Clinical Trial Protocol: MIM-728

A Phase 3, Multi-Center, Randomized, Double-Masked, Vehicle-Controlled Clinical Study to Assess the Safety and Efficacy of 1% Tavilermide and 5% Tavilermide Ophthalmic Solutions for the Treatment of Dry Eye

Sponsor: Mimetogen Pharmaceuticals USA, Inc.

Protocol Number: MIM-728

NCT Number: NCT03925727

Document Date: 03 July 2019

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1 GENERAL INFORMATION

Protocol Title:	A Phase 3, Multi-Center, Randomized, Double-Masked, Vehicle-Controlled Clinical Study to Assess the Safety and Efficacy of 1% Tavilermide and 5% Tavilermide Ophthalmic Solutions for the Treatment of Dry Eye
Protocol Number:	MIM-728
Study Phase:	3
Investigational Product Name:	Tavilermide Ophthalmic Solution
IND Number:	105181
Indication:	Dry Eye Disease (*keratoconjunctivitis sicca*)
Investigators:	Multi-Center
Sponsor:	Mimetogen Pharmaceuticals USA, Inc. 67 Batterymarch St., 5th Floor Boston, MA 02110
Contract Research Organization:	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810
IRB/IEC:	Alpha IRB 1001 Avenida Pico Suite C, #497 San Clemente, CA 92673

	Date
Original Protocol:	07 March 2019
Amendment 1:	03 July 2019

Confidentiality Statement

SPONSOR PERSONNEL

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Department Vice President:	[redacted]
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MEDICAL MONITOR

Medical Monitor:	[redacted]

PROTOCOL SYNOPSIS

Title:	A Phase 3, Multi-Center, Randomized, Double-Masked, Vehicle-Controlled Clinical Study to Assess the Safety and Efficacy of 1% Tavilermide and 5% Tavilermide Ophthalmic Solutions for the Treatment of Dry Eye
Number:	MIM-728
Primary Objective:	To compare the efficacy and safety of 5% tavilermide ophthalmic solution to placebo for the treatment of the symptoms and signs of dry eye disease (DED).
Secondary Objective:	To compare the efficacy and safety of 1% tavilermide ophthalmic solution to placebo for the treatment of the symptoms and signs of DED.
Design:	Multi-center, double-masked, randomized, vehicle-controlled, parallel-group study.
Study Duration	An individual's participation is approximately 100 days (i.e., about 14 weeks). This includes a 2-week run-in period and a 12-week treatment period.
Summary of Visit Schedule:	Visit 1 (Day -14 ± 2): Screening Visit 2 (Day 1): Baseline and Randomization Visit 3 (Day 15 ± 2): 2-Week Follow-Up Visit 4 (Day 29 ± 2): 4-Week Follow-Up Visit 5 (Day 57 ± 3): 8-Week Follow-Up Visit 6 (Day 85 ± 4): 12-Week Follow-Up and Study Exit
Interventions:	1) 5% tavilermide ophthalmic solution 2) 1% tavilermide ophthalmic solution 3) Placebo ophthalmic solution (vehicle of tavilermide ophthalmic solution) Subjects are to administer 1 drop (GTT) of their assigned treatment to both eyes (OU), topically (TOP), and twice per day (BID).

Number of Subjects	Approximately 1034 subjects are to be screened to enroll approximately 600 subjects at 15 to 20 sites.

Study Population Characteristics – Inclusion Criteria:

Each subject must:

a. Be at least 18 years of age;

b. Provide written informed consent;

c. Have a subject-reported history of dry eye disease in both eyes for at least 6 months prior to Visit 1;

d. Have a history of use of artificial tear eye drops for dry eye symptoms;

e. Report a total score (i.e., the square root of the product of the scores for each question) of [redacted] in Dry Eye (SANDE) Questionnaire at Visits 1 and 2;

f. Have a tear film break up time (TFBUT) [redacted] at Visits 1 and 2;

g. Have a total corneal fluorescein staining (CFS) score of [redacted] NEI scale [redacted] at Visits 1 and 2

h. Have a total conjunctival lissamine green staining score of [redacted] according to the NEI scale [redacted] at Visits 1 and 2;

i. Have an Unanesthetized Schirmer's Test score of [redacted] at Visit 1; and

j. Have at least one eye, the same eye, satisfy all criteria for i at Visit 1 and f, g, and h at Visits 1 and 2.

Study Population Characteristics – Exclusion Criteria:

Each subject must not:

a. Have any clinically significant (CS) anterior chamber findings that may include active ocular infection (bacterial, viral, or fungal), lid margin inflammation/disorders (e.g., clinically significant blepharitis including staphylococcal, demodex, or seborrheic; clinically significant meibomian gland disease; floppy eye syndrome), clinically significant ocular rosacea , active ocular inflammation (iritis, uveitis), follicular conjunctivitis, or allergic conjunctivitis (seasonal and/or perennial) that require therapeutic treatment, and/or in the opinion of the Investigator may interfere with study parameters;

b. Have any clinically significant (CS) posterior chamber findings, or a history of such findings/disorders, that may include exudative (i.e., wet) age-related macular degeneration, retinal vein occlusion, diabetic retinopathy, glaucoma, ocular hypertension, or any other retinal or optic nerve disease/disorder that require therapeutic treatment and/or in the opinion of the Investigator may interfere with study parameters;

c. Have worn contact lenses within 30 days of Visit 1 or anticipate using contact lenses during the study;

d. Have had laser-assisted in situ keratomileusis (LASIK) or similar type of corneal refractive surgery and/or any other ocular surgical procedure within 12 months prior to Visit 1; or have any ocular surgical procedure scheduled to be conducted during the study period;

e. Have had eyelid surgery within 12 weeks prior to Visit 1 or planned eyelid surgery during the study period;

f. Have a history of lacrimal duct obstruction in either eye within 12 months prior to Visit 1;

g. Have used temporary (i.e., collagen) punctal plugs within 12 weeks prior to Visit 1 or anticipate their use during the study period;

h. Have had permanent punctal plugs inserted or removed – including falling out – or have had surgical punctal occlusion within 12 weeks prior to Visit 1 or anticipate any such event at any time during the study period;

i. Have used any of the following treatments in the period indicated before Visit 1 or anticipate their use at any time during the study.

Day of Visit 1

1. All topical ophthalmic preparations (e.g., medications for glaucoma, over-the counter-solutions, artificial tears, gels, scrubs, ointments)

72 hours prior to Visit 1

2. Antihistamines (including topical ophthalmic antihistamines)

30 days prior to Visit 1

3. Topical ophthalmic non-steroidal anti-inflammatories
4. Topical ophthalmic corticosteroids
5. Topical ophthalmic autologous serum
6. Topical ophthalmic antibiotics
7. Mast cell stabilizers
8. Oral aspirin or aspirin-containing products except in the case that it was taken on a stable dosing regimen for at least 30 days prior to Visit 1 and is expected to be taken on the same regimen throughout the study period
9. Any other medication known to cause ocular drying (e.g., antidepressants, beta blockers) except in the case that it was taken on a stable dosing regimen for at least 30 days prior to Visit 1 and is expected to be taken on the same regimen throughout the study period

12 weeks prior to Visit 1

10. Restasis®
11. Xiidra®
12. CEQUA™
13. LipiFlow® or other similar meibomian gland dysfunction (MGD) therapy
14. TrueTear®
15. Corticosteroids (e.g., systemic steroids including intravenous, intramuscular, intraarticular, and oral steroids; facial topical steroids; dermatological steroids with high potency or large treatment areas);
16. Tetracyclines (tetracycline, doxycycline, minocycline, etc.)

j. Be monocular or have best corrected visual acuity [redacted] as assessed by the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale at Visit 1;

k. Have a severe/serious systemic disease, chronic illness or uncontrolled medical condition including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, poorly controlled diabetes and/or clinically significant (CS) hematologic, renal or liver disease that in the opinion of the Investigator could interfere with study assessments or limit compliance;

l. Be a woman who is pregnant, nursing or planning a pregnancy;

m. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or is post-menopausal (i.e., without menses for 12 consecutive months);

n. Be a woman of childbearing potential who is not using an acceptable means of birth control. Acceptable methods of contraception include hormonal (e.g., oral, implantable, injectable, or transdermal contraceptives), mechanical (e.g., spermicide in conjunction with a barrier such as a diaphragm or a condom), intrauterine device (IUD), or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;

o. Have a known hypersensitivity or contraindication to the investigational products (IPs) or their components;

p. Have a condition or be in a situation which the Investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study (e.g., any planned procedure or surgery during the study period);

q. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 45 days prior to Visit 1;

r. Have previously participated in a clinical trial with tavilermide (MIM-D3);

s. Be, in the opinion of the Investigator, unable or unwilling to comply with the study protocol, including participation in all study assessments, visits, and dosing, or be unable to instill eye drops successfully. Subject non-compliance with dosing during the run-in period, [redacted] may be exclusionary if, in the opinion of the Investigator, the subject is likely to be non-compliant with subsequent dosing regimens or other study assessments; or

t. Be an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.

Efficacy Measures and Endpoints:

Primary Endpoints:

The following primary endpoints will be tested in order using hierarchical fixed sequence testing:

- Change from baseline in the Eye Dryness Score (EDS) at Visit 6 (Day 85) as measured by the Visual Analog Scale (VAS), comparing 5% tavilermide ophthalmic solution to placebo.
- Change from baseline in total CFS score at Visit 6 (Day 85) as measured by the NEI scale for grading of fluorescein staining, comparing 5% tavilermide ophthalmic solution to placebo.

