A Phase 4 Study to Assess the Clinical Efficacy and Safety of Intense Pulse Light Treatment with Meibomian Gland Expression of the Upper Eyelids in Dry Eye

Protocol Number: TCLUM-0012

National Clinical Trial (NCT) Identified Number:

Principal Investigator:Melissa Toyos, M

Sponsor: Toyos Clinic

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STATEMENT OF COMPLIANCE

(1) [The trial will be conducted in accordance with International Conference on HarmonisationGood Clinical Practice (ICH GCP) and applicableUnited 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

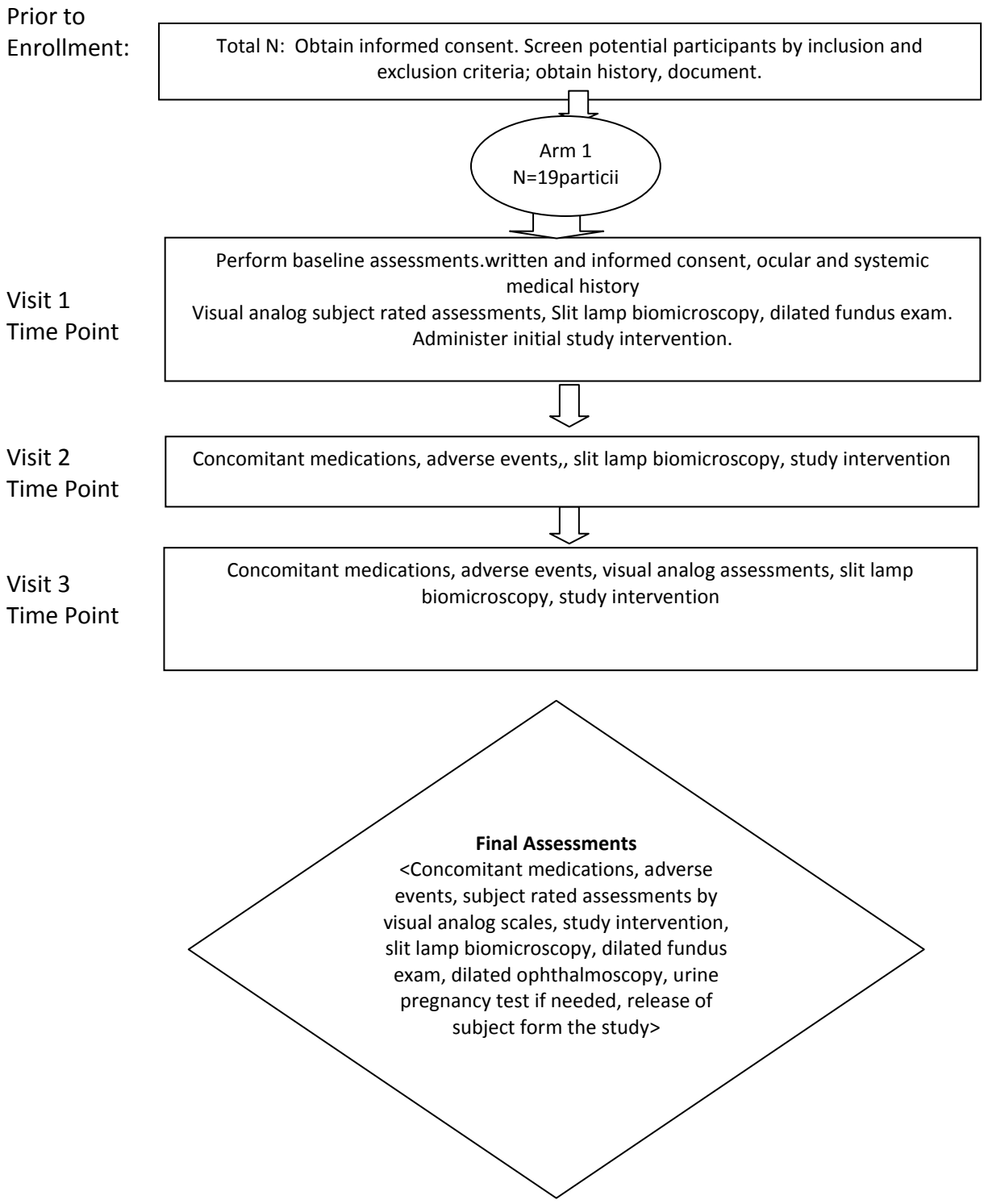
1.1 SYNOPSIS

Title:	A Phase 4 Study to Assess the Clinical Efficacy and Safety of Intense Pulse Light with Meibomian Gland Expression of the Upper Eyelids in Dry Eye Disease
Study Description:	*This study will test the efficacy and safety of application of light and expression of meibomian glands in upper eyelids in eyes of patients suffering with meibomian gland disease unrelieved by traditional dry eye treatments.*
Objectives:	*The primary objective of the study is to investigate the safety and efficacy of intense pulse light with Meibomian gland expression of the upper eyelids in dry eye disease.*
Endpoints:	Primary Endpoint: Improvement of tear break up time over the length of the study Secondary endpoint: patient comfort over the length of the study using a validated dry eye comfort questionnaire, VAS, over the past 2 weeks. 0= no pain and 100 = maximal discomfort, Improvement of patient comfort over the past 24 hours using a validated dry eye comfort questionnaire, VAS, where 0=no pain and 100= maximal pain, and a VAS scale of frequency of ocular discomfort over the past 24 hours where 0=no episodes and 100 = constant and continuous painful ocular episodes.
Study Population:	*19 study subjects 18-85 will be enrolled with male or female in the*

	Memphis, 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, cyclosporine, lifitegrast, loteprednol, artificial tears and warm compresses
Phase:	4
Description of Sites/FacilitiesEnrolling Participants:	*Single site study in Memphis, TN and surrounding areas.*
