A randomized, double-masked, vehicle-controlled, phase 2 study to evaluate the efficacy and safety of OTX-DED (dexamethasone intracanalicular ophthalmic insert) for the short-term treatment of signs and symptoms of dry eye disease (DED)

Investigational Product

OTX-DED

Version 02

15 December 2020

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

A randomized, double-masked, vehicle-controlled, phase 2 study to evaluate the efficacy and safety of OTX-DED (dexamethasone intracanalicular ophthalmic insert) for the short-term treatment of signs and symptoms of dry eye disease (DED)

I hereby agree to participate in the clinical investigation of OTX-DED (dexamethasone 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
09 November 2020	01	Original Issue	N/A
15 December 2020	02	1. Entered correct name of KPI-121. 2. Added CCLRU grading entry criterion to Visit 2 list. 3. Added unanesthetized Schirmer to Visit 2. 4. Added unscheduled visit.	1. Corrected typographical errors. 2. Item was inadvertently omitted from initial version. 3. Added to align with the endpoint. 4. Item was inadvertently omitted from initial version.

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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
CCLRU	Cornea and Contact Lens Research Unit
CFB	Change from Baseline
CFR	Code of Federal Regulations
CFS	Corneal Fluorescein Staining
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum Vitae
DED	Dry Eye Disease
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
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
NDA	New Drug Application
NEI	National Eye Institute
NSAID	Nonsteroidal Anti-Inflammatory Drug
PP	Per Protocol
OD	Right Eye
OS	Left eye
OSDI	Ocular Surface Disease Index
OTX	Ocular Therapeutix
OTX-DED	Dexamethasone Ophthalmic Insert
PK	Pharmacokinetics
QD	quaque die (one a day)
SAE	Serious Adverse Event/Experience
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBUT	Tear Film Break Up Time
tCFS	Total Corneal Fluorescein Staining
UPT	Urine Pregnancy Test
US	United States
VA	Visual Acuity
VAS	Visual Analog Scale
WOCBP	Women of Childbearing Potential

2 SYNOPSIS

<table>
<tr><td>Protocol Title</td><td>A randomized, double-masked, vehicle-controlled phase 2 study to evaluate the efficacy and safety of OTX-DED (dexamethasone intracanalicular ophthalmic insert) for the short-term treatment of signs and symptoms of dry eye disease (DED)</td></tr>
<tr><td>Protocol Number</td><td>OTX-DED-2020-201</td></tr>
<tr><td>Phase of Clinical Study</td><td>2</td></tr>
<tr><td>Investigational Products</td><td>
<table>
<tr><th>Name</th><th>Dry Dimensions</th><th>Hydrated Dimensions</th></tr>
<tr><td>OTX-DED 0.2mg Dexamethasone Ophthalmic Insert</td><td>Diameter: 0.41-0.49mm Length: 2.14-2.36 mm</td><td>Diameter: 1.35-1.80mm Length: 1.8mm</td></tr>
<tr><td>OTX-DED 0.3mg Dexamethasone Ophthalmic Insert</td><td>Diameter: 0.44-0.55mm Length: 2.14-2.36mm</td><td>Diameter: 1.35-1.80 mm; Length: 1.8mm</td></tr>
<tr><td>Hydrogel Vehicle (HV) Insert</td><td>Diameter: 0.38mm Length: 2.25mm</td><td>Diameter: 1.5 mm; Length: 1.8mm</td></tr>
</table>
</td></tr>
<tr><td>Study Objective</td><td>To assess the efficacy and safety of OTX-DED for the short-term treatment of signs and symptoms of Dry Eye Disease.</td></tr>
<tr><td>Efficacy Endpoints</td><td>Primary:
Photographic assessment of bulbar conjunctival hyperemia change from baseline (CFB) at 15 days (evaluated via central reading center).
Secondary:
Severity of Eye Dryness Score (visual analogue scale [VAS]) CFB at 15 days
Frequency of Eye Dryness (VAS) CFB at 15 days.
Severity of Eye Dryness Score (VAS), CFB and absolute values at each post-baseline visit.
Frequency Eye Dryness Score (VAS), CFB and absolute values at each post-baseline visit.
Investigator assessment of bulbar conjunctival hyperemia CFB at each post-baseline visit.
Total Corneal Fluorescein Staining (tCFS) [National Eye Institute (NEI) scale], CFB and absolute values at each post-baseline visit.
CFS sub-regions using NEI scale, CFB and absolute values at each post-baseline visit.</td></tr>
</table>

<table>
<tr><td></td><td>

Ocular Surface Disease Index questionnaire (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.

<u>Exploratory</u>:

Presence of OTX-DED or HV insert at all post-baseline visits
Ease of insertion as assessed by the Investigator
Ease of visualization as assessed by the Investigator
Schirmer Test without anesthesia CFB

</td></tr>
<tr><td>Safety Evaluations</td><td>

Adverse Events (Ocular and Non-ocular)
Best-Corrected Visual Acuity (BCVA)
Slit Lamp Biomicroscopy (including punctum assessment)
Intraocular Pressure (IOP)
Fundus Examination
Rescue artificial tear use during the study

</td></tr>
<tr><td>Pharmacokinetics (PK) Parameters</td><td>Tear Film PK</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 150 subjects (300 eyes) will be enrolled</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, double-masked, vehicle-controlled, phase 2 clinical study designed to evaluate the efficacy and safety, of OTX-DED for the short-term treatment of subjects with signs and symptoms of DED. Approximately 150 subjects (300 eyes) will be enrolled in this study at approximately 15 sites in the US. Subjects will be enrolled into one of three arms as noted in the table below.
<table>
<tr><th>Arm</th><th>Number of Subjects (Bilateral insertion)</th><th>Duration of IP Release</th></tr>
<tr><td>OTX-DED 0.2mg Dexamethasone Intracanalicular Ophthalmic Insert</td><td>50</td><td>2 weeks</td></tr>
<tr><td>OTX-DED 0.3mg Dexamethasone Intracanalicular Ophthalmic Insert</td><td>50</td><td>3 weeks</td></tr>
<tr><td>Hydrogel Vehicle Intracanalicular Insert</td><td>50</td><td>N/A</td></tr>
</table>
</td></tr>
</table>