Key Secondary Endpoints:

The following key secondary endpoints will be tested in order following the two primary endpoints using hierarchical fixed sequence testing:

- Change from baseline in the EDS at Visit 4 (Day 29) [redacted].
- Change from baseline in total CFS score at Visit 4 (Day 29) [redacted]
- Change from baseline in the EDS at Visit 6 (Day 85) [redacted].
- Change from baseline in total CFS score at Visit 6 (Day 85) [redacted]
- Change from baseline in the EDS at Visit 4 (Day 29) [redacted].
- Change from baseline in total CFS score at Visit 4 (Day 29) [redacted]

Other Secondary Endpoints:

- Eye dryness, discomfort, grittiness, pain, blurred vision, and photophobia [redacted]
- Frequency, severity, and total score [redacted]
- [redacted] at Visits 3, 4, 5, and 6, and the [redacted] at Visits 3, 4, 5, and 6.
- CFS in the inferior, superior, central, temporal, nasal, and corneal (i.e., sum of all regions) regions [redacted]
- Conjunctival lissamine green staining in the temporal, superior temporal, inferior temporal, superior nasal, inferior nasal, nasal, and conjunctival (i.e., sum of all regions) regions [redacted]
- [redacted] scores at Visit 6 and the [redacted] (Visit 1) at Visit 6.

Safety Measures:

- Concomitant Medication Review
- Visual Acuity (ETDRS)
- Slit-Lamp Biomicroscopy
- Intraocular Pressure (IOP)
- Dilated Fundoscopy
- Ora Calibra® Drop Comfort Scale and Questionnaire
- Adverse Event (AE) Query

General Statistical Methods and Types of Analyses

Analysis Populations

- [redacted]

[redacted]

Sample Size

[redacted]

Multiplicity Considerations

[redacted]

Primary Efficacy Analyses

[redacted]

[redacted]

Key Secondary Efficacy Analyses

[redacted]

Other Secondary Efficacy Analyses

[redacted]

Safety Analyses

[redacted]

[redacted]

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LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	Analysis of Covariance
BID	twice daily
CAE	Controlled Adverse Environment
CFR	Code of Federal Regulations
CFS	corneal fluorescein staining
CI	confidence interval
CS	clinically significant
DED	dry eye disease
DHHS	Department of Health and Human Services
eCRF	electronic case report form
EDC	electronic data capture
EDS	eye dryness score
ERC	Ethical Review Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GTT	drop
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug application
IOP	intraocular pressure
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
KCS	keratoconjunctivitis sicca
kg	kilogram
LASIK	laser in situ keratomileusis
LDPE	low-density polyethylene
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution

MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MGD	meibomian gland dysfunction
mL	milliliter
mm	millimeter
mmHg	millimeter of mercury
NCS	not clinically significant
NEI	National Eye Institute
NGF	nerve growth factor
NOAEL	no-observed-adverse-effect-level
OU	both eyes
PP	per protocol
QID	four times each day
SAE	serious adverse event
SANDE	Symptom Assessment in Dry Eye
SDC	Statistics and Data Corporation
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment emergent adverse event
TFBUT	tear film break-up time
TMF	trial master file
TOP	topically
TrkA	tropomyosin receptor kinase A
VA	visual acuity
VAS	Visual Analog Scale

2 BACKGROUND INFORMATION

2.1 Characterization of Tavilermide

Tavilermide (previously designated by its laboratory name, MIM-D3) ophthalmic solution is a proteolytically stable, cyclic peptidomimetic that mimics a β-turn region of nerve growth factor (NGF) formulated as a preservative-free, aqueous, sterile ophthalmic solution. Biochemical and cellular assays showed that tavilermide is a partial tropomyosin-related kinase A (TrkA) receptor agonist, activating and potentiating the effects of suboptimal concentrations of the natural ligand NGF,[1] and acts synergistically with NGF *in vivo*.[2–4] Tavilermide is a new chemical entity.

Mimetogen Pharmaceuticals USA, Inc. (Sponsor) is developing tavilermide as a potential therapeutic agent for the treatment of dry eye disease (DED).

2.2 Summary of the Nonclinical Program

Nonclinical data have demonstrated that tavilermide has physiologic effects that lead to amelioration of the signs associated with dry eye[5] without causing any significant ocular, systemic, genotoxic, embryo-fetal development or safety concerns related to any organ system.

Intravenous toxicity studies in rats and dogs (28 days) revealed no adverse findings and no target organ toxicity for doses up to 150 and 40 mg/kg tavilermide, respectively. No evidence of mutagenicity or genotoxicity was observed, nor were any significant effects noted on the central nervous system, respiratory system or cardiovascular system.

Repeat-dose ocular toxicity studies of up to 6-months duration were conducted in rabbits at concentrations up to 5% administered topically four times per day (QID). No test article-related morbidity/mortality was noted, and no test article-related ocular effects were observed macroscopically or microscopically. No marked or significant toxicological effects were noted in any organ system, and the product did not accumulate in the body after repeated topical ocular instillations. No significant gender-related effects were noted for tavilermide.

In an embryo-fetal development study in rats, a slight reduction in maternal body weight gain was apparent at the high dose (350 mg/kg). There was no evidence of effects on fetal growth and embryo-fetal mortality. Fetal abnormalities noted at 100 and 350 mg/kg did not indicate a clear effect of tavilermide. The no-observed-adverse-effect-level (NOAEL) for maternal toxicity was considered to be 350 mg/kg/day and for embryo-fetal development was considered to be 35 mg/kg/day. In a rabbit embryo-fetal development study, there were no effects on embryo-fetal growth or dysmorphology (teratogenicity) or embryo-fetal mortality at the highest dose. The NOAEL for maternal toxicity and embryo-fetal development was considered to be 200 mg/kg/day.

2.3 Summary of the Clinical Program

To date, one Phase 2 and three Phase 3 multicenter, randomized, double-masked, vehicle-controlled studies conducted in adult subjects with dry eye disease in the U.S. of similar design are completed. The Phase 2 study was 7 weeks in duration, whereas the Phase 3 studies were 10 weeks. There was a one-week open-label run-in with Bausch & Lomb Sensitive Eyes® Drops followed by a 4-week and 8-week treatment period in the Phase 2 and Phase 3 studies, respectively. The Phase 2 study also had a 2-week follow up after treatment cessation. Treatment in each study was administered as a single drop twice daily (morning and evening) in each eye. These previous studies used the Controlled Adverse Environment® (CAE®) model both for screening and efficacy endpoints.

In the Phase 2 study (MIM-724), 150 subjects with dry eye were randomized to 1% tavilermide ophthalmic solution, 5% tavilermide ophthalmic solution, or placebo ophthalmic solution (i.e., vehicle of tavilermide ophthalmic solution). The 1% and 5% tavilermide ophthalmic solutions were numerically superior to placebo in reducing the signs and symptoms of dry eye, but not for the study pre-specified primary efficacy endpoints.[6] Post hoc analyses suggested that the greatest treatment effect was observed with the 1% tavilermide ophthalmic solution. Therefore, 1% tavilermide ophthalmic solution was chosen for further investigation in Phase 3 studies.

In each of the three Phase 3 studies (MIM-725, MIM-726, and MIM-727), 400 subjects with dry eye were randomized to 1% tavilermide ophthalmic solution or placebo ophthalmic solution. 1% tavilermide ophthalmic solution was numerically superior to placebo in reducing the signs and symptoms of dry eye, but not for the study pre-specified primary efficacy endpoints.

2.4 Summary of Known and Potential Risks and Benefits

In the Phase 2 study (MIM-724), which investigated the 1% and 5% concentrations of tavilermide versus placebo, there were no deaths or serious ocular treatment emergent adverse events (TEAEs). The total TEAEs reported during the study were distributed fairly evenly among the treatment groups: 1% tavilermide had 22 TEAEs, 5% tavilermide had 35, and placebo had 30. Furthermore, ocular TEAEs also were distributed somewhat evenly among the treatment groups: 1% tavilermide had 10 TEAEs, 5% tavilermide had 8, and placebo had 8. The majority of the ocular TEAEs were mild. Ophthalmic examinations yielded no concerns. The MIM-724 trial suggested that the tavilermide ophthalmic solutions, both 1% and 5%, are safe and well-tolerated.

In the Phase 3 studies, no deaths or serious ocular TEAEs occurred; TEAEs occurred in less than 5% of subjects. No clinically significant (CS) safety findings were observed by intraocular pressure (IOP) measurement, slit-lamp biomicroscopy, or dilated fundoscopy, and there were no changes in safety parameters due to the tavilermide or vehicle treatments. All abnormal findings reported at baseline were considered not clinically significant (NCS).

1% tavilermide ophthalmic solution was well tolerated, and there was no difference in the comfort of 1% tavilermide ophthalmic solution compared to placebo, as reported by subjects.

Results from the previous Phase 2 and Phase 3 trials suggest that tavilermide ophthalmic solution is a promising new treatment for DED with an acceptable safety profile.

2.5 Dose Selection and Study Rationale

Tavilermide ophthalmic solution is to be administered as a single drop, bilaterally (i.e., both eyes), and twice daily (morning and evening). The previous Phase 3 studies were performed with 1% tavilermide for 8 weeks and did not meet the pre-specified primary endpoints. Consequently, this trial is powered to study the efficacy of 5% tavilermide with a longer treatment period of 12 weeks, while simultaneously continuing to examine 1% tavilermide.

2.6 Compliance Statement

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonisation (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of investigational product (IP) in the countries involved will be adhered to.

2.7 Intended Study Population

The population for this study will be patients with moderate DED who are at least 18 years of age and of any gender and race who satisfy all of the inclusion criteria and meet none of the exclusion criteria outlined in this protocol.

3 STUDY OBJECTIVES

3.1 Primary Objective

To compare the efficacy and safety of 5% tavilermide ophthalmic solution to placebo for the treatment of the symptoms and signs of DED.

3.2 Secondary Objective

To compare the efficacy and safety of 1% tavilermide ophthalmic solution to placebo for the treatment of the symptoms and signs of DED.

