



CLINICAL STUDY PROTOCOL

**A Multicenter, 2 Part Study to Assess the Efficacy and Safety of [REDACTED]
Acthar [REDACTED] Gel in Subjects With Rheumatoid Arthritis With Persistently
Active Disease**

Protocol Number: MNK14294063

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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, PhD PRA Health Sciences 4130 ParkLake Ave. Suite 400 Raleigh, North Carolina 27612 United States of America	Telephone: [REDACTED] E-mail: (not for emergencies): [REDACTED]
Secondary Contact:		
Back-Up Medical Monitor	[REDACTED] MD PRA Health Sciences Bollingbrook, IL United States of America	Telephone: [REDACTED] E-mail: (not for emergencies): [REDACTED]

Please see next page for additional telephone contact numbers in [Section 2.2](#).

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

SAE reporting fax: +1 314-654-5759

SAE confirmation email: GlobalPV@mallinckrodt.com

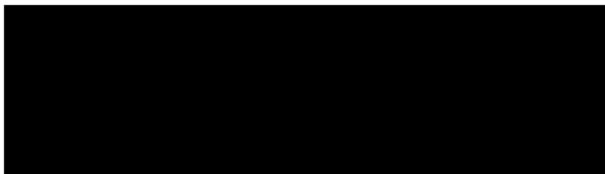
2.2 Additional Contacts

Role in Study	Name	Contact Information
Sr. Clinical Trial Manager	MS, M.Phil.	Telephone: E-mail:
Clinical Technical Lead	MD	Telephone: + Cell phone: E-mail:

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 Conference on 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

4 Aug 2016
Date of Signature

(DD Month YYYY)



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 Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR) (where appropriate), all applicable national and local regulations, protections for privacy, and generally accepted ethical principles such as the Declaration of Helsinki.

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

Investigator's Signature

Date of Signature
(DD Month YYYY)

Investigator's Name and Title (print)

5 ABBREVIATIONS

Abbreviation	Term
2x/week	Twice a week
ACTH	Adrenocorticotrophic hormone
ACR	American College of Rheumatology
ACR20	20% improvement in ACR criteria
ACR50	50% improvement in ACR criteria
ACR70	70% improvement in ACR criteria
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CDAI	Clinical Disease Activity Index
CFR	Code of Federal Regulations
CIA	Collagen-induced arthritis
CRP	C-reactive protein
CTX-I	C-terminal crosslinking telopeptide of Type I collagen
CTX-II	C-terminal crosslinking telopeptide of Type II collagen
DA	Disease activity
DMARD	Disease modifying antirheumatic drug
eCRF	Electronic case report form
DAS28-ESR	Disease Activity Score with 28 joint count and ESR
ED	Emergency Department
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HAQ-DI	Health Assessment Questionnaire-Disability Index
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
ICF	Informed consent form
ICTP	I collagen telopeptide
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IGRA	Interferon gamma release assay
IMP	Investigational medicinal product

Abbreviation	Term
IRB	Institutional Review Board
IXRS	Interactive Phone/Web Response System
JAK	Janus kinase
LDA	Low disease activity
MCR	Melanocortin receptor
mITT	Modified intent to treat
MM	Medical monitor
MTX	Methotrexate
OPG	Osteoprotegerin
PINP	N-terminal propeptide of Type I collagen
QD	Per day, daily
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear kappa β ligand
SAE	Serious adverse event
SC	Subcutaneous
TB	Tuberculosis
TNF- α	Tumor Necrosis Factor-alpha
TEAE	Treatment-emergent adverse event
U	Unit(s)
US	United States of America
ULN	Upper limit of normal
VAS	Visual Analog Scale
WPAI	Work Productivity and Activity Impairment Questionnaire

6 SYNOPSIS

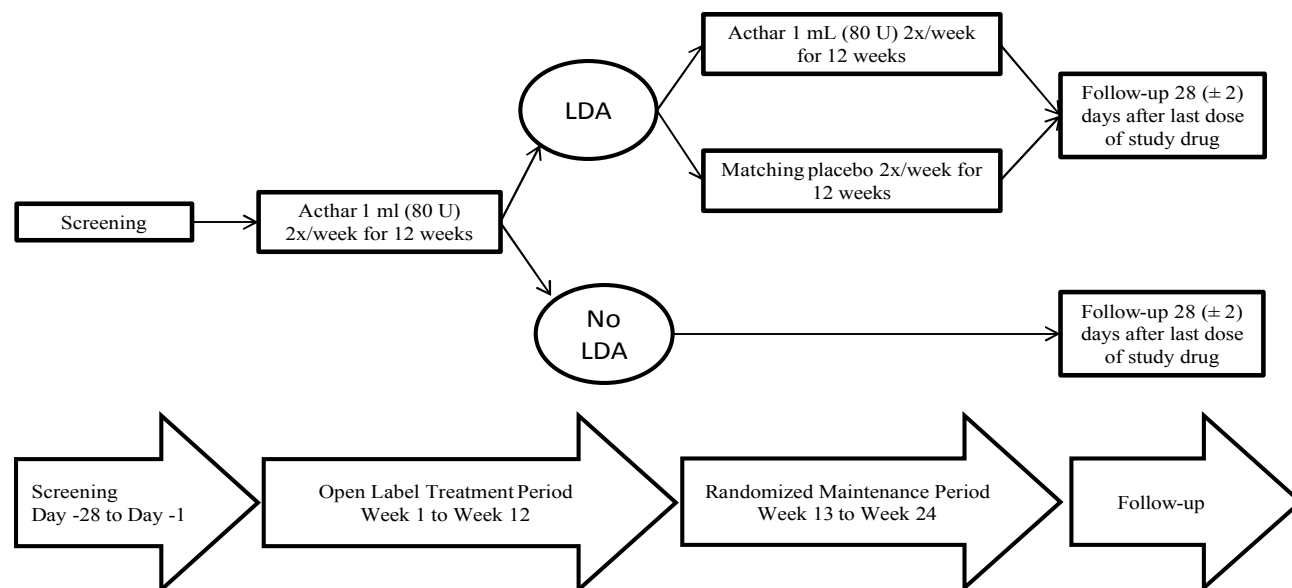
Study Title: A Multicenter, 2 Part Study to Assess the Efficacy and Safety of Acthar [®] Gel in Subjects With Rheumatoid Arthritis With Persistently Active Disease	
Protocol Number: MNK14294063	Type: Phase 4 (US)/Phase 2 (all other countries)
Condition/Disease:	Rheumatoid Arthritis
Approximate Number of Subjects: 232	Approximate Duration of Subject Participation: 32 weeks
Approximate Number of Study Centers: 100 globally	Approximate Duration of Study: 4.5 years
Design: This is a 2 part multicenter study to examine the effect of Acthar in adult subjects with rheumatoid arthritis (RA) with persistently active disease. In Part 1 (Open Label Period), following a screening period of up to 28 days, all subjects will receive open label treatment with 1 mL (80 Units [U]) of Acthar [®] Gel (hereafter referred to as Acthar) subcutaneously (SC) 2 times per week (2x/week) for 12 weeks. After 12 weeks of treatment with Acthar, subjects will be evaluated for treatment response using the Disease Activity Score in 28 Joints - Erythrocyte Sedimentation Rate (DAS28-ESR). Subjects who have achieved low disease activity (LDA), defined as DAS28-ESR < 3.2, will enter a double-blind randomized maintenance period (Part 2) and be randomized in a 1:1 ratio to receive either Acthar 1 mL (80 U) SC or matching placebo 1 mL SC 2x/week for an additional 12 weeks. Subjects who do not achieve LDA at Week 12 will be discontinued from further study participation. All subjects will have a follow-up visit 28 (± 2) days after the last dose of study drug, regardless of treatment group.	
Objectives: Primary Objective <ul style="list-style-type: none">To assess the efficacy of Acthar given as a 1 mL (80 U) dose 2x/week for 12 weeks as determined by DAS28-ESR in subjects with RA with persistently active disease. Secondary Objectives <ul style="list-style-type: none">To assess the safety and tolerability of Acthar in subjects with RA with persistently active disease.To assess the efficacy of Acthar in maintaining LDA in subjects with RA with persistently active disease who have achieved LDA after 12 weeks of treatment. Exploratory Objectives <ul style="list-style-type: none">	
Entry Criteria: Male or nonpregnant, nonlactating female subjects 18 years of age or older meeting the definition of RA in accordance with the 2010 Rheumatoid Arthritis Classification Criteria (American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] Collaborative Initiative. Subjects must have active disease defined as a score of > 3.2 on DAS28-ESR at screening and baseline. Subjects must have been on a corticosteroid for at least 12 weeks prior to screening and on a stable dose of 5 to 10 mg of prednisone (or prednisone equivalent) for at least 4 weeks prior to screening. In addition to prednisone subjects must be on a stable dose of ≤ 20 mg per week of methotrexate (MTX) and a stable dose of 1 biologic or nonbiologic disease modifying antirheumatic drug (DMARD), or be on a stable dose of 1 biologic DMARD for at least 12 weeks prior to screening. Subjects with current rheumatic disease or inflammatory joint disease other than RA will be excluded. Subjects with any history of use of adrenocorticotrophic hormone (ACTH) for the treatment of RA, and subjects who have taken B-cell mediated therapies in the 24 weeks prior to screening will be excluded. Subjects must be negative for hepatitis B, hepatitis C, and tuberculosis. Subjects may not have any other	

