Clinical Study Protocol

ProSpective StUdy on DEXTENZA® SafeTy And EffIcacy following coNcomitant MIGS and Cataract Surgery

The SUSTAIN Study

Compound:	Sustained Release Dexamethasone, 0.4 mg
IND Number:	146602
NCT:	04200651
Study Name:	Prospective Study on DEXTENZA® Safety and Efficacy following concomitant MIGS and Cataract Surgery
Clinical Phase:	Phase IV open label prospective
Date of Issue:	10/18/2020
Primary Investigator:	Nathan M. Radcliffe, MD
Sub Investigator:	Nicholas Tan
Site Name & Location:	New York Eye Surgery Center, 1101 Pelham Pkwy N, The Bronx, NY 10469

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	Prospective Study on DEXTENZA® Safety and Efficacy following concomitant MIGS and Cataract Surgery
SITE LOCATION(S)	New York Eye Surgery Center, 1101 Pelham Pkwy N, The Bronx, NY 10469
PRINCIPAL INVESTIGATOR	Nathan M. Radcliffe, MD
OBJECTIVE(S)	To compare dexamethasone insert to topical corticosteroid use through 90 days in glaucomatous eyes undergoing MIGS and cataract surgery as measured by: visual acuity, IOP control, adverse events, control of inflammation, macular health, and patient comfort.
STUDY DESIGN	Prospective Fellow-Eye, Randomized Open-label Interventional Study
STUDY DURATION	Fourteen months, including enrollment period
ESTIMATED STUDY COMPLETION DATE	February 2022
POPULATION	
Sample Size:	40 eyes
Target Population:	Patients with cataract and glaucoma
TREATMENT(S)	
Study Drug	Sustained Release Dexamethasone, 0.4 mg
Dose/Route/Schedule:	All study eyes will receive cataract extraction, IOL placement, minimally-invasive glaucoma surgery, and a postoperative topical antibiotic prescription. 20 eyes will be randomized to receive Sustained Released Dexamethasone, 0.4 mg. 20 eyes will be prescribed a prednisolone acetate 1% regimen.
ENDPOINT(S)	
Primary:	1. Reduction in IOP at 1 and 3 months 2. BCVA at 1 and 3 months 3. Difference in adverse events between groups 4. Difference in # of glaucoma meds at 3 months
Secondary:	1. Number of patients requiring supplemental prednisolone acetate 1% eye drops 2. Incidence of CME at 90 days as seen on OCT 3. Difference in Ocular Comfort Index between groups at 1 month and 3 months 4. Difference in % of patients with absence of

anterior chamber cells at 30 days between groups

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1. INTRODUCTION

1.1 Type of study

This is a drug study. The IND number is: 146602.

1.2 Introduction

Following cataract surgery, the standard of care for controlling ocular inflammation has historically been a topically applied anti-inflammatory eye drop regimen. Such drops utilize steroids or non-steroidal anti-inflammatory drugs, with steroid drops being more commonly prescribed (Juthani et al. 2017). Sustained-release steroid inserts, such as the FDA-approved intracanicular dexamethasone insert DEXTENZA®, have provided a "dropless" alternative to steroid eye drop regimens. DEXTENZA® was shown to be safe and effective following cataract surgery, in terms of ocular pain and anterior chamber cell clearance, in a multi-center trial (Tyson et al. 2018). However, in prior studies of DEXTENZA®, none have specifically examined the safety and efficacy of the insert in a glaucoma patient population. Furthermore, none have examined the outcomes of the insertion of DEXTENZA® following both cataract surgery and a minimally invasive glaucoma surgery (MIGS). DEXTENZA® may be of utility to glaucoma patients because it can simplify one's combined eye drops regimen. A complicated medication schedule is a significant risk factor for poor adherence to glaucoma medication instructions (Newman-Casey et al. 2015). Furthermore, given that steroid eye drops are already administered after concomitant cataract and MIGS surgery, it is highly plausible that DEXTENZA (which uses a steroid as its active ingredient) should be similar in safety. This prospective fellow-eye study will thus target glaucomatous eyes to explore the further applications of DEXTENZA®.

