over 50 years. In the BLISS 52 Phase 3 study, approximately 58% of Benlysta patients (10 mg/kg) responded to treatment and 19% were able to decrease prednisone to < 7.5 mg/day (Navarra et al, 2011). This is compared to approximately 44% of placebo patients who responded to treatment and 12% were able to decrease prednisone to < 7.5 mg/day. Despite the recent approval of Benlysta, a significant unmet need remains for treatments that can improve disease activity and decrease dependence on chronic prednisone use.

As described in the Package Insert, [redacted]Acthar® Gel (repository corticotropin injection, hereafter referred to as Acthar) contains a highly purified adrenocorticotropic hormone (ACTH) analogue (Mallinckrodt, 2015). It is approved by the FDA for use during an acute exacerbation or as maintenance therapy in selected cases of SLE. ACTH is a member of the family of structurally related peptides known as melanocortin peptides. Melanocortin peptides, which in addition to ACTH include α-, β-, and γ-melanocyte stimulating hormones, are derived from the natural protein pro-opiomelanocortin and exert their physiologic effects by binding to cell surface G-protein coupled receptors known as melanocortin receptors (MCR) (Mountjoy et al, 1992). Five subtypes of MCRs have been identified to date (MC1R-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). Stimulation of cortisol by ACTH is mediated by activation of the MC2R expressed on

adrenal cortical cells. However, biologic activity of ACTH may extend beyond stimulation of adrenal corticosteroid production. MC1, 3, 4 and 5R are expressed on multiple leukocytes subpopulations (eg, T & B cells, macrophages), as well as within target organs (eg, skin, kidney, central nervous system [CNS]) relevant to SLE (Catania et al, 2004).

Experimental evidence suggests that MCR ligands such as ACTH and α-MSH may possess steroid-independent anti-inflammatory and immune modulatory activity relevant to SLE pathophysiology (Decker et al, 2014; Botte et al, 2014). In a murine model, Acthar has been shown to reduce B-cell differentiation and development, and to decrease circulating auto-antibodies, proteinuria, renal lymphocyte infiltration and glomerular immune complex deposition (Decker et al, 2014). Similarly, other investigators demonstrated that alpha-MSH attenuated manifestations of pristine-induced lupus in mice (Botte et al, 2014). Effects of Acthar on human B cell function were studied in vitro using peripheral blood B cells isolated from healthy human subjects. Acthar dose dependently inhibited interluekin-4/CD40 ligand-induced B-cell proliferation and immunoglobulin G production without enhancing cell death. These data suggest direct effects of Acthar on human B-cell function and provide supportive evidence for steroid independent effects of Acthar when used as a treatment for SLE, an autoimmune disease characterized by B-cell activation and humoral autoimmunity (Olsen et al, 2015). Historically, ACTH preparations have been used as a treatment option in SLE, with and without corticosteroids (cortisone or prednisone) (Harris-Jones, 1956).

In a recent publication (Fiechtner et al, 2014), the results of an open label, single arm study supported the use of Acthar as a treatment for SLE. A total of 10 female patients with chronic, moderate to severe SLE who were receiving a stable dose of prednisone (or equivalent) ≤ 20 mg/day and/or stables doses of azathioprine, antimalarials, mycophenolate mofetil/mycophenolic acid, or methotrexate were enrolled. Patients self-administered a 1 mL SC injection daily of Acthar (80 Units [U]) over 10 days with an optional 5 day rescue period for partial or nonresponders. All patients were assessed weekly from baseline (Day 0) through Week 4 (Day 28). There were significant improvements at all follow-up visits in Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) scores and other measures of disease activity. These results suggested that Acthar may be a therapeutic option for SLE patients and may provide significant disease activity reduction.

The sponsor recently completed a pilot study to explore the effects of Acthar on disease activity in SLE (Furie et al, 2015; Becker et al, 2016). The study consisted of 2 treatment periods: an 8 week double blind, placebo controlled period followed by an optional 44 week open label period, and was performed to examine the effects of Acthar in patients with steroid dependent, persistently active SLE with arthritic and/or cutaneous involvement. Subjects received 0.5 mL (40 U) SC daily or 1 mL (80 U) SC every other day of Acthar or volume

matched placebo for 4 weeks, followed by dose tapering to 2 times per week (2x/week) during Weeks 5 to 8. Subjects who completed the double blind period were given the option to continue into the 44 week open label extension period where all subjects received Acthar. From Weeks 9 to 20, Acthar regimen adjustments were permitted based on safety and efficacy with a goal of achieving a stable Acthar regimen by no later than Week 28, which was to be maintained for the remainder of the open label extension.

The majority of patients in this study were white (63.9%), while 33% were black or African-American and 16.7% were of Hispanic or Latino ethnicity. Mean baseline Hybrid Systemic Lupus Erythematosus Disease Activity Index (hSLEDAI) total scores ranged from 8.7 to 11.3 across treatment groups and mean total British Isles Lupus Assessment Group-2004 (BILAG-2004) total scores ranged from 13.1 to 18.6.

A novel responder index that had not been validated was used as the primary endpoint. It was defined as the proportion of patients responding to treatment at Week 4, with response defined by a decrease in hSLEDAI score from 4 to 0 for arthritis, or from 2 to 0 for rash, with no worsening in other organ systems as assessed by BILAG-2004. Although the primary endpoint was not met in this pilot study, Acthar was associated with significant improvements in several measures of disease activity, including hSLEDAI and BILAG-2004. The response to treatment with Acthar was seen as early as Week 6 for improvements from baseline in total hSLEDAI score, and by Week 8 significant improvements were seen in the remaining measures of disease activity (total BILAG-2004, improvement in BILAG A and B mucocutaneous and musculoskeletal scores, Cutaneous SLE Disease Area and Severity Score (CLASI)-Activity, and both tender and swollen joint count). Furthermore, in post hoc analyses, the proportion of responders as defined by the SLE Responder Index (SRI), a widely accepted and validated composite index (Furie et al, 2009), was significantly higher in the combined Acthar group than in the combined Placebo group at Week 8.

In the open label extension, hSLEDAI, BILAG, and Physician's Global Assessment (PGA) scores generally decreased over time from Week 8 for both treatment groups (Acthar/Acthar and Placebo/Acthar). Subjects randomized to Acthar during the double blind period who continued on Acthar throughout the 44 week open label extension had a durable response to therapy, while subjects who crossed over from placebo to Acthar experienced improvements in several measures of disease activity during the open label extension. These improvements were generally comparable to the improvements seen with Acthar treatment from the blinded period of the trial by 12 to16 weeks after Acthar was initiated. A notable proportion of subjects were able to taper exogenous corticosteroid therapy by Week 52 (Furie et al, 2015; Becker et al, 2016).

In general, Acthar was safe and well tolerated at the doses administered in this pilot study. In the double blind period, the most commonly reported treatment-emergent adverse event (TEAE) was increased weight, for which the incidence in the combined placebo cohort was comparable to that in the Acthar 0.5 mL (40 U) and Acthar 1 mL (80 U) cohorts. Two patients treated with Acthar had serious TEAEs (moderate viral infection and Klebsiella sepsis), and 4 patients (11.1% overall, 16.0% of the combined Acthar cohort) reported 4 TEAEs leading to study drug withdrawal. There were no unexpected adverse events in the open label extension.

