A Phase 4 Study to Assess the Clinical Efficacy of H.P. Acthar Gel 80 u/ml to Improve the Signs and Symptoms in Subjects with Dry Eye Disease

Protocol Number: MMT-4233

National Clinical Trial (NCT) Identified Number: NCT03287635

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Sponsor: Toyos Clinic

Funded by: unrestricted grant from Mallinkrodt Pharmaceuticals

Version Number: v.1

10 May 2018

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STATEMENT OF COMPLIANCE

(1) [The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Phase 4 Study to Assess the Clinical Efficacy of H.P. Acthar Gel 80 U/ml to Improve the Signs and Symptoms in Subjects with Dry Eye Disease
Study Description:	*This study will test the efficacy of a systemic intervention and adrenocorticotropin injection for severe dry eye unrelieved by traditional dry eye treatments.*
Objectives:	*The primary objective of the study is to investigate the safety and efficacy of H.P. Acthar gel injections in subjects who have a documental clinical diagnosis of dry eye disease. Secondary objective is to demonstrate safety for use of Acthar H.P. Gel in dry eye subjects.*
Endpoints:	Primary Endpoint: Improvement of patient comfort over the length of the study using a validated dry eye comfort questionnaire, OSDI and improvement of spk in cornea over study treatment period Secondary Endpoints: conjunctival staining with lissamine green
Study Population:	*12 study subjects 18-85 will be enrolled with male or female in the Nashville, TN area who are generally healthy but have persistent signs and symptoms of dry eye diseases after treatment with traditional dry eye treatments including but not limited to: IPL, cyclosporing, lifitegrast, loteprednol, artificial tears and warm compresses*
Phase:	4

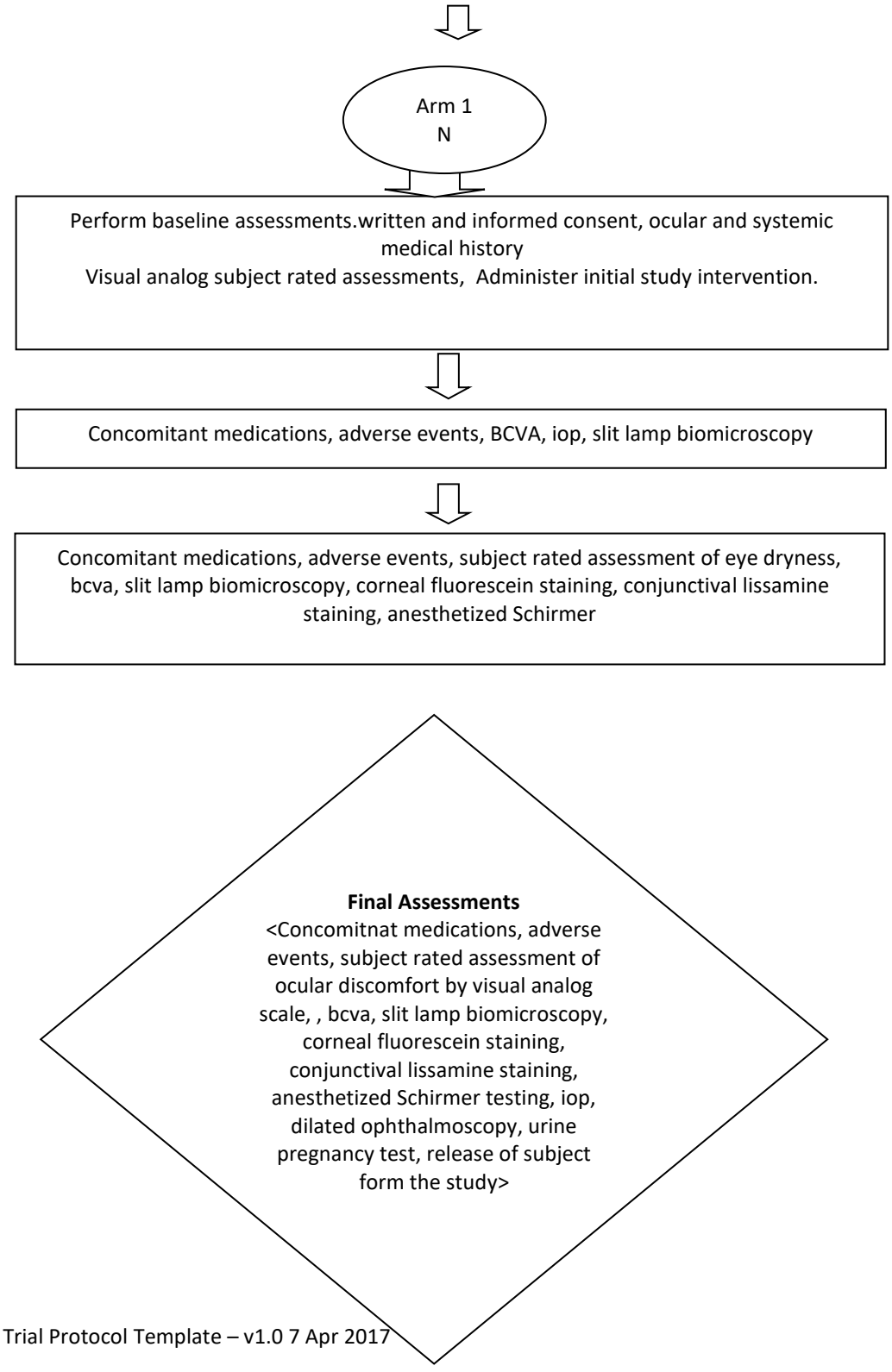
Description of Sites/Facilities Enrolling Participants:	*Single site study in Nashville, TN and surrounding areas.*
Description of Study Intervention:	*Acthar is an adrenocorticotropic hormone given subcutaneously twice weekely.*
Study Duration:	*6 months*
Participant Duration:	*12 weeks*