1.3 Rationale

Glaucoma and cataract surgery patients face an outsize postoperative burden. In addition to taking frequent anti-inflammatory eye drops, they often continue their glaucoma medications. This can cause patient confusion and nonadherence, potentially leading to poor healing, slower recovery period, and/or cystoid macular edema. DEXTENZA®, as a sustained release anti-inflammatory insert, could help preclude adherence difficulties and increase comfort by reducing eye drop load. However, glaucoma surgeons may hesitate to adopt DEXTENZA® due to concerns regarding safety with respect to elevated intraocular pressure. This prospective study will address those concerns directly, providing timely and high-quality clinical evidence comparing DEXTENZA® to standard-of-care steroid eye drops. For physicians and patients, the results of this study will prove immediately useful for therapeutic decision-making.

1.4 Purpose

The purpose of this study is to compare the safety and efficacy of sustained-release dexamethasone insert (DEXTENZA®) to steroid eye drops after glaucoma and cataract surgery.

1.5 Rationale for Study Design

This prospective study will enroll 40 eyes from a variable number of total patients. The total patient number may vary due to the enrollment of both eyes from some patients where possible. All eyes will receive concomitant cataract and MIGS surgery. Each eye will be randomized to receive either insertion at the end of the surgery or to a standard of care prednisolone acetate 1% eye drop regimen. All eyes will receive the standard of care topical ofloxacin antibiotic regimen. The experimental group will consist of the 20 eyes receiving DEXTENZA® insertion. The control group will consist of the 20 eyes placed on the prednisolone eye drop regimen.

In terms of study procedures, the majority are among cataract and MIGS preoperative, perioperative, and postoperative standards of care. Such procedures include: pachymeter, indirect ophthalmoscope, slit lamp exam, BCVA, IOP, visual field, OCT RNFL, corneal endothelial microscopy and gonioscopy. The ocular response analyzer will record corneal hysteresis data. Corneal hysteresis, as a measure of the cornea's ability to dampen in response to an external force, has been shown in multiple studies to serve as an independently valuable risk factor indicating glaucoma progression (Lam et al. 2010; Agarwal et al. 2012; Medeiros et al. 2013). To better inform the treatment of glaucoma patients during this study, the ocular response analyzer is a valid and useful tool.

In terms of primary study endpoints, change in IOP values at 1 and 3 months are crucial for quantifying glaucoma outcome differences between groups. We will use three methods to comprehensively assess IOP changes, including Goldmann applanation tonometry, CATS tonometer prism, and the automatic IOP readings provided by the ocular response analyzer. Goldmann is the current standard of care, and thus will be the primary measure. However, CATS tonometry is a valuable supplement because it utilizes a modified prism that may better account for central corneal thickness and corneal hysteresis when providing IOP measurements (McCaffertey et al. 2019). Change in number of glaucoma medications from preop to 3 months postop will be serve as an additional metric to compare glaucoma outcomes. BCVA measurements using an ETDRS chart at 4 meters will indicate whether DEXTENZA® placement in this population affects the visual acuity improvement conferred by an IOL and MIGS. Recording adverse events is necessary not only for the integrity of the study, but also for evaluating the safety of the DEXTENZA® insert for this study population.

In terms of secondary endpoints, the number of patients requiring

supplementary prednisolone acetate 1% eye drops will be recorded to compare ocular inflammation between groups. Checking for absence of anterior chamber cells at 30 days will provide another measure of control of inflammation. Incidence of cystoid macular edema at three months will be used to compare macular health between groups.

