NCT02633046

CLINICAL STUDY PROTOCOL

Treatment of Proteinuria Due to Treatment Resistant or Treatment Intolerant Idiopathic Focal Segmental Glomerulosclerosis: A Prospective Study of Acthar (PODOCYTE)

Protocol Number: MNK14224049

Date of Original Protocol: 02 December 2015

Date of Protocol Amendment 1: 20 April 2016

Date of Protocol Amendment 2.0: 22 August 2017

Date of Protocol Amendment 2.1: 12 October 2017

Date of Protocol Amendment 3: 3 June 2019

Mallinckrodt ARD LLC

1425 US Route 206

Bedminster, NJ 07921 United States of America

SUMMARY OF CHANGES

PROTOCOL AMENDMENT 3.0 DATED 3 June 2019

Summary of Important Changes in Amendment 3.0

A separate Summary of Changes document is available with a comprehensive list of changes from Amendment 2.1 to Amendment 3.0.

- The title page was updated to reflect the regulatory requirement to use the Mallinckrodt ARD LLC corporate headquarters address in Bedminster, New Jersey.
- Changed enrolled population from 236 to 60 subjects.
- Removed the double-blind, placebo-controlled randomization maintenance period (week 26, including removing the forced taper starting at Week 26, to Week 50) to extend the open label/open-label extension period (Week 26 to Week 50).
- Changed primary objective from confirmation of efficacy to confirmation of safety and tolerability.
- Changed primary endpoints to
  - Severity and frequency of AEs
  - Changes in physical findings
  - Changes in clinical laboratory findings
  - Changes in vital signs
- Removed all secondary objectives and endpoints.
- Removed all exploratory objectives in Amendment 2.1. Replaced with [redacted]
- Removed all exploratory endpoints from Amendment 2.1. Replaced with
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

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

- Descriptive statistics only.
- Reformatted to new Mallinckrodt format. Section numbering, table and figure numbering, and internal section references were adjusted in the amended protocol

PROTOCOL AMENDMENT 2.1 DATED 12 OCTOBER 2017

Summary of Changes in Amendment 2.1

The following changes from protocol Amendment 2 to Amendment 2.1 where made:

1. The title page was updated to reflect the regulatory requirement to use the Mallinckrodt ARD, Inc. corporate headquarters address in Hazelwood, Missouri.
2. Section 2 (Contacts) was deleted. This information will be supplied in the Study Operations Manual with updates to that document as needed. The Emergency Contacts list in the Study Operations Manual will be revised to remove [redacted] as medical monitors. [redacted] will remain as regional medical monitors. Section numbering and internal section references were adjusted in the amended protocol based on this deletion.
3. International Council on Harmonisation was changed to International Council for Harmonisation globally.
4. Week 24 is noted as Visit 8 throughout the protocol.
5. Corresponding appropriate changes were made to the study synopsis (Section 1.1).
6. The abbreviation [redacted] was added to abbreviation list. [redacted] was used throughout the protocol.
7. Serum sampling for cortisol determination was removed as an safety assessment from Table 1 (Schedule of Study Events, Section 1.4), Section 8 (Procedures), Section 10 (Safety Assessments and Procedures), Section 10.7 (Clinical Laboratory Tests, HbA1c, [redacted], IGRA, Urinalysis, and Pregnancy Tests), and Section 24.1 (Attachment 1: Clinical Laboratory Tests). It was recognized that there is no endpoint associated with the assessment and [redacted].
8. [redacted]on was added to screening at Visit 1. Table 1 (Schedule of Study Events, Section 1.4) was revised to add a separate row for [redacted] with a determination

indicated at Visit 1. Section 8 (Procedures) was revised to include the [redacted] determination to the Visit 1.

9. The timing of the Baseline Visit/Visit 2 was revised if the subject had no treatment at Screening Visit/Visit 1 to "Eligibility is confirmed and IMP is on-site" in Table 1 (Section 8.2).
10. Willingness to undergo [redacted], was added to Inclusion Criterion 5 (Section 6.1). Table 1 (Schedule of Study Events, Section 1.4) and Section 6.1 (Inclusion Criteria) were revised to reflect this new criterion. Section 13 (Procedures) was revised to include the [redacted] at Visit 1.
11. Male contraception was removed from Inclusion Criterion 4 (Section 6.1). There is no relevant data to indicate a teratogenic, or genotoxic risk of ACTH peptides in Acthar.
12. The qualifying urine protein creatinine ratio in Inclusion Criterion 6 (Section 6.1) was changed from greater than 3.5 mg/mg to greater than 3.0 mg/mg.
13. Cyclophosphamide was added to medications prohibited 24 weeks before screening at Visit 1 Exclusion Criterion 24 (Column 1, Table 2) was revised to add "cyclophosphamide" to the column. Cyclophosphamide was added to prohibited medications because of its long pharmacodynamic half-life. The title to Table 2 was inadvertently changed from "Screening Visit/Visit 1" to "Screening Visit/Visit."
14. The title to Table 2 was corrected from "Screening Visit/Visit" to "Screening Visit/Visit 1."
15. Mathematical operators were removed globally for better readability. Inadvertent errors in Exclusion Criterion 27 (Section 6.2) were made in the conversion of mathematical symbols to text in Protocol Amendment 2.0; these have been corrected.
16. The definition of screen failures was revised to allow only one repeat measurement (Section 6.3 and Section 8.1). The following text was added to Section 8.1: "A screening procedure can be repeated only once; if the repeat procedure continues to be exclusionary, the subject will be a screen failure."
17. Prohibited concomitant medications (Section 7.1) were revised to include any long-acting corticotropin, other than Acthar, and to allow intraocular immunosuppressive medications.
18. Expanded the information to be conveyed during the IXRS contact (Section 9.1). Replaced the text "The investigator or designee must contact the IXRS to update the subject's status" with the text "[redacted] during the IXRS contact; appropriate kit assignment will be made following this determination."
19. Time durations in Table 5 (Section 9.3, Dosing Procedures) were revised in Column 1. Footnotes b and c to Table 5 were changed from Week 23 to Week 24.
20. Dosing procedures (Section 9.3) were updated to include information regarding restrictions on dosing. The text "Throughout the trial, IMP cannot be taken on 2

consecutive days and cannot be taken more than 3 days apart, regardless of dosing frequency," was added.

21. The text "The investigator or designee must contact the IXRS to update the subject's status" was removed from Section 9.1 (Methods of Assigning Subjects to Treatment Groups).
22. Added the following text reporting and recording of AEs to Section 10.1, "AEs occurring prior to the administration of IMP will only be reported if they are related to study procedures."
23. The text "…Screening Visit/Visit and…" was changed to "…Screening Visit/Visit 1 and…" in Section 10.5.
24. Definitions relating to [redacted] was added.
25. The exploratory endpoints [redacted]
26. Refined the definition of visits to the emergency department in Section 13.2 so that they are not considered SAEs in Mallinckrodt clinical studies.
27. Clarified the collection times for AEs and SAEs will begin from the time of signing of the informed consent form through the end-of-study/early termination visit in Section 13.4. Also added the text, "All AEs and SAEs should be recorded in source documents; all AEs and SAEs that occur following the first dose of IMP should also be recorded in the eCRF."
28. Carbon dioxide and sodium were inadvertently removed from the listing of clinical laboratory tests in Attachment 1 (Section 24.1). These analytes will be collected.
29. Additional unspecified minor changes to punctuation, style, and formatting.

PROTOCOL AMENDMENT 2 DATED 22 AUGUST 2017

SUMMARY OF CHANGES

Protocol Amendment 2 was developed primarily to add [redacted] as a screening procedure. Additional revisions were made to clarify other specific protocol issues. The protocol changes are summarized below:

1. Section 2 (Contacts) was deleted. Remaining sections located after Section 1 were renumbered.

2. Section 1.4 (Schedule of Study Events) and Section 6.1 (Inclusion Criteria) were revised to add [redacted] as a screening procedure unless performed in the prior 3 years (new inclusion criterion #5).
3. Section 6.2 (Table 2) was revised to add a separate row for [redacted] with an extra 'X' at the Screening Visit.
4. Section 6.1 (Inclusion Criteria) Inclusion criterion #4 was revised to remove the requirement for male contraception. Inclusion criterion #6 was revised to change [redacted]
5. Section 6.1 (Inclusion Criteria - inclusion criterion #9) and Section 7.2 (Permitted During Study) were revised to delete "DRI" since DRI drugs have not been shown to improve renal function.
6. Section 6.2 (Exclusion Criteria) - Exclusion criterion #9 was revised to change "senescence" to "sclerosis". Exclusion criterion #24 (Table 11-1, column 1) was revised to add "cyclophosphamide" to the *24 weeks before Screening Visit/Visit 1* column, since cyclophosphamide is used as a treatment for FSGS and has a very long pharmacodynamic half-life. Exclusion criterion #27 was revised for better readability.
7. Section 12.3.1 (Primary Efficacy Endpoint). Table 6 was revised, [redacted]
8. Section 13.4 was revised to clarify the reporting and recording of AEs.
9. Corresponding appropriate changes were also made to Section 1.1 (Study Synopsis).
10. Global edits were made to revise the number of study sites from 80 to 100 and the study duration from 4 years to 5 years.
11. Formatting changes were made globally as necessary for medical writing style guide compliance.

