Safety and Efficacy of Dexamethasone Ophthalmic Insert (Dextenza®) in the Management of Clinically Significant Dry Eye

NCT04498468

Date: September 21, 2020

Clinical Study Protocol

Safety and Efficacy of Dexamethasone Ophthalmic Insert (Dextenza®) in the Management of Clinically Significant Dry Eye

Compound:	Sustained Release Dexamethasone, 0.4 mg.
Study Name:	Safety and Efficacy of Dexamethasone Ophthalmic Insert (Dextenza®) in the Management of Clinically Significant Dry Eye.
Clinical Phase:	Phase IV, prospective, masked trial.
Date of Issue:	September 21, 2020
Principal Investigator:	Esen K. Akpek, MD.
Sub Investigators:	Sezen Karakus, MD. Lee Guo, OD.
Site Name & Location:	Ocular Surface Diseases and Dry Eye Clinic, The Wilmer Eye Institute, The Johns Hopkins University School Of Medicine, Baltimore, Maryland.

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	Safety and Efficacy of Dexamethasone Ophthalmic Insert (Dextenza®) in the Management of Clinically Significant Dry Eye.
SITE LOCATION(S)	Ocular Surface Diseases and Dry Eye Clinic, The Wilmer Eye Institute, The Johns Hopkins University School Of Medicine, Baltimore, Maryland.
PRINCIPAL INVESTIGATOR	Esen K. Akpek, MD.
OBJECTIVE(S)	To determine efficacy and safety profile of dexamethasone 0.4mg lacrimal insert in dry eye related ocular surface inflammation.
STUDY DESIGN	Prospective, double-masked, interventional clinical trial.
STUDY DURATION	42 Days per patient, There will be 5 visits (run in, Day 1, 14, 28, and 42) with 12 months of active enrollment. Start-up period (finalizing the protocol and case report forms, obtaining approvals from institutional review board, etc): 3 months. Enrollment period: 12 months. Close-out (data completion and lock, statistical analyses, and multiple manuscript preparations etc): 3 months. Interim data analysis at 6 months. *Total of 18 months*
ESTIMATED STUDY COMPLETION DATE	December 31, 2021
POPULATION	Adult patients with significant dry eye or keratoconjunctivitis sicca, requiring topical steroid treatment.
Sample Size:	85 patients [1 treatment eye/1 control eye = 170 eyes] will be enrolled at a single site.
Treatment(s)	

Study Drug	Sustained release dexamethasone, 0.4 mg
DOSE/ROUTE/SCHEDULE:	Each patient's right eye will be randomized to receive either the treatment or the control. The left eye will automatically receive the alternative. For example if the right eye of the patient gets randomized to receive the study medication, left eye will automatically be the control eye. If the right eye gets randomized to receive the control treatment, the left eye will receive the study medication. Control eye will receive a sham treatment: commercially available tear duct plug without the dexamethasone (Vera90TM EXTENDED WEAR SYNTHETIC ABSORBABLE PUNCTAL PLUG made of E-Caprolactone-L-Lactide copolymer (PCL). Absorbs in 60 to 180 days. Size 0.5mm which is comparable to the study treatment) RESCUE MEDICINE: In patients with worsening of signs or symptoms, topical loteprednol 0.5% (Lotemax) drops up to 4 times a day, mimicking the usual practice, can be used at the discretion of the principle investigator. In patients with increased intraocular pressure (more than 5 points greater than baseline or more than 5 points higher than the fellow eye) treatment with topical beta blocker/betaxolol 0.5% (Betoptic) drops can be used 2 times a day to bring down the pressure at the discretion of the principle investigator.
Endpoint(s)	

PRIMARY EFFICACY: Efficacy will be measured at 28 days.)

We have two co-primary end points:

1- Dry eye Sign: Corneal staining score measured using OSS scale on Day 28. The difference between the average corneal staining in the treated arm versus the average corneal staining in the sham arm will be compared statistically.