In previous trials of sustained-release ocular therapeutics, authors have commented on the need to explore patient experience as an additional measure (Kindle et al. 2018). Two modalities will be used to evaluate patient experience between groups. The Ocular Comfort Index (OCI) will be used to quantify ocular comfort. The OCI is a 12-item Likert-style questionnaire designed to assess the severity of ocular surface irritation. Authors compared the OCI against the Ocular Surface Disease Index and tear-break up time (TBUT) values, and also examined changes in OCI scores after application of lubricant to dry eyes (Johnson and Murphy 2007). Statistical analysis of those three constructs support the use of the OCI to help quantify dry eye disease severity. Although participants in this study will not represent a dry eye disease population, the OCI nevertheless provides quantifiable data on general discomfort in each eye. For sustained released dexamethasone specifically, some physicians may be wary that its location in the punctum may contribute to discomfort in a way that an intracameral or intravitreal steroid would not. The OCI would address such concerns directly. From a clinical utility standpoint, the OCI is favorable due to the questionnaire's free access, an included Excel calculator for rudimentary data analysis, and the brevity of the 12-item questionnaire. Administering the OCI at 1 month postop and 3 months postop will offer insight into both the immediate and delayed changes in ocular comfort for each group.

2. STUDY OBJECTIVES

2.1 Primary Objective

To determine the effect of dexamethasone insert through 90 days as measured by –

- Visual acuity
- IOP control
- Adverse events

2.2 Secondary Objectives

To determine the effect of dexamethasone insert through 90 days as measured by –

- Control of inflammation
- Macular health
- Patient comfort

3. STUDY DESIGN

3.1 Study Description and Duration

This prospective, open-label, single-center, randomized, fellow-eye,

investigator-initiated clinical study seeks to investigate the safety and efficacy of the dexamethasone insert in glaucoma patients after concomitant MIGS and cataract surgery. After screening a given patient for inclusion and exclusion criteria, and gaining informed consent, the patient's eligible eye will be randomized to either receive the dexamethasone insert after concomitant cataract-MIGS or to receive prednisolone acetate 1% eye drops after concomitant cataract-MIGS. For participants who enroll only a single eye, block randomization will be performed to ensure that the type of MIGS surgeries will be balanced between the two treatment groups. This stratification is necessary because it is possible that different MIGS devices can confound endpoint measurements, such as IOP control. A stratified block randomization schedule will be developed in advance by the sub-investigator through a computer program, and each assignment will be placed in opaque, sealed envelopes that will be labeled with the stratifying MIGS category. The primary investigator will only open an envelope after a patient is enrolled and the MIGS type that is suitable for the patient is determined. In the few cases where a patient enrolls both eyes, the same MIGS surgery will be performed for each eye. Under such a circumstance, simple randomization will be sufficient to determine whether the first or second eye operated on will receive the dexamethasone insert. The other eye will be placed in the prednisolone acetate 1% eye drops group.

Per enrolled eye, the study period will last for approximately 90 days after surgery, consisting of four postop follow-up visits. At Day 1, Day 7, Day 30, and Day 90, primary and secondary endpoints will be assessed alongside standard-of-care procedures. Adjusting for enrollment period, the study will last a total of approximately twelve months.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Study Population

This study aims to enroll 40 eyes from patients with both cataract and glaucoma.

4.1.1 Inclusion Criteria

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

- At or over the age of 21
- Cataract surgery candidate and glaucoma present in at least one eye
- Minimally-invasive glaucoma surgery candidate in at least one eye. Defined by having ocular hypertension requiring a medication, OR as by having mild, moderate, or severe glaucoma that is sufficiently stable and appropriate for operation.

4.1.2 Exclusion Criteria

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

- Maintains regular use (daily or more) of systemic or ocular steroids at time of enrollment
- Maintains regular use (daily or more) of systemic or ocular non-steroidal anti-inflammatory drugs at time of enrollment
- Anterior chamber cells present at time of enrollment
- Recent febrile illness that precludes or delays participation for 3 months
- Pregnancy or lactation
- Known allergy to dexamethasone
- Known allergy to prednisolone
- Treatment with another investigational drug within the last 20 years
- Current recreational drug use
- Preexisting ocular pathology likely to confound the visual acuity or comfort endpoints including but not limited to: severe corneal scarring, ocular surface disease, diabetic retinopathy, or macular edema
- Corneal or retinal procedures (laser or incisional) during the study period and 6 months prior in either eye

