A randomized, controlled study to evaluate the safety and effectiveness of treatment with an intracanalicular dexamethasone (0.4mg) ophthalmic insert in the operating room following cataract surgery/intraocular lens implant (IOL) with or without iStent/Hydrus/Goniotomy when placed in the lower punctum vs the upper punctum

Investigational Product

Dexamethasone Ophthalmic Insert (0.4mg)

Version 01

26 April 2022

Sponsor

IWorks Laser and Vision Center

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations of specialist terms are used in this protocol:

Abbreviation	Meaning
AE	Adverse event
COVID-19	Coronavirus disease 2019
CRF	Case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
VA	Visual acuity

2 SYNOPSIS

Protocol Title	A randomized, controlled study to evaluate the safety and effectiveness of treatment with an intracanalicular dexamethasone (0.4mg) insert in the operating room following cataract surgery/intraocular lens implant (IOL) with or without iStent/Hydrus/Goniotomy when placed in the lower punctum compared to the upper punctum.
Phase of Clinical Study	Phase 4, Collaborative Study ✓
Investigational Product	DEXTENZA (dexamethasone ophthalmic insert, 0.4mg) for intracanalicular use
Study Objective	To assess the safety and effectiveness of treatment with an intracanalicular dexamethasone (0.4mg) insert in the operating room following cataract surgery/intraocular lens implant (IOL) with or without iStent/Hydrus/Goniotomy when placed in the lower punctum compared to the upper punctum.
Efficacy and Safety Endpoints	Primary Efficacy: • Absence of anterior chamber cells at Day 14 as measured by Summed Ocular Inflammation Score (0 to 4) • Absence of ocular pain at Day 8 as measured by ocular pain assessment numerical grading scale (0 to 10) Secondary Efficacy: • Mean change in BCVA from Baseline • Number and percentage of subjects with complete absence of pain • Number and percentage of subjects with complete absence of cell • Measuring cell, pain, and flare on Day 8, 14, 30 • Physician ease of insertion and visualization • Number of attempts to successfully insert Dextenza • Dry eye severity as measured by VAS at baseline, Day 8 and Day 30 • Record insert retention up to 30 days Safety: • Adverse events (AEs) • Intraocular pressure (IOP)
Number of Sites	Single site, United States (US)

Number of Subjects Planned	Up to 80 eyes; at least 60 eyes
Study Population	Subjects undergoing non-complicated CCI CE/PCIOL in one or both eyes with or without iStent/Hydrus/Goniotomy.
Study Design and Overview	This is a randomized, controlled study to evaluate the safety and effectiveness of treatment with an intracanalicular dexamethasone (0.4mg) insert in the operating room following cataract surgery/intraocular lens implant (IOL) with or without iStent/Hydrus/Goniotomy when placed in the lower punctum compared to the upper punctum. There will be approximately 80 eyes with two groups: **Group 1** (up to 40 eyes) will receive the insert in the lower punctum on the day of surgery in the OR. **Group 2** (up to 40 eyes) will receive the insert in the upper punctum on the of surgery in the OR. Each subject's participation is expected to last for approximately 1 month and will be required to complete six scheduled visits over the course of the study period: Baseline (Screening Visit), Operative Visit/Insertion Day (Day 0), Day 1, Day 8, Day 14 and Day 30.
Inclusion Criteria	Subjects will be eligible for study participation if they: 1. Are planning to undergo non-complicated CCI CE/PCIOL in one or both eyes with or without iStent/Hydrus/Goniotomy 2. Are willing and able to comply with clinic visits and study related procedures 3. Are willing and able to sign the informed consent form
Exclusion Criteria	Subjects are not eligible for study participation if they: 1. Have active infectious systemic disease 2. Have active infectious ocular or extraocular disease 3. Have unobstructed nasolacrimal duct in the study eye(s) (dacrocystitis) 4. Have known hypersensitivity to dexamethasone or are a known steroid responder 5. Have a history of ocular inflammation or macular edema 6. Are currently being treated with immunomodulating agents in the study eye(s) 7. Are currently being treated with immunosuppressants and/or oral steroids 8. Are currently being treated with corticosteroid implant (i.e. Ozurdex)