4 STUDY DESIGN

4.1 Type of Study

This Phase 3 trial is a multi-center, double-masked, randomized, vehicle-controlled, parallel-group clinical study. There will be two active treatment groups – 1% tavilermide ophthalmic solution and 5% tavilermide ophthalmic solution – and one control group – placebo ophthalmic solution (vehicle of tavilermide ophthalmic solution).

Figure 1 (Page 21) provides an outline of the study assessments and phases of the trial.

A subject's participation is to start with screening and baseline safety measurements at Visit 1. If the subject is considered eligible for the study at the end of Visit 1, the subject will participate in a 14-day run-in period. Isotonic ophthalmic solution – also known as placebo ophthalmic solution (vehicle of tavilermide ophthalmic solution) – is the designated run-in and is to be administered to both eyes (OU), topically (TOP), and twice per day (BID) throughout the run-in period.

Baseline efficacy measurements are to be obtained at Visit 2. Should a subject qualify for final study entry at the end of Visit 2, they are to be randomly assigned to one of three treatment groups:

- 5% tavilermide ophthalmic solution,
- 1% tavilermide ophthalmic solution, or
- Placebo ophthalmic solution.

During the treatment period, the subject is to dose with their assigned treatment OU, TOP, and BID for approximately 85 days.

4.2 Number of Subjects

Approximately 1034 subjects are to be screened to enroll approximately 600 subjects. A maximum of 40 subjects will be enrolled at each of 15 to 20 sites in the United States.

4.3 Expected Duration of Study

The duration of an individual's participation in the study, from the start of subject screening to study exit, is six clinic visits over approximately 100 days (i.e., about 14 weeks).

The duration of the study – from first patient, first visit to last patient, last visit – is expected to be approximately 10 months.

Visit 1 (Day -14 ± 2): Screening	Informed Consent / HIPAA Medical / Medication History and Demographics Urine Pregnancy Test (as needed) Sign and Symptom Assessments Safety Assessments Dispensation of Run-In
Visit 2 (Day 1): Baseline and Randomization	Run-In Collection and Accountability Medical Status Update / AE Query Sign and Symptom Assessments Safety Assessments Randomization Dispensation of Randomized Treatment Kit In-Office Randomized Treatment Dose Drop Comfort Assessments
Visit 3 (Day 15 ± 2): 2-Week Follow-Up	IP Collection and Accountability Medical Status Update / AE Query Sign and Symptom Assessments Safety Assessments Dispensation of Randomized Treatment Kit
Visit 4 (Day 29 ± 2): 4-Week Follow-Up	IP Collection and Accountability Medical Status Update / AE Query Sign and Symptom Assessments Key Secondary Sign and Symptom Assessments Safety Assessments Dispensation of 2 Randomized Treatment Kits
Visit 5 (Day 57 ± 3): 8-Week Follow-Up	IP Collection and Accountability Medical Status Update / AE Query Sign and Symptom Assessments Safety Assessments Dispensation of 2 Randomized Treatment Kits In-Office Randomized Treatment Dose Drop Comfort Assessments
Visit 6 (Day 85 ± 4): 12-Week Follow-Up and Study Exit	IP Collection and Accountability Medical Status Update / AE Query Urine Pregnancy Test (as needed) Primary Endpoint Assessment Key Secondary Sign and Symptom Assessments Other Sign and Symptom Assessments Safety Assessments

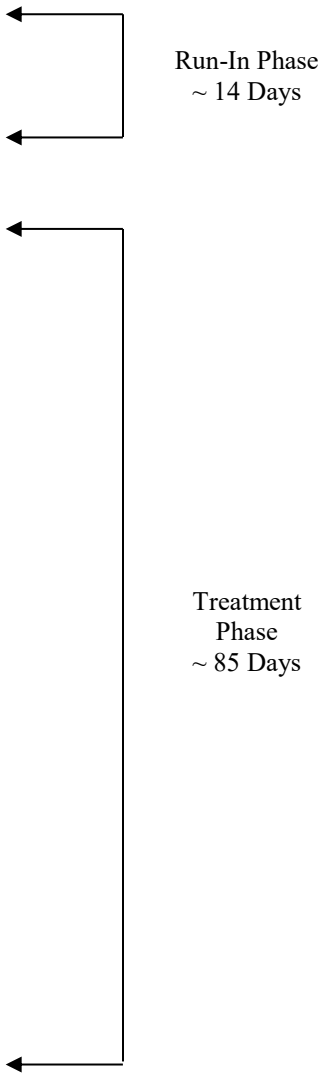


Figure 1 Trial design, procedure outline, and phases.

4.4 Primary and Secondary Outcome Measures

4.4.1 Primary Endpoints

The following primary endpoints will be tested in order using hierarchical fixed sequence testing:

- Change from baseline in the Eye Dryness Score (EDS) at Visit 6 (Day 85) [redacted]
- Change from baseline in total corneal fluorescein staining score (CFS) at Visit 6 (Day 85) [redacted].

Clinical Hypotheses:

The hierarchical clinical hypotheses for the primary endpoint, to be tested in the order indicated below, are that the 5% tavilermide ophthalmic solution is superior to the placebo for the treatment of the symptoms and signs of DED at Day 85.

1. Subjects receiving 5% tavilermide ophthalmic solution will have a statistically significantly lower change from baseline in EDS when compared to placebo [redacted]

If the above hypothesis is successful at the 0.05 confidence level, then the second hypothesis is to be tested.

2. Subjects receiving 5% tavilermide ophthalmic solution will have a statistically significantly lower total change from baseline in total CFS score when compared to placebo [redacted]

4.4.2 Key Secondary Endpoints

The following key secondary endpoints will be tested in order following the two primary endpoints using hierarchical fixed sequence testing:

- Change from baseline in the EDS at Visit 4 (Day 29) [redacted]
- Change from baseline in total CFS score at Visit 4 (Day 29) [redacted]
- Change from baseline in the EDS at Visit 6 (Day 85) [redacted]
- Change from baseline in total CFS score at Visit 6 (Day 85) [redacted]
- Change from baseline in the EDS at Visit 4 (Day 29) [redacted]

- Change from baseline in total CFS score at Visit 4 (Day 29) [redacted]

Clinical Hypotheses:

The hierarchical clinical hypotheses for the key secondary endpoint, to be tested in the order indicated below following the primary clinical hypotheses, are that the 5% tavilermide ophthalmic solution is superior to the placebo for the treatment of the symptoms and signs of DED at Day 29 and that the 1% tavilermide ophthalmic solution is superior to the placebo for the treatment of the symptoms and signs of DED at Day 85.

If the second primary hypothesis is successful [redacted] then the third hypothesis is to be tested.

3. Subjects receiving 5% tavilermide ophthalmic solution will have a statistically significantly lower change from baseline in EDS when compared to placebo as measured by the VAS at Visit 4 (Day 29).

If the above hypothesis is successful [redacted], then the fourth hypothesis is to be tested.

4. Subjects receiving 5% tavilermide ophthalmic solution will have a statistically significantly lower total change from baseline in total CFS score when compared to placebo as measured by the NEI scale at Visit 4 (Day 29).

If the above hypothesis is successful [redacted], then the fifth hypothesis is to be tested.

5. Subjects receiving 1% tavilermide ophthalmic solution will have a statistically significantly lower change from baseline in EDS when compared to placebo as measured by the VAS at Visit 6 (Day 85).

If the above hypothesis is successful [redacted], then the sixth hypothesis is to be tested.

6. Subjects receiving 1% tavilermide ophthalmic solution will have a statistically significantly lower total change from baseline in total CFS score when compared to placebo as measured by the NEI scale at Visit 6 (Day 85).

If the above hypothesis is successful [redacted], then the seventh hypothesis is to be tested.

7. Subjects receiving 1% tavilermide ophthalmic solution will have a statistically significantly lower change from baseline in EDS when compared to placebo as measured by the VAS at Visit 4 (Day 29).

If the above hypothesis is successful [redacted], then the eighth hypothesis is to be tested.

8. Subjects receiving 1% tavilermide ophthalmic solution will have a statistically significantly lower total change from baseline in total CFS score when compared to placebo as measured by the NEI scale at Visit 4 (Day 29).

5 STUDY TREATMENTS

5.1 Description and Labelling of Investigational Product

5.1.1 Study Treatment Formulation

The trial has three investigational products:

- 5% tavilermide ophthalmic solution (10 mg/day total dose),
- 1% tavilermide ophthalmic solution (2 mg/day total dose), and
- Placebo ophthalmic solution (vehicle of tavilermide ophthalmic solution).

The active ingredient in the 5% and 1% tavilermide ophthalmic solutions is tavilermide hydrochloride salt. The vehicle for tavilermide is a sterile, preservative-free, buffered, isotonic solution for topical administration. Tavilermide ophthalmic solution contains drug substance and pharmaceutically acceptable excipients commonly used in ophthalmic solutions. The manufacturer of the IP is Holopack Verpackungstechnik GmbH, which has a place of business at Bahnhofstraße 20, 73453 Abtsgmünd, Germany.

The IP is contained in sterile, single-use, low-density polyethylene (LDPE) vials (0.3 mL/vial). A card of five vials of the same formulation is sealed in a foil pouch. Eight foil pouches containing vials of the same formulation are packaged into a box to make one clinical kit. One clinical kit is sufficient for 14 days of dosing with an additional 12 extra vials. All IP is labeled according to applicable regulatory requirements.

IP for the treatment phase of the study is labeled as “Tavilermide Ophthalmic Solution or Placebo Ophthalmic Solution.” Kit packaging and labeling, except for an identifier, are identical for each of the three treatment arms. Treatment kits are identifiable by a unique, five-digit kit number. Kit numbers are randomly associated with clinical kits from the three treatment arms and range from 30001 to 36600.