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 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 1	Day 7	Day 30	3 MTH post-op	Early Termination
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5**	**VISIT 6**	
Windows for Visits	**(Day -90 to -1)**		**(+/- 2 days)**	**(+/- 2 days)**	**(+/- 7 days)**	**(+/- 14 days)**	
Inclusion/Exclusion	X						
Informed Consent	X						
Demographics	X						
Medical History and Concurrent Illnesses	X						
Concomitant Medications (inc. glaucoma meds and supp. prednisolone)	X		X	X	X	X	
BCVA (ETDRS at 4m)	X		X	X	X	X	
Visual field mean deviation	X					X	
Ophthalmic Examination (dilated fundus exam)	X		X	X	X	X	
Cataract density grade (scale 1 to 4) and type	X						
Glaucoma type and severity	X						
OCT RNFL & Macula	X					X	
Intraocular Pressure (Goldmann and CATS)	X		X	X	X	X	
Corneal Endothelial Specular Microscopy	X					X	
Gonioscopy	X					X	
Ocular Response Analyzer	X					X	
Pachymeter	X						
Indirect Ophthalmoscope	X					X	
Indicate the incision type, location, and size (mm)		X					
Type of IOL (e.g. monofocal, toric, multifocal, etc.) and lens power	X	X					
Type of MIGS device	X	X					
Record any surgical complications		X					X
Subject reported AEs prior to or after surgery	X		X	X	X	X	X
Intracanalicular dexamethasone insert		X					
Ocular Comfort Index					X	X	
Anterior chamber cell count			X	X	X	X	
Anterior chamber cell flare			X	X	X	X	
Insert Visualization			X	X	X	X	
Prescribe post-operative topical therapy regimen			X				

5.2 Study Visit Descriptions

5.2.1 Study Procedures

Screening/Baseline (Day -90 to -1)

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

1. Inclusion/exclusion
2. Demographics
3. Medical history and concurrent illnesses
4. Concomitant medications
5. Best-corrected visual acuity as measured by ETDRS chart at 4m
6. Visual field mean deviation
7. Ophthalmic examination
8. Grade cataract density and identify type
9. Glaucoma type and severity
10. OCT RNFL & Macula
11. Goldmann Intraocular pressure and CATS intraocular pressure
12. Corneal endothelial specular microscopy
13. Gonioscopy
14. Ocular Response Analyzer
15. Pachymeter
16. Indirect ophthalmoscope
17. Type of IOL
18. Type of MIGS device (Hydrus, iStent, canaloplasty, or Kahook Dual-Blade)
19. Subject reported AEs prior to surgery

Surgical visit/Day 0

1. Indicate the incision type, location, and size
2. Type of IOL
3. Type of MIGS device (Hydrus, iStent, canaloplasty, or Kahook Dual-Blade)
4. Record any surgical complications
5. Intracanicular dexamethasone insert

Day 1 postop (+/- 2 days)

1. Concomitant medications
2. Best-corrected visual acuity as measured by ETDRS chart at 4m
3. Ophthalmic examination
4. Goldmann Intraocular pressure and CATS intraocular pressure
5. Subject reported AEs after surgery
6. Anterior chamber cell count
7. Anterior chamber cell flare
8. Insert Visualization
9. Prescribe post-operative topical therapy regimen

Day 7 postop (+/- 2 days)

1. Concomitant medications

2. Best-corrected visual acuity as measured by ETDRS chart at 4m
3. Ophthalmic examination
4. Goldmann Intraocular pressure and CATS intraocular pressure
5. Subject reported AEs after surgery
6. Anterior chamber cell count
7. Anterior chamber cell flare
8. Insert Visualization

Day 30 postop (+/- 7 days)

1. Concomitant medications
2. Best-corrected visual acuity as measured by ETDRS chart at 4m
3. Ophthalmic examination
4. Goldmann Intraocular pressure and CATS intraocular pressure
5. Subject reported AEs after surgery
6. Anterior chamber cell count
7. Anterior chamber cell flare
8. Insert Visualization
9. Ocular Comfort Index

3 month postop (+/- 14 days)

1. Concomitant medications
2. Best-corrected visual acuity as measured by ETDRS chart at 4m
3. Ophthalmic examination
4. Goldmann Intraocular pressure and CATS intraocular pressure
5. Corneal endothelial specular microscopy
6. Subject reported AEs after surgery
7. Anterior chamber cell count
8. Anterior chamber cell flare
9. Insert Visualization
10. OCT RNFL & Macula
11. Visual field mean deviation
12. Gonioscopy
13. Ocular Response Analyzer
14. Ocular Comfort Index
15. Indirect ophthalmoscope

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.

