A randomized, multi-center, double-masked, vehicle-controlled, Phase 1/2 study to evaluate the safety, tolerability, and efficacy of OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use for the treatment of subjects with dry eye disease (DED)

Investigational Product

CLN-Protocol-0054

Version 05

03 June 2021

Sponsor
Ocular Therapeutix, Inc.
24 Crosby Drive
Bedford, MA 01730 USA

A randomized, multi-center, double-masked, vehicle-controlled, Phase 1/2 study to evaluate the safety, tolerability, and efficacy of OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use for the treatment of subjects with dry eye disease (DED)

I hereby agree to participate in the clinical investigation of OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use sponsored by Ocular Therapeutix, (hereinafter "Study Sponsor"). I agree to conduct this investigation in accordance with the agreement, the investigational plan, and applicable regulations. I agree to protect the rights, safety, and welfare of subjects under my care; I agree to adhere to the regulations outlined in 21 CFR Part 312, other applicable United States Food and Drug Administration (FDA) regulations, and conditions of approval imposed by the reviewing IRB and the FDA. I agree to supervise all use of the investigational product and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee of the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor. I am also aware that I may be inspected by a representative of the FDA to verify compliance with applicable federal regulations related to clinical research on human subjects. I am aware that my contact for all matters related to this investigation is the Ocular Therapeutix Clinical Department at (781) 357-4000.

I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time. In the event that I decide to discontinue my participation as an Investigator in this study, I will notify the Study Sponsor 30 days prior of my intent to discontinue. I understand that I am obligated to complete the follow up of the subjects already participating in the investigation.

Any data generated as a result of this investigation will be the exclusive property of the Study Sponsor who retains all rights of publication. I understand that the Study Sponsor encourages me to pursue independent publications related to my experience with this investigational product with the understanding that Study Sponsor reserves the right of prior review and approval of these publications.

I agree to provide to the Study Sponsor my current curriculum vitae along with the current curriculum vitae of those physicians at this institution who will be using this investigational product or participating in this study as Sub-Investigators under my supervision. These CVs include education, training, and the extent and type of our relevant experience with pertinent dates and locations. I certify that I have not been involved in an investigation that was terminated for noncompliance at the insistence of a Study Sponsor, an IRB or the FDA.

I understand that this investigation, protocol, and trial results are confidential, and I agree not to disclose any such information to any person other than a representative of the Study Sponsor or FDA without the prior written consent of the Study Sponsor.

I will provide financial information, as indicated in 21 CFR Part 312.64(d) and 21 CFR Part 54.

Accepted by:

Principal Investigator Signature	Date	Printed Name

PROTOCOL REVISION HISTORY

Date	Version	Description of Modifications	Rationale for Modification
02 December 2019	01	Original Issue	N/A
31 January 2020	01	Version 01 dated 02 December 2019 was not initiated in the clinic 1. Extended follow-up timeframe for Cohort 1 subjects. 2. Updated statistical section to include planned methods of analyses for the primary and secondary efficacy endpoints. 3. Add language regarding replacement of inserts.	1. To have Cohort 1 subjects follow the same schedule as the Cohort 2 subjects. 2. To specify planned analyses. 3. To allow for reinsertion due to early loss of insert.
7 July 2020	02	1. Updated Screening visit to include wait time for Schirmer test. 2. Updated Appendices to refer to Lab Manual for Schirmer test and Tear Film PK.	1. To ensure screening Schirmer is same as other visits. 2. To ensure alignment within the protocol and across the protocol and other study documents.
25 August 2020	03	1. Updated Section 7.4 to note both eyes. 2. Removed Impression Cytology assessment from the protocol. 3. Added secondary efficacy endpoint for Schirmer Test. 4. Moved TBUT from Week 16 visit to Week 12 visit.	1. Any subject with an insert should be followed in the study. 2. Decided to include Impression Cytology in another study. 3. This efficacy endpoint should have been included previously. 4. Correction needed to align with the associated exploratory endpoint.

Date	Version	Description of Modifications	Rationale for Modification
23 November 2020	04	1. Study Design, Sections 4.7 and 6.1 changed to reflect increase in subject population from 105 to 140 cohort 2. 2.Updated Section 7.4 to state that any subject with a successful unilateral insertion should return within three days to reattempt insertion in the unsuccessful eye. 3. Inclusion #7 added to include post-menopausal women 4. OTC decongestants added to Exclusion #14. 5.Procedural Exclusion Criteria updated to specify that subjects with unilateral insertion will be followed throughout study. 6.For Visit 1 procedures, Urine pregnancy test specifies it is for Women of Child Bearing Potential (WOCBP) only. 7. Section 8.4.10 updated to state Replacement of inserts is not permitted for subjects enrolled in Cohort 2.	1. Increase in subject population total. 2. To specify that reinsertion should be attempted when possible. 3. To specify post-menopausal women can be included. 4.To clarify that over-the-counter decongestants as well as prescription ones are excluded. 5. Clarification. 6. Clarification. 7. Clarification.
03 Jun 2021	05	1. Removal of all 'Rescue' Language referring to Artificial Tears. 2. Removal of sentence from Section 11.6 regarding subjects data after sustained usage of rescue medication. 3. Addition of the word 'procedural' to the body of the section named	1. Artificial Tears are commonly used in Dry Eye Disease studies and not viewed in this study as a rescue therapy. 2. All data will be used. 3.Clarification.

Date	Version	Description of Modifications	Rationale for Modification
		'**Procedural Exclusion Criteria'.** 4. Addition of the phrase 'procedural screen failures' to section 7.4.	4.Clarification.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	Adverse Event/Experience
AT	Artificial Tears
BCVA	Best Corrected Visual Acuity
C	Celsius
CD	Compact Disc
CFB	Change from Baseline
CFR	Code of Federal Regulations
CFS	Corneal Fluorescein Staining
CMO	Chief Medical Officer
CRF	Case Report Form
CRO	Contract Research Organization
CsA	Cyclosporine A
CV	Curriculum Vitae
DED	Dry Eye Disease
DLT	Dose-Limiting Toxicity
e	Electronic
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
FCS	Fluorescein Corneal Scoring
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HED	Human Equivalent Dose
HV	Hydrogel Vehicle Insert
ICH	International Council on Harmonization
ICF	Informed Consent Form
ID	Subject Identification
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intra-Uterine Device
KCS	Keratoconjunctivitis Sicca
LogMAR	Logarithm of the Minimum Angle of Resolution
mg	Milligram
ml	Milliliter
mm	Millimeter
mmHg	Millimeters of Mercury
NDA	New Drug Application
NEI	National Eye Institute
NOAEL	No Observed Adverse Event Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
NSR	Non-Significant Risk
PP	Per Protocol
PRN	As Needed
OD	Right Eye
OS	Left eye
OSDI	Ocular Surface Disease Index
OTX	Ocular Therapeutix
OTX-CSI	Cyclosporine Ophthalmic Insert
PK	Pharmacokinetics
SAE	Serious Adverse Event/Experience

Term	Definition
SPEED	Standard Patient Evaluation of Eye Dryness
SRG	Safety Review Group
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBUT	Tear Film Break Up Time
tCFS	Total Corneal Fluorescein Staining
µg	Microgram
UPT	Urine Pregnancy Test
US	United States
VA	Visual Acuity
VAS	Visual Analog Scale
VKC	Vernal Keratoconjunctivitis
WOCBP	Women of Child-Bearing Potential

2 SYNOPSIS

<table>
<tr><td>Protocol Title</td><td>A randomized, multi-center, double-masked, vehicle-controlled, Phase 1/2 study to evaluate the safety, tolerability, and efficacy of OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use for the treatment of subjects with dry eye disease (DED)</td></tr>
<tr><td>Protocol Number</td><td>CLN-Protocol-0054</td></tr>
<tr><td>Phase of Clinical Study</td><td>1/2</td></tr>
<tr><td>Investigational Products</td><td>
<table>
<tr><th>Formulation Number</th><th>Name</th><th>Approximate Persistence</th></tr>
<tr><td>1</td><td>OTX-CSI 0.36 mg Cyclosporine Ophthalmic Insert</td><td>2 to 3 months</td></tr>
<tr><td>2A</td><td>OTX-CSI 0.36 mg Cyclosporine Ophthalmic Insert</td><td>3 to 4 months</td></tr>
<tr><td>2B</td><td>Hydrogel Vehicle Insert</td><td>3 to 4 months</td></tr>
<tr><td>3</td><td>Hydrogel Vehicle Insert</td><td>1 week</td></tr>
</table>
</td></tr>
<tr><td>Study Objective</td><td>To assess the safety, tolerability, and efficacy of OTX-CSI in subjects with DED.</td></tr>
<tr><td>Safety Evaluations</td><td>Primary:
Non-ocular and Ocular Adverse Events (AEs)
Secondary:
Best-Corrected Visual Acuity (BCVA)
Slit Lamp Biomicroscopy (including punctum assessment)
Intraocular Pressure (IOP)
Fundus Examination
Artificial tear use during the study</td></tr>
<tr><td>Efficacy Endpoints</td><td>Primary:
Schirmer Test (without anesthesia) change from baseline (CFB) and absolute value at Week 12.
Secondary:
<u>Signs</u>:
Percent of subjects with ≥10 mm increase in Schirmer at Week 12.
Total Corneal Fluorescein Staining (tCFS) using NEI scale, CFB and absolute values at each post baseline study visit.
CFS sub-regions using NEI scale, CFB and absolute values at each post-baseline visit.
Conjunctival Lissamine Green Staining using NEI Scale, CFB and absolute values at each post-baseline visit.</td></tr>
</table>

<table>
<tr><td></td><td>Symptoms (subject-reported):
Eye Dryness Score (visual analogue scale [VAS]), CFB and absolute values at each post-baseline visit.
Ocular Surface Disease Index (OSDI©) questionnaire, CFB and absolute values at each post-baseline visit (total score, each of the three domains, and individual questions).
SPEED questionnaire (overall score and individual questions), CFB at each post-baseline visit.
Exploratory:
Tear Film Break Up Time (TBUT), CFB at Week 12
Presence of OTX-CSI or HV insert at all post-baseline visits
Ease of insertion as assessed by the Investigator
Ease of visualization as assessed by the Investigator</td></tr>
<tr><td>Pharmacokinetics (PK) Parameters</td><td>Systemic PK (at selected sites)
Tear Film PK (all sites)</td></tr>
<tr><td>Number of Investigational Sites</td><td>Approximately 15 sites in the United States (US)</td></tr>
<tr><td>Number of Subjects Planned</td><td>Approximately 145 subjects (290 eyes) will be enrolled in two cohorts.</td></tr>
<tr><td>Study Population</td><td>Subjects with signs and symptoms of DED.</td></tr>
<tr><td>Study Design and Overview</td><td>This is a randomized, multi-center, double-masked, vehicle-controlled, phase 1/2 clinical study designed to evaluate the safety, tolerability, and efficacy of OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use for the treatment of subjects with DED. Approximately 145 subjects (290 eyes) will be enrolled in this study at approximately 15 sites in the US. Subjects will be enrolled in two cohorts. Cohort 1 will be an open-label group consisting of approximately 5 subjects. Cohort 2 will be a randomized, double-masked group consisting of approximately 140 subjects (280 eyes)treated with 2 different hydrogel formulations of OTX-CSI and 2 different formulations of hydrogel vehicle inserts (HV). Both eyes will be treated with the same treatment/formulation.
<table>
<tr><th>Cohort Number</th><th>Number of Subjects</th><th>Treatment</th><th>Formulation Number</th></tr>
<tr><td>1
Open-label</td><td>5</td><td>OTX-CSI</td><td>2A</td></tr>
<tr><td rowspan="4">2
Randomized, double-masked</td><td>40</td><td>OTX-CSI</td><td>1</td></tr>
<tr><td>40</td><td>OTX-CSI</td><td>2A</td></tr>
<tr><td>40</td><td>HV</td><td>2B</td></tr>
<tr><td>20</td><td>HV</td><td>3</td></tr>
</table>
The recommendation to progress to Cohort 2 will be the responsibility of the Safety Review Group (SRG). The SRG will review Cohort 1 data to</td></tr>
</table>

	evaluate the safety of OTX-CSI Formulation 2A after all subjects have been followed for at least 2 weeks and will issue a recommendation on whether or not to open enrollment in Cohort 2. Once subject eligibility has been determined, OTX-CSI or HV insert, as applicable, will be placed bilaterally, into either the superior or inferior canaliculus (per investigator's preference), during the Insertion/Day 1 (Visit 2) for all subjects who meet the eligibility criteria. **Cohort 1** Subjects in Cohort 1 will undergo Screening 14 days prior to Insertion/Day 1 (Visit 2) to determine eligibility and eligibility will be re-confirmed at Visit 2 (Insertion/Day 1). The treatment follow-up visits will occur at Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), Week 9 (Visit 6), Week 12 (Visit 7), and Week 16 (Visit 8). All subjects in Cohort 1 will be followed until Week 16 (Visit 8), whether or not an insert is visualized. **Cohort 2** Subjects in Cohort 2 will undergo Screening 14 days prior to Insertion/Day 1 (Visit 2) to determine eligibility. At Visit 2 (Insertion/Day 1) eligibility will be confirmed and subjects who are eligible will be randomly assigned to one of four treatment groups (OTX-CSI Formulation 1, OTX-CSI Formulation 2A, HV Formulation 2B or HV Formulation 3) in a 2:2:2:1 ratio. Should only a unilateral insertion be possible, Visit 2B will occur within 3 days to attempt the insertion again. The treatment follow-up visits will occur at Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), Week 9 (Visit 6), Week 12 (Visit 7), and Week 16 (Visit 8). All subjects in Cohort 2 will be followed until Week 16 (Visit 8), whether or not an insert is visualized. For both cohorts, if an OTX-CSI or HV insert is visualized at Week 16 (Visit 8), the subject will return to the clinic in 30 days (± 10 days; Visit 9) and will continue returning to the clinic every 30 days as needed, until an insert can no longer be visualized and the physician has determined that there is no evidence of biological activity. Additionally, subjects may be exited any time at the investigator's discretion. If an OTX-CSI or HV insert cannot be visualized at Week 16 (Visit 8) and the physician has determined that there is no evidence of biological activity, the subject will exit the study.
Inclusion Criteria	Subjects will be eligible for study participation if they: 1. Provide written informed consent prior to performing any study procedures and are willing to comply with study requirements and the study visit schedule. 2. Are 18 years of age or older. 3. Have a self-reported history or clinically confirmed diagnosis of DED by an eye care professional in both eyes for ≥6 months. 4. Have ongoing DED, in the study eye at screening visit as defined by the following criteria:

a. VAS eye dryness severity score ≥ 30.

And in the same qualifying eye or both eyes:

b. Total Corneal Fluorescein Staining Score of ≥6 (NEI scale) and <15.

c. Have a Schirmer score (unanesthetized) of >0 mm and ≤10 mm wetting at 5 minutes.