1.2 SCHEMA

Example #1 Flow diagram *(e.g., randomized controlled trial)*

Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.

Prior to Enrollment



Example #3 provided as a guide, customize as needed: Timeline diagram *(e.g., randomized controlled trial)*

1.3 SCHEDULE OF ACTIVITIES (SOA)

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Procedures	Screening Day -7 to -1	Enrollment/Baseline Visit 1, Day 1	Study Visit 2 Day 7 +/-1 day	Study Visit 3 Day 14 +/- 1 day	Final Study Visit 13 Day 84 +/-1 day
Informed consent	X				
Demographics	X				
Medical history	X				
Randomization	X				
Administer study intervention		X			
Concomitant medication review	X	X---------- ---------- X			
Bcva	X	X	x	x	X
Slit lamp biomicroscopy	X	x	x	x	x
IOP	X	X	x	X	X
Corneal fluorescein stain	X	X		X	X
Conjunctival liissamine stain	X	X		X	X
	X	X		X	X
anesthetized schirmer	X	x		x	x
Dilated ophthalmoscopy	X				x
Training on study medications	X				
Discpense study meds \	X				

2 INTRODUCTION

2.1 STUDY RATIONALE

Many people suffer from dry eye disease and are incompletely relieved of signs and symptoms with traditional treatments like artificial tears, warm compresses, prescription eye drops, and IPL. Those most severely affected may find relief using a systemic medication that increases the body's endogenous production of corticosteroid to reduce surface inflammation. This study will attempt to demonstrate improvement in both signs and symptoms of dry eye and the safety of use of this medicine in patients suffering with moderate to severe dry eye.