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 7.

5.3 Rescue Criteria

Rescue criteria include any of the following: moderate to severe photophobia, moderate to severe ciliary or conjunctival injection, or excessive anterior chamber cells or flare.

Rescue treatment would include supplementary prednisolone acetate 1% drops and/or topical NSAIDs, at the discretion of the study doctor.

6. Risk/Benenfit Assessment

6.1 Risks

Use of corticosteroids on the eye, whether they are steroid drops or sustained-release inserts like DEXTENZA®, can worsen glaucoma with damage to the optic nerve by increasing intraocular pressure. Corticosteroids may suppress the host immune system and increase risk for bacterial infection, fungal infection, and viral infection. The use of steroids after eye surgery may delay healing and increase the incidence of bleb formation. DEXTENZA® may be ineffective. DEXTENZA® may cause discomfort in the eye. DEXTENZA® may involve unforeseeable risks. DEXTENZA® may involve additional risks that are currently unknown. Because DEXTENZA® is FDA approved for the treatment of postoperative ocular inflammation and pain, minimal overall risk to patients is anticipated.

6.2 Prevention of Risks

At each follow-up visit, risks will be monitored through conversations with the participant regarding their postoperative issues and visualized thorough all components of the ophthalmic exam (please see Table 1). Rescue treatment will be administered as per the criteria of section 5.3.

6.3 Benefits

For the eye receiving DEXTENZA®, a potential benefit is that the participant will not have to take steroid eye drops in that eye after surgery. DEXTENZA® may potentially be more comfortable and/or convenient than steroid eye drops. The results of this study will benefit future patients by providing clinical evidence comparing the safety and efficacy of DEXTENZA® to steroid eye drops in eyes with glaucoma and a cataract.

6.4 Alternative Treatments

Steroid eye drops are the standard-of-care alternative to DEXTENZA®. Also, DEXYCU® is another type of sustained-release dexamethasone drug that is currently FDA-approved for the same indication as DEXTENZA®. DEXYCU® is injected inside the eye, behind the iris of the eye. No currently published study has compared DEXTENZA® to DEXYCU®, so the relative advantages and disadvantages are not clearly known.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1 Definitions

7.1.1 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.

7.1.2 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.

7.2 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.

8. STUDY VARIABLES

8.1 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.

8.2 Primary and Secondary Endpoints

Primary Endpoints

Effect of dexamethasone insert through Day 90 as measured by –

1. Mean Reduction in IOP at 1 and 3 months as measured by Goldmann Applanation Tonometer and comparison between groups
2. Mean change in ETDRS BCVA at 1 and 3 months and comparison between groups
3. Difference in adverse events between the two groups
4. Difference in number of glaucoma medications between the wo groups at 3 months

Secondary Endpoints

Through Day 90 as measured by –

1. Number of patients requiring supplemental prednisolone acetate 1% eye drops
2. Incidence of CME at 90 days as seen on OCT

3. Difference in Ocular Comfort Index between the two groups at 1 month and 3 months
4. Difference in percentage of patients with absence of anterior chamber cells at 30 days between groups

9. STATISTICAL PLAN

Primary endpoints and secondary endpoints will be analyzed through statistical hypothesis testing. Demographic and baseline characteristics will be summarized descriptively. Continuous variables will be summarized with mean, median, and standard deviation. Categorical variables will be summarized with frequency and percentage.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1 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.