	9. Have a history of herpes simplex virus keratitis or present active bacterial, viral, or fungal keratitis in either eye 10. Have a history of complete punctal occlusion in one or both punctum 11. Currently use topical ophthalmic steroid medications 12. Are unwilling or unable to comply with the study protocol 13. Are determined by the Investigator to not be included for reasons not already specified (e.g., systemic, behavioral, or other ocular disease/abnormality) or if the health of the subject or the validity of the study outcomes may be compromised by the subject's enrollment
Sample Size Considerations	No formal sample size calculations were performed.
Statistical Methods	No formal statistical testing will be done. All data will be descriptive in nature. 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. Data will be displayed overall, as applicable.

3 PRINCIPAL CONTACTS

Please reference the Contact List.

4 BACKGROUND INFORMATION

4.1 Introduction

The Food and Drug Administration (FDA) has approved DEXTENZA, an ophthalmic insert containing 0.4 mg of dexamethasone, for the treatment of ocular inflammation and pain following ophthalmic surgery and for the treatment of ocular itching associated with allergic conjunctivitis. The ophthalmic insert is placed through the punctum, a natural opening in the eye lid, and into the canaliculus and is designed to provide a sustained and tapered release of dexamethasone to the ocular surface for up to 30 days. Following treatment, DEXTENZA resorbs and exits the nasolacrimal system without the need for removal.

In three randomized, multicenter, double-masked, parallel group, vehicle-controlled trials, patients received DEXTENZA or its vehicle immediately upon completion of cataract surgery. In all four trials, DEXTENZA had a higher proportion of patients than the vehicle group who were pain-free on postoperative Day 8. In two of the three trials, DEXTENZA had a higher proportion of patients than the vehicle group who achieved an absence of inflammation at Day 14. The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were anterior chamber inflammation including iritis and iridocyclitis (10%), intraocular pressure increased (6%), visual acuity reduced (2%), cystoid macular edema (1%), corneal edema (1%), eye pain (1%), and conjunctival hyperemia (1%) (Dextenza [package insert], 2021).

In a randomized, prospective, open-label interventional clinical study, DEXTENZA was evaluated and compared to topical prednisolone in patients undergoing bilateral laser-assisted in situ keratomileusis (LASIK) surgery. One eye was randomized to receive the dexamethasone insert or topical prednisolone acetate 1% four times daily for one week and 2 times daily for a second week; the fellow eye received the alternate therapy. After 1 month, 80% of patients preferred the dexamethasone insert to topical prednisolone acetate for post-operative treatment (Greenwood, et al. 2020). Additionally, the insert produced comparable ocular comfort, corneal staining, and visual acuity outcomes to topical prednisolone (Greenwood, et al. 2020).

4.2 Rationale for Study Design

Following ophthalmic surgery the current standard of care is to prescribe corticosteroid drops to treat both ocular pain and inflammation. Typically, a dose of topical corticosteroids is prescribed and tapered through the post-operative period, generally 2 to 4 weeks. Patients are expected to administer multiple drops, with differing administration regimens, through the days and weeks following surgery. There are limitations with the standard of care, including: patient noncompliance, difficulty in administration and poor accuracy of drop administration onto the ocular surface resulting in suboptimal doses of drug administered.

The hydrogel platform that allows for DEXTENZA to be a sustained release, dexamethasone delivery system, allows patients to eliminate topical corticosteroid medication which is associated with lack of compliance and difficulty with use. This clinical study will evaluate the safety and effectiveness of treatment with an intracanalicular dexamethasone (0.4mg) insert in the operating room following cataract surgery/intraocular lens implant (IOL) with or without iStent/Hydrus/Goniotomy when placed in the lower punctum compared to the upper punctum.