2.2 BACKGROUND

Acthar is approved by the FDA for the treatment of severe allergic and inflammatory eye conditions. Dry eye disease is a disease that affects millions of Americans and may be underdiagnosed. Dry eye disease is diagnosed by evaluating the signs and symptoms of dry eye including self-reported ocular comfort and staining of both the cornea and the conjunctiva by special stains. Moderate to severe dry eye disease is characterized by a self-perpetuating and progressive increase in inflammation of the ocular surface. For patients that continue to experience bothersome symptoms and/or loss of function due to dry eye despite compliance with current and traditional therapies, the use of corticotropin hormone may offer some relief.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Known risks of Acthar use include
Infections
Cushing's syndrome
High blood pressure
Bleeding stomach ulcers
Irritability
Depression
Insomnia
Mood swings
Loss of diabetic control
Cataracts
Glaucoma
Allergy to acthar
Long term use can affect children's growth and development
Osteoporosis
Birth defects

The most common side effects are
Increased blood sugar
Increased blood pressure
Fluid retention
Changes in appetite
Weight gain
Cardiac hypertrophy

2.3.2 KNOWN POTENTIAL BENEFITS

By activating the release of endogenous cortisol and impacting steroid independent immunomodulatory and anti-inflammatory pathways, Acthar reduces inflammation in the body without synthetic steroids. Immediate benefits in dry eye disease would be reduced symptomatology and improvement of function which would be expected to extend long term and help to prevent and reduce future damage from chronic inflammation.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Moderate to severe dry eye can cause significant discomfort and interfere with even daily normal function. Patients can experience depression, reduced function at work, social anxiety if others incorrectly interpret red eyes as staying out too late, use of illegal drugs or episodes of crying. Patients who have exhausted all currently available therapies and still experience bothersome signs and symptoms especially if symptoms interfere with jobs and normal daily function may feel that the increased risk of systemic anti-inflammatory may be worth the benefits of reduced ocular surface inflammation.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective is the efficacy of H.P. Acthar gel injections in subjected with documented moderate to severe dry eye disease who have failed traditional therapies.	*The primary endpoint(s) are improvement in comfort over the course of the trial with a validated dry eye comfort questionnaire, OSDI and improvement in the number of corneal spk using fluorescein stain over the course of the trial.*	*Both endpoints have been validated in recent dry eye approvals (lifitegrast).*
Secondary		
The secondary objective is improvement in conjunctival staining with lissamine green and demonstration of safety of use of in dry eye subjects.	*Conjunctival staining with lissamine green is another method of measuring ocular surface inflammation and safety will be measured by collecting intraocular pressure, assessing AEs, slit lamp biomicroscopy, BCVA and dilated ophthalmoscopy*	*Lissamine green staining has also been used in recent approvals (lifitegrast) and safety of adrenocorticotropic stimulators must measure common side effects of steroid like glaucoma, cataract and potential change in vision.*
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4 STUDY DESIGN

4.1 OVERALL DESIGN

- *The hypothesis is that use of H.P. Acthar gel subcutaneously has the ability to reduce ocular surface inflammation in moderate to severe dry eye and improve the signs and symptoms over the course of the trial.*

- *Single site pilot study Pilot study*

- *H.P. Acthar gel will be dosed two or three times weekly to control signs and symptoms at the discretion of the primary investigator.*

- *One study arm of active intervention for up to 89 days*
- *Single site*
- *Study intervention is use of H.P. Acthar Gel)*
- *No interim analysis is planned*

There are no planned stratifications.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a small single site study with no control designed to show efficacy in moderate to severe dry eye disease which may be used in the future as a basis for a larger, multi-site, randomized placebo controlled study. Potential pitfalls include the small number of participants, the variable nature of the disease and the often inverse relationship of signs to symptoms in dry eye disease.

4.3 JUSTIFICATION FOR DOSE

H.P. Acthar gel will be injected subcutaneously two or three times weekly. Subjects will self-administer the dose recommended by the treating physician which may range from 80 international units two to three times per week. Nursing support from Mallinkrodt to train study coordinator and study personnel who will train subjects on proper administration techniques will be available at all times points in the study. Patients will self-inject the study medicine for the length of the study, 12 weeks.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form and HIPPA authorization.
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18 and older.
4. Diagnosed with moderate to severe dry eye in one or both eyes.
5. History of persistent symptoms despite use of artificial tears and one or more of the following ophthalmic drops: loteprednol, cyclosporine or lifitegrast.
6. At least 40 mm on the ocular discomfort scale.
7. At least 5 spk on one or both corneas.

