NCT04169061

CLINICAL STUDY PROTOCOL

A Multicenter, Open-Label Study to Assess the Efficacy and Safety of Acthar® Gel in Subjects with Severe Keratitis

Protocol Number: MNK14084113

Date of Original Protocol: 08 August 2019

Date of Protocol Amendment 1: 12 August 2019

Date of Protocol Amendment 2: 11 September 2019

Mallinckrodt ARD LLC
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AMENDMENT HISTORY

Protocol Amendment 2 Summary of Changes:

Protocol Amendment 2 was created to:

1. Remove asessments and language in the protocol related to [redacted] due to its proprietary nature
2. Include a 4 week Acthar tapering period, which followed the 12 week treatment period of the study
    a. Because of the addition of an Acthar tapering period, Visit 7 was changed from a safety phone call to an in-person safety visit
3. Stringency of Hepatitis C virus (HCV) assay reporting by the clinical testing laboratory is less detailed than was originally planned for the study, so details on the HCV assay were updated to highlight the more qualitative nature of the assay results

Protocol Amendment 1 Summary of Changes:

Protocol Amendment 1 was created to remove [redacted] from the screening assessment.

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 guidance documents and regulations including, but not limited to:

* ICH E6(R2): Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, which has its ethical foundation in the Declaration of Helsinki

* the US Code of Federal Regulations (CFR) (as appropriate, including 42 CFR 11: Final Rule for Clinical Trials Registration and Results Information Submission)

* NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

* all applicable national and local regulations (as appropriate, including the EU Clinical Trials Regulation)

* protections for privacy (as appropriate, including the EU General Data Protection Regulation (GDPR)

* provisions of all local ethics committees

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

[redacted]
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Reason: I am approving this document
Date: 2019.09.11 15:34:48 -04'00'
Adobe Acrobat version: 11.0.19

Sponsor Signature

11 September 2019

Date of Signature
(DD Month YYYY)

[redacted], PhD

Sponsor Name (print)

INVESTIGATOR SIGNATURE

I have read the MNK14084113 clinical study protocol and pledge that this study will be conducted in accordance with the protocol. In addition, by completing and signing the Statement of Investigator (FDA-Form 1572), I agree to abide, for the duration of this clinical trial, by all applicable guidance documents laws and regulations including, but not limited to:

* ICH E6(R2): Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, which has its ethical foundation in the Declaration of Helsinki

* the US Code of Federal Regulations (CFR) (as appropriate, including 42 CFR 11: Final Rule for Clinical Trials Registration and Results Information Submission)

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

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ACTH	adrenocorticotropic hormone
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BCVA	Best corrected visual acuity
CFR	Code of Federal Regulations
CI	Confidence interval
eCRF	Electronic case report form
ET	Early Termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HbA1c	glycosylated hemoglobin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
IDEEL	Impact of Dry Eye on Everyday Life
ICF	Informed consent form
ICH	International Council for Harmonisation
IGRA	Interferon gamma release assay
ID	Identification
IEC	Independent Ethics Committee
INR	International normalized ratio
IOP	Intraocular pressure
IRB	Institutional Review Board

Abbreviation	Term
IXRS	Interactive Phone/Web Response System
LASIK	Laser-assisted in situ keratomileusis
logMAR	Logarithm of the Minimum Angle of Resolution
MCR	Melanocortin receptors
MM	Medical monitor
ODS	Ocular Discomfort Score
OTC	Over-the-counter
PRO	Patient-reported outcomes
QOL	Quality of life
QTcF	QT interval corrected using Fridericia's Formula
SAE	Serious adverse event
SC	Subcutaneously
SD	Standard deviation
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor- alpha
U	Units
ULN	Upper limit of normal
US	United States
VAS	Visual Analogue Scale

SYNOPSIS

Study Title: A Multicenter, Open-label Study to Assess the Efficacy and Safety of Acthar® Gel in Subjects with Severe Keratitis	
Protocol Number: MNK14084113	Type: Interventional/Phase 4
Condition/Disease: Severe or Recalcitrant Keratitis	
Approximate Number of Subjects: Up to 36 subjects enrolled	Approximate Duration of Subject Participation: 22 weeks
Approximate Number of Study Centers: 6	Approximate Duration of Study: 1 year

Rationale:

Noninfectious keratitis can result from many different etiologies including systemic autoimmune disorder. Inflammatory cells express melanocortin receptors (MCRs) and anecdotal evidence suggests that adrenocorticotropic hormone (ACTH) gel, a MCR agonist, is beneficial in treating ocular inflammation and alleviating the associated symptoms (Perez, 2019). Acthar is believed to exert its effect through the activation of multiple MCRs present in immune cells, as well as in the eye, and the induction of cortisol in the adrenocortex. The introduction of Acthar to the treatment algorithm for keratitis may provide a treatment option when early treatments have failed or were not well tolerated.

The study is being conducted to explore the efficacy and safety of Acthar in subjects with severe keratitis to better understand how different clinical parameters observed within the spectrum of this condition might be impacted by treatment with Acthar® Gel.

Objectives and Endpoints:

To evaluate the safety and efficacy of Acthar in subjects with severe keratitis when treated with Acthar gel. Efficacy endpoints include corneal staining, conjunctival staining, conjunctival redness, tear production, tear film stability, dryness, ocular discomfort, grittiness, burning, stinging, Quality of Life, and cytokine array levels. Safety endpoints include the incidence and severity of ocular adverse events (AEs), incidence and severity of other AEs, new or worsening cataracts, and the mean change in intra-ocular pressure (IOP).

Outcome Measures:

Primary: The proportion of responders who improved on the IDEEL score.

Secondary: Not applicable.

Overall Design:

This is a multicenter, multiple dose, open-label study to examine the efficacy of Acthar in adult subjects 18 years of age or older with a diagnosis of keratitis sicca. Up to 36 subjects with severe or recalcitrant keratitis who did not respond or tolerate treatment with topical cyclosporine or any immunosuppressant to treat keratitis will be enrolled. Subjects who meet entry criteria will be treated with Acthar 1 mL (80 units [U]) subcutaneously (SC) 2x (twice) per week for 12 weeks. After this 12 weeks, Acthar will be tapered over 4 weeks. The 80 U dose will be reduced to 40 U 2x/week for 2 weeks, followed by 40 U 1x/week for 2 additional weeks. Subjects will be reassessed at an in-clinic

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safety visit, 4 weeks after the last treatment dose for AE assessments and concomitant medication use. Endpoints will be measured at Baseline (Visit 2 [Day 1]), and Visit 3 through 6.	
Number of Subjects: Up to 36 subjects will be enrolled in this study at approximately 6 sites in the US.	
Treatment Groups and Duration: Subjects with severe or recalcitrant keratitis who did not respond or tolerate treatment with topical cyclosporine or any immunosuppressant to treat keratitis will be enrolled. Subjects will participate in the study for approximately 22 weeks, including a screening period of up to 28 days, an active treatment period of 12 weeks, an Acthar taper period of 4 weeks, and a follow up in-person safety visit 4 weeks after the last dose of study drug.	