The IP for the three arms are visually distinct. The discrepancies in appearance mandate that there is at least one technician designated as unmasked at each clinical site. Once open, a treatment kit is to be handled by only the subject to which it was assigned and unmasked designees.

5.1.2 Run-In Formulation

The run-in is the placebo ophthalmic solution. The run-in is packaged in the same manner as randomized treatment kits.

IP for the run-in phase of the study is labeled “Isotonic Ophthalmic Solution.” Run-in kits are identifiable by a unique, four-digit kit number. Run-in kit numbers range from 1001 to 3880.

Subjects are not to be made aware that the run-in is the placebo ophthalmic solution because the placebo is visually distinct from the active treatments. Should a subject note an appearance change from the run-in phase to the treatment phase, and be aware that the placebo ophthalmic solution is the IP for the run-in phase and one of the three randomized treatment arms, they may infer that they were assigned to one of the active

treatments. Therefore, IP for the run-in phase is to be labeled as "Isotonic Ophthalmic Solution" so as to mask from the subjects that the run-in is the placebo ophthalmic solution.

5.2 Dosage and Route of Administration

5.2.1 Run-In Period

For the run-in phase of the trial, subjects qualified at the end of Visit 1 to continue to Visit 2 are to administer 1 drop (GTT) of isotonic ophthalmic solution (i.e., placebo ophthalmic solution) OU, TOP, and BID – morning and evening before bed – for approximately 14 days. The first dose of run-in is to be in the evening before bed on the day of Visit 1. The last dose of run-in is to be in the evening before bed on the day before Visit 2.

The subject is **not to dose** with run-in on the day of Visit 2 before their appointment. Should a subject dose with run-in on the day of Visit 2 before their appointment, the time of the dose is to be recorded, and the subject should wait at least 4 hours from the time of the dose to the start time of any efficacy assessments.

The subject is to return their run-in kit, including used and unused vials at Visit 2.

5.2.2 Treatment Period

At the end of Visit 2, enrolled subjects are to be randomly assigned one of the three IPs to use during the treatment phase of the trial (i.e., Visit 2 to Visit 6). During the treatment phase, subjects are to administer 1 GTT of their assigned treatment OU, TOP, and BID – morning and evening before bed – for approximately 85 days. The first dose of the assigned treatment is to be in the office at Visit 2. The first at-home dose is to be in the evening before bed on the day of Visit 2. The last dose is to be in the evening before bed on the day before Visit 6.

On the days of Visits 3, 4, 5, and 6, subjects are **not to dose** with IP before their appointments. Should a subject dose with IP on the day of a visit before their appointment, the time of the dose is to be recorded, and the subject should wait at least 4 hours from the time of the dose to the start time of any efficacy assessments.

Subjects are to self-administer an in-office dose of their assigned treatment at Visits 2 and 5. After Visits 2 and 5, subjects are to take their next dose of IP in the evening before bed. Subjects will not dose in-office at Visits 3 and 4. After Visits 3 and 4, subjects are to resume dosing at home immediately following the visit and take a second dose in the evening before bed.

Subjects are to return each kit, used and unused vials, the visit after which it was originally assigned. Used vials are to be returned to the site in a resealable, opaque bag. The bag and the unused vials should be kept in the closed kit box. Furthermore, subjects are to be instructed not to show their drops to, or discuss the drops with, clinical trial staff – unless specifically told otherwise – or other subjects.

Escape medications and special diet or activities are not applicable.

The follow-up period for the IP in the run-in and treatment phases ends with the subject's exit from the study. Adverse Events (AEs) ongoing at the end of Visit 6 are to be followed as specified in Section 9.5.

5.3 Storage and Dispensation of Investigational Product

The IP must be stored in a secure area accessible only to the Investigator and his/her designees. The IP will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

IP is to be stored at 15-25 ℃ and protected from light; IP is never to be frozen or refrigerated.

Subjects are to be instructed on the proper use and storage of the IP at the end of each visit at which IP is dispensed. Written instructions detailing the proper use and storage of the IP are also to be provided to the subjects.

Kits are to be dispensed in their entirety to the appropriate subjects. At Visit 1, each eligible subject is to receive one run-in kit. Run-in kits should be assigned in sequential order to subjects as they become eligible from the list of available kits at the site.

At Visits 2 and 3, each eligible subject is to receive one kit of their randomly assigned treatment. At Visits 4 and 5, each eligible subject is to receive two kits of their randomly assigned treatment. Randomized treatment kits are to be assigned by the Interactive Response Technology (IRT) system. Subjects are to return all used vials and unused IP at the visit after the one at which the IP was originally dispensed.

Replacement kits are available as needed for dispensation. Replacement kits are to be assigned using the IRT system after receiving approval from Ora and the Sponsor.

5.4 Investigational Product Accountability

The IP is only to be prescribed by the Principal Investigator or his/her named Sub-Investigator(s) and is only to be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

The Investigator must keep an accurate record and accounting of the IP on site received from the supplier, including dates of receipt. In addition, accurate records will be kept regarding the amount of IP dispensed to subjects, amount of IP returned to the Investigator by the subjects, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the IP, and reasons for departure from the expected dispensing regimen will be recorded.

At the end of the study, there will be a final reconciliation of unused investigational product that was returned to the site by subjects or was not dispensed by the site. There is to be no reconciliation of used or missing vials. Any discrepancies will be investigated, resolved and documented by the study team. All IP, used and unused, will be returned to the Sponsor or their designee in compliance with applicable regulations. The return of IP will be specified in writing.

5.5 Subject Compliance with Protocol

The compliance and accountability guidelines below are to be used by the Investigator for determining subject compliance with this protocol and for recording deviations from the stated compliance. The site-calculated dosing compliance is not to be transcribed to the electronic Case Report Forms (eCRFs).

Run-in is to be collected at Visit 2. A technician is to calculate dosing compliance from Visit 1 to Visit 2 by dividing the number of used vials by the number of expected doses and [redacted] Non-compliance with dosing during the run-in phase may be grounds for screen failure at Visit 2 as determined by the Investigator (Section 6.2, Exclusion s).

Randomized treatment is to be collected at Visits 3, 4, 5, and 6. At each of these visits, the subject compliance with dosing from the previous visit is to be calculated. At Visits 3 and 6, the in-office doses at Visits 2 and 5 will be included in the expected vial count for the purpose of site-calculated dosing compliance, respectively. [redacted]

5.6 Prohibited Medications/Treatments

Disallowed medications and treatments during the study and applicable washout periods are outlined in the Exclusion Criteria (Section 6.2). In addition, the site is responsible for reviewing subject-reported concomitant medications for prohibited treatments such as medications with ocular drying effects, antihistamines, mast cell stabilizers, corticosteroids, or other exclusionary medications.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

5.6.1 Concomitant Medications

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

Common medications that may be permissible for use as needed by trial subjects for pain relief or the treatment of a cold or flu during the study are outlined below. The site is responsible for reviewing any medication taken by the subject for compliance with the disallowed medications as listed in the Exclusion Criteria (Section 6.2).

- Pain Relief / Fever Reducers

- Active Ingredients: acetaminophen, ibuprofen, naproxen sodium
- Brands: Tylenol®, Advil®, Aleve®

- Daytime Cold Medicines
  - Active Ingredients: acetaminophen, phenylephrine, dextromethorphan, guaifenesin
  - Brands: Tylenol® Cold Multi-Symptom Daytime, DayQuil® Cold and Flu
- Nasal Decongestants
  - Active Ingredients: phenylephrine
  - Brands: Sudafed® PE Maximum Strength Congestion & Sinus Pressure Relief
- Expectorants
  - Active Ingredients: guaifenesin
  - Brands: Mucinex®
- Cough Suppressants
  - Active Ingredients: dextromethorphan
  - Brands: Robitussin®

5.7 Non-IP Study Supplies

Additional, non-IP study supplies required at each site include urine pregnancy tests, medical examination gloves, urine collection cups, clear 100 mm rulers, ETDRS Series 2000 Chart 1, occluder, alcohol swabs, pipette(s), pipette tips, stopwatch(es), 2% preservative free fluorescein sodium, Wratten #12 yellow filter, lissamine green ophthalmic strips, sterile saline solution, Schirmer's tear test strips, timer(s), fluorescein sodium and benoxinate hydrochloride ophthalmic solution (e.g., Fluress®, Altafluor Benox), and 1% tropicamide ophthalmic solution.

6 SUBJECT ENROLLMENT AND RANDOMIZATION

Before performing any study-specific procedure – including screening procedures to determine eligibility – a signed informed consent form (ICF) will be obtained for each subject. The consent form will describe the purpose of the study, the procedures to be performed, and the risks and potential benefits of participation. The Investigator or an appropriately trained and delegated staff member is to conduct the informed consent discussion, check that the subject comprehends the information provided, and answer any questions about the study. The subject and the individual that conducted the consent discussion are to sign the ICF. A copy of the consent form is to be given to the subject and consent is to be documented on the subject's record.

Each subject who signs an ICF is to be assigned a screening number. All screening numbers are to be assigned in strict numerical sequence at each site, and no numbers are to be skipped or omitted. The first screening number at each site is to be 001. A unique, two-digit, numeric identifier is to be assigned to each site (e.g., 70). The site number and the screening number are to be concatenated to create a unique subject identifier (e.g., 70-001).

