Investigator-Initiated Study Protocol

A **R**andomized, Controlled, Masked (Reading Center) Prospective Study of the **E**ffectiveness and **S**afety of the Ocular **T**herapeutix Dextenza (dexamethasone **O**phthalmic insert) 0.4 mg for the treatment of post-operative inflammation and pain in patients who have undergone Photo**RE**fractive Keratectomy (PRK)

The **RESTORE** Study

Compound:	DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg for intracanalicular use
Study Name:	A Randomized, Controlled, Masked (Reading Center) Prospective Study of the Effectiveness and Safety of the Ocular Therapeutix Dextenza (dexamethasone ophthalmic insert) 0.4 mg for the treatment of post-operative inflammation and pain in patients who have undergone Photorefractive Keratectomy (PRK)- The RESTORE Study
Clinical Phase:	Prospective, Randomized, Controlled, Masked Investigator-Initiated Trial
Date of Issue:	December 17, 2019
Primary Investigator:	John Berdahl, MD
Sub Investigator:	Mitch Ibach, OD
Site Name & Location:	Vance Thompson Vision Center 3101 West 57th Street Sioux Falls, South Dakota 57108

CLINICAL STUDY PROTOCOL SYNOPSIS	
TITLE	A Randomized, Controlled, Masked (Reading Center) Prospective Study of the Effectiveness and Safety of the Ocular Therapeutix Dextenza (dexamethasone ophthalmic insert) 0.4 mg for the treatment of post-operative inflammation and pain in patients who have undergone Photorefractive Keratectomy (PRK)
SITE LOCATION(S)	Vance Thompson Vision Center 3101 West 57th Street Sioux Falls, South Dakota 57108
PRINCIPAL INVESTIGATOR	John Berdahl, MD
OBJECTIVE(S)	To determine patient preference and treatment outcomes with an intracanalicular dexamethasone (0.4mg) insert compared to standard steroid drop regimen in the contralateral eye following bilateral PRK surgery.
STUDY DESIGN	Prospective Open-label Interventional Study Randomized, self-controlled design in which one eye (Group A) receives Dextenza and the second eye (Group B) receives prednisolone acetate 1% QID 1 week, BID 1 week following bilateral PRK surgery. All eyes will receive topical moxifloxacin QID for one week. Moxifloxacin in used post-op regardless of the research. Post-operative evaluations to be performed on Day 3 and Day 4, Month 1, and Month 3. Phone call survey to be performed on Week 2.
STUDY DURATION	3 months
ESTIMATED STUDY COMPLETION DATE	January 2021
POPULATION Sample Size: Target Population:	 N=20 (40 eyes) Patients planning to undergo bilateral Photorefractive Keratectomy (PRK) surgery.
TREATMENT(S)	

Study Drug	DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg for intracanalicular use
Dose/Route/Schedule:	All patients will be enrolled for bilateral PRK surgery. The first eye will be randomized to Group A or B; the second eye will be selected for the opposite group. Group A will receive Dextenza at the time of PRK surgery while Group B will receive prednisolone acetate 1% QID 1 week, BID 1 week following bilateral PRK surgery. All eyes will receive topical moxifloxacin QID for 1 week. Moxifloxacin is used post-op regardless of the research.
ENDPOINT(S)	
Primary:	Adapted COMTOL Survey
Secondary:	Percentage of eyes epithelialized at POD 4 Corneal Staining Corneal haze Ocular Pain Assessment Uncorrected distance visual acuity Corrected distance visual acuity Manifest refraction spherical equivalent Modified SPEED questionnaire
Safety:	IOP spikes (increase of 10 mm Hg or greater than baseline) Adverse events

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1. INTRODUCTION AND RATIONALE

1.1 Introduction

Photorefractive Keratectomy (PRK) is a well-studied, FDA approved, refractive surgery option for many patients. Post-operatively patients are commonly treated with antibiotic drops for infection prophylaxis, steroid drops for inflammation and corneal haze prevention, and finally NSAIDs (non-steroidal anti-inflammatory drugs) for pain management. Although the types of medications are standardized, there are many different protocols that vary based on surgeon and practice preference.

Post-operative drop regimens frequently induce both concerns and questions for patients undergoing ocular surgery. Poor compliance with post-operative medications can lead to unexpected and or unsatisfactory outcomes. With refractive surgery visual outcomes and safety at such a high level, patient satisfaction and experience can be altered by post-operative convenience.