SCHEDULE OF STUDY EVENTS

Table 1: Schedule of Study Events

Study procedures	Visit 1 Screening Day -28 to-1	Visit 2 Baseline Day 1	Visit 3 Phone Day 15 ±1	Visit 4 In Clinic Day 29 ±2	Visit 5 In Clinic Day 43 ±2	Visit 6 In Clinic Day 85 ±3	Visit 7 In Clinic / End of Acthar Taper Day 113 ±3	Early Termination
Informed consent	X							
Urine pregnancy test	X							
Demographic data, medical, surgical, ophthalmic history	X							
Patient-Reported Outcomes								
ODS	X	X		X	X	X		X
IDEEL and VAS		X	X	X	X	X		X
Ophthalmic examination								
Visual Acuity	X	X		X	X	X	X	X
Slit Lamp Evaluation	X	X		X	X	X	X	X
Conjunctival redness	X	X		X	X	X		X
Tear film breakup time	X	X		X	X	X		X
Inferior corneal staining score	X	X		X	X	X		X

Study procedures	Visit 1 Screening Day -28 to-1	Visit 2 Baseline Day 1	Visit 3 Phone Day 15 ±1	Visit 4 In Clinic Day 29 ±2	Visit 5 In Clinic Day 43 ±2	Visit 6 In Clinic Day 85 ±3	Visit 7 In Clinic / End of Acthar Taper Day 113 ±3	Early Termination
Superior, central and total corneal staining score (fluorescein)	X	X		X	X	X		X
Nasal, temporal and total conjunctival staining score (lissamine green)	X	X		X	X	X		X
Schirmer's Test	X	X		X	X	X		X
IOP	X					X	X	X
Undilated Fundoscopy	X					X	X	X
Inclusion/Exclusion critera review	X	X						
Height [a] and weight	X	X				X	X	X
Vital signs [b]	X	X		X	X	X	X	X
Physical examination	X					X		X
Laboratory testing								
Chemistry and others [c]	X	X		X	X	X		X
HbA1c	X	X		X	X	X		X
Serum Pregnancy	X	X		X	X	X		X

Study procedures	Visit 1 Screening Day -28 to-1	Visit 2 Baseline Day 1	Visit 3 Phone Day 15 ±1	Visit 4 In Clinic Day 29 ±2	Visit 5 In Clinic Day 43 ±2	Visit 6 In Clinic Day 85 ±3	Visit 7 In Clinic / End of Acthar Taper Day 113 ±3	Early Termination
Hepatitis Serology [d]	X							
IGRA for TB	X							
Immunological protein assay [e]	X	X				X		X
IXRS contact	X	X		X	X			X
Study Therapy								
Study drug and injection record training		X						
Dispense study drug		X		X	X			
Administer first dose in clinic [f]		X						
Adverse event assessment	X	X	X	X	X	X	X	X
Injection record review				X	X	X	X	X
Concomitant treatment review		X	X	X	X	X	X	X
Start Acthar Taper						X		
End Acthar Taper							X	
Study exit							X	X

AE = adverse events; ET = early termination; HbA1c = glycosylated hemoglobin; IDEEL = Impact of Dry Eye on Everyday Life; IGRA = Interferon gamma release assay; IOP = Intraocular Pressure; ODS = Ocular Discomfort Score; TB = tuberculosis; VAS = Visual Analogue Scale.

[a] Height at screening only. Weight at screening, Visits 2, 6, and ET.

[b] Blood pressure, respiratory rate, pulse rate and body temperature. For blood pressure, an average of 2 readings after the subject has been seated for ≥ 5 minutes at the Screening and Baseline Visits. Single readings after subject has been seated for ≥ 5 minutes at all other time points.

[c] Refer to Section 9.2.

[d] HBsAg, HBcAb, and HCV.

[e] Refer to Table 2.

[f] The first dose will be administered at the clinic and the subject should be observed for at least 1 hour after dosing.

1. BACKGROUND INFORMATION AND RATIONALE

1.1. Disease/Condition Under Study

Keratitis is a painful inflammation of the cornea which can result in partial or total loss of vision if left untreated and is a significant cause of ocular morbidity around the world (Sharma, 2001). It can result from infectious agents (eg, microbes including bacteria, fungi, amebae, and viruses) (Collier, 2010) or from noninfectious causes (eg, eye trauma, chemical exposure, and ultraviolet exposure). Conditions that affect the integrity of the ocular surface epithelium (exposure keratitis, neurotrophic keratitis, keratomalacia, recurrent corneal erosions) may also lead to development of sterile corneal ulcers. Non-infectious corneal ulcers may be associated with various collagen vascular or other autoimmune diseases, sometimes as the presenting sign of the disease (Donzis, 1987).

As described in the Package Insert, Acthar® Gel (repository corticotropin injection, hereafter referred to as Acthar) is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH) analogues and other pituitary peptides (Mallinckrodt Package Insert, 2019) currently approved for the treatment of ocular inflammatory conditions including keratitis. ACTH is a member of the family of structurally related peptides known as melanocortin peptides. Melanocortin peptides, which include ACTH, as well as, α-, β-, and γ-melanocyte stimulating hormones, are derived from the natural protein pro-opiomelanocortin and exert their physiologic effects by binding to cell surface G-protein coupled receptors known as melanocortin receptors (MCRs) (Mountjoy, 1992). Five subtypes of MCRs have been identified to date (MC1R to MC5R), each with different tissue distributions, binding affinity characteristics, and physiological roles (Getting, 2006) (Montero-Melendez, 2015). ACTH binds to all 5 subtypes of MCR (Schioth, 1995).

