Clinical Study Protocol

Assessing the efficacy of DEXTENZA, Sustained release dexamethasone 0.4 mg Insert, when placed within the lower eye lid canaliculus in comparison to topical prednisolone acetate following bilateral small incision lenticule extraction (SMILE).

WILEY STUDY Protocol #WW-2020-DexSMILE

Compound:	Sustained Release Dexamethasone, 0.4 mg (DEXTENZA)
Study Name:	A randomized controlled clinical trial assessing the efficacy of DEXTENZA, sustained release dexamethasone 0.4 mg insert, when placed within the lower eye eyelid canaliculus in comparison to topical prednisolone acetate following bilateral small incision lenticule extraction (SMILE).
Sponsor:	William Wiley, MD
Clinical Phase:	Open label prospective
Date of Issue:	18OCT2019
Primary Investigator:	William Wiley, MD
Sub Investigator:	Kathleen Jee MD
Site Name & Location:	Cleveland Eye Clinic 7001 S Edgerton Rd suite b, Brecksville, OH 44141

CLINICAL STUDY PROTOCOL SYNOPSIS	
TITLE	A randomized controlled clinical trial assessing the efficacy of DEXTENZA, sustained release dexamethasone 0.4 mg insert, when placed within the lower eye eyelid canaliculus in comparison to topical prednisolone acetate following bilateral small incision lenticule extraction (SMILE).
SITE LOCATION(S)	Toledo LASIK & Cataract
PRINCIPAL INVESTIGATOR	Dr. William Wiley
OBJECTIVE(S)	Assessing DEXTENZA efficacy when placed within the lower eyelid canaliculus post SMILE in comparison to topical prednisolone acetate.
STUDY DESIGN	A randomized controlled clinical trial assessing the efficacy of DEXTENZA, sustained release dexamethasone 0.4 mg insert, when placed within the lower eye eyelid canaliculus in comparison to topical prednisolone acetate following bilateral small incision lenticule extraction (SMILE).
STUDY DURATION	3 months
ESTIMATED STUDY COMPLETION DATE	3 months
POPULATION **Sample Size:** **Target Population:**	 20 Patients undergoing bilateral SMILE
TREATMENT(S) **Study Drug** **Dose/Route/Schedule:**	 Sustained Release Dexamethasone, 0.4 mg All patients will receive: First eye randomized for either topical prednisolone acetate (Control eye) or lower eyelid canaliculus DEXTENZA insertion (Study Eye) insertion and the contralateral eye receiving the opposite treatment in the OR following SMILE
ENDPOINT(S)	

Primary:

- Patient preference as measured by Patient Symptoms Questionnaire
- Mean change in pain score
  - Post op pain scores as measured on a scale from 0-10 (Days 1,7,30)
- Mean change in AC cell and flare score
  - Post op inflammation scores as measured on a scale of 0-4 (Days 1,7,30)
    - Absence of cell to be defined as a grade of: 0-0.5
    - Absence of flare to be defined as a grade of: 0-1

Secondary:

- Mean change BCVA
- Mean change in UCVA
- Proportion of patient call backs on post-operative management per eye (E.H.R. chart documentation)

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1. INTRODUCTION AND RATIONALE

1.1 Introduction

Drug delivery platforms are an innovative exciting advancement in ophthalmology. They allow patients to eliminate topical medications which are generally associated with lack of compliance, difficulty of use and requiring help from family members. These delivery systems can be applied easily during refractive surgeries, and patients do not have to worry about drop insertion in their post-operative regimen.

1.2 Rationale

Following SMILE surgery, the current standard of care is to prescribe corticosteroid drops to treat both ocular pain and inflammation. Typically, a tapering dose of topical corticosteroids is prescribed and tapered throughout the post-operative period, generally 2 weeks. Patients are expected to administer multiple drops throughout the days and weeks following surgery. There are limitations with the standard of care, these include; patient noncompliance, difficulty in administration and poor accuracy of drops getting into the eye.

1.2.1 Rationale for Study Design

This study will compare and evaluate the benefit of treatment with a physician administered intracanalicular dexamethasone insert, in the lower canaliculus (study eye) compared to topical corticosteroids (control eye) following bilateral SMILE surgery. In addition, the study will evaluate physician assessment of ease of DEXTENZA insertion

2. STUDY OBJECTIVES

2.1 Primary Objective

To determine the effect of dexamethasone insert through Week 12 as measured by:

- Patient preference
- Mean change in pain score
    - Post op pain scores as measured on a scale from 0-10 (Days 1,7,30)
- Mean change in AC cell and flare score
    - Post op inflammation scores as measured on a scale of 0-4 (Days 1,7,30)
        - Absence of cell to be defined as a grade of: 0-0.5
        - Absence of flare to be defined as a grade of: 0-1

2.2 Secondary Objectives

To determine the effect of dexamethasone insert through Week 12 as measured by:

- Mean change BCVA
- Mean change in UCVA
- Proportion of patient call backs on post-operative management per eye (E.H.R. chart documentation

3. STUDY DESIGN

3.1 Study Description and Duration

This three-month prospective, open-label, single-center, randomized investigator initiated clinical study seeks to investigate the efficacy of DEXTENZA when placed in the lower canaliculus (study eye) compared to topical corticosteroids (control eye) following bilateral SMILE surgery. In addition, the study will evaluate physician assessment of ease of DEXTENZA insertion

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Study Population

The study aims to enroll 20 patients undergoing bilateral SMILE.

4.1.1 Inclusion Criteria

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

- Age 18 years and older
- Scheduled for bilateral SMILE 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.
- Pregnancy (must be ruled out in women of child-bearing age with pregnancy test)
- Active infectious systemic disease
- Active infectious ocular or extraocular disease
- Obstructed nasolacrimal duct in the study eye(s)
- Hypersensitivity to dexamethasone
- Patients being treated with immunomodulating agents in the study eye(s)
- Patients being treated with immunosuppressants and/or oral steroids Patients with severe disease that warrants critical attention, deemed unsafe for the study by the investigator

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 -30 to -1)**			**+/- 3 day**	**+/- 5 days**	**+/- 7 days**	
Inclusion/Exclusion	x						
Informed Consent	x						
Demographics	x						
Medical History and Concurrent Illnesses	x						
Concomitant Medications	x	x	x	x	x	x	
Distance UCVA testing	x		x	x	x	x	
BCVA (ETDRS at 4m)	x			x	x	x	
Ophthalmic Examination (w or w/o dilated fundus exam)	x	x	x	x	x	x	
Pentacam	x						
Intraocular Pressure	x			x	x	x	
Indicate the incision type, location, and size (mm)			x	x	x	x	
Record any surgical complications	x	x	x	x	x	x	
Subject reported AEs prior to or after surgery	x	x	x	x	x	x	
Intracanalicular dexamethasone insert*		x					
Patient Treatment Preference			X	X	X	x	
Ocular Pain Assessment	x		x	x	x	x	
Anterior chamber cell count	x		x	x	x	x	
Anterior chamber cell flare	x		x	x	x	x	
Insert Visualization		x	x	x	x	x	

5.2 Study Visit Descriptions

5.2.1 Study Procedures

Screening/Baseline

- Inclusion/Exclusion Criteria
- Informed consent
- Demographics
- Medical history and concurrent illnesses
- Concomitant medications
- Ocular Pain Assessment Scale
- Distance UCVA (OD, OS, OU)
- Best-corrected visual acuity as measured by ETDRS chart at 4m
- Intraocular Pressure
- Ophthalmic Examination (including dilated fundus exam)
    - anterior chamber cell count
    - anterior chamber cell flare
- Pentacam
- IOP
- Subject reported AE's prior to or after surgery

Visit 2 (Surgery Day)

- Concomitant medications
- Ophthalmic exam
- Intracanalicular dexamethasone insert
- Insert visualization
- Record any surgical complications
- Subject reported AE's prior to or after surgery
- Physician ease of use

Visit 3 (Day 1 post op)

- Concomitant medications
- Ophthalmic exam
- Distance UCVA (OD, OS, OU)
- Record any surgical complications
- Indicate the incision type, location and size (mm)
- Subject reported AEs after surgery
- Patient Treatment Assessment
- Ocular Pain assessment
- Ocular inflammation assessment
- Insert visualization

Visit 4-6 (1 week- 3months after surgery)

- Concomitant medications
- Ophthalmic exam
- Distance UCVA (OD, OS, OU)
- BCVA (ETDRS at 4m) at Visit 4,5,6 (OD, OS, OU)
- IOP at Visit 4,5,6
- Record any surgical complications
- Indicate the incision type, location and size (mm)
- Subject reported AEs after surgery
- Patient Symptoms Questionnaire
- Ocular Pain Assessment Scale
- Ocular inflammation assessment
- Insert visualization

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

- Patients should be rescued at any time at the discretion of the investigator.
- The following rescue criteria are to be applied by the investigator on post operative visit 1 or later:
  - ≥ Grade 2+ anterior chamber cells
  - ≥ Grade 3+ anterior chamber flare
  - ≥ Grade 4+ pain

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.

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

1. DEXTENZA (dexamethasone insert) Prescribing Information, Ocular Therapeutix,Inc.2019http://www.dextenza.com/wp-content/uploads/2019/06/NDA-208742-S001-Dextenza-labeling-19Jun19.pdf
2. Tyson, SL, Bafna, S., Gira, J.P. et al. Multicenter randomized phase 3 study of a sustained-release intracanalicular dexamethasone insert for treatment of ocular inflammation and pain after cataract surgery. J Cataract Refract Surg. 2018; 45(2): 204-12
3. Walters TR, 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): 572.