PROTOCOL AMENDMENT 1 DATED 20 APRIL 2016
SUMMARY OF CHANGES

Protocol Amendment 1 was developed primarily to modify eligibility criteria. Additional revisions were made to adjust other procedures and descriptions. The major protocol changes are summarized below:

- Deleted "(US and Canada only)" as the location of where [redacted] would be conducted.
- Revised the Emergency Contacts list to remove [redacted] as a backup medical monitor, and to add [redacted] as medical monitors.
- Revised Inclusion Criterion #5 to allow time from [redacted]
- Added Exclusion Criterion #8: Subjects cannot have failed to achieve [redacted], as determined by the investigator, on more than 2 prior immunosuppressive therapies with different mechanisms of action.
- The following Secondary Endpoints were deleted or revised:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

– [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- The following Exploratory Endpoints were deleted or revised:

[redacted]

- The following Secondary Efficacy Endpoints were added/revised:

- [redacted]

- The following Secondary Safety Endpoint was added:
  - 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.
- The following Exploratory Endpoints were added/revised:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

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DISCLOSURE STATEMENT

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.

SPONSOR SIGNATURE

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

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

[redacted]@mallinckrodt.com Digitally signed by [redacted]@mallinckrodt.com
DN: cn[redacted]@mallinckrodt.com
Reason: I am approving this document
Date: 2019.06.03 16:44:32 -04'00'

Sponsor Signature | Date of Signature (DD Month YYYY)

Sponsor Name (print)

INVESTIGATOR SIGNATURE

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

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

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

ABBREVIATIONS

Abbreviation	Term
2x/week	Twice a week
3x/week	Three times a week
ACEi	Angiotensin-converting enzyme inhibitor
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
BMI	Body mass index
CFR	Code of Federal Regulations
CNI	Calcineurin inhibitor
CR	Complete remission
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
FDA	Food and Drug Administration
FSGS	Focal segmental glomerulosclerosis
GCP	Good Clinical Practices
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody

Abbreviation	Term
HCV	Hepatitis C virus antibody
HCV PCR	Hepatitis C virus polymerase chain reaction
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IGRA	Interferon gamma release assay
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intent-to-treat
IXRS	Interactive Phone/Web Response System
KDIGO	Kidney Disease Improving Global Outcomes
LDL	Low density lipoprotein
MCR	Melanocortin receptor
MDRD	Modification of Diet in Renal Disease
MMF	Mycophenolate mofetil
PR	Partial remission
SAE	Serious adverse event
SC	Subcutaneous
SF-36	Short Form (36) Health Survey
TB	Tuberculosis

Abbreviation	Term
TEAE	Treatment-emergent adverse event
U	Unit(s)
US	United States
ULN	Upper limit of normal
uPCR	Urine protein creatinine ratio

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Study Title: Treatment of Proteinuria Due to Treatment Resistant or Treatment Intolerant Idiopathic Focal Segmental Glomerulosclerosis: A Prospective Study of Acthar (PODOCYTE)	
Protocol Number: MNK14224049	**Type: Phase 4 (US)/Phase 2 (all other countries)**
Condition/Disease: Idiopathic focal segmental glomerulosclerosis (FSGS)	
Approximate Number of Subjects: 60	**Approximate Duration of Subject Participation:** Up to 65 weeks
Approximate Number of Study Centers: 100 globally	**Approximate Duration of Study:** 5 years
Design: This is a multicenter, multiple dose study to examine the effect of Acthar (repository corticotropin injection, hereafter referred to as Acthar) in adult subjects with idiopathic focal segmental glomerulosclerosis (FSGS) who have failed to achieve remission with, or who are intolerant of, 1 or more previous immunosuppressive therapies. All enrolled subjects will be treated in an unblinded fashion with Acthar 1 mL (80 U) subcutaneously (SC) 3 times per week (3x/week) for 50 weeks to assess the safety and tolerability of Acthar. Taper to 1 mL SC twice a week (2x/week) for tolerability reasons will be allowed. All subjects will have an End of Study/Early Termination Visit 4 weeks after discontinuing Investigational Medicinal Product (IMP).	
Objectives and Endpoints:	
Primary Objective	**Primary Endpoints**
To confirm the safety and tolerability of Acthar in the induction of remission of proteinuria in subjects with primary FSGS who are resistant to, or intolerant of, at least 1 prior immunosuppressive therapy	• Severity and frequency of adverse events (AEs) • Changes in physical findings • Changes in clinical laboratory findings • Changes in vital signs
Secondary Objective	**Secondary Endpoint**
None	None
Exploratory Objective	**Exploratory Endpoints**
• To demonstrate [redacted]	• [redacted]

Study Title: Treatment of Proteinuria Due to Treatment Resistant or Treatment Intolerant Idiopathic Focal Segmental Glomerulosclerosis: A Prospective Study of Acthar (PODOCYTE)	
Protocol Number: MNK14224049	**Type: Phase 4 (US)/Phase 2 (all other countries)**
Condition/Disease: Idiopathic focal segmental glomerulosclerosis (FSGS)	
	• [redacted]

Entry Criteria:

Male or nonpregnant, nonlactating female subjects 18 years of age or older with primary FSGS (confirmed by renal biopsy) who are nephrotic (uPCR > 3.0 mg/mg and estimated glomerular filtration rate [eGFR] at least 30 mL/min/1.73 m^2) and who have failed to achieve sustained CR or PR of proteinuria with at least 1 prior immunosuppressive therapy OR intolerance at least 1 prior immunosuppressive therapy will be enrolled in the study. Subjects must be treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker (or have documentation of intolerance), for at least 4 weeks prior to Screening Visit/Visit 1 with blood pressure no more than 150/90. Subjects also must be negative for hepatitis B, hepatitis C, have no history of tuberculosis (TB) or other contraindication as per the United States (US) Prescribing Information for Acthar, have no history of Type 1 or Type 2 diabetes mellitus, or have any clinically significant infection. Subjects cannot have taken Rituximab or cyclophosphamide 24 weeks prior to Screening Visit/Visit 1, any investigational treatments for FSGS or oral corticosteroids (unless used to treat FSGS) for 12 weeks prior to Screening Visit/Visit 1, any intravenous/intramuscular corticosteroids (unless used to treat FSGS) for 8 weeks prior to Screening Visit/Visit 1, or have been involved in a therapeutic drug/device trial (other than for FSGS) 4 weeks prior to Screening Visit/Visit 1.

Concomitant Medications and Treatments:

A stable dose of angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker is required throughout study participation. Subjects requiring other antihypertensive medications must be on a stable dose at least 4 weeks prior to the first dose of Acthar.

Subjects are not permitted to take any enteral or parenteral corticosteroid, live or live-attenuated vaccine or systemic immunosuppressive medication during the study.

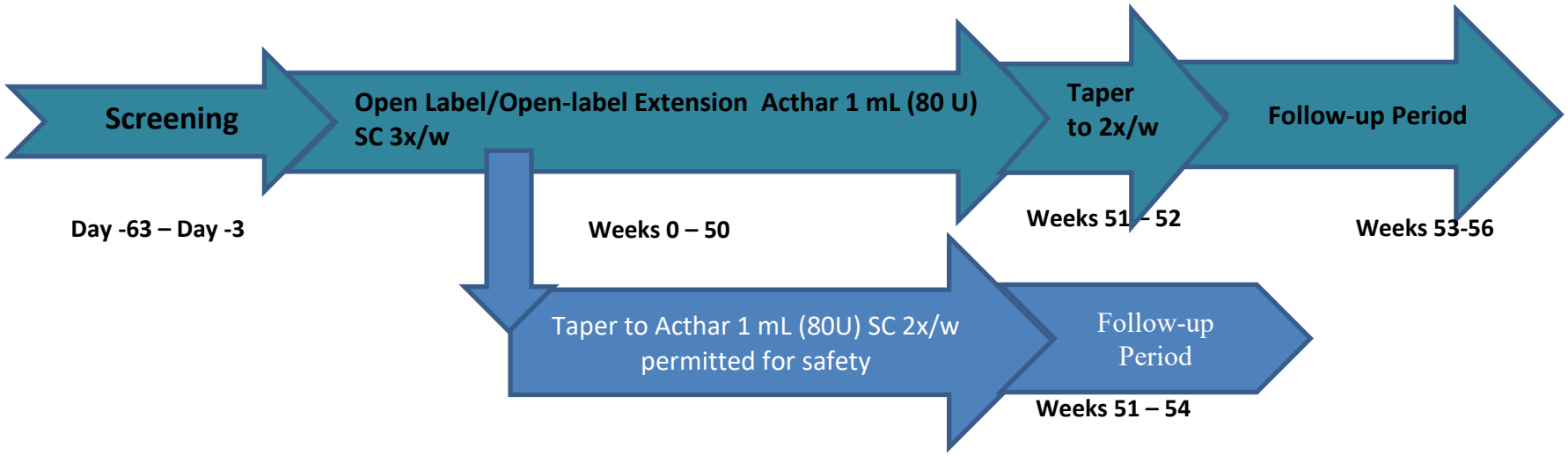
All medications and nondrug therapies (eg, blood transfusions, oxygen supplementation) at Screening Visit/Visit 1 and throughout the study will be recorded.