	Subjects will undergo Screening within 14 ±2 days prior to Insertion/Day 1 (Visit 2). At Visit 2 (Insertion/Day 1) subjects confirmed to be eligible will be randomly assigned to one of three treatment groups (OTX-DED 0.2 mg, OTX-DED 0.3 mg, or HV) in a 1:1:1 ratio. OTX-DED or HV insert, as applicable, will be placed bilaterally, into either the superior or inferior canaliculus (per investigator's preference). The treatment follow-up visits will occur at Week 1/Day 8 (Visit 3), Week 2/Day 15 (Visit 4), Week 3/Day 22 (Visit 5) and Week 4/day 29 (Visit 6). All subjects will be followed until Week 8/Day 57 (Visit 7) to evaluate whether or not the insert is visualized.
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, at screening visit as defined by the following criteria: a. VAS Eye Dryness severity score ≥ 40. And in the same qualifying eye or both eyes: b. Investigator assessment of bulbar conjunctival hyperemia grade ≥ 2 (CCLRU; 0 – 4 scale). c. Unanesthetized Schirmer of > 0 and ≤ 10 mm. 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 childbearing 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. e. Alternatively, are post-menopausal women (i.e. no menstrual cycle for at least one year prior to Visit 1/Screening) or are women who have undergone one of the following sterilization procedures at least 6 months prior to screening: i. Bilateral tubal ligation ii. Hysterectomy iii. Bilateral oophorectomy 7. Agree to the removal of non-dissolvable punctal plugs 4 weeks prior to the insertion visit (Day 1, Visit 2) and 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 be placed within 6 weeks prior to insertion (Day 1, Visit 2). 8. Agree to restrict the use of artificial tears (AT) through Day 29 of the trial.
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. In the judgement of the investigator uncontrolled anterior blepharitis or posterior blepharitis or blepharitis requiring the use of systemic or antibiotic therapy. c. Uveitis 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 within 6 months or require penetrating intraocular surgery during the study, eyelid surgery within 6 months, corneal laser refractive surgery within the last 1 year, cauterization of the punctum resulting in complete occlusion of both punctum in both eyes, glaucoma surgery or corneal transplantation (full thickness, anterior or posterior) 11. Have taken any of the following in either eye within 30 days prior to the screening visit: a. Topical ocular corticosteroids b. Topical ocular antibiotics c. Topical ocular NSAID d. Topical ocular antihistamines and/or mast cell stabilizers e. Topical ocular or nasal vasoconstrictors f. Topical ocular cyclosporine (e.g., Cequa®, Restasis®) g. Lifitegrast (Xiidra®) h. Autologous tears i. Intranasal Tear Neurostimulation 12. 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 13. 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), or dermatological steroids (use is allowed if applied to <4 locations for < 4 continuous days). 14. 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) 15. Have taken isotretinoin (Accutane) or systemic immunosuppressive agents within 6 months prior to the screening visit. 16. 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. 17. Are an employee of the site or an immediate family member of an employee of the site. 18. Are a current smoker (including marijuana, cigar, cigarette, and/or e-cigarettes). 19. 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). 20. Are unwilling or unable to comply with the study protocol. 21. 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 ≥35. 2. Investigator assessment of bulbar conjunctival hyperemia grade ≥ 2 (CCLRU; 0 – 4 scale). 3. Subjects must not have taken prohibited medications and have completed the appropriate washout of prior medications, if necessary. 4. Subjects who require rescue AT must not have administered > 3 time/day for 3 consecutive days during the washout period. NOTE: AT use is not permitted unless absolutely necessary as rescue therapy. If subject requires rescue AT 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-DED or HV Intracanalicular Ophthalmic insert in both eyes (i.e. neither eye has an insert). Subject will be followed per protocol if the investigator successfully places one insert.
Rescue Therapy	Preservative-free AT will be supplied by the sponsor and will be provided only as rescue therapy if absolutely required. If AT is administered, subjects will be instructed not to administer AT within 2 hours prior to any study visit. Preservative-free AT use if needed will be recorded by subjects in a daily diary.
Sample Size Considerations	This study is not powered to show statistical significance but will provide initial estimates and trends of the endpoints for use in future trial designs. Statistical analyses will be descriptive.
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-DED minus HV and change from baseline will be calculated as follow-up visit minus baseline visit values. The study eye will be the eye with the higher grade from the photographic assessment of bulbar conjunctival hyperemia. If both eyes have the same bulbar conjunctival hyperemia grades, the study eye will be determined by the biostatistician prior to the analysis and will be detailed in the Statistical Analysis Plan. Efficacy and safety summaries will be presented for the study eye. Safety summaries of the non-study eye will also be included, and additional analyses may be presented for the non-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-DED will be combined and summarized

	Primary Hypothesis: Statistical hypothesis for the primary efficacy endpoint of photographic assessment of bulbar conjunctival hyperemia at 15 days is as follows: H_{10}: There is no difference in mean change from baseline in photographic assessment of bulbar conjunctival hyperemia grades between OTX-DED and HV treated subjects at 15 days. H_{1a}: There is a difference in mean change from baseline in photographic assessment of bulbar conjunctival hyperemia grades between OTX-DED and HV treated subjects at 15 days. **Primary Efficacy Analyses:** The primary efficacy analyses will be conducted on the intent-to-treat (ITT) population with multiple imputation using Markov Chain Monte Carlo (MCMC) for missing data. An analysis of covariance (ANCOVA) model will be run to estimate least square (LS) treatment means. This model will include the baseline value as a covariate for adjustment and treatment group as the sole factor. LS means will be used to make treatment comparisons using Dunnett's adjustment for multiple comparisons to a control. Statistical significance of treatment differences will be determined using a two-sided significance level of $\alpha = 0.10$. Two-sample t-tests will be used as an unadjusted sensitivity analysis, as well as non-parametric Wilcoxon rank sum tests. If both OTX-DED treatment groups have similar results, they will be combined and compared to HV using a two-sample t-test and Wilcoxon rank sum test. Sensitivity analyses will be conducted on the ITT population with last observation carried forward (LOCF), as well as using observed data only for the ITT and per protocol (PP) populations. **Secondary Efficacy Analyses:** The secondary efficacy endpoints including change from baseline of: severity of eye dryness score at 15 days, frequency of eye dryness score at 15 days, severity of eye dryness score at each post-baseline visit, frequency of eye dryness score at each post-baseline visit, investigator assessment of bulbar conjunctival hyperemia at each post-baseline visit, total corneal fluorescein staining (tCFS) at each post-baseline visit, CFS sub-regions at each post-baseline visit, Ocular Surface Disease Index questionnaire (OSDI©) at each post-baseline visit (total score, each of the three domains, and individual questions) and SPEED questionnaire (overall score and individual questions), CFB at each post-baseline visit will be analyzed in a manner similar to the primary efficacy variable using ANCOVA model. The secondary efficacy analyses of severity of eye dryness scores, frequency of eye dryness scores and photographic assessment of bulbar conjunctival hyperemia will be analyzed in a similar manner as the primary efficacy analyses. The remaining secondary efficacy analyses will be conducted using observed data only on the ITT and PP populations.

3 PRINCIPAL CONTACTS

Please reference the OTX-DED-2020-201 Contact List.

4 BACKGROUND INFORMATION

4.1 Dry Eye Disease (DED)

Dry eye disease (DED) is a multifactorial disorder of the tears and ocular surface characterized by symptoms of dryness and irritation. Although the pathogenesis of dry eye disease is not fully understood, it is recognized that inflammation has a prominent role in the development and propagation of this debilitating condition. Factors that adversely affect tear film stability and osmolarity can induce ocular surface damage and initiate an inflammatory cascade that generates innate and adaptive immune responses. These immunoinflammatory responses lead to further ocular surface damage and the development of a self-perpetuating inflammatory cycle.

DED flares are rapid-onset, inflammation driven responses to a variety of triggers that typically cannot be adequately managed with patients ongoing maintenance therapy – such as artificial tears and chronic prescribed therapies (ASCRS, 2019). Ocular surface inflammation plays a key role in all types of DED and conjunctival hyperemia in DED is a good indicator of inflammation (Baudouin, 2018). Acute DED flares are driven by both innate and adaptive immune responses (Perez et al., 2020) and corticosteroids targets both innate and adaptive immune response (Jones et al., 2017). With that in mind, many different groups of patients with DED may benefit from a short-term treatment of corticosteroids. Patients on artificial tears and/or other palliative treatments who experience episodic flares, patients requiring induction therapy while initiating chronic treatment for dry eye, patients experiencing breakthrough flares who are on chronic treatment such as cyclosporine and lifitegrast, patients requiring treatment of dry eye before cataract and refractive surgery to improve outcomes/satisfaction and short-term treatment of signs and symptoms of dry eye after cataract or refractive surgery.

Furthermore, corticosteroids have a fast onset and effective treatment for both signs and symptoms of DED as they target inflammation driven by both innate and adaptive immune responses (Perez et al., 2020). Despite the efficacy of corticosteroids there is only one currently FDA approved (Kala Pharmaceuticals) for safe and efficacious short-term treatment of episodic DED. Steroid pre-treatment before initiating long term therapy for chronic DED can lead to faster resolution of signs and symptoms of DED and have been reported to reduce some side effects such as ocular burning from cyclosporine. In a multicenter randomized controlled clinical trial, the use of 0.5% loteprednol therapy two weeks before the initiation of long-term topical cyclosporine provided more rapid improvement in symptoms, corneal fluorescein staining, lissamine green staining and Schirmer score, than topical cyclosporine or artificial tears alone (Sheppard, et al., 2014). Furthermore, induction therapy with loteprednol etabonate decreased the incidence of severe stinging and discontinuation of topical cyclosporine (Sheppard, et al., 2014). In another study, treatment with topical 1% methylprednisolone and cyclosporine for an initial three-week period provided faster symptom relief and improvement in ocular signs than topical cyclosporine alone (Byun et al., 2012).

