Randomized, Controlled, Multicenter, Double-Masked, Parallel, Phase 3 Trial to Evaluate the Safety and Efficacy of TP-03 for the Treatment of *Demodex* Blepharitis (Saturn-2)

Protocol Number: TRS-010

IND Sponsor: Tarsus Pharmaceuticals, Inc.

Funded by: Tarsus Pharmaceuticals, Inc.

[redacted]

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Registration No: NCT04784091

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of clinical trials 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 Institutional Review Board (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. In addition, 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:	Randomized, Controlled, Multicenter, Double-Masked, Parallel, Phase 3 Trial to Evaluate the Safety and Efficacy of TP-03 for the Treatment of *Demodex* Blepharitis (Saturn-2)
Test Article:	TP-03, lotilaner ophthalmic solution, 0.25%
Study Description and Hypotheses:	This Phase 3 study is a randomized, controlled, multicenter, double-masked, parallel trial to compare the safety and efficacy of TP-03 to vehicle control for the treatment of *Demodex* blepharitis. The hypothesis for the study is the proportion of participants cured at Day 43 with treatment by TP-03, 0.25%, is greater than the proportion cured by treatment with vehicle.
Control Article:	Vehicle of TP-03
Study Design:	Prospective, randomized, double-masked, multicenter, two-arm, parallel vehicle-controlled study
Objective:	To demonstrate the safety and efficacy of TP-03, 0.25%, for the treatment of *Demodex* blepharitis

Endpoints:	Primary Efficacy Endpoint: Cure based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43. Secondary Endpoints: • *Demodex* mite eradication (mite density of 0 mites/lash) from the analysis eye at Day 43. • Composite cure based on collarette score (0) and erythema score (0) for the upper eyelid of the analysis eye at Day 43. • Erythema cure based on erythema score (0) for the upper eyelid of the analysis eye at Day 43 [redacted] Safety will be determined by assessing adverse effects related to the active treatment [redacted]
Phase:	3
Number of Participants:	Up to 418 participants will be enrolled [redacted]
Study Population:	Participants with blepharitis due to *Demodex* infestation defined as having an elevated mite density, collarettes and erythema
Description of Sites:	Up to 25 sites in the United States
Description of Study Treatment:	Participants eligible to be randomized will receive one of the following treatments administered bilaterally BID for 43 days: TP-03, 0.25%, or TP-03 vehicle
Study Duration:	Approximately six months

Participant Duration:	The study duration for an individual participant is estimated to be approximately three months
Summary of Visit Schedule:	Screening, Day 1, Day 8, Day 15, Day 22, Day 43, Day 57 [redacted] and Day 90. The Day 90 visit should only be conducted at sites that performed specular microscopy.

1.2 SCHEMA

At the Screening visit, potential participants will be evaluated for eligibility. Prior to performing any study specific procedures, potential participants must provide informed consent using the current IRB-approved informed consent form. [redacted]

[redacted]

[redacted] Screening

- Obtain informed consent
- Obtain demographics, medical/ophthalmic history, concomitant medications
- Corrected distance visual acuity (CDVA)
- Slit lamp biomicroscopy
- Collarette grading; erythema assessment
- *Demodex* count
- Urine pregnancy test, as required

Day 1 Initiation of study treatment

- Concomitant medication review if required
- CDVA [redacted]
- Slit lamp biomicroscopy [redacted]
- Corneal staining
- Intraocular pressure
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Randomization
- Dispense study drug; [redacted]
- [redacted]

- Adverse event review and evaluation

Day 8 ± 3 days **Follow-up assessments of study endpoints and safety**

- Concomitant medication review
- [redacted]
- CDVA
- Slit lamp biomicroscopy
- Collarette grading; erythema assessment
- Corneal staining
- [redacted]
- Collection of study drug and return to participant
- Adverse event review and evaluation

Day 15 ± 3 days **Follow-up assessments of study endpoints and safety**

- Concomitant medication review
- [redacted]
- CDVA
- Slit lamp biomicroscopy
- Collarette grading; erythema assessment
- Corneal staining
- *Demodex* count
- [redacted]
- Collection of study drug and return to participant
- Adverse event review and evaluation

Day 22 -3/+4 days **Follow-up assessments of study endpoints and safety**

- Concomitant medication review
- [redacted]
- CDVA
- Slit lamp biomicroscopy
- Collarette grading; erythema assessment
- Corneal staining
- *Demodex* count
- [redacted]
- Collection of study drug and return to participant
- Adverse event review and evaluation

Day 43 -3/+7 days **Day 43 study assessments** [redacted]

- Concomitant medication review
- [redacted]
- CDVA
- Slit lamp biomicroscopy
- Collarette grading; erythema assessment
- Corneal staining
- Intraocular pressure
- [redacted]
- *Demodex* count
- [redacted]
- [redacted]
- [redacted]
- Urine pregnancy test, as required
- Adverse event review and evaluation
- Collect unused study drug, [redacted]
- [redacted]

Day 57 -6/+14 days **Observational study assessment** [redacted]

- Concomitant medication review
- CDVA
- Slit lamp biomicroscopy
- Collarette grading; erythema assessment
- Corneal staining
- Intraocular pressure
- *Demodex* count
- [redacted]
- Adverse event review and evaluation
- [redacted]

Day 90 ± 14 days **Safety assessment and (end of study at sites performing specular microscopy)**

- Concomitant medication review
- CDVA
- Slit lamp biomicroscopy
- [redacted]
- Adverse event review and evaluation
- [redacted]

[redacted]

[redacted]

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic blepharitis is an ocular inflammation that primarily involves the eyelid margin and is a common cause of chronic ocular irritation.[1] Blepharitis may affect the eyelid skin, base of the eyelashes, the eyelash follicles, the meibomian glands and gland orifices. It is estimated that up to 19 million patients may have blepharitis in the US alone.[2] A meta-analysis of the results of 13 controlled studies performed

by Zhao et al. has shown that the rate of *Demodex* infestation in blepharitis subjects is 44.5% compared to 16.7% in normal controls.[3] *Demodex* infestation increases with age, being observed in 84% of the population at age 60 and 100% of the population over the age of 70,[4] but it can affect either sex and any age group.