Study Title: Treatment of Proteinuria Due to Treatment Resistant or Treatment Intolerant Idiopathic Focal Segmental Glomerulosclerosis: A Prospective Study of Acthar (PODOCYTE)	
Protocol Number: MNK14224049	**Type: Phase 4 (US)/Phase 2 (all other countries)**
Condition/Disease: Idiopathic focal segmental glomerulosclerosis (FSGS)	
Investigational Medicinal Product and Treatment Administration: Acthar 1 mL (80 U) SC 3x/week will be administered to all subjects from Week 0 to 50. Tapering of dose to 1 mL SC 2x/week will be allowed for safety and/ tolerability issues. Once the dose is tapered to 1 mL SC 2x/week it must remain at this level. Subjects unable to tolerate 1 mL SC 2x/week will be discontinued.	
Efficacy Evaluations: There are no efficacy assessments.	
Safety Evaluations: The following safety assessments will be evaluated: adverse events, physical examinations, clinical laboratory tests, vital signs, medical and surgical history, height and height.	
Exploratory Evaluations: The following exploratory assessments will be evaluated: [redacted]	
Statistical Methods: **Analysis Populations:** Intent-to-Treat (ITT) Population: All enrolled subjects who receive 1 or more doses of IMP and who contribute any exploratory data to the study. Per-Protocol Population: the subset of the ITT population who complete the study as per protocol. Completer populations will be further defined in the statistical analysis plan. Safety Population: all enrolled subjects who receive 1 or more doses of IMP. **Sample Size:** Approximately 60 subjects will be enrolled. Formal sample size calculations were not performed. **Assessments:** **Efficacy:** There are no efficacy endpoints. **Safety:** The following safety assessments will be evaluated: adverse events, physical examinations, clinical laboratory tests, vital signs, medical and surgical history, height and height. **Exploratory:** Exploratory endpoints will be summaries with descriptive statistics only. [redacted]	

1.2. STUDY SCHEMATIC AND SCHEDULE OF EVENTS

1.3. Study Schematic

Figure 1: Study Overview



1.4. Schedule of Study Events

Table 1: Schedule of Study Events

Period	Screening (Day -63 to -3)	Baseline	Open Label/Open-label Extension													Taper Safety Visit[a]	End of Study/Early Termination[b]
VISIT #: Visit window is ± 5 days starting with Visit 2 (except at V9 where window is + 5 days only)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		
Week		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**30**	**34**	**38**	**42**	**46**	**50**		**54 or 56**
Informed consent[c]	X																
Inclusion/exclusion criteria review	X	X															
Demographics	X																
Medical/surgical history	X																
Current medical condition review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X																X
Limited physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (screening only) and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (serum chemistry and CBC w/diff)	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X[d]	X
HbA1c	X				X			X				X			X		
Nonfasting lipid panel		X			X			X				X			X		
[redacted]		X		X		X		X			X		X		X		
[redacted]	X	X		X		X		X			X		X		X		

Period	Screening (Day -63 to -3)	Baseline	Open Label/Open-label Extension													Taper Safety Visit[a]	End of Study/Early Termination[b]
VISIT #: Visit window is ± 5 days starting with Visit 2 (except at V9 where window is + 5 days only)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		
Week		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**30**	**34**	**38**	**42**	**46**	**50**		**54 or 56**
[redacted]	X																
[redacted]		X		X		X		X			X		X		X		
Serum pregnancy test	X																
IGRA for TB	X																
[redacted]	X	X		X		X		X			X		X		X		X
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
[redacted]s	X						X							X			
[redacted]		X						X							X		
[redacted]	X																
IXRS contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
IMP and diary training		X						X							X[f]		
IMP accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]
Dispense IMP kits		X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]		
Administer first dose[g]		X															
Diary review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X						X							X		

Period	Screening (Day -63 to -3)	Baseline	Open Label/Open-label Extension													Taper Safety Visit[a]	End of Study/Early Termination[b]
VISIT #: Visit window is ± 5 days starting with Visit 2 (except at V9 where window is + 5 days only)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**		
Week		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**30**	**34**	**38**	**42**	**46**	**50**		**54 or 56**
[redacted]		X						X							X		
Concomitant medications/adverse events	----------X----------																

[a]If IMP is tapered from 3x/week to 2x/week for safety and/or tolerability issues, a Taper Safety Visit will be conducted 2 weeks later (See Section 8.17).

[b]Subjects receiving 2x/week dosing (tapered for safety) will return at Week 54 + 5 days and subjects dosing 3x/week will return at Week 56 + 5 days.

[c]Subjects (US only) with stored [redacted] will be reconsented after implementation of Amendment 3 to allow for sponsor/site contact and permission for additional sample examination.

[d]Clinical laboratory tests will be done if the reason for discontinuation was related to laboratory test results.

[e]R[redacted]

[f]For subjects requiring IMP taper only.

[g]Subject or subject's caregiver will administer the first dose of IMP in the clinic under the supervision of the study staff. The subject will be observed in the clinic for at least 1 hour postdose to monitor for allergic or anaphylactic reactions.

2. ETHICAL CONSIDERATIONS

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

2.1. 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 SAEs 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).

2.2. 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 GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

2.3. 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/Visit 1, 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.

3. BACKGROUND INFORMATION AND RATIONALE

3.1. Overview

Focal segmental glomerulosclerosis (FSGS) is a pattern of histologic renal injury marked by segmental glomerular sclerosis and hyalinosis and may be either primary (idiopathic) or secondary. The renal injury results from insults directed at or within the podocyte that eventually lead to a rearrangement of the actin cytoskeleton and effacement of foot processes in the glomerular basement membrane. The histologic lesions differ in their location relative to the glomerular vascular and tubular poles and in the morphologic features of hyalinosis, capillary collapse, and hypercellularity (D'Agati et al, 2011).

Primary, or idiopathic, FSGS is defined by the exclusion of another identifiable cause of FSGS. The glomerulosclerosis of secondary FSGS usually results from an adaptive response to scarring from a previous injury or direct toxic injury to the podocytes. Secondary FSGS may be associated with viral infections, be drug induced, or result from conditions marked by either reduced renal mass or elevated glomerular capillary pressures. It is important to distinguish primary from secondary FSGS as the latter is treated only with renin angiotensin system blockade and not immunosuppressive therapy. In addition to clinical history and laboratory findings such as hypoalbuminemia and hyperlipidemia, histological findings may help differentiate primary from secondary FSGS, with the former exhibiting more widespread foot process effacement under electron microscopy (D'Agati et al, 2011).

Eighty percent of cases of FSGS are primary and the incidence of primary FSGS has dramatically increased over the past 20 to 30 years (D'Agati et al, 2011). Primary FSGS is usually a progressive disorder with a low likelihood of spontaneous remission. Approximately 50% of patients will reach end stage renal disease (ESRD) over a period of 5 to 8 years from the time of biopsy if either unresponsive to treatment or not treated (Korbet, 1999). Five to 10 percent of all pediatric and adult patients who progress to ESRD will have FSGS as their primary cause of renal failure (Malaga-Diequez et al, 2015). The prognosis of patients with primary FSGS is best predicted by the severity of proteinuria and the response to therapy. Patients who undergo a complete remission (CR) or partial remission (PR) have a much better chance of renal survival, 80% or greater over a 10-year period, than those who are unresponsive (Troyanov et al, 2005).

The goal of therapy is to induce CR of proteinuria that in turn leads to the preservation of renal function. The achievement of PR or even substantial reductions in proteinuria translates into less rapid loss of renal function. Adult patients with primary FSGS who have nephrotic range proteinuria are usually treated with renin angiotensin system blockade and immunosuppressive

therapy. Seventy percent of adults with primary FSGS will have nephrotic range proteinuria (Kitiyakara et al, 2003). The initial Kidney Disease Improving Global Outcomes (KDIGO) recommended immunosuppressive therapy for most adults with primary FSGS is oral prednisone, with calcineurin inhibitors (CNI) reserved for those at high risk for glucocorticoid-induced toxicity. There is no universal agreement on the dose and duration of prednisone therapy, though the current KDIGO Clinical Practice Guidelines for glomerulonephritis recommends treatment with high doses of prednisone, 1 mg/kg/day or 2 mg/kg every other day, for between 4 and 16 weeks or until CR. If CR occurs, prednisone is then tapered slowly over a 6-month period. If the FSGS is steroid resistant, the KDIGO recommended second-line treatment is a CNI for 4 to 6 months, although CNI are not FDA-approved for this indication. If PR or CR occurs, it is recommended that the CNI be slowly tapered over at least 12 months. A combination of mycophenolate mofetil (MMF) and high dose dexamethasone is the KDIGO recommended alternative for patients who do not tolerate or respond to the CNI, although MMF is also not FDA-approved for this indication (KDIGO Work Group, 2012).