8. A grade of 1 or greater in the nasal or temporal areas of one or both eyes.
9. Have normal lid anatomy.
10. Ability to take subcutaneous injected medication and be willing to adhere to the study regimen
11. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional 4 weeks after the end of Acthar administration
12. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner
13. Are postmenopausal (no menstrual cycle for at least one year prior to Visit 1) or have undergone bilateral tubal ligation, hysterectomy, hysterectomy with uni or bilateral oophorectomy, or bilateral oophorectomy.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Have a known hypersensitivity or contraindication to the investigational product or their components.
2. Have used topical or nasal vasoconstrictors within 14 days prior to screening.
3. Pregnancy or lactation
4. Subjects can be on the following medications if they have been on a stable dose for 12 weeks: topical cyclosporing, topical liftigrast and/or topical loteprednol etabonate. Tetracycline compounds, omega 3s, anticholinergics, anticonvulsants, antidepressants, retinoids, systemic immunosuppressive agents including oral corticosteroids, non-steroidals, antihistamines, or mast cell stabilizers, punctal plugs, contact lens wear and glaucoma medications.
5. Subjects must be unwilling to abstain from eyelash growth medications for the duration of the trial.
6. Subjects must not have had penetrating intraocular surgery, refractive surgery or corneal transplantation, eyelid surgery within 12 weeks prior to Visit 1.
7. Febrile illness within one week.
8. Treatment with another investigational drug or other intervention within *one month.*
9. *Subjects with a history of herpetic keratitis.*
10. Have serious or severe disease or uncontrolled medical condition that in the judgement of the investigator could confound study assessments or limit compliance.

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of OSDI score may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Anticipate 25 screenings for 12 enrolled subjects.

- *One site in the US.*
- *Source of participants will be outpatient clinics and general public*
- *Potential participants will be identified and approached by chart review, during regular dry eye clinic visits and self-identified by general dry eye study signs within our clinics*

6 STUDY INTERVENTION

The study intervention is H.P. Acthar Gel (repository corticotropin injection) an adrenocorticotropic hormone (ACTH) analogue used on label as currently approved by the FDA for ocular inflammation. *This study will be used to gather data specifically about the efficacy and safety of use of Acthar in moderate to severe dry eye.*

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

There is no control, only study intervention with H.P. Acthar gel used subcutaneously 80 IU 2-3 times weekly. The drug is currently approved for all ocular inflammation and will be studied in this investigation specifically for moderate to severe dry eye disease.

6.1.2 DOSING AND ADMINISTRATION

Each participant will be started at 80 IU subcutaneously 2-3 weekly and the dosing increased to up to three times weekly at the discretion of the primary investigator. The dosing will remain consistent unless the investigator decides to reduce or escalate the dosing at the one month mark. The dosing may be stopped altogether and the subject followed only for safety in the event of uncontrolled hypertension, blood sugar, glaucoma or other serious adverse events in the opinion of the investigator The dosing of study drug will continue for 12 weeks.

Missed or delayed doses should be taken as soon as realized unless it would result in two doses being given at once, in which case the investigator should be contacted for a modified dosing schedule.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Study drug will be provided by Mallinkrodt and shipped to the investigative site from Mallinkrodt . It will be dispensed to the subject at the time of enrollment by the study coordinator. Unused or expired study drug will be returned to Mallinkrodt.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Study drug formulation, appearance, packaging, and labeling will be as normally supplied by the manufacturer, Mallinkrodt Pharmaceuticals. .