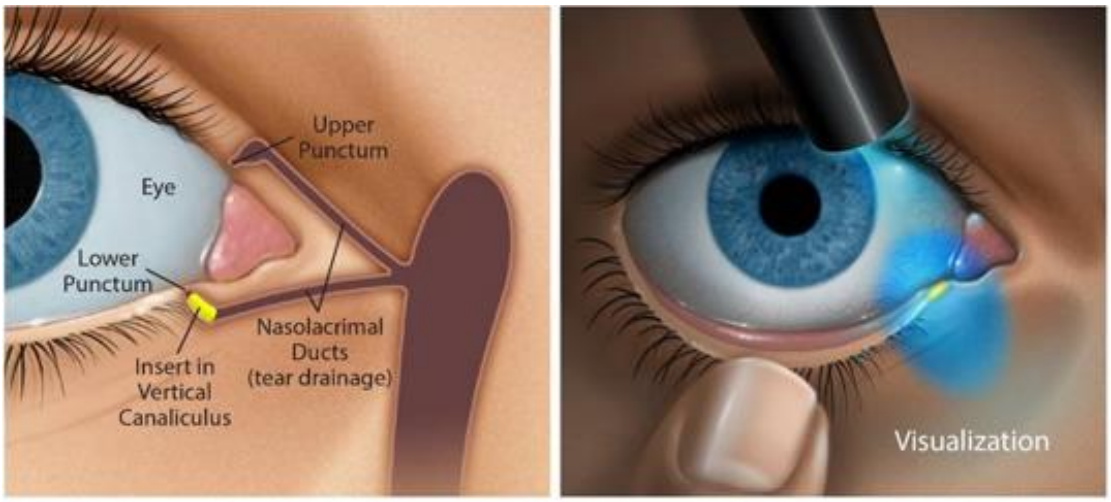
On 10/27/2020, EYSUVIS (KPI-121-loteprednol etabonate ophthalmic suspension) 0.25%, developed by Kala Pharmaceuticals was FDA approved. KPI-121 a preserved eyedrop delivered 4x/day for 2 weeks was approved for the short term (up to 2 weeks) treatment of the signs and symptoms of dry eye disease (Kala Pharmaceuticals, 2020).

4.2 Investigational Product Rationale

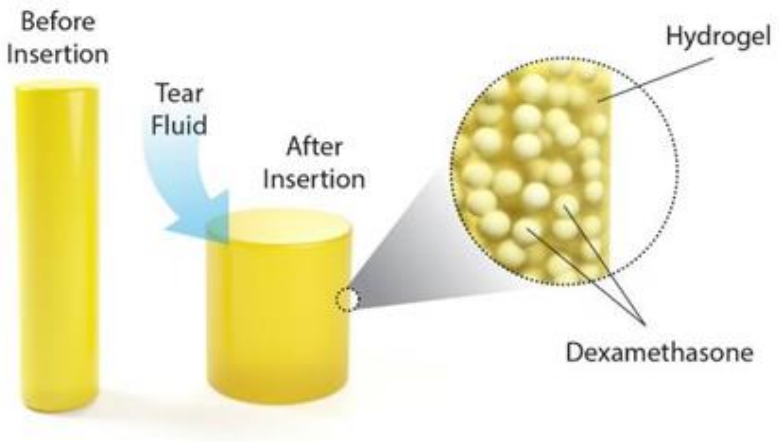
Given limitations of topical ocular treatments and devices indicated for treatments of DED, there is a rational for novel therapies. Ocular Therapeutix has designed a resorbable intracanalicular insert as the platform for drug delivery products which can be used to deliver various active pharmaceutical ingredients approved by the Food and Drug Administration (FDA).

OTX-DED is an intracanalicular insert that consists of two main components: dexamethasone and polyethylene glycol (PEG) based hydrogel conjugated with fluorescein. OTX-DED contains approximately 0.2 mg or 0.3 mg of dexamethasone and is designed to provide a sustained and tapered release of dexamethasone for up to 14 and 21 days, respectively. Over this time and through hydrolysis, OTX-DED softens, liquefies and is cleared through the nasolacrimal duct without the need for removal. The fluorescent PEG illuminates when excited with a blue light source to allow for visualization of product presence.

Figure 1 Dexamethasone Entrapped in the Hydrogel Intracanalicular Insert



Name	Dry Dimensions	Hydrated Dimensions
OTX-DED 0.2mg Dexamethasone Ophthalmic Insert	Diameter: 0.41-0.49mm Length: 2.14-2.36 mm	Diameter: 1.35-1.80mm Length: 1.8mm
OTX-DED 0.3mg Dexamethasone Ophthalmic Insert	Diameter: 0.44-0.55mm Length: 2.14-2.36mm	Diameter: 1.35-1.80 mm Length: 1.8mm
Hydrogel Vehicle (HV) Insert	Diameter: 0.38mm Length: 2.25mm	Diameter: 1.5 mm Length: 1.8mm



The insert is designed to be placed in the inferior or superior punctum and is retained in the canaliculus for the entire duration in which the drug is being delivered. Over time the insert softens and liquefies via hydrolysis, resulting in clearance through the nasolacrimal duct.

Anti-inflammatory effects of corticosteroids make them interesting development candidates for acute (short-term) DED. The drug and PEG-hydrogel technology used in OTX-DED is the same as that approved by the FDA in 2018 for DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg for intracanalicular use but contains lower dexamethasone dose of 0.2 or 0.3 mg and shorter intended therapy. Dexamethasone is already approved by FDA for treatment of steroid responsive inflammatory ocular conditions (MAXIDEX®, Alcon, Inc. NDA 013422, approved June 20, 1962). OTX-DED combines the benefits of dexamethasone with punctal occlusion, which is an established effective therapy for DED (McCabe, 2009). Recent clinical trials have demonstrated the efficacy using a topical corticosteroid treatment KPI-121 (loteprednol etabonate ophthalmic suspension) as a pharmacological treatment for acute episodes of DED.

There is significant prior experience with the marketed product dexamethasone. .OTX-DED offers several potential advantages over current therapies and/or standard of care regimens such as: tapered delivery of low doses of dexamethasone, single administration by a physician which provides for hands free drug delivery, contains no anti-microbial preservatives which may cause damage to the ocular surface and provides punctal occlusion . Moreover, OTX-DED is physician administered which eliminates the potential to abuse or misuse steroids and therefore eliminates long-term risks including glaucoma, cataract formation.

4.3 Nonclinical Findings

The sustained and then tapered drug release rate from dexamethasone inserts (OTX-DED) is regulated by drug solubility in the hydrogel matrix and transfer at the interface in contact with the tear fluid lavage. Nonclinical studies demonstrated that dexamethasone concentrations in the tear fluid and

aqueous humor of beagle dogs delivered from early development versions of dexamethasone inserts were similar to those achieved from Maxidex® (0.1% dexamethasone suspension) eye drops.

Pharmacokinetic (PK) dosing studies of dexamethasone inserts performed in beagle dogs produced sustained AH and TF concentrations which then decreased and tapered to zero (complete release) over time. The average amount of dexamethasone released from the dexamethasone insert in beagle dogs during the sustained release phase is approximately 0.20 mg per day. The OTX-DED dexamethasone doses are proposed to contain either 0.2 or 0.3 mg and is designed to provide a sustained release of dexamethasone for up to 14 or 21 days, respectively.

Dexamethasone inserts containing a maximum feasible dose of 0.737 mg dexamethasone, was evaluated in a GLP toxicology study in Beagle dogs. Daily clinical examinations, and histology performed at 36 and 50 days following implantation was generally well tolerated. Adverse findings included some mild and/or local ocular irritation. Otherwise no significant ocular toxicity was detected. Notably, there were no toxic effects observed on the posterior segment and no significant increases in IOP. No indication of systemic toxicity was observed, and absorption of the drug is negligible.

Additional details about non-clinical findings can be found in the Investigator's Brochure (IB).

4.4 Risk-Benefit Analysis

OTX-DED has several potential advantages over topical corticosteroid drops, assuming such a treatment is approved for the signs and symptoms of dry eye disease, given that OTX-DED does not contain any anti-microbial preservatives, may treat the signs and symptoms of episodic dry eye with a single application that is relatively easy to insert, eliminates complexity with daily drops, and delivers therapeutic levels of dexamethasone continuously for the intended duration of therapy. OTX-DED combines two currently used therapies for DED (steroid and punctal plug occlusion).