A detailed description of the chemistry, pharmacology, efficacy, and safety of Acthar is provided in the (Acthar® Gel Package Insert, 2019)

1.2. Study Rationale

Noninfectious keratitis can result from many different etiologies including systemic autoimmune disorder. Inflammatory cells express melanocortin receptors (MCRs) and anecdotal evidence suggests that Acthar Gel, a MCR agonist, is beneficial in treating ocular inflammation and alleviating the associated symptoms (Perez, 2019). Acthar is believed to exert its immunomodulatory effect through the activation of multiple MCRs present in immune cells, as well as in the eye, and the adrenocortex. The introduction of Acthar to the treatment algorithm for keratitis may provide a treatment option when early treatments have failed or were not well tolerated.

The study is being conducted to explore the efficacy and safety of Acthar in subjects with severe keratitis to better understand how different clinical parameters observed within the spectrum of this condition might be impacted by treatment with Acthar® Gel.

1.3. Assessment of Potential Benefits and Risks

Common adverse reactions for Acthar include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.

Prolonged use of Acthar may produce posterior subscapular cataracts, glaucoma with possible damage to the optic nerves, and may enhance establishment of secondary ocular infections due to fungi and viruses. For a complete reference of known potential risks, refer to the Acthar® Gel Package Insert, 2019. More detailed information about the known and expected benefit, risks, and reasonably expected adverse events (AE) can be found in the Acthar® Gel Package Insert, 2019.

2. OBJECTIVES

To further evaluate the safety and efficacy of Acthar in subjects with severe keratitis when treated with Acthar gel.

2.1. Assessments of Efficacy

Table 2: Efficacy Assessments for Study MNK14084113

Efficacy Assessments	
Corneal Staining	Inferior, superior, central and total cornea regions as measured by the Ora Calibra™ Corneal Staining Scale (0 - 4)
Conjunctival Staining	Nasal, temporal and total conjunctiva regions as measured by the Ora Calibra™ Conjunctival Staining Scale (0-4)
Conjunctival Redness	As measured by the Ora Calibra™ Conjunctival Redness Scale (0 - 4)
Tear Production	Schirmer's Test (mm)
Tear Film Stability	Tear Film Break-Up Time (seconds)
Dryness	As measured by the 0 - 100 mm Visual Analogue Scale (VAS)
Ocular Discomfort	As measured by the Ora Calibra™ Ocular Discomfort Scale (0 - 4)
Ocular discomfort, dryness, grittiness, burning and stinging	As measured by the Ora Calibra™ 4-symptom Questionnaire (0 - 5)
Quality of Life	As measured by IDEEL (Impact of Dry Eye on Everyday Life)
Immunological protein assay	Protein assay to detect levels of the cytokine array [interleukin 1,6,17; interferon-ɤ]; ratio of T helper cells to T regulatory cells

2.2. Assessment of Safety

The frequency of adverse events (AEs), AEs of special interest (AESIs); clinical laboratory tests; metabolic panel; vital signs; physical examination; and ophthalmic findings (best corrected visual acuity, intraocular pressure, slit lamp examination, undilated eye examination) will be used to detect the presence of a safety signal(s).

2.3. Outcome Measures

The primary outcome measure is the proportion of responders who improved on the IDEEL score. There are no secondary outcome measures.

3. STUDY DESIGN

3.1. Overall Design

This is a multicenter, multiple dose, open-label study to examine the efficacy of Acthar in adult subjects 18 years of age or older with a diagnosis of keratitis sicca. Up to 36 subjects with severe or recalcitrant keratitis who did not respond or tolerate treatment with topical cyclosporine or any immunosuppressant to treat keratitis will be enrolled. Subjects who meet entry criteria will be treated with Acthar 1 mL (80 units [U]) subcutaneously (SC) 2x (twice) per week for 12 weeks, followed by a 4 week taper period of 40 U 2x/week for 2 weeks then 40 U 1x/week for 2 more weeks. Subjects will be reassessed at an in-clinic safety visit, 4 weeks after the last treatment dose for AE assessments, and concomitant medication use. Endpoints will be measured at Baseline and all other visits.

3.2. Duration of Subject Participation

Subjects will participate in the study for approximately 22 weeks, including a screening period of up to 28 days, an active treatment period of 12 weeks, an Acthar taper period of 4 weeks, and a follow up in-person safety visit 4 weeks after the last treatment dose of study drug.

3.3. 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 1 year to complete.

3.4. Number of Subjects

Up to 36 subjects will be enrolled in this study at approximately 6 sites in the US.

3.5. Treatment/Dose Rationale

According to the Acthar Package Insert, the dosage should be individualized depending on the disease under treatment and the medical condition of the patient. The usual dose of Acthar is 40 to 80 U (0.5 to 1 mL) given subcutaneously every 24 to 72 hours (Acthar® Gel Package Insert, 2019). In a survey of patients with ocular inflammatory disease that had been treated with Acthar and had registered with the sponsor's patient support services, those with keratitis were most often treated with a subcutaneous injection of 80 U mL of Acthar 2x/week. To take into account the patient survey results, 80 U 2x/week was selected as the dose for this study. (Mallinckrodt Acthar Data Compendium, 2018).

Following the 12 week period of treatment with 80 U, Acthar will be tapered over a 4 week period. The 80 U dose will be reduced to 40 U 2x/week for 2 weeks, followed by 40 U 1x/week for 2 additional weeks.

3.6. End of Study Definition

A subject is considered to have completed the study if the subject has completed the final assessments at Visit 7.

The end of the study is defined as the completion of the final assessment for the last subject enrolled in the trial.

4. STUDY POPULATION

Prospective approval of protocol deviations in recruitment and enrollment criteria, also known as protocol waiver or exemption, is not permitted.

4.1. Inclusion Criteria

To be eligible to participate in the study, at the Screening Visit and the Baseline Visit (except as noted below) each subject must:

1. 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. Be 18 years of age or older at the Screening Visit and may be male or female;
3. Have normal lid anatomy;
4. Have a reported history of severe keratitis in one or both eyes and a history of previous treatment for keratitis within the previous 6 months;
5. Did not respond adequately or did not tolerate previous treatment with topical cyclosporine or LFA-1 antagonist;
6. Have all the following in at least one eye (the same eye) at screening and baseline:
    a. Have an inferior corneal fluorescein staining score of at least 2 points in any field (Ora Calibra™ Scale) in at least one eye at the Screening and Baseline visits;
    b. Have a sum corneal fluorescein staining score ≥ 4, based on the sum of the central, superior, and inferior regions of the cornea (Ora Calibra™ Scale) in at least one eye at the Screening and Baseline Visits;
    c. Have a sum lissamine green conjunctival score of ≥ 2, based on the sum of the temporal and nasal regions of the conjunctiva (Ora Calibra™ Scale) in at least one eye at Screening and Baseline visits;
    d. Have a conjunctival redness score ≥ 1 (0-4 point Ora scale) in at least one eye at the Screening and Baseline Visits;
    e. Have a Schirmer score ≥ 1 mm and ≤ 10 mm/5min in at least one eye at the Screening and Baseline Visits;
    f. Have an Ocular Discomfort Score (ODS) of ≥ 2 (0-4 point Ora scale) in at least one eye at the Screening and Baseline Visits;
7. If female, of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation; or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating, and agree to use 2 forms of effective contraception when with a male partner for the duration of the study (through Visit 6). 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, surgical sterilization of the male partner), and abstinence;