2- Patient reported symptom: Most bothersome symptom (any one of the (1)eye dryness, (2)eye discomfort, or (3)eye fatigue will be established as the most bothersome symptom at baseline for each eye) measured using visual analogue scale (0 to 100). The difference between the average most bothersome symptom in the treated arm versus the average most bothersome symptom in the sham arm will be compared statistically.

Secondary Efficacy:

We have two secondary end points:

1- Corneal staining responder analysis. Responder is defined as one full severity grade improvement in corneal staining. The percentage of subjects achieving 1 severity grade improvement in corneal staining (responders) in the treated arm versus sham arm will be compared statistically.

2- Symptom responder analysis. Responder is defined as 30% improvement in the most bothersome symptom. The percentage of subjects achieving a 30% improvement in their most bothersome symptom (responders) in the treated arm versus the sham arm will be compared statistically.

Safety: **Safety Endpoint(s):** Safety measures will be performed at 42 days. IOP measurement using applanation tonometry, cataract formation or worsening of cataract, other local adverse events (AEs) such as redness, pain, stinging, etc will be recorded.

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1. INTRODUCTION AND RATIONALE

1.1 Introduction

Dry eye is a common public health problem with an estimated 25 million Americans affected by this condition (1). It is a chronic, possibly progressive inflammatory condition that leads to symptoms of ocular discomfort as well as blurred vision (2). Regardless of the underlying etiology, dry eye has been shown to be associated with abnormalities in the pre-corneal tear film and subsequent inflammatory changes in the entire ocular surface including the adnexa, conjunctiva and cornea (3). Since the recognition of the role of inflammation in dry eye, a number of anti-inflammatory treatments have been investigated designed to inhibit various inflammatory pathways. Previously loteprednol etabonate 0.5% and dexamethasone 0.1% drops have been shown to improve ocular surface inflammation and benefit patients with dry eye (4-7).

1.2 Rationale

Previous studies showed that dexamethasone and loteprednol topical drops have led to favorable results (4-7). However, the requirement of frequent instillation of drops by the patients is problematic causing discomfort and blurring of vision and requires remembering and dexterity for instillation, poor compliance is not uncommon (7). In addition we believe that instillation of drops disturbs the homeostasis of the natural tear film due to physical and chemical trauma due to large drop volume (50 microliters) hammering on the eye surface (which can only hold 7 to 10 microliters). Particularly washing away of the mucin layer that holds all the "good ingredients" in the tears is harmful to the ocular surface. Therefore, "dropless" treatment of dry eye is desirable.

Dextenza® (dexamethasone ophthalmic insert, Ocular Therapeutix Inc., Bedford, MA) is a corticosteroid intracanalicular insert approved by US-FDA in November 2018 for the treatment of post-surgical ocular inflammation and pain. It is inserted into the lower lacrimal punctum and into the canaliculus. A single insert releases a 0.4 mg dose of dexamethasone for up to 30 days following insertion. Dextenza® is resorbable and does not require removal. We hypothesize that Dextenza® could mimic short-term topical steroid use in a tapering manner in patients with clinically significant dry eye and show efficacy in improving its symptoms and signs, as was previously shown with other steroid preparations. If proven, the use of Dextenza® may shift paradigms in the management of the clinically significant ocular surface disease. To test this hypothesis, we propose to study the effects of Dextenza® in the treatment of clinically significant dry eye. This proposal has several strengths over a non-masked protocol:

1- We have identified a tear duct plug with a comparable size (size 0.5mm) that lasts 60-180 days (Vera90TM). This would serve as an excellent comparison to Dextenza and allow the study to be a double-masked design. Both devices are not visible at the slit-lamp once inserted.
2- The investigator enrolling the patient (inserting the study treatment versus the control treatment) will be different than the examining investigator for each patient to allow the study to be truly double masked.
3- Because each patient will have one Dextenza eye and one control eye, the efficacy and safety of the treatment will be fairly, effectively, and accurately assessed. The

"patient" related factors in this small scale study (such as difference in use of computers or sleep/wake hours, environmental factors such as humidity during this short-term study, or severity of ocular surface inflammation particularly whether underlying Sjögren's syndrome is present or not, as well as the severity of evaporative component of the dry eye) will be comparable between the treatment and the control.