10.2 Recruiting

Participants will be recruited from the New York Eye Surgery Center in the Bronx, NY. Potential participants will be identified based on information in their medical records and most recent exam findings. The investigator will discuss the study with potential participants at their check-up appointment. The potential participant will be provided with information on the study device, the study protocol, risks and benefits, patient data security, procedures if an adverse event occurs, travel compensation, and the informed consent form. The investigator will present reasonable alternatives to the study device. The investigator will emphasize that participation is entirely voluntary, and that neither the patient's relationship with the investigator nor his/her quality of care will be impacted by the decision to or to not participate. The investigator will encourage the potential participant to ask questions, and will respond to whatever questions arise.

10.3 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.

10.4 Storage of Data

Data from the study will be stored in paper files and electronically. The investigator, sub-investigator, study staff, and Ocular Therapeutix will have access to the data purely for research purposes. Microsoft Excel and the Medflow electronic medical record system will be used to manage and extract patient data.

10.5 Confidentiality of Data

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.

Paper files will be secured in a locked drawer accessible only to the investigator, the research assistant, and study staff. Medflow data will be stored under password protection in the servers of the New York Eye Surgery

Center. Excel spreadsheet data will be stored locally in the sub-investigator's password-protected and antivirus-secured Macbook laptop. Participant names will be coded by randomized numbers.

10.6 Participant Comprehension and Capacity

To assess comprehension, the potential participant will be asked to "teach back" to the principal investigator what he/she learned about the study from the informed consent form. At minimum, they will be quizzed on: 1) What DEXTENZA® does; 2) Risks to participating; 3) How many follow-up visits they are expected to attend; 4) How late the participant's second eye's surgery can be scheduled after the first eye surgery; and 5) What happens in the event of a complication. Potential participants will also be asked to voice any questions they have to the principal investigator.

10.7 Costs to Participants

The study doctor, Dr. Radcliffe, will be covering the costs of all procedures and necessary follow-ups associated with the study.

10.8 Compensation to Participants

Participants will receive $10 at each post-surgical follow up visit, per eye, in order to cover the costs of travel. If a participant completes all four post-surgical follow-up visits in one eye, the participant will have received $40 in total. If a participant enrolls two eyes and completes a total of eight post-surgical follow-up visits, he or she will have received $80 in total.

10.9 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

Agarwal DR, Ehrlich JR, Shimmyo M, et al. The relationship between corneal hysteresis and the magnitude of intraocular pressure reduction with topical prostaglandin therapy. *Br J Ophthalmol.* 2012 Feb;96(2):254-7.

Johnson ME, Murphy PJ. Measurement of Ocular Surface Irritation on a Linear Interval Scale with the Ocular Comfort Index. *Invest Ophthalmol Vis Sci*. 2007;48(10):4451.

Juthani VV, Clearfield E, Chuck RS. Non-steroidal anti-inflammatory drugs versus corticosteroids for controlling inflammation after uncomplicated cataract surgery. *Cochrane Database Syst Rev*. 2017;7(7):CD010516.

Kindle T, Ferguson T, Ibach M, et al. Safety and efficacy of intravitreal injection of steroid and antibiotics in the setting of cataract surgery and trabecular microbypass stent. *Journal of Cataract & Refractive Surgery*. 2018;44(1):56-62.

Lam A, Chen D, Tse J. The usefulness of waveform score from the Ocular Response Analyzer. *Optomet Vis Sci.* 2010;87:195–199.

McCafferty SJ, Tetrault K, McColgin A, Chue W, Levine J, Muller M. Modified Goldmann prism intraocular pressure measurement accuracy and correlation to corneal biomechanical metrics: multicentre randomised clinical trial. *Br J Ophthalmol*. 2019;103(12):1840.

Medeiros FA, Meira-Freitas D, Lisboa R, et al. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. *Ophthalmology*. 2013;120:1533-1540.

Newman-Casey PA, Robin AL, Blachley T, et al. The most common barriers to glaucoma medication adherence: a cross-sectional survey. *Ophthalmology*. 2015;122(7):1308–1316.

Potvin R, Fisher B. Transzonular vitreous injection vs a single drop compounded topical pharmaceutical regimen after cataract surgery. *Clinical Ophthalmology*. 2016;Volume 10:1297-1303.