8. If male with reproductive potential, agree to use 2 forms of effective contraception (abstinence, surgical sterilization [vasectomy], or condom with spermicide) with a female partner for the duration of the study (through Visit 6);
9. Subjects must have a mean systolic blood pressure ≤ 150 mm Hg and a diastolic blood pressure of ≤ 90 mm Hg determined by the average of 2 seated readings taken at least 5 minutes apart at the Screening and Baseline Visits;
10. Be able to communicate effectively with study personnel;
11. Be able and willing to follow all protocol requirements and study restrictions;
12. Be able and willing to return for all study visits

4.2. Exclusion Criteria

A subject is ineligible for study participation if the subject meets any of the following criteria at the Screening or Baseline Visit:

1. Subject is from a vulnerable population, as defined by the US CFR Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc.) or a family member of the research staff conducting the study, or of the sponsor, or of the clinical research organization, or of the IRB/IEC;
2. Have any ocular condition that, in the opinion of the investigator, could affect study parameters including, but not limited to, glaucoma, diabetic retinopathy, blepharitis, meibomian gland disease, lid margin inflammation, ocular allergies, follicular conjunctivitis, iritis, uveitis, neuropathic pain and/or active ocular inflammation not related to keratitis;
3. Have a history of laser-assisted in situ keratomileusis (LASIK) or similar type of corneal refractive surgery within 12 months prior to the Baseline visit, and/or any other ocular surgical procedure (eg, cataract surgery, eyelid surgery) within 12 months prior to the Baseline Visit; or any scheduled ocular surgical procedure during the study phase;
4. Have active or any history of ocular herpes; and other ocular infection within 30 days prior to the Baseline visit;
5. Have current punctal plugs (within 30 days prior to Screening visit), punctal occlusion, or history of nasolacrimal duct obstruction;
6. Be unwilling to avoid wearing contact lenses for 7 days prior to the Screening visit and for the duration of the study phase;
7. Have best corrected visual acuity < 0.7 Logarithm of the Minimum Angle of Resolution (logMAR) in each eye at the Screening and Baseline Visits;
8. Use prohibited prescription or over-the-counter (OTC) medications or devices and be unable to discontinue their use for the required period before entry into the study as follows:

a. Ophthalmic cyclosporine (Restasis®) or ophthalmic lymphocyte function-associated antigen-1 (LFA-1) antagonist (Xiidra®): 12 weeks prior to the Screening visit;

b. Corticosteroids (topical and systemic), ocular autologous serum, antibiotics (topical and systemic), mast cell stabilizers (topical and systemic), vasoconstrictors (topical and systemic): 30 days prior to the Screening visit;

c. Systemic tetracycline compounds (tetracycline, doxycycline or minocycline), unless the dose has been stable for at least 30 days prior to the Screening visit and will remain stable during the study phase, in which case this is permitted;

d. Any medication (topical and systemic) known to cause ocular drying, such as the use of systemic anticholinergic medications (eg, antihistamines and antidepressants), unless the dose has been stable for at least 30 days prior to the Screening visit and will remain stable during the study phase;

e. Antihistamines (topical and systemic): 7 days prior to the Screening visit;

f. Topical or nasal vasoconstrictors within 14 days prior to screening;

g. Unable to refrain from using artificial tears

h. Subject has received glucocorticosteroid implants such as Retisert®, Iluvien®, or Yutiq™ within 3 years prior to the Baseline Visit or has had complications related to the device and/or subject has had a glucocorticoid implant removed within 90 days prior to the Baseline Visit or has had complications related to the removal of the device;

i. Any FDA-approved medical devices other than punctal plugs (eg Lipiflow® and Truetear®) for dry eye 12 weeks prior to the Screening visit;

9. Subject is unwilling to receive, or is intolerant of, SC injections;
10. Subject has a history of sensitivity to ACTH preparations or sensitivity to porcine protein products;
11. Subject has Type 1 or Type 2 diabetes mellitus or is taking antidiabetic medication (a history of gestational diabetes mellitus is not exclusionary);
12. Subject has proliferative or severe nonproliferative diabetic retinopathy, clinically significant macular edema due to diabetic retinopaty, or neovascular/wet age-related macular degeneration;
13. Subject has a history of chronic active hepatitis including active or chronic hepatitis B, or acute or chronic hepatitis C;
14. Subject has a history of tuberculosis (TB) infection, any signs/symptoms of TB, or any close contact with an individual with an active TB infection;
15. Subject has an active corneal infection, any other systemic infection;
16. Subject has received a live or attenuated-live vaccine within 30 days prior to screening;
17. Subject had ocular trauma, penetrating intraocular surgery, refractive surgery, corneal transplantation, or eyelid surgery within 12 weeks prior to screening;