Description of StudyIntervention:	*Upper eyelid intense pulse light is given tragus to tragus including nose for 2 passes using standardized light settings and expression of Meibomian glands is done immediately following using cotton tip applicators.*
Study Duration:	*6 months*
Participant Duration:	*8-12 weeks*

1.2 SCHEMA

Flow diagram


Prior to Enrollment:
Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Arm 1
N=19particii
Visit 1 Time Point
Perform baseline assessments.written and informed consent, ocular and systemic medical history
Visual analog subject rated assessments, Slit lamp biomicroscopy, dilated fundus exam.
Administer initial study intervention.
Visit 2 Time Point
Concomitant medications, adverse events,, slit lamp biomicroscopy, study intervention
Visit 3 Time Point
Concomitant medications, adverse events, visual analog assessments, slit lamp biomicroscopy, study intervention
Final Assessments
<Concomitant medications, adverse events, subject rated assessments by visual analog scales, study intervention, slit lamp biomicroscopy, dilated fundus exam, dilated ophthalmoscopy, urine pregnancy test if needed, release of subject form the study>

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 14 +/-1 day	Study Visit 3 Day 28 +/- 1 day	Final Study Visit 4 Day 44 +/-1 day
Informed consent	X				
Demographics	X				
Medical history	X				
Randomization	X				
Concomitant medication review	X	X---------- X			
Bcva	X	X			X
Slit lamp biomicroscopy	X	x	X	x	X
Intense pulse light to upper lids		x	X	X	X
Expression of upper Meibomian glands	X	X		X	X
Non-invasive tear break up time	X	X		X	X
	X	X	x	X	X
Dilated ophthalmoscopy	X				X
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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

In 2002, Toyos and colleagues observed that rosacea subjects treated with IPL showed improvement in symptoms of dry eye disease. They hypothesized that IPL application to the malar region and nose closes the abnormal telangiectasias, decreasing the secretion of inflammatory substances and improving the function of Meibomian glands and the quality of their secretions.