4- Also, this design allows both eyes of the same patients enrolled as study eyes thereby decreasing the sample size, hence the cost.

1.2.1 Rationale for Study Design

We determined the sample size using STATA Statistical Software (STATA Release 12.1; STATA Corp., College Station, TX). Standard deviations from previously published data sets were used for calculations (8).

Efficacy There will be two primary efficacy measures performed at day 28. The improvement in corneal staining score (using the OSS scale) and improvement in the most bothersome symptom (using the VAS scale between 0 to 100).

Efficacy Endpoint 1: Improvement in the corneal staining score measured using OSS scoring system (0-6). With a power of 80% and significance level of 0.05, 23 persons in each group (having both eyes eligible) need to be enrolled to detect a clinically significant 3 point difference in the mean corneal staining between the treated arm versus the sham arm at day 28.

Efficacy Endpoint 2: Improvement in most bothersome dry eye symptom as measured using VAS (0 to 100). With power of 80% and significance level of 0.05, 85 persons in each group (having both eyes eligible) need to be enrolled to detect a clinically meaningful 30 point difference in the most bothersome dry eye symptom Assuming that there will be a clinically significant 30% difference in the mean most bothersome symptom between the treated arm versus the sham arm at day 28.

One problematic issue in the field of dry eye is the lack of widely agreed upon core outcomes (9). It is currently not well known for example whether improving corneal staining is clinically meaningful and how much improvement would be necessary to make a difference in what the patient is experiencing. Our previous investigator initiated studies demonstrated that corneal fluorescein staining directly relates to impairment of visual function, and reduction in reading speed (10). The relationship is linear and for each 1 severity grade increase in corneal staining (0-6), we found an average of two words per minute reduction in reading speed, using iRest out loud testing and 10 words per minute reduction in reading speed using the sustained silent reading test. Therefore, perhaps corneal staining can be used as a clinically meaningful core outcome.

2. STUDY OBJECTIVES

2.1 Primary Objectives

To determine the safety and efficacy of dexamethasone insert at Day 28 and Day 42 respectively, as measured by –

- Improvement in the corneal fluorescein staining in the treatment arm versus the sham arm
- Improvement in most bothersome dry eye symptoms ((1) eye dryness, or (2) eye fatigue, or (3) eye discomfort) as measured using VAS (0 to 100) in the treatment arm versus sham arm
- We also will determine efficacy of the treatment by determining the responder rate in the treatment versus sham arm.
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- 1- One full severity grade improvement in corneal staining. The percentage of subjects achieving 1 severity grade improvement in corneal staining (responders) in the treated arm versus sham arm will be compared statistically

2- 30% improvement in the most bothersome symptom (responders). The percentage of subjects achieving a 30% improvement in their most bothersome symptom in the treated arm versus the sham arm will be compared statistically.

2.2 Secondary Objectives

To determine the safety of dexamethasone insert through Day 42, as measured by –

- Intraocular pressure monitoring
- Cataract formation or worsening of existing cataract as determined by slit-lamp examination and best spectacle corrected visual acuity.
- Other adverse events (unsolicited, but volunteered by the subjects)

3. STUDY DESIGN

3.1 Study Description and Duration

This prospective, double-masked, randomized, sham-controlled, single-center, phase IV investigator-sponsored clinical study seeks to investigate the safety and efficacy of dexamethasone 0.4 mg lacrimal insert over a 42 day period.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Study Population

The study aims to enroll 85 Patients (170 eyes) with dry eye syndrome (DES) or keratoconjunctivitis sicca (KCS), requiring topical steroid treatment.

