Investigator-Initiated Trial Study Protocol

Safety and Efficacy of an Intracanalicular Dexamethasone Insert compared to Topical Loteprednol Etabonate Ophthalmic gel 0.38% in Patients with Keratoconus (KC) wearing Rigid Gas Permeable (RGP) Contact Lenses who have been diagnosed with Allergic Conjunctivitis and underlying Dry Eye Disease (DED)

The HARTHAN Study

Compound:	DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg, for intracanalicular use
Study Name:	The HARTHAN STUDY
Clinical Phase:	Open-label, Prospective, Interventional
Date of Issue:	February 20, 2020
Primary Investigator:	Jennifer Harthan, OD JHarthan@ico.edu
Research Coordinator:	Elyse Nylin Senior Research Coordinator
Site Name & Location:	Cornea Center for Clinical Excellence Illinois College of Optometry Illinois Eye Institute 312-949-7137

CLINICAL STUDY PROTOCOL SYNOPSIS	
TITLE	Safety and Efficacy of an Intracanalicular Dexamethasone Insert compared to Topical Loteprednol Etabonate Ophthalmic gel 0.38% in Patients with Keratoconus (KC) wearing Rigid Gas Permeable (RGP) Contact Lenses who have been diagnosed with Allergic Conjunctivitis and underlying Dry Eye Disease (DED)- The HARTHAN Study
SITE LOCATION(S)	Cornea Center for Clinical Excellence Illinois College of Optometry Illinois Eye Institute 312-949-7137
PRINCIPAL INVESTIGATOR	Jennifer Harthan,OD JHarthan@ico.edu
OBJECTIVE(S)	To determine if physician administered intracanalicular dexamethasone insert improve the signs and symptoms of ocular allergy and dry eye disease in KC patients compared to topical loteprednol etabonate ophthalmic gel 0.38%.
STUDY DESIGN	Prospective Open-label Interventional Study
STUDY DURATION	4 months after IRB approval
ESTIMATED STUDY COMPLETION DATE	3 months after DEXTENZA insertion
POPULATION **Sample Size:** **Target Population:**	 20 patients (40 eyes) Patients with bilateral keratoconus, wearing RGP contact lenses in both eyes, who have been diagnosed with bilateral allergic conjunctivitis and underlying dry eye disease
TREATMENT(S) **Study Drug** **Dose/Route/Schedule:**	 DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg, for intracanalicular use Patients with Keratoconus, with Allergic Conjunctivitis and underlying Dry Eye Disease, wearing RGP contact lenses will have one eye randomized to receive the Sustained Release Dexamethasone, 0.4mg intracanalicular insert (study eye). The fellow-eye will receive topical loteprednol (control eye) on a 4,3,2,1 weekly taper schedule.
ENDPOINT(S)	

Primary:

To determine the effect of dexamethasone intracanalicular insert through Day 90 as measured by:

- Mean change in itching score from Baseline measured at all visits (Visits 1-5)
    - Graded on a scale of 0-4 and determined by asking the patient
- Mean change in palpebral conjunctivitis papillae score from Baseline measured at all visits (Visits 1-5)
    - Graded using the Papillae Efron Scale as graded by the physician
- Mean change in conjunctival injection score from Baseline measured at all visits (Visits 1-5)
    - Graded on a scale of 0-4 as graded by the physician
- Mean change in corneal staining score from Baseline measured at all visits (Visits 1-5)
    - Graded using the NEI Fluorescein Staining Scale as graded by the physician

Secondary:

To determine the effect of dexamethasone, insert through Day 90 as measured by:

- Physician ease of insertion as measured by a 0-10-point scale
- Vision-related Quality of Life (QOL) assessment as measured with OSDI Questionnaire measured at all visits (Visits 1-5)
- Uncorrected and corrected VA mean change from Baseline measured at all visits (Visits 1-5)
- Patient`s therapy of preference as measured by the Comparison of Ophthalmic Medications for Tolerability Questionnaire (COMTOL) at final visit (Visit 5)
- Mean change in MMP9/osmolarity from Baseline measured at all visits (Visits 1-5)
- Incidence of IOP spikes (IOP increased >or = 10mmHg from baseline)

TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION AND RATIONALE

1.1 Introduction

Keratoconus is a bilateral, asymmetric, non-inflammatory corneal ectasia characterized by progressive thinning of the corneal stroma resulting in corneal bulging and distortion.[iii] Such pathological changes to the cornea not only cause decreased visual acuity, but also have been associated with reduced tear film quality[iii] and overall ocular discomfort.[iv] A recent study demonstrated that keratoconic patients have a greater incidence of dry eye pathology – specifically, greater tear instability and corneal staining as well as decreased tear volumes.[v] There is emerging evidence demonstrating that the predominance of dry eye is evaporative in nature[vi]—the major cause being meibomian gland dysfunction (MGD).[vii] Eye rubbing, family history of keratoconus, allergy, asthma, and eczema have been demonstrated to be important risk factors according to the most recent systematic review and meta-analysis.[v]

Ocular allergy can alter the dry eye disease cycle including tear film instability, ocular surface inflammation and neurosensory abnormalities. The TFOS DEWS II Report has included allergic conjunctivitis among one of the likely risk factors for dry eye disease. Both allergic conjunctivitis and dry eye are associated with inflammation. Inflammation may be present before the clinical signs of dry eye, contributing to increased corneal desquamation and corneal surface irregularity.

Steroids play an important role in in the treatment of both allergic conjunctivitis and dry eye disease. The anti-inflammatory properties of dexamethasone and other synthetic glucocorticoids can benefit the status of dry eye and allergic conjunctivitis via modification of a wide variety of immune functions.[viii] The immune-modifying properties of dexamethasone can improve dry eye and allergy status not only by inhibiting the inflammation that has already occurred as a result of the initiated immunological priming, but also by potentially preventing initiating immune responses from recurring.

1.2 Rationale

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 in office, and patients do not have to worry about drop insertion in their post-operative regimen.

The results of this research project should help to answer the following question: Does the use of a physician administered intracanalicular dexamethasone insert improve the signs and symptoms of ocular allergy and dry eye disease in KC patients compared to the use of topical loteprednol etabonate ophthalmic gel 0.38%?

1.2.1 Rationale for Study Design

This prospective study will use a fellow-eye design for 20 participants (40 eyes) with bilateral keratoconus, wearing RGP contact lenses in both eyes, who have been diagnosed with bilateral allergic conjunctivitis and underlying dry eye disease. Per participant, one eye will be randomized to receive the intracanalicular dexamethasone insert at the baseline visit (study eye), while the other eye will be assigned to receive the standard of care topical lotemax etabonate ophthalmic gel 0.38% (control eye). Thus, for every eye in the study group, there will be a paired eye with similar baseline characteristics in the control group sourced from the same participant. The fellow-eye design allows for greater control of potential confounders tied to participants' systemic and ocular health.

2. STUDY OBJECTIVES

2.1 Primary Objective

To determine the effect of dexamethasone intracanalicular insert through Day 90 as measured by:

- Mean change in itching score from Baseline measured at all visits (Visits 1-5)
    - Graded on a scale of 0-4 and determined by asking the patient
- Mean change in palpebral conjunctivitis papillae score from Baseline measured at all visits (Visits 1-5)
    - Graded using the Papillae Efron Scale as graded by the physician
- Mean change in conjunctival injection score from Baseline measured at all visits (Visits 1-5)
    - Graded on a scale of 0-4 as graded by the physician
- Mean change in corneal staining score from Baseline measured at all visits (Visits 1-5)
    - Graded using the NEI Fluorescein Staining Scale as graded by the physician

2.2 Secondary Objectives

To determine the effect of dexamethasone, insert through Day 90 as measured by:

- Physician ease of insertion as measured by a 0-10-point scale
- Vision-related Quality of Life (QOL) assessment as measured with OSDI Questionnaire measured at all visits (Visits 1-5)
- Uncorrected and corrected VA mean change from Baseline measured at all visits (Visits 1-5)
- Patient`s therapy of preference as measured by the Comparison of Ophthalmic Medications for Tolerability Questionnaire (COMTOL) at final visit (Visit 5)
- Mean change in MMP9/osmolarity from Baseline measured at all visits (Visits 1-5)