5. Have corrected visual acuity better than or equal to logarithm of the minimum angle of resolution (logMAR), +0.7 as assessed with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts in both eyes.
6. Are women of child-bearing potential (WOCBP) who are non-pregnant, non-lactating, and sexually inactive (abstinent) for 14 days prior to screening. And are willing to remain so through the last study visit. Alternatively, WOCBP who are not abstinent must have been using one of the following acceptable methods of birth control for the times specified:
    a. Intra-uterine device (IUD) in place for at least 3 months prior to screening and the desire to continue this method through the last study visit.
    b. Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to screening and the desire to continue this method through the last study visit.
    c. Stable hormonal contraceptive for at least 3 months prior to screening and the desire to continue this method through the last study visit.
    d. Surgical sterilization (vasectomy) of partner for at least 6 months prior to Day 1.
7. Are postmenopausal women [i.e., no menstrual cycle for at least one year prior to Visit 1 (Screening)] or are women who have undergone 1 of the following sterilization procedures at least 6 months prior to Visit 1 (Screening):
    a. Bilateral tubal ligation
    b. Hysterectomy
    c. Hysterectomy with unilateral or bilateral oophorectomy
    d. Bilateral oophorectomy
8. Agree to the removal of non-dissolvable punctal plugs 4 weeks prior to the insertion visit (Day 1, Visit 2). Long-term dissolvable punctal plugs were not placed within 4 months prior to insertion visit (Day 1, Visit 2) and short-term dissolvable punctual plugs were not placed within 6 weeks prior to insertion (Day 1, Visit 2).

Pre-Procedural Exclusion Criteria	Subjects are not eligible for study participation if they: 1. Have a known or suspected allergy to any component of the study product. 2. Are unwilling to discontinue use of contact lenses for 4 weeks prior to the screening visit and throughout the study period. 3. Have any active systemic disease and/or systemic infection (e.g., fever or current antibiotic use), or uncontrolled medical condition that in the judgment of the investigator could confound study assessments or limit compliance. 4. Have a documented history of ocular allergies, which, in the judgment of the investigator, are likely to have an acute increase in severity during the duration of this trial. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted. 5. Have a history of neuropathic pain related to dry eye. 6. Have corneal erosive disease (e.g., multiple filaments, recurrent erosion syndrome) or other conditions suggestive of extensive damage of the cornea. 7. Have a history of glaucoma or ocular hypertension or have intraocular pressure (IOP) < 5 mmHg or > 24 mmHg or a history of elevated IOP within the past 6 months prior to the screening visit. 8. Have abnormal lid anatomy that may confound study data, in the judgement of the investigator. 9. Have a diagnosis of any of the following: a. Active ocular infection b. Uveitis c. Uncontrolled blepharitis (including severe MGD), in the judgement of the investigator d. Moderate to severe pinguecula or pterygia, in the judgement of the investigator e. Stevens-Johnson syndrome f. Mucous membrane pemphigoid g. Significant conjunctival scarring, in the judgement of the investigator h. Chemical burn i. Herpetic or neurotrophic keratitis j. Congenitally absent lacrimal gland or meibomian glands k. Nasolacrimal duct obstruction in either eye

	10. Have had penetrating intraocular surgery in the past 6 months or require penetrating intraocular surgery during the study. 11. Have had eyelid surgery within 6 months prior to the screening visit. 12. Have had corneal laser refractive surgery, glaucoma surgery or corneal transplantation (full thickness, anterior or posterior). 13. Have had cauterization of the punctum resulting in complete occlusion of the punctum. 14. Have taken any of the following in either eye within 30 days prior to the screening visit: a. Topical ocular cyclosporine (e.g., Cequa®, Restasis®) b. Lifitegrast (Xiidra®) c. Autologous tears d. Topical ocular corticosteroids e. Topical ocular antibiotics f. Topical ocular NSAID g. Topical ocular antihistamines and/or mast cell stabilizers h. Topical or nasal vasoconstrictors i. Over The Counter (OTC) decongestants j. Intranasal Tear Neurostimulation 15. Have taken any of the following in either eye prior to the screening visit: a. Periocular injection of any corticosteroid solution – 3 months b. Corticosteroid intra-vitreal depot injection– 3 months c. Ozurdex– 6 months d. Retisert– 40 months 16. Have altered the dose of the following within 30 days prior to the screening visit (i.e., should keep dose stable throughout the study): a. Nutraceuticals or multivitamins b. Tetracycline compounds (tetracycline, doxycycline or minocycline) c. Inhaled, intramuscular or intra-articular corticosteroids (mouth or nasal spray form) 17. Have altered the dose of the following within 6 months prior to the screening visit (i.e., should keep dose stable throughout the study): a. Systemic anticholinergics b. Antidepressants (with the exception of rare usage as a sleep aid)

	c. Oral corticosteroids (e.g., prednisone. Prednisone dose must be less than 11 mg/day) 18. Have taken isotretinoin (Accutane) or systemic immunosuppressive agents within 6 months prior to the screening visit. 19. Are unwilling to withhold use of artificial tears (AT) for the duration of the trial. 20. Have participated in any other investigational study within 30 days of the screening visit or plans to participate in any other investigational study during the follow-up period. 21. Are an employee of the site or an immediate family member of the site. 22. Are a current smoker (including marijuana, cigar, cigarette, and/or e-cigarettes). 23. Have a known history of alcohol and/or drug abuse or are currently using illicit drugs or plan to use illicit drugs for the duration of the study. Recreational or medicinal marijuana allowed if oral consumption (no inhaled use). 24. Are unwilling or unable to comply with the study protocol. 25. The Investigator determines that the subject should not be included for reasons not already specified (e.g., systemic, behavioral, or other ocular disease/abnormality) if the health of the subject or the validity of the study outcomes may be compromised by the subject's enrollment.
Entry/Randomization Criteria	To qualify for insertion at Day 1 (Visit 2), a subject must continue to meet all screening inclusion/exclusion criteria with the following exceptions/additions: 1. VAS eye dryness severity score ≥25 2. CFS total score ≥5 (NEI scale) and <15 in the same qualifying eye as Visit 1. 3. Subject must not have taken prohibited medications and have completed the appropriate washout of prior medications, if necessary. 4. Subjects who require AT use must not have administered >3 times/day for 3 consecutive days during the washout period. NOTE: AT use is not permitted unless absolutely necessary. If subject requires AT use and has administered >3 times/for 3 days during the Screening period, they are not eligible for randomization.
Procedural Exclusion Criteria	Subjects are considered procedural screen failures if the investigator is unsuccessful at placing the OTX Ophthalmic insert in both eyes (i.e. neither eye has an insert). Subjects will be followed per protocol if the investigator successfully places one insert.

Sample Size Considerations	No formal sample size calculations were performed. The proposed sample size will allow for initial estimates of efficacy as well as provide for sufficient safety information to be obtained, while still limiting the number of subjects exposed to the IP.
Statistical Methods	Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum and maximum. Summaries for discrete variables will include frequencies and percentages. The baseline visit will be defined as the last non-missing measure prior to initiation of IP. Differences between treatment groups will be calculated as OTX-CSI minus HV and change from baseline will be calculated as follow-up visit minus baseline visit values. Efficacy summaries will be presented for the primary study eye for Cohort 2 only. Cohort 1 will be included for all safety summaries and will include summaries of the secondary study eye. Additional analyses may be presented for the secondary study eye. All summaries will be presented by treatment group and visit, where appropriate. In addition to looking at the individual formulations, the two formulations of OTX-CSI and HV will be combined and summarized.

3 PRINCIPAL CONTACTS

Please reference the CLN-Protocol-0054 Contact List.

4 BACKGROUND INFORMATION

4.1 Dry Eye Disease (DED)

Dry eye disease (DED), also known as Keratoconjunctivitis Sicca (KCS), is one of the most common ophthalmic disorders presenting to the clinician (American Academy of Ophthalmology, 2018). It is estimated that more than 16 million United States (US) adults have been diagnosed with the disorder with 9 million being classified as moderate to severe (Farrand et al, 2017; Prevent Blindness, 2019). Prevalence of dry eye is higher among women than men (8.8% or approximately 11.1 million compared to 4.5% or 5.3 million, respectively) (Farrand et al, 2017). Prevalence also increases with age with 2.7% of Americans age 18 to 34 years and 18.6% of Americans ≥75 years diagnosed with DED (Farrand et al, 2017).

DED is a multifactorial disorder of the tear film and ocular surface that results in eye discomfort (such as burning sensation, itching, redness, stinging, pain, and foreign body sensation), visual disturbances, tear film instability, and often ocular surface damage (Perry, 2008; Schultz, 2014). Inflammation of both the lacrimal gland and ocular surface has been shown to play a role in dry eye, resulting in a reduction in tear production (Salib et al, 2006; Sall et al, 2000; Stevenson et al, 2000; Willen et al, 2008). In animal models, T-cell-mediated inflammation was both a cause and result of dry eye (Niederkorn et al, 2006). In humans, dry eye was found to be associated with the presence of conjunctival T-cells and elevated levels of inflammatory cytokines in the tears compared with controls (Massingale et al, 2009; Lee et al, 2013).

4.2 Investigational Product Rationale

Cyclosporine for ophthalmic use was first approved in 1995 for the treatment of KCS in dogs. In 2003, it was approved for ophthalmic use in humans as Restasis® (cyclosporine ophthalmic emulsion 0.05%) and is indicated for increased tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS (Restasis® NDA #021023). Cyclosporine A is a cyclic polypeptide immunosuppressive agent. Cyclosporine exerts its effect by lowering the activity of T-cells suppressing the associated immune response. Cyclosporine is thought to act as a partial immunomodulator. Topical cyclosporine eye drops were shown to decrease inflammatory mediators (Turner et al, 2000) and increase tear production (Stevenson et al, 2012).

Commercial and marketed topical cyclosporine eye drops are sold around the world for the treatment of DED/KCS, Vernal Keratoconjunctivitis (VKC), and ocular inflammation (Appendix 17); however, there are limitations with the application of topical drops, which affect patient management. These limitations include difficulty with handling the bottle, limited instillation accuracy, potential washout of drops (Winfield, et al, 1990), and limited bioavailability of topical eye drops (Aldrich et al, 2013). In humans, the bioavailability from topical eye drops reaching the ocular tissues is less than 5% (Aldrich et al, 2013) which estimates to a bioavailable amount of less than 1.4 µg cyclosporine per day from Restasis® eye drops. Other limitations include the length of time (up to 6 months) for patients to be relieved from symptoms of DED and adverse reactions, such as ocular burning, associated with topical cyclosporine eye drops (Restasis® NDA #021023).

In order to address the limitations of topical ophthalmic eye drops, Ocular Therapeutix has developed OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use. OTX-CSI combines the benefits of cyclosporine with punctal occlusion, an effective therapy for DED (McCabe, 2009). OTX-CSI contains

approximately 0.36 mg of cyclosporine and is designed to deliver therapeutic levels of cyclosporine onto the ocular surface for a duration of approximately 12 weeks. Continuous release of cyclosporine from the hydrogel inserts may result in higher daily concentrations of cyclosporine delivered to the ocular surface than is found with topical Restasis. In a beagle dog study, the average cyclosporine release rate from OTX-CSI was 3.5 µg/day, exceeding the estimated daily bioavailable dose from Restasis of <1.4 µg cyclosporine per day. Tear fluid concentrations of cyclosporine measured in the beagle dog studies were typically 1 to 3 µg/mL. It is known that cyclosporine accumulates with repeat dosing in the cornea and lacrimal gland in animal studies (Acheampong et al, 1999), and this may be the case with sustained cyclosporine delivery from OTX-CSI. However, considering the low cyclosporine concentrations required at the ocular surface, OTX-CSI, offers promise as a potential sustained release treatment for patients with signs and symptoms of DED for approximately 12 weeks with a single insert.

The two active formulations of OTX-CSI being studied in this clinical trial contain the same cyclosporine dose and release drug at the same daily rates but differ in their hydrogel composition. These two formulations are designed to have different breakdown periods of the hydrogel with one formulation designed to last approximately 2 to 3 months (Formulation 1) and the other approximately 3 to 4 months (Formulation 2A). These formulations have been evaluated in prior human clinical trials conducted by the sponsor either with an active molecule or in a non-significant risk (NSR) study. The difference between these two OTX-CSI hydrogel formulations will be studied for retention and persistence in this Phase 1/2 clinical study.

The two HV insert formulations being studied contain no active drug but differ in their hydrogel formulation. These two formulations are designed to have different hydrogel breakdown periods with one formulation designed to last approximately 1 week (Formulation 3) and the other approximately 3 to 4 months (Formulation 2B). The difference between these two HV formulations will be studied in the clinical study as they provide for a short-acting and long-acting placebo.

4.3 Nonclinical Findings

The safety, efficacy, and pharmacology of topical cyclosporine eye drops have been studied extensively by other Sponsors in animals (most notably rabbits and dogs). The study results have been extensively published in the scientific literature and in supporting regulatory submissions (Cequa NDA 210913, Restasis NDA 021023, Optimmune NADA 141 052). See Section 4 of the Investigator's Brochure for more details.

OTX-CSI has been assessed by Ocular Therapeutix in 2 non-GLP pharmacokinetic (PK) studies and 1 GLP (Good Laboratory Practice) study to determine the PK of cyclosporine drug release from OTX-CSI into tear fluid over time. OTX-CSI was assessed in the GLP nonclinical study in a beagle dog model to determine its safety and toxicokinetics in a 90-day toxicology study with a 104-day recovery period compared to controls (hydrogel vehicle). The study designs are presented in Table 5 of Investigator's Brochure.

The average daily release rate of 3.5 µg/day released from OTX-CSI in the beagle dog PK study is 270-fold less than demonstrated to be safe in 12-month repeat-dose toxicology study performed in support of Restasis (NDA 021023) and 68,000-fold less than the daily oral maintenance dose of cyclosporine used in transplantation therapy in patients.

Ocular Therapeutix performed a GLP-compliant single-dose toxicity study for OTX-CSI (TP1408/CSI-NC-Tox-2019-001 "Tox Study") in beagle dogs, summarized in Table 5 of the Investigator's Brochure. The two test article formulations (OTX-CSI-1A and OTX-CSI-2A) contained approximately 0.7 mg of cyclosporine, which approximates a 2X dose relative to the proposed clinical dose, and the vehicle hydrogels (HV-1B and HV-2B) contained no drug; both inserts (with and without active ingredient)

were manufactured in a similar fashion. The number 1 (OTX-CSI-1A; HV-1B) and number 2 (OTX-CSI-2A; HV-2B) designated hydrogel formulations are designed to persist in vivo for approximately 2 to 3 months, and 3 to 4 months, respectively.

This study evaluated the potential ocular toxicity, ocular irritation, and systemic toxicity of the OTX-CSI test articles and vehicle hydrogels following insertion over a 90-day period in 27 male and 27 female beagle dogs. This study also evaluated the reversibility, persistence, and delayed occurrence of toxic effects after a 14-day recovery period.