4.3 Risk-Benefit Analysis

4.3.1 Benefit

Dextenza has several potential advantages over topical corticosteroid drops given that it requires a single application that is relatively easy to insert using standard dilator and blunt, non-tooth forceps, helps potentially eliminate subject non-compliance with daily drops, delivers therapeutic levels of dexamethasone continuously for the intended duration of therapy, and is free of anti-microbial preservatives.

Dextenza demonstrated a statistically significant improvement over control treatment for both pain and inflammation in double-masked clinical trials. In addition, Dextenza was shown to be generally safe and well-tolerated in studies to date.

4.3.2 Risks

The following adverse reactions are typical adverse events that are known to be expected with the insertion procedure using a standard dilator and blunt, non-toothed forceps: eye pain and discomfort, tearing or epiphora (with or without mucopurulent discharge), eye inflammation, allergic reaction, dacrocystitis, canaliculitis, decreased/impaired visual acuity, stenosis (narrowing/closing of the punctum and/or canaliculus), perforation of or trauma to the punctum and/or surrounding tissues, inability to remove test article, need for surgery on the lacrimal system, infection or intraocular infection that if severe could lead to temporary or permanent impairment of eye sight.

Additionally, 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 DEXTENZA 0.4 mg dexamethasone insert. The following AEs and/or risks have been observed with the administration of corticosteroids: IOP increase/glaucoma/ocular hypertension, masking of infection or enhancing existing infections, delayed healing, cataracts. Other common risks (occurring in ≥1% of safety population) included anterior chamber inflammation, iritis, visual acuity reduced, corneal oedema, cystoid macular oedema, conjunctival hyperemia, eye pain, ocular discomfort, posterior capsule opacification, intraocular pressure increased, and corneal abrasion.

4.3.3 Minimization of Risks

With any product, there is always a chance of developing problems from the treatment. However, the risks associated with DEXTENZA have been minimized by 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 DEXTENZA Phase 2 and 3 studies, biocompatibility and preclinical testing, DEXTENZA has been shown to be safe and well tolerated in the eye.

The risks described above will be minimized via selection of experienced and board eligible or board-certified ophthalmologists/optometrists skilled in the use of intracanalicular inserts. All Investigators that will use the investigational product will undergo training per the instructions provided under separate cover. 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 study 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. Appropriate therapeutic intervention following standard medical practices will be used in the event of medical complications.

4.4 Compliance

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), including the International Council on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, adherence to all applicable local, state, and federal requirements relevant to the use of investigational products is required.

4.5 Trial Population

There will be approximately up to 80 eyes enrolled in this study that are planned to undergo non-complicated CCI CE/PCIOL in one or both eyes with or without iStent/Hydrus/Goniotomy.

5 TRIAL OBJECTIVES

The study objectives are to evaluate the safety and effectiveness of treatment with an intracanalicular dexamethasone (0.4mg) insert in the operating room following cataract surgery/intraocular lens implant (IOL) with or without iStent/Hydrus/Goniotomy when placed in the lower punctum compared to the upper punctum.

6 TRIAL DESIGN

6.1 Description of Trial

This is a randomized, controlled study to evaluate the safety and effectiveness of treatment with an intracanalicular dexamethasone (0.4mg) insert in the operating room following cataract surgery with or without iStent/Hydrus/Goniotomy when placed in the lower punctum compared to the upper punctum.

Each subject's participation is expected to last for approximately 1 month from the DEXTENZA insertion. Visit 1 is the surgical visit; subjects will return for post-operative visits on Day 1, Day 8, Day 14 and Day 30.