- Incidence of IOP spikes (IOP increased >or = 10mmHg from baseline)

3. STUDY DESIGN

3.1 Study Description and Duration

This prospective, open-label, single-center, randomized, fellow-eye, investigator-sponsored clinical study seeks to investigate the safety and efficacy of the dexamethasone insert in the treatment of allergic conjunctivitis and DED signs and symptoms in patients with Keratoconus using RGP contact lenses when compared to topical standard of care loteprednol etabonate ophthalmic gel 0.38%. After screening a given patient for inclusion and exclusion criteria, and gaining informed consent, one eye will be randomized to receive the dexamethasone insert as determined by a coin flip at the screening visit. The remaining eye will be prescribed a loteprednol etabonate ophthalmic gel 0.38% following a 4,3,2,1 weekly taper. Per enrolled eye, the study period will last for approximately 90 days, consisting of five visits. At Screening/ Baseline, Day 0, 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 3 months. An abstract with preliminary results will be submitted by May 2020 for the AAOpt conference.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Study Population

The study aims to enroll 20 patients with keratoconus, wo have been diagnosed with allergic conjunctivitis and underlying dry eye disease.

4.1.1 Inclusion Criteria

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

- 18 years of age or older
- Bilateral Keratoconus
- Bilateral RGP contact lenses
- Bilateral allergic conjunctivitis as determined by the Papillae Efron Scale score of at least 1 and symptoms of itching
- Bilateral underlying dry eye disease as determined by the NEI Fluorescein Staining Scale score of at least 1 and a TBUT of less than 10 and must correlate with dryness on OSDI

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^{o} C and 8^{0} C. Intracanalicular dexamethasone insert contains 0.4 mg dexamethasone and is designed to provide a sustained and tapered release of therapeutic levels of dexamethasone to the ocular surface for up to 30 days for the reduction of post-surgical inflammation and pain associated with ocular surgery. Dexamethasone is an anti-inflammatory 9-fluoro-glucocorticoid (also termed a glucocorticoid agonist) and is the active ingredient found in MAXIDEX® 0.1% (dexamethasone ophthalmic suspension), which contains approximately 50 µg of dexamethasone per drop.

Study inserts will be supplied by Ocular Therapeutix in a sealed foil pouch containing one intracanalicular dexamethasone insert in a foam carrier.

Study inserts will be shipped to the site via overnight shipping using cold packs to maintain a temperature of 2° to 8° C. The Investigator, or an approved representative (e.g. pharmacist), will ensure that all study drug inserts are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. The shipping box is to be opened and stored immediately at the site in a refrigerator intended for investigational products at a temperature of 2° to 8°C.

When the insert is removed from the refrigerator, it should be visually inspected. Exposure of the insert to temperatures outside these limits it not recommended. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.

4.2.2 Supply and Disposition of Treatments

Study insert will be shipped at a temperature of 2° to 8°C to the investigator as needed during the study.

4.2.3 Treatment Accountability

All study insert accountability records will be kept current.

The investigator will account for all opened and unopened packaging of study inserts. These records will contain the dates, quantity, and study medication

- Inserted in each patient,
- disposed of at the site or returned to Ocular Therapeutix

All accountability records will be made available for inspection by regulatory agency inspectors.

4.3 Concomitant Medications and Procedures

At the discretion of their physician, patients may continue to receive all medications and standard treatments administered for other conditions.

5. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

5.1 Schedule of Events

Study assessments and procedures are presented by visit in Table 1.

Table 1 Schedule of Events

Study Procedure	Screening/ Baseline	Insertion Visit Day 0	Day 7	Day 30	Day 90	Early Termination
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5**	
Windows for Visits	**(Day -30 to -1)**		**(+/- 2 days)**	**(+/- 3 days)**	**(+/- 3 days)**	
Inclusion/Exclusion	X					
Informed Consent	X					
Demographics	X					
Medical History and Concurrent Illnesses	X					
Concomitant Medications	X	X	X	X	X	X
Uncorrected Distance VA testing (ETDRS at 4m)	X	X	X	X	X	X
MR/BCVA (ETDRS at 4m)	X	X	X	X	X	X
Ophthalmic Examination (with or without dilation)	X	X	X	X	X	X
QOL Assessment (OSDI questionnaire)	X	X	X	X	X	X
Osmolarity (Needs to be done prior to any drop instillation)	X	X	X	X	X	X
MMP9 (Needs to be done prior to any drop instillation)	X	X	X	X	X	X
Grading of itching (Scale 0-4)	X	X	X	X	X	X
Papillae conjunctivitis assessment (Efron Scale)	X	X	X	X	X	X
Conjunctival Injection (Scale 0-4)	X	X	X	X	X	X
Corneal staining (NEI Fluorescein Scale)	X	X	X	X	X	X
TBUT	X	X	X	X	X	X
Intraocular Pressure (IOP)	X	X	X	X	X	X
Intracanalicular dexamethasone insert*		X				
Insert Visualization		X	X	X	X	X
Subject reported AEs after insertion		X	X	X	X	X
Physician ease of insertion as measured on a 0-10 point scale		X				

COMTOL					X	X

5.2 Study Visit Descriptions

5.2.1 Study Procedures

Screening/Baseline (Visit 1)

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

- Inclusion/Exclusion
- Demographics
- Medical History and Concurrent Illnesses
- Concomitant Medications
- Uncorrected and best-corrected visual acuity with manifest refraction as measured by ETDRS chart at 4 meters
- Ophthalmic Examination (with or without dilation)
- QOL assessment as measured by OSDI questionnaire
- Osmolarity (Needs to be done prior to any drop instillation)
- MMP9 (Needs to be done prior to any drop instillation)
- Grading of itching (scale 0-4)
- Papillae conjunctivitis assessment (Efron Scale)
- Conjunctival Injection
- Corneal Staining
- TBUT
- Intraocular Pressure

Insertion Visit/Day 0 (Visit 2)

- Concomitant Medications
- Uncorrected and best-corrected visual acuity with manifest refraction as measured by ETDRS chart at 4 meters
- Ophthalmic Examination (with or without dilation)
- QOL assessment as measured by OSDI questionnaire
- Osmolarity (Needs to be done prior to any drop instillation)
- MMP9 (Needs to be done prior to any drop instillation)
- Grading of itching (scale 0-4)
- Papillae conjunctivitis assessment (Efron Scale)
- Conjunctival Injection
- Corneal Staining
- TBUT
- Intraocular Pressure
- Insertion of Dextenza (intracanalicular dexamethasone insert)
- Insert Visualization
- Subject reported AEs after insertion
- Physician ease of insertion grading

Day 7 (Visit 3)

- Concomitant Medications

- Uncorrected and best-corrected visual acuity with manifest refraction as measured by ETDRS chart at 4 meters
- Ophthalmic Examination (with or without dilation)
- QOL assessment as measured by OSDI questionnaire
- Osmolarity (Needs to be done prior to any drop instillation)
- MMP9 (Needs to be done prior to any drop instillation)
- Grading of itching (scale 0-4)
- Papillae conjunctivitis assessment (Efron Scale)
- Conjunctival Injection
- Corneal Staining
- TBUT
- Intraocular Pressure
- Insert Visualization
- Subject reported AEs after insertion

Day 30 (Visit 4)

- Concomitant Medications
- Uncorrected and best-corrected visual acuity with manifest refraction as measured by ETDRS chart at 4 meters
- Ophthalmic Examination (with or without dilation)
- QOL assessment as measured by OSDI questionnaire
- Osmolarity (Needs to be done prior to any drop instillation)
- MMP9 (Needs to be done prior to any drop instillation)
- Grading of itching (scale 0-4)
- Papillae conjunctivitis assessment (Efron Scale)
- Conjunctival Injection
- Corneal Staining
- TBUT
- Intraocular Pressure
- Insert Visualization
- Subject reported AEs after insertion

Day 90 (Visit 5) or Early Termination

- Concomitant Medications
- Uncorrected and best-corrected visual acuity with manifest refraction as measured by ETDRS chart at 4 meters
- Ophthalmic Examination (with or without dilation)
- QOL assessment as measured by OSDI questionnaire
- Osmolarity (Needs to be done prior to any drop instillation)
- MMP9 (Needs to be done prior to any drop instillation)
- Grading of itching (scale 0-4)
- Papillae conjunctivitis assessment (Efron Scale)
- Conjunctival Injection
- Corneal Staining

- TBUT
- Intraocular Pressure
- Insert Visualization
- Subject reported AEs after insertion
- COMTOL

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 Criteria

Patients can be rescued at any time at the discretion of the investigator with loteprednol etabonate ophthalmic gel 0.38%. Rescue criteria includes:

- A score greater than or equal to 2+ in one or more of the following categories:
    - Itching
    - Papillae
    - Injection
    - Staining

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. ETHICAL AND REGULATORY CONSIDERATIONS

7.1 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.

7.2 Informed Consent

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

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

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF will be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF will be retained by the investigator as part of the patient's study record, and a copy of the signed ICF will be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated appropriately. All study patients will be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF will be maintained in the patient's study record and a copy will be given to the patient.

7.3 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.

7.4 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.

APPENDICES

I. Itching Score

The physician will ask the patient to grade their current level of itching on a 0 to 4-point scale. The Investigator will record patient graded level of itching on the appropriate Case Report Form.

0 = None

1 = Mild

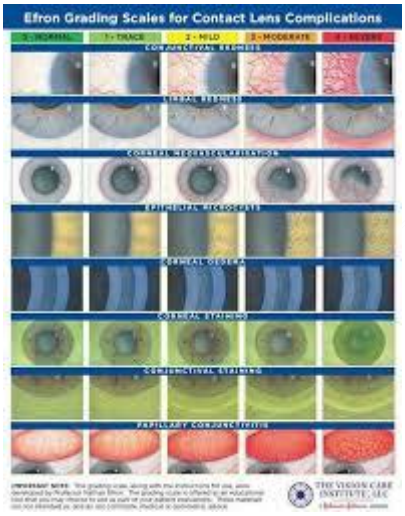
2 = Moderate

3 = Severe

4 = Extremely Severe

II. Palpebral Conjunctivitis Papillae Score

The investigator will grade the level of papillae with the Papillae Efron scale.



III. Conjunctival Injection Score

The investigator will grade the level of ocular injection on a 0 to 4-point scale.

0 = None

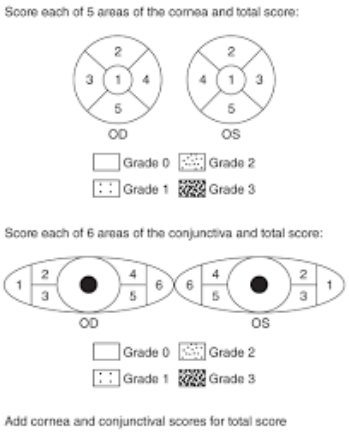
1 = Mild – Slightly dilated blood vessels; color of vessels is typically pink; can be quadrantal

2 = Moderate – More apparent dilation of blood vessels; vessel color is more intense (redder); involves the majority of the vessel bed

3 = Severe – Numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red, may be less red or pink in presence of chemosis, is not quadrantic

4 = Extremely Severe – Large, numerous, dilated blood vessels characterized by unusually severe deep red color, regardless of grade of chemosis, which involves the entire vessel bed

IV. NEI Fluorescein Corneal Staining Scale



V. Ocular Surface Disease Index (OSDI)

PDF attached

VI. Comparison of Ophthalmic Medications for Tolerability Questionnaire (COMTOL Adapted)

PDF attached

VII. Physician Ease of Insertion Grading

The investigator will grade the level of ease of insertion of the intracanalicular insert on a 0 to 10-point scale. The Investigator will record ease of insertion procedure on the appropriate Case Report Form.

0	1	2	3	4	5	6	7	8	9	10

Very Easy Very Hard

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