Study Title: A Multicenter, 2 Part Study to Assess the Efficacy and Safety of Acthar Gel in Subjects With Rheumatoid Arthritis With Persistently Active Disease	
Protocol Number: MNK14294063	Type: Phase 4 (US)/Phase 2 (all other countries)
Condition/Disease:	Rheumatoid Arthritis
contraindication as per the United States (US) Prescribing Information for Acthar. Subjects cannot have any history of Type 1 or Type 2 diabetes, or have any clinically significant infection.	
Concomitant Medications/Nondrug Therapies: Subjects must remain on their current stable doses of DMARDs and corticosteroid throughout the study. Intraarticular corticosteroids; live or live-attenuated vaccines; enteral or parenteral immunosuppressive medications including, but not limited to azathioprine, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, rituximab (or other B-cell inhibitors); and any investigational drug, device, or procedure administered as part of a research study are prohibited during this study. Opioid use is allowed during the study but prohibited in the 24 hours prior to each study visit. All medications (including vaccinations) and nondrug therapies (eg, blood transfusions, oxygen supplementation) received by subjects from the Screening Visit through the Follow-up Visit will be recorded.	
Investigational Medicinal Product and Treatment Administration: Acthar contains a highly purified porcine ACTH analogue currently approved by the Food and Drug Administration (FDA) in multiple indications. Acthar and its matching placebo will be supplied by the sponsor and administered SC as follows in this study: <i>Part 1 (Open Label Period):</i> Acthar 1 mL (80 U) administered 2x/week for 12 weeks. <i>Part 2 (Randomized Maintenance Period):</i> Acthar 1 mL (80 U) administered 2x/week for 12 weeks, OR Placebo 1 mL administered 2x/week for 12 weeks.	
Efficacy Evaluations: The following efficacy assessments will be evaluated: DAS28-ESR, ACR core criteria for defining RA improvement, Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F).	
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Safety Evaluations: The following safety assessments will be evaluated: adverse events, physical examinations, clinical laboratory tests, pregnancy testing, and vital signs.	
Statistical Methods: Analysis Populations <ul style="list-style-type: none"> The Modified Intent to Treat (mITT) Population will include all enrolled subjects who receive 1 or more doses of study drug and who contribute any efficacy data to the study. 	

7 STUDY SCHEMATIC AND SCHEDULE OF EVENTS

7.1 Study Schematic

Figure 7-1: Study Overview



7.2 Schedule of Study Events

Table 7-1: Schedule of Study Events

Assessment/Procedure	Screening (Day -28 to Day -1)	Part 1 Open Label Period				Part 2 Randomized Maintenance Period			Unscheduled Visit ^a	Follow-up 28 (± 2) Days After Final Dose of Study Drug
		0/Base- line	4 (± 5 days)	8 (± 5 days)	12 (± 2 days)	16 (± 5 days)	20 (± 5 days)	24 (± 5 days) /Early Termination		
Informed Consent	X									
Inclusion/Exclusion Criteria Review	X	X								
Medical/Surgical History	X									
Current Medical Condition Review		X	X	X	X	X	X	X	X	X
Demographics	X									
Complete Physical Examination	X							X		
Limited Physical Examination		X	X	X	X	X	X		X	X
28 Joint Count	X	X	X	X	X	X	X	X		
Height and Weight ^b	X	X	X	X	X	X	X	X	X	X
Vital Signs ^c	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests ^d	X	X	X	X	X	X	X	X		X
HbA1c	X				X			X		
ESR and CRP	X	X	X	X	X	X	X	X		
Serum Pregnancy Test	X							X		
Urine Pregnancy Test		X	X	X	X	X	X			X
Hepatitis Serology	X									
IGRA for TB	X									
		X			X			X		
and Urine Creatinine Samples		X			X			X		
General Health VAS	X	X	X	X	X	X	X	X		
Patient Assessment of Pain (VAS)		X	X	X	X	X	X	X		
Patient Global Assessment of Disease Activity (VAS)		X	X	X	X	X	X	X		
Physician Global Assessment of Disease Activity (VAS)		X	X	X	X	X	X	X		

Assessment/Procedure	Screening (Day-28 to Day -1)	<u>Part 1</u> Open Label Period				<u>Part 2</u> Randomized Maintenance Period			Unscheduled Visit ^a	Follow-up 28 (± 2) Days After Final Dose of Study Drug
		0/Base- line	4 (± 5 days)	8 (± 5 days)	12 (± 2 days)	16 (± 5 days)	20 (± 5 days)	24 (± 5 days) /Early Termination		
HAQ-DI		X	X	X	X	X	X	X		
FACIT-F		X	X	X	X	X	X	X		
WPAI		X	X	X	X	X	X	X		
Hospital Admissions, ED and Nonstudy Outpatient Visits			X	X	X	X	X	X		
IXRS Contact	X	X	X	X	X	X	X			
Discontinue Subjects Who Have Not Achieved LDA, Randomize Subjects With LDA					X					
Study Drug and Diary Training		X								
Study Drug Accountability			X	X	X	X	X	X		
Dispense Study Drug		X	X	X	X	X	X			
Administer First Dose ^e		X								
Diary Review			X	X	X	X	X	X		
Adverse Events and Concomitant Treatments		X								

^aChecked assessments are required at any unscheduled visit. Additional assessments may be done at the investigator's discretion.

^bHeight is required at screening only.

^c Blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure will be measured in triplicate at the Screening and Baseline Visits

^dChemistry, hematology, urinalysis.

^eThe first dose will be administered clinic and the subject will be observed for at least 1 hour after dosing.