6.2 Study Endpoints

6.2.1 Primary Efficacy Endpoint

- Absence of anterior chamber cells at Day 14 as measured by Summed Ocular Inflammation Score (0 to 4)
- Absence of ocular pain at Day 8 as measured by ocular pain assessment numerical grading scale (0 to 10)

6.2.1.1 Secondary Efficacy Endpoint

- Mean change in BCVA from Baseline
- Number and percentage of subjects with complete absence of pain
- Number and percentage of subjects with complete absence of cell
- Measuring cell, pain, and flare on Day 8, 14, 30
- Physician ease of insertion and visualization

- Number of attempts to successfully insert Dextenza
- Dry eye severity as measured by VAS at baseline, Day 8 and Day 30
- Record insert retention up to 30 days

6.2.2 Safety Endpoints

- Adverse events (AEs)
- Intraocular pressure (IOP)

6.3 Randomization and Masking

This is an open-label study. All subjects will receive DEXTENZA. Subjects will be randomized to one of two treatment groups. Group 1 will receive the insert in the lower punctum on the day of surgery in the OR and Group 2 will receive the insert in the upper punctum on the day of surgery in the OR.

6.4 Trial Treatment

DEXTENZA (0.4 mg dexamethasone) will be administered into the canaliculus of the eye. The 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 for the reduction of post-operative inflammation and pain associated with ocular surgery. 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.

Insertion instructions will be provided under separate cover.

6.5 Trial Duration

Each subject's participation is expected to last for approximately 1 month from the DEXTENZA insertion.

6.6 Trial Material Handling and Accountability

The trial material used in this study is DEXTENZA (0.4 mg dexamethasone).

The trial material will be provided by Ocular Therapeutix, Inc. or its designee, and will be supplied in a sealed foil pouch containing one single DEXTENZA insert.

The trial material 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 the investigational product is 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 trial material at a temperature of 2° to 8°C.

The trial material 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. The trial material should be stored at controlled refrigerated temperatures from 2°C to 8°C. When the trial material is removed from the refrigerator, it should be visually inspected. Exposure of the trial material to temperatures outside these limits is not recommended.

The recipient will acknowledge receipt of the trial material indicating shipment content and condition. Damaged supplies may be replaced upon notification to Ocular Therapeutix, Inc. or its designee.

Accurate records of all trial material used by study site (e.g., dates, subject number, kits used, kits unused, etc.) should be maintained and recorded. A study team member will periodically check the supplies of trial material held at the site to verify accountability of all trial material. The Investigator must keep an accurate accounting of trial material received from the supplier by maintaining a detailed inventory. This includes the amount of trial material received by the site, amount used, the amount destroyed by the site, and the amount returned to the Sponsor or designee (as applicable) upon completion of the trial. All trial material that is used during the trial must be accounted for on a drug accountability form, or equivalent.

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

7 SELECTION AND WITHDRAWAL OF SUBJECT

There will be up to 80 eyes enrolled in this study.

7.1 Inclusion Criteria

Subjects will be eligible for study participation if they:

1. Are planning to undergo non-complicated CCI CE/PCIOL in one or both eyes with or without iStent/Hydrus/Goniotomy.
2. Are willing and able to comply with clinic visits and study related procedures
3. Are willing and able to sign the informed consent form

7.2 Exclusion Criteria

Subjects are not eligible for study participation if they:

1. Have active infectious systemic disease
2. Have active infectious ocular or extraocular disease
3. Have unobstructed nasolacrimal duct in the study eye(s)
4. Have known hypersensitivity to dexamethasone or are a known steroid responder
5. Have a history of ocular inflammation or macular edema
6. Are currently being treated with immunomodulating agents in the study eye(s)
7. Are currently being treated with immunosuppressants and/or oral steroids
8. Are currently being treated with corticosteroid implant (i.e Ozurdex)
9. Have a history of herpes simplex virus keratitis or present active bacterial, viral, or fungal keratitis in either eye
10. Have a history of complete punctal occlusion in one or both punctum
11. Currently use topical ophthalmic steroid medications
12. Are unwilling or unable to comply with the study protocol
13. Are determined by the Investigator to 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 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 2-digit subject number. The subject ID will be used as the primary subject identifier for the duration of the study. For example, Site 01 with the first subject would be 01-01.

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. 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 team members at any time, and a copy will be given to each subject.