About 50% of patients with primary FSGS will be resistant to therapy with corticosteroids (Bose and Cattran, 2014). The prolonged duration of high doses of prednisone is frequently associated with significant side effects including the development or worsening of diabetes, weight gain, fluid retention, osteoporosis, behavioral changes, and infection. Between 30% and 40% of patients resistant to steroids will also be resistant to CNIs, and in those who respond, relapse is common (Cattran et al, 2007). CNIs are also associated with significant side effects, such as hypertension and glucose intolerance, and the long-term nephrotoxicity associated with their use may potentially abrogate the benefit from the reduction in proteinuria. These side effects make a number of patients with FSGS intolerant to the therapies. Thus a significant unmet need for efficacious therapies exists for both children and adults diagnosed with primary FSGS.

As described in the Package Insert, H.P. Acthar® Gel (repository corticotropin injection, hereafter referred to as Acthar) is a highly purified porcine adrenocorticotropic hormone (ACTH) analogue (Mallinckrodt ARD LLC, 2015). Acthar is a purified sterile preparation of the ACTH formulated in 16% gelatin to provide a prolonged release after intramuscular or subcutaneous injection. ACTH is a member of the family of structurally related peptides known as melanocortin peptides. Melanocortin peptides, which in addition to ACTH include the α-, β-, and γ-melanocyte stimulating hormones, are derived from the natural protein pro-opiomelanocortin. They bind to cell surface G-protein coupled receptors known as melanocortin receptors (MCRs). 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 is a known agonist for all 5 subtypes of MCR (Schioth et al, 1995) and recent experiments demonstrate that Acthar also has agonist activity for all 5 MCRs (Wright, 2018).

The kidney is a major target of the melanocortin hormone system. MCRs have been expressed throughout the kidney, including on glomerular podocytes, and receptor activations initiate downstream signaling cascades that ultimately lead to amelioration of renal injury (Gong and Dworkin, 2010). Agonists of the MC1R receptor were shown to reduce oxidative stress and improve glomerular morphology in nephrotic rats with passive Heymann nephritis (Lindskog et al, 2010). Acthar has been shown to diminish podocyte injury and apoptosis and reduce foot process effacement in a rodent subtotal nephrectomy model, an animal model of FSGS (Gong and Dworkin, 2010). In addition to improved podocyte structure and function, glomerulosclerosis,

tubule-interstitial nephritis, renal inflammation, tubular injury and tubular epithelial to mesenchymal transformation were all reduced in this model.

Clinical studies on patients with primary FSGS have provided evidence for the therapeutic effect of ACTH (including Acthar) on proteinuria. In an observational study, 1 patient with FSGS and nephrotic range proteinuria who was resistant to steroid and cytotoxic therapy was treated with synthetic ACTH and attained PR (Berg and Arnadottir, 2004). A published case report documented the development of PR in a young woman with FSGS and massive proteinuria (greater than 10 grams) who was treated with Acthar (80 units [U] subcutaneously [SC] twice weekly for 6 months) after having failed to respond to corticosteroids, mycophenolate and a CNI (Bomback et al, 2011). In a prospective open label study, 3 patients with FSGS resistant to at least 2 previous therapies were treated with Acthar 80 U SC twice a week for 6 months and 1 patient attained CR (Bomback et al, 2012).

The largest experience of treating primary FSGS with Acthar is in 24 adult patients with nephrotic syndrome and FSGS where 16 patients were studied prospectively. Twenty-two patients had received prior immunosuppressive therapy, 21 of which had received at least one course of corticosteroids. Patients had received a mean of 2.2 ± 1.2 immunosuppressives prior to receiving Acthar. During treatment with Acthar, 19 patients received no other immunosuppressives. Data was available for 23 of 24 patients with 1 patient being lost to follow up after 5 weeks of Acthar. Seven of the 24 patients had remission of proteinuria, 5 with PR and 2 with CR and 5 of the 7 patients had sustained remission with a median follow up time of 90 weeks (Hogan et al, 2013).

3.2. Product Description

Acthar is currently approved in the US for inducing a diuresis or remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus (Mallinckrodt ARD LLC, 2015). Acthar is a proprietary ACTH mixture isolated from porcine pituitary extracts.

3.3. Dosage and Administration

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

In this study all subjects will receive open label treatment with Acthar 1 mL (80 U) SC 3 times per week (3x/week) for 50 weeks. Taper to 1 mL SC twice a week (2x/week) for safety and/or tolerability reasons will be allowed. If the dose is tapered to 1 mL SC 2x/week it must remain at this level for the remainder of the study. Subjects unable to tolerate 1 mL SC 2x/week will be discontinued.

3.4. Rationale

The doses for this study were chosen based on safety and feasibility data. 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 LLC, 2015). The maximal dose is 80 to 120 U SC daily, which has been used safely for the treatment of acute multiple

sclerosis exacerbations over a period of 2 to 3 weeks. 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).

Higher doses of Acthar and longer periods of exposure are well tolerated and associated with improved outcomes in patients with idiopathic nephrotic syndrome. In the largest published experience of Acthar in FSGS, patients received treatment for 16 to 56 weeks and the side effect profile was considered acceptable (Hogan et al, 2013). A case report of 10 patients with treatment resistant FSGS documented that prolonged therapy with synthetic ACTH for a median of 18 months was well tolerated (Berg et al, 2012). In a study of patients with membranous nephropathy, another cause of idiopathic nephrotic syndrome, higher exposure to Acthar was well tolerated and associated with higher rates of remission of proteinuria (Hladunewich et al, 2014).

3.5. Risk/Benefit

Known potential risks of Acthar include potential Cushing's Syndrome, hypertension, gastrointestinal perforation and bleeding, behavioral and mood disturbances, hyperglycemia, enhanced risk for infection, decrease in bone density and/or worsening of peripheral edema (Mallinckrodt ARD LLC, 2015).

Primary FSGS is a progressive disorder associated with a low likelihood of spontaneous remission and high risk of reaching ESRD if not treated or unresponsive to treatment. The incidence of primary FSGS is increasing, as is the number of patients reaching ESRD because of the disorder. Current therapies are inefficacious in a large number of patients and are associated with significant side effects that limit their use and potentially abrogate their benefit. Evidence suggests that Acthar will be beneficial in reducing proteinuria and the subsequent deterioration in renal function in patients who are resistant or intolerant to currently recommended treatments.

4. OBJECTIVES

4.1. Primary Objective

Primary Objective	Primary Endpoints
To confirm the safety and tolerability of Acthar in the induction of remission of proteinuria in subjects with primary FSGS who are resistant to, or intolerant of, at least 1 prior immunosuppressive therapy	• Severity and frequency of adverse events (AEs) • Changes in physical findings • Changes in clinical laboratory findings • Changes in vital signs

4.2. Secondary Objectives

There are no secondary objectives or endpoints.

4.3. Exploratory Objective(s)

Primary Objective	Primary Endpoints
Exploratory Objectives	**Exploratory Endpoints**
• To demonstrate [redacted]	• [redacted]

5. STUDY DESIGN

5.1. Description

This is a multicenter, multiple dose study to examine the effect of Acthar in adult subjects with FSGS who have failed to achieve remission with, or who are intolerant of, one or more previous immunosuppressive therapies. Approximately 60 subjects will be enrolled.

All enrolled subjects will be treated with Acthar 1 mL (80 U) SC 3x/week for 50 weeks. Taper to 1 mL SC 2x/week for safety and/or tolerability reasons will be allowed. If the dose is tapered to 1 mL SC 2x/week it must remain at this level for the remainder of the study. Subjects unable to tolerate 1 mL SC 2x/week will be discontinued.

All subjects will participate in the Follow-up Period at the conclusion of their participation in the study (including those who terminate early). The Follow-up Period will be 4 to 6 weeks in duration, depending on the dose of Investigational Medicinal Product (IMP).

For subjects receiving IMP 3x/week, the dose of IMP will be tapered to 2x/week for 2 weeks and then discontinued. For subjects receiving IMP 2x/week (tapered from 3x/week to 2x/week for safety), the IMP will be discontinued without a taper. All subjects, including those who terminate early, will then have an End of Study/Early Termination Visit 4 weeks after their last dose of IMP.

5.2. Approximate Duration of Subject Participation

Subjects will participate in the study for a total of approximately 65 weeks, including a Screening Visit/Visit 1 period of up to 9 weeks, and active treatment period of up to 50 weeks, and a follow-up visit of up to 6 weeks after discontinuation of IMP.

5.3. 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 5 years to complete.

5.4. Approximate Number of Subjects

Approximately 60 subjects will be enrolled at approximately 100 sites globally.