Qualified subjects are to be assigned to a randomized study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

6.1 Subject Inclusion Criteria

Subjects may be of either gender and of any race. Each subject must meet all of the following criteria to be enrolled in this study:

a. Be at least 18 years of age;

b. Provide written informed consent;

c. Have a subject-reported history of dry eye disease in both eyes for at least 6 months prior to Visit 1;

d. Have a history of use of artificial tear eye drops for dry eye symptoms;

e. Report a total score (i.e., the square root of the product of the scores for each question) of [redacted] in Dry Eye (SANDE) Questionnaire at Visits 1 and 2;

f. Have a tear film break up time (TFBUT) [redacted] Visits 1 and 2;

g. Have a total corneal fluorescein staining (CFS) score of [redacted] according to the NEI scale [redacted] at Visits 1 and 2

h. Have a total conjunctival lissamine green staining score of [redacted] with a score of [redacted] according to the NEI scale [redacted] at Visits 1 and 2;

i. Have an Unanesthetized Schirmer's Test score of [redacted] at Visit 1; and

j. Have at least one eye, the same eye, satisfy all criteria for I at Visit 1 and f, g, and h at Visits 1 and 2.

6.2 Subject Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

a. Have any clinically significant (CS) anterior chamber findings that may include active ocular infection (bacterial, viral, or fungal), lid margin inflammation/disorders (e.g., clinically significant blepharitis including staphylococcal, demodex, or seborrheic; clinically significant meibomian gland disease; floppy eye syndrome), clinically significant ocular rosacea , active ocular inflammation (iritis, uveitis), follicular conjunctivitis, or allergic conjunctivitis

(seasonal and/or perennial) that require therapeutic treatment, and/or in the opinion of the Investigator may interfere with study parameters;

b. Have any clinically significant (CS) posterior chamber findings, or a history of such findings/disorders, that may include exudative (i.e., wet) age-related macular degeneration, retinal vein occlusion, diabetic retinopathy, glaucoma, ocular hypertension, or any other retinal or optic nerve disease/disorder that require therapeutic treatment and/or in the opinion of the Investigator may interfere with study parameters;

c. Have worn contact lenses within 30 days of Visit 1 or anticipate using contact lenses during the study;

d. Have had laser-assisted in situ keratomileusis (LASIK) or similar type of corneal refractive surgery and/or any other ocular surgical procedure within 12 months prior to Visit 1; or have any ocular surgical procedure scheduled to be conducted during the study period;

e. Have had eyelid surgery within 12 weeks prior to Visit 1 or planned eyelid surgery during the study period;

f. Have a history of lacrimal duct obstruction in either eye within 12 months prior to Visit 1;

g. Have used temporary (i.e., collagen) punctal plugs within 12 weeks prior to Visit 1 or anticipate their use during the study period;

h. Have had permanent punctal plugs inserted or removed – including falling out – or have had surgical punctal occlusion within 12 weeks prior to Visit 1 or anticipate any such event at any time during the study period;

i. Have used any of the following treatments in the period indicated before Visit 1 or anticipate their use at any time during the study.

<u>Day of Visit 1</u>

1. All topical ophthalmic preparations (e.g., medications for glaucoma, over-the counter-solutions, artificial tears, gels, scrubs, ointments)

<u>72 hours prior to Visit 1</u>

2. Antihistamines (including topical ophthalmic antihistamines)

<u>30 days prior to Visit 1</u>

3. Topical ophthalmic non-steroidal anti-inflammatories
4. Topical ophthalmic corticosteroids
5. Topical ophthalmic autologous serum
6. Topical ophthalmic antibiotics
7. Mast cell stabilizers

8. Oral aspirin or aspirin-containing products except in the case that it was taken on a stable dosing regimen for at least 30 days prior to Visit 1 and is expected to be taken on the same regimen throughout the study period
9. Any other medication known to cause ocular drying (e.g., antidepressants, beta blockers) except in the case that it was taken on a stable dosing regimen for at least 30 days prior to Visit 1 and is expected to be taken on the same regimen throughout the study period

12 weeks prior to Visit 1

10. Restasis®
11. Xiidra®
12. CEQUA™
13. LipiFlow® or other similar meibomian gland dysfunction (MGD) therapy
14. TrueTear®
15. Corticosteroids (e.g., systemic steroids including intravenous, intramuscular, intraarticular, and oral steroids; facial topical steroids; dermatological steroids with high potency or large treatment areas);
16. Tetracyclines (tetracycline, doxycycline, minocycline, etc.)

j. Be monocular or have best corrected visual acuity [redacted] in either eye as assessed by the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale at Visit 1;

k. Have a severe/serious systemic disease, chronic illness or uncontrolled medical condition including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, poorly controlled diabetes and/or clinically significant (CS) hematologic, renal or liver disease that in the opinion of the Investigator could interfere with study assessments or limit compliance;

l. Be a woman who is pregnant, nursing or planning a pregnancy;

m. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or is post-menopausal (i.e., without menses for 12 consecutive months);

n. Be a woman of childbearing potential who is not using an acceptable means of birth control. Acceptable methods of contraception include hormonal (e.g., oral, implantable, injectable, or transdermal contraceptives), mechanical (e.g., spermicide in conjunction with a barrier such as a diaphragm or a condom), intrauterine device (IUD), or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;

o. Have a known hypersensitivity or contraindication to the investigational products (IPs) or their components;

p. Have a condition or be in a situation which the Investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study (e.g., any planned procedure or surgery during the study period);

q. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 45 days prior to Visit 1;

r. Have previously participated in a clinical trial with tavilermide (MIM-D3);

s. Be, in the opinion of the Investigator, unable or unwilling to comply with the study protocol, including participation in all study assessments, visits, and dosing, or be unable to instill eye drops successfully. Subject non-compliance with dosing during the run-in period, defined as [redacted] of expected doses taken, may be exclusionary if, in the opinion of the Investigator, the subject is likely to be non-compliant with subsequent dosing regimens or other study assessments; or

t. Be an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.

6.3 Randomization Procedures

A patient who meets all of the inclusion criteria and none of the exclusion criteria is eligible for randomization at Visit 2. Subjects are to be randomized to one of three treatment arms:

1) 5% tavilermide ophthalmic solution,
2) 1% tavilermide ophthalmic solution, or
3) Placebo ophthalmic solution.

A statistician not directly involved in the analysis of the study results will prepare the randomization schedule using block randomization to maintain balance between treatment arms. Randomization is to be done in a [redacted] respectively, by the IRT system.

Subjects are to be stratified by site and EDS as measured by the VAS at Visit 2 using the following strata:

[redacted]

Details required for stratification are to be entered into the IRT which will randomize the subject and assign a randomization number. Randomization numbers are to be four digits and will allow for the identification of a subject's treatment arm. The IRT is also to be used to assign treatment kits; each treatment kit is identifiable by a five-digit kit number.

The randomization number and all treatment kit numbers are to be recorded on the subject's source document and the appropriate eCRFs.

6.4 Arrangements Taken to Prevent Unmasking

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments.

Randomization is to be accomplished by IRT. A dedicated IRT manager is to be responsible for overseeing the IRT system including randomization and treatment kit assignment.

The discrepancies in visual appearance among the IP mandate that there is at least one technician designated as unmasked at each clinical site. Once open, a treatment kit is to be handled by only the subject to which it was assigned and unmasked designees.

Unmasked technicians are uniquely delegated for facilitating the in-office dose and drop comfort assessments and performing randomized treatment kit accountability. Unmasked technicians may not participate in any other aspect of the trial that has a bearing on trial efficacy including symptom questionnaires, scribing for the Investigator, and data transcription. Unmasked technicians are not to have access to the electronic data capture (EDC) system. Clinical trial monitors who are designated as unmasked are to be responsible for reviewing randomized IP accountability. After unmasking, a clinical trial monitor is not to participate in other aspects of trial monitoring.

6.5 Procedures for Unmasking

When medically necessary, the Investigator may need to determine what treatment has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the Sponsor should be notified before unmasking IP.

If the Investigator identifies a medical need for unmasking the assigned treatment of a subject, they should, if possible, contact Ora and/or the Medical Monitor before completing the unmasking. Ora is to ask the site to complete the appropriate parts of the Unmasking Request Form and then to return the form. After receiving the form, Ora is to notify Mimetogen, and jointly they are to determine whether to approve the unmasking; Ora or Mimetogen may consult with the Medical Monitor as needed during this process. The result of the request is to be documented on the Unmasking Request Form.

If the request to unmask a subject is approved, the Investigator is to be provided the approval in writing via the Unmasking Request Form. The Investigator is to unmask the subject using the IRT and complete the Unmasking Memo. The Unmasking Memo is to be filed with the subject's study file, and a copy is to be sent to project management so that it may be included in the Trial Master File (TMF). For each unmasking request, the reason for the request, the date of the request, and the name and signature of the individual unmasking the subject are to be noted in the subject's study file.

6.6 Early Termination

6.6.1 Reasons for Discontinuation

Subjects may be discontinued by the Investigator, Sponsor, or Medical Monitor prior to their completion of the study due to:

- AEs,
- Protocol violations,
- Administrative reasons (e.g., inability to continue due to scheduling, lost to follow-up),
- Sponsor termination of study, or
- Other.

If at any time, the Investigator determines that a subject's safety has been compromised, the Investigator may discontinue the subject from the study treatment. The Investigator, Sponsor, or Medical Monitor may discontinue any subject for any valid medical reason or non-compliance.

Ora, the Sponsor, or the Investigator may terminate the trial at any time with appropriate notification.

6.6.2 Reasons for Withdrawal

Subjects may choose to end their participation in the study at any time by withdrawing consent (i.e., subject choice).

6.6.3 Documenting Early Termination and Subjects Lost to Follow-Up

The site is to notify Ora of any subject discontinuation or withdrawal and the reason. The discontinuation or withdrawal and the reason are to be clearly documented in the subject source and eCRF.

If a subject is discontinued or withdraws from the study before Visit 6, all safety and efficacy evaluations performed at Visit 6 are to be done on the day of discontinuation or at the discretion of the Investigator. Sites are to use the Visit 6 section of the source document to record an early termination visit.