10.2 Product Description

Acthar is a sterile preparation of a purified ACTH analogue formulated in 16% gelatin to provide a prolonged release after intramuscular or subcutaneous (SC) injection. Acthar contains 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH, and water for injection. Acthar is obtained from processing porcine pituitary using an FDA approved process. Acthar is currently labeled for use during an exacerbation or as maintenance therapy in selected cases of SLE (Mallinckrodt, 2015).

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

10.3 Dosage and Administration

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

Following a screening period of up to 28 days, subjects with persistently active disease SLE despite treatment with moderate dose corticosteroids will be randomized to receive either Acthar or placebo. Acthar 1 mL (80 U) or placebo (1 mL) will be administered as SC doses every other day for 4 weeks, followed by Acthar 1 mL (80 U) or placebo (1 mL) SC doses 2x/week for an additional 20 weeks.

10.4 Rationale

Recent studies (Fiechtner et al, 2014; Furie et al, 2015; Becker et al, 2016) support the efficacy of Acthar as a treatment for SLE. This study will provide additional data to support the efficacy and safety of Acthar in SLE, [redacted]

The Acthar dose and dosing regimen for this study are based on results from the pilot Phase 4 study exploring the efficacy, safety and pharmacodynamics of Acthar in subjects with SLE and a history of persistently active disease (Furie et al, 2015; Becker et al, 2016). In that study, subjects received 0.5 mL (40 U) SC daily or 1 mL (80 U) SC every other day of Acthar or volume matched placebo for 4 weeks, followed by dose tapering to 2x/week during Weeks 5 to 8. Subjects who completed the double blind period were given the option to continue into the 44 week, open label extension period where all subjects received Acthar. From Weeks 9 to 20, Acthar regimen adjustments were permitted based on safety and efficacy with a goal of achieving a stable Acthar regimen, no later than Week 28, which was to be maintained for the remainder of the open label period.

The Acthar dosing regimens studied during the pilot trial led to clinically meaningful improvements in disease activity measures such as hSLEDAI and BILAG-2004 as early as 8 weeks after initiation of Acthar in the double blind period, and 12 to16 weeks after initiating Acthar therapy in the open label extension. In general, Acthar was safe and well tolerated at the doses administered in the double blind and open label extension periods. No unexpected adverse events were observed. These results support the efficacy of Acthar as a treatment option in steroid dependent patients with persistently active SLE.

10.5 Risks and Benefits

The common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain. For a complete reference of known potential risks please refer to the Acthar product labeling (Mallinckrodt, 2015).

SLE is a chronic, autoimmune disease characterized by excess production of autoantibodies, immune complex deposition and pro-inflammatory cytokines that can cause inflammation and tissue damage in a range of organ systems. Although early diagnosis and advances in disease-specific therapies have improved 5- to 10-year survival rates to more than 90% (Kasitanon et al, 2006; Trager and Ward, 2001), there remain significant unmet needs in the management of SLE, particularly among patients with persistent, treatment-refractory disease (Holloway et al, 2014). Preclinical data (Decker et al, 2014; Olsen et al, 2015) support the potential for Acthar to reduce circulating autoantibodies and disease activity. Additionally, a recently published case series (Fiechtner, 2014) and the safety and efficacy data generated from a recently completely randomized controlled double blind pilot study with an optional open label extension (Furie et al, 2015; Becker et al, 2016) support the potential benefits of Acthar for reducing disease activity in the patient population to be studied.

11 OBJECTIVES

11.1 Primary Objective

The primary objective of this study is:

- To determine the ability of Acthar to reduce disease activity as measured by SRI in subjects with SLE requiring moderate dose corticosteroids for persistently active disease.

11.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the impact of Acthar on disease activity, measured by the SLEDAI-2K, BILAG-2004, and PGA, in subjects with SLE requiring moderate dose corticosteroids for persistently active disease.
- To assess the time to response to Acthar in subjects with SLE requiring moderate dose corticosteroids for persistently active disease.
- To further assess the safety and tolerability of Acthar in subjects with SLE requiring moderate dose corticosteroids for persistently active disease.

11.3 Exploratory Objectives

- [redacted]
- [redacted]

11.4 Approximate Duration of Subject Participation

Subjects will participate in the study for a total of up to approximately 32 weeks, including a screening period of up to 28 days, an active treatment period of 24 weeks, and a follow-up visit 28 (± 5) days after the last dose of study drug.

12 STUDY DESIGN

12.1 Description

This is a randomized, placebo controlled, double blind study. Following a screening period of up to 28 days, subjects with persistently active SLE and moderate to severe rash and/or arthritis despite receiving corticosteroids (7.5 mg to 30 mg per day of prednisone or equivalent) for ≥ 4 weeks prior to screening, will be randomized in a 1:1 ratio to receive 1 mL (80 U) of Acthar or

matching placebo. At randomization, subjects will be stratified by prednisone equivalent dose (≤ 20 mg/day vs > 20 mg/day). During Weeks 1 to 4, 1 mL (80 U) of Acthar or volume matched placebo will be administered SC every other day. For the remainder of the study (Weeks 5 to 24), Acthar 1 mL (80 U) or volume matched placebo will be administered SC 2x/week. The primary efficacy endpoint is the SRI at Week 16. Corticosteroid taper may be attempted and is encouraged between Weeks 16 and 24 if medically appropriate; the taper rate and schedule will be at the discretion of the individual investigator. All subjects will have a follow-up visit 28 (± 5) days after the last dose of study drug.

12.2 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 3 years to complete.

12.3 Approximate Number of Subjects

It is expected that approximately 270 subjects will be screened and 162 subjects will be randomized at approximately 60 sites globally.

13 SELECTION OF SUBJECTS

13.1 Inclusion Criteria

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

1. Subjects must be adequately informed and understand the nature and risks of the study and must be able to provide a signature and date on the ICF.
2. Subjects must be ≥ 18 years of age at Screening Visit and can be male or female.
3. Female subjects must be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit); or if of childbearing potential must be nonpregnant, nonlactating and agree to use effective contraception when with a male partner throughout study participation (through the Follow-up Visit). Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), and abstinence.
4. Male subjects with a female partner of childbearing potential must have been surgically sterilized (vasectomy) or agree to use a double barrier for contraception (condom plus

diaphragm, condom or diaphragm plus spermicidal gel or foam) or remain abstinent throughout their study participation (through the Follow-up Visit).

