Intracanalicular Dexamethasone used in conjunction with LipiFlow for the treatment of meibomian gland dysfunction in patients with evaporative dry eye disease and evidence of clinically significant inflammation.

The DIERKER Study

Compound:	DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg for intracanalicular use
Study Name:	The DIERKER Study (NCT04413279)
Clinical Phase:	Open label prospective
Date of Issue:	12MAR2020
Primary Investigator:	Dr. Damon Dierker
Consultant:	Dr. Scott Hauswirth
Site Name & Location:	Eye Surgeons of Indiana 9202 N Meridian St, Indianapolis, IN 46260

CLINICAL STUDY PROTOCOL SYNOPSIS	
TITLE	Intracanalicular Dexamethasone used in conjunction with LipiFlow for the treatment of meibomian gland dysfunction in patients with evaporative dry eye disease and evidence of clinically significant inflammation.
SITE LOCATION(S)	Eye Surgeons of Indiana 9202 N Meridian St, Indianapolis, IN 46260
PRINCIPAL INVESTIGATOR	Dr. Damon Dierker
OBJECTIVE(S)	To evaluate the benefit of treatment with a physician administered intracanalicular dexamethasone insert in evaporative dry eye disease (DED) patients with meibomian gland disfunction (MGD) and underlying inflammation undergoing LipiFlow Thermal Pulsation.
STUDY DESIGN	Prospective Open-label Interventional Study
STUDY DURATION	3 months
ESTIMATED STUDY COMPLETION DATE	3 months after date of insertion
POPULATION	
Sample Size:	20 patients (40 eyes)
Target Population:	Patients with bilateral evaporative DED and MGD with evidence of clinically significant inflammation.
TREATMENT(S)	
Study Drug	Sustained Release Dexamethasone, 0.4 mg
Dose/Route/Schedule:	All eyes will undergo LipiFlow Thermal Pulsation for the treatment of evaporative DED secondary to MGD. Patients will have their most symptomatic eye selected to receive the dexamethasone intracanalicular insert at the day of the LipiFlow Thermal Pulsation treatment (study eye). The fellow-eye will receive a punctal "sham" dilation (control eye). If there is no obvious symptomatic difference, the right eye will receive the intracanalicular insert. Screening Visit Treatment Visit 1 week follow up 1 month follow up 3 month follow up
ENDPOINT(S)	

Primary:	• Change from baseline in meibomian gland scores (expressibility and quality) at week 1, week 4 and week 12. • Patient preference for therapy as measured by COMTOL at week 12
Secondary:	• Mean change in MMP-9 from baseline at week 1, week 4 and week 12 as measured by InflammaDry • Mean change in ocular surface staining (sodium fluorescein and lissamine green) from baseline at week 1, week 4 and week 12 as measured by the NEI grading scale and • Mean change in tear break-up time (TBUT) from baseline at week 1, week 4 and week 12 • Mean change in tear osmolarity from baseline at week 1, week 4 and week 12 as measured by Tear Lab • Mean change in DEQ-5 from baseline at week 1, week 4 and week 12 • Mean change in Best-corrected Visual Acuity (BCVA) from baseline at week 1, week 4 and week 12 as measured by ETDRS chart

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1. INTRODUCTION AND RATIONALE

1.1 Introduction

Secretions from the meibomian gland are important in reducing ocular surface water evaporation and preventing dry eye. Patients with dry eye disease frequently have meibomian gland dysfunction with loss of meibomian glands.[4] This process is thought to be driven by both inflammation and obstruction of the meibomian glands. LipiFlow, also known as vectored thermal pulsation, was the first device aimed specifically at MGD-related evaporative dry eye. It combines heat with physical massage to liquefy and express the meibomian gland contents to get the lipid layer of the ocular surface back to normal again.[5] Patients do not usually experience instant relief after LipiFlow treatment because the glands need 6-8 weeks to start producing good quality meibum. During this time, it is recommended that patients use artificial tears to keep the eye moisturized during the healing process.

1.2 Rationale

Although use of topical steroids in the post-operative regimen following LipiFlow is not the standard of care, these agents are often prescribed to provide faster symptomatic relief and potentially act synergistically with meibomian gland obstruction removal.

This study seeks to explore the benefit of managing patients with DED secondary to MGD with a sustained release intracanalicular dexamethasone (0.4 mg) insert in addition to LipiFlow Thermal Pulsation compared to LipiFlow Thermal Pulsation alone. In addition, this study will evaluate the ease of Dextenza insertion and the patient preference for therapy.