The presence of *Demodex folliculorum* in the eyelid structures of man has been recognized for more than a century[5] and has been implicated as a cause of chronic blepharitis.[1,6,7] *Demodex folliculorum,* which is classified as an arthropod because of its eight jointed, rudimentary legs,[8] is the most common ectoparasite found in humans[9] and can inhabit the eyelash follicles, meibomian glands and sebaceous glands.[10] The association of blepharitis and *Demodex* infestation has been examined in several studies.[4,7,8] In *Demodex* blepharitis, mites inhabit the eyelash follicles where they feed on sebum and can cause microscopic epithelial abrasions, resulting in epithelial hyperplasia and reactive hyperkeratinization.[4,11] Undigested regurgitated material from the mites, combined with epithelial cells, keratin and eggs are thought to contribute to the formation of collarettes (cylindrical dandruff), which are pathognomonic for *Demodex* blepharitis.[7,11–16] Gao et al[7] found that lashes with collarettes had an average *Demodex* density of 2 to 4 mites per lash, which was significantly higher than the 0.2 mites per lash found in lashes without collarettes. This finding indicated that the extent of *Demodex* infestation correlated with the clinical severity of collarettes.

Currently there are no FDA approved treatments for *Demodex* blepharitis. Management can include a combination of lid scrubs and removal of the eyelash collarettes.[11] *Demodex* mites are resistant to a wide range of antiseptics including 75% alcohol, 10% povidone iodine and antibiotics such as erythromycin.[17] In previous clinical trials, systemic ivermectin, metronidazole, their combination and topical tea tree oil have been used to treat blepharitis due to *Demodex* infestation with varying degrees of success[18–21] and in spite of the ocular discomfort and irritation associated with these treatments.[22] However, studies have shown that no single management option fully eradicates *Demodex* after four weeks of therapy.[11,23] Thus, there remains an unmet medical need for an efficacious and safe treatment option for individuals with *Demodex* blepharitis.

This Phase 3 study is a randomized, controlled, multicenter, double-masked, parallel trial to compare the safety and efficacy of TP-03 to vehicle control for the treatment of *Demodex* blepharitis. The primary objective of the study is to assess the safety and efficacy of TP-03, 0.25%, compared to its vehicle from Day 1 (Baseline) to Day 43 in adult participants with mild to severe *Demodex* blepharitis. The primary efficacy endpoint will be cure based upon collarettes. Safety will be determined by assessing adverse effects related to the active treatment as well as evaluating any changes in visual acuity, intraocular pressure, slit lamp biomicroscopy, endothelial cell density, hematology, blood chemistry, drug concentration analysis and urinalysis.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks for participation in this study include mild: ocular irritation (inflammation), conjunctival hyperemia, ocular discomfort, ocular burning, ocular soreness, transitory pain, and ocular surface staining following instillation of TP-03 or vehicle. Other potential risks include a mild, transitory medicinal taste following instillation of TP-03 or vehicle.

2.3.2 KNOWN POTENTIAL BENEFITS

Potential benefits for those participants randomized to treatment with TP-03 include a reduction in *Demodex* density and improvement in the signs of *Demodex* blepharitis. Participants randomized to the control arm may not receive any direct benefit.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

[redacted] The benefits of treatment with an efficacious anti-infective that can eradicate *Demodex folliculorum* is believed to outweigh the potential risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To demonstrate the safety and efficacy of TP-03, 0.25%, as a cure for *Demodex* blepharitis	Primary Efficacy Endpoint: Cure based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43 Primary Safety Endpoint: The assessment of treatment-related adverse effects	The presence of collarettes are pathognomonic of *Demodex* infestation. The elimination of collarettes is definitive evidence of a cure. Adverse events are a direct indication of the safety of the treatment.
Secondary		
To demonstrate the efficacy of TP-03, 0.25%, to eradicate *Demodex* mites from the eyelid margin	Secondary Endpoint: *Demodex* mite eradication (mite density of 0 mites/lash) from the analysis eye, at Day 43	Determining *Demodex* density provides direct evidence of the presence of mites. The eradication of mites provides definitive evidence that the source of inflammation has been eliminated.
To demonstrate the efficacy of TP-03, 0.25%, to eliminate collarettes and erythema from the eyelid margin	Secondary Endpoint: Composite cure based on collarette score (0) and erythema score (0) for the upper eyelid of the analysis eye at Day 43	The composite of both signs, collarettes and erythema provides additional evidence of underlying mite eradication and improvement in blepharitis.
To demonstrate the efficacy of TP-03, 0.25%, to eliminate erythema from the eyelid margin	Secondary Endpoint: Erythema cure based on erythema score (0) for the upper eyelid of the analysis eye at Day 43	Erythema is a primary sign of blepharitis and the elimination of erythema is another indication of improvement.