4.1.1 Inclusion Criteria

A patient's study eye must meet the following criteria to be eligible for inclusion in the study:

1) Male or Female Age 18-100
2) Capacity to give informed consent
3) Ability to follow study direction and complete all study visits
4) A previous or current diagnosis of dry eye by an eye care specialist, whereas treatment is requiring the use of a topical steroid
5) Able to have a lacrimal plug placement into both lower puncta. If lower puncta are already plugged or cauterized/sealed, upper puncta will be used

6) Females of childbearing potential unwilling to use reliable form(s) of birth control throughout study period
7) Clinical diagnosis of dry eye syndrome (DES) or keratoconjunctivitis sicca (KCS), in which the following has been bilaterally documented in the ophthalmic and medical histories:
    i. history/diagnosis of dry eye
    ii. has taken or is on prescription drops (including but not limited to topical steroids, cyclosporine or lifitegrast)
8) Presence of all of the following in both eyes at Baseline (Day 1):
    i. Total OSS of 3 or more with at least 2+ corneal staining (0-6)
    ii. Unaesthetized Schirmer level of <10 mm at 5 minutes
    iii. Presence of significant symptoms defined as 30mm or higher score of (1) eye dryness, or (2) eye fatigue, or (3) eye discomfort as measured using VAS, in both eyes. At the baseline visit, the most bothersome symptom (of the three) will be determined and used as the main symptom outcome measure throughout the study.

4.1.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:
1) Use of Contact lenses within 1 week of screening visit or during the study
2) Any ocular surgery (including tear duct cauterization) within the 3 months
3) Inability to place a lacrimal device into upper or lower puncta of both eyes (if upper in R eye should be upper in the left eye and vice versa)
4) Inability to participate in the wash out period
5) Use of topical glaucoma medications (With exception of rescue medication)
6) Pregnancy, nursing or intention of pregnancy or nursing in the study period.
7) Monocular patients
8) Uncontrolled systemic disease (defined as frequent or recent change in the medication regimen)
9) Patients who are currently on with stable doses of oral steroids, topical cyclosporine or lifitigrast, topical tacrolimus or pimecrolimus are eligible as long as there has been no change in the dose in the last 3 months
10) Patients who are on topical steroids (with the exception of rescue medication) Patients who have used steroids recently but have been off for at least 2 weeks will be eligible.
11) Current enrollment in any other investigational drug or device study or participation of study within 30 days of baseline visit.
12) Known allergy or sensitivity to any of the clinical or experimental drugs used in this study including history of steroid response.

4.2 Treatment Logistics and Accountability

4.2.1 Packaging, Labeling, and Storage

Intracanalicular dexamethasone insert must be stored in a secure area accessible only to the Investigator and their designee(s) and refrigerated and stored between 2![ ]"C and 8#"C. Intracanalicular dexamethasone insert contains 0.4 mg dexamethasone and is designed to provide a sustained and tapered release of therapeutic levels of dexamethasone to the

ocular surface for up to 30 days. Dexamethasone is an anti-inflammatory 9-fluoro-glucocorticoid (also termed a glucocorticoid agonist) and is the active ingredient found in MAXIDEX® 0.1% (dexamethasone ophthalmic suspension), which contains approximately 50 µg of dexamethasone per drop.

Study inserts will be supplied in an unmasked fashion by Ocular Therapeutix in a sealed foil pouch containing one intracanalicular dexamethasone insert in a foam carrier.

Study inserts will be shipped to the site via overnight shipping using cold packs to maintain a temperature of 2° to 8° C. The Investigator, or an approved representative (e.g. pharmacist), will ensure that all study drug inserts are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. The shipping box is to be opened and stored immediately at the site in a refrigerator intended for investigational products at a temperature of 2° to 8°C.

When the insert is removed from the refrigerator, it should be visually inspected. Exposure of the insert to temperatures outside these limits it not recommended. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.

4.2.2 Supply and Disposition of Treatments

Study insert will be shipped at a temperature of 2° to 8°C to the investigator by sponsor as needed during the study.

4.2.3 Treatment Accountability

All study insert accountability records will be kept current.