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 prior or post ophthalmic surgeries, and patients do not have to worry about drop insertion in their post-operative regimen.[1]

1.2.1 Rationale for Study Design

This prospective study will use a fellow-eye design for 20 participants, 40 eyes. All eyes will receive bilateral LipiFlow Thermal Pulsation. The most symptomatic eye will be selected to receive DEXTENZA® insertion on the day of the procedure (study eye), while the other eye will be assigned to receive sham punctum dilation (control eye). If there is no obvious symptomatic difference, the right eye will receive the intracanalicular insert. The study group will consist of 20 eyes receiving DEXTENZA® insertion. The control group will consist of 20 eyes receiving sham punctum dilation. 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. This fellow-eye design allows for greater control of potential confounders tied to participants' systemic and ocular health.

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2. STUDY OBJECTIVES

2.1 Primary Objective

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

- Change from baseline in meibomian gland scores (expressibility and quality) at week 1, week 4 and week 12.
- Patient preference for therapy as measured by COMTOL at week 12

2.2 Secondary Objectives

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

- Mean change in MMP-9 from baseline at week 1, week 4 and week 12 as measured by InflammaDry
- Mean change in ocular surface staining (sodium fluorescein and lissamine green) from baseline at week 1, week 4 and week 12 as measured by the NEI grading scale and
- Mean change in tear break-up time (TBUT) from baseline at week 1, week 4 and week 12
- Mean change in tear osmolarity from baseline at week 1, week 4 and week 12 as measured by Tear Lab
- Mean change in DEQ-5 from baseline at week 1, week 4 and week 12
- Mean change in Best-corrected Visual Acuity (BCVA) from baseline at week 1, week 4 and week 12 as measured by ETDRS chart

3. STUDY DESIGN

3.1 Study Description and Duration

This prospective, open-label, single-center, non-randomized, investigator-sponsored clinical study seeks to investigate the benefit of managing patients with DED secondary to MGD with a sustained release intracanalicular dexamethasone (0.4 mg) insert in addition to LipiFlow Thermal Pulsation compared to LipiFlow Thermal Pulsation alone. In addition, this study will evaluate the ease of Dextenza insertion and the patient preference for therapy.

After screening a given patient for inclusion and exclusion criteria, and gaining informed consent, each eye will undergo LipiFlow Thermal Pulsation on the same day. The most symptomatic eye will be selected to receive DEXTENZA® insertion on the day of the procedure (study eye), while the other eye will be assigned to a receive a sham punctum dilation (control eye). If there is no obvious symptomatic difference, the right eye will receive the intracanalicular insert. Per patient, the study period will last for approximately 12 weeks after the LipiFlow procedure, consisting of one screening visit, one treatment v4isit and 3 post-procedure follow-up visits (week 1, week 4 and week 12). At week 1, week 4 and week 12, primary and secondary endpoints will be assessed alongside standard-of-care procedures. Adjusting for enrollment period, the study will last a total of approximately 4 months.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Study Population

The study aims to enroll 20 patients (40 eyes) with evaporative DED secondary to MGD.

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
- Evaporative DED with MGD and clinically significant inflammation
- 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
- Altered nasolacrimal flow of either acquired, induced, or congenital origin
- Hypersensitivity to dexamethasone
- Patient being treated with either topical, oral, or intravenous 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**	**Lipiflow Visit**	**Week 1**	**Week 4**	**Week 12**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5**
Windows for Visits	**(Day -30 to -1)**		**+/- 1 day**	**+/- 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
UCVA Testing	x	x	x	x	x
MR/BCVA (ETDRS at 4m)	x	x	x	x	x
Ophthalmic Examination (w/ or w/o dilation)	x	x	x	x	x
Meibomian gland assessment (expressibility and quality)	x	x	x	x	x
MMP9 with InflammaDry	x		x	x	x
Tear Osmolarity with Tear Lab	x		x	x	x
NaFl Staining	x		x	x	x
TBUT	x		x	x	x
Lissamine Green Staining	x		x	x	x

Intraocular Pressure	x		x	x	x
LipiFlow procedure		x			
Record any surgical complications		x			
Subject reported AEs prior to or after surgery	x	x	x	x	x
Intracanalicular dexamethasone insert*		x			
Physician ease of insertion questionnaire		x			
Insert Visualization		x	x	x	x
DEQ-5	x		x	x	x
Patient preference questionnaire					x