18. Subject is unwilling to abstain from eyelash growth medications for the duration of the trial;
19. Subject is under treatment with any corticosteroids, immunosuppressants, immunomodulators, or biologic agents for a concomitant condition (eg, rheumatoid arthritis under treatment with a tumor necrosis factor- alpha [TNF-α] drug). Subjects are specifically excluded for any of the following;
    a. Subject has received intraocular or periocular corticosteroids within 30 days prior to Baseline Visit;
    b. Subject has received Ozurdex® (dexamethasone implant) within 6 months prior to the Baseline Visit;
    c. Subject has received intravitreal anti-VEGF therapy within 45 days of the Baseline Visit with Lucentis® (ranibizumab) or Avastin® (bevacizumab) or has received anti-VEGF Trap (aflibercept) within 60 days of the Baseline Visit;
    d. All others, subject has received treatment within 30 days prior to baseline;
20. Subject has any known contraindication(s) to Acthar® Gel Package Insert, 2019 including, but not limited to:
    a. Any known history of scleroderma, osteoporosis, or ocular herpes simplex. For the purposes of this study, osteoporosis is defined as evidence of current vertebral or long bone fracture, or lumbar T-score > 2.0 standard deviations (SD) below the mean of the reference population;
    b. Any primary adrenocortical insufficiency, or adrenal cortical hyperfunction,
    c. Any current congestive heart failure (defined as New York Heart Association Functional Class III to IV),
    d. Peptic ulcer (within 24 weeks prior to the Screening Visit);
    e. Recent major surgery (within 24 weeks prior to the Screening Visit);
21. Subject has a clinically significant infection requiring administration of intravenous antibiotics or hospitalization in the 4 weeks prior to the Screening Visit or between the Screening Visit and the first dose of study drug;
22. Subject has known immune-compromised status (not related to disease/condition under study), including but not limited to, individuals who have undergone organ transplantation or who are known to be positive for the human immunodeficiency virus;
23. Subject has any solid tumor malignancy currently diagnosed or undergoing therapy, or has received therapy for any solid tumor malignancy in the 5 years prior to the Screening Visit; with the exception of treated and cured basal cell carcinoma, treated and cured squamous cell carcinoma of the skin, and treated and cured carcinoma in situ of the cervix;
24. Subject has a diagnosis of, is undergoing therapy for, or has received therapy for a hematologic malignancy in the 5 years prior to the Screening Visit;

25. Subject has current or recent (within 24 weeks prior to the Screening Visit) drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders , 2013, Fifth Edition, Diagnostic Criteria for Drug and Alcohol Abuse;
26. Subject has any of the following laboratory abnormalities at the Screening Visit:
    a. Hemoglobin ≤ 8.0 g/dL;
    b. Platelet count ≤ 50,000 cells/µL;
    c. Absolute neutrophil count (ANC) ≤ 1000 cells/µL;
    d. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin > 2 times upper limit of normal (ULN);
    e. Glycosylated hemoglobin (HbA1c) > 6.5;
    f. Positive Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb), or positive or indeterminant Hepatitis C virus antibody (HCV);
    g. Systolic blood pressure > 150 mm Hg and diastolic blood pressure > 90 mm Hg (average of 2 assessments) at the Screening or Baseline Visits does not qualify for the study;
    h. Positive or indeterminate interferon gamma release assay (IGRA) for TB;
27. Subject has any other clinically significant disease, disorder or laboratory abnormality (including those listed on the Prescribing Information Section 5: Warnings and Precautions [Acthar® Gel Package Insert, 2019]) 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;
28. Subject is participating in or plans to participate in any other interventional research study from the time of screening and throughout this study.

4.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently treated.

Subjects will be allowed to repeat any single screening assessment/procedure once, if necessary, if it is within the screening window. However, laboratory results indicating a positive or indeterminant TB test, positive hepatitis B surface antigen, hepatitis B core antibody and positive or indeterminant hepatitis C antibody cannot be rescreened. The subject will not be considered a screen failure unless the repeat assessment/procedure result does not meet eligibility criteria. The period from the start of screening related procedures at the Screening Visit to the Baseline Visit must not exceed 28 days, inclusive of any repeat screening procedures.

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

Rescreening

A subject who is a screen failure at the Screening or Baseline Visit may be rescreened. The subject must repeat all screening procedures. The period from the start of rescreening related

procedures to the first dose of study drug must not exceed 28 days. Subjects may be rescreened only once.

5. STUDY TREATMENT

Acthar is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH) analogues and other pituitary peptides used to provide a prolonged release after intramuscular or subcutaneous (SC) injection. Acthar contains 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH, and water for injection.. Acthar is currently labeled for use in keratitis (Acthar® Gel Package Insert, 2019). Acthar is supplied as 5 mL multidose vials containing 80 U of ACTH per mL.

5.1. Treatment Administration

Following a screening period of up to 28 days, subjects who meet entry criteria will be treated with Acthar 1 mL (80 units [U]) subcutaneously (SC) 2x (twice) per week for 12 weeks. After this 12 week period of treatment with 80 U, Acthar will be tapered over a 4 week period. The 80 U dose will be reduced to 40 U 2x/week for 2 weeks, followed by 40 U 1x/week for 2 additional weeks. An in-clinic safety visit will also take place 4 weeks after the last treatment dose. The subject or subject's caregiver will receive training/instructions and will administer the first dose of study drug in the clinic under the supervision of study staff. The subject will remain in the clinic for at least 1 hour postdose to monitor for allergic, including anaphylactic, reactions. Thereafter, all doses will be administered by the subject or the subject's caregiver at home. If a subject misses a dose, that dose will be skipped and the reason for the missed dose will be recorded.

5.2. Study Treatment Preparation/Handling/Accountability

Study treatment will be provided by the sponsor or sponsor's representative and will be labeled as required by local and national regulations.

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.

The investigator or designee will confirm that appropriate temperature control conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved prior to study treatment administration.

The study treatment will be maintained in a monitored, environmentally controlled (in accordance with treatment labeling), secure, locked area with restricted access at the study site.

Only subjects enrolled in the study will receive study treatment and only authorized study staff will dispense study treatment.

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

5.3. Storage of Clinical Supplies

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

5.4. Measures to Minimize Bias

This is an open label study, no randomization or stratification will be employed in treatment assignment.

5.4.1. Interactive Phone/Web Response System

The investigator or designee will contact interactive phone/web response system (IXRS) to register subjects at screening. The subject's identification (ID) number will be determined by the IXRS and will be used to identify the subjects for the duration of the study within all systems and documentation.

Each subject will be assigned a unique ID number. If the subject is not eligible to receive study treatment, or should discontinue from the study, the subject ID number will not be reassigned to another subject.

In the event that a subject repeats any evaluation during the screening window, they will not receive a new ID number. In addition, subjects who fail screening and are rescreened will not receive a new subject ID number. At the Baseline Visit, qualified subjects who meet all of the eligibility criteria will be enrolled into the study.

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

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.

5.4.2. Emergency Identification of Study Treatment

Not applicable.

5.5. Study Treatment Compliance

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

5.6. Prior and Concomitant Therapy

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 30 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through Visit 7) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

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

5.6.1. Permitted Concomitant Therapies

Permitted concomitant medications include lid hygiene, warm compresses and artificial tears or any medication not mentioned in the exclusion criteria provided the subject has been on a stable dose for at least 4 weeks prior to the Screening Visit. Patients should be instructed not to use ophthalmic preparations 2 hours prior to each study visit.