6. SELECTION OF SUBJECTS

6.1. Inclusion Criteria

Subjects must meet all of the following criteria for inclusion in the study at the Screening Visit/Visit 1 and the Baseline Visit/Visit 2:

1. 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. Must be ≥ 18 years of age at Screening Visit/Visit 1 and can be male or female.

3. Female subjects must be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, or are postmenopausal with no history of menstrual flow in the 12 months prior to Screening Visit/Visit 1), or if of childbearing potential must be nonpregnant, nonlactating and agree to use effective contraception with a male partner throughout study participation and for 4 weeks after ending study participation. 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. Must have a history of primary FSGS confirmed by a renal biopsy.
5. Must be willing to undergo a renal biopsy unless the most recent renal biopsy ≤ 3 years of the Screening Visit/Visit 1.
6. Must have a total urine protein creatinine ratio (uPCR) > 3.0 mg/mg at Screening Visit/Visit 1.
7. Must have an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 at the Screening Visit/Visit 1 as calculated by the 4-variable modification of diet in renal disease (MDRD) study equation.
8. Must have failed to achieve sustained CR or PR of proteinuria as determined by the investigator with ≥ 1 prior immunosuppressive therapy, or must have intolerance to ≥ 1 prior immunosuppressive therapy.
9. Must have been treated with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for ≥ 4 weeks prior to Screening Visit/Visit 1 and on stable maintenance dose(s) for ≥14 days prior to Screening Visit/Visit 1 and are expected to remain on that dose for the duration of the study **or** have a documented intolerance to ACEi or ARB with approval from the MM prior to enrollment. Subjects taking other antihypertensive medication(s), must be on a stable dose of for ≥ 4 weeks prior to the Screening Visit/Visit 1.
10. Must have a mean systolic blood pressure ≤ 150 mm Hg and a diastolic blood pressure of ≤ 90 mm Hg determined by the average of ≥ 3 seated readings taken at least 5 minutes apart at Screening Visit/Visit 1 and at the Baseline Visit/Visit 2.
11. Must be able to communicate effectively with study personnel.
12. Must be able and willing to follow all protocol requirements and study restrictions.
13. Must be able and willing to return for all study visits.

6.2. Exclusion Criteria

Subjects are ineligible for study participation if they meet any of the following criteria at the Screening Visit/Visit 1 or Baseline Visit/Visit 2:

1. 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. Is unwilling to receive, or is intolerant of, subcutaneous injections.
3. Has any history of use of ACTH preparations for treatment of nephrotic syndrome (including but not limited to Acthar and Synacthen®).
4. Has a history of sensitivity to ACTH preparations (including but not limited to Acthar and Synacthen).
5. Has a history of sensitivity to porcine protein products.
6. Has a body mass index (BMI) >45 kg/m^2 at Screening Visit/Visit 1.
7. Has secondary FSGS, including but not limited to, obesity, known genetic cause, reduced kidney mass, Human Immunodeficiency Virus (HIV), intravenous heroin abuse, or sickle cell anemia (a full list of secondary causes of FSGS is included in Section 24.3).
8. Cannot have failed to achieve sustained CR or PR of proteinuria, as determined by the investigator, on more than 2 prior immunosuppressive therapies with different mechanisms of action.
9. Has had a renal biopsy demonstrating > 50% global glomerular sclerosis, or > 50% cortical interstitial fibrosis, or collapsing FSGS.
10. Has any known contraindication(s) to Acthar (Mallinckrodt ARD LLC, 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 6 months prior to Screening Visit/Visit 1).
    - Recent major surgery (within 6 months prior to Screening Visit/Visit 1, renal biopsy is not considered an exclusionary surgical procedure).
11. Has a history of chronic active hepatitis; acute or chronic hepatitis B; or acute or chronic hepatitis C.
12. Has a history of tuberculo/sis (TB) infection, any signs/symptoms of TB, or any close contact with an individual with an active TB infection.
13. Has a clinically significant infection requiring intravenous administration of antibiotics and hospitalization in the 4 weeks prior to Screening Visit/Visit 1.
14. Has known immune compromised status, including but not limited to, individuals who have undergone organ transplantation or who are known to be positive HIV.

15. Has Type 1 or Type 2 diabetes mellitus (prior diagnosis of gestational diabetes mellitus is not exclusionary).
16. Has had any of the following in the 12 weeks prior to Screening Visit 1/Visit 1: unstable angina confirmed by a cardiologist, myocardial infarction, coronary artery bypass graft, percutaneous trans-luminal coronary angioplasty, transient ischemic attack or cerebrovascular disease, unstable cardiac arrhythmia, or resuscitated sudden cardiac death.
17. Has any solid tumor malignancy currently diagnosed or undergoing therapy, or has received therapy for any solid tumor malignancy in the 5 years prior to Screening Visit/Visit 1, with the exception of treated and cured basal cell carcinoma, treated and cured squamous cell carcinoma of the skin, and treated and cured carcinoma in situ of the cervix.
18. Has a diagnosis of, is undergoing therapy for, or has received therapy for a hematologic malignancy in the 5 years prior to Screening Visit/Visit 1.
19. Has been treated with any of the medications outlined in Table 2 within the specified timeframe prior to the Screening Visit/Visit 1.

Table 2: Prohibited Medications Relative to Screening Visit/Visit 1

24 weeks before Screening Visit/Visit 1	12 weeks before Screening Visit/Visit 1	8 weeks before Screening Visit/Visit 1	4 weeks before Screening Visit/Visit 1
Rituximab	Investigational treatment for FSGS	Intravenous/intramuscular corticosteroids[a, c]	Therapeutic drug/device trial (except FSGS)
Cyclophosphamide	Chronic oral corticosteroids[a,b]		

[a]Does NOT include corticosteroids (enteral or parenteral) used for the treatment of FSGS.
[b]Chronic use is defined as any dose of corticosteroid taken > 4 consecutive weeks.
[c]Any dose of parenteral corticosteroids 8 weeks prior to Screening Visit/Visit 1.

20. Has been treated with any of the medications outlined in Table 3 within the specified timeframe prior to Baseline Visit/Visit 2.

Table 3: Prohibited Medications Relative to Baseline Visit/Visit 2

FSGS Treatment at Screening Visit/Visit 1[a]	Days Prior to Baseline/Visit 2
CNI	> 49 days
Corticosteroids[b], Mycophenolate, Mofetil	> 30 days

[a]If subject is not currently receiving immunosuppressant treatment for FSGS at the Screening Visit/Visit 1, the Baseline Visit/Visit 2 will occur >2 days and < 63 days after the Screening Visit/Visit 1.
[b]Corticosteroids used for the treatment of FSGS (see exclusion Criterion 14 for corticosteroid use to treat other conditions).

21. Has current or recent (within 6 months of the Screening Visit/Visit 1) drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Diagnostic Criteria for Drug and Alcohol Abuse (American Psychiatric Association, 2013).
22. Has any of the following laboratory abnormalities at the Screening Visit/Visit 1:
    - Hemoglobin ≤ 8.0 g/dL.
    - Platelets ≤ 50,000 cells/μL.
    - Absolute neutrophil count (ANC) ≤ 1,000 cells/μL.
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin > 2 times the upper limit of normal (ULN).
    - Glycosylated hemoglobin (HbA1c) > 6.5%.
    - Positive Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb).
    - Positive Hepatitis C virus antibody (HCV) and HCV polymerase chain reaction (PCR) ≥ 25 IU/mL (HCV PCR will be automatically analyzed if HCV is positive).
    - Positive or indeterminate interferon gamma release assay (IGRA).
23. Has any other clinically significant disease, disorder or laboratory abnormality (including those listed on the Prescribing Information Section 5: Warnings and Precautions [Mallinckrodt ARD LLC, 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.

6.3. Screen Failure

Subjects will be allowed to repeat any screening procedure once, as long as the results of the repeated procedure will be available within the screening visit window. This will not be considered a screen failure. The period from the start of the screening visit to the baseline visit must not exceed 63 days, inclusive of any repeated procedures.

A subject who is a screen failure at the Screening Visit/Visit 1 or at the Baseline Visit/Visit 2 may be rescreened once. During the rescreening period, subjects will be allowed to repeat any screening procedure once, as long as the results of the repeated procedure will be available within the screening visit window. The period from the start of the rescreening visit to the baseline visit must not exceed 63 days, inclusive of any repeated procedures.

Subjects may only be rescreened once.

7. PRIOR AND CONCOMITANT MEDICATION

The start and stop date, dose, unit, frequency, route of administration, and indication for prior medications and concomitant medications taken within the past 30 days will be recorded.

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

7.1. Prohibited Concomitant Medications

The following treatments will not be permitted during the study:

- Any long-acting corticotropin other than IMP.
- Any enteral or parenteral corticosteroid use (topical, inhaled and intra-articular corticosteroids are allowed).
- Administration of live or live-attenuated vaccines.
- Enteral or parenteral immunosuppressive medications including, but not limited to methotrexate, azathioprine, cyclophosphamide, cyclosporine, tacrolimus, MMF, rituximab (or other B-cell inhibitors), and tumor necrosis factor inhibitors (eg, Enbrel®, Humira®, Remicade®); intraocular immunosuppressive medications are allowed.
- 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 MM must be informed immediately so the sponsor may determine whether to continue the subject in the study.