6.2.3 PRODUCT STORAGE AND STABILITY

H.P. Acthar gel is stored under refrigeration 2-8 degrees Celsius or 36-46 degrees Fahrenheit. Study drug temperature stability will be monitored with downloadable temperature monitors to ensure safety.

6.2.4 PREPARATION

Study drug should be warmed to room temperature before using. It is supplied in 5 ml multi-dose vials with 80 USP units per ml. Subjects will be instructed to withdraw 1ml.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All subjects will receive active drug with no control.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to the protocol will be assessed by verbally discussing with the subject and return of participant drug log.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

6.5.1 RESCUE MEDICINE

The study site will not supply rescue medication.

The use of rescue medications is allowable at any time during the study and the date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation during study does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is

identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Subject rated assessment of eye dryness, use of concomitant medications since last visit, occurrence of AEs since last visit, unused investigational product will be collected, BCVA, slit lamp biomicroscopy, iop, dilated fundus exam and pregnancy test for women of childbearing potential.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for 14 days.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 72 hours and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

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8.1 EFFICACY ASSESSMENTS

List and describe all study procedures and evaluations to be done as part of the study to support the determination of efficacy, as per the primary and secondary objectives outlined in this protocol. Discuss the sequence of events that should occur during the screening process and any decision points regarding participant eligibility. Include the time frame prior to enrollment within which screening procedures/ evaluations must be performed (e.g., within 28 days prior to enrollment).

In addition, indicate where appropriate, that procedures/evaluations will be performed by qualified personnel.

- *Once enrolled, initial study visit will occur within one week and can occur on the same day. Study assessments on each study day will occur in this order:*
- ***Subject rated assessment of ocular discomfort by visual analog scale. Subjects will be asked to subjectively rate their eye dryness at Visit 1,2, and 3. Subjects will be instructed to rate eye dryness using the scale below. The total length of the line from "no dryness" to "maximal dryness" is 100 mm. The length of the line between the "no dryness" starting point and the first point at which the subject mark crosses the line will be measured in mm. This assessment is a general assessment of both eyes.***

  Instantaneous Evaluation of Eye Dryness

  Please place a single line across the line below to indicate the severity of your eye dryness at the present time:

  *No dryness*_____*Maximal dryness*
- ***Significant non-ocular and significant ocular medical history***
- ***Concomitant medication usage and significant medications taken 6 months prior to screening***
- ***Inclusion/Exclusion criteria***
- ***Urine pregnancy test if required***
- ***BCVA Subjects will be placed at the predetermined mark for ETDRS testing***
- ***. LogMAR will be assessed with ETDRS or modified ETDRS charts and with subjects own corrective lenses or BCVA measured in office whichever is better. Scores are recorded according to ETDRS protocol and right eyes tested first.***
- ***Slit lamp biomicroscopy – 8 mm x 2 mm slit lamp beam wil be used right to left and left to right to examine thoroughly the structures of the anterior segment: lids, lashes, conjunctiva, corea, iris, anterior chamber, and lens. Results will be recorded as normal or abnormal. Abnormal findings will be followed by explanation of pathology.***
- ***Corneal fluorescein staining. One drop of tetracaine or properacaine will be applied to the surface of the eye. One drop of Fluress will be applied to the eye, excess blotted and 60 seconds elapsed before the examiner looks for spk. Alternatively, one drop of properacaine or tetracaine can be applied to a fluorescein strip, holding the strip to the inferior fornix for 10***

seconds and allow 120 seconds elapsed prior to examination. Cobalt filter will be used to count discrete and macropunctate staining.