In summary, there was no evidence of systemic toxicity. No cyclosporine was observed in plasma. Cyclosporine concentrations in the tear fluid over the study duration demonstrated a sustained steady state release of cyclosporine for both formulations achieving average concentrations in the tear fluid ranging from 2.2 to 4.1 µg/mL over 90 days. Monthly clinical ophthalmic examinations demonstrated no clinically relevant abnormalities for all eyes. Microscopic observations of relevant ocular tissues and surrounding adnexa was normal (score of 0) for all study groups with the single occurrence of an iris cyst deemed incidental. Findings of minimal to mild inflammation were due to localized tissue irritation at the site of the insert (punctal region) for both control and test article groups or frequent eyelid manipulation, as evidenced in the sham group and were not considered adverse. When present, any noted localized inflammation demonstrated reversal upon removal of the insert. Histopathology findings were comparable between active and control groups. The presence of the control and test articles in the puncta was generally well tolerated. Please see the Investigator's Brochure (section 4.4.3) for additional details.

Relative to the proposed clinical dose of 0.36 mg per insert, this GLP toxicity study in male and female beagle dogs over 90-days assessed high cyclosporine doses of 0.70 mg (OTX-CSI-1A) and 0.68 mg (OTX-CSI-2A) in two hydrogel formulations. A maximum feasible dose in the test articles was formulated by increasing the percentage of drug in each insert and increasing the length from 2.7 mm (clinical formulation) to 3.5 mm (test articles). A maximum tolerated dose (MTD) was not established in this study despite exaggerated dosing, thereby supporting the use of a 0.36 mg cyclosporine dose in clinical studies.

4.4 Risk-Benefit Analysis

OTX-CSI has the potential to deliver an efficacious cyclosporine dose to the ocular surface as a sustained release treatment for patients with signs and symptoms of DED; the dose selected is based on pre-clinical and clinical data. The risks associated with OTX-CSI have been minimized by formulating the ophthalmic insert with constituents that have a long history of use in medical devices and pharmaceuticals. Furthermore, results of biocompatibility and preclinical testing at a comparable dose, which will be used in the clinic, confirmed that OTX-CSI has no difference in inflammatory or toxic response of ocular tissues in the canine model compared with controls.

The most common adverse events (AEs) associated with topical cyclosporine (see Appendix 1 Cyclosporine Package Insert in the Investigator's Brochure)

- Ocular burning (17%)
- Conjunctival hyperemia (1-5%)
- Discharge (1-5%)
- Epiphora (1-5%)
- Eye pain (1-5%)
- Foreign body sensation (1-5%)
- Pruritus (1-5%)
- Stinging (1-5%)

- Visual disturbance (most often blurring; 1-5%)

The following adverse reactions have also been identified during post approval use of Restasis®: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema and dyspnea) and superficial injury of the eye (from the vial tip touching the eye during administration). Since these reactions are voluntarily reported by a population of an uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following AEs and/or risks have been observed with the insertion procedure:

- Perforation of or trauma to the punctum and/or surrounding tissues
- Punctoplasty
- Tearing or epiphora
- Eye inflammation
- Allergic reaction
- Dacrocystitis
- Canaliculitis
- Eye pain and discomfort, including foreign body sensation
- Decreased/impaired visual acuity
- Tearing with mucopurulent discharge
- Stenosis
- Inability to remove test article
- Infection or intraocular infection that if severe could lead to temporary or permanent impairment of eyesight
- Need for surgery on the lacrimal system

Overall, the risk-benefit analysis supports the evaluation of OTX-CSI and HV inserts as planned for administration in this trial.

4.5 Dose and Administration Justification

OTX-CSI planned clinical dose contains approximately 0.36 mg of cyclosporine designed to provide a sustained release of therapeutic levels of drug over approximately 12 weeks. Based on the size of the human canalicular system, this is the maximum dose that can be loaded into the insert without increasing the size of the insert. Using a lower or higher concentration of cyclosporine in the insert would not change the daily release of cyclosporine from the insert but would result in a shorter or longer duration of release, respectively, since low drug solubility (10 µg/mL) at physiological conditions and low tear fluid volume effectively regulates the rate of drug delivery to the ocular surface rather than concentration of cyclosporine in the implant.

The purpose for studying the two active hydrogel formulations (Formulation 1 and Formulation 2A) in this clinical study is to ensure an adequate duration of hydrogel retention and persistence to allow drug delivery to the ocular surface for approximately 12 weeks prior to hydrogel degradation. Cyclosporine not released to the ocular surface and remaining within OTX-CSI will clear through the nasolacrimal duct when the insert softens and liquefies via hydrolysis.

In humans, the bioavailability from topical Restasis eye drops reaching the ocular tissues is estimated to be less than 1.4 µg cyclosporine per day. Low cyclosporine concentrations (≥ 0.24 µg/mL) at the ocular surface are required for immunomodulation (Tang-Liu and Acheampong, 2005). The average daily cyclosporine release rate from OTX-CSI in the beagle PK study (see Table 8 in the Investigator's Brochure) approximates 3.5 µg/day (range: 2.7 to 4.4 µg/day), so this daily dose should be sufficient for therapy in the treatment of DED. Assuming a maximum exposure of 4.4 µg cyclosporine/day/eye

delivered from OTX-CSI then this amount is approximately 218 times lower than the dose demonstrated to be safe in beagle dogs in the 12 month repeat-dose toxicology study performed in support of Restasis® (NDA 021023).

Considering the highest daily cyclosporine release seen in the PK studies, the 4.4 µg/day release of cyclosporine from OTX-CSI (administered bilaterally) is approximately 68,000 times lower than the typical maintenance dose of 10 mg/kg/day in patients administered oral cyclosporine in transplantation treatment (Cequa NDA 210913). If all cyclosporine was released immediately following bilateral OTX-CSI administration, then this would still be 750-fold less than the daily maintenance dose of oral cyclosporine. A rat carcinogenicity study was performed in support of Sandimmune (NDA 050573), and the NOAEL was 0.5 mg/kg/day.

Because beagle dogs have an approximate 7-fold higher tear production rate than humans (7.8 vs 1.1 µL/min, respectively; (Williams, 2005; Tomlinson, 2005), the total amount of cyclosporine released in humans could be less than 3.5 µg/day due to reduced tear fluid lavage at the interface of the hydrogel matrix. On the other hand, the cyclosporine concentrations on the human ocular surface may be expected to be higher due to less tear fluid dilution. Human PK studies with OTX-CSI will be conducted to confirm the actual daily cyclosporine release in humans.

Ocular Therapeutix demonstrated ocular and systemic safety of bilateral administration of OTX-CSI in a single dose toxicity study in beagle dogs that were administered an exaggerated dose of 0.7 mg cyclosporine per eye, total of 1.4 mg per animal as summarized in Table 1. The inserts tested in the toxicity studies were much higher compared with the proposed clinical dose. Inserts in the GLP toxicology study were larger in size and greater in dose to achieve a maximal feasible dose of cyclosporine within the beagle canaliculus to attain a safety margin. A maximum feasible dose of approximately 0.7 mg cyclosporine per insert in the OTX-CSI assessed in the 90-day toxicity study in beagle dogs did not establish a maximum tolerated dose, thereby supporting the safe use of a 0.36 mg cyclosporine dose in clinical studies.

No systemic drug levels were observed in the beagle dog toxicology study and these results are consistent with studies evaluating topical eye drops. Therefore, there is no systemic safety concerns beyond those established for the oral dosing formulations.

Calculations of human equivalent dose (HED) of NOAELs and applications of safety factors used to calculate the ocular and systemic safety factors for the planned clinical dose of 0.36 mg/eye are presented in Table 1. Ocular HED is based on equivalence of eyes between humans and beagle dogs, and systemic HED is based on the dog to human conversion factor (1.8X) dose per unit weight per guidance (FDA, 2005).

The dose of 0.36 mg cyclosporine in OTX-CSI to be evaluated in the proposed clinical trial is appropriate and safe for testing based on OTX-CSI nonclinical studies performed by Ocular Therapeutix and supported by cyclosporine topical eye drops and oral dosage form studies in support of regulatory submissions and reported in the literature.

Table 1 Safety Margins for Ocular and Systemic Toxicity

NOAEL Study	Dose per Eye	Ocular Safety Factor for 0.36 mg Human Dose per Eye	Total Systemic Dose	Systemic HED	Systemic Safety Factor for 0.36 mg Bilateral Human Dose
"Tox Study" OTX-CSI 90-Day Toxicity Study with a 14 Day Recovery Period in male and female dogs (TP1408/ CSI-NC-Tox-2019-001)	0.7 mg/eye	1.9×[a]	0.18 mg/kg	0.10 mg/kg[b]	8.3×[c]
12-month repeat dose toxicology study in beagles from RESTASIS NDA 021023	0.96 mg/eye/day	218×[d]	NA	NA	NA
Oral cyclosporine maintenance dose in transplantation therapy patients	NA	NA	10 mg/kg/day	NA	68,000[e]

[a] Ocular safety factor is a direct comparison between beagle and human eyes.
[b] Systemic HED is derived by converting total systemic dose to mg/kg in beagles (8 kg) then dividing by a factor of 1.8 consistent with Example 3 in *FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*.
[c] The systemic safety factor is the systemic HED (0.10 mg/kg) times human weight (60 kg) divided by the proposed clinical dose of 0.36 mg administered bilaterally in patients.
[d] Ocular safety factor is a direct comparison between daily cyclosporine exposure in beagle eyes from Restasis repeat-dose 12-month safety studies compared to maximal daily amounts (4.4 µg/day) released from OTX-CSI in PK studies.
[e] Systemic safety factor is a direct comparison between daily cyclosporine dose used in transplantation therapy compared to maximal daily amounts (4.4 µg/day) released from OTX-CSI in beagle PK studies.

4.6 Compliance

This trial will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including the International Council on Harmonization (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 IPs in the countries involved will be adhered to.

4.7 Trial Population

Cohort 1 will consist of approximately 5 subjects diagnosed with DED enrolled into an open-label active study arm. In Cohort 2 approximately 140 subjects diagnosed with DED will be screened and randomly assigned to four treatment arms.

5 TRIAL OBJECTIVES

The objectives of the trial with respect to Cohort 1 are to assess the safety and tolerability of OTX-CSI in subjects with DED. The objectives of the trial with respect to Cohort 2 are to assess the safety, tolerability, and efficacy of OTX-CSI in subjects with DED.

6 TRIAL DESIGN

6.1 Description of Trial

This is a randomized, multi-center, double-masked, vehicle-controlled, phase 1/2 clinical study designed to evaluate the safety, tolerability, and efficacy of OTX-CSI (cyclosporine ophthalmic insert) for intracanalicular use for the treatment of subjects with DED. Approximately 145 subjects (290 eyes) will be enrolled in this study at approximately 15 sites in the US. Subjects will be enrolled in two cohorts. Cohort 1 will be an open-label group consisting of approximately 5 subjects. Cohort 2 will be a randomized, double-masked group consisting of approximately 140 subjects treated with 2 different hydrogel formulations of OTX-CSI and 2 different formulations of HV. Both eyes will be treated with the same treatment/formulation. If both eyes qualify, the eye having the higher total corneal fluorescein staining score will be designated as the study eye and the other eye designated as the non-study eye. If both eyes have the same total corneal fluorescein staining score, the study eye will be determined by the biostatistician prior to the analysis and will be detailed in the Statistical Analysis Plan. If only one eye qualifies, that eye will be the study eye, but both eyes will still receive the same treatment/formulation. Table 2 reflects the treatment assignment paradigm for both Cohorts.

Table 2 Treatment Assignment Paradigm for Cohorts 1 and 2

Cohort Number	Number of Subjects	Treatment	Formulation Number
1 Open-label	5	OTX-CSI	2A
2 Randomized, double-masked	40	OTX-CSI	1
	40	OTX-CSI	2A
	40	HV	2B
	20	HV	3

The recommendation to progress to Cohort 2 will be the responsibility of the Safety Review Group (SRG) which will be minimally comprised by a Principal Investigator(s) in the study, the study Medical Monitor and the Chief Medical Officer (CMO) at Ocular Therapeutix, Inc. The SRG (Appendix 2) may request the participation of an independent statistician and/or independent medical expert to assist in the assessment of the safety of the IP and the recommendation to progress. The SRG will review the Cohort 1 data to evaluate the safety of OTX-CSI Formulation 2A after all subjects have been followed for at least 2 weeks and will issue a recommendation whether or not to open enrollment in Cohort 2. The SRG may further convene at any time during the study if necessary.

Once subject eligibility has been determined, OTX-CSI or HV insert, as applicable, will be placed bilaterally, into either the superior or inferior canaliculus (per investigator's preference), during the Insertion/Day 1 (Visit 2) for all subjects who meet the eligibility criteria.

Cohort 1

Subjects in Cohort 1 will undergo Screening 14 days prior to Insertion/Day 1 (Visit 2) to determine eligibility and eligibility will be re-confirmed at Visit 2 (Insertion/Day 1). The treatment follow-up visits will occur at Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), Week 9 (Visit 6), Week 12 (Visit 7), and Week 16 (Visit 8). All subjects in Cohort 1 will be followed until Week 16 (Visit 8) whether or not an insert is visualized.

Cohort 2

Subjects in Cohort 2 will undergo Screening 14 days prior to Insertion/Day 1 (Visit 2) to determine eligibility. At Visit 2 (Insertion/Day 1) eligibility will be confirmed and subjects who are eligible will

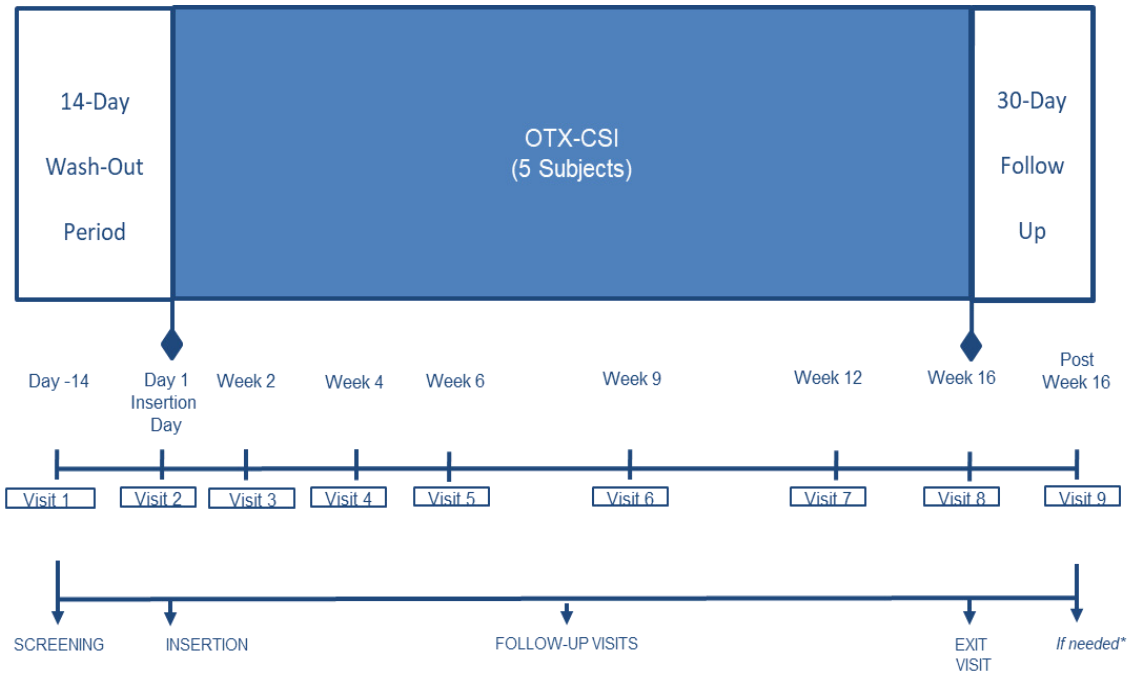
be randomly assigned to one of four treatment groups (OTX-CSI Formulation 1, OTX-CSI Formulation 2A, HV Formulation 2B or HV Formulation 3) in a 2:2:2:1 ratio. Should only a unilateral insertion be possible, Visit 2B will occur within 3 days to attempt the insertion again. The treatment follow-up visits will occur at Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), Week 9 (Visit 6), Week 12 (Visit 7), and Week 16 (Visit 8). All subjects in Cohort 2 will be followed until Week 16 (Visit 8) whether or not an insert is visualized.