The investigator will account for all opened and unopened packaging of study inserts. These records will contain the dates, quantity, and study medication

- Inserted in each patient,
- disposed of at the site or returned to Ocular Therapeutix

All accountability records will be made available for inspection by regulatory agency inspectors.

4.3 Concomitant Medications and Procedures

At the discretion of their physician, patients may continue to receive all medications and standard treatments administered for other conditions.

4.4 Potential Risks of Study

Steroids are known to increase eye pressure, which might be a finding of glaucoma, which is a vision threatening disease if not treated appropriately and promptly. In order to detect this, eye pressure will be checked at every visit as explained in sections: Schedule of Events (5.1), Study procedures (5.1.1), and rescue medications (5.2).

Additionally, steroids may mask signs of and enhance or and exacerbate the severity of ocular bacterial, viral, and fungal infections. The use of ocular steroids may slow the rate of ocular healing.

5. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

5.1 Schedule of Events

Study assessments and procedures are presented by visit in Table 1

Table 1 Schedule of Events

Procedure	Run In* (Day -14 to -7)	Visit 1* (Day 1)	Visit 2 (Day 14)	Visit 3 (Day 28)	Visit 4 (Day 42)	Early Termination
Informed Consent	X	X**				
Inclusion/Exclusion/Demographics	X	X**				
Medical history and concurrent illnesses	X	X**				
Concomitant medications	X	X	X	X	X	X
Pregnancy Test		X			X	X
Log/Dispense Rescue Meds	X	X	X	X	X	
Insert Study Drug/Control		X				
BSCVA		X			X	X
VAS	X	X		X	X	X
Schirmer (W/O anesthesia)	X	X			X	X
OSS (corneal and conjunctival)	X	X	X	X	X	X
IOP	X	X	X	X	X	X
SLE	X	X	X	X	X	X
Dilated Fundus Exam	X	X**			X	X
Rescue med recording	X		X	X	X	X
AE recording		X	X	X	X	X

*If no run-in required, patient will start at baseline visit/ Day 1

**Required in absence of run-in visit

After having obtained an informed consent patients will be assigned a unique patient number and undergo the below procedures in the order they are listed.

1. Medical History and Review of Systems
    i. Contact lens and glasses wearing (contact lens wear has to be discontinued 1 week prior and for the duration of the study)
    ii. Current eye drops used:
        a. Patients who are on dry eye drops, such as artificial tears, cyclosporine, or lifitigrast treatment will be eligible as long as the doses have been stable for at least 3 months
        b. Patients who are on steroid drops will be placed in a 14 day wash-out period, in both eyes, before they can be eligible. If in the discretion of the principle investigator, discontinuation of the topical treatment could pose any harm to the patient's ocular health, the patient will be excluded.
        c. Patients who are on anti-histamines, oral (doxycycline or azithromycin) or topical antibiotics (bacitracin or erythromycin ointment) are eligible for as long as the doses have been stable in the past 2 weeks

d. Patients who are on oral steroids or other anti-inflammatory or immunomodulatory medications are eligible for as long as the doses have been stable in the past 3 months
e. Patients using glaucoma drops in either eye will be excluded (with the exception of rescue medication)

iii. Current systemic medications (see above)
iv. History of eye diseases and previous eye or eyelid surgery
a. Patients who had eye surgery in the past 3 months prior to study are ineligible
b. Patients who had penetrating corneal transplantation are not eligible
c. Patients who had endothelial corneal transplantation are eligible as long as the surgery was 3 months or longer ago

v. History of other inflammatory or autoimmune medical disease (GVHD, RA, SLE, etc), in particular presence of SS (primary or secondary), and related symptoms.
a. These patients are eligible as long as they do not have cicatrizing conjunctivitis (such as SJS, MMP, etc)

2. Informed consent

Informed consent will be given to the patient to review at the time of approach in the clinical setting, or sent to the patients home if identified via chart review. The patient will be given ample time review the consent form, and will return on the day of the study visit with any questions. All questions will be answered and a discussion will be had with the person obtaining consent prior to the consent form being signed.