Since this discovery, Toyos and colleagues have used IPL off-label to treat hundreds of rosacea subjects presenting with dry eye disease. A case report from 2002 demonstrated the potential of IPL technology for treatment of dry eye disease. Prior to the IPL sessions, the subjects reported unbearable drdy eye symptoms unresponsive to other conservative means of therapy (artificial tears, punctal plugs, cyclosporine, etc). After 4 monthly applications of IPL, there was a dramatic improvement in tear break up time and in Schirmer's test. A more recent study showed improvements in TBUT and the OSDI questionnaire, shifting the level of disease downwards towards less symptoms.

The M22 is modular. The M22 comprises the IPL module (treatment head and handpiece – Universal IPL Sapphire Cool Light Guide 6 mm KT-1007656) hereby referred to as the M22 with Optimal Pulse Technology, or M22-OPT.

The IPL treatment head emits light in the range of 515-1200 nm. The light is emitted perpendicular to the handpiece axis. The tip (lightguide) is made of sapphire and provides coverage of 6 mm. The lightguide is cooled by a thermos-electric cooler (also referred to as a chiller).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWNPOTENTIAL RISKS

Known risks of IPL on skin and Meibomian expression include
Skin redness
Eye redness
Skin blistering
Skin pigmentation
Skin swelling
Lid swelling
Lid tenderness
Increased mucus production
Skin scarring

2.3.2 KNOWN POTENTIAL BENEFITS

IPL is known to improve the signs and symptoms of dry eye disease including OSDI scores, tear break up time and eye comfort when four or more treatments are utilized over time. IPL also appears to improve the quality of Meibomian secretion and the function of Meibomian glands.

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 topical light therapy to affected periocular skin coupled with Meibomian gland expression 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 safety and efficacy of intense pulse light treatment with meibomian gland expression in upper lids with documented moderate to severe dry eye disease who have failed traditional therapies.	*The primary endpoint is the improvement in non-invasive tear break up time over the course of the study.*	*Endpoint has been validated in prior dry eye approvals.*
Secondary		
The secondary objectives are improvement in ocular pain and reduction of episodes of eye pain due to dry eye.	*The secondary endpoint(s)are improvement in eye pain due to dry eye over the course of the trial with a validated dry eye comfort questionnaire, measuring VAS pain scale over the past 2 weeks and 24 hours on a scale of 0-100 with 0 being no pain and 100 being maximal continuous pain. Also VAS scale measurement at each study visit measuring the frequency of ocular pain episodes over the previous 2 weeks on a scale of 0-100 with 0 being no episodes of eye pain due to dry eye and 100 being continuous maximal eye pain due to dry eye.*	*Endpoints have been validated in recent dry eye approvals (lifitegrast).*
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4 STUDY DESIGN

4.1 OVERALL DESIGN

- *The hypothesis is that use of upper eyelid IPL coupled with Meibomian gland expression 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*
- *Intense pulse light with Meibomian gland expression will be applied tragus to tragus including the nose four times every two weeks to control signs and symptoms at the discretion of the primary investigator.*

- *One study arm of active intervention for up to 12 weeks*
- *Single site*
- *Study intervention is use of intense pulse light with Meibomian gland expression of both upper eyelids*
- *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 safety and 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

Recommended IPL settings correlate to the Fitzpatrick skin type and are the Toyos settings utilized in previous trials and in current practice. These values are recommended and can be modified at the discretion of the investigator.