Any subject who is discontinued or withdraws is to be instructed to return all IP to the clinic for accountability.

Subjects who are discontinued or withdraw from the study are not to be replaced.

Follow-up for subjects who end treatment with IP is to be performed at the Investigator's discretion. Any AEs that are ongoing as of withdrawal or discontinuation are to be followed as outlined in Section 9.5.

In the case that the site is unable to contact a subject, the site is to make two documented phone calls to the subject and send a certified letter before deeming the subject lost to follow-up.

7 STUDY VISITS AND PROCEDURES SCHEDULE

The following outlines the order of procedures to be performed at the indicated visit with regard to the study objectives. See Appendix 2 for detailed descriptions of the procedures.

Visit 1 (Day -14 ± 2): Screening	**Visit 2 (Day 1): Baseline and Randomization**
• Informed consent / HIPAA • Medical / medication history and demographics • Urine pregnancy test for women of childbearing potential • VAS questionnaire • SANDE questionnaire • Visual acuity (ETDRS) • Slit-lamp biomicroscopy • TFBUT • Fluorescein staining (NEI scale) • Lissamine staining (NEI scale) • Unanesthetized Schirmer's Test • IOP • Dilated fundoscopy • Review of qualification criteria • Run-in kit assignment and dispensation • AE query	• Run-in collection and kit accountability • Medical status update / AE query • Concomitant medication review • VAS questionnaire • SANDE questionnaire • Visual acuity (ETDRS) • Slit-lamp biomicroscopy • TFBUT • Fluorescein staining (NEI scale) • Lissamine staining (NEI scale) • Review of qualification criteria • Randomization • Randomized treatment kit assignment and dispensation (1 kit) • In-office randomized treatment dose • Ora Calibra® Drop Comfort Scale and Questionnaire • AE query

Visit 3 (Day 15 ± 2): 2-Week Follow-Up	**Visit 4 (Day 29 ± 2): 4-Week Follow-Up**
• Randomized treatment kit collection and accountability • Medical status update / AE query • Concomitant medication review • VAS questionnaire • SANDE questionnaire • Visual acuity (ETDRS) • Slit-lamp biomicroscopy • TFBUT • Fluorescein staining (NEI scale) • Lissamine staining (NEI scale) • Randomized treatment kit assignment and dispensation (1 kit) • AE query	• Randomized treatment kit collection and accountability • Medical status update / AE query • Concomitant medication review • VAS questionnaire • SANDE questionnaire • Visual acuity (ETDRS) • Slit-lamp biomicroscopy • TFBUT • Fluorescein staining (NEI scale) • Lissamine staining (NEI scale) • Randomized treatment kit assignment and dispensation (2 kits) • AE query

Visit 5 (Day 57 ± 3): 8-Week Follow-Up • Randomized treatment kit collection and accountability • Medical status update / AE query • Concomitant medication review • VAS questionnaire • SANDE questionnaire • Visual acuity (ETDRS) • Slit-lamp biomicroscopy • TFBUT • Fluorescein staining (NEI scale) • Lissamine staining (NEI scale) • Randomized treatment kit assignment and dispensation (2 kits) • In-office randomized treatment dose • Ora Calibra® Drop Comfort Scale and Questionnaire • AE query	**Visit 6 (Day 85 ± 4): 12-Week Follow-Up and Study Exit** • Randomized treatment kit collection and accountability • Medical status update / AE query • Concomitant medication review • Urine pregnancy test for women of childbearing potential • VAS questionnaire • SANDE questionnaire • Visual acuity (ETDRS) • Slit-lamp biomicroscopy • TFBUT • Fluorescein staining (NEI scale) • Lissamine staining (NEI scale) • Unanesthetized Schirmer's Test • IOP • Dilated fundoscopy • AE query • Study exit

7.1 Unscheduled Visits

An Unscheduled Visit may be performed in order to ensure subject safety or at the Investigator's discretion. Assessments performed at an Unscheduled Visit are to be documented on the Unscheduled Visit pages of the subject source document and then transcribed to the Unscheduled Visit eCRFs. Any assessment listed as a potential Unscheduled Visit assessment in the subject source or the EDC that is not performed is to be documented as "Not Done."

Evaluations that may be conducted at an Unscheduled Visit include

- Urine pregnancy test,
- Visual acuity (ETDRS),
- Slit-lamp biomicroscopy,
- Intraocular pressure (IOP),
- Dilated fundoscopy,
- Unanesthetized Schirmer's Test
- Assessment of Adverse Events,
- Assessment of concomitant medications and/or treatments, or
- Any other assessments needed in the judgment of the Investigator.

8 ASSESSMENT OF EFFICACY

8.1.1 Primary and Key Secondary Endpoints

Parameters for assessing efficacy for the primary and key secondary endpoints are EDS [redacted] fluorescein staining at Visit 2 (Day 1), Visit 4 (Day 29) and Visit 6 (Day 85). Instructions for the completion of these assessments are in Appendix 2.

8.1.2 Other Secondary Endpoints

Other secondary endpoints for assessing efficacy are below. Instructions for the completion of these assessments are in Appendix 2.

- Eye dryness, discomfort, grittiness, pain, blurred vision, and photophobia [redacted]
- Frequency, severity, and total score [redacted]
- [redacted] at Visits 3, 4, 5, and 6, and the [redacted] at Visits 3, 4, 5, and 6.
- CFS in the inferior, superior, central, temporal, nasal, and corneal (i.e., sum of all regions) regions [redacted]
- Conjunctival lissamine green staining in the temporal, superior temporal, inferior temporal, superior nasal, inferior nasal, nasal, and conjunctival (i.e., sum of all regions) regions [redacted]
- [redacted] Visit 6 and the [redacted] (Visit 1) at Visit 6.

9 ASSESSMENT OF SAFETY

AEs (both elicited and observed) will be monitored throughout the study. All AEs (both elicited and observed) will be promptly reviewed by the Investigator for accuracy and completeness. All AEs will be documented on the appropriate source document pages and eCRF.

9.1 Safety Parameters

The safety parameters are concomitant medication monitoring/review, visual acuity (ETDRS), slit-lamp biomicroscopy, IOP, dilated fundoscopy, Ora Calibra® Drop Comfort Scale and Questionnaire, and AE query. Instructions for completing the safety assessments are in Appendix 2.

Procedure ↓ Visit →	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Day -14 ± 2	Day 1	Day 15 ± 2	Day 29 ± 2	Day 57 ± 3	Day 85 ± 4
Concomitant Medication Review		X	X	X	X	X
Visual Acuity (ETDRS)	X	X	X	X	X	X
Slit-Lamp Biomicroscopy	X	X	X	X	X	X
Intraocular Pressure (IOP)	X					X
Dilated Fundoscopy	X					X
Ora Calibra® Drop Comfort Scale and Questionnaire		X			X	
Adverse Event (AE) Query	X	X	X	X	X	X

9.2 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release, and anatomic fit) associated with medical device use.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, seriousness, severity, relationship to IP, expectedness, action taken with IP, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning.

Surgical interventions are not adverse events; surgical interventions are therapeutic measures for medical conditions for which they are required. The medical condition that

necessitates surgical intervention is to be considered an adverse event if the occurrence or detection of the condition is temporally associated with the use of study drug.

The worsening of a medical condition that was present before the administration of study drug is to be considered a new adverse event and reported as such. The improvement or lack of change of a medical condition that was present before the administration of study drug is not to be recorded as a TEAE at subsequent visits unless it worsens during treatment.

The worsening of DED is to be considered an adverse event only if the exacerbation of the signs or symptoms exceed what the subject has previously experienced. The determination to record worsening of DED as an AE is to be made by the Investigator and the subject.

Study drug includes the IP under evaluation, any comparator drug, the vehicle, and any other medications required by the protocol given during any stage of the study. Therefore, AE reporting begins with the administration of the topical, local anesthetic used to measure IOP at Visit 1.

9.2.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

- ***Mild*:** Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- ***Moderate*:** Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- ***Severe*:** Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.2.2 Relationship to Investigational Product

The relationship of each AE to the IP should be determined by the Investigator using these explanations:

- ***Suspected*:** A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:
  - *Definite*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
  - *Probable*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.

- *Possible*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.

- ***Not Suspected:*** A reasonable possibility does not exist that the IP caused the AE.
  - *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

9.2.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- ***Unexpected:*** An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- ***Expected:*** An AE that is listed in the IB at the specificity and severity that has been observed.
- ***Not applicable:*** An AE unrelated to the IP.

AEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The Investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

9.2.4 Action Taken with Investigational Product

If an AE occurs and the Investigator alters the IP dose or administration in any way, this should be documented in the source document and reported in the eCRF.

Available options within the eCRF for reporting actions taken with the IP due to an AE include:

- Dose Not Changed
- Drug Interrupted
- Drug Withdrawn
- Not Applicable (if subject has not been exposed to IP)

9.2.5 Outcome

The outcome of an AE should be documented in the source document and in the eCRF using the following categories:

- Fatal
- Not Recovered/Not Resolved

- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

9.3 Serious Adverse Events

An AE 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;

Note: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the Investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or

Note: A serious adverse event (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.4 Procedures for Reporting Adverse Events

9.4.1 Reporting an Adverse Event

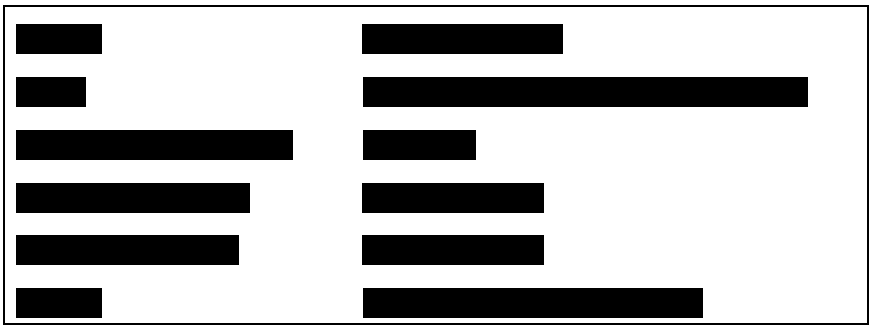
All AEs and their outcomes must be reported to Ora, the Sponsor, and the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) as required by the IRB/IEC,

federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF. AEs are to be collected from the first administration of study drug to the subject's exit from the study.