For both cohorts, if an OTX-CSI or HV insert is visualized in either eye or both eyes at Week 16 (Visit 8) the subject will return to the clinic in 30 days (± 10 days; Visit 9) and will continue returning to the clinic every 30 days as needed until an insert can no longer be visualized and the physician has determined that there is no evidence of biological activity. Additionally, subjects may be exited any time at the investigator's discretion. If an OTX-CSI or HV insert cannot be visualized at Week 16 (Visit 8) and the physician has determined that there is no evidence of biological activity, the subject will exit the study.

This study will be conducted per the schedule shown in Figure 1.

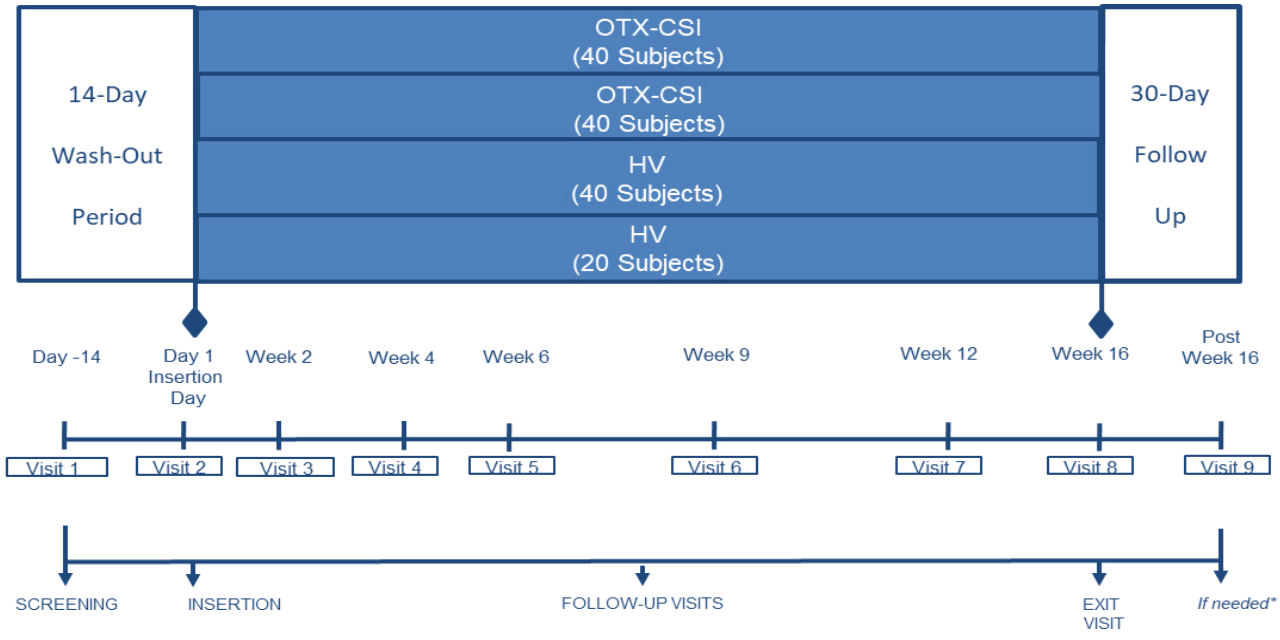
Figure 1 Cohort 1 and Cohort 2 Study Schematic

Cohort 1



*Subject remains in study until insert is no longer visible and no evidence of biological activity.

Cohort 2



*Subject remains in study until insert is no longer visible and no evidence of biological activity.

6.2 Study Endpoints

6.2.1 Safety Evaluations (Cohorts 1 and 2)

Primary:

- Non-ocular and Ocular Adverse Events (AEs)

Secondary:

- Best-Corrected Visual Acuity (BCVA)
- Slit Lamp Biomicroscopy (including punctum assessment)
- Intraocular Pressure (IOP)
- Fundus Examination
- Artificial tears use during the study

6.2.2 Efficacy Endpoints (Cohort 2 only):

6.2.2.1 Primary Efficacy Endpoints

- Schirmer Test (without anesthesia) change from baseline (CFB) and absolute value at Week 12.

6.2.2.2 Secondary Efficacy Endpoints

Signs:

- Percent of subjects with ≥10 mm increase in Schirmer at Week 12.
- Total Corneal Fluorescein Staining (tCFS) using NEI scale, CFB and absolute values at each post baseline study visit.
- CFS sub-regions using NEI scale, CFB and absolute values at each post-baseline visit.
- Conjunctival Lissamine Green Staining using NEI Scale, CFB and absolute values at each post-baseline visit.

Symptoms (subject-reported):

- Eye Dryness Score (visual analogue scale [VAS]), CFB and absolute values at each post-baseline visit.
- Ocular Surface Disease Index questionnaire (OSDI©) questionnaire, CFB and absolute values at each post-baseline visit (total score, each of the three domains, and the individual questions).
- SPEED questionnaire (overall score and individual questions), CFB at each post-baseline visit.

6.2.2.3 Exploratory Efficacy Endpoints

- Tear Film Break Up Time (TBUT), CFB at Week 12
- Presence of OTX-CSI or HV insert at all post-baseline visits
- Ease of insertion as assessed by the Investigator
- Ease of visualization as assessed by the Investigator

6.2.3 Supplementary Objectives

Systemic PK will be collected and analyzed from subjects at a subset of sites. Tear Film PK will be collected and analyzed at all sites.

6.3 Randomization and Blinding

Cohort 1 will be open-label and treatment assignment will be known to the sponsor, investigator and subjects. All 5 enrolled subjects in Cohort 1 will receive OTX-CSI Formulation 2A.

Cohort 2 will be randomized to treatment assignment and double-masked. If unmasking is required, the integrity of the study assessments and objectives will be maintained by limiting access to the unmasked data to the two individuals in the Safety Review Group (Sponsor Medical Monitor and Sponsor Statistician) who are not involved in the study conduct or directly by the investigator if required in an emergency.

A randomization schedule will be computer-generated by a qualified biostatistician independent of the study conduct or project team and uploaded into the EDC system. The EDC/IRT system will be used for randomization and unmasking.

The HV and OTX-CSI inserts administered to subjects at randomization in the double-masked treatment phase will be comparable in appearance. Study subjects and investigators and their staff will be masked to the identity of treatment until the final database is locked. The Sponsor's personnel involved with the conduct and monitoring of the study will remain masked until completion of the study and database lock.

Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme. Unless the subject's safety requires otherwise and if time permits, the decision to unmask a treatment assignment is to be made jointly by the Investigator and Sponsor's medical monitor.

6.4 Trial Treatment

Formulation 1– OTX-CSI 0.36 mg Cyclosporine Ophthalmic Insert

Formulation 2A – OTX-CSI 0.36 mg Cyclosporine Ophthalmic Insert

Formulation 2B – Hydrogel Vehicle Insert

Formulation 3 – Hydrogel Vehicle Insert

6.5 Trial Duration

An individual subject's participation in Cohort 1 and Cohort 2 will last approximately 18 weeks. After the trial, subjects will be treated per the standard of care, at the discretion of their physician.

Ongoing clinical investigational data will be reviewed by the Medical Monitor and/or the SRG. The clinical investigation may be suspended if the Medical Monitor and/or SRG, upon review and evaluation of the clinical data, finds the severity or incidence of adverse events or complications unacceptable for continuation of the investigation.

6.6 Trial Material Accountability

All IP required for this study will be provided by Ocular Therapeutix, Inc., or its designee. The recipient will acknowledge receipt of study drug, indicating shipment content and condition. Damaged supplies may be replaced upon notification to Ocular Therapeutix, Inc., or its designee. Accurate records of all IP administered by study site should be maintained and recorded. A study monitor will periodically check the supplies of IP held at the site to verify accountability of all IP. All used and unused IP (non-dispensed) will either be returned to Ocular Therapeutix, Inc., or its designee, or destroyed at the site upon written confirmation from Ocular Therapeutix, according to site procedures. The investigator must keep an accurate accounting of IP received from the supplier by maintaining a detailed inventory. This includes the amount of IP received by the site, amount administered to subjects, the amount destroyed

by the site and the amount returned to the sponsor or designee (as applicable), upon completion of the trial. All IP that is used during the course of the trial must be accounted for on a drug accountability form.

Accurate records of receipt and disposition of the IP (e.g., dates, subject number, kits used, kits unused, etc.) must be maintained by designated site personnel.

OTX-CSI and HV Inserts are sterile, ophthalmic inserts that are without antimicrobial preservatives. OTX-CSI and HV Inserts are provided in sterile, single use packages. The product is packaged in a hermetically sealed aluminum/polyester laminate pouch to maintain stability and sterility over time. The product is terminally sterilized and stored refrigerated.

At the investigational site, IP must be kept in a safe storage area with limited access (e.g., in a refrigerator in a locked/limited access area). The refrigerator should be temperature monitored. IP should be stored at controlled refrigerated temperatures from 2°C to 8°C and protected from light.

The IP must not be used outside of this clinical trial. The investigator or site personnel may not supply IP to other clinical sites, investigators, or subjects, or allow the IP to be used other than as directed by this protocol without prior authorization from Ocular Therapeutix, Inc.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

The trial will include approximately 145 subjects from approximately 15 sites.

7.1 Inclusion Criteria

Subjects will be eligible for study participation if they:

1. Provide written informed consent prior to performing any study procedures and are willing to comply with study requirements and the study visit schedule.
2. Are 18 years of age or older.
3. Have a self-reported history or clinically confirmed diagnosis of DED by an eye care professional in both eyes for ≥6 months.
4. Have ongoing DED, in the study eye at screening visit as defined by the following criteria:
    a. VAS eye dryness severity score of at least ≥30.

In the same qualifying eye or both eyes:

    b A Total Corneal Fluorescein Staining Score of ≥6 (NEI scale) and <15.

    c. Have a Schirmer score (unanesthetized) of >0 mm and ≤10 mm wetting at 5 minutes.

5. Have corrected visual acuity better than or equal to logarithm of the minimum angle of resolution (logMAR), +0.7 as assessed with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts in both eyes.
6. Are women of child-bearing potential (WOCBP) who are non-pregnant, non-lactating, and sexually inactive (abstinent) for 14 days prior to screening. And are willing to remain so through the last study visit. Alternatively, WOCBP who are not abstinent must have been using one of the following acceptable methods of birth control for the times specified:
    a. Intra-uterine device (IUD) in place for at least 3 months prior to screening and the desire to continue this method through the last study visit.

b. Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to screening and the desire to continue this method through the last study visit.

c. Stable hormonal contraceptive for at least 3 months prior to screening and the desire to continue this method through the last study visit.

d. Surgical sterilization (vasectomy) of partner for at least 6 months prior to Day 1.

7. Are postmenopausal women [i.e., no menstrual cycle for at least one year prior to Visit 1 (Screening)] or are women who have undergone 1 of the following sterilization procedures at least 6 months prior to Visit 1 (Screening):

   a. Bilateral tubal ligation

   b. Hysterectomy

   c. Hysterectomy with unilateral or bilateral oophorectomy

   d. Bilateral oophorectomy

8. Agree to the removal of non-dissolvable punctal plugs 4 weeks prior to the insertion visit (Day 1, Visit 2). Long-term dissolvable punctal plugs were not placed within 4 months prior to insertion visit (Day 1, Visit 2) and short-term dissolvable punctual plugs were not placed within 6 weeks prior to insertion (Day 1, Visit 2).

7.2 Exclusion Criteria

Subjects are not eligible for study participation if they:

1. Have a known or suspected allergy to any component of the study product.
2. Are unwilling to discontinue use of contact lenses for 4 weeks prior to the screening visit and throughout the study period.
3. Have any active systemic disease and/or systemic infection (e.g., fever or current antibiotic use), or uncontrolled medical condition that in the judgment of the investigator could confound study assessments or limit compliance.
4. Have a documented history of ocular allergies, which, in the judgment of the investigator, are likely to have an acute increase in severity during the duration of this trial. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted.
5. Have a history of neuropathic pain related to dry eye.
6. Have corneal erosive disease (e.g., multiple filaments, recurrent erosion syndrome) or other conditions suggestive of extensive damage of the cornea.
7. Have a history of glaucoma or ocular hypertension or have intraocular pressure (IOP) < 5 mmHg or > 24 mmHg or a history of elevated IOP within the past 6 months prior to the screening visit.
8. Have abnormal lid anatomy that may confound study data, in the judgement of the investigator.
9. Have a diagnosis of any of the following:

   a. Active ocular infection

   b. Uveitis

   c. Uncontrolled blepharitis (including severe MGD), in the judgement of the investigator

d. Moderate to severe pinguecula or pterygia, in the judgement of the investigator
e. Stevens-Johnson syndrome
f. Mucous membrane pemphigoid
g. Significant conjunctival scarring, in the judgement of the investigator
h. Chemical burn
i. Herpetic or neurotrophic keratitis
j. Congenitally absent lacrimal gland or meibomian glands
k. Nasolacrimal duct obstruction in either eye

10. Have had penetrating intraocular surgery in the past 6 months or require penetrating intraocular surgery during the study.
11. Have had eyelid surgery within 6 months prior to the screening visit.
12. Have had corneal laser refractive surgery, glaucoma surgery or corneal transplantation (full thickness, anterior or posterior).
13. Have had cauterization of the punctum resulting in complete occlusion of the punctum.
14. Have taken any of the following in either eye within 30 days prior to the screening visit:
    a. Topical ocular cyclosporine (e.g., Cequa®, Restasis®)
    b. Lifitegrast (Xiidra®)
    c. Autologous tears
    d. Topical ocular corticosteroids
    e. Topical ocular antibiotics
    f. Topical ocular NSAID
    g. Topical ocular antihistamines and/or mast cell stabilizers
    h. Topical or nasal vasoconstrictors
    i. Over The Counter (OTC) decongestants
    j. Intranasal Tear Neurostimulation
15. Have taken any of the following in either eye prior to the screening visit:
    a. Periocular injection of any corticosteroid solution – 3 months
    b. Corticosteroid intra-vitreal depot injection– 3 months
    c. Ozurdex– 6 months
    d. Retisert– 40 months
16. Have altered the dose of the following within 30 days prior to the screening visit (i.e., should keep dose stable throughout the study):
    a. Nutraceuticals or multivitamins
    b. Tetracycline compounds (tetracycline, doxycycline or minocycline)
    c. Inhaled, intramuscular or intra-articular corticosteroids (mouth or nasal spray form)

17. Have altered the dose of the following within 6 months prior to the screening visit (i.e., should keep dose stable throughout the study):
    a. Systemic anticholinergics
    b. Antidepressants (with the exception of rare usage as a sleep aid)
    c. Oral corticosteroids (e.g., prednisone. Prednisone dose must be less than 11 mg/day)
18. Have taken isotretinoin (Accutane) or systemic immunosuppressive agents within 6 months prior to the screening visit.
19. Are unwilling to withhold use of artificial tears (AT) for the duration of the trial.
20. Have participated in any other investigational study within 30 days of the screening visit or plans to participate in any other investigational study during the follow-up period.
21. Are an employee of the site or an immediate family member of an employee of the site.
22. Are a current smoker (including marijuana, cigar, cigarette, and/or e-cigarettes).
23. Have a known history of alcohol and/or drug abuse or are currently using illicit drugs or plan to use illicit drugs for the duration of the study. Recreational or medicinal marijuana allowed if oral consumption (no inhaled use).
24. Are unwilling or unable to comply with the study protocol.
25. The Investigator determines that the subject should not be included for reasons not already specified (e.g., systemic, behavioral, or other ocular disease/abnormality) if the health of the subject or the validity of the study outcomes may be compromised by the subject's enrollment.