Dextenza (dexamethasone 0.4mg ophthalmic insert) is a steroid eluting intracanalicular plug approved on-label for the treatment of pain and post-operative inflammation in patients who've undergone ocular surgery. Utilizing Dextenza, in place of ophthalmic steroid drops, will provide patients with a lessened number of post-operative drops which decreases both contamination possibilities and improper drug installation. Dextenza's hydrogel technology is proposed to offer patients a gradual sustained delivery of steroid to the ocular surface which may decrease subjective post-operative pain.

The tear film is a key component in corneal epithelial healing as well as refractive outcomes in PRK. In many studies, inflammation and inflammation markers are a driver to decreasing tear film homeostasis. With an intracanalicular steroid plug there is potential benefit to restoring tear film homeostasis sooner, combined with increased tear volume, leading to improved epithelialization and refractive outcomes. Finally, intracanalicular steroid plugs offer patients a preservative free steroid option to further promote epithelial health by decreasing topical preservatives.

1.2 Rationale

DEXTENZA (dexamethasone 0.4mg ophthalmic insert) has increasing research and evidence for post-cataract surgery patients, but a gap remains in many other ophthalmic surgeries. Refractive surgery, similar to cataract surgery, has post-operative visual acuity as a major determinant of surgery success. Dextenza's ability to treat post-operative inflammation while also increasing remaining tear volume by punctal occlusion has potential to improve visual outcomes for patients while also decreasing post-operative drop inconvenience.

1.2.1 Rationale for Study Design

This prospective contralateral eye study will compare the outcomes of 20 patients undergoing bilateral PRK. In one eye the patient will receive a topical steroid and the contralateral eye will receive a Dextenza ophthalmic insert. Both eyes will receive a topical antibiotic.

The primary endpoint of patient preference and pain was chosen based on previous studies that have shown decreasing topical medications increases patient satisfaction. Secondary endpoints including SPEED survey and corneal staining were chosen to test the hypothesis of less ocular surface disease with Dextenza. Time to epithelialization will be studied to see the positive or neutral effects of steroid plus punctal occlusion on epithelialization. Finally, the other secondary endpoints are standard measures for PRK.

The study inclusion and exclusion criteria were chosen based on patients who normally would be successful with laser refractive surgery. The study follow-up visits were based on the Vance Thompson Vision standard post-operative follow-up protocols.

2. STUDY ENDPOINTS

2.1 Primary Endpoint

To determine at Month 1 (Day 28 +/-3 days):

- Patient preference as measured by adapted COMTOL survey at Month 1 following surgery.

2.2 Secondary Endpoints

To determine at Post-Operative Day 3 and 4:

- Percentage of eyes epithelialized at Day 3 and Day 4.

To determine through Month 1 (Day 28 +/- 3 days):

- Mean pain score per eye (Group A vs. Group B) as measured by the Numerical Rating Scale (NRS) at Day 3, Day 4, Week 2 (collected via telephone survey), and Month 1.
- Patient preference as measured by a modified SPEED questionnaire at Pre-op Visit and Month 1.

To determine through Month 3 (+/- 4 days):

- Incidence and grade of post-operative corneal haze as measured by Heidelberg Anterior Segment OCT at Pre-op Visit, Month 1, and Month 3.
- Post-operative corneal staining score as measured by the National Eye Institute (NEI) grading system at Day 3, Day 4, Month 1, and Month 3.

- Uncorrected visual acuity as measured by ETDRS chart at 4m at Month 1 and Month 3.
- Best-corrected visual acuity as measured by ETDRS chart at 4m at Month 1 and Month 3
- Manifest Refraction Spherical Equivalent as measured by the Optometrist at Month 1 and Month 3.

2.3 Safety Endpoints

To determine through Month 3 (+/- 4 days):

- Incidence of increased IOP >10 mmHg above baseline at all timepoints
- Occurrence of adverse events at all timepoints

3. STUDY DESIGN

3.1 Study Description and Duration

This prospective, open-label, single-center, randomized, investigator-sponsored clinical study seeks to investigate the outcomes of patients undergoing bilateral PRK surgery with the treatment of a dexamethasone intracanalicular insert compared to topical standard of care steroid. All eyes will receive treatment. Additionally, all eyes will receive topical moxifloxacin QID for 1 week. Moxifloxacin is used post-op regardless of the research.

Twenty patient eyes undergoing bilateral PRK surgery will be randomized to receive either Dextenza (Group A) OR standard of care prednisolone acetate 1% QID for 1 week, BID for 1 week (Group B). The contralateral eye will receive treatment with either Dextenza or topical prednisolone as a comparator based on randomization of first eye to Group A or Group B. Post-operative evaluations to be performed on Day 3, Day 4, phone call survey at Week 2, Month 1, and Month 3.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Study Population

The study aims to enroll 20 patients planning to undergo bilateral PRK surgery.