5.6.2. Prohibited Concomitant Therapies

The following treatments will not be permitted during the study (from the Baseline Visit through Visit 7):

- Administration of live or live-attenuated vaccines.
- Use of eyelash growth medications.
- Topical, inhaled, intra-articular, or intra-ocular corticosteroids.
- Any systemic corticosteroids, immunosuppressants, immunomodulators, or biologic agents for a concomitant condition (eg, rheumatoid arthritis being treated with a TNF-α drug).
- Any investigational drug, device, or procedure administered as part of a research study.

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

6. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1. Discontinuation of Study Treatment

Subjects who discontinue, or are withdrawn from study treatment for any reason, will be encouraged to complete the Early Termination (ET) Visit and provide any additional follow-up information as required by the study, unless the subject specifically indicates that they will not participate in any further evaluations.

Permanent study treatment discontinuation is required for any of the following:

- Elevated blood pressure (defined as systolic blood pressure not more than 180 *and* diastolic blood pressure not more than 100 mm Hg).
- Hyperglycemia (HbA1c greater than 6.5%, or fasting plasma glucose greater than 126 mg/dL, or classic symptoms of hyperglycemia with random plasma glucose greater than 200 mg/dL).
- Infections that are considered SAEs or lead to treatment discontinuation.
- The subject becomes pregnant during the active treatment phase of the study.
- Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a subject meets one of the conditions outlined in Section 9.5.
- The reason for study treatment discontinuation will be recorded.

6.2. Subject Discontinuation/Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent. If a subject withdraws from the study, the subject may request destruction of any samples taken and not tested and the investigator must document this in the site study records.

The reason for study discontinuation/withdrawal 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.

Adverse Event

If a dosed subject suffers an adverse event (AE) that, in the judgment of the investigator, sponsor, or MM; presents an unacceptable consequence or risk to the subject, the subject will be discontinued from study drug.

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 at least 3 attempts to reach the subject by phone and no response to a certified letter (or equivalent) sent to the last known address of the subject, if possible. Efforts to contact the subject should be noted in the source documentation.

Met Withdrawal Criteria

Discontinuation for safety and/or tolerability issues is outlined in Section 6.1.

Other

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

7. STUDY ASSESMENTS AND PROCEDURES

7.1. Efficacy Assessments

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

7.1.1. Ophthalmic Examination

An ophthalmic examination will be completed at specified times during the study and will include the following:

- Best corrected visual acuity (BCVA) measured using the using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Hilton, 2009).
- Intra-ocular pressure (IOP) will be measured using Goldmann Applanation Tonometry (Ramakrishnan, 2009).
- Complete Slit lamp examination (including evaluation of the cornea and lens and grading of superficial puncta.
- Undilated funduscopic evaluation.

7.1.2. Patient-reported Outcomes (PROs)

The following 4 questionnaires were used to assess quality of life (QOL) measures (Sheppard, 2014):

Impact of Dry Eye on Everyday Life (IDEEL) Questionnaire: The IDEEL comprises 57 questions and 3 modules: the impact on daily life module (activity/work limitations and emotional impact), the treatment satisfaction module, and the symptom bother module. Each module is scored from 0 to 100; higher scores on the impact on daily life and treatment satisfaction modules indicate a better quality of life (QOL) and higher treatment satisfaction. In contrast, higher scores on the symptom bother module indicate more bothersome dry eye symptoms. A 12-point difference in symptom bother module scores indicates a clinically important change in bothersome dry eye symptoms (Grubbs, 2014).

Ocular Discomfort Score (ODS): The ODS is a scale in which subjects are asked to subjectively rate 5 areas of ocular discomfort: ocular discomfort, dryness, grittiness, burning, and stinging. Subjects are asked to grade their discomfort on a 5-point scale where 0 is no discomfort and 4 is constant discomfort (Stonecipher, 2016).

Visual Analog Scale (VAS) of Eye Dryness: The VAS is a 7-item, patient-reported symptom index with items of eye dryness, burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, and pain. Subjects are asked to subjectively rate each ocular symptom by placing a vertical mark on the horizontal line from 0 to 100 (0 = no discomfort, 100 = maximal discomfort) to indicated their level of discomfort (Holland, 2017).

7.1.3. Corneal and Conjunctival Staining Score

Corneal and conjunctival staining using fluorescein or lissamine green dye is an objective assessment of the inferior, superior, central, and total regions of the cornea as well as the nasal,

temporal and total regions of the conjunctiva. Both fluorescein and lissamine green scores are obtained using the Ora Calibra™ Scale for each region that is scored from 0 to 4 where 0 = none and 4 = confluent.

7.1.4. T-Cell Assessments

Blood samples for T-cell assessments (T-cell effector total number, T-cell regulatory, and regulatory/effector T-cell ratio) will be collected at specified times during the study and shipped to a central laboratory. Detailed instructions for the collection, handling, storage and shipment of the samples will be provided in a separate laboratory manual.

7.2. Safety Assessments

All safety assessments will be performed at times outlined in the Schedule of Study Events (Table 1). Safety assessments that will be evaluated include adverse events, ophthalmic examinations, physical examination, clinical laboratory test results, metabolic panel, pregnancy testing, and vital signs.

Additional (unscheduled) safety assessments may be performed as needed.

7.2.1. Medical, Ophthalmic, and Surgical History

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

Ophthalmic history will include the date and approximate time of onset, suspected cause, symptoms, course, laterality, and any treatment (drug name, dose, how administered, tapering scheme) for the current keratitis episode; and the date of any previous episodes with treatment given and response to treatment; as well as any previous or antecedent ocular trauma or surgery and any previous or antecedent ocular conditions.

7.2.2. Physical Examination

The complete physical examination will include 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.

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

7.2.3. Height and Weight

Height and weight will be collected at baseline (Visit 2), Visit 6, and Early Termination.

7.2.4. Vital Signs

Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. The results, date, and time for all vital sign assessments will be recorded. Additionally, at the Screening and Baseline Visits, blood pressure will be measured with an average of 2 readings, with at least 5 minutes between assessments after the subject has been seated for a minimum of 5 minutes prior to the initial blood pressure assessment. A subject with systolic blood pressure > 150 mm Hg and diastolic blood pressure > 90 mm Hg (average of 3 assessments) at the Screening or Baseline Visits does not qualify for the study (Section 4.2).

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

7.2.5. Clinical Laboratory Tests

Required clinical laboratory tests are listed in Section 9.2. Specific instructions for collection, processing, storage, and shipment of clinical laboratory samples will be provided in separate laboratory manual(s).