7.3 Entry/Randomization Criteria:

To qualify for insertion at Day 1 (Visit 2), a subject must continue to meet all screening inclusion/exclusion criteria with the following exceptions/additions:

1. VAS eye dryness severity score ≥25
2. CFS total score ≥5 (NEI scale) and <15 in the same qualifying eye as Visit 1.
3. Subject must not have taken prohibited medications and have completed the appropriate washout of prior medications, if necessary.
4. Subjects who require AT use must not have administered >3 times/day for 3 consecutive days during the washout period (i.e. period between the screening and Day 1 visits.).

   NOTE: AT use is not permitted unless absolutely necessary. If subject requires AT use and has administered >3 times/for 3 days during the Screening period, they are not eligible for randomization.

7.4 Procedural Exclusion Criteria

Subjects are considered procedural screen failures if the investigator is unsuccessful at placing the OTX Ophthalmic insert in both eyes (i.e. neither eye has an insert). Procedural screen failures will be exited from the study at that time and will be included in the disposition tables as 'randomized, not treated'. Subjects will be followed per protocol if the investigator successfully places one insert.

Note: A subject with a successful unilateral insertion should return within three days to re-attempt insertion in the unsuccessful eye.

7.5 Subject Recruitment and Screening

Each subject that is screened will be assigned a Subject Identification (ID) consisting of a 2-digit Site number plus a 3-digit Subject number. The Subject ID will be used as the primary subject identifier for the duration of the study. For Cohort 2, once all inclusion and exclusion criteria are met at Visits 1 and 2, each qualifying subject will be randomized via the IRT system and will be assigned a randomization number.

The subject must sign the Informed Consent Form (ICF) before his or her participation in the study. A copy of the ICF must be provided to the subject or the subject's legal guardian. If applicable, it will be provided in a certified translation of the subject's first or native language. The original signed ICF for each participating subject shall be filed with records kept by the investigator and must be available for verification by study monitors at any time, and a copy will be given to each subject.

7.6 Withdrawal Criteria

Any subject who wishes to voluntarily discontinue study drug or withdraw from participation in the study for any reason is entitled to do so without obligation.

IP may be discontinued (insert removed) and any subject may be discontinued from study participation at any time during the study at the discretion of the Investigator or the Sponsor for any reason.

7.6.1 Withdrawal Methods

The Sponsor may terminate this study at any time. Reasons for termination may include but are not limited to, the following:

- The incidence or severity of adverse events (AE) in this or other studies point to a potential health hazard for trial subjects.
- Insufficient subject enrollment.
- Any information becoming available during the study that substantially changes the expected benefit risk profile of the study treatments.

7.6.2 Collection of Data from Withdrawn Subjects

In the event that study discontinuation of a randomized subject is necessary, the Investigator should make every attempt to have the subject complete Visit 8 assessments as soon as possible. The reason for premature discontinuation should be recorded in the subject chart and entered in the eCRF.

7.6.3 Subject Replacement

Subjects who withdraw from Cohort 1 will be replaced. Subjects who withdraw from Cohort 2 will not be replaced.

8 SUBJECT TREATMENT

8.1 Treatment Regimen

OTX-CSI contains 0.36 mg of micronized cyclosporine in a resorbable hydrogel matrix. It is intended to be inserted at Visit 2 and retained in the inferior or superior vertical canaliculus where it then provides sustained release of therapeutic levels of cyclosporine over approximately 12 weeks.

8.2 Prior and Concomitant Therapy

Only sponsor provided preservative free artificial tears may be used as needed (PRN), if absolutely needed, during the study. Use of AT will be discouraged, and subjects will be counseled to administer only if absolutely necessary. Further, if used, subjects will be instructed not to administer AT with 2 hours prior to any study visit. Preservative-free AT use will be recorded by subjects in a daily diary. All other tears substitutes are not permitted.

Table 3 List of Prohibited Medications

Medication	Minimum Washout Period Prior to Screening (Visit 1)
Topical ocular cyclosporine (e.g., Cequa®, Restasis®)	30 days
Lifitegrast (Xiidra®)	30 days
Autolgous tears	30 days
Topical ocular corticosteroids	30 days
Topical ocular antibiotics	30 days
Topical ocular NSAID	30 days
Topical ocular antihistamines and/or mast cell stabilizers	30 days
Topical or nasal vasoconstrictors	30 days
Intranasal Tear Neurostimulation	30 days
Periocular injection of any corticosteroid	90 days
Corticosteroid intra-vitreal depot injection	90 days
Ozurdex	6 months
Retisert	40 months
Isotretinoin	6 months
Systemic Immunosuppressants	6 months

8.3 Study Assessments by Visit

For every visit, perform study procedures as referenced in the Schedule of Events (Appendix 1) in the order specified below in both eyes. Note: Procedures will apply to both Cohort 1 and Cohort 2 unless otherwise indicated. An asterisk (*) indicates the assessment may occur at any time during the visit.

8.3.1 Visit 1 (14 days prior to Day 1) Screening/Baseline Visit

Note: In rare cases, the Screening Visit can be split into 2 consecutive days.

- Informed consent
- Demographics *
- Medical/ophthalmic history *
- Record concomitant medications *
- Urine pregnancy test * (may be performed at any time during the visit for WOCBP only)
- VAS for Eye Dryness (Appendix 3)
- OSDI (Appendix 4)
- SPEED assessment (Appendix 5)
- BCVA assessment (Appendix 8)
- Slit lamp biomicroscopy (including punctum assessment) (Appendix 9)
- TBUT (Appendix 11)
- Corneal fluorescein staining (NEI scale) (Appendix 6)

Conjunctival Lissamine Green Staining (NEI scale) (Appendix 7)

- Schirmer Test (without anesthesia) (Appendix 12)

Note: Wait 20 minutes prior to conducting Schirmer

- IOP
- Dilated fundus exam
- Determine Eligibility
- Dispense artificial tears (as needed)
  Note: Subjects will be provided with sponsor supplied Preservative Free Artificial Tear Substitutes but instructed to use only if necessary. If used, instillation will be recorded in a daily diary. Subjects will also be asked to withhold the tears within two hours of study visits.
- Dispense Daily Subject Diary for Artificial Tears Use (as needed) (Appendix 16)

Note: All ophthalmic assessments must be performed on both eyes.

8.3.2 Visit 2 Insertion/Day 1

- Record concomitant medications *
- Record AEs
  Note: Any signs, symptoms or conditions captured prior to the insertion of IP, will be recorded as medical history.
- Collect and review Subject Daily Diary for Artificial Tears Use (as needed)
  Note: Subjects using AT > 3x/day for 3 consecutive days will be ineligible for randomization.
- VAS for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
  Note: Prior to insertion, a clinical determination of the absence of infection will be made based on the lack of erythema or discharge at the punctum.
- Punctum Size Assessment
- TBUT
- Corneal fluorescein staining (NEI scale)
- Conjunctival Lissamine Green Staining (NEI scale)
  Schirmer Test (without anesthesia)
  Note: Wait 20 minutes prior to conducting Schirmer
- IOP
- Determine Eligibility for Insertion (Cohort 1 and 2) and Randomization (Cohort 2)
- OTX-CSI or HV Insert Placement (Appendix 13)
  Note: If placement is only successful in one eye, subjects should be asked to return within 0-3 days to re-attempt insertion in the other eye.
- Ease of Insertion Assessment
- Systemic PK (at selected sites – to be collected 2 hours (±30 minutes) **or** 4 hours (±30 minutes) post-insertion) (Appendix 10)
- Tear film PK (to be collected 1 hour (±30 minutes), 2 hours (±30 minutes) and 4 hours (±30 minutes) post-insertion)
- Dispense artificial tears (as needed)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed)

Note: All ophthalmic assessments must be performed on both eyes.

8.3.3 Visit 2B (Day 1 + 1 to 3 days)

This visit should be conducted for subjects with a successful unilateral insertion at Visit 2 (Day 1) to re-attempt insertion in the other eye. The following assessments should be performed at this visit:

- OTX-CSI or HV Insert Placement (Appendix 13)
- Ease of Insertion Assessment
- Systemic PK (at selected sites – to be collected 2 hours (±30 minutes) **or** 4 hours (±30 minutes) post-insertion) (Appendix 10)
- Tear film PK (to be collected 1 hour (±30 minutes), 2 hours (±30 minutes) and 4 hours (±30 minutes) post-insertion)

8.3.4 Follow-Up Visit 3 (Week 2 ±2 days)

- Record concomitant medications *
- Record AEs *
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed) *
- VAS for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- OTX-CSI or HV Insert Presence by visual Assessment
- Ease of Visualization by Investigator (Appendix 14)
- Corneal fluorescein staining (NEI scale)
- Conjunctival Lissamine Green Staining (NEI scale)
- Systemic PK (at selected sites)

Note: Wait 20 minutes prior to conducting Schirmer/Tear Film PK

- Schirmer Test (without anesthesia) and Tear Film PK
- Dispense artificial tears (as needed)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed)

Note: All ophthalmic assessments must be performed on both eyes.

8.3.5 Follow-Up Visit 4 (Week 4 ±2 days)

- Record concomitant medications *
- Record AEs*
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed) *
- VAS for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- OTX-CSI or HV Insert Presence by visual Assessment
- Ease of Visualization by Investigator
- Corneal fluorescein staining (NEI scale)
- Conjunctival Lissamine Green Staining (NEI scale) Schirmer Test (without anesthesia) and Tear Film PK

Note: Wait 20 minutes prior to conducting Schirmer/Tear Film PK

- Dispense artificial tears (as needed)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed)

Note: All ophthalmic assessments must be performed on both eyes.

8.3.6 Follow-Up Visit 5 (Week 6 ±3 days)

- Record concomitant medications *
- Record AEs *
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed) *
- VAS for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- OTX-CSI or HV Insert Presence by visual Assessment
- Ease of Visualization by Investigator
- TBUT
- Corneal fluorescein staining (NEI scale)

  Conjunctival Lissamine Green Staining (NEI scale)Schirmer Test (without anesthesia)/Tear Film PK

  Note: Wait 20 minutes prior to conducting Schirmer/Tear Film PK

- Dispense artificial tears (as needed)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed)

Note: All ophthalmic assessments must be performed on both eyes.

8.3.7 Follow-Up Visit 6 (Week 9 ±3 days)

- Record concomitant medications *
- Record AEs *
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed) *
- VAS for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- OTX-CSI or HV Insert Presence by visual Assessment
- Ease of Visualization by Investigator
- Corneal fluorescein staining (NEI scale)
- Conjunctival Lissamine Green Staining (NEI scale)
- Schirmer Test (without anesthesia) and Tear Film PK

Note: Wait 20 minutes prior to conducting Schirmer/Tear Film PK

- Dispense artificial tears (as needed)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed)

Note: All ophthalmic assessments must be performed on both eyes.

8.3.8 Follow-Up Visit 7 (Week 12 ±3 days)

- Record concomitant medications *
- Record AEs *
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed) *
- VAS for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- OTX-CSI or HV Insert Presence by visual Assessment
- Ease of Visualization by Investigator
- TBUT
- Corneal fluorescein staining (NEI scale)
- Conjunctival Lissamine Green Staining (NEI scale)
- Schirmer Test (without anesthesia) and Tear Film PK
  Note: Wait 20 minutes prior to conducting Schirmer/Tear Film PK
- Dispense artificial tears (as needed)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed)

Note: All ophthalmic assessments must be performed on both eyes.

8.3.9 Final Visit 8 (Week 16 ±3 days)

- Record concomitant medications *
- Record AEs *
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed) *
- Urine pregnancy test (WOCBP only)
- VAS for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- OTX-CSI or HV Insert Presence by visual Assessment
- Ease of Visualization by Investigator
- Corneal fluorescein staining (NEI scale)
- Conjunctival Lissamine Green Staining (NEI scale)
- Schirmer Test (without anesthesia) and Tear Film PK

Note: Wait 20 minutes prior to conducting Schirmer/Tear Film PK

- Undilated Fundus Exam (*may be performed before or after IOP)
- IOP
- Punctum Size Assessment
- Dispense artificial tears (as needed)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed)

Note: All ophthalmic assessments must be performed on both eyes.

8.3.10 30-day Follow-Up Visit (Week 20 ± 10 days)

This visit will be conducted every 30 days (± 10 days) until an insert can no longer be visualized and the physician has determined that there is no evidence of biological activity.

- Record concomitant medications *
- Record AEs *
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed) *
- VAS for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- OTX-CSI or HV Insert Presence by visual Assessment
- Ease of Visualization by Investigator
- Corneal fluorescein staining (NEI scale)
- Conjunctival Lissamine Green Staining (NEI scale)
  Schirmer Test (without anesthesia) and Tear Film PK
  Note: Wait 20 minutes prior to conducting Schirmer/Tear Film PK
- Dispense artificial tears (as needed)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed)

Note: All ophthalmic assessments must be performed on both eyes.

8.3.11 Replacement of Inserts

For Cohort 1 subjects only, within the first six weeks post treatment, if an insert is not visualized in one or both eyes by the Investigator, the Investigator should place a new insert in the respective eye(s) after confirming patency. Refer to Appendix 13 for placement instructions. Replacement of inserts is not permitted for subjects enrolled in Cohort 2.

8.3.12 Unscheduled Visit

An unscheduled visit may be performed during the course of the trial in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages.

Evaluations that may be conducted at an Unscheduled Visit may include:

- Slit lamp biomicroscopy
- BCVA assessment
- IOP
- Dilated or Undilated fundus exam
- Urine pregnancy test (if applicable)
- Assessment of AEs
- Assessment of concomitant medications and/or treatments
- Any other assessments needed in the judgment of the investigator

9 ASSESSMENT OF EFFICACY

9.1 Efficacy Parameters

The efficacy assessments of the study are listed below and will be performed per the Schedule of Events in Appendix 1. All clinical efficacy assessments should be performed in both eyes. Efficacy assessments should be performed by the same person, e.g., FCS scoring for a given subject should be performed by the same person at each visit if possible.