5. Subjects must have a diagnosis of SLE according to the American College of Rheumatology revised criteria (fulfilled ≥ 4 criteria) (Hochberg, 1997; Tan et al, 1982).
6. Subjects must have active SLE as demonstrated by a SLEDAI-2K score of ≥ 6 at the Screening Visit and a clinical SLEDAI (excluding laboratory results) score ≥ 4 at the Screening and Randomization Visits. Points for arthritis and/or rash must be present at both the Screening and Randomization Visits.
7. Subjects must have moderate to severe rash and/or arthritis as demonstrated by BILAG-2004 score A or B in the in the mucocutaneous and/or musculoskeletal body systems at both Screening and Randomization Visits.
8. A documented history of positive antinuclear antibody (ANA)
   OR
   A screening result of positive ANA test by immunofluorescent assay (IFA) with titer ≥ 1:80 or an equivalent assay
   OR
   A documented history or positive screening result of elevated anti-dsDNA or ENA antibodies (e.g., anti-Smith, SSA, SSB, RNP).
9. Subjects must have been on prednisone (or prednisone equivalent) for ≥ 8 weeks prior to the Screening Visit and on a stable dose of 7.5 mg to 30 mg of prednisone (or prednisone equivalent) for ≥ 4 weeks prior to the Screening Visit.
10. Subjects must have a mean systolic blood pressure ≤ 150 mm Hg and a 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 Randomization Visits.
11. Subjects using antimalarials and NSAIDs must have been on a stable dose for at least 4 weeks prior to the Screening Visit and remain on that dose throughout the study.
12. Subjects using methotrexate, azathioprine and/or mycophenolate mofetil must have been a stable dose for at least 8 weeks prior to the Screening Visit and remain on that dose throughout the study.
13. Subjects must be able to communicate effectively with study personnel.
14. Subjects must be able and willing to follow all protocol requirements and study restrictions.
15. Subjects must be able and willing to return for all study visits.

13.2 Exclusion Criteria

Subjects are ineligible for study participation if they meet any of the following criteria at the Screening Visit or the Randomization Visit.

1. Subject is from a vulnerable population, as defined by the US CFR Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the clinical research organization, or of the IRB/IEC.
2. Subject is unwilling to receive, or is intolerant of, SC injections.
3. Subject has a history of sensitivity to ACTH preparations (including but not limited to Acthar and Synacthen).
4. Subject has a history of sensitivity to porcine protein products.
5. Subject has severe active lupus nephritis defined as serum creatinine > 2.5 mg/dL or protein creatinine ratio > 1.5 g/g, or subject has required hemodialysis within 3 months prior to the screening visit or is likely to require hemodialysis throughout the study.
6. Subject has active CNS manifestations of lupus (as evidenced by seizures, psychoses, organic brain syndrome, cerebrovascular accident, cerebritis, or CNS vasculitis) within the 3 months prior to the Screening Visit or develops CNS lupus between the Screening Visit and the first dose of study drug
7. Subject has Type 1 or Type 2 diabetes mellitus or is taking hypoglycemic medication (a history of gestational diabetes mellitus is not exclusionary). Subjects must not have glycosylated hemoglobin (HbA1c) > 6.5 at the Screening Visit.
8. Subject has received any steroid injection (intramuscular, intraarticular or intravenous [IV]) within 4 weeks prior to the Screening Visit (use of topical and/or inhaled steroids is not exclusionary).
9. Subject has received oral prednisone > 30 mg per day or equivalent, cyclosporine, or any nonbiologic investigational drug within 3 months prior to the Screening Visit.
10. Subject has received IV immunoglobulin (Ig) or plasmapheresis within 4 months prior to the Screening Visit.

11. Subject has received cyclophosphamide, abatacept, B cell targeted therapy (anti-CD-22 [epratuzumab] or belimumab), B cell depleting therapy (rituximab or other anti-CD20 agent, or anti-CD52 agent [alemtuzumab]), or any biologic investigational agent within 6 months prior to the Screening Visit.
12. 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. For the purposes of this study, osteoporosis is defined as evidence of vertebral or long bone fracture, or lumbar T-score > 2.0 SD below the mean of the reference population.
    - Any primary adrenocortical insufficiency, or adrenal cortical hyperfunction.
    - Any current congestive heart failure (defined as New York Heart Association Functional Class III to IV).
    - Peptic ulcer (within 24 weeks prior to the Screening Visit).
    - Recent major surgery (within 24 weeks prior to the Screening Visit).
13. Subject has a history of chronic active hepatitis including active or chronic hepatitis B, or acute or chronic hepatitis C. Subjects must have negative Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb) and negative Hepatitis C virus antibody (HCV) or HCV polymerase chain reaction (PCR) < 25 IU/mL (HCV PCR will be automatically analyzed if HCV is positive) at the Screening Visit.
14. Subject has a history of tuberculosis (TB) infection, any signs/symptoms of TB, or any close contact with an individual with an active TB infection. Subjects must not have a positive or indeterminate interferon gamma release assay (IGRA) for TB at the Screening Visit.
15. Subject has a clinically significant infection requiring administration of IV antibiotics or hospitalization in the 4 weeks prior to the Screening Visit or between the Screening Visit and the first dose of study drug.
16. Subject has known immune compromised status (not related to SLE or therapies for SLE), including but not limited to, individuals who have undergone organ transplantation or who are known to be positive for the human immunodeficiency virus.
17. 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.

18. 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.
19. 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).
20. 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).
21. 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 patient at risk due to participation in the study, or may influence the results of the study or the subject's ability to complete the study.

13.3 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 Randomization 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 Randomization 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 Randomization 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.

14 PRIOR AND CONCOMITANT MEDICATIONS/TREATMENTS

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

In addition, all prior treatments for SLE will be recorded with start and stop date, dose, unit, frequency and route of administration.

14.1 Permitted Concomitant Medications

The use of antimalarials and NSAIDs is permitted provided the subject has been on a stable dose for at least 4 weeks prior to the Screening Visit and will remain on that dose throughout the study.

The use of methotrexate, azathioprine and mycophenolate mofetil is permitted provided the subject has been on a stable dose for at least 8 weeks prior to the Screening Visit and will remain on that dose throughout the study.

The use of topical and/or inhaled corticosteroids is allowed during the study.

14.2 Prohibited Concomitant Medications

The following treatments will not be permitted during the study:

- Administration of live or live-attenuated vaccines.
- Oral prednisone (or equivalent) > 30 mg/day.
- Steroid injections (intramuscular, intraarticular, or IV).
- IV Ig or plasmapheresis.
- Cyclosporine.
- Cyclophosphamide.
- Abatacept.
- B cell targeted therapy, anti-CD-22 (epratuzumab) or belimumab.
- B cell depleting therapy (rituximab or other anti-CD20 agent, or anti-CD52 agent [alemtuzumab]).
- Any other new immunosuppressant therapy or any other new treatment for SLE (initiated after the Screening Visit).

- Any investigational drug, device, or procedure administered as part of a research study.

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

15 PROCEDURES

The detailed schedule of study procedures is summarized in the Schedule of Study Events (Table 8-1). What follows is a general outline of required procedures and a suggested order for completion.

15.1 Screening Visit (Study Days -28 to -1) Procedures

Screening assessments must be performed within 1 to 28 days prior to the Week 0 Visit.

The following procedures will be performed at the Screening Visit:

- Informed consent.
- Inclusion/exclusion criteria.
- SLEDAI-2K and BILAG-2004.
- Medical and surgical history, including the first day of the last menstrual period for women of childbearing potential.
- Demographics.
- Complete physical examination.
- Height and Weight.
- Vital signs.
- 12-lead electrocardiogram (ECG).
- Clinical laboratory tests (chemistry, hematology, and urinalysis).
- Lipid panel.
- HbA1c.
- Serum pregnancy test.
- Hepatitis serology.
- IGRA test for TB.