Skin Type	Fluence	Filter nm	Pulse structure	Pulse duration msec	Delay msec	Chiller
I	10	590	triple	6	50	On
II	10	590	triple	6	50	On
III	10	590	triple	6	50	On
IV	10	590	triple	6	50	On

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 -85.
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. Tear break up time of 7 seconds or less
7. Have normal lid anatomy.
8. Fitzpatrick skin type I-IV.
9. Subject is able and willing to comply with the treatment, follow up schedule and requirements.
10. 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 the study.
11. For males of reproductive potential:use of condoms or other methods to ensure effective contraception with partner
12. 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 components.
2. Pregnancy or lactation
3. Subjects can be on the following medications if they have been on a stable dose for 12 weeks: topical cyclosporine, topical liftigrast and/or topical loteprednoletabonate. 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.
4. Subjects must be unwilling to abstain from eyelash growth medications for the duration of the trial.
5. Subjects must not have had penetrating intraocular surgery, refractive surgery or corneal transplantation, eyelid surgery within 12 weeks prior to Visit 1.
6. Febrile illness within one week.
7. Treatment with another investigational drug or other intervention within *one month.*
8. *Subjects with a history of herpetic keratitis.*
9. Have serious or severe disease or uncontrolled medical condition that in the judgement of the investigator could confound study assessments or limit compliance.
10. Neuro-paralysis or pre-cancerous lesions in the area to be treated.
11. Prior history of cold sores or rashes in the area to be treated.
12. Use of photosensitizing medication within the past 90 days including isotretinoin, tetracycline, doxycycline and St. John's Wort.
13. Radiation to the head or neck within past 12 months.
14. Planned radiation therapy or chemotherapy.

15. Anticipated relocation or extensive travel outside of the local study area preventing compliance with study procedures.
16. Legally blind in either eye.
17. Facial IPL treatment within 12 months of treatment.
18. Expression of Meibomian glands within 6 months prior to treatment.

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).

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Anticipate 20 screenings for 15 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 the use of intense pulse light with M22 machine with 6 mm light guide applied across bilateral upper lids tragus to tragus including the nose followed by expression of the meibomian glands with fingers and/or cotton q-tips. Patients will be given one drop of bromfenac and one drop of brimonidine following the treatment and given one bottle of bromfenac to be used once daily for four days following the procedure.

6.1 STUDY INTERVENTION(S)ADMINISTRATION

6.1.1 STUDY INTERVENTIONDESCRIPTION

There is no control, only study intervention with intense pulse light and Meibomian gland expression of bilateral upper lids. This treatment will be studied in this investigation specifically for moderate to severe dry eye disease.

6.1.2 ADMINISTRATION OF TREATMENT

Each eligible participant will undergo IPL therapy using the M22 OPT machine. Eye shields will be placed on the lower lids, leaving upper lids exposed for the treatment. Ultrasound coupling gel applied 1-2 mm

thick across the area of treatment will be applied tragus to tragus across the area to be treated. Two passes of light at a power setting of 10 mJ were used across the upper eyelids.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION

The investigative site will provide M22, specified lightguide, coupling agent, bromfenac, brimonidine and Honeywell adhesive eye protection as well as eye protection glasses for operators.

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6.2.2 TRAINING

Investigators and study staff will be fully trained on the protocol and the appropriate study techniques by Dr. Rolando Toyos or doctors trained by directly by Dr. Rolando Toyos.

6.2.3 PRODUCT STORAGE

The M22 and corresponding handpiece will be stored in the clinic at room temperature between 65-80 degrees Fahrenheit.

6.2.4 PREPARATION

Before treatment, the subjects face will be cleaned with a mild cleansing agent like soap, facial wipes or dilute medical grade alcohol. Clinicians will be trained to identify Fitzpatrick skin types, apply a thin film of coupling gel and use appropriate eye protection for subjects as well as staff. The treatment area will include the upper eyelids from tragus to tragus including the nose.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All subjects will receive active drug with no control.

6.4 STUDY INTERVENTIONCOMPLIANCE

Adherence to the protocol will be assessed by documenting study visits.

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 sitewill notsupply 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 INTERVENTIONDISCONTINUATIONAND PARTICIPANTDISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuationduring 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 willbe 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, past 2 weeks and 24 hours, subject assessment of frequency of eye pain related to dry eye, use of concomitant medications since last visit, occurrence of AEs since last visit, BCVA, slit lamp biomicroscopy, dilated fundus exam and pregnancy test for women of childbearing potential.