The following efficacy measures will be assessed:

Signs

- Percent of subjects with ≥10 mm increase in Schirmer at Week 12.
- Schirmer Test (without anesthesia) change from baseline (CFB) and absolute value at Week 12.
- Total Corneal Fluorescein Staining (tCFS) using NEI scale, CFB and absolute values at each post baseline study visit.
- CFS sub-regions using NEI scale, CFB and absolute values at each post-baseline visit.
- Conjunctival Lissamine Green Staining using NEI Scale, CFB and absolute values at each post-baseline visit.

Symptoms (subject-reported)

- Eye Dryness Score (visual analogue scale [VAS]), CFB and absolute values at each post-baseline visit.
- Ocular Surface Disease Index questionnaire (OSDI©) questionnaire, CFB and absolute values at each post-baseline visit (total score and each of the three domains).
- SPEED questionnaire, CFB at each post-baseline visit.

Other Efficacy Evaluations

- Tear Film Break Up Time (TBUT), CFB at Week 12.
- Presence of OTX-CSI or HV insert at all post-baseline visits.
- Ease of insertion as assessed by the Investigator.
- Ease of visualization as assessed by the Investigator.

10 ADVERSE EVENTS

The investigator and study staff are responsible for detecting and recording AEs and SAEs, during scheduled safety evaluations and whenever such information is brought to their attention.

This section of the protocol provides definitions and detailed procedures to be followed.

During each visit, the Investigator will question the subject about adverse events using an open question taking care not to influence the subject's answers. Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided. At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

10.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Examples of an AE include:

- Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after IP administration even though it may have been present prior to the start of the study.
- Signs, symptoms of a drug interaction.

- Signs, symptoms of a suspected overdose of either IP or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- A laboratory abnormality occurring after the start of the study (i.e., after insertion) that results in subject withdrawal from the study or medical treatment or further follow-up.

10.2 Definition of Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
  Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalizations for elective surgeries do not constitute an SAE.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered SAEs, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above.

10.3 Disease-Related Events or Outcomes Not Qualifying as AE/SAE's

Not applicable.

10.4 Monitoring and Recording of AEs and SAEs

10.4.1 Adverse Events

Any AE experienced by the subject from Visit 2 (Insertion/Day 1) through Visit 9 (30-day follow-up visit) is to be recorded in the eCRF, regardless of the severity of the event or its relationship to study treatment.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits, as necessary. If these have resolved, this should be documented.

Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started).

10.4.2 Serious Adverse Events

Any SAE experienced by the subject from Visit 2 (Insertion/Day 1) through Visit 9 (30-day follow-up visit) is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment.

Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

10.4.3 All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 10.2.

- The severity of the event as defined in Section 10.7.1.
- The relationship of the event to study treatment as defined in Section 10.7.2.

10.5 Immediate Reporting of Serious Adverse Events and Pregnancies

In order to adhere to all applicable laws and regulations for reporting an SAE or pregnancy, the study site must formally notify the pharmacovigilance team within 24 hours of the study site staff becoming aware of the SAE or pregnancy. It is the Investigator's responsibility to ensure that the SAE or pregnancy reporting information is emailed or faxed as described in Figure 2. It may be necessary for the pharmacovigilance team to directly communicate with the Investigator if additional information is required.

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to the pharmacovigilance team on the subject's condition within 24 hours. New or updated information will be recorded on the SAE reporting form. The updated SAE reporting form should be sent to the pharmacovigilance team within 24 hours as described in Figure 2.

All additional follow-up evaluations must be reported to the pharmacovigilance team. Such data should be sent by fax or email (Figure 2) within 10 calendar days. All SAEs will be followed until the Investigator and Ocular Therapeutix agree that the event is satisfactorily resolved.

10.6 Death

The death must be recorded on the appropriate eCRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the pharmacovigilance team.

Figure 2 Reporting Information for SAEs and Pregnancies

To report initial or follow up SAE or Pregnancy information email or fax a copy of the SAE or Pregnancy report form to the following:

ProPharma Group

Email: clinicalsafety@propharmagroup.com

Fax: +1-866-681-1063

10.7 Evaluating AEs and SAEs

10.7.1 Severity

The following definitions should be considered when evaluating the severity of AEs and SAEs.

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.

For AEs that change in intensity, the start and stop date of each intensity should be recorded.

An AE that is assessed as severe should not be confused with a SAE. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.2 Definition of a SAE.

10.7.2 Relationship to OTX-CSI or Hydrogel Vehicle product or procedure

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Unrelated	This category applies to those (S)AEs which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.); there is no reasonable probability that the (S)AE may have been caused by the insertion procedure or the ophthalmic insert. If the investigator determines that the AE is unlikely to be related to the study drug, then this would be the appropriate category.
Related	The following criteria should be applied in considering inclusion of an (S)AE in this category: i. It bears a reasonable temporal relationship to the insertion procedure or the presence of the ophthalmic insert ii. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other factors (e.g., disease under study, concurrent disease(s) and concomitant medications) and modes of therapy administered to the subject iii. It disappears or decreases on removal of the ophthalmic insert iv. It follows a known pattern of response to the insertion procedure or the ophthalmic insert

10.7.3 Expectedness of Events

Expectedness of all AEs will be determined according to the Investigator's Brochure as determined by Ocular Therapeutix, Inc.

10.8 Pre-scheduled or elective Procedures or Routinely Scheduled Treatments

A pre-scheduled or elective procedure or routinely scheduled treatment will not be allowed during the study period.

10.9 Procedures for Handling Special Situations

10.9.1 Pregnancy

Females should not become pregnant during the study period. If this occurs the subject should notify the Investigator immediately. The Investigator must report the pregnancy as outlined in Section 10.5. In addition, the Investigator or study site staff must report the outcome of the pregnancy to the pharmacovigilance team.

10.9.2 Unmasking for Medical Emergencies

In the case of a medical emergency or occurrence of an SAE, the randomization code may be unmasked and made available to the Investigator, Sponsor, and/or other study personnel involved in the conduct of

the study. In the absence of medical need, the randomization code will not be available to the above individuals until after the study is completed and the database is locked.

In the event of a medical need, the Investigator will treat each subject, as medically required. If the Investigator feels it is necessary to unmask a subject's treatment assignment after an emergency situation, the Investigator may call the Medical Monitor and notify the Sponsor. The treatment assignment will be revealed on a subject-by-subject basis with the approval of the Medical Monitor and Sponsor, thus leaving the masking of the remaining subjects intact. Ocular Therapeutix will make the final determination if the unmasking request will be granted. Once the unmasking request is granted the investigator or designee should use the IRT system to unmask the subject's randomization code. The investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with breaking the mask must be recorded and reported as specified in this protocol.

Subjects will have the IP removed (Appendix 15) immediately if treatment assignment is unmasked.

10.9.3 Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Ocular Therapeutix to be associated to the study treatment administered. Ocular Therapeutix will report SUSARs to the appropriate authorities within the required regulatory timeframes. Reports of SUSARs will be made to IRBs, and Investigators, as needed.

11 STATISTICAL METHODS AND DATA ANALYSIS

11.1 Statistical Methods

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Summaries for discrete variables will include frequencies and percentages. The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment. Differences between treatment groups will be calculated as OTX-CSI minus HV and change from baseline will be calculated as follow-up visit minus baseline visit values.

11.2 Unit of Analysis

Both eyes will be treated with the same treatment/formulation. If both eyes qualify, the eye having the higher total corneal fluorescein staining score will be designated as the study eye and the other eye designated as the non-study eye. If both eyes have the same total corneal fluorescein staining score, the study eye will be determined by the biostatistician prior to the analysis and will be detailed in the Statistical Analysis Plan. If only one eye qualifies, that eye will be the study eye, but both eyes will still receive the same treatment/formulation.

The unit of analysis in this study will be the primary study eye for all efficacy summaries. Efficacy summaries will be presented for the primary study eye for Cohort 2 only. Cohort 1 will be included for all safety summaries and will include summaries of the secondary study eye. Additional analyses may be presented for the secondary study eye. All summaries will be presented by treatment group and visit, where appropriate. In addition to looking at the individual formulations, the two formulations of OTX-CSI and HV will be combined and summarized.

11.3 Sample Size Determination

No formal sample size calculations were performed. The proposed sample size will allow for initial estimates of efficacy as well as provide for sufficient safety information to be obtained, while still limiting the number of subjects exposed to the IP.

11.4 Statistical Significance

All statistical testing will be done at the two-sided alpha level of 0.05. As this is a Phase 1/2 study, no adjustments to alpha will be made for testing of multiple endpoints.

11.5 Trial Termination

Should it become apparent during the trial that there is a significant safety concern or there is an issue with enrollment, the trial may be terminated. In addition, should information become known during the course of the trial that would negatively impact the trial, the trial may be terminated. In addition, the FDA or another regulatory authority may terminate the trial.

11.6 Missing Data

The primary analyses of efficacy data will use Markov Chain Monte Carlo (MCMC) multiple imputation methodology to impute missing data. Sensitivity analyses, to determine robustness of results, will be performed using last observation carried forward (LOCF) and observed data only.

11.7 Efficacy Analyses

The primary efficacy endpoint analysis of Schirmer Test will use a linear model with fixed effects of baseline Schirmer Test value and treatment will be used to compare Schirmer Test change from baseline and absolute values with least square means comparing OTX-CSI treatment groups to HV treatment groups at each visit. In addition to looking at the individual formulations, the two formulations of OTX-CSI and HV will be combined and a linear model, two-sample t-test and Wilcoxon rank sum test will be performed at each visit.

Secondary efficacy endpoint analyses of Total Corneal Fluorescein Staining (tCFS) using NEI scale, CFS sub-regions using NEI scale, Conjunctival Lissamine Green Staining using NEI scale, Eye Dryness Score (VAS) and Ocular Surface Disease Index questionnaire (total score, each of the three domains and the individual questions) will be analyzed similar to the Schirmer Test. Speed measures (overall score and individual questions) will also be analyzed similarly, however only change from baseline will be presented. Percent of subjects with ≥10 mm increase in Schirmer at Week 12 will be analyzed using a chi-squared test.

11.8 Exploratory Analyses

Tear Film Break Up Time at Week 12 will be analyzed similar to the Schirmer Test, however only observed data will be used. Presence of insert, ease of insertion as assessed by the Investigator and ease of visualization as assessed by the Investigator at all post-baseline visits will be summarized using discrete statistics and will be tested between treatment groups (all treatment groups separately and combined) using the Pearson chi-squared statistic.

11.9 Reporting Deviations

Should there be changes in any analyses described in the protocol, the statistical analysis plan will document them. Should there be changes in any analyses described in the statistical analysis plan, the final clinical study report will describe them.

11.10 Subject Population(s) for Analysis

Intent-to-Treat (ITT): The ITT population will include all randomized subjects. Analysis on the ITT population will be used as the primary efficacy analysis and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized.

Per Protocol (PP): The PP population will include all ITT subjects who do not deviate from the protocol in any way likely to seriously affect the efficacy outcomes of the study. Analysis on the PP population will be used as secondary efficacy analysis and will be performed for select efficacy endpoints, analyzing subjects under the treatment actually received. Important protocol deviations will be identified prior to locking the study database.

Safety: The Safety population will include all subjects who received IP (OTX-CSI or HV). Analyses performed on the Safety population will be according to the treatment the subject actually received.

12 STUDY MANAGEMENT AND DATA COLLECTION

12.1 Confidentiality

All trial subject data collected and processed for the purposes of this trial 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 CRO, drug safety, the sponsor, the IRB/IEC approving this trial, the FDA, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the trial subject's original medical and trial 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 trial 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.

12.2 Source Documents

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

12.3 Case Report Forms

All subject data will be captured in the subject source documents which will be transcribed to the eCRFs. The investigator is responsible for ensuring that trial data is completely and accurately recorded on each subject's eCRF, source documents, and all trial-related materials. All trial data should also be attributable, legible, contemporaneous, original, accurate and complete. Recorded data 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.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements and will be performed only by staff that have been trained on the system and have access

to the system. Minimal data will be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the trial and database lock, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each investigator site to be maintained on file by the investigator.

12.4 Records Retention

All trial related correspondence, subject records, consent forms, record of the distribution and use of all IP and copies of case report forms 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. The investigator must notify the sponsor prior to destroying trial documentation even after the above-mentioned time has passed.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping trial 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.

13 STUDY MONITORING, AUDITING, AND INSPECTING

13.1 Study Monitoring Plan

Each investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by Ocular Therapeutix, Inc., prior to seeking approval from the IRB/Ethics Committee. Investigators' proficiency in observing and scoring ophthalmic observations will be established and documented via review of academic training and experience, prior to examining subjects. Each investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. During study conduct, Ocular Therapeutix, Inc and/or its representative will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors may review source documents to confirm that the data recorded on the electronic case report forms (eCRFs) are accurate. Further details of the trial monitoring (including medical monitoring) will be outlined in a monitoring plan.

The investigator and institution will allow Ocular Therapeutix, Inc., monitors or its representatives and appropriate regulatory authorities direct access to source documents and CRFs to perform this verification. Data Managers will also review data and may interact with site personnel for clarifications.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

14 ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of International Council on Harmonization, Good Clinical Practice Guideline, Research Ethics Committee regulations, any applicable government regulations, Trust and Research Office policies and procedures.

This protocol, the ICF, relevant supporting information, and all types of subject recruitment or advertisement information must be submitted to the IRB/Ethics Committee for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the IRB/Ethics Committee prior to implementing changes in the study. The investigator is responsible for

keeping the IRB/Ethics Committee apprised of the progress of the study, any SAEs, and any changes made to the protocol according to the requirements of the site's IRB.

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Appendix 1 Time and Events Schedule

See Section 8.3 for order of assessments.