- C3, C4 and anti-ds DNA antibodies.
- Serology (ANA, ENA; if history is unavailable)
- Contact the Interactive Phone/Web Response System (IXRS).
- Adverse events and concomitant medications.

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

15.2 Randomization Visit (Week 0) and First Dose Procedures

All evaluations will occur prior to the first dose of study drug, except as noted.

- Inclusion/exclusion criteria review.
- [redacted]
- [redacted]
- 28 Joint Count, SLEDAI-2K, BILAG-2004, PGA, and CLASI -Activity.
- Current medical condition review.
- Limited physical examination.
- Weight.
- Vital signs.
- Clinical laboratory tests.
- Lipid panel.
- Urine pregnancy test.
- C3, C4, and anti-ds DNA antibodies.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Subject diary and study drug administration training.
- Contact IXRS and dispense study drug kits.

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

15.3 Week 2 (± 3 days) and 6 (± 3 days) Procedures

- SLEDAI-2K.
- Current medical condition review.
- Limited physical examination.
- Weight.
- Vital signs.
- Clinical laboratory tests [redacted]
- C3, C4, and anti-ds DNA antibodies.
- Hospital admissions.
- Subject diary review.
- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- Adverse events and concomitant medications.

15.4 Week 4 (± 3 days) and 20 (± 5 days) Procedures

- 28 Joint Count, SLEDAI-2K, BILAG-2004, PGA, CLASI- Activity, and Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) Flare Index (SFI).
- Current medical condition review.
- Limited physical examination.
- Weight.
- Vital Signs.
- Clinical laboratory tests.
- C3, C4, and anti-ds DNA antibodies.
- Hospital admissions.
- Subject diary review.

- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- Adverse events and concomitant medications.

15.5 Week 8 (± 3 days) and 16 (± 5 days) Procedures

- [redacted]
- [redacted]
- 28 Joint Count, SLEDAI-2K, BILAG-2004, PGA, CLASI-Activity, and SFI.
- Current medical condition review.
- Limited physical examination.
- Weight.
- Vital Signs.
- Clinical laboratory tests.
- Urine pregnancy test.
- C3, C4 and anti-DS DNA antibodies.
- [redacted]
- [redacted]
- Serum cortisol and aldosterone.
- Hospital admissions.
- Subject diary review.
- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- Adverse events and concomitant medications.

15.6 Week 12 (± 5 days) Procedures

- 28 Joint Count, SLEDAI-2K, BILAG-2004, PGA, CLASI-Activity, and SFI.
- Current medical condition review.
- Limited physical examination.
- Weight.

- Vital Signs.
- Clinical laboratory tests.
- Lipid panel.
- C3, C4 and anti-DS DNA antibodies.
- HbA1c.
- [redacted]
- Hospital admissions.
- Subject diary review.
- Study drug accountability.
- Contact IXRS and dispense study drug kits.
- Adverse events and concomitant medications.

15.7 Week 24 (± 5 days)/Early Termination Procedures

- [redacted]
- [redacted]
- 28 Joint Count, SLEDAI-2K, BILAG-2004, PGA, CLASI-Activity, and SFI.
- Current medical condition review.
- Complete physical examination.
- Weight.
- Vital Signs.
- 12-lead ECG.
- Clinical laboratory tests.
- Lipid panel.
- Serum pregnancy test.
- HbA1c.
- [redacted]
- C3, C4 and anti-DS DNA antibodies.
- [redacted]

- [redacted]
- [redacted]
- Hospital admissions.
- Subject diary review.
- Study drug accountability.
- Contact IXRS
- Adverse events and concomitant medications.

15.8 Follow-up Visit - Week 28 (± 5 days)

The following procedures will be completed at the follow-up visit 28 (± 5) days after the final dose of study drug:

- Current medical condition review.
- Limited physical examination.
- Weight.
- Vital signs.
- Clinical laboratory tests.
- Urine pregnancy test.
- Adverse events and concomitant medications.

16 INVESTIGATIONAL MEDICINAL PRODUCT (Study Drug)

16.1 Methods of Assigning Subjects to Treatment Groups

16.1.1 Randomization and Stratification

Subjects will be randomized according to computer-generated allocation scheme to receive either Acthar 1 mL (80 U) or placebo 1 mL administered every other day for 4 weeks followed by 2x/week for 20 weeks. The randomization will be stratified by location (US or outside the US) and prednisone equivalent dose (≤ 20 and > 20 mg/day). For each stratum, a separate randomization scheme will be produced. Both investigators and the subjects will be blinded to the treatment assignment. A block randomization will be performed. The biostatistician will decide on the details at the time of the creation of the randomization scheme.

16.1.2 IXRS

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

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

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

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

The investigator or designee must contact IXRS to record each subject visit, to receive the study drug 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.

16.2 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 by the IXRS vendor. 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, time, and reason for breaking the blind.

16.3 Dosing Procedures

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

The following treatments will be administered:

- Acthar 1 mL (80 U) SC doses every other day for 4 weeks, followed by 1 mL (80 U) SC 2x/week for an additional 20 weeks.
- Placebo (1 mL) SC doses every other day for 4 weeks, followed by 1 mL SC 2x/week for an additional 20 weeks.

The subject or subject's caregiver will administer the first dose of Acthar in the clinic under the supervision of study staff. The subject will remain in the clinic for at least 1 hour postdose to monitor for allergic or anaphylactic reactions. Thereafter, all doses will be administered by the subject or the subject's caregiver at home.

16.3.1 Treatment Discontinuation

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

- Development of accelerated hypertension (defined as systolic blood pressure ≥ 180 *and* diastolic blood pressure ≥ 100 mm Hg) that cannot be managed by the adjustment of concomitant medications such as antihypertensive medications.
- Development of congestive heart failure (Class III or IV) 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.
- Development of any other adverse event (AE) of at least moderate intensity and possibly, probably or definitely related to study drug that cannot be managed by the adjustment of concomitant medications.

Missed doses of study drugshould be discussed with the medical monitor.

16.4 Storage of Clinical Supplies

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

Study drug will be supplied in kits containing the appropriate amount of vials. 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.

16.5 Drug Accountability

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

16.6 Compliance Monitoring

Prior to beginning the administration of study drug, subjects and/or their caregiver will be trained on dosing administration and must exhibit proper technique. Subjects and/or their caregiver will be trained on the completion of the study diary and will complete study diary entries to record all study drug administration and will bring it, along with all study drug kits including used vials to each visit. Each time study drug is dispensed compliance will be encouraged. Subject diary training is an ongoing process as the diary will be reviewed with the subject at each visit to monitor compliance with study drug administration.

17 EFFICACY ASSESSMENTS AND PROCEDURES

Efficacy assessments will be evaluated at times specified in the Schedule of Study Events (Table 8-1). Below is a general instruction of the administration of these assessments. Specific instructions and questionnaires/forms (where appropriate) will be provided in a separate document.