5.2 Study Visit Descriptions

5.2.1 Study Procedures

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
- UCVA and MR/BCVA as measured by ETDRS chart at 4m
- Ophthalmic Examination with dilation
- Intraocular pressure
- Meibomian gland assessment (expressibility and quality)
- DED Assessment
    - MMP9
    - Osmolarity
    - TBUT
    - Ocular surface staining (sodium fluorescein and lissamine green)
- Subject reported AE's

- DEQ-5

Surgery Day/Insertion day

- Concomitant medications
- UCVA and MR/BCVA as measured by ETDRS chart at 4m
- Ophthalmic Examination without dilation and without IOP
- Meibomian gland assessment (expressibility and quality)
- Bilateral LipiFlow procedure
- Dextenza insertion in one eye
- Sham dilation in the other eye
- Insert visualization
- Record any procedure complications
- Subject reported AE's
- Physician ease of insertion questionnaire

Week 1

- Concomitant medications
- UCVA and MR/BCVA as measured by ETDRS chart at 4m
- Ophthalmic Examination without dilation
- Intraocular pressure
- Meibomian gland assessment (expressibility and quality)
- Meibomian gland assessment (expressibiblity and quality)
- DED Assessment
    - MMP9
    - Osmolarity
    - TBUT
    - Ocular surface staining (sodium fluorescein and lissamine green)
- Insert visualization
- Subject reported AE's
- DEQ-5

Week 4

- Concomitant medications
- UCVA and MR/BCVA as measured by ETDRS chart at 4m
- Ophthalmic Examination without dilation
- Intraocular pressure
- Meibomian gland assessment (expressibility and quality)
- Meibomian gland assessment (expressibility and quality)
- DED Assessment
    - MMP9
    - Osmolarity
    - TBUT

    - Ocular surface staining (sodium fluorescein and lissamine green)
- Insert visualization
- Subject reported AE's
- DEQ-5

Week 12

- Concomitant medications
- UCVA and MR/BCVA as measured by ETDRS chart at 4m
- Ophthalmic Examination without dilation
- Intraocular pressure
- Meibomian gland assessment (expressibility and quality)
- DED Assessment
    - MMP9
    - Osmolarity
    - TBUT
    - Ocular surface staining (sodium fluorescein and lissamine green)
- Insert visualization
- Subject reported AE's
- DEQ-5
- 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 will be rescued at any time at the investigator's discretion by removal of Dextenza by manual expression or flushing down the nasolacrimal duct.

6. SAFETY DEFINITIONS, REPORTING, AND MONITORING

6.1 Definitions

6.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (i.e. any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

6.1.2 Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (e.g. a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or prolongation of existing hospitalization. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse). Any malignancy (other than basal cell skin cancers) would be considered a medically important event.

6.2 Recording and Reporting Adverse Events

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

All SAEs, regardless of assessment of causal relationship to study insert will be reported to Ocular Therapeutix.

To report an SAE, Ocular Therapeutix will be contacted at the following:

ocutx.pharmacovigilance@propharmagroup.com
SAE hotline: 844-668-3948

The investigator will promptly report to the IRB all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study insert. All SAEs will be reported to the IRB, regardless of assessed causality.

7. STUDY VARIABLES

7.1 Demographic and Baseline Characteristics

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

8. ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Good Clinical Practice Statement

It is the responsibility of the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

8.2 Informed Consent

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

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

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

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

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

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

8.3 Patient Confidentiality and Data Protection

The investigator will take all appropriate measures to ensure that the anonymity of each study patient will be maintained.

The patient's and investigator's personal data will be treated in compliance with all applicable laws and regulations.

8.4 Institutional Review Board

An appropriately constituted IRB, as described in ICH Guidelines for GCP, will review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (e.g. advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB will be informed as soon as possible

Ongoing studies will be reviewed by the IRB/EC on an annual basis or at intervals appropriate to the degree of risk.

In addition, the IRB will be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB approval letter will be sent to Ocular Therapeutix prior to shipment of drug insert supplies to the investigator. The approval letter will include the study title, the documents reviewed, and the date of the review.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) will be kept on file by the investigator.