Study Parameter*	Screening/ Baseline Visit Day -14	Insertion Day Day 1	Follow-up Week 2 ±2 days	Follow-up Week 4 ±2 days	Follow-up Week 6 ±3 days	Follow-up Week 9 ±3 days	Follow-up Week 12 ±3 days	Final Visit Week 16[8] ±3 days	30-Day Follow-Up Visit[9] (± 10 days)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Informed Consent	X								
Determine Eligibility	X	X							
Demographic Information	X								
Medical/Ophthalmic History	X								
Record Medications	X	X	X	X	X	X	X	X	X
Record Adverse Events[10]		X	X	X	X	X	X	X	X
Urine Pregnancy Test[1]	X							X	
OSDI	X	X	X	X	X	X	X	X	X
VAS for Eye Dryness	X	X	X	X	X	X	X	X	X
SPEED	X	X	X	X	X	X	X	X	X
Corneal Fluorescein Staining Using the NEI Scale	X	X	X	X	X	X	X	X	X
Conjunctival Lissamine Green Staining Using the NEI Scale	X	X	X	X	X	X	X	X	X
Assessment of BCVA	X	X	X	X	X	X	X	X	X
Slit Lamp Biomicroscopy (including punctum assessment)	X	X[4]	X	X	X	X	X	X	X
OTX-CSI or HV Insert Presence by Visual Assessment			X	X	X	X	X	X	X
Ease of Visualization as assessed by Investigator			X	X	X	X	X	X	X
Systemic PK sample collection[2] (at selected sites)		X[5]	X						
Tear Film PK sample collection[7] (at all sites)		X[6]	X	X	X	X	X	X	X
Measurement of TBUT	X	X			X		X		
Schirmer Test (without anesthesia)	X	X	X	X	X	X	X	X	X
IOP Measurement	X	X						X	
Fundus Exam[3]	X							X	

Study Parameter*	Screening/ Baseline Visit Day -14	Insertion Day Day 1	Follow-up Week 2 ±2 days	Follow-up Week 4 ±2 days	Follow-up Week 6 ±3 days	Follow-up Week 9 ±3 days	Follow-up Week 12 ±3 days	Final Visit Week 16[8] ±3 days	30-Day Follow-Up Visit[9] (± 10 days)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Punctum Size Assessment		X						X	
Randomization (Cohort 2)		X							
OTX-CSI or HV Insert Placement		X[11 & 12]							
Ease of Insertion as assessed by the Investigator		X							
Dispense Artificial Tears (as needed)	X	X	X	X	X	X	X	X	X
Dispense Daily Subject Diary for Artificial Tear Use (as needed)	X	X	X	X	X	X	X	X	X
Collect/review Daily Subject Diary for Artificial Tear Use (as needed)		X	X	X	X	X	X	X	X

*All examinations need to be performed on both eyes. See Section 8.4 to confirm the order that the assessments should be performed.

1 A negative UPT is required for women of childbearing potential to be included in the study.
2 Select sites will collect Systemic PK. All sites will collect Tear Film PK.
3 Dilated fundus examination at screening; undilated fundus examination at Week 16.
4 Prior to insertion, a clinical determination of the absence of infection will be made based on the lack of erythema or discharge at the punctum.
5 Systemic PK sample on Day 1 will be collected after successful insertion at 2 hours (±30 minutes) **or** 4 hours (±30 minutes) post-insertion.
6 Tear Film PK will be collected at 1 hour (±30 minutes), 2 hours (±30 minutes), and 4 hours (±30 minutes) post insertion on Day1. Tear Film PK should be collected using Schirmer strips.
7 Tear Film PK will be collected using Schirmer Tests strips. These will be collected and sent to the central lab for analysis. See lab manual.
8 Early termination subjects should complete assessments based on the final visit (Visit 8) schedule of assessments.
9 Post week 16 visit will be conducted every 30 days (± 10 days) until an insert can no longer be visualized and the physician has determined that there is no evidence of biological activity. Additionally, subjects may be exited at the investigator's discretion.
10 Signs, symptoms, conditions occurring prior to insertion on Day 1 should be captured as medical history.
11 For Cohort 1 subjects only, within the first six weeks post treatment, if an insert is not visualized in one or both eyes by the Investigator, the Investigator should place a new insert in the respective eye(s) after confirming patency. Refer to Appendix 13 for placement instructions. Replacement of inserts for Cohort 2 subjects is not permitted.
12 If placement is only successful in one eye, subjects should be asked to return within 1-3 days to attempt insertion in the other eye. The following items should be repeated at the return visit, Insert Placement, Ease of Insertion, Tear Film PK and AEs.

Appendix 2 Safety Review Group Charter

The recommendation to continue into Cohort 2 (double-masked, vehicle-controlled, portion of the study) will be the responsibility of a Safety Review Group constituted by the Principal Investigator(s) of the study, the Medical Monitor and the Chief Medical Officer at Ocular Therapeutix, Inc. The SRG, may request the participation of an independent statistician and/or independent medical expert to assist in the assessment of the safety of the IP and the recommendation to progress.

In order to maintain the integrity of the trial, unless it is absolutely necessary, the safety review should be conducted using masked subject-specific information. The Safety Review Group will convene after all subjects in Cohort 1 have been followed for at least 2 weeks (or at any time during the study if necessary) to evaluate the safety of the IP. Upon review and evaluation, the SRG will issue a recommendation to Ocular Therapeutix, Inc.

General guidelines for the recommendation to escalate to the next cohort:

A recommendation to escalate to the next cohort may be issued if no more than 1 dose limiting toxicity (DLT) is found during or at the end of the cohort.

Indicators of DLT in this study will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0, Published November 27, 2017).

A DLT is defined as one of the following events at the specified toxicity level deemed by the Investigator to be related to OTX-CSI and based on CTCAE (version 5.0)[1]

- Any Grade 3 or higher adverse event
- Any Grade 2 or higher adverse event that in the judgment of the Investigator or Sponsor requires discontinuation of dosing
- Any Grade 2 or higher adverse event that in the judgment of the Investigator or Sponsor requires further investigation before determining dose escalation.

Events, including serious adverse events (SAEs), deemed by the Investigator to be related to the subject's underlying medical condition, will not be considered DLTs and used for determination of dose escalation, e.g., hyperglycemic event.

[1] Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE.

Recommendations:

The recommendations of the Safety Review Group to Ocular Therapeutix, Inc. may include:

- Escalate to Cohort 2
- Repeat Cohort 1
- Amend the protocol
- Stop the study

If the safety data obtained in Cohort 1 warrants continuation of the study and initiation of Cohort 2, the Safety Review Group will issue a memorandum to Ocular Therapeutix, Inc. recommending continuing to Cohort 2.

If a review of Cohort 2 data is required and upon the review of the masked safety information, the Safety Review Group requires unmasked information in order to ensure the safeguard of the interests of the study subjects, the unmasked information will be provided. Please refer to Section 10.9.2 for unmasking procedures.

The Safety Review Group will make every effort to arrive to a recommendation by consensus.

Ocular Therapeutix, Inc. representatives then will make a decision that is consistent primarily with the safeguard of the interests of the study subjects.

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images. **Navigational Note:** -					
Cataract	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); glare symptoms affecting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated. **Navigational Note:** -					
Corneal ulcer	-	-	Corneal ulcer without perforation in the affected eye	Perforation in the affected eye	-
Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber. **Navigational Note:** -					
Dry eye	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	-	-
Definition: A disorder characterized by dryness of the cornea and conjunctiva. **Navigational Note:** If corneal ulcer is present, grade under Eye disorders: Corneal ulcer.					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Extraocular muscle paresis	Asymptomatic; clinical or diagnostic observations only	Unilateral paresis without double vision	Bilateral paresis or unilateral paresis causing double vision in peripheral gaze, but not in central gaze	Bilateral paresis requiring head turning to see beyond central 60 degrees or double vision in central gaze	-
Definition: A disorder characterized by incomplete paralysis of an extraocular muscle. **Navigational Note:** -					
Eye pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the eye. **Navigational Note:** -					
Eyelid function disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by impaired eyelid function. **Navigational Note:** -					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light. **Navigational Note:** Also consider Eye disorders: Retinal tear or Retinal detachment					
Floaters	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens. **Navigational Note:** Also consider Eye disorders: Retinal tear or Retinal detachment					
Glaucoma	Less than 8 mmHg of elevated intraocular pressure (EIOP); no visual field deficit	EIOP which can be reduced to 21 mmHg or under with topical medications and no visual field deficit	EIOP causing visual field deficits	Visual field deficit within the central 10 degrees of the visual field in the affected eye	-
Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Keratitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self care ADL	Perforation; best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation to the cornea of the eye. **Navigational Note:** Also consider Eye disorders: Corneal ulcer					
Night blindness	Symptomatic but not limiting ADL	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by an inability to see clearly in dim light. **Navigational Note:** -					
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve). **Navigational Note:** -					
Papilledema	Asymptomatic; no visual field deficit	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by swelling around the optic disc. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face. **Navigational Note:** -					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of light. **Navigational Note:** -					
Retinal detachment	-	-	Macular sparing rhegmatogenous detachment	Macula-off rhegmatogenous retinal detachment	-
Definition: A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium. **Navigational Note:** -					
Retinal tear	No retinal detachment and treatment not indicated	No retinal detachment and treatment indicated	-	-	-
Definition: A disorder characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters. **Navigational Note:** If retinal detachment is present, grade under Eye disorders: Retinal detachment					
Retinal vascular disorder	-	Retinal vascular disorder without neovascularization	Retinal vascular disorder with neovascularization	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects vision. **Navigational Note:** If vitreous hemorrhage is present, report under Eye disorders: Vitreous hemorrhage.					
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder involving the retina. **Navigational Note:** If vitreous hemorrhage is present, report under Eye disorders: Vitreous hemorrhage.					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Scleral disorder	No change in vision from baseline	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by involvement of the sclera of the eye. **Navigational Note:** -					
Uveitis	Anterior uveitis with trace cells	Anterior uveitis with 1+ or 2+ cells	Anterior uveitis with 3+ or greater cells; intermediate posterior or pan-uveitis	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye. **Navigational Note:** -					
Vision decreased	-	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by a decrease in visual acuity. **Navigational Note:** If etiology is known, use a more specific CTCAE term.					
Vitreous hemorrhage	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL; vitrectomy indicated	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by bleeding into the vitreous humor. **Navigational Note:** -					

Appendix 3 VAS for Eye Dryness

The following procedures should be followed for conducting the study assessments. The Visual Analog Scale (VAS) should be performed prior to all other ocular assessments.

To complete the VAS questionnaire, ask the subject to rate the severity and the frequency of symptom of eye dryness (0%-100%) by placing a vertical mark (|) on the horizontal line to indicate the level of eye discomfort that they are experiencing in both eyes currently (i.e., right now) and how often the eye dryness is experienced.

0% corresponds to: “no discomfort”

100% corresponds to: “maximal (the most) discomfort”

Eye Dryness Severity

0% **100%**

|_____|

Eye Dryness Frequency

0% **100%**

|_____|

Appendix 4 OSDI

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?.	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?.	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?.	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?. . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

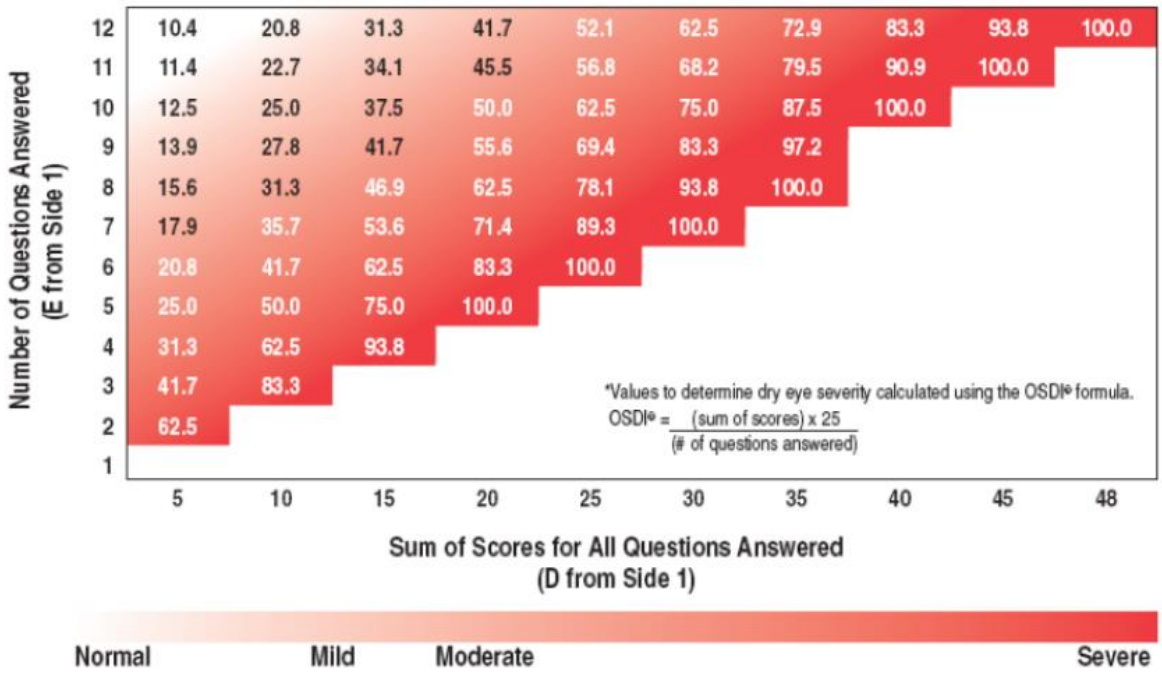
Please turn over the questionnaire to calculate the patient's final OSDI® score.

Evaluating the OSDI® Score[1]

The OSDI® is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI® is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

Appendix 5 Standard Patient Evaluation of Eye Dryness (SPEED) Questionnaire

The following procedure should be followed for conducting the study assessments.

Report the type of **SYMPTOMS** you experience and when they occur:

	At This Visit		Within Past 72 Hours		Within Past 3 Months	
Symptoms	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Dryness, Grittiness, or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye Fatigue						

Report the **FREQUENCY** of the above-checked symptoms as Never, Sometimes, Often, or Constant using the numbering system below:

Symptoms	**0**	**1**	**2**	**3**	
Dryness, Grittiness, or Scratchiness					0 = Never 1 = Sometimes 2 = Often 3 = Constant
Soreness or Irritation					
Burning or Watering					
Eye Fatigue					

Report the **SEVERITY** of your symptoms using the rating list:

Symptoms	**0**	**1**	**2**	**3**	**4**	
Dryness, Grittiness, or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye Fatigue						

0 = No problems

1 = Tolerable – not perfect but not uncomfortable

2 = Uncomfortable – irritating but does not interfere with my day

3 = Bothersome – irritating and interferes with my day

4 = Intolerable – unable to perform my daily tasks

Appendix 6 Corneal Fluorescein Staining (CFS) Procedure - Using NEI Scale

The procedure for evaluating corneal staining should be completed after the Tear Film Breakup Time (TBUT). If the CFS is done closely following the TBUT, then an additional application of fluorescein dye is not required. If a long time has elapsed between the TBUT and the CFS then an additional application of fluorescein dye may be required.

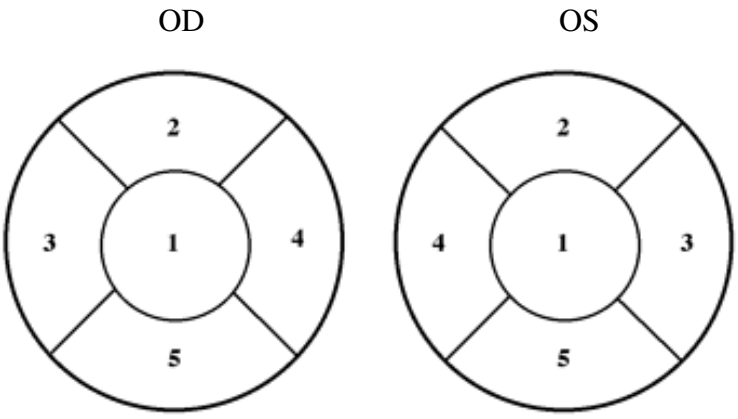
The process of completing the TBUT followed by the CFS may be completed right eye first followed by the left eye. A second fluorescein strip to apply dye to the left eye is required with this technique. If preferred, the TBUT followed by the CFS may be performed by alternating between the right and left eye. Starting first with the TBUT right eye, followed by TBUT left eye, then CFS right eye, then CFS left eye. Using this technique only one fluorescein strip is required to apply the dye to both the right and left eye.