17.1 Physician Completed Assessments

The SLEDAI-2K, BILAG-2004, PGA, SFI, CLASI-Activity and 28 Joint Count are assessments to be completed by the investigator or designee. When these assessmentsare required, they should be the done immediately after subject reported outcome/questionnaire completion (if applicable) and must be completed prior to any study drug dosing.

17.1.1 Systemic Lupus Erythematosus Disease Activity Index-2000

The SLEDAI-2K is a modified version of a composite score based on the presence or absence of clinical signs, clinical symptoms, and immunologic laboratory results taken within 10 days of the evaluations (Bombardier et al, 1992; Gladman et al, 2002). Disease activity is based on 24 questions weighted across 9 organ systems with total scores ranging from 0 to 105 but are generally < 20 with very active disease. The Clinical SLEDAI-2K score is derived without the inclusion of points attributed to laboratory test results.

17.1.2 British Isles Lupus Assessment Group 2004

The BILAG scores disease involvement within each organ system based upon the intent to treat premise (Isenberg et al, 2005). The major difference between the BILAG and other disease activity indices is that disease activity in different organs/systems is reported separately. Specific manifestations in 9 organ systems are scored (there are a total of 97 items). Each item is rated as 0 (not present), 1 (improving), 2 (same), 3 (worse), or 4 (new) in the last 4 weeks compared with the previous 4 weeks.

The numerical scores are used to categorize each organ system by an alphabetical score: ‘A’ reflecting severe disease requiring increases in prednisone to > 20 mg daily and/or addition of immunosuppressive agents, ‘B’ indicated less active disease, requiring low-dose prednisone and/or symptomatic treatment with NSAIDs and/or antimalarials, ‘C’ reflecting mild disease requiring only symptomatic therapy, ‘D’ reflecting previous organ system involvement without current disease activity, and ‘E’ reflecting no prior or no current disease involvement in that organ system.

BILAG 2004 is a revised version of the original BILAG. The revised index removed the vasculitis section, placing individual clinical features more appropriately within the other organs or systems. It now incorporates sections on gastrointestinal disease and has an ophthalmology section, both missing from the original. Furthermore, some items related to damage were removed.

17.1.3 Physicians Global Assessment

PGA is a 100 mm visual analogue scale anchored at 0 (none) and 3 (severe) with intermediate lines at 1 (mild) and 2 (moderate). It was designed for physicians to provide an overall assessment of a patient’s wellbeing (Petri et al, 1999).

17.1.4 SELENA Flare Index

The SFI categorizes SLE flare as mild, moderate or severe based on the following 6 variables (Buyon et al, 2005):

- Change in SELENA SLEDAI score from the most recent assessment to current.
- Change in signs or symptoms of disease activity.
- Change in prednisone dosage.
- Use of new medication for disease activity or hospitalization.
- Change in PGA score.
- Hospitalization for SLE activity.

A severe flare is defined as 1 or more of the following: a) SLEDAI score greater than 12; b) new or worsening CNS involvement, vasculitis, glomerulonephritis, myositis, thrombocytopenia (platelet count < 60,000/mL), or hemolytic anemia (hemoglobin level < 70 g/L or decrease in hemoglobin level > 30 g/L), each requiring doubling of corticosteroid dosage to a final dosage > 0.5 mg/kg per day or acute hospitalization; c) any manifestation requiring an increase in dosage of prednisone or equivalent drug to greater than 0.5 mg/kg per day, or initiation of therapy with cyclophosphamide, azathioprine, mycophenolate mofetil, or methotrexate; d) hospitalization for lupus activity; and e) PGA score greater than 2.5 points.

17.1.5 Cutaneous Lupus Erythematosus Disease Area and Severity Score-Activity

The CLASI was developed to specifically track cutaneous activity and damage in SLE (Klein et al, 2010). The CLASI uses separate activity and damage scores as indicators of disease burden. The activity score reflects ongoing inflammation that can be treated, with points given for the presence of erythema, scale, mucous membrane lesions, recent hair loss, and inflammatory alopecia. The damage score represents the irreversible aftermath of inflammation. Only the CLASI activity score will be used in the study.

17.1.6 28 Joint Count

The 28 Joint Count includes assessment of swelling and tenderness in the shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints and knees.

17.2 SLE Responder Index

An SRI responder is defined as a subject with a 4 point reduction from baseline in SLEDAI-2K, with no new BILAG A and no more than 1 new BILAG B organ domain scores compared

with baseline, and no worsening in PGA (≤ 10% increase from baseline) (Furie et al, 2009). This index will be calculated by the sponsor.

[redacted]

[redacted]

19 SAFETY ASSESSMENTS AND PROCEDURES

The following safety assessments will be evaluated: AEs, physical examinations, clinical laboratory test results (chemistry, lipid panel, hematology, and urinalysis), HbA1c, vital signs, [redacted] medical history, weight, concurrent medical conditions, and hospital admissions. All safety assessments will be performed at times outlined in the Schedule of Study Events (Table 8-1). Additional (unscheduled) safety assessments may be performed as needed.

19.1 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.

19.2 Medical and Surgical History

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

19.3 Current Medical Conditions

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

19.4 Physical Examination

A complete physical examination will be performed at the Screening and Week 24/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 completed prior to the Randomization visit will be recorded as Medical History..

19.5 Height and Weight

Height will be collected at screening only. Weight will be collected at all visits.

19.6 Vital Signs

Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. Additionally, at the Screening and Randomization Visits, blood pressure will be measured 3 times, with at least 5 minutes between assessments after the subject has been seated for a minimum of 5 minutes prior to the initial blood pressure assessment.

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

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

Screening/Randomization

A subject with systolic blood pressure > 150 mm Hg and diastolic blood pressure > 90 mm Hg (average of 3 assessments) at the Screening or Randomization Visits does not qualify for the study.

On Study Assessments

If an on-study systolic blood pressure is > 150 mm Hg and diastolic blood pressure is > 90 mm Hg, an AE will be recorded if the investigator determines the change is clinically significant or requires a change in the subject's clinical management.

19.7 Clinical Laboratory Tests (Chemistry, Hematology and Urinalysis), HbA1c, IGRA, Direct Coombs test, Pregnancy Tests, [redacted]; and C3, C4, and anti-ds DNA antibodies

The clinical laboratory tests are listed in Attachment 1. All clinical laboratory tests will be done at a central laboratory facility except urine pregnancy (at the site) and [redacted] Specific instructions for collection, processing, storage, and shipment of clinical laboratory samples will be provided in a separate laboratory manual, where appropriate.

Samples for laboratory testing at all visits may be collected under fasted or nonfasted conditions. Fasting early morning samples are preferred, but a random daytime sample is acceptable. The date and time of the sample collection must be documented on the laboratory report. Investigators must review and sign laboratory reports. The clinical significance of each laboratory abnormality will be documented. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs.

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

In addition:

- All female subjects of child-bearing potential will have a serum pregnancy test at the Screening and Follow-up Visits. A positive urine test after randomization will be confirmed by a serum pregnancy test. Urine pregnancy tests will be done at other specified 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 Randomization) or withdrawn from the study. Any

female subject that becomes pregnant during the study will be immediately withdrawn and the pregnancy reported as per Section 21.6.

If applicable, the subject's agreement to use contraception throughout their study participation, and for 28 days after ending study participation, will be documented.

- A lipid panel (high density lipoprotein, low density lipoprotein, triglycerides, and total cholesterol) will be done at the Screening, Randomization, Week 12, and Week 24 Visits.
- 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 protocol.
- [redacted]
- C3, C4, and anti-ds DNA antibody samples will be taken at specified times during the study. -

Out-of-Range Laboratory Values

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

Laboratory values that fall outside the reference range from samples collected at the Randomization Visit and throughout the study will be assessed by the investigator for clinical significance. If the out of range value is deemed clinically significant by the investigator, an AE will be recorded.

19.8 Hospital Admissions

The number of hospital admissions and the reason for each admission will be collected at specified times in the study.

[redacted]

21 STATISTICAL METHODS AND PLANNED ANALYSIS

21.1 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. [redacted]

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

All data will be summarized by treatment groups as appropriate. Data summary and analyses will be performed with SAS 9.2 or higher.

21.2 Analysis Populations

- The Modified Intent-to-Treat (mITT) Population will include all randomized subjects who receive at least 1 dose of study drug and who contribute any postbaseline efficacy data to the study.
- The Per-Protocol Population will include the subset of the mITT population who complete the study as per protocol, have no missing primary endpoint data, and do not have any major protocol deviations.
- The Safety Population will include all subjects who receive 1 or more doses of study drug.

The safety analyses will be performed using the safety populations. The efficacy and pharmacodynamic analyses will be performed using the mITT and Per Protocol populations; analyses performed on the mITT population will be considered primary.

21.3 Efficacy Endpoints

21.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be proportion of responders as assessed by SRI at Week 16.

21.3.2 Secondary Efficacy Endpoints

- Change from baseline over time in SLEDAI-2K (Week 0 to 16).
- Time to first response as assessed by SRI.
- Change from baseline over time in total BILAG-2004 (Week 0 to 16).
- Change from baseline over time in PGA (Week 0 to 16).
- Proportion of subjects with decrease from baseline of ≥ 4 points in SLEDAI-2K over time (Week 0 to 16).
- Change from baseline in CLASI-Activity score over time (Week 0 to 16) in subjects with CLASI-Activity at baseline.
- Change from baseline (Week 0 to 16) in 28 Joint Count (tender and swollen) in subjects with tender and swollen joints at baseline.

21.3.3 Exploratory Endpoints

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

21.4 Safety Endpoints

- Summary of general safety profile, including adverse events (serious and non-serious), vital signs and laboratory assessments by study period and over the entire study.

21.5 Subject Characteristics

21.5.1 Demographics

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

21.5.2 Medical and Surgical History

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

21.5.3 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.

21.5.4 Subject Disposition and Exposure to Study Drug

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

21.6 Efficacy Analysis

Subjects will be included in the efficacy analyses based on their treatment assignment. The primary endpoint is the proportion of SRI responders at Week 16. The proportions of SRI responders for the 2 treatment groups will be summarized descriptively by visit and treatment group in tabular format and compared using a 2-sided Pearson's chi-square test at a significance level of 0.05. If the responder or nonresponder count falls to equal or below 5 in either treatment group, 2-sided Fisher's exact test will be used instead. All quantitative secondary and exploratory endpoints will be analyzed using analysis of covariance models with treatment group as a factor and the baseline value of the corresponding endpoint as a covariate. Mixed model with repeated measurement will be performed as deemed necessary. Secondary and exploratory endpoints that are proportions will be analyzed using Pearson's chi-square test or Fisher's exact tests.

For the primary efficacy endpoint, subjects who do not provide data to allow classification as responders will be considered nonresponders, that is, missing data will be imputed as non-responder. A similar approach will be applied to secondary efficacy endpoints that are proportions; missing will be classified as not satisfying the conditions described for that endpoint. A full description of missing data imputation method for all endpoints will be described in the statistical analysis plan.

[redacted]

[redacted]

21.8 Safety Analysis

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

21.8.1 Adverse Events

Adverse events will be coded using MedDRA (version 19.0 or higher) by preferred term within system organ class. The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by body system, preferred term, severity, and causality for each treatment group. Only TEAEs (events that are new in onset or aggravated in severity following treatment) will be included in all summaries. SAEs (including death) will be summarized.

21.8.2 Clinical Laboratory Tests; [redacted] and C3, C4, and anti-ds DNA Antibodies

Clinical laboratory tests (hematology, lipid panel, blood chemistry, and urinalysis); [redacted] and C3, C4, and anti-ds DNA antibodies results will be listed by subject and summarized by visit and treatment group. Categorical laboratory results will be presented with the frequency and percentage in each category by treatment group. Change from baseline at each visit will also be summarized. Shift tables will be generated if applicable. Select laboratory parameters may be presented graphically. Abnormal laboratory values will be identified and analyzed.

21.8.3 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.

21.8.4 Hospital Admissions

Hospital admissions and the reason for each admission will be listed and summarized descriptively by visit and treatment. The cumulative number of hospital admissions will be compared between treatment groups at Week 24 with a 2-sided Pearson's chi-square test or Fisher's exact test at a significance level of 0.05.

21.8.5 Other Safety Analysis

Other safety assessments including physical examinations, weight, pregnancy testing, and HbA1c will be listed and summarized descriptively or graphically, as appropriate.

[redacted]

21.10 Interim Analysis

Blinded aggregate data analyses will be completed when 25%, 50% and 75% of subjects complete Week 16. No other interim analyses are planned for this study.

21.11 Statistical Power and Sample Size Considerations

It is expected that approximately 270 subjects will be screened to randomize a total of 162 subjects into 1 of the 2 treatment groups: 1 mL (80 U) of Acthar every other day for 4 weeks followed by 1 mL (80 U) of Acthar for 20 weeks or 1 mL of placebo every other day for 4 weeks followed by 1 mL of placebo 2 times per week for 20 weeks in a 1:1 ratio (81 per group). The primary efficacy analysis will compare the SRI response rate in the Acthar 1 mL (80 U) group to the SRI response rate in the placebo group. Assuming 2 subjects might not qualify for the mITT analysis population after randomization, with 80 mITT subjects in each treatment group (160 total) and a response rate of 30% in the placebo group and 55% in the Acthar group, the study will have a 90% power to detect a treatment difference at the 0.05 level of significance.

21.12 Deviations From Statistical Analysis Plan

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

22 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

22.1 Safety

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

22.2 Definitions

Adverse Event

An AE is any untoward or undesirable medical occurrence in a subject who is administered 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.

SLE Activity Changes

All changes in SLE activity that are unequivocally due to progression of disease should not be reported as an AE unless they result in a SAE as defined below.

Serious Adverse Event

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

- Death.
- A life-threatening AE.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject 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).

22.3 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 22-1).

Table 22-1: Adverse Event Relationships

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

Severity Assessment

For purposes of consistency, if required the investigator may use the intensity grades presented in Table 22-2.

Table 22-2: 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.

22.4 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. The investigator must follow up on all AEs and SAEs reported to have occurred through the Follow-up Visit 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 Follow-up Visit.
- Report all SAEs on an SAE Report Form to Global Pharmacovigilance.
- Report all pregnancies to Global Pharmacovigilance on the Pregnancy Surveillance Form.
- Submit any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction from Global Pharmacovigilance to the IRB/IEC.

The reporting requirements for AEs are summarized in Table 22-3.

Table 22-3: 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 fax it to Mallinckrodt at +1 314-654-5759 or email at PVClinical@mallinckrodt.com 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.

- Should the investigator or designee have any difficulty in sending the SAE Report, they may contact Mallinckrodt contacts listed in Section 2.2.

- 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 are submitted to the FDA and other regulatory agencies as appropriate.

Follow Up Reporting

The investigator or designee must complete an SAE Report Form for all follow-up information received and fax or e-mail it to Mallinckrodt at +1 314-654-5759 or PVClinical@mallinckrodt.com within 24 hours of receipt. The investigator(s) or designee will receive acknowledgement of receipt for each SAE Report Form from Mallinckrodt.

- The investigator or designee is required to provide all related information/supporting documentation of an SAE until the SAE is resolved or stabilized or the subject has been referred to a nonstudy physician for follow-up treatment.

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

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

22.5 Adverse Events of Special Interest

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

- Elevated blood pressure (defined as systolic blood pressure ≥ 180 *and* diastolic blood pressure ≥ 100 mm Hg).
- Hyperglycemia (HbA1c > 6.5%, or fasting plasma glucose > 126 mg/dL, or classic symptoms of hyperglycemia with random plasma glucose > 200 mg/dL).
- MedDRA System Organ Class infection/infestation that are considered SAEs or lead to treatment discontinuation.
- 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).

22.6 Pregnancy Reporting

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

Pregnancy exposure to an investigational medicinal product, except for exposure to prenatal vitamins. Subjects should not become pregnant during the study. If the subject becomes pregnant, study treatment must be discontinued immediately. The investigator must report the pregnancy by submitting the appropriate form to Global Pharmacovigilance (fax at +1 314-654-5759 or email at PVClinical@mallinckrodt.com) 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 Global Pharmacovigilance (fax at +1 314-654-5759 or email at PVClinical@mallinckrodt.com) 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 Global Pharmacovigilance (fax at +1 314-654-5759 or email at PVClinical@mallinckrodt.com) 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 Global Pharmacovigilance (fax at +1 314-654-5759 or email at PVClinical@mallinckrodt.com), 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 Global Pharmacovigilance (fax at +1 314-654-5759 or email at PVClinical@mallinckrodt.com) 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 Pharmacovigilance (fax at +1 314-654-5759 or email atPVClinical@mallinckrodt.com) within 24 hours of the study site becoming aware of the follow-up information.

23 SUBJECT DISCONTINUATION OR WITHDRAWAL

23.1 Subject Withdrawal

Subjects who discontinue, or are withdrawn from the study for any reason, will be considered early termination. All subjects who terminate early will be required to have the Early Termination safety assessments (see Section 14.7) to assess their continued well-being.

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

Withdrawal by Subject

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

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 study drug. In addition, subjects who experience any of the adverse events described in Section 15.3.1 will be discontinued.

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 develops a condition that meets any of the exclusion criteria (Section 13.2) or fails to meet an inclusion criteria (Section 13.1) during the study that is not considered to be an AE or is noncompliant (eg, has a positive pregnancy), the subject will be discontinued from study drug. Discontinuation from study drug is also mandated for safety and/or tolerability issues as outlined in Section 15.3.1).

Worsening of Disease Activity

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

Other

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

24 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.

25 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.

26 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 IB, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study. During these study site visits, information recorded in the eCRFs will be verified against source documents.

26.1 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 or evaluation 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.

27 DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

27.1 Investigator

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

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

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

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

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

27.2 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.

28 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.

29 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.

[redacted]

31 PUBLICATION POLICY

31.1 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.

31.2 Investigator's Ability to Publish

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

32 REFERENCES

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

Becker, P.; Furie, R.; Mitrane, M.; Zhao, E. Repository Corticotropin Injections (RCI) Attenuates Disease Activity in Patients with Persistently Active Systemic Lupus Erythematosus (SLE) Requiring Corticosteroids: Results From a 44 Week Open-Label Extension Study. To be presented at the 2016 Annual Congress of Rheumatology; June **2016**; London, England.

Bombardier, C.; Gladman, D.D.; Urowitz, M.B.; Caron, C.; Chang, C.H. Description of the SLEDAI: A Disease Activity Index for Lupus Patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum.* **1992**, 35, 630-640.

Botte, D.A.C.; Noronha, I.L.; Malheiros, D.M.A.C.; Peixoto, T.V.; de Mello, S.B.V. Alpha-melanocyte Stimulating Hormone Ameliorates Disease Activity in Induced Murine Lupus-like Model. *Clin. Exp. Immun.* **2014**, 177, 381-390.

Buyon, J.P.; Petri, M.A.; Kim, M.Y.; Kaluniam, K.C.; Grossman, J.; Hahn, B.H.; et al. The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in SLE: A Randomized Trial. *Ann. Internal Med.* **2005**, 142, 953-962.

Catania, A.; Gatti, S.; Colombo, G.; Lipton, J.M. Targeting Melanocortin Receptors as a Novel Strategy to Control Inflammation. *Pharmacol. Rev.* **2004**, 56, 1-29.

Decker, D.; Grant, C.; Oh, L.; Becker, P.; Young, D.; Jordan, S. Immunomodulatory Effects of H. P. Acthar Gel on B Cell Development in the NZB/W F1 Mouse Model of Systemic Lupus Erythematosus. *Lupus*, **2014**, 23, 802-12.

Fiechtner, J.J.; Montroy, T. Treatment of Moderately to Severely Active Systemic Lupus Erythematosus With Adrenocorticotropic Hormone: A Single-site, Open-label Trial. *Lupus.* **2014**, 23, 905-12.

Furie, R.A.; Das, M.; Li, D.; Smythe, S.; Mathura, E.; Becker, P. Repository Corticotropin Injections (H.P. Acthar® Gel) Attenuates Disease Activity in Patients With Persistently Active Systemic Lupus Erythematosus (SLE) Requiring Corticosteroids, *Arthritis Rheumatol.* **2015**, 67, S10.

Furie, R.A.; Petri, M.A.; Wallace, D.J.; Ginzler E.M.; Merrill, J.T.; Stohl, W.; et al. Novel Evidence-Based Systemic Lupus Erythematosus Responder Index. *Arthritis Rheum*. **2009**, 61, 1143-1151.

Getting, S.J. Targeting Melanocortin Receptors as Potential Novel Therapeutics. *Pharmacol. Ther*. **2006**, 111, 1-15.

Gladman, D.D.; Ibanez, D.; Urowitz, M.B. Systemic Lupus Erythematosus Disease Activity Index 2000.*J. Rheumatol.* **2002**, 29, 288-291.

Gordon, C.; Isenberg, D.; Lerstrom, K.; Norton, Y.; Enkeleida, N.; Pushparajah, D.S. The Substantial Burden of Systemic Lupus Erythematosus on the Productivity and Careers of Patients: a European Patient-driven Online Survey. *Rheumatol.* **2013**, 52, 2292-2301.

Harris-Jones, J.N. The role of ACTH and Cortisone in the Treatment of Systemic Lupus Erythematosus. *Postgrad. Med. J.* **1956**, 32, 145-149.

Helmick, C.G.; Felson, D.T.; Lawrence, R.C.; Gabriel, S.; Hirsh, R.; Kwoh, C. K.; et al. Estimates of the Prevalence of Arthritis and Other Rheumatic Conditions in the United States. Part I. *Arthritis Rheum*. **2008**; 58, 15-25.

Hochberg, M.C. Updating the American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus Erythematosus. *Arthritis Rheum.* **1997**, 40, 1725.

Holloway, L.; Humphrey, L.; Heron, L.; Pilling, C.; Kitchen, H.; Hojbjerre, L.; et al. Patient-reported Outcome Measures for Systemic Lupus Erythematosus Clinical Trials: A Review of Content Validity, Face Validity, and Psychometric Performance. *Health Qual. Life Outcomes.* **2014**, 12, 116.

Isenberg, D. A.; Rahman, A.; Allen E.; Farwell, V.; Akl, M.; Bruce, I.M. BILAG 2004. Development and Initial Validation of the British Isles Lupus Assessment Group's Disease Activity Index for Patients with Systemic Lupus Erythematosus. *Rheumatol.* **2005**, 44, 902-906.

Jolly, M.; Pickard, A.S.; Wilke, C.; Mikolaitis, R.A.; Teh, L-S.; McElhine, K.; et al. Lupus-specific Health Outcomes Measure for US Patients: The Lupus QOL.-US Version. *Ann. Rheum. Dis.* **2010**, 69, 29-33.

Kasitanon, N.; Magder, L.S.; Petri, M. Predictors of Survival in Systemic Lupus Erythematosus. *Medicine (Baltimore).* **2006**, 85, 147-156.

Klein, R.S.; Morganroth, P.A.; Werth, V.P. Cutaneous Lupus and the CLASI instrument. *Rheum. Dis. North Am.* **2010**, 36, 33-51.

Mallinckrodt Inc. Acthar Data Compendium. RD-010-00 internal data on file.

Mallinckrodt Inc. *H.P. Acthar® Gel*; Package Insert: Hazelwood, MO, **2015**.

Mallinckrodt Inc. *H.P. Acthar® Gel*; Investigator's Brochure: Hazelwood, MO, **2016**.

McElhone, K.; Abbott, J. Shelmerdine, J.; Bruce, J.; Ahmad, Y.; Gordon, C.; et al. Development and Validation of Disease-specific Health-related Quality of Life Measure, the Lupus QOL, for Adults With Systemic Lupus Erythematosus. *Arthritis Care Res.* **2007**, 57, 972-979.

Mountjoy, K.G.; Robbins, L.S.; Mortrud, M.T.; Cone, R.D. The Cloning of a Family of Genes That Encode the Melanocortin Receptors. *Scienc*e. **1992**, 257, 1248-1251.

Navarra, S.V.; Guzmán, R.M.; Gallacher, A.E.; Hall, S.; Levy, R.A.; Jimenez, R.E.; et al. Efficacy and Safety of Belimumab in Patients With Active Systemic Lupus Erythematosus: A Randomized, Placebo-controlled, Phase 3 Trial. *Lancet*. **2011**, 377, 721-731.

Olsen, N.J.; Decker, D.A.; Becker, P.A.; McAloose, C.A.; Benko, A.L.; Kovacs, W.J. Direct Effects of HP Acthar Gel on Human B Lymphocyte Activation In Vitro. *Arthritis Res. Ther.* **2015**, 17, 300.

Petri, M.; Buyon, J.; Kim, M.; Classification and Definition of Major Flares in Systemic Lupus Erythematosus Clinical Trials. *Lupus*. **1999**, 8, 685-691.

Petri, M. Clinical Research in Systemic Lupus Erythematosus: Immediate Relevance to Clinical Practice. *Int. J. Rheum. Dis.* **2011**, 14, 1-5.

Schiöth, H.B.; Muceniece, R.; Wikberg, J.E.; Chhajlani, V. Characterization of melanocortin receptor subtypes by radioligand binding analysis. *Eur. J. Pharmacol*. **1995**, 15, 311-317.

Tan, E.M.; Cohen, A.S.; Fries, J.F., Masi, A.T.; McShane, D.J.; Rothfield, N.F.; at al. The 1982 Revised Criteria for the Classification of Systemic Lupus Erythematosus. *Arthritis Rheum.* **1982**, 25, 1271-1277.

Trager, J.; Ward, M.M. Mortality and Causes of Death in Systemic Lupus Erythematosus. *Curr. Opin. Rheumatol.* **2001**, 13, 345-351.

Urowitz, M.B.; Bookman, A.A.; Koehler, B.E.; Gordon, D.A.; Smythe, H.A.; Ogryzlo, M.A.; The Bimodal Mortality Pattern of Systemic Lupus Erythematosus. *Am. J. Med.* **1976**, 60, 221-225.

Von Feldt, J.M. Systemic Lupus Erythematosus. Recognizing its Various Presentations. *Postgrad. Med*. **1995**, 97, 79-86.

Zhang, W.; Bansback, N.; Boonen, A.; Young, A.; Singh, A.; Anis, A.H. Validity of the Work Productivity and Activity Impairment Questionnaire – A General Health Version in Patients With Rheumatoid Arthritis. *Arthritis Res. Ther.* **2010,** 12, R177.

33 Attachments

33.1 Attachment 1: Clinical Laboratory Tests

Serum Chemistry	
Alanine aminotransferase (ALT)	Creatine phosphokinase
Albumin (total)	Creatinine
Alkaline phosphatase	Glucose
Aspartate aminotransferase (AST)	Phosphorus
Bilirubin (total)	Potassium
Bicarbonate	Protein, total
Blood urea nitrogen	Sodium
Calcium	Uric acid
Chloride	
Lipid Profile	
High density lipoprotein	Triglycerides
Low density lipoprotein	Total cholesterol
Hematology Assays	
Direct Coombs Test (local laboratory)	Mean corpuscular volume
Hematocrit	Platelet count
Hemoglobin	Red blood cell count
Haptoglobin	Reticulocyte count
Mean corpuscular hemoglobin	White blood cell count, including differential
Mean corpuscular hemoglobin concentration	
Urinalysis	
Color	Ketones
Clarity	Protein
Albumin	pH
Bilirubin	Specific gravity
Blood	Protein:creatinine ratio
Creatinine	Microscopy (WBC/ high power field (HPF), RBC/HPF and urinary casts)
Glucose	
Diabetes Screen	
HbA1c	
Hormones	
Serum and urine beta-human chorionic gonadotropin (pregnancy test; conducted on site)	
Other	
[redacted]	
C3, C4, and ant-ds DNA antibodies	

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)	