9.4.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate eCRFs. The Investigator is obligated to pursue and obtain information requested by Ora and/or the Sponsor in addition to that information reported on the eCRF. All subjects experiencing an SAE must be followed until the SAE is resolved or reaches a clinically stable outcome, with or without sequelae, and the outcome reported.

In the event of an SAE, the Investigator should inform the clinical project manager, [redacted], that an SAE occurred by phone, fax, or email immediately.

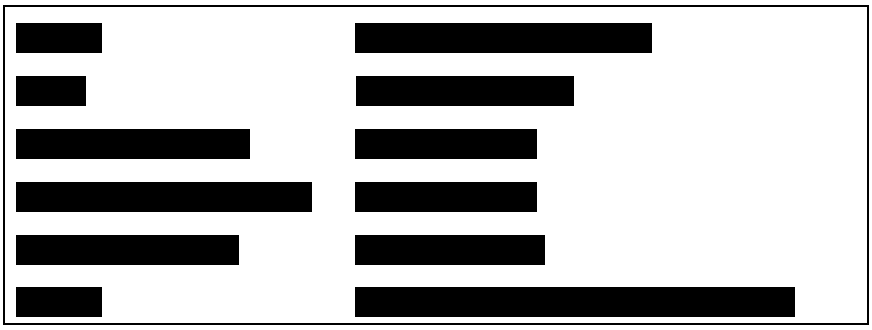


The site is to complete the initial SAE Report Form and submit the form to the clinical project manager as soon as is feasible but no more than 24 hours after becoming aware of the event. Furthermore, the site is to transcribe the requisite SAE information to the appropriate eCRF no more than 24 hours after becoming aware of the event. After the initial report, all additional follow-up evaluations must be reported to Ora within one business day of receipt of the information.

The Ora clinical project manager will notify the Medical Monitor and the Sponsor of the SAE as soon as is feasible but no more than 24 hours after becoming aware of the event.

The Investigator must obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the Sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the IP; and inform the IRB of the SAE within their guidelines for reporting SAEs. If an SAE is considered reportable per Alpha IRB's guidelines, the site should report the SAE promptly but no more than 10 business days after becoming aware of the event.

For questions regarding the seriousness of an AE, the site is to contact the Medical Monitor directly. The site may also consult with the Medical Monitor additionally as needed.



9.4.3 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, the Sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.5 Type and Duration of Follow-Up of Subjects after Adverse Events

AEs that are ongoing at the subject's exit from the study are to be marked as such in the subject's source document and eCRF. Sites are to follow AEs ongoing at the subject's exit from the study until resolution or until the condition is considered ongoing and stable. Documentation of AE follow-up is to be maintained at the clinical site.

9.6 Pregnancy

Pregnancy in itself is not considered an AE or SAE (unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication), but it is an important medical event that must be followed up. Any pregnancy that occurs during the clinical trial where the fetus could have been exposed to the study drug(s) must be followed through the outcome of the pregnancy.

If a female has a positive pregnancy test during the study, then the Investigator will notify Ora immediately. The Investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The Investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to Ora.

10 STATISTICS

10.1 Analysis Populations

10.1.1 Intent-to-Treat Population

[redacted].

10.1.2 Per Protocol Population

[redacted]

10.1.3 Safety Population

[redacted]

10.2 **Statistical Hypotheses**

10.2.1 Primary Endpoints

[redacted]

[redacted].

10.2.2 Key Secondary Endpoints

[redacted]

[redacted]

10.3 **Sample Size**

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

10.3.1 Multiplicity Considerations

[redacted]

10.4 Statistical Analysis

10.4.1 General Considerations

[redacted]

[redacted]

10.4.2 Unit of Analysis

[redacted]

[redacted]

[redacted]

10.4.3 Missing Data

[redacted]

10.4.4 Primary Efficacy Analyses

[redacted]

10.4.5 Key Secondary Efficacy Analyses

[redacted]

[redacted]

[redacted]

10.4.6 Other Secondary Efficacy Analyses

[redacted]

10.4.7 Safety Analyses

[redacted]

[redacted]

10.4.8 Interim Analyses

[redacted]

11 DATA HANDLING AND RECORDKEEPING

11.1 **Data Collection**

The Investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and

writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when by adding to the correction his/her initials as well as the date of the correction.

Source document entries are to be transcribed to eCRFs. iMedNet is to be the EDC system and Statistics & Data Corporation (SDC) is the contracted data management firm. Transcription to eCRFs is to be accomplished using software that conforms to 21 CFR Part 11 requirements. Only staff who are masked and who have received training on the iMedNet system and the study-specific eCRFs will be allowed access to this study's EDC environment. The EDC system is to maintain an audit trail to capture all changes made to the eCRFs. Each investigative site is to be supplied with their subject data on compact disks that are to be maintained on file by the Investigator.

Source documents may include a subject's medical records, hospital charts, clinic charts, the Investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and EKGs. The Investigator's copy of the eCRFs serves as the Investigator's record of a subject's study-related data.

11.2 Data Directly Recorded on the Electronic Case Report Forms

The results of all trial assessments are to be documented and then transcribed to the eCRFs. No data is to be recorded directly on the eCRFs and considered source data with the exception of the IRT-assigned randomization number, the treatment arm, and any kit numbers.

11.3 Retention of Documentation

All study-related correspondence, subject records, consent forms, record of the distribution and use of all IP, and copies of eCRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

12 ADMINISTRATIVE ASPECTS

12.1 Ethics

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

This study will be conducted in compliance with the protocol and current GCPs, including the ICH Guidelines. In addition, all applicable local, state, and federal requirements relevant to the use of IP in the countries involved will be adhered to.

12.2 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the Sponsor, the IRB/IEC approving this study, the US Food and Drug Administration (FDA), the US Department of Health and Human Services (DHHS), other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

12.3 Institutional Review Board Approval

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved in accordance with IRB regulations (U.S. 21 CFR Part 56.103). The Investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB/IEC approved version of the informed consent form will be used.

12.4 Subject Informed Consent

Informed consent/assent must take place before any study-specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent forms must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form

requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (e.g., oral informed consent), then the procedures to be followed must be determined by Ora and/or Sponsor and provided in writing by Ora and/or Sponsor prior to the consent process.

12.5 Modifications of the Protocol

This study will be conducted in compliance with the most recently approved version of the protocol. Any change to the protocol or ICF that affects the scientific intent, study design, or subject safety or may affect a subject's willingness to continue participation in the study is considered an amendment to this protocol and/or ICF. All such amendments will be submitted to the IRB for approval prior to becoming effective.

12.6 Quality Control and Quality Assurance

Each Investigator and site participating in this clinical trial are to permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections and provide direct access to source data/documents and trial records.

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess IP accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, Ora, Inc. quality assurance, the Sponsor and/or the designees of these parties may carry out on-site inspections and/or audits which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

12.7 Financing and Insurance

Financing and insurance are addressed in an agreement separate from this clinical trial protocol.

13 PUBLICATION POLICY

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Ora and the Sponsor will have the final decision regarding the manuscript and publication.

14 REFERENCES

1. Maliartchouk S, Feng Y, Ivanisevic L, et al. A Designed Peptidomimetic Agonistic Ligand of TrkA Nerve Growth Factor Receptors. *Mol Pharmacol*. 2000;57(2):385-391.

2. Bruno MA, Clarke PBS, Seltzer A, et al. Long-lasting rescue of age-associated deficits in cognition and the CNS cholinergic phenotype by a partial agonist peptidomimetic ligand of TrkA. *J Neurosci*. 2004;24(37):8009-8018. doi:10.1523/JNEUROSCI.1508-04.2004

3. Lebrun-Julien F, Morquette B, Douillette A, Saragovi HU, Di Polo A. Inhibition of p75(NTR) in glia potentiates TrkA-mediated survival of injured retinal ganglion cells. *Mol Cell Neurosci*. 2009;40(4):410-420. doi:10.1016/j.mcn.2008.12.005