4.1.1 Inclusion Criteria

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

- Any adult patient who is planned to undergo bilateral PRK surgery.
- Willing and able to comply with clinic visits and study related procedures
- Willing and able to sign the informed consent form

4.1.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

- Patients under the age of 18.
- Patients who are pregnant (must be ruled out in women of child-bearing age with pregnancy test).
- Active infectious ocular or systemic disease.
- Patients with active infectious ocular or extraocular disease.
- Patients actively treated with local or systemic immunosuppression including systemic corticosteroids.
- Patients with known hypersensitivity to Dexamethasone.
- Patients with severe disease that warrants critical attention, deemed unsafe for the study by the investigator.
- Patients with a history of ocular inflammation or macular edema.
- Patients with allergy or inability to receive intracameral antibiotic.
- Patients on systemic non-steroidal anti-inflammatory drugs (NSAID) greater than 1,200 mg/day
- Patients with a corticosteroid implant (i.e. Ozurdex).
- Patient with corneal pathology which pre-disposes them to unsatisfactory outcomes.
- Patients who do not have 20/20 snellen visual acuity potential pre-operatively.
- MRSE greater than 6 diopters.
- Greater than 2 diopters anisometropia.

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^{o} C and 8^{0} 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 for the reduction of post-surgical 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.

Study inserts will be supplied 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 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.

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

Study Procedure	Screening/ Baseline	Surgical Visit Day 0	Day 3	Day 4	Day 14	Day 28	3 MTH post-op	Early Termination
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**Phone call 1**	**VISIT 5**	**VISIT 6**	
Windows for Visits	**(Day -30 to -1)**				**(+/- 2 days)**	**(+/- 3 days)**	**(+/- 3 days)**	
Inclusion/Exclusion	X							
Informed Consent	X							
Demographics	X							
Medical History and Concurrent Illnesses	X							
Concomitant Medications	X	X	X	X		X	X	
Randomization	X							
Confirm Treatment Group		X						
Uncorrected Distance VA testing	X					X	X	
Manifest Refraction	X					X	X	
BCVA (ETDRS at 4m)	X					X	X	
Corneal Haze (via AS-OCT)	X					X	X	
Intraocular Pressure	X		X	X		X	X	
Corneal Staining	X		X	X		X	X	
Slit Lamp Exam	X		X	X		X	X	
Ophthalmic Examination (dilated fundus exam)	X							
Ocular Pain Assessment	X		X	X	X	X		
SPEED Questionnaire	X					X		
COMTOL Survey						X		
Record any surgical complications		X						
Subject reported AEs prior to or after surgery	X	X	X	X	X	X	X	
Intracanalicular dexamethasone insert*		X						
Prescribe post-operative topical therapy regimen**		X						
Insert Visualization			X	X		X	X	

*Eye Randomized to Group A

**Specific for each eye based on Group A or B

5.2 Study Visit Descriptions

5.2.1 Study Procedures

Visit 1: Screening/Baseline (Day -30 to -1)

After the patient has provided informed consent, the following information will be collected:

- Inclusion/exclusion

- Demographics
- Medical History and Concurrent Illnesses
- Concomitant Medications
- Randomization
- Uncorrected Distance visual acuity as measured by ETDRS chart at 4m
- Manifest Refraction
- Best-corrected visual acuity as measured by ETDRS chart at 4m
- Corneal haze (via AS-OCT)
- Intraocular pressure
- Corneal Staining
- Slit Lamp Exam
- Ophthalmic Examination (dilated fundus exam)
- Subject reported AEs prior to or after surgery
- Ocular pain assessment
- Modified Speed questionnaire

Visit 2: Surgical Day 0

- Concomitant medications
- Confirm treatment group
- Record any surgical complications
- Subject reported AEs prior to or after surgery
- Intracanalicular dexamethasone insert
- Prescribe post-operative topical therapy regimen

Visit 3: Day 3

- Concomitant medications
- Intraocular pressure
- Corneal staining
- Slit lamp exam
- Subject reported AEs prior to or after surgery
- Insert visualization
- Ocular pain assessment

Visit 4: Day 4

- Concomitant medications
- Intraocular pressure
- Corneal staining
- Slit lamp exam
- Subject reported AEs prior to or after surgery
- Insert visualization
- Ocular pain assessment

Phone Call 1: Day 14 (+/- 2 days)

- Subject reported AEs prior to or after surgery
- Ocular pain assessment

Visit 5: Day 28 (+/- 3 days)