[redacted]

4 STUDY DESIGN

4.1 OVERALL DESIGN

The Phase 3 study is a randomized, controlled, multicenter, double-masked, parallel trial to evaluate the safety and efficacy of TP-03, 0.25%, for the treatment of *Demodex* blepharitis. The primary objective of the study is to demonstrate the safety and efficacy of TP-03, 0.25%, compared to its vehicle for the treatment of mild to severe *Demodex* blepharitis. The primary efficacy endpoint will be cure based upon collarettes as evaluated by the study grading scale (see Appendix A: Collarette Grading). Safety will be determined by assessing adverse effects related to the active treatment [redacted]

The sample size is planned to be a minimum of 300 participants. The plan is to enroll up to 418 subjects in a 1:1 ratio of active: vehicle to allow for possible loss to follow-up and the possibility that up to two clinical sites need to close due to COVID-19 before completion of the study. This sample size is based primarily upon safety considerations and is designed to ensure a minimum of 300 subjects treated with TP-03, 0.25%, for 43 days across two pivotal studies. Based upon prior clinical studies conducted in Mexico City and the previous Phase 2b/3 (Saturn-1) in the US with TP-03, 0.25%, for the treatment of *Demodex* blepharitis, this Phase 3 study should be adequately powered to demonstrate a difference between TP-03, 0.25%, and vehicle treatment arms.

Treatment assignment will be randomly assigned to reduce bias and the treatment assignment will be double-masked, unknown to the study participant, investigators and site staff performing study assessments.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is designed to demonstrate the superiority of TP-03, 0.25%, to vehicle for the treatment of *Demodex* blepharitis. The vehicle of TP-03 was selected as the control since there are no approved pharmaceutical treatments for *Demodex* blepharitis. The vehicle as the control will provide evidence that the active ingredient is responsible for the response, not the vehicle alone.

[redacted]

[redacted]

[redacted]

[redacted]

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the last visit. The end of the study is defined as completion of the last visit by all participants at all sites.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Screening is defined as the study visit where baseline assessments are performed prior to first administration of the study drug.

Participants who participated in the Saturn-1 clinical trial should not participate in the Saturn-2 clinical trial. Participants who meet all of the following criteria may be enrolled.

1. Male or female, aged ≥18 years of age
2. Be willing to sign the informed consent and deemed capable of complying with the requirements of the study protocol
3. Has blepharitis*
4. Meet all of the following criteria <u>in at least one eye</u>:
    a. Have more than 10 lashes with collarettes present on the upper lid (score of 2 or greater)
    b. Have at least mild erythema of the upper eyelid margin
    c. Have a *Demodex* density, upper and lower eyelids combined, of 1.5 or more mites per lash

    Note: All three criteria (a to c) must be met in the **same** eye. Only one eye must qualify for the participant to be eligible.
5. [redacted]
6. Stated willingness to comply with all study procedures and availability for the duration of the study

[1] Perks D. (2015) AHC 2224920: 13 Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 4-Week Treatment-free Period. (Report No. 8275617). [redacted]

[redacted]

* The blepharitis diagnosis can be made on the date of screening.

[redacted]

5.2 EXCLUSION CRITERIA

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

1. Have had prescription: systemic, nasal, inhaled, ocular topical or topical anti-inflammatory steroid treatment; antibacterial treatment; or antiparasitic treatment within 14 days of Screening
2. Have had topical tea tree oil or hypochlorous acid treatment of the ophthalmic area within 14 days of Screening or unwilling to forego the use of these treatments during the study
3. Have used lid hygiene products (e.g., lid scrubs) within 14 days of Screening or unwilling to forego the use of lid hygiene products during the study
4. Have initiated treatment with an ocular topical prostaglandin analogue within 30 days of Screening or have any plans to change or discontinue treatment during the study
5. Have used a prostaglandin analogue to promote eyelash growth within 30 days of Screening or any plans to initiate treatment during the study
6. Have used artificial eyelashes, eyelash extensions or had other cosmetic eyelash or eyelid procedures (e.g., eyeliner tattooing, eyelash tinting, eyelash curling perm, etc.) within 7 days of Screening or be unwilling to forego their use during the study

[redacted]

8. Have an acute ocular infection or have an active ocular inflammation other than blepharitis

[redacted]

11. Have hypersensitivity to lotilaner or any of the formulation components
12. Have participated in any clinical trial with an investigational drug or device within 30 days of Screening or concurrent enrollment in such a trial with the exception of treatment with the investigational drug or device having been completed at least three months prior
13. Be pregnant or lactating at the time of Screening

[redacted]

[redacted]

[redacted]

5.4 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 treatment 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).

[redacted]

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

It is anticipated that at least 500 patients will be screened in order to reach target enrollment. The source of participants is expected to come primarily from outpatient clinics and the general public. As *Demodex* positive patients are widely available, participants are expected to come from in-office visits of participating investigators. In the general public, participants may be identified by their symptoms (e.g., itching and burning of the lids margins) and can be reached through print advertisements (e.g., newspaper, magazine advertisement, flyer, poster, etc.); social media; radio or television advertisement; and/or telephone screening script.

As the risk to participants is considered minimal, employees of the study site and family members of site staff may be invited to participate in the clinical trial. Site staff who work on the clinical trial are not eligible to participate.

To retain participants, participants may receive visit reminders and some reimbursement for their time and travel expenses.

In the event prohibited medications / treatments are indicated for care, participants will not be discontinued.

6 STUDY TREATMENT

6.1 STUDY TREATMENT(S) ADMINISTRATION

6.1.1 STUDY TREATMENT DESCRIPTION

TP-03

Lotilaner is the investigational product substance. Lotilaner is an isoxazoline and inhibits the γ-aminobutyric acid (GABA)-gated chloride channels (GABACls) of arthropods. The GABA-mediated chloride influx leads to hyperpolarization of the cellular membrane and generates an inhibitory

postsynaptic potential, which decreases the probability of an action potential.[24] Ectoparasites exposed to isoxazolines will exhibit a spastic paralysis leading to their starvation and death. Isoxazolines as a chemical class have been shown to have no to very low affinity to the human GABA receptor and the GABA pathway is not activated in humans.