It is not required for laboratory samples to be collected under fasted conditions. The date and time of the sample collection must be documented on the laboratory report. Investigators must review and sign laboratory reports and document the clinical significance of each laboratory abnormality. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs.

Hematology with differential, serum chemistry, lipid profile, and urinalysis samples will be collected at the specific times starting at screening and throughout the study according to the schedule of events (Table 1).

In addition: all female subjects of childbearing potential will have a serum pregnancy test at Screening, all other site visits except for Visit 3 which is by phone, and Visit 6/Early Termination Visits. Urine pregnancy tests will be done only at Screening. Any positive urine pregnancy test will be confirmed with a serum pregnancy test. Results must be available prior to protocol mandated study treatment. Subjects with positive results at the Screening or Baseline Visits will be ineligible for study entry. Any female subject that becomes pregnant during the study will be immediately withdrawn and will have the pregnancy reported as per Section 9.4.

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

HBsAg and HBcAb will be performed at the Screening Visit. Results of these tests must be negative or nonreactive for subjects to qualify for the study.

HCV antibody testing will be performed at the Screening Visit. Results of this test must be negative for subjects to qualify for the study.

IGRA testing for tuberculosis will be performed at the Screening Visit. Results of this test must be negative for subjects to qualify for the study.

Thyroid stimulating hormone (TSH) will be measured at the Screening Visit. Results of this test must be within the normal range for subjects to qualify for the study.

Hemoglobin A1c (HbA1c) testing will be performed at the Screening Visit. HbA1c must be ≤ 6.5% for subjects to qualify for the study. Additional HbA1c tests will be done at specified times during the protocol.

Out-of-Range Laboratory Values

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

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

7.3. Adverse Events

Adverse events will be recorded from signing of the ICF and followed by the investigator until the AE is resolved, resolved with sequela, or stabilized. 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 9.3.4 for additional details on the handling of AEs and SAEs.

7.4. Treatment Overdose

For this study, any dose of Acthar greater than 80 U within a 24 (± 1) hour time period will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or designee should:

- Contact the MM immediately.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities until the treatment can no longer be detected (at least 48 hours).
- Document the quantity of the excess dose, as well as the duration of the overdose.

7.5. Pharmacokinetic Assessments

Not applicable for this study.

7.6. Genetics

Not applicable for this study.

7.7. Biomarkers

Not applicable for this study.

7.8. Health Economics and Outcomes Research Assessments

Not applicable for this study.

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size Determination

Approximately 36 subjects will be screened in order to have 30 analysable subjects enrolled in this study. No formal sample size calculations will be performed. The sample size was determined empirically.

8.2. Populations for Analysis

For the purposes of analysis, the following populations are defined

- The Modified Intent-to-Treat (mITT) population will include all subjects who receive at least 1 dose of study drug and who contribute any postbaseline efficacy data to the study.
- The Per-Protocol (PP) population will include a subset of the mITT population with subjects who do not have any major protocol deviations.
- The Safety Population will include all subjects who receive 1 or more doses of study drug.

8.3. Statistical Analyses

This section provides a general summary of the statistical methods to be used in analyzing study data. A more detailed statistical analysis plan will be provided in a separate document that will be finalized prior to database lock.

8.3.1. Efficacy Analyses

All efficacy analyses will be performed on the mITT population. Selected analyses may be performed on the Per-Protocol population.

Baseline and change from baseline at each posttreatment visit will summarized for all numerical variables with descriptive statistics. Frequency and percentage will be calculated for categorical variables. The nominal p-values along with the 95% confidence intervals (CI) will be provided as appropriate. For subjects who have both eyes affected, the change from baseline will be determined based on the eye with the worst severity at baseline. If both eyes have the same severity at baseline, the right eye will be used to determine change from baseline.

8.3.2. Safety Analyses

All safety data will be summarized with descriptive statistics or frequency tables as appropriate. Safety analyses will be performed on the safety population. Safety endpoints include the incidence and severity of ocular AEs, incidence and severity of other AEs, new or worsening cataracts, and the mean change in IOP.

AEs will be coded using MedDRA version 22.0 by preferred term within system organ class. The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by system organ class, preferred term, severity, and causality for each treatment group. Only treatment-emergent adverse events (TEAE) (events that are new in onset or aggravated in severity following treatment) will be included in all summaries. Serious adverse events (SAE) (including death) will be summarized.

Other safety assessments include vital signs (heart rate, diastolic/systolic blood pressures, respiratory rate, and body temperature), clinical laboratory tests, ophthalmology examinations, physical examinations, HbA1c, pregnancy test, hepatitis serology, IGRA for TB, etc. All of these assessments will be listed and summarized descriptively.

8.3.3. Interim Analyses

No formal interim analyses are planned for this study.

8.3.4. Handling Missing Data

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

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

9.1.1. Regulatory and Ethical Considerations

The study will be conducted in full compliance with applicable international, national and local regulatory requirements; US Food and Drug Administration (FDA) regulations including 21 Code of Federal Regulations (CFR) 314.106 and 312.120, (where applicable), ICH guidelines for GCP, in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and European regulation 536/2014/EU (where applicable).

It is the responsibility of the investigator to obtain the approval of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before the start of the study. A copy of the approval letter along with a roster of IRB/IEC members and compliance letter and/or the US Department of Health and Human Services general assurance number (if applicable) will be provided to the sponsor and 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, ICF, advertisements (if any), and amendments (if any) will be approved by the IRB/IEC in conformance with international, national and local regulatory requirements.

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, if appropriate.

9.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after the end of the study.

9.1.3. 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 (and at other time as may be required by the study or when changes are made to the consent form), subjects will read the consent form(s) and any privacy authorization as required by local and national regulations (such as the Health Insurance Portability and Accountability Act [HIPAA] authorization form), if applicable after being given an explanation

of the study. Before signing the consent form(s) and the privacy 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 and all applicable national and international regulations, before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time. Subjects unable to give written informed consent must orally assent to the procedures, and written informed consent must be obtained from a legally authorized representative in accordance with national and local laws, as applicable.

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

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

9.1.4. Data Protection

Study subjects will be assigned a unique identifier by the sponsor or designee. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure (in accordance with local and/or national law) must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.1.5. Committees Structure

No monitoring committees will be used for this study.

9.1.6. Dissemination of Clinical Study Data

Study results and de-identified individual subject data will be protected as required by local and/or national regulation.

9.1.7. Data Quality 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 Prescribing Information (Mallinckrodt Package Insert, 2019), the electronic case report forms (eCRF) 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.