7.2. Permitted During Study

If any medication is taken during the study, all pertinent information will be recorded in source documents and the eCRF.

Subjects should remain on stable doses of ACEi and/or ARB during the study. An adjustment in the dose of these medications would represent a protocol deviation, but would not necessarily mandate study termination. Adjustments in dose of a concomitant medication should be documented in the subject's source documents and eCRF.

8. PROCEDURES

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

8.1. Screening Visit/Visit 1 (Study Days -63 to -3) Procedures

Screening assessments must be performed within 3 to 63 days prior to the Baseline Visit/Visit 2.

The following procedures will be performed at the Screening Visit/Visit 1:

- Informed consent.
- Note: Subjects (US only) with stored renal biopsy samples will be reconsented after implementation of Amendment 3 to allow for sponsor contact and permission for additional sample examination.
- Inclusion/exclusion criteria.
- Contact the Interactive Phone/Web Response System (IXRS).
- Medical and surgical history.
- Current medical condition review.
- Demographics.
- Vital signs.
- Height and Weight.
- Complete physical examination.
- Clinical laboratory tests.
- [redacted]
- HbA1c.
- Serum pregnancy test.
- Hepatitis serology.
- IGRA test for TB (to be performed locally).
- Urinalysis.
- [redacted]
- [redacted]
  NOTE: A separate consent is required for this procedure.
- Dispense 24-hour urine collection materials.
- Adverse events (AEs) and concomitant medications.

Subjects who are taking immunosuppressant medication for FSGS at the time of the Screening Visit/Visit 1 must discontinue their use and complete a washout period of appropriate length before the Baseline Visit/Visit 2 (Table 4).

Table 4: Timing of Baseline Visit/Visit 2 Relative to FSGS Treatment at Screening

FSGS Treatment at Screening Visit/Visit 1	Timing of Baseline Visit/Visit 2
CNI	> 49 days and < 63 days after drug discontinuation
Corticosteroids, MMF	> 30 days and < 63 days after drug discontinuation
No treatment	Eligibility is confirmed and IMP is on-site.

Subjects will be allowed to repeat any screening procedure, if necessary, if it is within the screening time window. A screening procedure can be repeated only once; if the repeat procedure continues to be exclusionary, the subject will be a screen failure.

8.2. Baseline Visit/Visit 2 Procedures

The timing of the Baseline Visit/Visit 2 will depend on the washout period for the immunosuppressives the subject is taking at screening. The subject will collect a 24-hour urine 3 days prior (± 2 days) to Baseline Visit/Visit 2.

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

- Inclusion/exclusion criteria review; subject must meet all eligibility criteria at Screening Visit/Visit 1 *and* Baseline Visit/Visit 2.
- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight (height from Visit 1 will be used to calculate BMI at Visit 2).
- Clinical laboratory tests.
- Nonfasting lipid panel.
- [redacted]
- Urine pregnancy test.
- Urinalysis.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted].
- Subject diary training.
- Contact IXRS and dispense IMP kits.
- IMP administration under supervision of study staff and observation for at least 1 hour thereafter.
- AEs and concomitant medications.

8.3. Visit 3 Procedures (Week 4 ± 5 Days)

- Current medical condition review.

- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- Urine pregnancy test.
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- AEs and concomitant medications.

8.4. Visit 4 Procedures (Week 8 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- [redacted]
- Urine pregnancy test.
- Urinalysis.
- [redacted]
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- AEs and concomitant medications.

8.5. Visit 5 Procedures (Week 12 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.

- Clinical laboratory tests.
- Nonfasting lipid panel.
- HbA1c.
- Urine pregnancy test.
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS, dispense IMP kits.
- AEs and concomitant medications.

8.6. Visit 6 Procedures (Week 16 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- [redacted]
- Urine pregnancy test.
- Urinalysis.
- [redacted].
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- AEs and concomitant medications.

8.7. Visit 7 Procedures (Week 20 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.

- Urine pregnancy test.
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- Dispense 24-hour urine collection materials.
- AEs and concomitant medications.

8.8. Visit 8 Procedures (Week 24 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- Nonfasting lipid panel.
- HbA1c.
- [redacted]
- Urine pregnancy test.
- Urinalysis.
- [redacted]
- [redacted]
- [redacted]
- IMP accountability.
- [redacted]
- [redacted]
- Study diary retraining.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- AEs and concomitant medications.

8.9. Visit 9 Procedures (Week 26 + 5 Days)

- Current medical condition review.

- Limited physical examination.
- Vital signs.
- Weight.
- Urine pregnancy test.
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- AEs and concomitant medications.

8.10. Visit 10 Procedures (Week 30 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- Urine pregnancy test.
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- AEs and concomitant medications.

8.11. Visit 11 Procedures (Week 34 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- [redacted]
- Urine pregnancy test.
- Urinalysis.

- [redacted]
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- AEs and concomitant medications.

8.12. Visit 12 Procedures (Week 38 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- Nonfasting lipid panel.
- HbA1c.
- Urine pregnancy test.
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- AEs and concomitant medications.

8.13. Visit 13 Procedures (Week 42 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- [redacted].
- Urine pregnancy test.
- Urinalysis.
- [redacted]

- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- AEs and concomitant medications.

8.14. Visit 14 Procedures (Week 46 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- Urine pregnancy test.
- [redacted]
- IMP accountability.
- Study diary review.
- Contact IXRS and dispense IMP kits.
- Dispense 24-hour urine collection materials.
- AEs and concomitant medications.

8.15. Visit 15 Procedures (Week 50 ± 5 Days)

- Current medical condition review.
- Limited physical examination.
- Vital signs.
- Weight.
- Clinical laboratory tests.
- Nonfasting lipid panel.
- HbA1c.
- [redacted]
- Urine pregnancy test.
- Urinalysis.
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Study diary review.
- IMP accountability.
- Contact IXRS.
- AEs and concomitant medications.

8.16. End of Study/Early Termination Visit Procedures

All subjects will have an End of Study/Early Termination Visit 4 weeks after their last dose of IMP.

Subjects receiving IMP 3x/week, will have IMP tapered to 2x/week for 2 weeks at Week 50 and then discontinued. These subjects will return at Week 56 + 5 days for their End of Study Visit.

Subjects receiving IMP 2x/week will discontinue dosing without a taper. These subjects will return at Week 54 + 5 days for their End of Study Visit.

Subjects who discontinue study participation at any other time in the study will have their dose tapered to 1 mL SC 2x/week (if required) and return for the Early Termination Visit 4 weeks after their last dose of IMP.

The following assessment will be done at the End of Study/Early Termination Visit

- Current medical condition review.
- Complete physical examination.
- Vital signs, including weight.
- Clinical laboratory tests.
- Urine pregnancy test.
- Urinalysis
- IMP accountability (subjects who required taper only).
- Study diary review.
- Contact IXRS.
- AEs and concomitant medications.

8.17. Taper Safety Visit

- Current medical condition review.
- Limited physical examination.

- Vital signs.
- Weight.
- Clinical laboratory tests (if the reason for discontinuation was related to laboratory test results).
- IMP accountability.
- Study diary review.
- AEs and concomitant medications.

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1. Methods of Assigning Subjects to Treatment Groups

The investigator or designee will contact IXRS to register subjects at Visit 1. 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 ID numbers will consist of 7 digits: the first 4 digits reflect the site number assigned to the Investigator and the last 3 digits are the subject number.

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

In the event that a subject is rescreened within the screening window, they do not need a new subject ID number. At the Baseline Visit/ Visit 2, qualified subjects who meet all of the eligibility criteria will be enrolled into the study. The investigator or designee must contact IXRS to record each subject visit and receive the IMP kit assignments.

The investigator or designee must contact the IXRS to report subjects as a screen failure if the enrolled subject does not meet eligibility criteria at the Baseline Visit/Visit 2.

The investigator or designee must contact the IXRS to report all subject visits and status changes.

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

9.2. Emergency Identification of Investigational Medicinal Product

This is an unblinded study.

9.3. Dosing Procedures

The following Acthar treatments are to be administered. The study treatment schedule is as noted in Table 5.

Table 5: IMP Treatment Schedule

Study Week	Study Period	Study Drug	Dose
Weeks 0 to 50	Open Label/Open-label Extension	Acthar	1 mL SC 3x/week[a]
Weeks 50 to 51[b]	Follow-up Period (taper)	Acthar	1 mL SC 2x/week

[a]Dose can be tapered to 1 mL SC 2x/week for safety and/or tolerability reasons. If a subject ends study participation prior to Week 50, the dose of Acthar should be tapered to 1 mL SC 2x/week for 2 weeks.

[b]Subjects receiving Acthar 1 mL (80 U) SC 3x/week should be tapered to 1 mL SC 2x/week for 2 weeks, with a final visit 4 weeks after the last dose of Acthar. Subjects in the open-label extension receiving 1 mL SC 2x/week at Week 49 will stop dosing at the conclusion of Week 49, with a final Visit 4 weeks after the last dose of Acthar.