- ***Conjunctival lissamine staining. One drop of lissamine green will be applied to each eye, excess blotted, and 60 seconds elapsed before staining is evaluated.***
- ***Anesthetized Schirmers. Fold the rounded ened of the test strip at the notched area. Instill 1-2 drops of properacaine or tetracaine and wait 5 minutes. Ask the subject to look up and away from the strip. Place the rounded ened of the strip towards the temporal one-third of the lower lid. Repeat procedure on contralateral eye. Instruct the subject to relax and gently close their eyes. Remove strips after 5 minutes and mark with ink the leading and lowest edges of moisture. Measure halfway between the 2 lines and record and the amount of wetting.***
- ***IOP measurements will be performed using Goldman applanation tonometry according to the investigators standard protocol. All pressures will be recorded in mm Hg. IOP will be measured at each time point and at the investigator's discretion.***
- ***Dilated ophthalmoscopy will occur at the first and last study visit and include assessment of the optic nerve head for pallor and cupping.***
- ***Training on study medication dosage will be done by specialists at Mallinkrodt directly with the subject until the subject is deemed by the specialist to be adequately trained and prepared for dosing.***
- ***Dispense study medications and temperature log. The study coordinator will dispense both the study medications and the temperature log with instructions on how to begin logging temperatures and when to return the thermometer for downloadable records.***

8.2 SAFETY AND OTHER ASSESSMENTS

- ***BCVA Subjects will be placed at the predetermined mark for ETDRS testing***
- ***LogMAR will be assessed with ETDRS or modified ETDRS charts and with subjects own corrective lenses or BCVA measured in office whichever is better. Scores are recorded according to ETDRS protocol and right eyes tested first.***
- ***Slit lamp biomicroscopy – 8 mm x 2 mm slit lamp beam wil be used right to left and left to right to examine thoroughly the structures of the anterior segment: lids, lashes, conjunctiva, cornea, iris, anterior chamber, and lens. Results will be recorded as normal or abnormal. Abnormal findings will be followed by explanation of pathology.***
- ***IOP measurements will be performed using Goldman applanation tonometry according to the investigators standard protocol. All pressures will be recorded in mm Hg. IOP will be measured at each time point and at the investigator's discretion.***
- ***Dilated ophthalmoscopy will occur at the first and last study visit and include assessment of the optic nerve head for pallor and cupping.***
  Adverse events will be collected at each time point

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8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.3

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or 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, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test

result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

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The primary investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Describe how AEs and SAEs will be identified and followed until resolved or considered stable. Specify

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the study coordinator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.]

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be informed about AEs and SAEs, and study-related results on an individual or aggregate level. Incidental findings associated with study procedures will be monitored by the primary investigator and reported appropriately as required.

8.3.8 EVENTS OF SPECIAL INTEREST

8.3.9 *N*REPORTING OF PREGNANCY

Should a participant become pregnant during the study, the primary investigator will create a plan to stop or taper the study drug as quickly as possible. The primary investigator will communicate with the physician managing the pregnancy and the subject and pregnancy will be followed to term.

8.4 UNANTICIPATED PROBLEMS

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8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems affecting the study or study participants will be reported to subjects by the primary investigator as soon as they are known.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

- Primary Efficacy Endpoint(s): the study will attempt to demonstrate the improvement in mean average from baseline to final visit of both corneal staining and subjective ocular discomfort as measured by the OSDI scale. Ed

- Secondary Efficacy Endpoint(s):improvement in mean average from baseline to final visit of conjunctival lissamine green staining. The study will demonstrate no change in baseline to final intraocular pressure, no worsened BCVA, and stable slit lamp biomicroscopy and dilated fundus exams.

9.2 SAMPLE SIZE DETERMINATION

This is a small pilot study of 12 participants completing the study assessments. There is no placebo and it is not powered to show statistical significance.

9.3 POPULATIONS FOR ANALYSES

- *Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)*
- *Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention)*

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

As a guide, the following should be addressed, as appropriate:

- *Categorical and continuous data will be presented as percentages, means with standard deviations, median, and range).*

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For each primary endpoint:

The improvement of patient comfort as measured by the dry eye comfort questionnaire OSDI defined as the mark listed in mm by the patient describing sensation of dryness. It will be measured at each study visit and reported as an ordinal endpoint. Descriptive statistics will be used for intent to treat patients and safety populations who receive at least one dose of the study drug.