APPENDICES

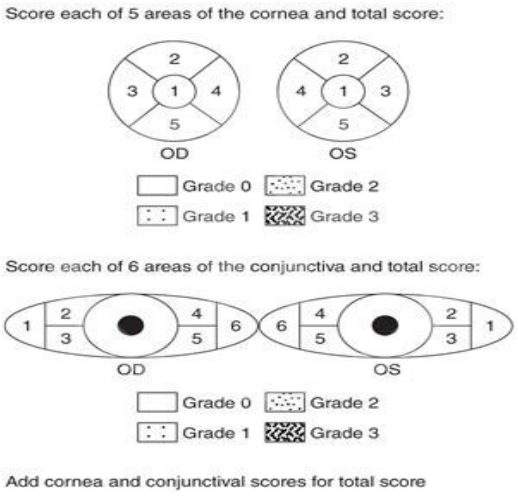
I. The investigator will evaluate the expressibility and quality of the meibomian glands at all visits.

Grade scale for meibomian gland dysfunction

Grade Scale	Percentage of blocked glands	Quality of meibomian secretion
Grade 1	40% - 50%	Clear to mild milky secretion
Grade 2	50% - 70%	Milky to pasty secretion
Grade 3	70% – 85%	Thick, pasty to very little secretion
Grade 4	85% – 90%	Very little to no secretion

Source: J Lee

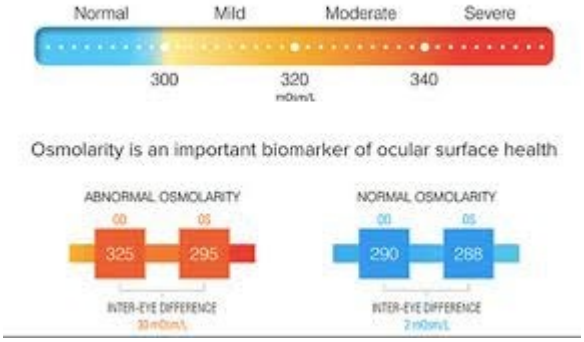
II. The investigator will use the NEI scale to grade the cornea using fluorescein and the conjunctiva using lissamine green at visits 1,3,4,5.



III. The investigator will use the InflammaDry to detect levels of MMP9 at visits 1,3,4,5.



IV. The investigator will use Tear Lab to assess tear osmolarity at visits 1,3,4,5.



V. The investigator will fill out the following questionnaire on the day of Dextenza insertion (visit 2):

Physician Ease of Insertion Questionnaire

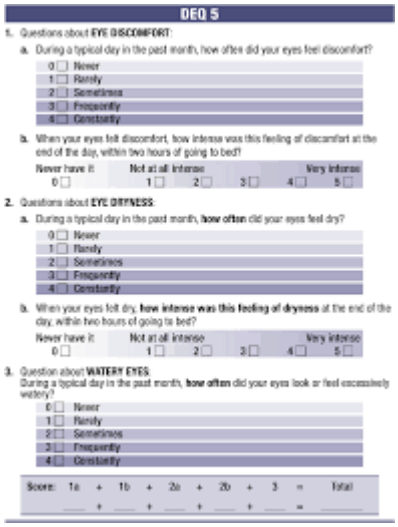
The investigator will grade the level of ease of insertion of the intracanalicular insert on a 0 to 10-point scale.

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

VI. The investigator will have the patient complete the DEQ-5 questionnaire at visits 1,3,4,5.



DEQ 5

1. Questions about **EYE DISCOMFORT**:
   a. During a typical day in the past month, how often did your eyes feel discomfort?
      0 ☐ Never
      1 ☐ Rarely
      2 ☐ Sometimes
      3 ☐ Frequently
      4 ☐ Constantly
   b. When your eyes felt discomfort, how intense was this feeling of discomfort at the end of the day, within two hours of going to bed?
      Never have it: 0 ☐ | Not at all intense: 1 ☐ 2 ☐ 3 ☐ | Very intense: 4 ☐ 5 ☐
2. Questions about **EYE DRYNESS**:
   a. During a typical day in the past month, **how often** did your eyes feel dry?
      0 ☐ Never
      1 ☐ Rarely
      2 ☐ Sometimes
      3 ☐ Frequently
      4 ☐ Constantly
   b. When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed?
      Never have it: 0 ☐ | Not at all intense: 1 ☐ 2 ☐ 3 ☐ | Very intense: 4 ☐ 5 ☐
3. Question about **WATERY EYES**:
   During a typical day in the past month, **how often** did your eyes look or feel excessively watery?
      0 ☐ Never
      1 ☐ Rarely
      2 ☐ Sometimes
      3 ☐ Frequently
      4 ☐ Constantly

Score: 1a + 1b + 2a + 2b + 3 = Total

____ + ____ + ____ + ____ + ____ = _____

VII. COMTOL Adapted (see attached, to be completed at visit 5 at the end of the study)

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