Based on several decades of use of topical ocular corticosteroids, risks have been identified with the use of dexamethasone, some of which have been observed in clinical trials with the higher dose 0.4 mg dexamethasone insert.

The following AEs and/or risks have been observed with the administration of corticosteroids:

1. IOP Increase/Glaucoma/Ocular hypertension
2. Masking of infection or enhancing existing infections
3. Delayed healing
4. Cataracts

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

1. Eye pain and discomfort, including foreign body sensation
2. Tearing or epiphora (with or without mucopurulent discharge)
3. Stenosis
4. Inability to remove test article
5. Perforation of or trauma to the punctum and/or surrounding tissues
6. Punctoplasty
7. Eye inflammation
8. Allergic reaction
9. Dacrocystitis
10. Canaliculitis
11. Decreased/impaired visual acuity
12. Infection or intraocular infection that if severe could lead to temporary or permanent impairment of eyesight

13. Need for surgery on the lacrimal system

Not all risks or problems of using OTX-DED are known. However, the risks associated with OTX-DED have been minimized by lowering the dose strength of the active ingredient dexamethasone and formulating the hydrogel intracanalicular insert with constituents that have a long history of safe use in ophthalmic drugs and medical devices. Furthermore, based on the results of a high dose (0.4 mg dexamethasone insert) in multiple Phase 2 and 3 studies and commercial experience with over 30,000 inserts placed, biocompatibility and preclinical testing, the highest dose (0.4 mg dexamethasone) has generally been shown to be safe and well tolerated in the eye. Moreover, OTX-DED is physician administered which eliminates the potential to abuse or misuse steroids and therefore eliminates long-term risks including glaucoma, cataract formation.

The risks described will be minimized via selection of experienced eye care professionals skilled in the use of intracanalicular inserts. All Investigators that will use the investigational product will undergo training per the product's Instructions for Use (IFU). Subjects will be selected and enrolled using clearly defined inclusion and exclusion criteria to ensure that patients with conditions/comorbidities that put them at higher risk for procedural complications are excluded. Treatment and follow up of the subjects will be performed consistent with current medical practices. Furthermore, risks will be minimized by requiring subjects to report for routine clinic visits allowing for prospective diagnosis of potential complications. Participants will be given instructions on whom to contact in the event they have any questions or are experiencing any problems.

4.5 Dose and Administration Justification

It is hypothesized that the efficacy of corticosteroid therapy may be enhanced by delivering a sustained low dose of dexamethasone compared to the typical eye drop. OTX-DED contains either 0.2 or 0.3 mg of dexamethasone, which has been designed to deliver dexamethasone in a sustained fashion for up to 14 – 21 days, respectively.

Preclinical studies have demonstrated compelling pharmacokinetics for OTX-DED compared to topically administered corticosteroids. There is a sustained presence of OTX-DED on the ocular surface. Dexamethasone levels will remain sustained until the insert is sufficiently depleted of dexamethasone at the interface, which results in the gradual tapering effect observed in tear fluid seen in the pharmacokinetic profiles. This pharmacokinetic profile may mark an efficacy improvement through steady and relatively low levels of drug delivered compared to the peak and trough model of topically administered corticosteroid eye drops.

The drug and PEG-hydrogel technology used in OTX-DED is the same as that approved by the FDA in 2018 for DEXTENZA (dexamethasone ophthalmic insert), 0.4 mg for intracanalicular use [NDA 208742] but contains a lower dexamethasone dose of 0.2 or 0.3 mg and are of a shorter intended duration of therapy. Clinical studies evaluating DEXTENZA (Phase 2: OTX-12-002; Phase 3: OTX-13-002, OTX-14-003 and OTX-15-003) that were double-masked, vehicle-controlled trials for the treatment of pain and inflammation following ophthalmic surgery demonstrated safety and efficacy of dexamethasone inserts in these patients.

Calculations of human equivalent dose (HED) of no observed adverse effect levels (NOAELs) and applications of safety factors used to calculate the ocular and systemic safety factors for the proposed clinical dose of 0.2 and 0.3 mg/eye are presented in Table 1. Ocular HED is based on equivalence of eyes between humans and beagles, and systemic HED is based on dose per unit weight.

Table 1 Safety Margins for Ocular and Systemic Toxicity

NOAEL Study	Beagle Dose per Eye	Ocular Safety Factor[a] for 0.2 mg and Human Dose per Eye	Ocular Safety Factor[a] for 0.3 mg Human Dose per Eye	Total Systemic Dose	Systemic HED[b]	Systemic Safety Factor for Bilateral 0.2 mg and Human Dose[c]	Systemic Safety Factor for Bilateral 0.3 mg Human Dose[c]
35-Day Toxicity Study of the Dexamethasone Punctum Plug with a 2 Week Recovery Period (TP/TR0161)	0.73 mg/eye	3.6 (0.2 mg dose)	2.4 (0.3 mg dose)	1.46 mg	5.41 mg	13.5 (0.4 mg dose)	9.0 (0.6 mg dose

[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 (9 kg) then dividing by a factor of 1.8 and multiplying by human weight (60 kg) consistent with Table 1 in FDA Guidance. [U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER)].
[c] The systemic safety factor is the systemic HED divided by the proposed doses of 0.2 and 0.3 mg.
[d] The ocular and systemic safety factors may vary by up to 10% to allow for the drug content specification range consistent with the label claim.

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

Approximately 150 subjects diagnosed with DED will be screened and randomly assigned to one of three treatment arms.

5 TRIAL OBJECTIVES

The objectives of the trial are to assess the efficacy and safety of OTX-DED for short term treatment of DED.

6 TRIAL DESIGN

6.1 Description of Trial

This is a randomized, multi-center, double-masked, vehicle-controlled, phase 2 clinical study designed to evaluate the efficacy and safety of OTX-DED (dexamethasone ophthalmic insert) for intracanalicular use for the short-term treatment of DED. Approximately 150 subjects (300 eyes) will be enrolled in this study at approximately 15 sites in the US. Subjects will be a randomized to one of three treatment groups as noted in Table 2. Both eyes will be treated with the same treatment.