The subject or subject's caregiver will administer the first dose of IMP in the clinic under the supervision of study staff. The subject will remain in the clinic for at least 1 hour post dose to monitor for allergic or anaphylactic reaction(s). After Visit 2, all doses will be administered by the subject or the subject's caregiver at home.

Throughout the trial, IMP cannot be taken on 2 consecutive days and cannot be taken more than 3 days apart, regardless of dosing frequency.

9.3.1. Dose Reduction

The dosing of Acthar should be tapered from 3x/week to 2x/week for safety reasons if a subject meets any of the following criteria:

- Development of accelerated hypertension (defined as systolic blood pressure ≥ 180 *and* diastolic blood pressure ≥ 100 mm Hg) that cannot be managed with adjustment of concomitant medications such as antihypertensive medications.
- Development of an edema score of 4 at any visit that cannot be managed with adjustment of concomitant medications such as diuretics (see Section 24.2).
- Development of congestive heart failure that cannot be managed with adjustment of concomitant medications such as diuretics and antihypertensive medications.
- Development of diabetic signs/symptoms (ie, HbA1c > 8%, or fasting plasma glucose > 126 mg/dL, or classic symptoms of hyperglycemia with random plasma glucose > 200 mg/dL).
- Development of any other AE of at least moderate intensity that cannot be managed with adjustment of concomitant medications.

Any subject whose dose is tapered for any of the reasons described above will have a Taper Safety Visit scheduled 2 weeks after the start of the taper.

9.3.2. Treatment Discontinuation

Treatment with Acthar should be discontinued for safety purposes if the reduction in dosing to 2x/week **and** adjustment of concomitant medications does not manage the following:

- Persistent accelerated hypertension (defined as systolic blood pressure ≥ 180 *and* diastolic blood pressure ≥ 100 mm Hg).
- Persistent edema score of 4 (see Section 24.2).
- Persistent congestive heart failure.
- Persistent diabetic signs/symptoms (ie, HbA1c > 8%, or fasting plasma glucose > 126 mg/dL, or classic symptoms of hyperglycemia with random plasma glucose > 200 mg/dL).
- Any other AE of at least moderate intensity that cannot be managed with adjustment of concomitant medications.

The investigator should discontinue subjects for safety purposes any time during the study if the subject meets any of the following criteria:

- Development of unexplained and sustained (2 consecutive visits) worsening of disease defined as unresolved progression or 30% decline in eGFR from baseline, or if the subjects remains at significant risk of sequelae of nephrotic syndrome (such as serum albumin < 2.8 mg/dL) and sustained worsening of uPCR (increase > 50% from baseline).
- Development of ESRD and requirement for chronic renal replacement therapy.
- Administration of live or live-attenuated vaccines after Screening Visit/Visit 1.
- Diagnosis of a malignancy or lymphoproliferative disorder.
- Pregnancy during the course of the study.
- Development of an independent disease that requires treatment with immunosuppressive therapy or plasma exchange therapy.
- Development of a contraindication to IMP use.
- Use of any investigational drug, device, or procedure as part of a research study.

9.4. Description of IMP

Acthar is a highly purified sterile preparation of prolonged-release porcine ACTH analogue in 16% gelatin for intramuscular or SC injection. Acthar contains 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH, and water for injection. Acthar is obtained from processing porcine pituitary using a FDA approved process.

Acthar is 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.

9.5. Storage of Clinical Supplies

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

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

9.6. Drug Accountability

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

9.7. Compliance Monitoring

Prior to beginning the administration of IMP, 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 a study diary entries to record all IMP administration and will bring it, along with all IMP kits including used vials to each visit. Each time IMP 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 IMP administration.

10. SAFETY ASSESSMENTS AND PROCEDURES

The following safety assessments will be evaluated: AEs, physical examinations, clinical laboratory test results (chemistry, hematology, HbA1c, [redacted], and urinalysis, [redacted] 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 1). Additional (unscheduled) safety assessments may be performed as needed.

10.1. Adverse Events

AEs will be collected from signing of the ICF and followed by the investigator until the AE is resolved or stabilized. AEs occurring prior to the administration of IMP will only be reported if they are related to study procedures. 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 13.4 for additional details on the handling of AEs and SAEs.

10.2. Medical and Surgical History

Medical and surgical history will be obtained at the Screening Visit/Visit 1. 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.

10.3. 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/Visit 1 will be recorded as AEs, as appropriate.

10.4. Physical Examinations

A complete physical examination will be performed at the Screening Visit/Visit 1 and the End of Study/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, extremities and assessment for edema will be done at all other visits.

The findings of the physical examinations will be recorded. Any change from the Screening Visit/Visit 1 physical examination that is considered clinically significant by the investigator will be recorded as an AE.

10.5. 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 Visit/Visit 1 and the Baseline Visit/Visit 2, 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.

At a minimum, the date of vital signs at the Screening Visit/Visit 1 will be recorded. The date and time for all other vital signs will be recorded.

Screening/Baseline

A subject with systolic blood pressure > 150 mm Hg and diastolic blood pressure > 90 mm Hg (average of 3 assessments) at the Screening Visit/Visit 1 or Baseline Visit/Visit 2 does not qualify for the study.

On Study Assessments

If an on-study vital sign is not in the 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.

10.6. Height and Weight

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

10.7. Clinical Laboratory Tests, HbA1c, Serum Cystatin C, Serum Electrolytes,IGRA, Urinalysis, and Pregnancy Tests

The clinical laboratory tests are listed in Section 24.1. 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, storage and shipment of clinical laboratory samples will be provided in a separate laboratory manual.

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 Visit/Visit 1, and a urine pregnancy test at the Baseline Visit/Visit 2 and at specified visits throughout the study. Results must be available prior to dosing with protocol mandated IMP. Subjects with positive results will be ineligible for study entry (Screening Visit/Visit 1) 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 13.5.

  If applicable, the subject's agreement to use contraception throughout their study participation, and for 4 weeks after ending study participation, will be documented.
- HBsAg and HBcAb will be performed at the Screening Visit/Visit 1. Results of these tests must be negative or nonreactive for subjects to qualify for the study.
- HCV will be performed at the Screening Visit/Visit 1. A positive HCV will automatically trigger a HCV PCR analysis. HCV PCR must be < 25 IU/mL to qualify for the study.

- IGRA for TB will be performed at the Screening Visit/Visit 1. Results of this test must be negative for subjects to qualify for the study.
- HbA1c.
- Non-fasting lipid panel including total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides.
- [redacted]

Out-of-range Laboratory Values

Laboratory values from samples collected at the Screening Visit/Visit 1 will be evaluated by the investigator for eligibility of the subject in the study.

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.

11. EXPLORATORY ASSESSMENTS

The following exploratory assessments will be evaluated at times specified in the Schedule of Study Events (Table 1).

[redacted]

[redacted]

12. STATISTICAL METHODS AND PLANNED ANALYSIS

12.1. General Considerations

Data will be listed, analyzed, and included in the clinical study report. Data will be analyzed as described in the statistical analysis plan. Descriptive statistics for continuous variables will include number of values, mean, SD, median, minimum, and maximum, unless otherwise noted. Frequency and percentages will be calculated for categorical variables. All statistical significance testing will be 2-tailed using $\alpha = 0.05$, unless otherwise specified. Data summary and analyses will be performed with SAS 9.2 or higher.

12.2. Analysis Populations

- The Intent to Treat (ITT) Population will include all enrolled subjects who receive 1 or more doses of IMP and who contribute any exploratory data to the study.
- The Per Protocol Population will include the subset of the ITT population who complete the study as per protocol. Completer populations will be further defined in the statistical analysis plan.
- The Safety Population will include all enrolled subjects who receive 1 or more doses of IMP.

12.3. Efficacy Assessments

12.3.1. Primary Efficacy Endpoint

There is no primary efficacy endpoint.

12.3.2. Secondary Efficacy Endpoints

There are no secondary efficacy endpoints.

12.4. Primary Safety Endpoints

The primary safety endpoints to be evaluated include a summary of the general safety profile including AEs (serious and non-serious), physical examinations, clinical laboratory tests, vital signs, medical and surgical history, height and height.

12.5. Exploratory Endpoints

Exploratory endpoints will examine [redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	

Exploratory endpoints include:

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

12.6. Subject Characteristics

12.6.1. Demographics

All dosed subjects enrolled in the study will be included in a listing of subject demographic characteristics. Summary statistics tables will present the data for all dosed subjects combined as well as for completers only.

12.6.2. Medical and Surgical History

The medical and surgical history data will not be summarized but will be presented in a data listing.

12.6.3. Concomitant Medications

Concomitant medications will not be summarized but will be presented in a data listing.

12.6.4. Subject Disposition and Exposure to IMP

The number of subjects who complete the study and who do not complete the study, both overall and according to reasons for discontinuation from the study, will be summarized for all dosed subjects. Subject disposition will be presented in a data listing.