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

Each subject's eCRF should be fully completed and submitted to the Sponsor in a timely fashion.

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 of protocol deviations in accordance with local regulatory and IRB requirements.

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

9.1.8. Source Documents

All subject information recorded in the eCRF will be attributable to source data from the investigational site.

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.

9.1.9. Study and Site Closure

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 the sponsor or designee standard operating procedures.

The sponsor, investigator, or local and national regulatory authorities may discover conditions during the study that indicate that the study or study site should be terminated. This action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study/study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- The decision on the part of the sponsor to suspend or discontinue testing or evaluation of the study drug.
- 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.

9.1.10. Publication Policy

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.

Terms and provisions of the investigator's publication rights are governed by the Publication Section in the Clinical Trial Agreement per site.

9.2. Appendix 2: Clinical Laboratory Tests

Serum Chemistry:	
Alanine aminotransferase (ALT)	Chloride
Albumin (total)	Creatinine
Alkaline phosphatase	Glucose
Aspartate aminotransferase (AST)	Phosphorus
Bilirubin (total)	Potassium
Blood urea nitrogen	Protein, total
Calcium	Sodium
Bicarbonate	Uric acid
Lipid Profile:	
High density lipoprotein	Triglycerides
Low density lipoprotein	Total cholesterol
Hematology Assays:	White blood cell count, including differential
Hematocrit	Platelet count
Hemoglobin	Red blood cell count
Urinalysis:	
Color	Ketones
Clarity	Protein
Albumin	pH
Bilirubin	Specific gravity
Blood	Urea
Creatinine Glucose	Microscopy (WBC/ high power field (HPF), RBC/HPF and urinary casts)
Diabetes Screen:	HbA1c
Hormones:	
Serum and urine beta-human chorionic gonadotropin (pregnancy test)	Thyroid Stimulating Hormone
Hepatitis and HIV Serology:	
Hepatitis B core antibody	Hepatitis C virus antibody (HCV)
Hepatitis B surface antigen	Human immunodeficiency virus (HIV)
TB Assay:	Interferon gamma release assay (IGRA)
Immunological protein assay:	Protein assay to detect levels of the cytokine array [interleukin 1,6,17; interferon-ɤ]; ratio of T helper cells to T regulatory cells

9.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up and Reporting

9.3.1. Safety

For safety information about Acthar, refer to the most recent version of the Prescribing Information (Mallinckrodt Package Insert, 2019).

9.3.2. Definitions

Adverse Event

An AE is any untoward or undesirable medical occurrence in a subject who is administered a study treatment, 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 study drug overdose whether accidental or intentional.
- An AE occurring from study drug abuse.
- An AE associated with study drug withdrawal.
- Unexpected Adverse Event.

An unexpected AE is defined as an AE, the nature and severity of which is not consistent with the applicable product information in the most recent version of the Prescribing Information (Mallinckrodt Package Insert, 2019).

Serious Adverse Event

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

- Death.
- 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.

Death

Death is an outcome of an event. The cause of 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 the sponsor or designee, or state not available.

Life-Threatening Event

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused 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. The following situations should not be reported as SAEs:

- 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.

Important Medical Events

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 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.

AEs (serious or non-serious) that commonly occur in the study population or background regimen will be considered anticipated events. Such events include known consequences of the condition under investigation (eg, symptoms, disease progression) and other events that may be common in this study population. Anticipated events are to be recorded on the eCRF and reported as SAEs when serious. These SAEs will not be expedited to health authorities, but included in aggregate safety reports.

9.3.3. Adverse Event and Serious Adverse Event Classifications

Study Drug Relatedness

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

Table 3: Adverse Event Relationships

Relationship	Definition
Not Related	No relationship between the AE and the administration of study treatment; the AE cannot be explained by other etiologies such as concomitant medications or subject's clinical state.

Relationship	Definition
Unlikely Related	The current state of knowledge indicates that a relationship to study treatment is unlikely.
Possibly Related	An AE that follows a plausible temporal sequence from administration of the study treatment to the start of the AE and follows a known response pattern to the suspected study treatment. The reaction might have been caused by the subject's clinical state or concomitant medications.
Related	The AE that follows a plausible temporal sequence from administration of the study treatment to the start of the AE and follows a known response pattern to the study treatment. The suspected causality can be confirmed with a positive re-challenge test or supporting laboratory data.

Severity Assessment

For purposes of consistency, the investigator may use the intensity grades presented in the following table, if required:

Table 4: 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

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.

If an AE increases in severity (eg, from moderate to severe); decreases in severity (eg, changes from moderate to mild); or if 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.

9.3.4. Adverse Event and Serious Adverse Event Recording and Reporting

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

During the period specified above, the investigator will:

- Record all AEs and SAEs from the signing of the ICF through the completion of the Follow-up Visit.
- Report all SAEs on an SAE Report Form to Mallinckrodt Global Pharmacovigilance or designee.
- Report all pregnancies to Mallinckrodt Global Pharmacovigilance or designee on the appropriate form.
- Submit any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction from Mallinckrodt Global Pharmacovigilance or designee to the IRB/IEC.

The reporting requirements for AEs are summarized in the following table:

Table 5: 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

9.3.5. Adverse Events of Special Interest

An adverse event of special interest is an event of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

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

- Increased IOP of 10 mm Hg or more from baseline confirmed upon repeat testing.
- New or worsening cataracts.
- New or worsening glaucoma.

9.4. Appendix 4: Pregnancy Reporting

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

Subjects should not become pregnant during the study. If a female subject, or the female partner of a male subject, becomes pregnant during any active treatment period, study treatment must be discontinued immediately and the investigator must report the pregnancy by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance, or designee, within 24 hours of confirmation of a pregnancy (ie, positive serum pregnancy test result). The outcome of pregnancy (eg, spontaneous abortion, live birth, still birth, congenital anomalies, birth defects) must be reported by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance,

or designee, within 24 hours of the pregnancy outcome being submitted to the study site. If the pregnancy results in a live birth, a postdelivery follow-up will be performed at least 28 days after the baby is born and must be reported to Mallinckrodt Global Pharmacovigilance, or designee, within 24 hours of the study site becoming aware of the follow-up information.

9.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

All events of alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) and with total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) >1.5 (if INR measured) which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE as outlined in Section 9.3.4.

Subjects with confirmed Hy's Law liver injury will be immediately withdrawn from study treatment and no rechallenge will be allowed.

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