3. Pregnancy test

A standard urine pregnancy test provided by Ocular Therapeutix will be performed on women of childbearing potential at Baseline and Exit visit. A positive test will exclude patient from enrollment into the study as well as will be considered a serious adverse event if occurred during the study period.

4. Dry eye symptoms as measured using Visual Analog Scale (VAS).

Patients will complete VAS questionnaires for each eye in regard to eye dryness, eye discomfort, and eye fatigue. The most bothersome symptoms will be determined (of the three symptoms) at baseline and used throughout the study as the main symptom.

Patients will be given the questionnaire and expected to complete on their own. Help may be given to patients who have difficulty reading or understanding of the definition of the questions which will accompany the three questions.

The patient marks on the line the point that they feel represents their perception of their current state at each visit.

The VAS score is determined by measuring in millimeters using a ruler from the left hand end of the line (0) to the point that the patient marks, to a maximum 100.

5. Visual acuity (VA)

Distance visual acuity will be measured under monocular conditions using the subjects' habitual correction for distance (if wearing). The Snellen Chart will be used. If less than 20/20, pt will have Best Spectacle Corrected Visual Acuity (BSCVA) measured via Manifest Refraction.

6. Schirmer's test without anesthesia.

This test involves placing a small piece of filter paper against the conjunctiva for 5 minutes to observe how much tear volume is being produced in the temporal part of the lower cul-de-sac. The filter paper is removed after 5 minutes, and the length of the paper wetted is measured to approximate tear production. The testing will be performed as minimally disturbing to the ocular surface as possible. Time will be recorded if Schirmer's are completely saturated prior to the 5 minutes.

7. Ocular surface staining (OSS).
    i. Corneal fluorescein staining: About 2.5 minutes after instillation of the fluorescein eye drops (one drop of saline placed on the commercially available fluorescein strips) the staining will be scored according to the criteria published by SICCA (11).
    ii. Conjunctival lissamine green staining: Within 1 minute after instillation of lissamine green eye drops (one drop of saline placed on the commercially available strips) the staining will be scored. Conjunctival staining will be measured based on SICCA criteria (11).

8. Dilated Fundus Examination (DFE)

1 drop of Tropicamide 1% and Phenylepherine 2.5% will be used in each eye for purpose of dilation. Macula, blood vessels and cup to disk ratio will be recorded.

9. Insertion of study drug.

Treatment eye will be randomized by a Randomization list made by the Biostat Center at Johns Hopkins School of Medicine (using REDcap database) contralateral eye of each patient will serve as the control

The Treatment Physician will place the study device and contralateral plug/sham treatment at Day 1. The Treatment or the Examining physician can do the baseline exam.

The Examining Physician will perform the study exams (Day 1 through 42) to preserve masking.

10. Unmasking procedures (Day 42 or for serious AE)

All tests require both eyes testing and will be performed in the right eyes first, then the left eyes.

5.1.1 Study Procedures

Patients will be instructed not to instill any eye drops one hour prior to any study visit.

SCREENING VISIT/RUN IN (Day -14 to -7) – Either Examining or Treating physician will perform.

The following information will be collected:

- Informed Consent
- Inclusion/exclusion
- Demographics
- Medical history and concurrent illnesses
- Concomitant medications
- Log/Dispense Rescue medications
- Ocular Surface Disease Index Questionnaire (OSDI)
- Schirmer test without anesthesia
- OSS (Corneal and conjunctival)
- Intraocular Pressure (IOP)
- Slit Lamp Examination (SLE)
- Dilated Fundus Exam (DFE)
- Rescue Med Recording

BASELINE VISIT (Day 1)- Treating Physician (Unmasked)

If run-in Visit was NOT performed:

- Informed Consent
- Inclusion/Exclusion
- Demographics

- Medical History and concurrent illnesses
- Dilated Fundus Exam (DFE)

Needed for all Baseline Day 1:

- Concomitant medications
- Urine Pregnancy Test
- Log/Dispense Rescue Meds
- Insert Study Drug/Control
- Best Corrected Spectacle Visual Acuity (BSCVA)
- VAS
- Schirmer without anesthesia
- OSS
- IOP
- SLE
- AE recording

VISIT 2 (14+/-3 days) – Examining Physician (Masked)

- Concomitant medications
- Log/Dispense Rescue Meds
- OSS
- IOP
- SLE
- Rescue med recording
- AE recording

VISIT 3 (28+/-3 days) – Examining physician (Masked)

- Concomitant medications
- Log/Dispense Rescue Meds
- VAS
- OSS
- IOP
- SLE
- Rescue med recording
- AE recording

VISIT 4 (42+/-3 days) – Examining Physician

- Concomitant Medications
- Log/Dispense Rescue Meds
- Pregnancy Test
- BSCVA
- VAS

- Schirmer W/O anesthesia
- OSS
- IOP
- SLE
- Dilated Fundus Exam
- Rescue med recording
- AE recording

5.1.2 Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results or clinical findings (high IOP), for follow-up of AEs, or for any other reason, as warranted.

5.1.3 Adverse Event Information Collection

The investigator (or designee) will record all AEs that occur during the study.
The definition of an AE and SAE, and information on the determination of severity and relationship to treatment are provided in Section 7.

5.2 Safety and Rescue Criteria.

In the opinion of investigator, if the patient is at harm due to the treatment such as high eye IOP or due to control such as worsening of dry eye parameters, rescue medications can be used. To start IOP lowering medication, the IOP should be about 5 points higher than baseline. For additional dry eye medications/treatments the corneal staining should worsen a full severity grade.

5.2.1 Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug/treatment which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (i.e. any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.
All AEs in this study are Physician documented signs or results or exam findings. Local instillation discomfort, burning, stinging, blurred vision, redness etc will not be necessarily queried but documented in response to “how are you feeling” or how are your eyes feeling” questions.

5.2.2 Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (e.g. a car accident in which a patient is a passenger).

- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or prolongation of existing hospitalization. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse). Any malignancy (other than basal cell skin cancers) would be considered a medically important event.

Serious AEs will be queried by asking "has anything changed in your medical or ocular history since the last visit".

5.3 Recording and Reporting Adverse Events

All AEs and SAEs will be recorded.

All SAEs, regardless of assessment of causal relationship to study insert will be reported to Ocular Therapeutix.

To report an SAE, Ocular Therapeutix will be contacted at the following:

ocutx.pharmacovigilance@propharmagroup.com
SAE hotline: 844-668-3948

The investigator will promptly report to the IRB all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study insert. All SAEs will be reported to the IRB, regardless of assessed causality.

6. STUDY VARIABLES

6.1 Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (e.g. age, race, etc.), disease characteristics including medical history, and medication history for each patient.

6.2 Primary and Secondary Endpoints

6.3 Primary Objective(s)

To determine the efficacy of dexamethasone insert through Day 28, as measured by –

- Improvement in corneal staining score in the treatment versus sham arm
- Improvement in worst/most bothersome symptom in the treatment versus control group

In addition

- % of patients with improvement of corneal staining score by one severity grade (clinically meaningful) in treatment versus control group
- % of patients with improvement of worst/most bothersome symptom by 30 points (clinically meaningful) in the treatment versus control group

6.4 Secondary Objectives

To determine the safety of dexamethasone insert through Day 42, as measured by –

- Improvement in Schirmer test without anesthesia
- Improvement of conjunctival lissamine green staining score
- Intraocular pressure monitoring
- Cataract Formation
- Adverse Events

7. ETHICAL AND REGULATORY CONSIDERATIONS

7.1 Good Clinical Practice Statement

It is the responsibility of the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

7.2 Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP. Standard Johns Hopkins Hospital template must be used.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The informed consent form (ICF) will be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF will be retained by the investigator as part of the patient's study record, and a copy of the signed ICF will be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated appropriately. All study patients will be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF will be maintained in the patient's study record and a copy will be given to the patient.