12.7. Safety Analysis

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

12.7.1. Adverse Events

AEs will be coded using MedDRA. All AEs will be presented in a data listing. Only treatment-emergent adverse events (TEAEs) will be included in all summaries.

TEAEs, treatment related TEAEs, severity of TEAEs, and TEAEs leading to early discontinuation will be summarized by system organ class and preferred term for all dosed subjects at the treatment level and overall. All TEAEs leading to early discontinuation will be presented in data listings.

12.7.2. Clinical Laboratory Tests

Clinical laboratory testing will be presented in data listings.

12.7.3. Physical Examination Findings

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

12.7.4. Vital Signs/Height and Weight

Vital sign measurements (diastolic blood pressure, systolic blood pressure, respiratory rate, pulse rate, body temperature, weight and height) will be presented in a data listing.

12.8. Interim Analysis

Not applicable.

12.9. Statistical Power and Sample Size Consideration

Formal sample size calculations were not performed.

12.10. 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.

13. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

13.1. Safety

For safety information about Acthar refer to the most recent version of the Prescribing Information (Mallinckrodt ARD LLC, 2015).

13.2. Definitions

Adverse Event

An AE is any untoward or undesirable medical occurrence in a subject who is administered an IMP, which does not necessarily have to have a causal relationship with this treatment. Examples of AEs include but are not limited to:

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

An unexpected AE is defined as an AE, the nature and severity of which is not consistent with the applicable product information in the most recent version of the Investigator's Brochure.

Serious Adverse Event

A serious adverse event (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 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) is not considered an SAE in Mallinckrodt clinical studies.

13.3. Adverse Event and Serious Adverse Event Classifications

IMP Relatedness

The following classifications should be used when evaluating the relationship of AEs or SAEs to study treatment (Table 7).

Table 7: 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

Relationship	Definition
	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 8.

Table 8: 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.

13.4. Adverse Event and Serious Adverse Event Recording and Reporting

AEs and SAEs will be collected from signing of the ICF through completion of the end of study/early termination visit. All AEs and SAEs should be recorded in source documents; all AEs and SAEs that occur following the first dose of IMP should also be recorded in the eCRF. 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 first dose at the Baseline Visit/Visit 2, only AEs and SAEs related to study procedures will be recorded on the eCRF. 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 9.

Table 9: 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

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

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

- For all SAEs, the investigator, or designee, must complete the SAE Report Form with the minimum information required by FDA and ICH and fax it to Mallinckrodt at +1 314-654-5759 or email at pvclinical@mnk.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.

13.5. Pregnancy Reporting

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

Pregnancy exposure to an investigational medicinal product, except for exposure to prenatal vitamins. Subjects should not become pregnant during the study. If the subject becomes pregnant, study treatment must be discontinued immediately. The investigator must report the pregnancy by submitting the appropriate form to Global Pharmacovigilance (fax at +1 314-654-5759 or email at pvclinical@mnk.com within 24 hours of confirmation of a pregnancy (ie, positive serum pregnancy test result). The outcome of pregnancy (eg, spontaneous abortion, live birth, still birth, congenital anomalies, birth defects) must be reported by submitting the

appropriate form to Global Pharmacovigilance (fax at +1 314-654-5759 or email at pvclinical@mnk.com within 24 hours of the pregnancy outcome being submitted to the study site. If the pregnancy results in a live birth, a postdelivery follow-up will be performed at least 28 days after the baby is born and must be reported to Global Pharmacovigilance (fax at +1 314-654-5759 or email at pvclinical@mnk.com) within 24 hours of the study site becoming aware of the follow-up information. Both maternal and paternal investigational medicinal product exposures are collected.

If the female partner of a male subject becomes pregnant during the study, the site will forward the Pregnancy Notification form and the Pregnancy Report Fax cover page to Global Pharmacovigilance (fax at +1 314-654-5759 or email at pvclinical@mnk.com), within 24 hours of being notified. The outcome of pregnancy (eg, spontaneous abortion, live birth, still birth, congenital anomalies, birth defects) must be reported by submitting the appropriate form to Global Pharmacovigilance (fax at +1 314-654-5759 or email at pvclinical@mnk.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 pvclinical@mnk.com) within 24 hours of the study site becoming aware of the follow-up information.

14. SUBJECT DISCONTINUATION OR WITHDRAWAL

14.1. 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 end of study/early termination safety assessments (see Section 8.16) 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 IMP 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.

Death

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

Lost to Follow-up

Every effort should be used to maintain contact with subjects during their participation in the study. A subject may be considered lost to follow-up if the there is no response to 3 attempts to

reach the subject by telephone and no response to a certified letter sent to the last known address of the subject. Efforts to contact the subject should be noted in source documentation.

Met Withdrawal Criteria

If a subject develops a condition that meets any of the exclusion criteria (Section 6.2) or fails to meet an inclusion criteria (Section 6.1) 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 9.3.2).

Other

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

For subjects who discontinue or are withdrawn from the study for any reason, the investigator will notify the sponsor and when possible, the subject will be required to have the early termination safety assessments (Section 8.16) to assess their continued well-being.

15. 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.

16. 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.

17. QUALITY CONTROL AND ASSURANCE

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

17.1. 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.

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

18.1. 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.

18.2. Sponsor

The eCRF data are stored in a database and processed electronically. The sponsor’s medical monitor 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.

19. 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.

20. 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.

21. BIOLOGICAL SAMPLES

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

22. PUBLICATION POLICY

22.1. 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.

22.2. Investigator's Ability to Publish

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

23. REFERENCES

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24. ATTACHMENTS

24.1. Attachment 1: Clinical Laboratory Tests

Serum Chemistry	
Alanine aminotransferase (ALT)	Creatinine
Albumin (total)	Cystatin C
Alkaline phosphatase	Glucose
Aspartate aminotransferase (AST)	Hemoglobin A1c
Bilirubin (total)	Phosphorus
Blood urea nitrogen	Potassium
Calcium	Protein, total
CO_2	Sodium
Chloride	Uric acid
Lipid Panel	
Total cholesterol	LDL
HDL	Triglycerides
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	

Serum Chemistry	
[redacted]	
[redacted]	
[redacted]	
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)	
[redacted]	
[redacted]	

24.2. Attachment 2: Evaluation of Edema

The presence of edema will be assessed using the following guidelines. Firm pressure should be applied by thumb for 5 to 10 seconds over a bony area.

Evaluation of Edema

Score*	**0**	**1**	**2**	**3**	**4**
Depth of pit	None	0-2mm	2-4 mm	4-6 mm	6-8 mm
Description of pit	none	slight pitting	somewhat deep pit	pit is noticeably deep	pit is very deep
Time to pit disappearance	none	disappears rapidly	10-15 seconds	1-2 minutes	> 2 minutes
Visible distortion	none	none	none readily detectable	dependent extremity appears fuller and swollen	dependent extremity is grossly distorted

*Assessment Chart for Pitting Edema adapted from the Guelph General Hospital Congestive Heart Failure Pathway.

Edema should also be categorized as 1 or more of the following types:

Categorization of Edema

Type	**Presacral**	**Anasarca**	**Brawny**
Localization	pelvis	general	skin
Edema	evaluated as above	generalized	accompanied by fibrotic skin changes that may not pit

24.3. Attachment 3: Secondary Causes of FSGS

1. Familial	a. Mutations in [redacted] b. Mutations in [redacted] c. Mutations in [redacted] d. Mutations in [redacted] e. Mutations in [redacted] f. Mutations in [redacted] g. Mutations in [redacted] h. Mutations in [redacted] i. [redacted]
2. Virus associated	a. HIV-associated nephropathy b. Parvovirus B19
3. Medication	a. Heroin-nephropathy b. Interferon-a c. Lithium d. Pamidronate/alendronate e. Anabolic steroids
4. Adaptive structural-functional responses likely mediated by [redacted]	4.1 Reduced kidney mass a. Oligomeganephronia b. Unilateral kidney agenesis c. Kidney dysplasia d. Cortical necrosis e. Reflux nephropathy f. Surgical kidney ablation g. Chronic allograft nephropathy h. Any advanced kidney disease with reduction in functioning nephrons 4.2 Initially normal kidney mass a. Diabetes mellitus b. Hypertension c. Obesity

1. Familial	a. Mutations in [redacted] b. Mutations in [redacted] c. Mutations in [redacted] d. Mutations in [redacted] e. Mutations in [redacted] f. Mutations in [redacted] g. Mutations in [redacted] h. Mutations in [redacted] i. [redacted]
	d. Cyanotic congenital heart disease e. Sickle cell anemia
5. Malignancy [redacted]	
6. Nonspecific pattern of FSGS caused by kidney scarring in glomerular disease	a. Focal proliferative glomerulonephritis (IgA nephropathy, lupus nephritis, pauci-immune focal necrotizing and crescentic glomerulonephropathy) b. Hereditary nephritis (Alport syndrome) c. Membranous glomerulopathy d. Thrombotic microangiopathy

Source: Adapted from Barsoni et al, 2007.