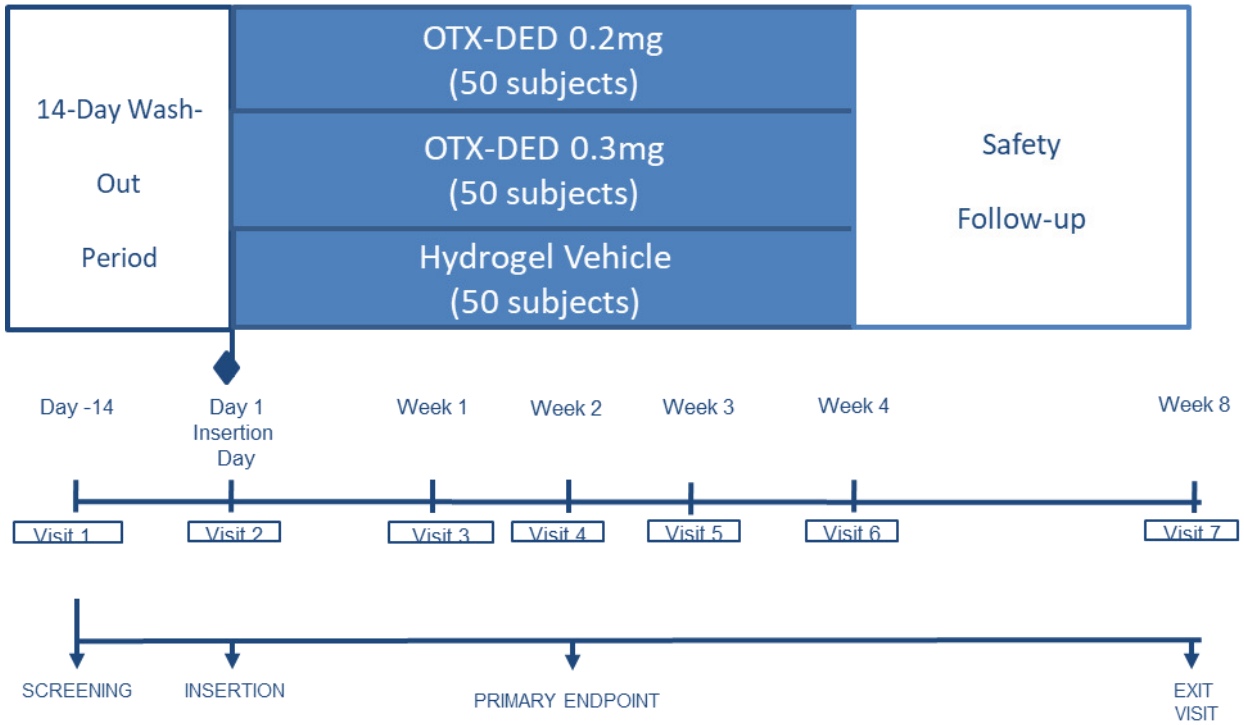
Table 2 Treatment Assignment Paradigm

Name	Number of Subjects
OTX-DED 0.2mg Dexamethasone Ophthalmic Insert	50
OTX-DED 0.3mg Dexamethasone Ophthalmic Insert	50
Hydrogel Vehicle (HV) Insert	50

Subjects will undergo Screening 14 days prior to Insertion/Day 1 (Visit 2). At Visit 2 (Insertion/Day 1) eligibility will be confirmed and subjects who are eligible will be randomly assigned to one of three treatment groups (OTX-DED 0.2mg, OTX-DED 0.3mg, or HV in a 1:1:1 ratio. The treatment follow-up visits will occur at Week 1 (Visit 3), Week 2 (Visit 4), Week 3 (Visit 5), Week 4 (Visit 6), and Week 8 (Visit 7).

This study will be conducted per the schedule shown in Figure 2.

Figure 2 Study Schematic



6.2 Study Endpoints

6.2.1 Efficacy Endpoints

6.2.2 Primary Efficacy Endpoints

- Photographic assessment of bulbar conjunctival hyperemia change from baseline (CFB) at 15 days (evaluated via central reading center).

6.2.2.1 Secondary Efficacy Endpoints

- Severity of Eye Dryness Score (visual analogue scale [VAS]) CFB at 15 days
- Frequency of Eye Dryness (VAS) CFB at 15 days.
- Severity of Eye Dryness Score (VAS), CFB and absolute values at each post-baseline visit.
- Frequency Eye Dryness Score (VAS), CFB and absolute values at each post-baseline visit.
- Investigator assessment of bulbar conjunctival hyperemia CFB at each post-baseline visit.
- Total Corneal Fluorescein Staining (tCFS) [National Eye Institute (NEI) scale], CFB and absolute values at each post-baseline visit.
- CFS sub-regions using NEI scale, 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 individual questions).
- SPEED questionnaire (overall score and individual questions), CFB at each post-baseline visit.

6.2.2.2 Exploratory Efficacy Endpoints

- Presence of OTX-DED or HV insert at all post-baseline visits
- Ease of insertion as assessed by the Investigator
- Ease of visualization as assessed by the Investigator
- Schirmer Test without anesthesia CFB

6.2.3 Safety Evaluations

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
- Rescue artificial tear use during the study

6.2.4 Supplementary Objectives

- Tear Film PK will be collected and analyzed at all sites.

6.3 Randomization and Masking

Subjects will be randomized to treatment assignment. If unmasking is required, the integrity of the study assessments and objectives will be maintained by limiting access to the unmasked data.

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 OTX-DED and HV 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

- OTX-DED 0.2 mg Dexamethasone Ophthalmic Insert
- OTX-DED 0.3 mg Dexamethasone Ophthalmic Insert
- Hydrogel Vehicle Insert

6.5 Trial Duration

An individual subject's participation will last approximately 10 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. The clinical investigation may be suspended if the Medical Monitor, 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-DED and HV Inserts are sterile, ophthalmic inserts that are without antimicrobial preservatives. OTX-DED 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 150 subjects (300 eyes) 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, at screening visit as defined by the following criteria:
    a. VAS Eye Dryness severity score ≥ 40.

And in the same qualifying eye or both eyes:

    b. Investigator assessment of bulbar conjunctival hyperemia grade ≥ 2 (CCLRU; 0 – 4 scale)
    c. Unanesthetized Schirmer of >0 and <10mm.
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.

e. Alternatively, are post-menopausal women (i.e. no menstrual cycle for at least one year prior to Visit 1/Screening) or are women who have undergone one of the following sterilization procedures at least 6 months prior to screening:

i. Bilateral tubal ligation

ii. Hysterectomy

iii. Bilateral oophorectomy

7. Agree to the removal of non-dissolvable punctal plugs 4 weeks prior to the insertion visit (Day 1, Visit 2) and 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).
8. Agree to restrict the use of artificial tears (AT) through Day 29 of the trial.

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. In the judgement of the investigator uncontrolled anterior blepharitis or posterior blepharitis or blepharitis requiring the use of systemic or antibiotic therapy.
    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 within 6 months or require penetrating intraocular surgery during the study, eyelid surgery within 6 months, corneal laser refractive surgery within the last 1 year, cauterization of the punctum resulting in complete occlusion of both punctum in both eyes, glaucoma surgery or corneal transplantation (full thickness, anterior or posterior)

11. Have taken any of the following in either eye within 30 days prior to the screening visit:

    a. Topical ocular corticosteroids

    b. Topical ocular antibiotics

    c. Topical ocular NSAID

    d. Topical ocular antihistamines and/or mast cell stabilizers

    e. Topical ocular or nasal vasoconstrictors

    f. Topical ocular cyclosporine (e.g., Cequa®, Restasis®)

    g. Lifitegrast (Xiidra®)

    h. Autologous tears

    i. Intranasal Tear Neurostimulation

12. 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 intravitreal depot injection– 3 months

    c. Ozurdex– 6 months

    d. Retisert– 40 months

13. 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) or dermatological steroids (use is allowed if applied to < 4 locations for < 4 continuous days).

14. 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)

15. Have taken isotretinoin (Accutane) or systemic immunosuppressive agents within 6 months prior to the screening visit.
16. 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.
17. Are an employee of the site or an immediate family member of an employee of the site.
18. Are a current smoker (including marijuana, cigar, cigarette, and/or e-cigarettes).
19. 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).
20. Are unwilling or unable to comply with the study protocol.
21. 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 ≥ 35.
2. Investigator assessment of bulbar conjunctival hyperemia grade ≥ 2 (CCLRU; 0 – 4 scale)
3. Subject must not have taken prohibited medications and have completed the appropriate washout of prior medications, if necessary.
4. Subjects who require rescue AT must not have administered >3 time/day for 3 consecutive days during the washout period

   Note: AT use is not permitted unless absolutely necessary as rescue therapy. If subject requires rescue AT and have 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-DED or HV intracanalicular 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.

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. 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 [see Appendix 13]) 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 7 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 will not be replaced.

8 SUBJECT TREATMENT

8.1 Treatment Regimen

OTX-DED contains 0.2 mg or 0.3mg of micronized dexamethasone 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 dexamethasone over approximately 14 - 21 days.

8.2 Prior and Concomitant Therapy

Only sponsor provided preservative free artificial tear use will be permitted as rescue therapy during the study. All other tear substitutes are not permitted.