7.4 Withdrawal Criteria

Subjects may withdraw from the clinical study at any time for any reason without jeopardy or prejudice and without compromising their clinical care by the Investigator. The Investigator also has the right to withdraw subjects from the trial in the event of an intercurrent illness, adverse event (AE), protocol deviation, and/or administrative reason.

If withdrawal occurs after insertion of DEXTENZA, but before all evaluations are completed, efforts should be made to complete the evaluations, and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation should be performed at the time of the subject's withdrawal with an explanation for the withdrawal. The reason for and date of the withdrawal must be recorded on the subject's case report form (CRF). If the reason for withdrawal is an AE, the AE should be monitored at the discretion of the Investigator (e.g., until the event is resolved or stabilized, the subject was referred to the care of a health care professional, or a determination of a cause unrelated to the trial material or insertion procedure). The specific event(s) or test result(s) are to be recorded in the CRF.

At least 3 documented attempts will be made to contact subjects who are non-compliant or lost to follow-up and such attempts will be documented in the subject's study record.

7.4.1 Withdrawal Methods

Ocular Therapeutix may terminate this study at any time if safety concerns arise. Reasons for termination may include but are not limited to, the following:

- The incidence or severity of AE in this or other studies point to a potential health hazard for trial subjects
- Any information becoming available during the study that substantially changes the expected benefit risk profile of the study product

7.4.2 Collection of Data from Withdrawn Subjects

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

7.4.3 Subject Replacement

Subjects who withdraw from the study after having DEXTENZA inserted will not be replaced.

8 SUBJECT TREATMENT

Appendix 3 VAS for Eye Dryness

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

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

0% corresponds to: "no discomfort"

100% corresponds to: "maximal (the most) discomfort"

Eye Dryness Severity	**0%**	**100%**
Eye Dryness Frequency	**0%**	**100%**

8.1 Treatment Regimen

The DEXTENZA insert will be administered, which is designed to be retained in the canaliculus where it provides sustained release of dexamethasone for approximately 30 days.

8.2 Prior and Concomitant Therapy

At the discretion of their physician, subjects may continue to receive all medications and standard treatments administered for other conditions. All medications will be collected, including those administered during the insertion procedure.

8.3 Product Quality Complaints

All product quality complaints should be reported to Ocular Therapeutix, by email to ocutx.productcomplaint@propharmagroup.com, or by phone: 1-800-339-8369, within 24 hours.

8.4 Study Assessment by Visit

8.4.1 Screening/Baseline Visit (Visit 1, Day -21 to -1)

At the Screening/Insertion Visit (Visit 1, Day -1), the following assessments will be performed. Ocular assessments will be performed in each eye:

- Informed consent
- Inclusion/exclusion criteria
- Demographics
- Medical and ocular history
- Prior and concomitant medications (record any medication that subject is taking as well as those taken in the previous 60 days)
- AEs (record incidence and severity of any adverse events that occur after the insertion)
- Distance VA
- Best-Corrected Visual Acuity
- Ocular pain assessment (0-10)
- Slit Lamp Examination (including anterior chamber cell count, and anterior chamber cell flare)
- Punctum examination (size and presence of any punctal plug)
- Grade cataract density (scale 1 to 4)
- Intraocular pressure
- Dilated fundus exam
- IOL measurement
- MAC OCT
- Dry eye severity as measured by VAS

8.4.2 Day of Surgery (Visit 2, Day 0)

At the Day of Surgery (Visit 2, Day 0), the following assessments will be performed:

- Prior and concomitant medication
- AEs (record incidence and severity of any adverse events that occur after the insertion)
- CE/PCIOL
- DEXTENZA insertion
- Indicate number of attempts to successfully insert DEXTENZA
- Insert visualization
- Record phacoemulsification time
- Indicate the incision type, location, and size (mm)
- Prescribe post-operative topical therapy regimen – No topical NSAID's
- Physician ease of insertion and visualization

8.4.3 Post-Operative Day 1 (Visit 3, Day 1)

At the Day after Surgery (Visit 3, Day 1), the following assessments will be performed:

- Prior and concomitant medication
- AEs (record incidence and severity of any adverse events that occur after the insertion)
- Distance visual acuity (VA)
- Ocular pain assessment (0 to 10)
- Slit lamp examination (including anterior chamber count and anterior chamber flare)
- Insert visualization

8.4.4 Post-Operative Day 8 (Visit 4, Day 8) Day 14 (Visit 5, Day 14) and Day 30 (Visit 6, Day 30)

At the Day 8, Day 14 and Day 30 Visits, the following assessments will be performed:

- Prior and concomitant medication
- AEs (record incidence and severity of any adverse events that occur after the insertion)
- Distance visual acuity (VA)
- Best-Corrected Visual Acuity
- Ocular pain assessment (0 to 10)
- Slit lamp examination (including anterior chamber count and anterior chamber flare)
- Intraocular pressure
- Insert visualization

- MAC OCT Day 30
- Dry eye severity as measured by VAS on Day 8 and Day 30

9 ADVERSE EVENTS

The Investigator and study staff are responsible for detecting and recording AEs and serious adverse events (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 AEs 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 subject 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 DEXTENZA 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 DEXTENZA or a concurrent medication (overdose per se should not be reported as an AE/SAE).

9.2 Definition of Serious Adverse Event

A 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 a 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/SAEs

Not applicable.

9.4 Monitoring and Recording of AEs and SAEs

9.4.1 Adverse Events

Any AE experienced by the subject from the Screening/Baseline Visit after insertion of the DEXTENZA, through the 29-Day PostInsertion Visit is to be recorded in the CRF, 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 the Screening/Insertion Visit through the 29-Day Post-Insertion Visit is to be recorded on a 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 a SAE as defined in Section9.2
- 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 a 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. It is the Investigator's responsibility to ensure that the SAE 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.

Figure 3 Reporting Information for SAEs and Pregnancies

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

Email: ocutx.pharmacovigilance@propharmagroup.com

Phone: 800-339-8369

Fax: 866-681-1063

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 3.

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 CRF. 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.

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

9.7.2 Relationship to Investigational 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 procedure or the product. If the Investigator determines that the AE is unlikely to be related to the study drug or procedure, then this would be the appropriate category.

Related The following criteria should be applied in considering inclusion of a (S)AE in this category:

a. It bears a reasonable temporal relationship to the procedure or the presence of DEXTENZA.

b. 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

c. It disappears or decreases on removal of the IP

d. It follows a known pattern of response to the procedure or the product

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.

9.7.4 Clarifications

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

Hospitalization Hospitalization for the elective treatment of a pre-existing condition (i.e., a condition present prior to the subject's signature of the informed consent) that did not worsen during the study is not considered a SAE. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or meets any of the other SAE criteria, the complication is a SAE.

Pre-existing Conditions Pre-existing conditions (i.e., conditions present or detected at the start of the study) which worsen during the study, exacerbation of a pre-existing illness or an increase in frequency or intensity of a pre-existing episodic event or condition are (S)AEs. Anticipated day-to-day fluctuations of pre-existing condition(s) that do not worsen with respect to baseline are not (S)AEs.

Medical or Surgical Procedure Medical or surgical procedures (e.g., colonoscopy) are not (S)AEs; however, the condition that leads to the procedure may be considered a (S)AE.

In the case of elective medical or surgical procedures, or pre-study planned medical or surgical procedures for pre-existing conditions (i.e., a condition present prior to the subject's signature of the ICF) that did not worsen during the study the condition that leads to the procedure does not need to be reported as a (S)AE.

Death Death is not a SAE; the condition that leads to the death is a SAE.

Abnormal Laboratory Value In the absence of a diagnosis, abnormal laboratory values that are judged by the Investigator to be clinically significant must be recorded as a (S)AE. Clinical significant abnormal laboratory findings that are present at baseline and significantly worsen following the start of the study will also be reported as a

(S)AE.