Lotilaner has the IUPAC name: 3-methyl-N-[2-oxo-2-(2,2,2-trifluoroethylamino)ethyl]-5-[(5S)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4H-1,2-oxazol-3-yl]thiophene-2-carboxamide. Lotilaner oral tablets were approved by the FDA for the treatment and control of flea and tick infestations in dogs and puppies in 2018 (Credelio, NADA 141-494). In addition, lotilaner is authorized for use as a veterinary medicine to treat flea and tick infestations in dogs and cats in the EU (Credelio, EMEA/V/C/004247).

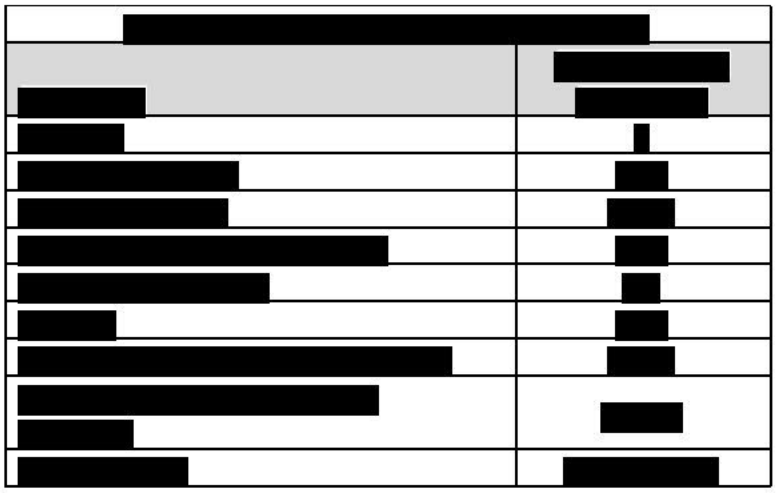
[redacted]

All excipients used are within the range of concentrations required to conform to the FDA's database of inactive ingredients.

Vehicle Control

The vehicle control treatment consists of the TP-03 vehicle. Specifically, the concentrations of the excipients match the vehicle for the TP-03, lotilaner ophthalmic solution, 0.25%.

[redacted]



All excipients used are within the range of concentrations required to conform to the FDA's database of inactive ingredients.

6.1.2 DOSING AND ADMINISTRATION

In this study, participants will be instructed to administer a single drop of the study product twice a day (e.g., morning and evening) in each eye. The treatment period will be for approximately 43 days. At Day 1, site staff will supervise the participant's first dose of the study medication. Participants will be asked to wash their hands prior to administration. Following drop instillation, the participant will be advised to close their eyes for approximately 15 to 30 seconds and apply gentle pressure to the upper lid to express the medication across the upper and lower lid margins. The participant should be instructed to let the medication air dry on the lid without dabbing with a tissue.

During waking hours, if a dose is missed in the morning, participants will be instructed to administer the drop if it is at least an hour prior to the second dose of the day. If it is less than an hour, the participant should simply dose the second drop of the day.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

[redacted] and its affiliates in [redacted] will perform the manufacturing, packaging, labeling and distribution of the investigational product. Expired or unused product will be returned to the sponsor or designee for disposal.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

TP-03, 0.25% (lotilaner ophthalmic solution, 0.25%), is a topical ophthalmic solution of 0.25% lotilaner.

[redacted]

6.2.3 PRODUCT STORAGE AND STABILITY

All preparations of both the study drug and vehicle control product should be stored at 15° to 30°C. There are no light or humidity requirements. Participants will be instructed to store the study drug at room temperature in a climate-controlled environment (15° to 30 °C) avoiding extreme heat or cold.

6.2.4 PREPARATION

Not applicable.

6.3 PARTICIPANT ID ASSIGNMENT AND MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND MASKING

A balanced (1:1) randomization will be used for this study. A computer-generated blocked randomization schedule will be generated by [redacted]. [redacted] will use the randomization schedule to package the study drug. The labelled study drug will be shipped to the US distribution center for distribution to the clinical sites.

[redacted]

If a potential study participant has provided written informed consent and met all eligibility criteria, the participant is considered eligible to participate. If the potential participant elects to participate in the study, they can continue with the Day 1 procedure or be scheduled to return for Day 1. At Day 1, they will be dispensed the next available study drug bottle from the current site inventory by the Interactive Response Technology (IRT) system [redacted], which uses block stratification by site. The participant will receive their assigned study drug at the completion of the Day 1 visit and the participant will be considered enrolled in the study. The participant will be assigned a unique identification number consisting of their site number followed by a hyphen and then the screening number.

Throughout the study, both the participant and site personnel performing study assessments will remain masked to the study medication. The active and vehicle control ophthalmic solutions will be indistinguishable in appearance and will be distributed in bottles identical in appearance.

Treatment assignments should only be unmasked if needed for proper care of the participant. Sites will be provided instructions on the procedure to be followed to unmask the treatment assignment for a participant. Inadvertent unmasking will be reported to the sponsor and IRB as required.

[redacted]

6.4 STUDY TREATMENT COMPLIANCE

Participants will be instructed on proper instillation and storage of the study drug and provided with written instructions. To assess adherence to the protocol regarding administration of the study product, participants will be instructed to record in a dosing compliance diary on a daily basis. Dosing compliance will be assured by an in-office review of a dosing diary. [redacted] Participants will be reinstructed on dosing compliance and this will be documented in the source documents.

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 recorded in the source document are concomitant prescription medications, over-the-counter medications, supplements, and relevant treatments and/or procedures (e.g., lid scrubs, tea tree oil, etc.). All concomitant medications including over-the-counter medications and nutritional supplements used within the 30 days prior to the first visit will be documented. Any changes to concomitant medication use or initiation of new medications will be reported throughout the study.