Table 3 List of Prohibited/Restricted Medications

Minimum Washout Period Prior to Screening (Visit 1)
30 days:
Topical ocular cyclosporine (e.g., Cequa®, Restatsis®)
Lifitegrast (Xiidra®)
Autologous tears
Topical ocular corticosteroids
Topical ocular antibiotics
Topical ocular NSAID
Topical ocular antihistamines and/or mast cell stabilizers
Topical ocular or nasal vasoconstrictors
Intranasal Tear Neurostimulation
Stable within 30 days of Visit 1 and stable throughout study:
Nutraceuticals or multivitamins
Tetracycline compounds (tetracycline, doxycycline or minocycline)
Inhaled, intramuscular or intra-articular corticosteroids (mouth or nasal spray form)
Stable within 6 months of Visit 1 and stable throughout study:
Systemic anticholinergics
Antidepressants (with the exception of rare usage as a sleep aid)
Oral corticosteroids (e.g., prednisone, prednisone dose must be less than 11mg/day)
90 days:
Periocular injection of any corticosteroid
Corticosteroid intra-vitreal depot injection
6 months:
Ozurdex
Isotretinoin
Systemic Immunosuppressants
40 months:
Retisert

8.3 Rescue Therapy

Use of preservative-free artificial tears (AT) should be discouraged, and subjects should be counseled to administer only if absolutely necessary as rescue. Further, if used, subjects will be instructed not to administer AT within 2 hours prior to any study visit. Preservative-free AT will be provided by the sponsor and use will be recorded by subjects in a daily diary.

8.4 Study Assessments by Visit

Perform study procedures as referenced in the Schedule of Events (Appendix 1) in the order specified below. Note: All subjects will have both eyes evaluated at all visits.

8.4.1 Visit 1 (14 ±2 days prior to Day 1) Screening/Baseline Visit

Note: The Screening Visit can be split into two (2) visits in rare cases, but both visits must be within the allowable window.

- Informed consent
- Demographics
- Medical/ophthalmic history
- Record concomitant medications
- VAS Severity and Frequency for Eye Dryness (Appendix 2)
- OSDI (Appendix 3)

- SPEED assessment (Appendix 4)
- BCVA assessment (Appendix 8)
- Slit lamp biomicroscopy (including punctum assessment) (Appendix 9)
- Investigator Rated Assessment of Bulbar Conjunctival Hyperemia (Appendix 5)
- CFS (Appendix 7)
  Note: Wait 15 minutes prior to conducting unanesthetized Schirmer test
- Unanesthetized Schirmer
- IOP
- Dilated fundus exam
- Determine Eligibility
- Dispense artificial tears (as needed and not to be administered within 2 hours of clinic visit.)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed) (Appendix 14)

8.4.2 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 Tear Use (if applicable)
  Note: Subjects using rescue AT > 3x/day for 3 consecutive days will be ineligible for randomization.
- VAS Frequency and Severity for Eye Dryness
- OSDI
- SPEED assessment
- Conjunctival Hyperemia Photography (Appendix 6)
- BCVA assessment
- Slit lamp biomicroscopy, including punctum evaluation
- Investigator Rated Assessment of Bulbar Conjunctival Hyperemia
- CFS
- IOP
- Punctum Size Assessment
- Urine pregnancy test (if applicable must be performed prior to treatment)
- Determine Eligibility for Insertion
- Randomization
- OTX-DED or HV Insert Placement (Appendix 11)*

  Note: If placement is only successful in one eye, the items with the asterisk should be performed on the same day. Subjects should be asked to return within 0-3 days to attempt insertion in the other eye. At the return visit, items with an asterisk should be performed on the second eye, and the AE review, Ease of Insertion Assessment and Tear film PK for the second eye should only be performed if the second eye has a successful insertion.

- Ease of Insertion Assessment*
- Tear film PK by Schirmer (to be collected 1 hour (±30 minutes), 2 hours (±30 minutes) and 4 hours (±30 minutes) post-insertion)* (Appendix 10)
- Dispense artificial tears (as needed and if used, not to be administered within 2 hours of the clinic visits)
- Dispense Daily Subject Diary for Artificial Tear Use (as needed)

8.4.3 Visit 3 (Week 1 ±2 days)

- Record concomitant medications
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed)
- Record AEs
- VAS Frequency and Severity for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- Investigator Rated Conjunctival Hyperemia Grade
- CFS
- OTX-DED or HV Insert Presence by visual assessment
- Ease of Visualization by Investigator (Appendix 12)
- Tear Film PK by Schirmer
- IOP
- Dispense artificial tears and diary (as needed)

8.4.4 Visit 4 (Week 2 ±2 days)

- Record concomitant medications
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed)
- Record AEs
- VAS Frequency and Severity for Eye Dryness
- OSDI
- SPEED assessment
- Conjunctival Hyperemia Photography
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- Investigator Rated Conjunctival Hyperemia Grade
- CFS
- OTX-DED or HV Insert Presence by visual assessment
- Ease of Visualization by Investigator
- Tear Film PK by Schirmer
- IOP
- Dispense artificial tears and diary (as needed)

8.4.5 Visit 5 (Week 3 ±2 days)

- Record concomitant medications
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed)
- Record AEs
- VAS Frequency and Severity for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- Investigator Rated Conjunctival Hyperemia Grade
- CFS
- OTX-DED or HV Insert Presence by visual assessment

- Ease of Visualization by Investigator
- Tear Film PK by Schirmer
- IOP
- Dispense artificial tears and diary (as needed)

8.4.6 Visit 6 (Week 4 ±3 days)

- Record concomitant medications
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed)
- Record AEs
- OSDI
- VAS Frequency and Severity for Eye Dryness
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- Investigator Rated Conjunctival Hyperemia Grade
- CFS
- OTX-DED or HV Insert Presence by visual assessment
- Ease of Visualization by Investigator
- Tear Film PK by Schirmer
- IOP
- Dispense artificial tears and diary (as needed)

8.4.7 Final Visit 7 (Week 8±10 days)

- Record concomitant medications
- Collect and review Subject Daily Diary for Artificial Tear Use (as needed)
- Record AEs
- Urine Pregnancy Test
- VAS Frequency and Severity for Eye Dryness
- OSDI
- SPEED assessment
- BCVA assessment
- Slit lamp biomicroscopy, including punctum assessment
- Investigator Rated Conjunctival Hyperemia Grade
- CFS
- Undilated Fundus Exam
- OTX-DED or HV Insert Presence by visual assessment
- Ease of Visualization by Investigator
- Tear Film PK by Schirmer
- IOP
- Punctum Size Assessment

8.4.8 Unscheduled Visits

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:

- BCVA assessment

- Slit lamp biomicroscopy
- 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 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.

9.1 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 screening) that results in subject withdrawal from the study or medical treatment or further follow-up.

9.2 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.

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

Not applicable.

9.4 Monitoring and Recording of AEs and SAEs

9.4.1 Adverse Events

Any AE experienced by the subject from Visit 2 (Insertion/Day 1) through Visit 7 (Week 8) 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).

9.4.2 Serious Adverse Events

Any SAE experienced by the subject from Visit 2 (Insertion/Day 1) through Visit 7 (Week 8) 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.

9.4.3 All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 9.2.
- The severity of the event as defined in Section 9.7.1.
- The relationship of the event to study treatment as defined in Section 9.7.2.

9.5 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 3. 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 3) within 10 calendar days. All SAEs will be followed until the Investigator and Ocular Therapeutix agree that the event is satisfactorily resolved.

9.6 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 3 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

9.7 Evaluating AEs and SAEs

9.7.1 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 9.2 Definition of a SAE.

9.7.2 Relationship to OTX-DED 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

9.7.3 Expectedness of Events

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

9.8 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.

9.9 Procedures for Handling Special Situations

9.9.1 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 9.5. In addition, the Investigator or study site staff must report the outcome of the pregnancy to the pharmacovigilance team.

9.9.2 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, 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.

9.9.3 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.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 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-DED minus HV and change from baseline will be calculated as follow-up visit minus baseline visit value.

10.2 Unit of Analysis

Both eyes will be treated with the same treatment/formulation. If both eyes qualify, the eye having the higher grade from the photographic assessment of conjunctival hyperemia will be designated as the study eye and the other eye designated as the non-study eye. If both eyes have the same conjunctival hyperemia grade, 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.

Efficacy and safety summaries will be presented for the study eye. Safety summaries of the non-study eye will also be included, and additional analyses may be presented for the non-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-DED will be combined and summarized.

10.3 Sample Size Determination

This study is not powered to show statistical significance but will provide initial estimates and trends of the endpoints for use in future trial designs. The sample size will allow for safety information to be obtained, while still limiting the number of subjects exposed to the IP. Statistical analyses will be descriptive.