9.8 Pre-scheduled or Elective Procedures or Routinely Scheduled Treatments

A pre-scheduled or elective procedure or routinely scheduled treatment will be allowed at the investigators discretion.

9.9 Procedures for Handling Special Situations

9.9.1 COVID-19 Pandemic

In response to the coronavirus disease 2019 (COVID-19) pandemic, study visits and procedures/assessments should be conducted in accordance with the protocol if at all possible. If a subject is unable to attend a scheduled study visit in the per-protocol timeframe due to COVID-19 restrictions, visit windows may be extended to accommodate subject availability. Alternatively, if a subject is unable to attend a study visit in-person due to COVID-19 restrictions, a televisit should be conducted (if possible) in accordance with the visit schedule, with a focus on completion of safety assessments.

9.10 Pregnancy

Not applicable. Age limitation will exclude the possibility of pregnancy.

9.10.1 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 Institutional Review Board (IRBs)/Independent Ethics Committee (IEC) and Investigators, as needed.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Statistical Methods

This study is designed to be descriptive in nature; therefore, there will be no formal statistical analyses completed. There will be a general statistical analysis plan (SAP) that will briefly summarize how the data will be presented. 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.

10.2 Sample Size Determination

No formal sample size calculations were performed.

10.3 Statistical Significance

There will be no formal statistical analyses performed. All summaries will be descriptive in nature.

10.4 Subject Population for Analysis

Subjects undergoing non-complicated CCI CE/PCIOL in one or both eyes with or without iStent/Hydrus/Goniotomy. All safety and efficacy analyses will be performed on the safety population.

10.5 Demographics and Baseline Data

Subject disposition will be presented, including the number of subjects screened, enrolled, and treated. The number of subjects who completed the study and reasons for discontinuation will be summarized.

Demographic and baseline characteristics (including medical history) will be summarized.

10.6 Primary Efficacy Analysis

The primary efficacy endpoints are:

- Absence of anterior chamber cells at Day 14 as measured by Summed Ocular Inflammation Score (0 to 4)
- Absence of ocular pain at Day 8 as measured by ocular pain assessment numerical grading scale (0 to 10)

Anterior chamber cells and ocular pain will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

10.7 Secondary Efficacy Analysis

Secondary Efficacy Endpoints are

- Mean change in BCVA from Baseline
- Number and percentage of subjects with complete absence of pain
- Number and percentage of subjects with complete absence of cell
- Measuring cell, pain, and flare on Day 8,14,30
- Physician ease of insertion and visualization
- Number of attempts to successfully insert Dextenza
- Dry eye severity as measured by VAS at baseline, Day 8 and Day 30
- Record insert retention up to 30 days

Mean change in BCVA from baseline will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

The number and percentage of subjects with complete absence of pain and with complete absence of cell will be summarized.

The number and percentage of investigators' responses to ease of insertion and visualization (easier, the same, and more difficult) will be summarized.

The number of attempts to successfully insert DEXTENZA will be summarized.

Dry eye severity as measured by VAS will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

Insert retention as measured by yes or no will be summarized.

10.8 Safety Analyses

10.8.1 Adverse Events

Incidence of adverse events will be tabulated by MedDRA System Organ Class and preferred term within each system organ class. Serious adverse events and adverse events related to study drug will be summarized similarly. Ocular and non-ocular adverse events will be summarized separately.

10.8.2 IOP

The observed values and change from baseline values for IOP will be summarized by visit.

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 SAP, the final clinical study report will describe them.

10.10 Trial Termination

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

11 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 contract research organization, drug safety, Sponsor, IRB/IEC approving this trial, FDA, 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 electrocardiograms.

11.3 Case Report Forms

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

corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled 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. Data will not be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the CRF database. After the end of the trial and database lock, electronic media containing copies of all applicable subjects' CRFs 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 2 years after the conclusion of this study. 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/IEC. 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 may conduct monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed.

13 COMPLIANCE WITH GOOD CLINICAL PRACTICES AND ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of ICH, GCP Guidelines, consistent with the 1996 version of the Declaration of Helsinki, and any applicable government regulations.