For the duration of the study, any therapy considered necessary for the participant's welfare may be given to the participant at the discretion of the investigator. Initiation of new medications or changes to concomitant medications should be recorded in the source document.

6.5.1 RESCUE MEDICINE

No rescue medication is available for this indication.

7 STUDY TREATMENT DISCONTINUATION AND PARTICIPANT DISCONTINUATION

7.1 DISCONTINUATION OF STUDY TREATMENT

Discontinuation from use of the study treatment 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 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 AE. Participants to be discontinued for AE(s) will be followed until the event is resolved or considered medically stable by the investigator.

The data to be collected at the time of study treatment discontinuation may include the following:

- An AE assessment and performance of safety assessments including visual acuity, IOP, slit lamp biomicroscopy, endothelial cell density, hematology, blood chemistry, drug concentration analysis and urinalysis
- Any follow-up evaluations required per investigator determination

Temporary discontinuation of the study treatment could include the onset of such conditions as an allergic conjunctivitis or signs or symptoms of eyelid allergy (e.g., injection, swelling, itching, etc.). Per investigator discretion, the study treatment could be discontinued until such a time that the allergic

conjunctivitis has shown sufficient improvement such that the study treatment could be re-started. Re-challenging with the study treatment could help to determine if the allergic response is related to the study drug.

The principal investigator reserves the right to discontinue the study at his/her site for any safety, ethical or administrative reason at any time.

7.2 PARTICIPANT DISCONTINUATION FROM THE STUDY

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

- Pregnancy
- If any clinical AE or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Reasons relating to COVID-19
- Other (specify reason)

The reason for participant discontinuation from the study will be recorded on the exit eCRF. Participants who sign the informed consent form and are randomized but do not receive the study treatment will not be replaced. Participants who sign the informed consent form, are randomized and receive the study treatment and subsequently discontinue, or are discontinued from the study, will not 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 their scheduled visit within the visit window 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 as soon as possible, counseling the participant on the importance of continuing the administration of the study drop and of maintaining the assigned visit schedule. In addition, the site should 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, three 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 discontinued from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The efficacy assessments performed include the following:

- Assessment of collarette grade
- Eyelash epilation and mite counts
- Assessment of erythema grade

The procedures are described in detail in Appendix A. All procedures/evaluations will be performed by qualified personnel. In addition, mite counts will be performed by trained clinical or SMO staff.

8.2 SAFETY AND OTHER ASSESSMENTS

The safety and other assessments to be performed include the following:

- Adverse events
- Corrected distance visual acuity
- Slit lamp biomicroscopy assessment
- Corneal staining
- IOP measurement
- [redacted]

The procedures are described in detail in Appendix A. All procedures/evaluations will be performed by qualified personnel.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An 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 AE, 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. Serious

adverse events include drug deficiencies that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

Events that are considered sight-threatening in the opinion of the investigator will be considered SAEs.

A planned hospitalization for a pre-existing condition without a serious deterioration in health is not considered to be an SAE. Hospitalization for less than 24 hours is not considered an SAE unless the precipitating event was unanticipated and also related to the investigational drug.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe the severity of AEs.

- **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." Severity is a measurement of intensity. Thus, a severe reaction is not necessarily a SAE. For example, a headache may be severe in intensity, but would not be serious unless it met one or more of the criteria for a serious adverse event.

8.3.3.2 RELATIONSHIP TO STUDY TREATMENT

All AEs must have their relationship to study treatment 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.

- **Definitely Related** – Evidence indicates a reasonable temporal sequence of the event with the study drug administration exists or that the association of the event with study drug administration is unknown and the event is not reasonably supported by other conditions such that:
  - There is a clinically plausible time sequence between onset of the AE and study treatment administration, and/or
  - There is a biologically plausible mechanism for study treatment causing or contributing to the AE, and
  - The AE cannot be reasonably attributed to concurrent/underlying illness, other drugs or procedures.
- **Potentially Related** – Evidence indicates a possible relationship to the study drug such that:

- The event occurs within a reasonable period of time relative to the treatment that makes a causal relationship possible, but plausible explanations may also be provided by other causes such as other drugs, products, chemicals, underlying disease, environment, etc.
- The event is possibly related to the study treatment.

- **Not Related** – Evidence indicates no plausible direct relationship to the study drug such that:
  - A clinically plausible temporal sequence is inconsistent with the onset of the AE and drug administration, and/or
  - A causal relationship is considered biologically implausible
  - The AE can be attributed to concurrent/underlying illness, other drugs or procedures.

8.3.3.3 EXPECTEDNESS

The investigator will be responsible for determining whether an 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 treatment. Expectedness should be determined if the AE is characterized as related to treatment and is serious (met one or more of the criteria for an SAE).

8.3.3.4 OUTCOME

The clinical outcome of an AE will be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Death
- Ongoing (i.e., continuing at time of study discontinuation)
- Unknown

8.3.3.5 TREATMENT OR ACTION TAKEN

The clinical treatment or action taken from an AE will be characterized as follows:

- None
- Medical intervention
- Surgical intervention
- Unknown
- Other (specify)

8.3.3.6 ACTION TAKEN WITH INVESTIGATIONAL PRODUCT

The action taken with the IP will be characterized as follows:

- None
- Drug temporarily withdrawn
- Drug discontinued
- Unknown

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

The occurrence of an AE or 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. At study visits, study personnel should pose general questions to the participant to ascertain if the participant experienced any issues prior to the visit.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate eCRF. Information to be collected includes event description, date 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 date of resolution/stabilization of the event. All AEs occurring while in the study must be documented appropriately regardless of relationship.

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.

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

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event (e.g., record congestive heart failure rather than dyspnea, rales and cyanosis). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual sign or symptom should be recorded as a separate AE. A diagnosis that is subsequently established should be reported as follow-up information.