1. Wet a sponsor supplied Fluorescein strip with the sponsor supplied saline solution/eye wash. Use enough liquid to wet the end of the strip without liquid falling from the end of the strip.
2. Ask the subject to look up and touch the moistened strip to the inferior palpebral conjunctiva without touching the strip to the bulbar conjunctiva.
3. Ask the subject to blink several times to distribute the fluorescein dye.
4. Wait between 2 to 3 minutes before evaluating the cornea for staining.
5. Use the cobalt blue illumination and the Wratten yellow filter to assess the corneal staining.
6. Record the staining for each of the 5 regions of the cornea, central, inferior, nasal, temporal, and superior using the NEI 0-3 scoring scale (see diagram). The CFS total score will be the sum of the five areas (0 to 15).

Grade each region, Central (1), Superior (2), Temporal (3), Nasal (4), Inferior (5), for each eye according to the following grading scale:

0 = No Staining
1 = Mild Staining
2 = Moderate Staining
3 = Severe Staining

NEI Corneal Staining Grading - Scale

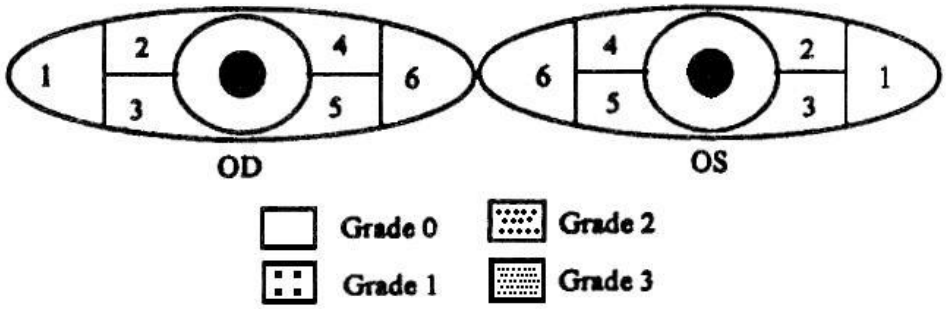


Appendix 7 Conjunctival Lissamine Green Staining (LGS) Procedure - Using the NEI Scale

Using this technique only one lissamine strip is required to apply the dye to both the right and left eye.

1. The goal is to moisten the strip without having a drop of dye ready to fall from the end of the strip. Wet a sponsor supplied Lissamine strip with the sponsor supplied saline solution/eye wash. If a drop of excess dye hangs from the end of the moistened strip, then shake off the excess over a paper towel. The moistened strip is now ready to use.
2. Ask the subject to look up and touch the moistened strip to the inferior palpebral conjunctiva without touching the strip to the bulbar conjunctiva.
3. Ask the subject to blink several times to distribute the lissamine dye.
4. Wait between 1 to 4 minutes before evaluating the conjunctiva for staining.
5. Use the moderate illumination to assess the conjunctival staining.
6. Record the staining for each of the 6 regions of the conjunctiva. The temporal conjunctive is divided into 3 sections, zones 1, 2, and 3, temporal, superior temporal, inferior temporal, respectively. The nasal conjunctive is divided into 3 sections, zones 4, 5, and 6, superior nasal, inferior nasal, and nasal, respectively. Grade the conjunctival staining using the NEI 0-3 scoring scale (see diagram). The LGS total score will be the sum of the six areas (0 to 18).
7. The staining produced by an elevated pinguecula may not improve. The staining associate with the pinguecula may be consistently excluded from the total Lissamine score.

NEI Conjunctival Staining Grading – Lissamine:



Appendix 8 Best Corrected Visual Acuity

BCVA will be conducted at all Visits.

Visual acuity testing should precede any examination requiring contact with the eye or instillation of study dyes. LogMAR visual acuity must be assessed using an ETDRS or modified ETDRS chart. Visual acuity testing should be performed with best correction using subject's own corrective lenses (spectacles only) or pinhole refraction.

An ETDRS or modified ETDRS chart may be used. If a Lighthouse chart is used (24.5" by 25"; either reflectance or retro-illuminated), the subject must view the chart from a distance of exactly 4 meters (13.1 feet). If smaller reproductions (18" by 18", e.g., Prevent Blindness) are used, the subject viewing distance should be exactly 10 feet. Reflectance wall charts should be frontally illuminated (60-watt bulb or a well-lit room).

The subject should be positioned according to the elevation of the chart (either seated or standing) so that the chart is at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter instead of the number. The subject should be asked to read slowly, about 1 letter per second, to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response. If the subject changes a response before he has read aloud the next letter, then the change must be accepted.

Maximum effort should be made to identify each letter on the chart; the subject should be encouraged to guess. When it becomes evident that no further meaningful readings can be made, the examiner should stop the test. The number of letters missed or read incorrectly should be noted.

In order to provide standardized and well-controlled assessments of visual acuity during the study, consistently use the same lighting conditions throughout the study.

<u>LogMAR Visual Acuity Calculations</u>

After each measurement of visual acuity, the visual acuity score for the visit is calculated. The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and included in the last line read. This total sum represents the logMAR visual acuity for that eye.

For Example: Subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 and line 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR VA	**= 0.18**

Appendix 9 Slit Lamp Biomicroscopy and External Eye Exam Procedures

Biomicroscopy

Fluorescein dye is to be instilled into the ocular cul-de-sac, or alternatively, fluorescein strips may be used to facilitate this examination.

The physician will examine the following using their usual technique:

- Eyelids (including punctum size)
- Lashes
- Conjunctiva
- Sclera
- Cornea
- Anterior Chamber
- Iris/pupil
- Lens

Except for Eyelids (Parameters below), findings will be reported as normal, abnormal non-clinically significant, or abnormal clinically significant. For any findings of "abnormal", the Investigator will provide all relevant explanation/comment.

Eyelid/Eyelid Margin Evaluations

Eyelid Vascularity

0 = Normal – Typical vascularity for patient age

1 = Mild vascular engorgement – Slightly dilated and pink blood vessels involving up to 1/3 of the lid margin

2 = Moderate vascular engorgement – Slightly more dilated pink/red blood vessels involving between 1/3 and 2/3 of the lid margin

3 = Severe vascular engorgement – Multiple significantly dilated red blood vessels involving between 1/3 and 2/3 of the lid margin

4 = Very Severe vascular engorgement – Multiple significantly dilated deep red blood vessels involving >2/3 of the lid margin

Meibomian glands (Out of 10 glands evaluated for the lower and upper eyelids)

1 = Normal: Clear orifices of meibomian glands

2 = Mild: Less than 1/3 of orifices plugged

3 = Moderate: Between 1/3 and 2/3 of orifices plugged

4 = Severe: More than 2/3 of orifices plugged

5 = Very severe: All orifices plugged

Appendix 10 PK Sample collection (Systemic and Tear Film Sample)

Systemic PK

Refer to laboratory manual for complete procedure.

Tear Film PK Sample

Tear fluid samples will be collected from both eyes at the same time.

Refer to the lab procedure manual for the complete procedure.

Appendix 11 Tear Film Break-Up Time

The time required for the tear film to break up following a blink is called TBUT. It is a quantitative test for measurement of tear film stability. The normal time for tear film breakup is over 15 seconds. A fluorescein strip is moistened with saline and applied to the inferior cul-de-sac. After a couple of blinks, the tear film is examined using a broad-beam of slit lamp with a blue filter for the appearance of the first dry spots on the cornea. TBUT values of less than 5–10 seconds indicate tear instability and are observed in patients with mild to moderate dry eye disease.

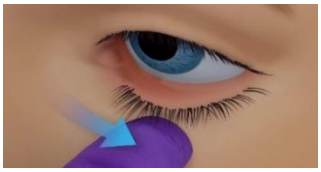
Appendix 12 Schirmer Test (without anesthesia)

Please refer to Tear Film PK Sample collection in the Lab Manual for measurement technique.

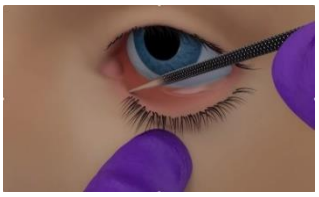
Appendix 13 OTX-CSI or HV Insert Placement

The following is the suggested placement technique and it can be modified based on investigator's medical judgment.

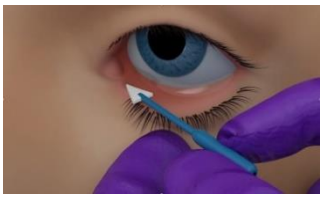
1. Apply lateral pressure to elongate the canalicular system. Pull the skin near the punctum down and temporally. A technician may assist if needed.



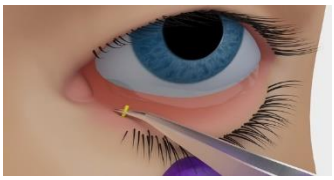
2. Dilate using the punctal dilator in towards the nose, ensuring the system is elongated. Dilate through the punctum deeper into the canaliculus, dilate for depth, as well as width. If desired, rotating the dilator in a spinning motion may help with the dilating process.



3. Dry the surface around the punctal opening using an ophthalmic sponge. More than one sponge may be necessary to ensure adequate drying of area. A technician may assist if needed.

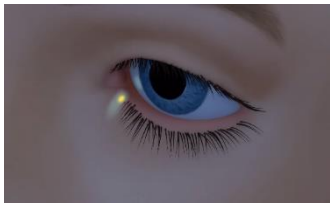


4. Grasp the OTX-CSI or HV insert with forceps and insert at a slight angle towards the nose. Aim for 70% of insertion within the first motion. Use forceps to tap or push insert the remainder of the way in. The insert should sit slightly beneath the punctal opening.

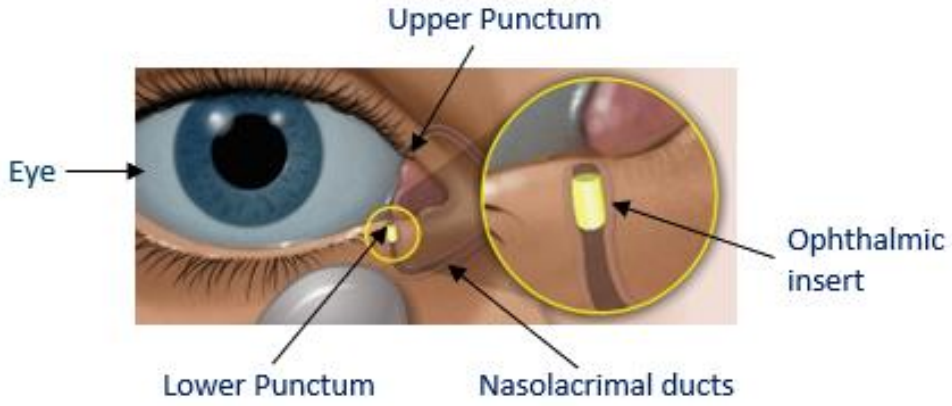


Note: Excessive squeezing of an OTX-CSI or HV may cause deformation. The product should be handled with care, so it maintains its original shape prior to insertion. If the insert hydrates before placement slightly below the punctal opening (resembling a trumpet shape), it should be discarded and a new insert should be used. If the insert hydrates before ideal positioning or if a portion of the insert is protruding and unable to be inserted, it should be removed, discarded and a new insert should be used.

5. An OTX-CSI or HV insert can be visualized when illuminated by a blue light source (e.g., slit lamp or hand-held blue light) with yellow filter.



Placement of OTX-CSI or HV insert in Canaliculus



The investigator will grade the level of ease of insertion of the ophthalmic insert as “easy” (1), “moderate” (2) or “difficult” (3).

Appendix 14 OTX-CSI or HV Insert Ease of Visualization

The Investigator will assess the presence of an OTX-CSI or HV insert at each study visit, using a blue light and yellow filter. The Investigator will be asked to grade the level of ease of visualization of the punctum plug as “easy”, “moderate”, or “difficult”.

Appendix 15 OTX-CSI or HV Insert Removal Instructions

An OTX-CSI or HV Insert can be removed either via application of manual pressure or saline irrigation, as described below.

Application of Manual Pressure

1. Identify the OTX-CSI or HV insert through the punctal tissue.
2. Place the blunt end of an instrument (e.g., punctum dilator or equivalent) next to the distal end of the test article.
3. Apply gentle pressure by pressing on the instrument in an outward motion towards the punctum until the test article is expressed out of the punctum.

Saline Irrigation

1. Ensure the punctum and canaliculus is sufficiently dilated.
2. Fill a sterile syringe and fixed cannula with sterile saline.
3. Insert the cannula into the vertical canaliculus.
4. Insert until it stops and simultaneously rotate the syringe horizontally.
5. Press slowly on the syringe plunger to flush the test article.
6. In order to help assess whether the flush is complete, it may be helpful to ask the subject to report when they taste saline or feel it in their nose.

The investigator will grade the level of ease of removal of the insert as “easy” (1), “moderate” (2) or “difficult” (3).

Appendix 16 Daily Subject Diary (For Artificial Tear Use)

If subjects are using artificial tears, they will be asked to complete a dosing diary for each administration. The dosing diary will collect the following information with respect to artificial tear administration:

Date	Time	Time	Time	Time	Time	Initials
DD/MMM/YYYY ___ /____ / _____	HR/MIN AM/PM	HR/MIN AM/PM	HR/MIN AM/PM	HR/MIN AM/PM	HR/MIN AM/PM	

Appendix 17 Marketed Cyclosporine

Product Name	Company	Indication	Region	Marketed since
Cequa™ (0.9 mg/ml)	Sun Ophthalmics	DED (KCS with presumed suppression of tear production)	US	2018
Restasis® (0.5 mg/ml)	Allergan	DED (KCS with presumed suppression of tear production)	US, Canada, and 33 other countries	2003
Ikervis® (1.0 mg/ml)	Santen Pharmaceutical	DED (Severe keratitis which has not improved with tear substitutes)	Europe	2015
Papilock Mini® (1.0 mg/ml)	Santen Pharmaceutical	VKC	Japan	2005
Modusik-A Ofteno® (1.0 mg/ml)	Laboratorios Sophia	KCS with a functional decrease of lacrimal glands	Mexico, Chile Columbia, Peru, Ecuador, Argentina	2003
TJ Cyporin® (0.5 mg/ml)	Taejoon Pharma Co, Ltd	Ocular inflammation associated with KCS	South Korea	2003
Lacrinmune® (0.5 mg/ml)	Bausch & Lomb, Inc.	KCS with a functional decrease of lacrimal glands	Argentina	NA
Cyporin® (0.5 mg/ml)	Aristopharma, Ltd	Ocular inflammation associated with KCS	Bangladesh, Myanmar	NA
Cyclorin® (0.5 mg/ml)	Ibn Sina Pharmaceutical Industry, Ltd.	Ocular inflammation associated with KCS	Bangladesh	NA

Adapted from Lallemand et al., 2017