7.2 PARTICIPANTDISCONTINUATION/WITHDRAWALFROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinueor 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 interventionfor 20 days.

The reason for participant discontinuationor 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 discontinuedfrom 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 willattempt 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 willmake 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.

- *Each subject will undergo 4 treatment sessions at 2 weeks intervals.*
- *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 for the past 2 weeks and the past 24 hours at Visit 1,2, 3 and 4. 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.***

  Past 2 week and 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

- ***Subject rated assessment of frequency of ocular discomfort by visual analog scale. Subjects will be asked to subjectively rate their eye dryness for the past 2 weeks at Visit 1,2, 3 and 4. Subjects will be instructed to rate the frequency of eye pain episodes using the scale below. The total length of the line from "no episodes" to "constant maximal episodes" 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.***

  Past 2 week and 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 eye pain episodes_____Maximal and continual eye pain episodes

- ***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***
- ***Slit lamp biomicroscopy – 8 mm x 2 mm slit lamp beam will 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.***
- ***Dilated ophthalmoscopy will occur at the first and last study visit and include assessment of the optic nerve head for pallor and cupping.***
- ***Non-invasive tear break up timewill be assessed subjectively by the investigator using a stop watch and the average of 3 measurements will recorded at each of the 4 study visits.***

8.2 SAFETY AND OTHER ASSESSMENTS

- ***Slit lamp biomicroscopy – 8 mm x 2 mm slit lamp beam will 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.***
- ***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 interventionassessed by the clinician who examines and evaluates the participantbased 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 interventioncaused the AE, or there is a temporal relationship between the study interventionand event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study interventionand the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study interventioncaused the event, there is no temporal relationship between the study interventionand 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 interventionadministration 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 interventionadministration 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 studyinterventionadministration, 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 coordinatorwill 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 interventionrelated, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study interventioncaused 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 interventionand 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 resultson 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 one week 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 7 business days 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: the study will attempt to demonstrate the improvement in mean average from baseline to final visit of measure of pain in past 2 weeks on visual analog scale (VAS) scale.
- Secondary Efficacy Endpoint(s): the study will attempt to demonstrate the improvement in mean average from baseline to final visit of visual analog scale of pain over the previous 24 hours an, the frequency of ocular discomfort over the past 2 weeks and the non-invasive tear break up time.

9.2 SAMPLE SIZE DETERMINATION

This is a small pilot study of 15 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

Paired t-tests will be conducted for each VAS scale and TBUT with standard deviations, error means, 95% confidence intervals and level of significance.

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)

The improvement of non-invasive tear break up time from the beginning of the study to the end. Descriptive statistics and paired t-tests will be applied.

- *MIssing 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 visual analog scale of pain over the past 2 weeks, the past 24 hours and the frequency of eye pain from dry eye over the past 2 weeks. Descriptive statistics and paired t-tests will be used where applicable.*

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 PARTICIPANTDATA

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

No exploratoryanalyses 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 partiessuch 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 aData and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, includingstudies and Actharspecifically..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 auditswill not be conductedto 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 HANDLINGANDRECORD 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 HarmonisationGood 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 reviewingInstitutional 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 theNIH 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
AR	Adverse Reaction
BCVA	Best Corrected Visual Acuity
CRF	Case Report Form
DED	Dry Eye Disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IPL	Intense Pulsed Light
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IPL	Intense pulse light
IRB	Institutional Review Board
IUD	Intrauterine Device
KCS	Keratoconjunctivitis Sicca
ITT	Intention-To-Treat
MG	Meibomian Gland
MGD	Meibomian Gland Dysfunction
MGX	Meibomian Gland Expression
mm	Millimeter
Mm Hg	Millimeter of mercury
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
OPT	Optimal pulse technology
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
SOP	Standard Operating Procedure
UPT	Urine pregnancy test
US	United States
VAS	Visual Analog Scale

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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