Adverse events occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example: Orthostatic hypotension $\Rightarrow$ fainting and fall to floor $\Rightarrow$ head trauma $\Rightarrow$ neck pain. The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.

Centralized safety oversight for this multi-site study will be provided by the Medical Monitor.

8.3.5 ADVERSE EVENT REPORTING

The investigator must record nonserious adverse events and submit on the eCRF in a timely manner.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor and Medical Monitor any SAE, whether or not considered study treatment-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 treatment caused the event [21 CFR 312.64(b)]. Serious adverse events must be reported immediately to the below listed individuals using the Serious Adverse Event Report (SAER) form. Sites will also be instructed to document the event in the Serious Adverse Event eCRF.

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

[redacted]	[redacted]

All 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 study sponsor and should be provided as soon as possible.

The study sponsor or designee 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 [21 CFR 312.32(c)(2)]. In addition, the sponsor must notify the 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 [21 CFR 312.32(c)(1)]. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to the FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the AE.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

It will be the responsibility of the principal investigator to inform participants of any AEs or SAEs deemed related to the study drug and of any study-related results.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Women of Childbearing Potential (WOCBP) includes any females who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or are not postmenopausal at least 12 months since last menses. WOCBP will be required to use designated methods of birth control during the course of the study. All women who are pregnant, nursing an infant or planning a pregnancy during the duration of this study will be excluded from participation.

If a participant or investigator suspects that the participant may be pregnant prior to study drug administration, the study drug should be withheld until the results of pregnancy testing are available. If pregnancy is confirmed, the participant should not administer the study drug and should not be enrolled in the study.

If a female participant becomes pregnant during the study, use of the study drug should be discontinued immediately. The investigator will notify the sponsor (or designee) immediately after the pregnancy is confirmed. The investigator will (1) obtain a consent from the female participant for pregnancy follow-up and (2) follow the progress of the pregnancy to term. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to the sponsor or designee. The sponsor or sponsor's designee will be responsible for reporting to the IRB and regulatory agencies as appropriate.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This study is designed to demonstrate the superiority of TP-03 to vehicle control.

- Population: Participants with *Demodex* blepharitis as defined by the enrollment criteria
- Primary Efficacy Endpoint: Cure based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43
- Secondary Efficacy Endpoints:
  - *Demodex* mite eradication (mite density of 0 mites/lash) from the analysis eye at Day 43
  - Composite cure based on collarette score (0) and erythema score (0) for the upper eyelid of the analysis eye at Day 43
  - Erythema cure based on erythema score (0) for the upper eyelid of the analysis eye at Day 43
- [redacted]
  - [redacted]

- [redacted]

- Hypotheses:

The primary efficacy hypothesis is:

H_{01}: The proportion of participants cured at Day 43, based on a collarette score of 0 for the upper eyelid of the analysis eye, by treatment with TP-03, 0.25%, is ≤ the proportion cured by treatment with vehicle.
H_{11}: The proportion of participants cured at Day 43, based on a collarette score of 0 for the upper eyelid of the analysis eye, by treatment with TP-03, 0.25%, is > the proportion cured by treatment with vehicle.

The secondary efficacy hypotheses are:

<u>*Demodex* Eradication</u>

H_{02}: The proportion of participants with *Demodex* eradicated at Day 43 (mite density of 0 mites/lash) in the analysis eye by treatment with TP-03, 0.25%, is ≤ the proportion with *Demodex* eradicated by treatment with vehicle.
H_{12}: The proportion of participants with *Demodex* eradicated at Day 43 (mite density of 0 mites/lash) in the analysis eye by treatment with TP-03, 0.25%, is > the proportion with *Demodex* eradicated by treatment with vehicle.

<u>Composite of Collarette and Erythema Cure</u>

H_{03}: The proportion of participants with a composite cure, collarette score of 0 and erythema score of 0, for the upper eyelid of the analysis eye at Day 43 by treatment with TP-03, 0.25%, is ≤ the proportion with a composite cure by treatment with vehicle.
H_{13}: The proportion of participants with a composite cure, collarette score of 0 and erythema score of 0, for the upper eyelid of the analysis eye at Day 43 by treatment with TP-03, 0.25%, is > the proportion with a composite cure by treatment with vehicle.

<u>Erythema Cure</u>

H_{04}: The proportion of participants with an erythema cure, score of 0, for the upper eyelid of the analysis eye at Day 43 by treatment with TP-03, 0.25%, is ≤ the proportion with an erythema cure by treatment with vehicle.
H_{14}: The proportion of participants with an erythema cure, score of 0, for the upper eyelid of the analysis eye at Day 43 by treatment with TP-03, 0.25%, is > the proportion with an erythema cure by treatment with vehicle.

9.2 SAMPLE SIZE DETERMINATION

A total sample size of 300 subjects (150 subjects per arm) yields approximately 99% power to establish superiority of TP-03 to vehicle in the participants meeting the primary efficacy endpoint assuming a response rate of 80.0% in TP-03 and 15.8% for vehicle treatments, respectively using Pearson chi-squared to test a 1-sided hypothesis with a significance level of 0.025. Response rates for sample size calculations are based upon a prior OUS clinical study of TP-03, 0.25%, for the treatment of *Demodex* blepharitis.

Based on the results of a more recent Phase 2b/3 study, TRS-009 (Saturn-1), with a response rate of 44.0% for the TP-03 treatment group and 7.4% for the vehicle treatment group, a total sample size of 300 subjects still provides greater than 99% power.