- Concomitant medications
- Uncorrected Distance visual acuity as measured by ETDRS chart at 4m
- Best-corrected visual acuity as measured by ETDRS chart at 4m
- Manifest refraction
- Corneal haze
- Intraocular pressure
- Corneal staining
- Slit lamp exam
- Subject reported AEs prior to or after surgery
- Insert visualization
- Ocular pain assessment
- Modified Speed questionnaire
- Adapted COMTOL Survey

Visit 6: Month 3 (+/- 3 days)

- Concomitant medications
- Uncorrected Distance visual acuity as measured by ETDRS chart at 4m
- Best-corrected visual acuity as measured by ETDRS chart at 4m
- Manifest refraction
- Corneal haze
- Intraocular pressure
- Corneal staining
- Slit lamp exam
- Subject reported AEs prior to or after surgery
- Insert visualization

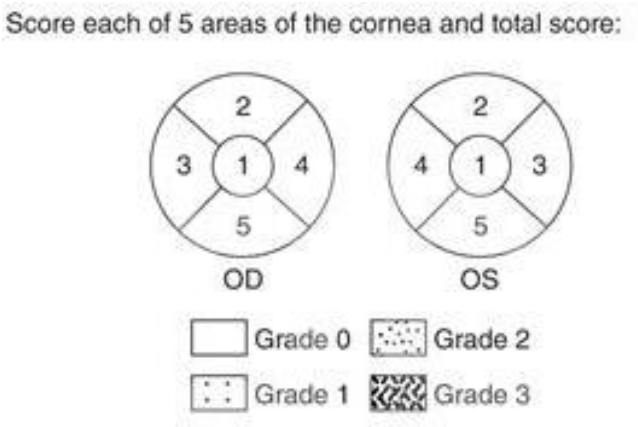
Medical and Ocular History obtained: The site will ask and document all past Ocular history, relevant medical history and surgical history. A list of current medications, dose, route, start date and indications will be obtained and documented for each subject. There will be a subsequent diagnosis and start date for each medication.

BCDVA on ETDRS chart: (manifest refraction performed if vision is worse than 20/20 with current MRx). The BCDVA will be captured on an ETDRS worksheet and calculated

Slit Lamp Examination (SLE): Slit lamp examination will be performed on the study eye and fellow eye of each subject by a masked examiner, and will include assessment of the lids and lashes, conjunctiva, tear film, cornea, anterior chamber, iris, and lens. At the screening/Day 0 visit, and 30 day/exit visit SLE will be performed both prior to and following application of the ELM or Lipiflow.

Corneal Staining: A drop of fluorescein will be instilled on the eye, then the masked examiner will use the cobalt blue filter on the slit-lamp to examine the cornea. A grading scale of 0 to 3 is used to evaluate each of the five areas on the cornea. 0 being no staining to 3 being severe staining. All areas are then added together for a maximum score of 15.

National Eye Institute/Industry Grading System



5.2.2 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, for follow-up of AEs, or for any other reason, as warranted.

If patient presents on POD 4 and have not epithelialized, patient will be brought in on POD 5 to re-assess epithelialization and remove bandage contact lens (BCL). This will be collected as an unscheduled visit.

5.2.3 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 6.

5.3 Rescue Criteria

If the investigator determines either eye requires additional post-operative treatment, topical prednisolone acetate 1% therapy may be added to the DEXTENZA eye or increased dosing frequency may be offered to eyes receiving topical prednisolone acetate 1%. The investigator may also prescribe either or both topical cyclosporine 0.05% or topical cyclosporine 0.09%.

6. SAFETY DEFINITIONS, REPORTING, AND MONITORING

6.1 Definitions

6.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug 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.

6.1.2 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.

6.2 Recording and Reporting Adverse Events

All AEs and SAEs will be recorded only if they are medically relevant.

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.

7. STUDY VARIABLES

7.1 Demographic and Baseline Characteristics

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

8. ETHICAL AND REGULATORY CONSIDERATIONS

8.1 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.

8.2 Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP.

Ocular Therapeutix will have the right to review and comment on the informed consent form.

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 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.

8.3 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.

8.4 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.

REFERENCES

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2. Walters TR, Bafna S, Vold S, et al. Efficacy and Safety of Sustained Release Dexamethasone for the Treatment of Ocular Pain and Inflammation after Cataract Surgery: Results from Two Phase 3 Studies. *J Clin Exp Ophthalmol*. 2016;7(4):1-11.
3. Tyson SL, Bafna S, Gira JP, et al. Multicenter randomized phase 3 study of a sustained-release intracanalicular dexamethasone insert for treatment of ocular inflammation and pain after cataract surgery. [published correction appears *in J Cataract Refract Surg*. 2019;45(6):895]. *J Cataract Refract Surg*. 2019;45(2):204-212.