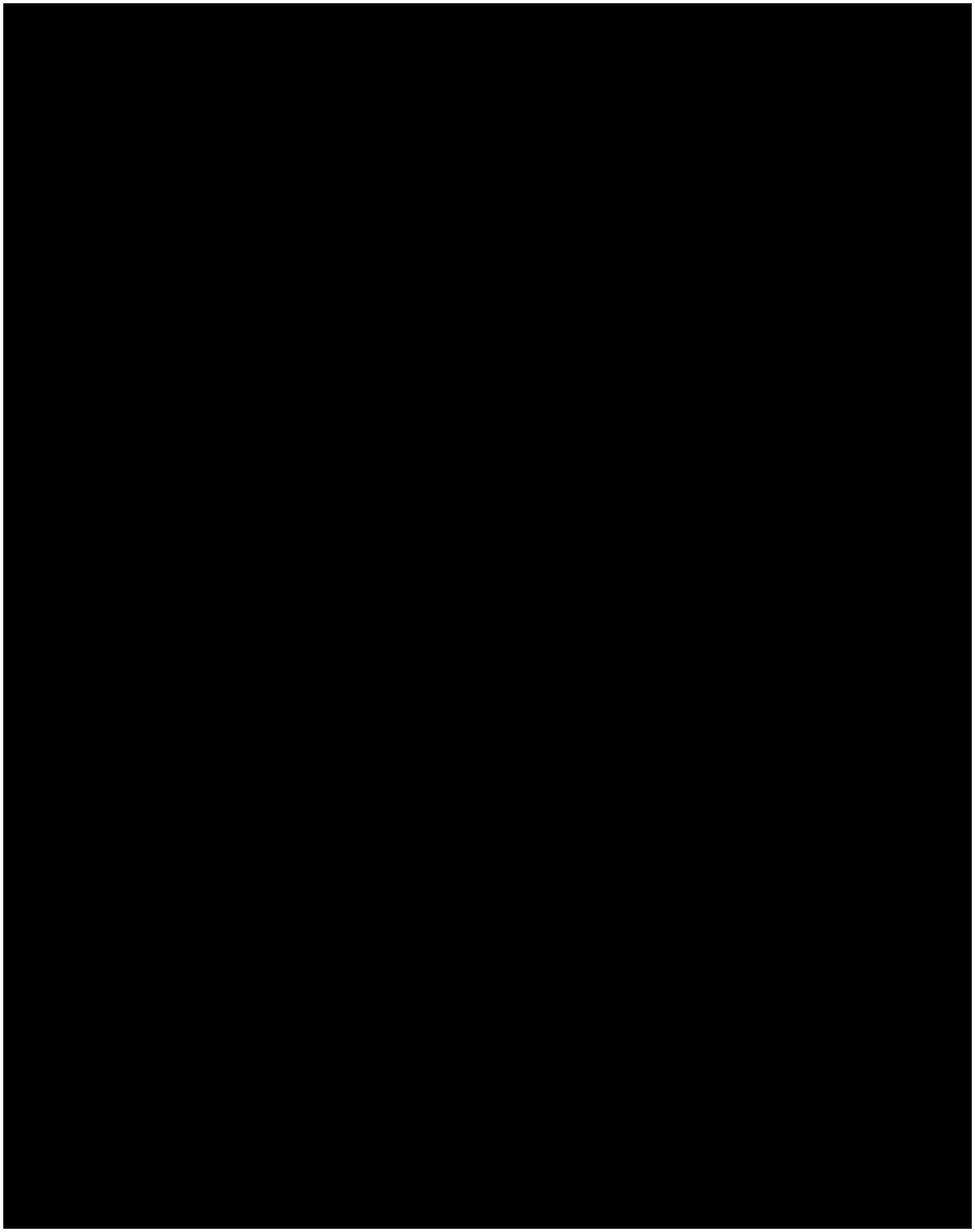
4. Shi Z, Birman E, Saragovi HU. Neurotrophic rationale in glaucoma: a TrkA agonist, but not NGF or a p75 antagonist, protects retinal ganglion cells in vivo. *Dev Neurobiol*. 2007;67(7):884-894. doi:10.1002/dneu.20360

5. Jain P, Li R, Lama T, Saragovi HU, Cumberlidge G, Meerovitch K. An NGF mimetic, MIM-D3, stimulates conjunctival cell glycoconjugate secretion and demonstrates therapeutic efficacy in a rat model of dry eye. *Exp Eye Res*. 2011;93(4):503-512. doi:10.1016/j.exer.2011.06.014

6. Meerovitch K, Torkildsen G, Lonsdale J, et al. Safety and efficacy of MIM-D3 ophthalmic solutions in a randomized, placebo-controlled Phase 2 clinical trial in patients with dry eye. *Clin Ophthalmol*. 2013;7:1275-1285. doi:10.2147/OPTH.S44688

15 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS



APPENDIX 2: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

Visual Analog Scale (VAS)

[redacted]

[redacted]

[redacted]

Symptom Assessment in Dry Eye (SANDE) Questionnaire

[redacted]

[redacted]

[redacted]

[redacted]

Visual Acuity Procedures (ETDRS Chart)

[redacted]

LogMAR Visual Acuity Calculations

[redacted]

Slit-Lamp Biomicroscopy Procedures

[redacted]

Tear Film Break-Up Time (TFBUT)

[redacted]

[redacted]

[redacted]

Fluorescein Staining

[redacted]

[redacted]

Lissamine Green Staining

Unanesthetized Schirmer's Test

[redacted]

Intraocular Pressure

[redacted]

Dilated Fundoscopy

[redacted]

[redacted]

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

[redacted]

Ora Proprietary Scale – Not for Distribution without Permission

APPENDIX 3: ADVERSE EVENT (AE) DEFINITIONS

Severity

- ***Mild*:** Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- ***Moderate*:** Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- ***Severe*:** Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

Relationship to Investigational Product (IP)

- ***Suspected*:** A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:
    - *Definite*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
    - *Probable*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.
    - *Possible*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- ***Not Suspected:*** A reasonable possibility does not exist that the IP caused the AE.
    - *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

Expectedness

- ***Unexpected:*** An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- ***Expected:*** An AE that is listed in the IB at the specificity and severity that has been observed.
- ***Not applicable:*** An AE unrelated to the IP.

APPENDIX 5: PROTOCOL AMENDMENT SUMMARY

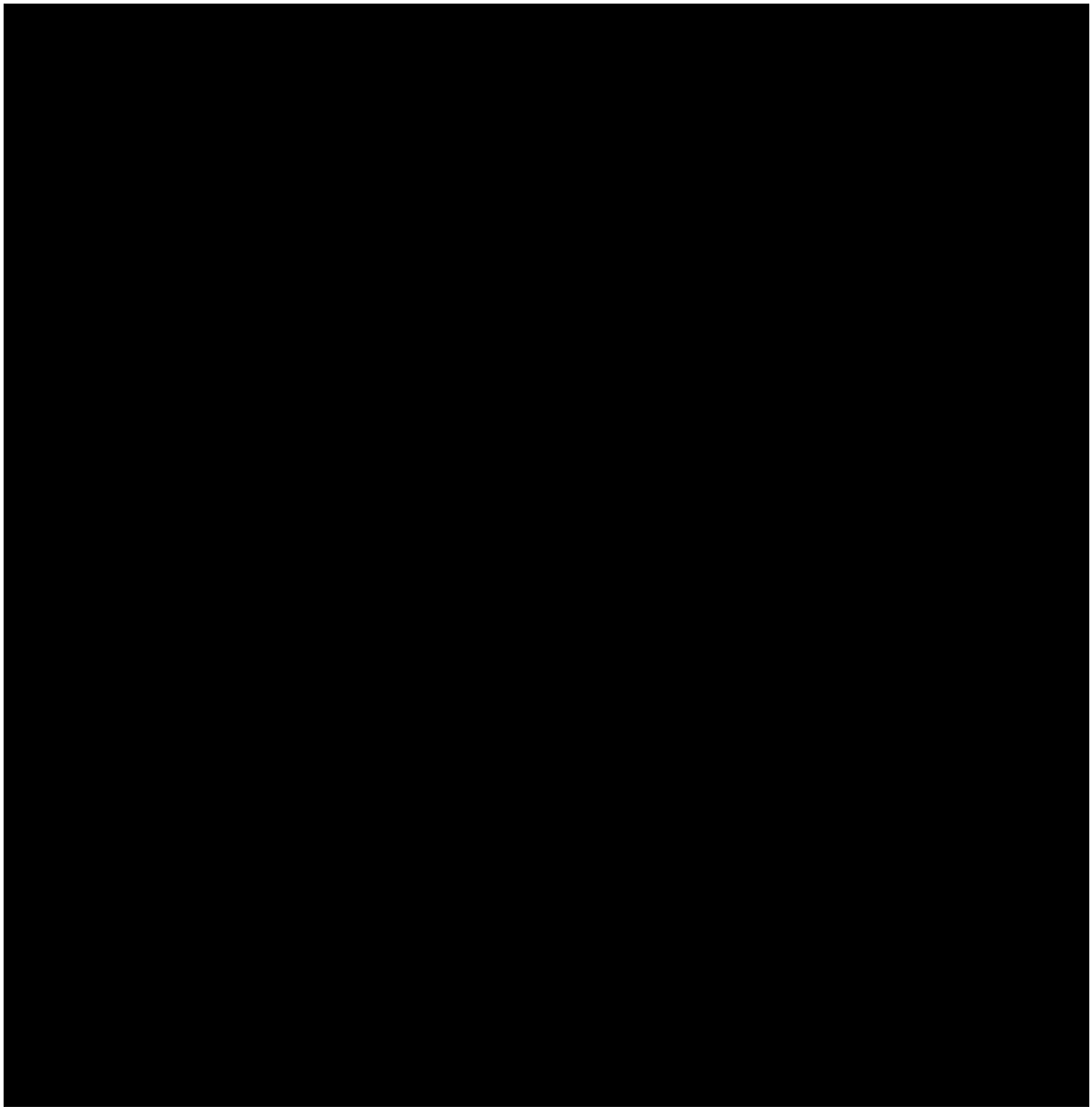
[redacted]

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

APPENDIX 6: SPONSOR AND ORA APPROVALS

Protocol Title:	A Phase 3, Multi-Center, Randomized, Double-Masked, Vehicle-Controlled Clinical Study to Assess the Safety and Efficacy of 1% Tavilermide and 5% Tavilermide Ophthalmic Solutions for the Treatment of Dry Eye
Protocol Number:	MIM-728
Final Date:	07 March 2019
Amendment 1:	03 July 2019

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol.



APPENDIX 7: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Phase 3, Multi-Center, Randomized, Double-Masked, Vehicle-Controlled Clinical Study to Assess the Safety and Efficacy of 1% Tavilermide and 5% Tavilermide Ophthalmic Solutions for the Treatment of Dry Eye
Protocol Number:	MIM-728
Final Date:	07 March 2019
Amendment 1:	03 July 2019

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by Ora and the Sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.