10.4 Statistical Significance

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

10.5 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.

10.6 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. Subjects who receive sustained rescue medication will have their data after receiving rescue medicine set to missing and will be imputed as described above.

10.7 Efficacy Analyses

Primary Hypothesis

Statistical hypothesis for the primary efficacy endpoint of photographic assessment of bulbar conjunctival hyperemia grade at 15 days is as follows:

H_{10}: There is no difference in mean change from baseline in photographic assessment of bulbar conjunctival hyperemia grades between OTX-DED and HV treated subjects at 15 days.

H_{1a}: There is a difference in mean change from baseline in photographic assessment of bulbar conjunctival hyperemia grades between OTX-DED and HV treated subjects at 15 days.

Primary Efficacy Analyses

The primary efficacy analysis will be conducted on the intent-to-treat (ITT) population with multiple imputation using Markov Chain Monte Carlo (MCMC) for missing data.

An analysis of covariance (ANCOVA) model will be run to estimate LS treatment means. This model will include the baseline value as a covariate for adjustment and treatment group as the sole factor. Least square means will be used to make treatment comparisons using Dunnett's adjustment for multiple comparisons to a control. Statistical significance of treatment differences will be determined using a two-sided significance level of $\alpha = 0.05$. Two-sample t-tests will be used as an unadjusted sensitivity analysis, as well as non-parametric Wilcoxon rank sum tests. If both OTX-DED treatment groups have similar results, they will be combined and compared to HV using a two-sample t-test and Wilcoxon rank sum test. Sensitivity analyses will be conducted on the ITT population with last observation carried forward (LOCF), as well as using observed data only for the ITT and PP populations.

Secondary Efficacy Analyses

The secondary efficacy variables including change from baseline of: severity of eye dryness score at 15 days, frequency of eye dryness score at 15 days, severity of eye dryness score at each post-baseline visit, frequency of eye dryness score at each post-baseline visit, investigator assessment of bulbar conjunctival hyperemia at each post-baseline visit, total corneal fluorescein staining (tCFS) at each post-baseline visit, CFS sub-regions at each post-baseline visit, Ocular Surface Disease Index questionnaire (OSDI©) at each post-baseline visit (total score, each of the three domains, and individual questions) and SPEED questionnaire (overall score and individual questions), CFB at each post-baseline visit will be analyzed in a manner similar to the primary efficacy variable using ANCOVA model. The secondary efficacy analyses of severity of eye dryness scores, frequency of eye dryness scores and photographic assessment of bulbar conjunctival hyperemia will be analyzed in a similar manner as the primary efficacy analyses. The remaining secondary efficacy analyses will be conducted using observed data only on the ITT and PP populations.

Exploratory Efficacy Analyses

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 using the Pearson chi-squared statistic. Change from baseline in Schirmer's test will be analyzed using an ANCOVA model similar to the primary analysis, on observed data.

Demographics and Baseline Data
The demographic and baseline medical history data will be summarized descriptively. For quantitative variables, the summaries will include the number of observations, mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

10.8 Safety Analyses

Incidence of adverse events will be tabulated by MedDRA System Organ Class and preferred term within each system organ class for ocular and non-ocular events, visual acuity, slit lamp biomicroscopy, IOP, dilated fundoscopy examination, and rescue medication use will be summarized descriptively using quantitative and qualitative summary statistics as appropriate.

10.9 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.

10.10 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-DED or HV). Analyses performed on the Safety population will be according to the treatment the subject actually received.

11 STUDY MANAGEMENT AND DATA COLLECTION

11.1 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.

11.2 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.

11.3 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 (eg, 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.

11.4 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.

12 STUDY MONITORING, AUDITING, AND INSPECTING

12.1 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.

13 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 8.4 for order of assessments.

Study Parameter	Screening/ Baseline Visit Day -14 (-16 to -12)	Insertion Day 1	Follow-up Day 8 Week 1 ±2 days	Follow-up Day 15 Week 2 ±2 days	Follow-up Day 22 Week 3 ±2 days	Follow-up Day 29 Week 4[6] ±3 days	Follow-Up Day 57 Week 8 (± 10 days)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Informed Consent	X						
Determine Eligibility	X	X					
Demographic Information	X						
Medical/Ophthalmic History	X						
Record Medications	X	X	X	X	X	X	X
Record Adverse Events[3,7]		X	X	X	X	X	X
Urine Pregnancy Test[1]		X					X
VAS for Eye Dryness	X	X	X	X	X	X	X
OSDI	X	X	X	X	X	X	X
SPEED	X	X	X	X	X	X	X
Conjunctival Hyperemia photography		X		X			
Assessment of BCVA	X	X	X	X	X	X	X
Slit Lamp Biomicroscopy (including punctum assessment)	X	X	X	X	X	X	X
Investigator Rated Conjunctival Hyperemia grade	X	X	X	X	X	X	X
Corneal Fluorescein Staining Using the NEI Scale	X	X	X	X	X	X	X
OTX-DED or HV Insert Presence by Visual Assessment			X	X	X	X	X
Ease of Visualization as assessed by Investigator			X	X	X	X	X
Unanesthetized Schirmer Tear Test	X						
Tear Film PK performed using Schirmer Strips[3,4,5]		X	X	X	X	X	X
IOP Measurement	X	X	X	X	X	X	X
Fundus Exam[2]	X						X
Punctum Size Assessment		X					X
Randomization		X					
OTX-DED or HV Insert Placement[3]		X					
Ease of Insertion as assessed by the Investigator[3]		X					
Dispense Sponsor Supplied Artificial Tears (if needed) and Daily Diary	X	X	X	X	X	X	
Collect/review Daily Subject Diary for Artificial Tear Use (as needed)		X	X	X	X	X	X

1 A negative UPT is required for women of childbearing age to be included in the study.

2 Dilated fundus examination at screening; undilated fundus examination at Week 8.
3 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. 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.
4 Tear Film PK will be collected at 1 hour (±30 minutes), 2 hours (±30 minutes), and 4 hours (±30 minutes) post insertion on Day 1. Tear Film PK should be collected using Schirmer strips.
5 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.
6 Early termination subjects should complete assessments based on the final visit (Visit 7) schedule of assessments.
7 Signs, symptoms, conditions occurring prior to insertion on Day 1 should be captured as medical history.

Appendix 2 VAS for Eye Dryness

The following procedures should be followed for conducting the study assessments. The Visual Analog Scale (VAS).

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 3 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)

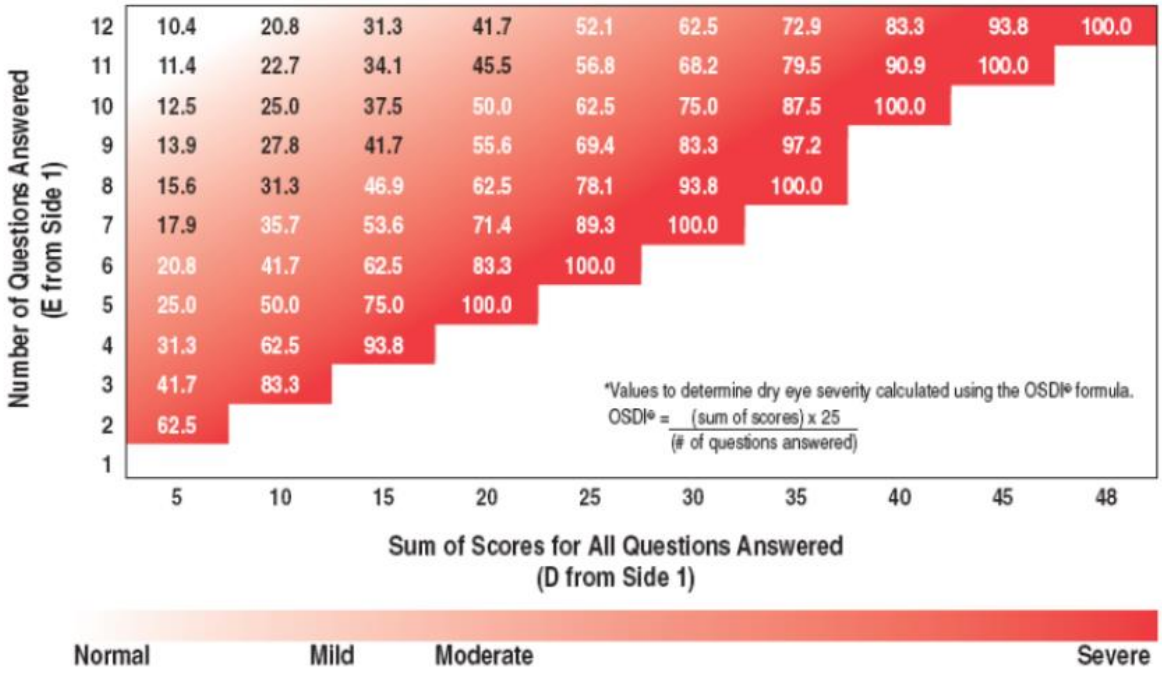
Please turn over the questionnaire to calculate the patient's final OSDI© score.