7.3 Patient Confidentiality and Data Protection

The investigator will take all appropriate measures to ensure that the anonymity of each study patient will be maintained.

The patient's and investigator's personal data will be treated in compliance with all applicable laws and regulations.

7.4 Institutional Review Board

An appropriately constituted IRB, as described in ICH Guidelines for GCP, will review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (e.g. advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB will be informed as soon as possible

Ongoing studies will be reviewed by the IRB/EC on an annual basis or at intervals appropriate to the degree of risk.

In addition, the IRB will be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB approval letter will be sent to Ocular Therapeutix prior to shipment of drug insert supplies to the investigator. The approval letter will include the study title, the documents reviewed, and the date of the review.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) will be kept on file by the investigator.

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APPENDICES

Appendix 1

Ocular Surface Staining:

SICCA Ocular Staining Score

	Right Eye		Left Eye	
Staining pattern score:	Lissamine Green (conjunctiva only)	Fluorescein (cornea only)	Lissamine Green (conjunctiva only)	Fluorescein (cornea only)
	Grade / Dots	Grade / Dots	Grade / Dots	Grade / Dots
	0 / 0-9	0 / 0	0 / 0-9	0 / 0
	1 / 10-32	1 / 1-5	1 / 10-32	1 / 1-5
	2 / 33-100	2 / 6-30	2 / 33-100	2 / 6-30
	3 / >100	3 / >30	3 / >100	3 / >30
Extra points–fluorescein only: (Mark all that apply and add to fluorescein score)	☐ +1 - patches of confluent staining ☐ +1 - staining in pupillary area ☐ +1 - one or more filaments		☐ +1 - patches of confluent staining ☐ +1 - staining in pupillary area ☐ +1 - one or more filaments	
Total Ocular Staining score:	☐☐		☐☐	

Total ocular staining scores of 0 to 12 per eye assess the range of severity for keratoconjunctivitis sicca..

Appendix 2: VAS Scales

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Eye Dryness

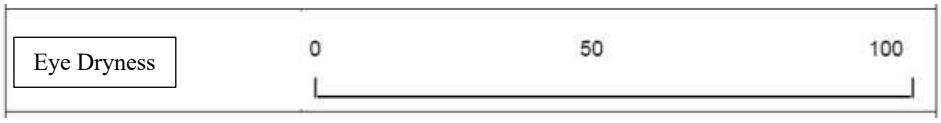
This questionnaire is in regards to your **current** eye dryness. Please remember to evaluate each eye separately.

Please rate your level of "eye dryness" by placing a vertical mark on the horizontal line on the below scale to indicate the level of dryness.

Please think of the feelings of dryness or "stickiness or the need for use of artificial tears BUT NOT sandiness/grittiness, sensitivity to light, redness, or itching.

Zero corresponds to "no dryness" and 100 correspond to "maximal dryness."

RIGHT EYE:



LEFT EYE:

Eye Discomfort

This questionnaire is in regards to your **current** eye discomfort. Please remember to evaluate each eye separately.

Please rate your level of "eye discomfort" by placing a vertical mark on the horizontal line on the below scale to indicate the level of discomfort.

Please think of pain, stinging, burning, sandiness/grittiness, sensitivity to light, itching, irritation or feeling that something is in the eye.

Zero corresponds to "no discomfort" and 100 correspond to "maximal discomfort."

Eye Fatigue

This questionnaire is in regards to your **current** eye fatigue. Please remember to evaluate each eye separately.

Please rate your level of "eye fatigue" by placing a vertical mark on the horizontal line on the below scale to indicate the level of fatigue.

Please think of feeling of heaviness in the lids, difficulty keeping eye open, difficulty reading, or just wanting to rest your eyes.

Zero corresponds to "no fatigue" and 100 correspond to "maximal fatigue."

RIGHT EYE:

LEFT EYE: