EvaluaTion of the Safety and Efficacy of SustaiNed Release Dexamethasone Intracanalicular Insert (DEXTENZA) in pEdiatric patients following Retinal surgery or laser treatment under anesthesia

The TENDER Study

Compound:	DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg, for intracanalicular use
Study Name:	The TENDER Study
Clinical Phase:	Investigator-Initiated Clinical Trial
Protocol Version:	2.0
Date of Issue:	9/12/2022
Primary Investigator:	Lejla Vajzovic, MD
Sub Investigator:	Xi Chen, MD
Site Name & Location:	Duke University Eye Center Durham, NC

NCT05620901

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Clinical Study Protocol Synopsis

Title	The EvaluaTion of the Safety and Efficacy of SustaiNed Release Dexamethasone Intracanalicular Insert (DEXTENZA) in pEdiatric patients following Retinal surgery or laser treatment under anesthesia
Site Location(s)	Duke University Eye Center
Principal Investigator	Lejla Vajzovic, MD
Objective(s)	To determine safety and efficacy of the dexamethasone ophthalmic insert in pediatric patients following retinal surgery or laser treatment under anesthesia
Study Design	Prospective Open-label Interventional Study
Study Duration	45 days postoperative
Estimated Study Completion Date	August 1, 2023
Population	
Sample Size:	30
Target Population:	Pediatric patients ages 3 to 17 undergoing routine retinal surgeries or laser treatment under anesthesia
Study Drug	DEXTENA (dexamethasone ophthalmic insert) 0.4 mg, for intracanalicular use
Dose/Route/Schedule:	All eyes will undergo routine retinal surgery or laser treatment under anesthesia. Patients in each treatment group (surgery or laser) will be randomized 2:1 at the time of surgery/laser to either: 1) Treatment Arm: Dextenza insert intraoperatively for perioperative ocular inflammation and pain. These patients will not be prescribed topical

steroid drops post-operatively, or

2) Control Arm: Prednisolone forte 1% steroid drop taper for 28 days post-operatively to treat perioperative ocular inflammation and pain; drops four times per day (QUID) on days 0-7, three times per day (TID) on days 7-14, twice per day (BID) on days 14-21 and once per day (QD) on days 21-28.

Each treatment group (surgery or laser) will include 15 patients total, 10 receiving Dextenza and 5 receiving the control drug.

Drops for dilation and antibiotic coverage will be used as clinically indicated in all groups and arms.

There will be a total of six visits for both treatment arms Screening/Baseline visit (day -30 to 0), Surgical Visit (day 0), and four post-operative follow up appointments occurring at post-op day 1, 7, 28/30 and 45 (+/- three days for all post-operative timepoints). Exams to be performed on these days are outlined in section 5.1.. Treatment Arm Schedule of Events in Table 1. Control Arm Schedule of Events in Table 2

Endpoint(s)

Primary Endpoint:

To evaluate if pediatric patients receiving retinal surgery or laser would benefit from DEXTENZA implant compared to topical ocular drop therapy to manage post-operative pain (measured with the Face, Legs, Activity, Cry Consolability (FLACC) Behavioral Pain Rating Scale). Pain will be measured at each visit with final outcome determined by the FLACC Pain Rating Scale score on day 45 (final visit).

Secondary Endpoints:

- Incidence and severity of adverse events from baseline through post-op day 45
- Degree of inflammation (AC cell count)
- Resolution of inflammation as defined as either 0

or 0.5 or less cell on follow up post op exams

- Resolution of pain using the Face, Legs, Activity, Cry, Consolability (FLACC) Behavioral Pain rating Scale. Ratio of Intraocular pressure increase with insert
- % of patients with rebound inflammation from baseline through post-op care
- % of patients that were given supplementary prednisolone drops and the number of drops needed in these patients
- Mean change in BCVA from baseline over time using either ETDRS or HOTV chart testing depending on age
- Primary caregiver's ability to adhere to treatment plan as prescribed and therapeutic preferences measured with primary caregiver satisfaction survey

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1. INTRODUCTION AND RATIONALE

Corticosteroids are routinely prescribed for the post-operative management of inflammation and pain following retinal surgery. Persistent ocular inflammation can increase the risk of ocular complications such as increased intraocular pressure (IOP), ocular pain, and reduced visual outcomes, where as untreated pain can affect overall patient satisfaction.[1] Despite the widespread use of topical eyedrops, this means of treatment is often associated with poor patient compliance. This issue is further complicated in pediatric patients, who often dislike eye drops leading to difficulty with administration in the post-op period by parents. Largely across preparations, there is poor bioavailability from eyedrops with less that 5% of the applied dose of topical preparations predicated to reach the intraocular tissues.[1]

To optimize the delivery of a corticosteroid after ocular surgery, a sustained-release intracanalicular dexamethasone insert (DEXTENZA, Ocular Therapeutix, Inc) has been approved by the FDA to treat ocular pain and to control inflammation after ocular surgery.[1]

2. STUDY OBJECTIVES

2.1 Primary Objective

To determine if pediatric retinal patients would benefit from the placement of the 0.4 mg sustained release Dexamethasone intracanalicular insert (DEXTENZA) in the inferonasal lacrimal system during surgery in the surgical/treated eye compared to topical ocular drop therapy to manage post-operative pain (measured with Face, Legs, Activity, Cry Consolability (FLACC) Behavioral Pain Rating Scale). Pain will be measured at each visit with final outcome determined by the FLACC Behavioral Pain Rating Scalescore on day 45.

2.2 Secondary Objectives

- Incidence and severity of adverse events from baseline through post-op day 45
- Degree of inflammation (AC cell count)
- Resolution of inflammation as defined as either 0 or 0.5 or less cell on follow up post op exams
- Resolution of pain using the FLACC Behavioral Pain Rating Scale
- Ratio of Intraocular pressure increase with insert
- % of patients with rebound inflammation from baseline through post-op care
- % of patients that were given supplementary prednisolone drops and the number of drops needed in these patients

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- Mean change in BCVA from baseline over time using either ETDRS or HOTV chart testing depending on age
- Primary caregiver's ability to adhere to treatment plan as prescribed and therapeutic preferences measured with primary caregiver satisfaction survey

3. STUDY DESIGN

3.1 Study Description and Duration

This prospective, open-label, single-center, randomized, investigator-initiated clinical study seeks to investigate the safety and efficacy of the DEXTENZA insert in pediatric patients following retinal surgery or laser treatment under anesthesia.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Study Population

The study aims to enroll 30 pediatric patients undergoing routine retinal surgery or laser treatment under anesthesia. Patients in each treatment group (surgery or laser) will be randomized 2:1 at the time of surgery/laser to receive either:

3) Treatment Arm: Dextenza insert intraoperatively for perioperative ocular inflammation and pain. These patients will not be prescribed topical steroid drops post-operatively, or

4) Control Arm: Prednisolone forte 1% steroid drop taper for 28 days post-operatively to treat perioperative ocular inflammation and pain; drops four times per day (QUID) on days 0-7, three times per day (TID) on days 7-14, twice per day (BID) on days 14-21 and once per day (QD) on days 21-28.

Each treatment group (surgery or laser) will include 15 patients total, 10 receiving Dextenza and 5 receiving the control drug. Drops for dilation and antibiotic coverage will be used as clinically indicated in all groups throughout the study period. Follow up will occur at post-op day 1, 7, 28/30 and 45 (+/- three days for all post-operative timepoints).

4.1.1 Inclusion Criteria

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

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- 3 to <17 year old pediatric patients undergoing routine retinal surgery or laser treatment under anesthesia for a variety of visual conditions. These conditions and procedures include but are not limited to:

    - Conditions:
        - Familial Exudative Vitreoretinopathy
        - Coats' Disease
        - Exudative Retinopathy
        - Lattice degeneration
        - Retinal holes
        - Sickler's syndrome
        - Retinal detachment, rhegmatogenous
        - Retinal detachment, exudative
        - Retinal detachment, tractional

    - Procedures
        - Laser photocoagulation
        - Cryotherapy
        - Retinal detachment repair with scleral buckle and cryotherapy
        - Retinal detachment repair with vitrectomy

- Written informed consent from parent/legal guardian

4.1.2 Exclusion Criteria

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

Preprocedural

- Subjects needing laser or ocular surgery in the fellow eye concurrently as the study eye.
- Active or history of chronic or recurrent inflammatory eye disease in either eye
- Any patient of reproductive potential that has a positive pregnancy test during pre-procedural testing
- Active or history of increased ocular pressure
- Patients with active corneal, conjunctival, and canalicular infections
- Patients with punctal stenosis or other punctal anatomical abnormalities that would not be conducive with device insertion
- Nasolacrimal duct obstruction
- Laser or incisional ocular surgery during the study period and 3 months prior in the study eye
- current use of systemic or topical steroids or NSAIDS on a regular basis

- History of autoimmune disease that may interfere with treatment/outcomes
- Ocular pain at the time of screening
- Known malignancy
- Current use of cyclosporin or a TNF blocker
- Ocular hypertension IOP >25, actively taking medications for ocular hypertension, any history of IOP spikes in either including steroid associated IOP elevation
- Congenital ocular lid and tear duct system abnormalities (e.g. congenital ectropion/entropion, trichiasis)
- Evidence of acute external ocular infection of the study eye
- Active or history of HSV
- Previous trauma causing deformity
- Previous enrollment or current enrollment with another clinical trial within the last 30 days that may interfere with treatment
- Known allergies to product under investigation
- Inability to engage in VA testing
- Investigator determines that the candidate is not eligible for participation based on clinical or historical factors that would interfere with treatment or impact patient safety not specified above
- Current artificial tear use >4x daily
- Anyone who, in the opinion of the investigator, would not be a good candidate for the study.

Intraoperatively

- Multiple and/ or extensive procedures required at the surgeon's discretion.
- Complication occurs that surgeon determines makes the patient ineligible for study inclusion
- Unsuccessful dilation of the punctum to 0.7mm when dilation attempted
- During the exam under anesthesia, if it is decided that periocular Kenalog injection is indicated this patient fails screen and will no longer be eligible for the study

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 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. Antibiotic regimen will not exceed 4x daily and will be the same in both treatment groups/arms.

Removal of insertion should occur if based on examination it is determined that patient is having AE directly related to DEXTENZA implant.

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5. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

5.1 Schedule of Events

Study assessments and procedures are presented by visit in Table 1 (treatment arm schedule of events) and Table 2 (control arm schedule of events).

Table 1 Treatment Arm Schedule of Events

Study Procedure	Screening/ Baseline	Surgical Visit Day 0	Day 1	Day 7	Day 28	Day 45
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
Windows for Visits	(Day -30 to 0)		+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days
Inclusion/Exclusion	X					
Informed Consent	X					
Demographics	X					
Medical History and Concurrent Illnesses	X					
Concomitant Medications	X					
Pregnancy testing as indicated/appropriate		X				
Subject reported AEs prior to or after surgery	X	X	X	X	X	X
Randomization with subsequent intracanalicular dexamethasone insert placement		X				
Easy of insertion		X				
If dilator was used		X				
Document administration of prescribed medications			X	X	X	X
Ocular Pain Assessment (FLACC)	X		X	X	X	X
Distance VA testing	X		X	X	X	X
BCVA (ETDRS at 4m)	X		X	X	X	X
Anterior chamber cell count	X		X	X	X	X

Study Procedure	Screening/ Baseline	Surgical Visit Day 0	Day 1	Day 7	Day 28	Day 45
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
Windows for Visits	(Day -30 to 0)		+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days
Anterior chamber cell flare	X		X	X	X	X
Punctum examination	X	X	X	X	X	X
Insert Visualization and ease of visualization score			X	X	X	X
Intraocular Pressure	X		X	X	X	X
Ophthalmic Examination (dilated fundus exam)	X		X	X	X	X
Satisfaction Survey						X

Table 2 Control Arm Schedule of Events

Study Procedure	Screening/ Baseline	Surgical Visit Day 0	Day 1	Day 7	Day 28	Day 45

Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
Windows for Visits	**(Day -30 to 0)**		**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**
Inclusion/Exclusion	X					
Informed Consent	X					
Demographics	X					
Medical History and Concurrent Illnesses	X					
Concomitant Medications	X					
Pregnancy testing as indicated/appropriate		X				
Subject reported AEs prior to or after surgery	X	X	X	X	X	X
Randomization without intracanalicular dexamethasone insert placement		X				
Document administration of prescribed medications			X	X	X	X
Ocular Pain Assessment (FLACC)	X		X	X	X	X
Distance VA testing	X		X	X	X	X
BCVA (ETDRS at 4m)	X		X	X	X	X
Anterior chamber cell count	X		X	X	X	X
Anterior chamber cell flare	X		X	X	X	X
Punctum examination	X	X				
Intraocular Pressure	X		X	X	X	X

Study Procedure	Screening/ Baseline	Surgical Visit Day 0	Day 1	Day 7	Day 28	Day 45
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
Windows for Visits	(Day -30 to 0)		+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days
Ophthalmic Examination (dilated fundus exam)	X		X	X	X	X
Satisfaction Survey						X

5.2 Study Visit Descriptions for control and treatment arms

5.2.1 Study Procedures

Visit 1 (Day -30 to 0) Screening/Baseline

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

- Inclusion/exclusion
- Demographics
- Medical history and concurrent illnesses
- Concomitant medications
- Subject reported AE's prior to surgery
- Ocular Pain Assessment (FLACC)
- Distance VA testing, when applicable
- Best-corrected visual acuity as measured by ETDRS or HOTV chart at 4m based on patient age (HOTV for pre-literate patients)
- Anterior chamber cell count
- Anterior chamber cell flare
- Punctum examination
- Intraocular pressure
- Ophthalmic Examination including dilated fundus exam

Visit 2 Surgical Visit (Day 0)

- Subject reported AE's prior to surgery
- Indicate the incision type, location, and size (mm)
- Punctum examination
- If you are a patient who could possibly be pregnant (you have started menstruation), a urine pregnancy test will be performed, and it must be negative in order to continue in the study.
- Randomization and potential placement of intracanalicular dexamethasone insert if assigned to treatment arm
- Record any surgical complications

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Visit 3 (Day 1 +/- 3 days) Visit 4 (Day 7 +/- 3 days) Visit 5 (Day 28 +/- 3 days) Visit 6 (Day 45 +/- 3 days)

- Subject reported AE's after surgery
- Document administration of prescribed medication (if used and number of drops used)
- Ocular Pain Assessment (FLACC)
- Distance VA testing, when applicable
- Best-corrected visual acuity as measured by ETDRS or HOTV chart at 4m based on patient age (HOTV for pre-literate patients)
- Anterior chamber cell count
- Anterior chamber cell flare
- Punctum examination and ease of insert visualization (for patients receiving DEXTENZA insert only)
- Intraocular pressure
- Ophthalmic Examination including dilated fundus exam
- Satisfaction Survey (at the end of visit 6 only)

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 6.

5.3 Rescue Treatment

Rescue treatment will be left to the discretion of the surgeon. Rescue treatment includes but is not limited to topical NSAID, oral and topical steroids. Rescue treatment will be adequately documented to include the dosage needed.

6. SAFETY DEFINITIONS, REPORTING, AND MONITORING

Safety will be assessed from surgery through 45 days post surgery. Safety will be assessed only by frequency and incidence of events of special interest (ESI) and SAEs.

Monitoring for ESIs and SAEs will occur from the initial study-specific procedure through 28 days post last study drug dose (including the weaning doses).

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**

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- 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.

6.1.3 Events of Special Interest

The patients enrolled in this trial will have trauma to the eye as a direct result of surgery with known and previously reported potential significant eye-related events. The following events will not be included in the primary safety outcome, but they are clinical events of special interest (ESI) that may relate to safety and that will be tracked and reported in the trial results. These AEs are to be reported to study database, regardless of whether these events meet serious criteria or unexpectedness:

- Elevated intraocular pressure
- Eye pain and local erythema
- Infection
- Allergic reaction
- Trauma to the punctum
- Eyelid swelling
- Hazy or cloudy vision
- Feeling like something is in the eye
- Increased sensitivity to light

6.2 Recording and Reporting Adverse Events

All ESIs and SAEs will be recorded in the study database.

All SAEs, regardless of assessment of causal relationship to study insert will be reported to the sponsor. The sponsor will provide these reports to Ocular Therapeutix.

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. STATISTICAL CONSIDERATIONS

8.1 Sample Size Considerations and Analysis Plan

This is a feasibility study and the sample size of 30 is not designed to provide power to determine any differences between arms.

Analysis results will be presented by study drug vs. standard of care topical drops overall and by surgical procedure group.

Descriptive statistics such as number of observations, mean, median, standard deviation, minimum and maximum will be presented by treatment arms for continuous variables (such as age, weight, etc.). Other descriptive statistics such as counts, proportions, and/or percentages will be presented by group to summarize discrete variables (such as race, sex, etc.).

8.1.1 Participant Disposition and Study Drug Exposure

Study disposition, demographic and baseline characteristics, and study medication exposure will be summarized for study patients. Study drug administration will be summarized, number of days of dosing, and reasons for final discontinuation of study drug.

Demographic and baseline characteristics will include race, age, sex, and selected clinical variables recorded prior to initiation of study drug.

8.1.2 Safety

The safety reports will be summarized.

Serious adverse events will be presented overall. Severity and relationship to study drug will be provided.

Events of special interest will be presented overall and summarized by participant characteristics.

Prior and concomitant medications will be summarized by World Health Organization (WHO) drug class.

9. ETHICAL AND REGULATORY CONSIDERATIONS

9.1 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.

The study will be conducted in accordance with US regulations (e.g. 45 CFR 46 and 21 CFR 312), the International Council for Harmonisation guidelines for Good Clinical Practice (GCP) (ICH E6),. The US Code of Federal Regulations (CFR) include but are not limited to:

- 45 CFR 46 (Human Subjects Protection)
- 45 CFR 160 and 164 Subparts A and E (Health Insurance Portability and Accountability Act [HIPAA] Privacy Rule)
- 21 CFR 312 (Investigational New Drug [IND] Application) as applicable
- 21 CFR 50 (Protection of Human Subjects, including Subpart D - Additional Safeguards for Children in Clinical Investigations)
- 21 CFR 56 (Institutional Review Boards [IRB])

9.2 Informed Consent

The principles of informed consent are described in 45 CFR 46 and 21 CFR 50.

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.

9.3 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.

9.4 Institutional Review Board

An appropriately constituted IRB, as described in 21 CFR 56 and 45 CFR 46 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.

10. APPENDICES

10.1 Primary caregiver satisfaction survey

Administer this questionnaire to the primary caregiver in charge of the child's post-operative eye drop administration at **day 45 (+/- 3 days) follow-up (Visit 6):**

#	Questions	Strongly Disagree 1	Disagree 2	Not Sure 3	Agree 4	Strongly Agree 5
1.	The instructions I was given on how to administer my child's eye drop treatment were clear and easy to follow					
2.	I did not have initial concerns regarding the administration instructions I was given on eye drop administration but some questions/issues arose for me after the dosing experience					
3.	It was difficult to fill and pick-up my child's eye drop prescription					
4.	My child's eye drops were expensive to purchase					
5.	My child cries or becomes upset when it is time to administer the eye drop treatment					
6.	Eye drop treatment appears to cause my child distress; my baby acts to avoid therapy					
7.	I sometimes forget to wash my hands prior to administering my child's eye drop treatment					
8.	It is difficult and/or frustrating to administer my child's eye drop treatment					
9	A second person is needed to help me administer my child's eye drop treatment					
10.	I worry my child is not receiving enough eye drop treatment when I administer it					
11.	I worry I am incorrectly administering the eye drop treatment to my child					

12.	I worry I will injure my child or cause infection trying to administer the eye drop treatment					
#	**Questions**	**Strongly Disagree**	**Disagree**	**Not Sure**	**Agree**	**Strongly Agree**
13.	It takes me a while (several minutes or longer) to soothe my child or get them to settle down after administering eye drop treatment					
14.	I sometimes forget to administer my child's eye drop treatment					
15.	Administering eye drops to my child causes me stress					
16.	I am the only capable person that can administer my child's eye drop treatment and I do not trust other caregivers to administer it, such as daycare personnel, the nanny/babysitter, grandparents, etc.					
17.	I have to adjust my daily schedule in order to correctly follow my child's eye drop schedule					
18.	I would prefer a post-operative treatment regimen for my child that has fewer eye drops or none at all					

10.2 HOTV Chart testing protocol and example (from Bernell Vision Therapy) [2]

HOTV Test Set Instructions

HOTV as objects by Dr. Otto Lippmann

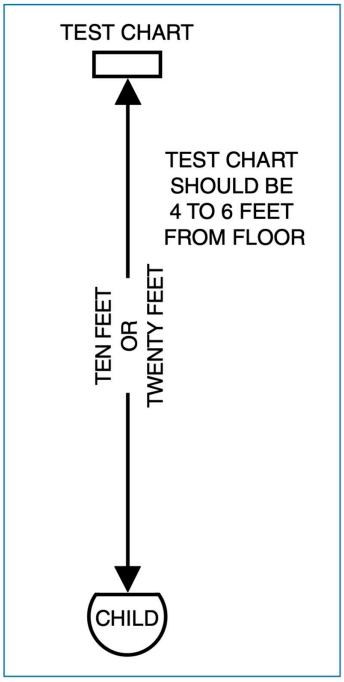
This test set consists of the following parts:

1. 9 in. x 14 in. HOTV test chart for 10 or 20 feet testing distance.
2. HOTV response panel.
3. HOTV flash cards.

Instructions

The HOTV matching method will determine the visual acuity more accurately and at a younger age than many other tests. It is accurate because four actual optotypes are used as matching objects. Children will learn to match them as readily as squares, triangles, etc. Because they are the same optotypes used by eye care professionals, they give meaningful results. Frequently children younger than 3 years and many handicapped can be tested.

The first step is to familiarize the child with the four optotypes (HOTV). This is best done by holding one of the flash cards a few feet in front of the child and have the child match the same optotype on the response panel. Several children can be familiarized at the same time. This step usually requires only a minute or two at most. Generally a verbal response is discouraged unless the child can easily and consistently name the optotypes. Once confidence in matching is established, move to the test chart.



- For the actual test the child is placed 10 feet (or 20 feet, depending on chart used) from the test chart. The test chart should be 4 to 6 feet from the floor. Proper illumination is critical for accurate and consistent testing.
- Use large optotypes on the test chart to gain the child's confidence.
- Point to the first optotype in each line in descending order.
- Move down until the child hesitates or misidentifies an optotype.
- Move back up one line and ask the child to identify all the optotypes on that line.
- If the child identifies all optotypes correctly go to the next line with smaller optotypes and ask the child to identify all optotypes on the line.
- If the child skips an optotype ask the child to try again while briefly pointing to that optotype.
- A child with an amblyopic eye may typically skip optotype within a line of objects.
- Visual acuity is recorded as the last line on which over 50% (3 of 5, 4 of 6) of the symbols are identified correctly.
- Many lines have less than 6 optotypes making repeating previously shown optotypes necessary.

10.3 FLACC Pain Rating Scale for measuring ocular pain[3]

The FLACC Scale will be used in the assessment of pain. BCVA and FLACC will occur prior to other visit assessments. The FLACC assessment will be performed by masked site personnel.

FLACC scale

Behavioral Observation Pain Rating Scale

Categories	Scoring		
	0	1	2
Face	No particular expression or smile; disinterested	Occasional grimace or frown, withdrawn	Frequent to constant frown, clenched jaw, quivering chin
Legs	No position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No crying (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or talking to. Distractable	Difficult to console or comfort
Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between 0 and 10.			

10.4 Ocular Inflammation Grading (AC cell and flare) [4]

- Use high intensity 1mm x 1mm slit beam based on Standardization of Uveitis Nomenclature Working Group (SUN grading scheme)

Anterior chamber cells		Anterior chamber flare	
Grade	**Cell count**	**Grade**	**Flare count**
0	0	0	Complete absence
0.5	1–5 cells (trace)	–	–
1	6–15	1	Very slight (barely detectable)
2	16–25	2	Moderate (iris and lens clear)
3	26–50	3	Marked (iris and lens hazy)
4	>50	4	Intense (fibrin clot)

11. REFERENCES

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3. Cable, Melissa. (2012). Comparison of bromfenac 0.09% QD to nepafenac 0.1% TID after cataract surgery: Pilot evaluation of visual acuity, macular volume, and retinal thickness at a single site. Clinical ophthalmology (Auckland, N.Z.). 6. 997-1004. 10.2147/OPTH.S32179.