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 4 Standard Patient Evaluation of Eye Dryness (SPEED) Questionnaire

The following procedure should be followed for conducting the study assessments. The Standard Patient Evaluation of Eye Dryness (SPEED) should be performed prior to all other ocular 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

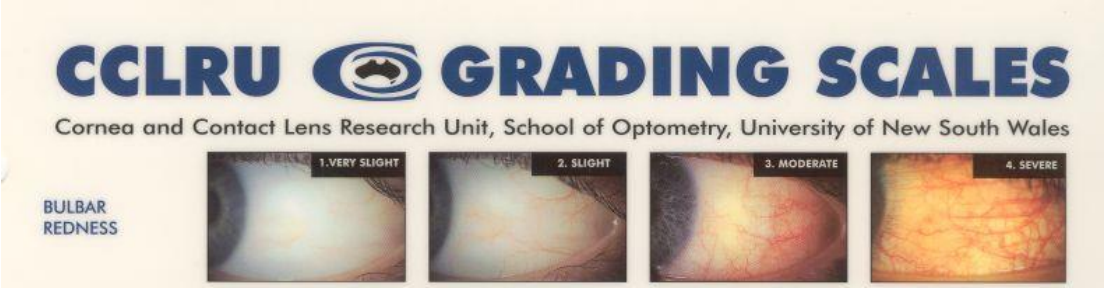
2 = Uncomfortable – irritating but does not interfere with my day

3 = Bothersome – irritating and interferes with my day

4 = Intolerable – unable to perform my daily tasks

Appendix 5 Investigator Rated Conjunctival Hyperemia Grade

Investigators will rate overall bulbar conjunctival hyperemia using the Cornea and Contact Lens Research Unit (CCLRU) Grading Scale.



0 = None

1 = Very Slight

2 = Slight

3 = Moderate

4 = Severe

Appendix 6 Bulbar Conjunctival Hyperemia Photography

The Investigator will obtain photographs of each eye at baseline and Day 15. These will be sent to a central reading center for assessment of bulbar conjunctival hyperemia. Procedures will be elaborated in a Photography Manual of Operations.

Appendix 7 Corneal Fluorescein Staining (CFS) Procedure - Using NEI Scale

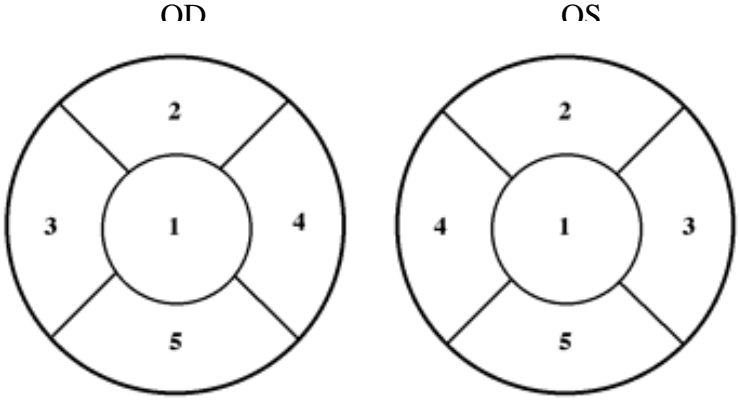
CFS may be completed right eye first followed by the left eye. Using this technique only one fluorescein strip is required to apply the dye to both the right and left eye.

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 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.

LogMAR Visual Acuity Calculations

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**

Letter Score	LogMAR Value	Snellen Equivalent
5	1.6	20/800
10	1.5	20/640
15	1.4	20/500
20	1.3	20/400
25	1.2	20/320
30	1.1	20/250
35	1.0	20/200
40	0.9	20/160
45	0.8	20/125
50	0.7	20/100
55	0.6	20/80
60	0.5	20/63
65	0.4	20/50
70	0.3	20/40
75	0.2	20/32
80	0.1	20/25
85	0.0	20/20
90	−0.1	20/15
95	−0.2	20/12

LogMAR = logarithm of the minimal angle of resolution.

Appendix 9 Slit Lamp Biomicroscopy and External Eye Exam Procedures

Biomicroscopy

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

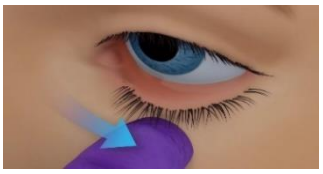
Appendix 10 Tear Film PK Sample collection

Refer to the lab procedure manual for the complete procedure.

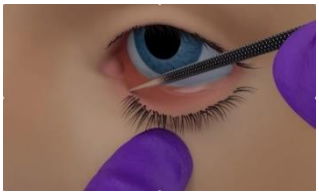
Appendix 11 OTX-DED or HV Insert Suggested Placement Technique

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.

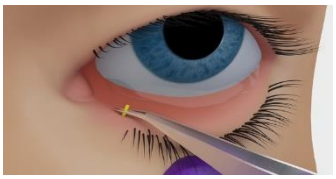


2. Dilate using the punctal dilator in towards the nose, ensuring the system is elongated. Dilate through the punctum deeper into the canaliculus, dilate for depth, as well as width. If desired, rotating the dilator in a spinning motion may help with the dilating process.



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.

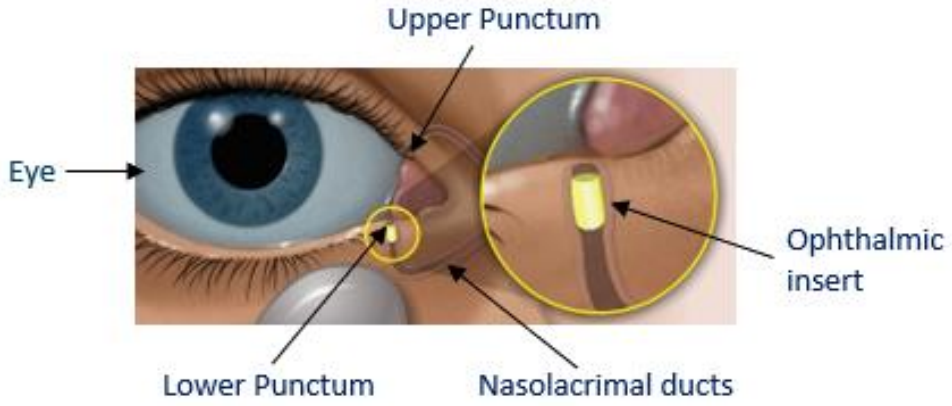
4. Grasp OTX-DED or HV insert with forceps and insert at a slight angle towards the nose. Aim for 70% of insertion within the first motion. Use forceps to tap or push insert the remainder of the way in. The insert should sit slightly beneath the punctal opening.



Note: Excessive squeezing of OTX-DED 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. (Note: cutting of the exposed insert is NOT allowed.)

5. OTX-DED 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-DED 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 12 OTX-DED or HV Insert Ease of Visualization

The Investigator will assess the presence of OTX-DED 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 13 OTX-DED or HV Insert Removal Instructions

OTX-DED 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-DED 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 14 Daily Subject Diary (For Artificial Tear Use)

If subjects are using artificial tears as a rescue, 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	