- *The improvement of corneal staining after fluorescein instillation in which discrete superficial punctate stains are counted.. Descriptive statistics will be used for intent to treat patients and safety populations who receive at least one dose of the study drug.*
- *MIissing data will be handled by imputation. Outliers will be evaluated by the primary investigator. Subjects who are nonadherent will be referred for re-training and those lost to follow up will be contacted by the study coordinator at least 3 times by phone and ultimately with certified letter if telephone contacts are unsuccessful.*

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary endpoint:

- *The improvement of conjunctival staining after lissamine green instillation in which discrete superficial punctate stains are counted.. Descriptive statistics will be used for intent to treat patients and safety populations who receive at least one dose of the study drug.*
- *IOPs wlll be analyzed for mm Hg increase from baseline, also noting 10 mm Hg increase from baseline It will be measured at each visit. Descriptive statistics will be used for intent to treat patients and safety populations who receive at least one dose of the study drug.*

9.4.4 SAFETY ANALYSES

Safety endpoints will be analyzed as summary statistics during treatment, coded as per Medical Dictionary for Regulatory Activities and counted once only for a given participant. Start/stop dates, severity as determined by the investigator, relationship, expectedness, outcome and duration will be reported. Adverse events leading to premature discontinuation from the study and serious treatment-emergent AEs will be presented separately in a listing.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Include content in this section if applicable, otherwise note as not-applicable.

Because all subjects will receive active intervention, Intervention groups will not be compared .

9.4.6 PLANNED INTERIM ANALYSES

No interim analysis is planned.

9.4.7 SUB-GROUP ANALYSES

No sub-group analyses are planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure and time point.
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9.4.9 EXPLORATORY ANALYSES

No exploratory analyses are planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol.: informed consent document.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The study coordinator and primary investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the

participants for their records if requested. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).]

10.1.3 CONFIDENTIALITY AND PRIVACY

- *Initials will be attached to data/samples*

- *Personally identifiable information will be released to third parties such as insurance carriers and primary physicians if warranted.*
- *Study coordinator, primary and sub-investigators will have access to records, data, and samples. Monitors or auditors outside of study investigators will need access as well.*

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in

strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Toyos Clinic. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinic site and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Toyos Clinic.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Toyos Clinic onsite at 2204 Crestmoor Nashville, TN or in appropriate storage facility where Toyos Clinic records are kept. After the study is completed, the de-identified, archived data will be transmitted to and stored at Toyos Clinic. for use by other researchers including those outside of the study.

When the study is completed, access to study data will be provided through Toyos Clinic.]

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator
Melissa Toyos, MD partner
Toyos Clinic
2204 Crestmoor Nashville, TN
615.327.44
mtoyos@toyosclinic.com

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an IRB and a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including studies and Acthar specifically.. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to Toyos Clinic.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The primary investigator will conduct the monitoring on-site, once, for random review of certain data,, safety. Independent audits will not be conducted by <insert text> to ensure monitoring practices are performed consistently.]

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.]

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered onto the CRF provided by Toyos clinic.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 14 working days of identification of the protocol deviation, or within 14 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to sponsor . . Protocol deviations must be sent to the reviewing Institutional

Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study is not funded by the NIH.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.]

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ACTH	Adrenocorticotropic hormone
AR	Adverse Reaction
BCVA	Best Corrected Visual Acuity
CRF	Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IOP	Intraocular Pressure
IPL	Intense Pulsed Light
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine Device
KCS	Keratoconjunctivitis Sicca
ITT	Intention-To-Treat
MLT	Micropulsed Laser Trabeculoplasty
mm	Millimeter
Mm Hg	Millimeter of mercury
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NSAID	Non-steroidal
OSDI	Ocular surface disease index
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SLT	Selective laser trabeculoplasty
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UPT	Urine pregnancy test
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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