[redacted]

[redacted]

[redacted]

The study will be considered a success and TP-03, 0.25%, will be considered superior to vehicle in clinical cure if H_{01} is rejected in favor of H_{11}. With this sample size, the study will have > 95% power to claim success for clinical cure. A closed hierarchical testing structure will be used such that the analysis will first be performed for the primary efficacy endpoint. [redacted]

Accounting for a 30% discontinuation, approximately 209 subjects per arm (approximately 418 total) will be randomized. The planned enrollment is much greater than typically planned to achieve 300

completed subjects due to concerns regarding the impact of COVID-19 and the possibility that up to two sites are unable to complete the study.

9.3 POPULATIONS FOR ANALYSES

The analysis datasets will include the following:

- Full Analysis Set – The full analysis set will include all randomized participants. Participants in the FAS will be analyzed as randomized.
- COVID-19 Analysis Set - The COVID-19 analysis set includes all randomized subjects, but excludes subjects that discontinued due to COVID-19 complications, subjects that would have discontinued due to COVID-19 had they remained on study, and subjects that had significant COVID-19-related protocol deviations. Subjects that would have discontinued due to COVID-19 had they remained on study will be determined and documented prior to unmasking. Protocol deviations will be assessed prior to unmasking for their significance based on their impact to primary endpoint data. Sensitivity analyses of the primary efficacy and key secondary analyses will be performed on the COVID-19 population and subjects will be analyzed as randomized if at least 5% of subjects met these criteria.
- Per Protocol Set – The per-protocol (PP) set will include participants in the FAS who do not have significant protocol deviations that effect the primary endpoint analyses. Protocol deviations will be assessed prior to unmasking. Participants in the PP set will be analyzed as treated.
- Safety Set – The safety set will include all participants who have received at least one dose of the investigational product. Participants in the safety population will be analyzed as treated.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

A formal Statistical Analysis Plan (SAP) will be completed prior to unmasking of the study data. If there are any discrepancies between the protocol and the SAP, the SAP will take precedence. Quantitative/continuous data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Qualitative/categorical data will be summarized using frequencies and percentages. Statistical testing, unless otherwise indicated, will be performed at a 1-sided 0.025 significance level.

When applicable, two-sided 95% confidence intervals will be reported. Baseline will be considered the last non-missing measure prior to initiation of study therapy. Change from baseline will be calculated as follow-up visit minus baseline.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy endpoint analysis will be conducted with the FAS, with intercurrent events handled as described in the missing data section. Descriptive statistics will be presented by treatment arm. Testing of the percentage of subjects cured at Day 43 based on the collarette grade will be completed using a difference of proportions test.

[redacted]

[redacted]

Multiplicity Adjustment

A closed hierarchical testing structure will be used where the analysis will be performed for the primary efficacy endpoint and, only if successful, the analysis will be performed for the three secondary efficacy endpoints using the Hochberg testing strategy. Specifically, if the null hypothesis, H_{01}, is rejected at a one-sided α of 0.025, the study will be considered a success for clinical cure and the family of three secondary efficacy endpoints will be tested using the Hochberg testing strategy with a familywise α of 0.025. If the secondary endpoint with the largest p-value is significant at the 0.025 level, then all three secondary endpoints will be declared statistically significant. If the secondary endpoint with the largest p-value is not significant at the 0.025 level, then the secondary endpoint with the next largest p-value will be tested at the 0.0125 level. If this secondary endpoint is significant at the 0.0125 level, then it and the remaining secondary variable will be declared statistically significant. If not, the remaining secondary will be tested at the 0.0083 level. If the null hypothesis, H_{01} is not rejected at a one-sided α of 0.025, testing will stop and the three secondary efficacy hypotheses will not be tested.

Missing Data

The primary efficacy analysis will be conducted with missing data and intercurrent events handled in the following manner:

- Discontinuation of study medication and non-optimal compliance is ignored [treatment policy strategy].
- Withdrawal due to lack of efficacy or adverse events: missing data will be imputed as failure [hypothetical strategy].
- Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: missing data will be imputed employing Multiple Imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology [hypothetical strategy].

Sensitivity analysis on the primary efficacy endpoint will be performed as specified in the Statistical Analysis Plan (SAP).

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The statistical approach for the secondary efficacy endpoints will be the same as for the primary efficacy endpoint analysis.

[redacted]

[redacted]

9.4.5 SAFETY ANALYSES

All safety analyses will be conducted using the safety set. Safety measures will be summarized for each treatment arm and visit (as appropriate) using descriptive statistics. Adverse events will be coded using

the Medical Dictionary for Regulatory Activities (MedDRA). Each MedDRA preferred term will be counted once only for a given participant. The severity, frequency, relationship of AEs to study treatment, expectedness if serious, duration, and outcome will be presented either in a table or listing. Adverse events leading to premature discontinuation from the study treatment and serious treatment-emergent AEs will be presented either in a table or a listing.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.4.10 FINAL REPORT

Once all study visits through Day 43 are complete and all associated study data has been received and corrected, the study data will be locked. Once the data has been locked and all exclusions from the PP analysis population and participants who would have discontinued due to COVID-19 had they remained on study have been determined, the treatment assignments will be unmasked for analysis. A complete analysis of the results will be performed and a final report will be prepared. When the last of the Day 90 visits have been completed and all associated study data has been received and corrected, the analysis of the endothelial cell density results will be performed. A report of the endothelial cell density results will be prepared and the report will be submitted to the NDA.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study treatment, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting study treatment. Consent materials submitted with this protocol could include questionnaires, printed or web-based advertisement materials, instruction sheets, and phone scripts.

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 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 discontinue from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. 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.

During the informed consent process, potential study participants will be informed that they have a 50% chance of being assigned to the vehicle control arm.

To obtain consent from speakers of languages other than English, the consent and applicable study-related materials will be translated into a language understandable to the participant. A member of the research team or non-family member interpreter will be available to interpret the initial and ongoing informed consent discussion for the participant. In case of emergencies, a member of the research team who is fluent in the participant's language will be available or the research team will have 24-hour access to a translation service that can sufficiently communicate with the participant.

[redacted]

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

10.1.1.3 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Possible reasons for termination or temporary suspension of the study could include:

- Study closure based on sponsor/funder decision, regulatory or other oversight bodies
- Review of serious, unexpected, and related AEs
- Noncompliance with protocol requirements
- Determination of unexpected, significant or unacceptable risk to participants due to COVID-19

Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to study participants, the investigator, the Investigational New Drug (IND) sponsor and regulatory authorities as required. 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 the study visit schedule.

The 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).

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples 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 will be shared with any parties other than those specifically identified in the ICF/HIPAA signed by the subject, without written permission from the subject.

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 [redacted]). 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 and their initials. The study data entry and study management systems used by clinical sites and by [redacted] research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at a location specified by the sponsor.

[redacted]

[redacted]

[redacted]

10.1.4 KEY ROLES AND STUDY GOVERNANCE

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

Study team roles and responsibilities of those involved in the conduct, management, or oversight of the trial will be established.

10.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Medical Monitor, an individual having appropriate expertise. The Medical Monitor will be independent from study conduct and free of conflict of interest.

10.1.6 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).

- Monitoring for this study will be performed by [redacted].
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

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 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.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 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.

Study participation should be captured in a participant's medical record. This is to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Electronic source data are data initially recorded in electronic form. Examples of source data include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, pharmacy dispensing records, audio recordings of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Hardcopies of the study visit worksheets may be provided for use as source document worksheets for recording data for each participant enrolled in the study.

Clinical data (including AEs and concomitant medications) and clinical laboratory data will be entered into [redacted], a 21 CFR Part 11-compliant data capture system managed by SDC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Data recorded in the electronic case report

form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Adverse events will be coded using MedDRA and concomitant medications will be coded using WHODrug for summarization and reporting.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment. 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. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 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 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 approximately 7 working days of identification of the protocol deviation, or within approximately 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the sponsor or its representative. Relevant 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.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

[redacted]

[redacted]

[redacted].

10.1.11 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 Ora, Inc. 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

AE	Adverse Event
APEC	Asociación para Evitar la Ceguera (Association to Prevent Blindness)
BID	Two times a day
CDVA	Corrected Distance Visual Acuity
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COVID	Corona virus disease
CONSORT	Consolidated Standards of Reporting Trials
eCRF	Electronic Case Report Forms
EDTA	Ethylenediaminetetraacetic acid
EMEA	European Medicines Evaluation Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	Europe
FAS	Full Analysis Set
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GABACLs	Gamma-aminobutyric acid-gated chloride channels
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IND	Investigational New Drug Application

IOP	Intraocular pressure
IP	Investigational product
IUPAC	International Union of Pure and Applied Chemistry
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDPE	Low-density polyethylene
logMAR	Logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
µL	Microliter
MD	Doctor of Medicine
NADA	New Animal Drug Application
NEI	National Eye Institute
NOAEL	No observed adverse effect level
OD	Doctor of Optometry
OUS	Outside United States
pH	Potential hydrogen
PI	Principal Investigator
PP	Per protocol
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDC	Statistics & Data Corporation
SMO	Site Management Organization
SOA	Schedule of Activities
TID	Three times a day
TP-03	Lotilaner ophthalmic solution
TRS	Tarsus
US	United States
WOCBP	Women of Childbearing Potential

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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12 APPENDIX A: EXAMS AND PROCEDURES

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12.2 CORRECTED DISTANCE VISUAL ACUITY

For distance visual acuity testing, participants will wear their own spectacles or may use a pinhole occluder for correction using the ETDRS-Fast procedure under standard illumination.[25] The participant will be asked to focus on an ETDRS visual acuity chart 4 meters away, checking one eye at a time. The number of letters read correctly will be used to compute the participant's logMAR score for corrected distance visual acuity (CDVA). The procedure used will be consistent with the recommendations provided for using the ETDRS-Fast method.

Visual acuity should be evaluated near the beginning of each study visit (i.e., prior to slit lamp examination). Participants should use their most recent correction to attain their corrected distance visual acuity (CDVA); if they forget their spectacles, this prescription can be placed in a trial frame or a pinhole can be used.

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12.3 SLIT LAMP BIOMICROSCOPY

A slit lamp examination will be performed and the following structures will be assessed for pathology:

- Eyelids and lashes (i.e., meibomian glands, lid margin, puncta, lashes)
- Cornea (NEI grading for staining)
- Conjunctiva
- Anterior chamber
- Iris

[redacted]

12.3.1 COLLARETTE GRADING

Grade	Clinical Interpretation
0	0 to 2 lashes have collarettes per eyelid
1	3 to 10 lashes have collarettes per eyelid
2	More than 10 but less than ⅓ of lashes have collarettes per eyelid
3	⅓ or more but less than ⅔ of lashes have collarettes per eyelid
4	⅔ or more of lashes have collarettes per eyelid
0.5 unit increments ARE NOT allowed	

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12.3.2 LID MARGIN ERYTHEMA GRADING

Erythema of the eyelid margin should be graded on a scale from 0 (normal) to 3 (severe erythema).

Grade	Severity	Clinical Interpretation
0	Normal	Normal age-related lid coloration
1	Mild	Pink capillary involvement along the lid edge, no patches of confluent capillary redness throughout the lid edge
2	Moderate	Deep pink or red confluent capillary redness present locally along the lid edge
3	Severe	Deep red, diffuse confluent capillary redness present along the lid edge
0.5 unit increments ARE NOT allowed		

12.3.3 CORNEAL FLUORESCEIN STAINING

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12.5 *DEMODEX* COUNT

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12.6 INTRAOCULAR PRESSURE

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12.10 URINE PREGNANCY TEST

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