13.1 Protection of Human Subjects

The protection of human subjects will follow the applicable regulations of the local health authority and will be the responsibility of the Principal Investigator.

13.2 Compliance with Informed Consent Regulations

An IRB/IEC approved ICF, signed and dated by both the subject and the approved study staff presenting the consent, is required from each subject prior to enrollment into the study and before any study specific procedures are initiated.

If at any point during the subject's participation in the study the ICF requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the revised ICF is approved by Ocular Therapeutix and the IRB/IEC. The updated and IRB/IEC approved ICF must be presented to the subject, and signed and dated by both the subject, and the study staff presenting the consent as per IRB/IEC requirements.

13.3 Compliance with IRB/IEC Regulations

This protocol, the ICF, relevant supporting information, and all types of subject recruitment or advertisement information will be submitted to the IRB/IEC for review and must be approved before the study is initiated and re-approved at least annually. Any amendments to the protocol must also be approved by the IRB/IEC prior to implementing changes in the study. The Investigator is responsible for keeping the IRB/IEC 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.

13.4 Subject Confidentiality

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

Monitors, auditors, and other authorized representatives of Ocular Therapeutix, the IRB/IEC approving this study, and other regulatory agencies, as appropriate, will be granted direct access to the study subjects' original medical and study records for verification of the data and/or clinical trial procedures.

14 REFERENCES

Dextenza [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2019.

Greenwood MD, Gorham RA, Boever KR. A randomized fellow-eye clinical trial to evaluate patient preference for dexamethasone intracanalicular insert or topical prednisolone acetate for control of postoperative symptoms following bilateral femtosecond laser in site keratomileusis (LASIK). Clin Ophthalmol. 2020;14:2223-8.

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Appendix 1 Table of Assessments

	Screening/Baseline Visit (Day -21 to -1)	Surgical Visit (Day 0)	Post-Operative Day 1 (Day 1)	Post-Operative Day 8 (Day 8)	Post Operative Day 14 (Day 14)	Post-Operative Day 30 (Day 30)	Early Termination Visit[5]
Visit Window				+/- 2 days	+/- 3 days	+/- 3 days	
Study Assessment	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	
Informed Consent	X						
Inclusion/Exclusion	X						
Demographics	X						
Medical & Ocular History	X						
Prior and Concomitant Medications	X[1]	X	X	X	X	X	X
Adverse Events	X[2]	X	X	X	X	X	X
Distance VA	X		X	X	X	X	X
BCVA	X		X	X	X	X	X
Ocular Pain Assessment	X		X	X	X	X	X
Slit Lamp Examination (including anterior chamber cell count & flare)	X		X	X	X	X	X
Punctum examination (size and presence of any punctal plug)	X						
Grade cataract density (1 to 4)	X						
Macular OCT	X					X	
Intraocular Pressure	X		X	X	X	X	X
Dilated Fundus Examination	X						X
IOL Measurement	X						
Cataract Extraction/IOL		X					
Intracanalicular Dexamethasone Insert Placement		X[3]					

Insert Visualization		X[4]	X	X	X	X	X
Phacoemulsification Time		X					
Indicate the incision type, location, and size (mm)		X					
Prescribe post-op topical therapy regimen		X					
VAS Dry Eye Severity	X			X	X	X	
Physician ease of insertion and visualization		X					
Record number of attempts to successfully insert DEXTENZA		X					

1. Record any medications the subject is taking, as well as those the subject has taken in the previous 60 days prior to Visit 1.
2. Record all adverse events that occur before and after the insertion of the intracanalicular dexamethasone insert in Visit 2 and all adverse events in Visits 3, 4 and 5.
3. To be done in the OR for Group 1 and Group 2
4. To be done after the insert is placed in the OR for Group 1 and Group 2. Visualization will continue to be done at all visits thereafter.
5. Early termination subjects should complete assessments based on the final visit schedule of assessments.