8 ETHICAL CONSIDERATIONS

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

8.1 Institutional Review Board/Independent Ethics Committee

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

8.2 Ethical Conduct of the Study

The study will be conducted in full compliance with applicable international, national and local regulatory requirements; United States (US) Food and Drug Administration (FDA) regulations including 21 CFR 314.106 and 312.120, (where applicable); and ICH guidelines for good clinical practice (GCP) and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

8.3 Subject Information and Consent

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

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

Subjects must assent understanding of and voluntarily sign these forms in compliance with ICH GCP guidelines and 21 CFR, Parts 50 and 312 (where applicable), before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time. Subjects unable to give written informed consent must orally assent to the procedures, and written informed consent must be obtained from a legally authorized representative in accordance with national and local laws, as applicable.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined in by national and local regulations including confidentiality. All versions of each subject's signed ICF must be kept on file by the site for possible inspection by regulatory authorities and/or authorized Mallinckrodt personnel. Signed copies of the ICF and the HIPAA authorization form, if applicable, will be given to the subject.

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

9 BACKGROUND INFORMATION AND RATIONALE

9.1 Overview

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic inflammation, articular erosions, and periarticular bone loss. Proinflammatory cytokines are the primary mediators of synovial inflammation and ensuing bone and cartilage destruction in multiple joints (Arend, 2001; Harris, 1990). Once considered simply a disease involving the joints, it is now recognized as a process involving multiple organ systems (Lévy et al, 2008; Wolfe et al, 1994; Mutru et al, 1976; Isomäki et al, 1975).

Rheumatoid arthritis has a significant negative impact on the ability to function in all settings, with increasing decline in functioning related to disease progression (Pincus et al, 1984), and is associated with increased morbidity and mortality (Wolfe et al, 1994; Wolfe et al, 2003). In developed countries, the prevalence of RA has been estimated at 0.5% to 1.0% of the adult population, with an annual incidence rate between 5 to 50 new cases per 100,000 (Scott et al, 2010).

The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) updated the classification of RA in order to identify patients earlier in the disease so that disease modifying therapy could be initiated to slow disease progression (Aletaha et al, 2010). The goal of treatment is a treat-to-target strategy, focused on achieving remission, defined

as the absence of inflammatory disease, with achievement of low disease activity (LDA) an acceptable alternative therapeutic goal ([Singh et al, 2016](#); [Smolen et al, 2010](#); [Smolen et al, 2013](#)).

The cornerstone in the management of RA is the use of disease modifying antirheumatic drugs (DMARDs) which have significantly reduced or even reversed disease progression, and improved symptoms as well as quality of life. Disease modifying antirheumatic drugs are often divided into nonbiologic and biologic agents ([Singh et al, 2016](#); [Smolen et al, 2010](#); [Smolen et al, 2013](#)). Nonbiologic agents are drugs that have been synthesized, and include methotrexate (MTX), sulfasalazine, hydrochloroquine, leflunomide and most recently tofacitinib ([Smolen et al, 2010](#); [Smolen et al, 2013](#)). With the exception of tofacitinib, the nonbiologic DMARDs are nonspecific drugs that disrupt the immune process; in contrast, tofacitinib is targeted at a specific immune pathway, namely the janus kinase (JAK) receptor ([Kytтарis, 2012](#)). Biologic agents are derived from living matter and target very specific genes or proteins ([Morrow and Felcone, 2004](#)). In RA, a deeper understanding of the pathophysiology of RA has led to the development of monoclonal antibodies and receptor decoys ([Kytтарis, 2012](#)). Tumor necrosis factor-alpha (TNF- α) is an inflammatory cytokine involved in RA. Blockade of TNF- α reduces production of numerous proinflammatory cytokines ([Feldmann and Maini, 2003](#)) and led to the development of a number monoclonal antibody anti-TNF agents, including etanercept, adalimumab, infliximab, certolizumab and golimumab ([Singh et al, 2016](#); [Arend, 2002](#)). Other biologic targets include proinflammatory cytokines (interleukin-1 and interleukin-6 [anakinra and tocilizumab, respectively]), the costimulatory signal for T-cell activation (abatacept), and the CD20 receptor on B-cells (rituximab) ([Arend, 2002](#); [Nishimoto et al, 2008](#); [Buch et al, 2009](#); [Taylor and Lindorfer, 2007](#)).

Methotrexate is considered to be the first-line DMARD of choice. When there is persistent disease activity the next step is use of MTX in combination with other nonbiologics such as leflunomide, or initiation of a biologic DMARD, with or without concomitant MTX, and consideration of low dose corticosteroids ([Rath and Rubbert, 2010](#); [Singh et al, 2016](#); [Smolen et al, 2010](#); [Smolen et al, 2013](#)). Despite significant advances in the treatment armamentarium for RA, 28% to 58% patients don't achieve even a minimal 20% improvement in ACR (ACR20) criteria ([Redlich et al, 2003](#)), and those that do achieve improvement can have a waning of treatment response ([Finckh et al, 2006](#)), demonstrating continued unmet need in the management of RA.

Corticosteroids are powerful immune suppressants, and have a significant impact on the immune system through multiple mechanisms including inhibition of proinflammatory cytokine production, inhibition of macrophage activation, and disruption of T-cell activity ([Townsend and Saag, 2004](#)). Dysfunction of the hypothalamic-pituitary-adrenal axis may have a role in the onset and continued presence of chronic inflammation in RA as evidenced by the observation that patients with RA have lower cortisol levels compared to healthy controls ([Imrich and Rovenský, 2010](#)). Corticosteroids have been shown to have benefit in RA, with reduction in inflammation as well as reduction in

disease progression (Graudal and Jürgens, 2010; Bijlsma et al, 2003; Kirwin, 1995), although the results are sometimes contradictory, especially in early RA (Capell et al, 2004). The use of corticosteroids is typically limited by adverse events (AE), including impaired glucose metabolism and frank diabetes, hypertension, osteoporosis, osteonecrosis, peptic ulcer disease, mood and behavioral effects, weight gain, increased risk of serious infections (Bijlsma et al, 2003), which has promulgated recommendations for limitations on dose and use of these agents in the management of RA (Bijlsma et al, 2003; Singh et al, 2016; Smolen et al, 2013). Additionally, up to 30% of patients are thought to be resistant to corticosteroids (Chikanza and Kozaci, 2004; Silverman and Sternberg, 2008), which further limits the potential benefit of this drug class.

As described in the Prescribing Information, Acthar Gel (repository corticotrophin injection, hereafter referred to as Acthar) contains a highly purified porcine adrenocorticotrophic hormone (ACTH) analogue (Mallinckrodt ARD, 2015). ACTH is a member of the family of structurally related peptides known as melanocortin peptides. Melanocortin peptides, which in addition to ACTH include α -, β -, and γ -melanocyte stimulating hormones, are derived from the natural protein pro-opiomelanocortin and exert their physiologic effects by binding to cell surface G-protein coupled receptors known as melanocortin receptors (MCR), activation of the JAK-signal transducer and inhibition of nuclear factor- κ B (Buggy, 1998; Mountjoy et al, 1992). Five subtypes of MCRs have been identified to date (MC1R-MC5R), each with different tissue distributions, binding affinity characteristics, and physiological roles (Getting, 2006). ACTH binds to all 5 subtypes of MCR (Schiöth et al, 1995) and recent experiments demonstrate that Acthar also has agonist activity for all 5 MCRs (Mallinckrodt, Unpublished Data).

From a mechanistic standpoint, Acthar has several potential pathways that may play a role in the effects in RA. ACTH has steroidogenic properties, which are exclusively mediated by MC2R (Cooray and Clark, 2011); as previously noted, corticosteroids are potent immunosuppressants (Bijlsma et al, 2003; Graudal and Jürgens, 2010; Kirwin, 1995; Townsend and Saag, 2004). However, there are other potential nonsteroidogenic targets that could impact immune regulation and inflammation. Activation of MC1R affects the Nuclear Factor- κ B pathway leading to down regulation of proinflammatory cytokines and chemokines (Ahmed et al, 2013). MC1R, MC3R and MC5R are expressed by multiple cells in the immune system (Ahmed et al, 2013; Cooray and Clark, 2011; Starowicz and Przewlocka, 2003), and MC1R and MC5R are present in the human articular chondrocytes and rheumatoid synovial fibroblasts (Ahmed et al, 2013). MC2R and MC4R are also expressed on human articular chondrocytes. MCRs are also expressed on osteoclasts and osteoblasts (Patel et al, 2010).

An evaluation of the effect of Acthar and etanercept in a collagen-induced arthritis (CIA) animal model administered alone and in combination was conducted. Overall efficacy of

corticotropin and etanercept used alone in established CIA were comparable, however corticotropin in combination with etanercept synergistically attenuated anti-collagen antibodies and both clinical and histopathologic measures of CIA vs etanercept alone (Decker et al, 2015). Further, the combination of Acthar and etanercept resulted in significant attenuation of CIA-induced reductions in average bone density, an effect that was not seen in either treatment when administered alone (Decker et al, 2015).

Clinical effects of ACTH in RA have been reported since the 1950's (Clark et al, 1953; Hench et al, 1950; Levin et al, 1953; Mason, 1953; Savage et al, 1959; Solem and Römcke, 1955). Preliminary results of an open label evaluation of Acthar in the treatment of subjects with RA who had not adequately responded to current biologic DMARD therapy and who had a history of inadequate response to at least 2 other biologic agents with different modes of action suggested positive response in Disease Activity Score in 28 Joints erythrocyte sedimentation rate (DAS28-ESR) when subjects were dosed for 12 weeks with Acthar 80 units (U) every 72 hours (Gillis et al, 2015). Preliminary data from another study evaluating the effect of Acthar (dosed as 80 U weekly or 80 U twice weekly) in combination with MTX in newly diagnosed RA subjects reported interim results in 10 subjects suggesting improvement in the Clinical Disease Activity Index (CDAI) for the majority of subjects, with half of the subjects achieving at least LDA as well as regression of osteitis, synovitis, and erosions in some patients (Gaylis et al, 2015). Additionally, a retrospective case series evaluated the adjunctive use of Acthar in 5 patients with RA that was refractory to 2 to 5 DMARDs, described improvement in inflammatory biomarkers and reported symptoms (Brown, 2015).

The current study seeks [REDACTED] the efficacy of Acthar in the management of RA in patients who have persistent disease activity, with secondary evaluation of potential benefit after LDA is achieved.

9.2 Product Description

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] Acthar is currently approved as adjunctive therapy (to tide the patient over in acute episode or exacerbation) in: Psoriatic arthritis, including juvenile RA (selected cases may require low dose maintenance therapy), ankylosing spondylitis (Mallinckrodt ARD, 2015).

Placebo is a sterile preparation of 16% gelatin for intramuscular or SC injection.

Placebo formulation is identical to Acthar except that it contains no active medication

9.3 Dosage and Administration

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

Following a screening period of up to 28 days, subjects with RA with persistently active disease will receive open label treatment with 1 mL (80 U) of Acthar SC 2x/week for 12 weeks in Part 1 (Open Label Period) of the study.

After 12 weeks of treatment with Acthar, subjects will be evaluated for treatment response using the DAS28 - ESR. Subjects who have achieved LDA, defined as DAS28-ESR < 3.2, will enter a double-blind randomized maintenance period (Part 2, Randomized Maintenance Period) and receive either Acthar 1 mL (80 U) SC or matching placebo SC 2x/week for an additional 12 weeks. Subjects who do not achieve LDA will be discontinued from study participation.

9.4 Rationale

The doses for this study were chosen based on safety and informed by prescribing patterns for RA.

Current small open label studies evaluating treatment refractory RA and newly diagnosed RA have a dosing strategy that ranges from Acthar 80 U weekly to 80 U every 72 hours ([Gillis et al, 2015](#); [Gaylis et al, 2015](#)).

The prescribing information for Acthar recommends the use of 40 to 80 U administered intramuscularly or SC every 24 to 72 hours in adults and children over 2 years of age; the specific dose is individualized according to the medical condition ([Mallinckrodt ARD, 2015](#)). The recommended dose is daily intramuscular or SC doses of 80 to 120 U for 2 to 3 weeks for acute exacerbations. Recently published data suggests that based on serum cortisol-equivalent exposure (assuming linearity), 80 U of Acthar equates to 30 mg of intravenous methylprednisolone ([Lal et al, 2015](#)).

9.5 Risk/Benefit

The most common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation of blood pressure, behavioral and mood changes, and increased appetite and weight gain. Acthar is also associated with increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infections ([Mallinckrodt ARD, 2015](#)).

Rheumatoid arthritis is a disorder characterized by progressive bone and cartilage damage, with impact on other organ systems ([Arend, 2001](#); [Lévy et al, 2008](#); [Harris, 1990](#); [Wolfe et al, 1994](#)), and is associated with substantial morbidity and mortality ([Wolfe et al, 1994](#); [Wolfe et al, 2003](#)). Treatment guidelines for RA state that the treatment target is complete remission or LDA ([Singh et al, 2016](#); [Smolen et al, 2013](#)). Current therapies are inefficacious in up to 58% patients ([Redlich et al, 2003](#)). [REDACTED]

10 OBJECTIVES

10.1 Primary Objective

The primary objective of this study is:

- To assess the efficacy of Acthar given as a 1 mL (80 U) dose 2x/week for 12 weeks as determined by DAS28-ESR in subjects with RA with persistently active disease.

10.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the safety and tolerability of Acthar in subjects with RA with persistently active disease.
- To assess the efficacy of Acthar in maintaining LDA in subjects with RA with persistently active disease who have achieved LDA after 12 weeks of treatment.

10.3 Exploratory Objectives

An exploratory objectives of this study are:

- [REDACTED]
- [REDACTED]

11 STUDY DESIGN

11.1 Description

This is a multicenter, multiple dose study to examine the effect of Acthar in adult subjects with RA with persistently active disease. Approximately 232 subjects will be enrolled.

During the first part of the study (Part 1-Open Label Period) all enrolled subjects will be treated with Acthar 1 mL (80 U) SC 2x/week for 12 weeks to assess the proportion of subjects who achieve LDA.

After 12 weeks of Acthar treatment, subjects who have achieved LDA (defined as DAS28-ESR < 3.2) will enter a double-blind randomized maintenance period (Part 2-Randomized Maintenance Period) and will be randomized in a 1:1 ratio into 2 groups:

- Group 1: Acthar 1 mL (80 U) SC 2x/week for an additional 12 weeks.
- Group 2: Placebo 1 mL SC 2x/week for an additional 12 weeks.

Subjects who do not achieve LDA at Week 12 will be discontinued from the study.

Subjects who experience a flare in disease activity will be discontinued from the study. Flare or worsening of disease activity is defined as:

- **Weeks 0 to 11:** DAS28-ESR ≥ 3.2 and increase of > 0.6 from the Week 0 assessment sustained over 2 consecutive study visits; **or** DAS28-ESR ≥ 3.2 and increased of > 1 from the Week 0 assessment at a single visit.
- **Weeks 13 to 23:** DAS28-ESR < 3.2 and increase of 1.2 from the Week 12 assessment; **or** DAS28-ESR ≥ 3.2 and increased of > 0.6 from the Week 12 assessment sustained over 2 consecutive study visits; **or** DAS28-ESR ≥ 3.2 and increase of > 1 from the Week 12 assessment at a single visit ([van der Maas, 2013](#)).

All subjects will have a Follow-up Visit 28 (± 2) days after their last dose of study drug.

11.2 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, and active treatment period of 24 weeks, and a follow-up visit of 28 (± 2) days after last dose of study drug.

11.3 Approximate Duration of Study

The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the sites to identify and enroll eligible subjects. The entire study is expected to require approximately 4.5 years to complete.

11.4 Approximate Number of Subjects

It is expected that approximately 360 subjects will be screened and 232 subjects will be enrolled at approximately 100 sites globally.

12 SELECTION OF SUBJECTS

12.1 Inclusion Criteria

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

1. Subjects must be adequately informed and understand the nature and risks of the study and must be able to provide a signature and date on the ICF.
2. Subjects must be ≥ 18 years of age at Screening Visit and can be male or female.
3. Female subjects must be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit), or if of childbearing potential must be nonpregnant, nonlactating and agree to use effective contraception with a male partner throughout study participation (through the Follow-up Visit). Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), and abstinence.
4. Male subjects with a female partner of childbearing potential must have been surgically sterilized (vasectomy) or agree to use a double barrier method 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 meet the criteria for RA as defined by the 2010 ACR/EULAR classification at the Screening Visit ([Aletaha et al, 2010](#)).
6. Subjects must have persistently active RA defined as a DAS28-ESR > 3.2 despite treatment with required biologic/nonbiologic DMARD(s) and a corticosteroid as defined below at the Screening and Baseline Visits.

7. Subjects must have been on a corticosteroid in the 12 weeks prior to the Screening Visit and on a stable dose of 5 mg to 10 mg of prednisone (or prednisone equivalent) for 4 weeks prior to the Screening Visit.
8. Subjects must have been on 1 of the following:
 - MTX \leq 20 mg per week and 1 additional allowed biologic or nonbiologic DMARD for at least 12 weeks prior to the Screening Visit and must remain on those doses throughout the study, OR
 - One allowed biologic DMARD for at least 12 weeks prior to the Screening Visit and must remain on that dose throughout the study.

Table 12-1 Allowed DMARDs

Allowed Nonbiologic DMARDs	Allowed Biologic DMARDs
Sulfasalazine 2 to 3 g per day (QD)	Infliximab 3 to 10 mg/kg every 4 to 8 weeks
Leflunomide 20 mg QD	Adalimumab 40 mg every other week
Hydroxychloroquine (HDQ) up to 200 mg twice a day	Entanercept 50 mg per week
Tofacitinib 10 mg QD	Certolizumab 200 mg per week to 400 mg every 4 weeks (inclusive)
	Golimumab 50 mg per month
	Abatacept 125 mg/mL SC per week or 500 to 1,000 mg intravenously every 4 weeks

9. Subjects taking non-steroidal anti-inflammatory drugs must be on a stable dose for 4 weeks prior to the Screening Visit, and remain on a stable dose throughout study participation.
10. Subjects must have a mean systolic blood pressure \leq 140 mm Hg and a diastolic blood pressure of \leq 90 mm Hg determined by the average of 3 seated readings taken at least 5 minutes apart at the Screening and Baseline Visits.
11. Subjects must be able to communicate effectively with study personnel.
12. Subjects must be able and willing to follow all protocol requirements and study restrictions.
13. Subjects must be able and willing to return for all study visits.

12.2 Exclusion Criteria

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

1. Subject is from a vulnerable population, as defined by the US CFR Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the clinical research organization, or of the IRB/IEC.
2. Subject has taken any investigational treatment for RA or any biologic investigational agent in the 24 weeks prior to the first dose of study drug or any nonbiologic investigational agent within 6 weeks prior to the first dose of study drug.
3. Subject is unwilling to receive, or is intolerant of, SC injections.
4. Subject has any history of use of ACTH preparations for treatment of RA (including but not limited to Acthar and Synacthen[®]).
5. Subject has a history of sensitivity to ACTH preparations (including but not limited to Acthar and Synacthen).
6. Subject has a history of sensitivity to porcine protein products.
7. Subject has any current rheumatic autoimmune disease other than RA.
8. Subject has current inflammatory joint disease other than RA.
9. Subject has used B-cell mediated therapies (including, but not limited to rituximab) in the 24 weeks prior to the Screening Visit or will use such treatments during the study.
10. Subject has used intraarticular corticosteroids in the 14 days prior to the Screening Visit.
11. Subject has any known contraindication(s) to Acthar ([Mallinckrodt ARD, 2015](#)) including, but not limited to:
 - Any known history of scleroderma, osteoporosis, or ocular herpes simplex.
 - Any current uncontrolled hypertension, primary adrenocortical insufficiency, or adrenal cortical hyperfunction.
 - Any current congestive heart failure (defined as New York Heart Association Functional Class III to IV).
 - Peptic ulcer (within 24 weeks prior to the Screening Visit).
 - Recent major surgery (within 24 weeks prior to the Screening Visit)

12. Subject has a history of chronic active hepatitis including active or chronic hepatitis B, or acute or chronic hepatitis C.
13. Subject has a history of tuberculosis (TB) infection, any signs/symptoms of active TB, or any close contact with an individual with an active TB infection.
14. Subject has had a clinically significant infection requiring intravenous administration of antibiotics and hospitalization in the 4 weeks prior to the Screening Visit.
15. Subject has known immune compromised status, including but not limited to, individuals who have undergone organ transplantation or who are known to be positive for the human immunodeficiency virus.
16. Subject has Type 1 or Type 2 diabetes mellitus (prior diagnosis of gestational diabetes mellitus is not exclusionary) or is currently taking hypoglycemic medications.
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 \leq 8.0 g/dL.
 - Platelets \leq 50,000 cells/ μ L.
 - Absolute neutrophil count (ANC) \leq 1000 cells/ μ L.
 - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin $>$ 2 times upper limit of normal (ULN).
 - Glycosylated hemoglobin (HbA1c) $>$ 6.5%.
 - Positive Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb).
 - Positive Hepatitis C virus antibody (HCV) and HCV polymerase chain reaction (PCR) \geq 25 IU/mL (HCV PCR will be automatically analyzed if HCV is positive).
 - Positive or indeterminate interferon gamma release assay (IGRA).

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 ARD, 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.

12.3 Screen Failure

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

Subjects who do not meet all of the eligibility criteria at the Screening or Baseline Visits will be deemed a screen failure and the reason for the screen failure will be documented. A subject who is a screen failure at the Screening or Baseline Visit may be rescreened. The subject must repeat all screening procedures. The period from the start of rescreening related procedures to the first dose of study drug must not exceed 28 days. Subjects may be rescreened only once.

13 PRIOR AND CONCOMITANT MEDICATION/NONDRUG THERAPIES

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 30 days prior to the first dose of study drug) and concomitant medications and nondrug therapies (eg, blood transfusions, oxygen supplementation) received will be recorded.

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

In addition, opioid use for pain management is allowed during the study, however, it cannot be used in the 48 hours prior to each study visit. Non-steroidal anti-inflammatory drugs for pain management are allowed during the study, however, subjects must have been on the medication for at least 4 weeks prior to the Screening Visit and remain on a stable throughout the study.

13.1 Prohibited Concomitant Medications/Nondrug Therapies

The following medications/ nondrug therapies will not be permitted during the study:

- Intraarticular corticosteroids.

- Live or live-attenuated vaccines.
- Enteral or parenteral immunosuppressive medications including, but not limited to azathioprine, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, rituximab (or other B-cell inhibitors).
- 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.

14 PROCEDURES/ASSESSMENTS

The schedule of study procedures is summarized in the Schedule of Study Events ([Table 7-1](#)).

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

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

The following procedures will be performed at the Screening Visit:

- Informed consent.
- Inclusion/exclusion criteria.
- General Health Visual Analog Scale (VAS).
- Medical and surgical history.
- Demographics.
- Complete physical examination.
- 28 Joint Count.
- Height and Weight.
- Vital signs.
- Clinical laboratory tests.
- HbA1c.
- ESR and C - reactive protein (CRP).
- Serum pregnancy test.
- Hepatitis serology.

- IGRA test for TB.
- Contact the Interactive Phone/Web Response System (IXRS) and confirm disease activity.
- Adverse events and concomitant medications.

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

14.2 Baseline Visit (Week 0) and First Dose Procedures/Assessments

Predose evaluations will occur prior to the first dose of study drug.

The investigator or designee will complete the following procedures predose:

- Inclusion/exclusion criteria review; subject must meet all eligibility criteria at screening and baseline.
- Efficacy Questionnaires: General Health (VAS), Patient Assessment of Pain (VAS), Patient Global Assessment of Disease Activity (VAS), Patient Assessment of Physical Function assessed using the Health Assessment Questionnaire- Disability Index [HAQ-DI]), Functional Assessment of Chronic Illness Therapy- Fatigue Scale (FACIT-F) and Physician Global Assessment of Disease Activity (VAS).
- Work Productivity and Activities Impairment (WPAI).
- Current medical condition review.
- Limited physical examination.
- 28 Joint Count.
- Weight.
- Vital signs.
- Clinical laboratory tests.
- ESR and CRP.
- Urine pregnancy test.
- Vectra Disease Activity (Vectra[®] DA) sample.

- Serum and urine samples for [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] and urine creatinine.
- Subject diary training.
- Contact IXRS and confirm disease activity eligibility.
- Dispense study drug kits.
- Study drug administration under supervision of study staff and observation for at least 1 hour thereafter. Administration of all other doses will be done at home by the subject/caregiver.
- Adverse events and concomitant medications.

14.3 Week 4 (\pm 5 days) and 8 (\pm 5 days) Procedures/Assessments

- Efficacy Questionnaires.
- WPAI.
- Current medical condition review.
- Limited physical examination.
- 28 Joint Count.
- Weight.
- Vital signs.
- Clinical laboratory tests.
- ESR and CRP.
- Urine pregnancy test.
- Hospital admissions, emergency department (ED) visits, and nonstudy outpatient visits.
- Subject diary review.
- Study drug accountability.
- Contact IXRS and confirm disease activity eligibility.
- Dispense study drug kits.

- Adverse events and concomitant medications.

14.4 Week 12 (\pm 2 days) Procedures/Assessments

- Efficacy Questionnaires.
- WPAI.
- Current medical condition review.
- Limited physical examination.
- 28 Joint Count.
- Weight.
- Vital signs.
- Clinical laboratory tests.
- HbA1c.
- ESR and CRP.
- [REDACTED].
- [REDACTED]/urine creatinine samples.
- Urine pregnancy test.
- Hospital admissions, ED visits, and nonstudy outpatient visits.
- Subject diary review.
- Study drug accountability.
- Contact IXRS and confirm disease activity eligibility.
- Dispense study drug kits (if appropriate).
- Adverse events and concomitant medications.

14.5 Week 16 (\pm 5 days) and 20 (\pm 5 days) Procedures/Assessments

- Efficacy Questionnaires.
- WPAI.
- Current medical condition review.
- Limited physical examination.
- 28 Joint Count.
- Weight.

- Vital signs.
- Clinical laboratory tests.
- ESR and CRP.
- Urine pregnancy test.
- Hospital admissions, ED visits, and nonstudy outpatient visits.
- Subject diary review.
- Study drug accountability.
- Contact IXRS and confirm disease activity eligibility.
- Dispense study drug kits.
- Adverse events and concomitant medications.

14.6 Week 24 (\pm 5 days)/Early Termination Procedures/Assessments

- Efficacy Questionnaires.
- WPAI.
- Current medical condition review.
- Complete physical examination.
- 28 Joint Count.
- Weight.
- Vital signs.
- Clinical laboratory tests.
- HbA1c.
- ESR and CRP.
- [REDACTED]
- [REDACTED]/urine creatinine samples.
- Serum pregnancy test.
- Hospital admissions, ED visits, and nonstudy outpatient visits.
- Subject diary review.
- Study drug accountability.

- Adverse events and concomitant medications.

14.7 Follow-up Visit Procedures/Assessments

The following procedures will be completed at the follow-up visit 28 (\pm 2) 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.

14.8 Unscheduled Visit Procedures/Assessments

Any time that an unscheduled visit is needed to assess the subject for the study (for example, for an adverse event), the following minimum evaluations must be completed:

- Current medical condition review.
- Limited physical examination.
- Weight.
- Vital signs.
- Adverse events and concomitant medications.

15 INVESTIGATIONAL MEDICINAL PRODUCT (Study Drug)

15.1 Methods of Assigning Subjects to Treatment Groups

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: [REDACTED]

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

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

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

The investigator or designee must contact IXRS to record each subject visit, to receive the study drug kit assignments, and to report any subject status changes. At visits where it is required, components of the DAS28-ESR (swollen joint count, tender joint count, ESR, General Health VAS) will be entered at into IXRS and the DAS28-ESR will be calculated.

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

15.2 Emergency Identification of Investigational Medicinal Product

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

15.3 Dosing Procedures

The following treatments will be administered:

- Weeks 0 to 12: Acthar 1 mL (80 U) SC 2x/week.
- Weeks 13 to 24: Acthar 1 mL (80 U) SC 2x/per week **OR** Placebo 1 mL SC 2x/week.

Throughout the trial, study drug cannot be taken on 2 consecutive days and cannot be taken more than 3 days apart.

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

15.3.1 Treatment Discontinuation

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

- Development of accelerated hypertension (defined as systolic blood pressure ≥ 180 *and* diastolic blood pressure ≥ 100 mm Hg) that cannot be managed by the adjustment of concomitant medications such as antihypertensive medications.
- Development of congestive heart failure that cannot be managed by the adjustment of concomitant medications such as diuretics and antihypertensive medications.
- Development of diabetic signs/symptoms (ie, HbA1c $> 6.5\%$, or fasting plasma glucose > 126 mg/dL, or classic symptoms of hyperglycemia with random plasma glucose > 200 mg/dL) that cannot be managed by the adjustment of concomitant medications such as insulin and oral hypoglycemic agents.
- Flare or worsening of disease activity, defined as:
 - **Weeks 0 to 11:** DAS28-ESR ≥ 3.2 and increase of > 0.6 from the Week 0 assessment sustained over 2 consecutive study visits; **or** DAS28-ESR ≥ 3.2 and increased of > 1 from the Week 0 assessment at a single visit.
 - **Weeks 13 to 23:** DAS28-ESR < 3.2 and increase of 1.2 from the Week 12 assessment; **or** DAS28-ESR ≥ 3.2 and increased of > 0.6 from the Week 12 assessment sustained over 2 consecutive study visits; **or** DAS28-ESR ≥ 3.2 and increase of > 1 from the Week 12 assessment at a single visit.
- Failure to achieve LDA at Week 12.

- Development of any other AE of at least moderate intensity and possibly, probably or definitely related to study drug that cannot be managed by the adjustment of concomitant medications.

15.4 Storage of Clinical Supplies

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

Study drug will be supplied in kits containing the appropriate amount of vials according to the treatment group to which the subject is assigned. Study drug will be stored under refrigeration between 2° to 8°C (36° to 46°F). Please refer to the Pharmacy Manual for complete information regarding storage and accountability of study drug.

15.5 Drug Accountability

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

15.6 Compliance Monitoring

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

16 SAFETY ASSESSMENTS AND PROCEDURES

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

16.1 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.

16.2 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.

16.3 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.

16.4 Physical Examination

A complete physical examination will be performed at the Screening Visit and the 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 will be recorded. Any change from the Screening Visit physical examination that is considered clinically significant by the investigator will be recorded as an AE.

16.5 Height and Weight

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

16.6 Vital Signs

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

The 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/Baseline Assessments

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

On Study Assessments

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

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

The clinical laboratory tests are listed in [Section 32.1](#). All clinical laboratory tests will be done at a central laboratory facility except urine pregnancy (at the site), and IGRA (local laboratory). Specific instructions for collection, processing, storage, and shipment of clinical laboratory samples will be provided in a separate laboratory manual, where appropriate.

Samples for laboratory testing at all visits may be collected under fasted or nonfasted conditions. The date and time of the sample collection must be documented on the laboratory report. Investigators must review and sign laboratory reports. The clinical significance of each

laboratory abnormality will be documented. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs, as appropriate.

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

In addition:

- All female subjects of child-bearing potential will have a serum pregnancy test at the Screening and Week 24/Early Termination Visits. Urine pregnancy tests will be done at all other visits throughout the study. Results must be available prior to dosing with protocol mandated study drug. Subjects with positive results will be ineligible for study entry (Screening Visit or Predose) or withdrawn from the study. Any female subject that becomes pregnant during the study will be immediately withdrawn and the pregnancy report as per [Section 21.6](#).

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

- HBsAg and HBcAb will be performed at the Screening Visit. Results of these tests must be negative or nonreactive for subjects to qualify for the study.
- HCV antibody testing will be performed at the Screening Visit. A positive HCV antibody 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 $\leq 6.5\%$ for subjects to qualify for the study. Additional HbA1c tests will be done at specified times during the protocol.

Out-of-Range Laboratory Values

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

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

17 EFFICACY ASSESSMENTS

Efficacy assessments will be evaluated at times specified in the Schedule of Study Events (Table 7-1) for composite indices including DAS28-ESR, ACR20/50/70, and CDAI; as well as FACIT-F and HAQ-DI.

The DAS28-ESR is a validated composite index to assess disease activity in RA (Prevoo et al, 1995; DAS28 Website, 2016). The components of DAS28-ESR include 28 Joint Count, General Health VAS, and ESR.

The ACR has developed a core set of criteria for defining improvement in RA that includes 28 Joint Count, Patient Assessment of Pain, Patient Global Assessment of Disease Activity, Physician Global Assessment of Disease Activity, Patient's Assessment of Physical Function using the HAQ-DI, and an acute phase reactant (ESR or CRP). Typical thresholds for ACR improvement are 20%, 50% and 70% (ACR20, ACR50, ACR70), with the percentages referring to the improvement in tender and swollen joints plus improvement in 3 of the 5 other components (Felson et al, 1995; Felson and LaValley, 2014; Pincus, 2005).

The CDAI is a validated composite index that was developed to simplify disease activity assessment in RA (Aletaha and Smolen, 2005) and consists of 28 Joint Count, Patient Global Assessment of Disease Activity, and Physician Global Assessment of Disease Activity.

The FACIT-F is validated to questionnaire used to assess fatigue in RA (Cella et al, 2005).

The HAQ-DI is a validated 20 item questionnaire to assess functional activity in specific tasks (Bruce and Fries, 2003).

Below are general instructions for the administration of these assessments. Specific instructions and questionnaires will be provided a separate document.

17.1 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. The 28 Joint Count will be completed by the investigator or designee. The same rater should assess the subject at every visit.

17.2 Subject Completed Efficacy Questionnaires

The General Health VAS, Patient Assessment of Pain, Patient Global Assessment of Disease Activity, Patient Assessment of Physical Function by HAQ-DI, and FACIT-F are questionnaires to be completed by subjects. When these assessments are required, they should be the first assessments done at any visit and must be completed prior to any study drug dosing. Subjects will be provided a quiet, private place to complete the assessments. Subjects will be instructed to answer all questions to the best of their ability and without help from others (including study staff, relatives, or friends). The study staff should review the questionnaires after they are completed and encourage the subjects to complete any missing information. Subjects may refrain from answering any question. Study staff will record the refusal of subjects to answer any questions in the source documents.

17.3 Physician Completed Efficacy Questionnaires

The Physician Global Assessment of Disease Activity is a questionnaire to be completed by the investigator or designee. When this assessment is required, it should be the first assessment done at any visit and must be completed prior to any study drug dosing.

17.4 ESR and CRP

Blood samples for evaluation of ESR and CRP will be collected at times specified in the Schedule of Study Events ([Table 7-1](#)). Samples for ESR will be analyzed at the site. CRP samples will be shipped to a central laboratory.

Specific instructions for collection, processing, storage, and shipment of samples for ESR and CRP will be provided in a separate laboratory manual.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

██████████

Bar Index	Relative Length (approximate)
1	95%
2	98%
3	97%
4	98%
5	100%
6	100%
7	99%
8	95%
9	98%
10	99%
11	75%

██████████

20 STATISTICAL METHODS AND PLANNED ANALYSIS

20.1 General Considerations

Unless otherwise specified, all statistical tests will be 2-sided with a significance level of 0.05. Summary statistics will be provided for all study variables with descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) for numerical (or continuous) variables. Frequency and percentages will be calculated for categorical variables. All data will be summarized for Part 1 with 1 treatment group and for Part 2 with 2 treatment groups as appropriate. Data summary and analyses will be performed with SAS 9.2 or higher.

20.2 Analysis Populations

- The Modified Intent to Treat (mITT) Population will include all enrolled subjects who receive 1 or more doses of study drug and who contribute any efficacy data to the study.
- The Per-Protocol Population will include the subset of the mITT population who complete the study as per protocol.
- The Safety Population will include all enrolled subjects who receive 1 or more doses of study drug.

20.3 Endpoints

20.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion of subjects with DAS28-ESR < 3.2 at Week 12.

20.3.2 Secondary Efficacy Endpoints

- Proportion of subjects who maintained DAS28-ESR < 3.2 from Week 12 through Week 24.
- Time to disease activity flare from Week 12 through Week 24.
- Proportion of subjects with CDAI \leq 10 at Week 12.
- Proportion of subjects who meet criteria for ACR20 at Week 12.

20.3.3 Secondary 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.

20.3.4 Exploratory Endpoints

Exploratory Efficacy Endpoints

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]

Exploratory Health Outcomes Related Endpoints

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Exploratory [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

20.3.5 Subject Characteristics

20.3.5.1 Demographics

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

20.3.5.2 Medical and Surgical History

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

20.3.5.3 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.

20.3.5.4 Subject Disposition and Exposure to Study Drug

Subject disposition will be summarized for all enrolled subjects in Part 1 and all randomized subjects in Part 2. The number of subjects who complete the study and who do not complete the study along with the reasons for discontinuation from the study will be summarized.

20.3.6 Safety Analysis

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

20.3.6.1 Adverse Events

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

20.3.6.2 Clinical Laboratory Tests

Hematology, blood chemistry, urinalysis and HbA1c results will be summarized at baseline and at each visit by treatment group. Change from baseline to each visit will also be summarized. Abnormal laboratory values will be identified and analyzed.

20.3.6.3 Vital Signs

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

20.3.6.4 Other Safety Analysis

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

20.3.7 Efficacy Analysis

All efficacy analyses will be performed on the mITT. Selected analyses will be performed on the Per-protocol Population.

For the primary endpoint, the proportion of subjects with LDA at Week 12 along with a 2-sided 95% confidence interval will be provided. The lower bound of the 95% confidence interval will be used to evaluate the response rate. The study will be deemed successful if the lower bound of the 95% confidence interval is greater than or equal to 10%.

For the secondary endpoints, the proportions of subjects who maintain LDA in Part 2 for the 2 treatment groups will be compared using a 2-sided Pearson's chi-square test at a significance level of 0.05. The time to disease activity flare in Part 2 will be analyzed using log-rank test. The proportion of subjects with CDAI ≤ 10 at Week 12 and the proportion of subjects who meet criteria for ACR 20 at Week 12 will be analyzed using the same method as that for the primary endpoint.

For the exploratory endpoints,

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20.6 Interim Analysis

The study results from Part 1 will be summarized when all subjects complete the Part 1 of the study. No other interim analyses are planned for this study.

20.7 Statistical Power and Sample Size Considerations

It is expected that 360 subjects will be screened and a total of 232 subjects will be enrolled in this study. It is estimated that 55% of subjects will either drop out before Week 12 or will not achieve LDA by Week 12. The remaining 45% of subjects will have achieved LDA after 12 weeks of treatment with Acthar and will be randomized into 2 treatment groups in Part 2 of the study. Based on results from previous studies ([Pincus, 2011](#)) and ([Ruperto et al, 2008](#)), it is estimated that 80% of the Acthar group and 50% of the placebo group will maintain LDA after the 12 additional weeks of treatment. Assuming that 52 subjects per group (104 subjects total) will complete Part 2, and based on the use of a 2-sided, 2-sample comparison of proportions at the $\alpha = 0.05$ level of significance, there will be 90% of power to detect a difference in the 2 treatment groups.

20.8 Deviations From Statistical Analysis Plan

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

21 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

21.1 Safety

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

21.2 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.

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).

21.3 Adverse Event and Serious Adverse Event Classifications

Study Drug Relatedness

The following classifications should be used when evaluating the relationship of AEs or SAEs to study treatment (Table 21-1).

Table 21–1: Adverse Event Relationships

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

Severity Assessment

For purposes of consistency, if required the investigator may use the intensity grades presented in [Table 21-2](#).

Table 21–2: Adverse Event Severity Grades

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

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

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

The term “severe” is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical importance (such as a severe headache). This is not the same as “serious,” which is based on the subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

21.4 Adverse Event and Serious Adverse Event Recording and Reporting

AEs and SAEs will be recorded from signing of the ICF through completion of the follow-up visit. The investigator is required to record the AE or SAE regardless of the severity of the event or its relationship to study treatment. Prior to the Baseline Visit/Visit 2, only AEs and SAEs related to study procedures will be recorded. The investigator must follow up on all AEs and SAEs reported to have occurred 30 days after study completion until the event has resolved or stabilized or at such time the investigator refers the subject to a nonstudy physician. The investigator will document the further follow-up information in the subject's source document.

During the period specified above, the investigator will:

- Record all AEs and SAEs from the signing of the ICF through the completion of the End of Study/Early Termination visit.
- Report all SAEs on an SAE Report Form to Global Pharmacovigilance.
- 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 21-3](#).

Table 21–3: Reporting Requirements for Adverse Events

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

Adverse Events

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

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

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

Serious Adverse Events

Initial Reporting

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

- For all SAEs, the investigator, or designee, must complete the SAE Report Form with the minimum information required by FDA and ICH and fax it to Mallinckrodt at +1 314-654-5759 or email at GlobalPV@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 based on the information in the Study Operations Manual.
- If there is any doubt about whether the information constitutes an SAE, the information is to be treated as an SAE.

The investigator(s) or designee is required to submit the any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction to the responsible IRB/IEC.

The sponsor will ensure that any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction 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 it to Mallinckrodt at +1 314-654-5759 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.

21.5 Adverse Events of Special Interest

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

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

21.6 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 globalpv@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 globalpv@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 globalpv@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 globalpv@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 globalpv@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 at globalpv@mallinckrodt.com) within 24 hours of the study site becoming aware of the follow-up information.

22 SUBJECT DISCONTINUATION OR WITHDRAWAL

22.1 Subject Withdrawal

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

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

Withdrawal by Subject

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

Adverse Event

If a dosed subject suffers an AE that, in the judgment of the investigator, sponsor or MM, presents an unacceptable consequence or risk to the subject, the subject will be discontinued from further participation in the study. In addition, adverse events outlined in [Section 15.3.1](#) will require subject withdrawal.

Death

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

Lost to Follow-up

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

Met Withdrawal Criteria

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

Worsening of Disease Activity

Subjects will be withdrawn if they have a flare/worsening of disease activity defined as:

- **Weeks 0 to 11:** DAS28-ESR ≥ 3.2 and increase of > 0.6 from the Week 0 assessment sustained over 2 consecutive study visits; **or** DAS28-ESR ≥ 3.2 and increased of > 1 from the Week 0 assessment at a single visit.

- **Weeks 13 to 23:** DAS28-ESR < 3.2 and increase of 1.2 from the Week 12 assessment; **or** DAS28-ESR \geq 3.2 and increased of > 0.6 from the Week 12 assessment sustained over 2 consecutive study visits; **or** DAS28-ESR \geq 3.2 and increase of > 1 from the Week 12 assessment at a single visit.

Other

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

23 STUDY SUSPENSION, TERMINATION, AND COMPLETION

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

24 PROTOCOL AMENDMENTS

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

25 QUALITY CONTROL AND ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the Investigator’s Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study. During these study site visits, information recorded in the eCRFs will be verified against source documents.

25.1 Study and Study Site Discontinuation Criteria

The sponsor, investigator, or local and national regulatory authorities may discover conditions during the study that indicate that the study or study site should be terminated. This action

may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study/study site include, but are not limited to:

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

26 DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

26.1 Investigator

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

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

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

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

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

26.2 Sponsor

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

27 SUBJECT INJURY

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

28 RECORDS RETENTION

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

29 BIOLOGICAL SAMPLES

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. After the study ends, the clinical laboratory samples will be destroyed, with the exception of

will be retained at a biologic storage facility for future testing. The subject may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from that sample will still be used for this research.

30 PUBLICATION POLICY

30.1 Sponsor's Publication Policy

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

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

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

30.2 Investigator's Ability to Publish

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

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32 Attachments

32.1 Attachment 1: Clinical Laboratory Tests

Serum Chemistry	
Alanine aminotransferase (ALT)	Chloride
Albumin (total)	Creatinine
Alkaline phosphatase	Glucose
Aspartate aminotransferase (AST)	Phosphorus
Bilirubin (total)	Potassium
Blood urea nitrogen	Protein, total
Calcium	Sodium
CO ₂	Uric acid
Diabetes Screen	
Hemoglobin A1c	
Hormones	
Serum and urine beta-human chorionic gonadotropin (pregnancy test)	
Hematology Assays	
Hematocrit	Platelet count
Hemoglobin	Red blood cell count
White blood cell count, including differential	Absolute neutrophil count
Urinalysis	
Blood	Nitrite
Clarity	Nitrite
Color	Protein
Glucose	pH
Leukocyte esterase	Specific gravity
Ketones	
Hepatitis Serology	
Hepatitis B core antibody	Hepatitis C virus antibody (HCV)
Hepatitis B surface antigen	Hepatitis C virus PCR (only if HCV +)
TB Assay	
Interferon gamma release assay (IGRA) (obtained at local lab)	