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Study ID: OCUN-029

Title: Prospective, Single-Arm Clinical Trial to Evaluate Acute Dry Eye Symptom Relief Assessed During Exposure to a Controlled Adverse Environment (CAE[®]) Following a 45 Day Period with Application of TrueTear[™]

Protocol Date: March 10, 2017

Prospective, Single-Arm Clinical Trial to Evaluate Acute Dry Eye Symptom Relief Assessed During Exposure to a Controlled Adverse Environment (CAE[®]) Following a 45 Day Period with Application of TrueTear[™]

Protocol Number: OCUN-029

Original Protocol: March 10, 2017

Device Name: TrueTear[™]

Sponsor: Allergan, Inc.

[Redacted]

Contract Research Organization:

[Redacted]

Confidentiality Statement

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MEDICAL MONITOR

[REDACTED]

SPONSOR PERSONNEL

Executive Director, Clinical Trial Management:

[REDACTED]

Executive Director, Clinical Development, Ophthalmology:

[REDACTED]

[REDACTED]

[REDACTED] PERSONNEL

Department Vice President:

[REDACTED]

Department Senior Manager:

[REDACTED]

Clinical Project Management:



SYNOPSIS

Protocol Title:	Prospective, Single-Arm Clinical Trial to Evaluate Acute Dry Eye Symptom Relief Assessed During Exposure to a Controlled Adverse Environment (CAE [®]) Following a 45 Day Period with Application of TrueTear [™]
Protocol Number:	OCUN-029
Study Device(s):	TrueTear [™]
Study Objective:	The objective of this study is to characterize acute dry eye symptom relief assessed during exposure to a Controlled Adverse Environment (CAE) following use of TrueTear for 45 days.
<u>Overall Study Design</u>	
Structure:	Prospective, single-arm, open-label study
Duration:	Approximate 21 day screening period and 45 day daily application period
Device Regimen:	Daily use of TrueTear per Instructions For Use (IFU) with in-office tear production assessment at Day 7 and CAE assessments taking place on Days 0 and 45.
Summary of Visit Schedule:	Up to four visits over the course of approximately 66 days Visit 1 (Day -21 ± 20) - Screening Visit Visit 2 (Day 0) - Day 0 CAE Visit Visit 3 (Day 7 ± 2) - Tear Production Assessment Visit Visit 4 (Day 45 ± 7) - Day 45 CAE Visit
<u>Study Population Characteristics</u>	
Number of Participants:	Approximately 45 participants are required to receive the device application in the CAE on Day 45. Approximately 60 participants may be enrolled at up to two sites to meet this goal.
Condition/Disease:	Dry Eye Disease
<u>Evaluation Criteria</u>	
Effectiveness Measures:	<u>Primary Effectiveness Measure:</u> The primary effectiveness measure will be Eye Dryness Score (EDS) using a visual analog scale (VAS) as assessed in the CAE at Day 45.

	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
Safety Measures:	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
Other Measures:	<ul style="list-style-type: none">[REDACTED] <p>[REDACTED]</p> <p>[REDACTED]</p>
General Statistical Methods and Types of Analyses	
<u>Sample Size</u>	
<p>Approximately 45 participants are required to receive the device application in the CAE on Day 45. Approximately 125 participants may be screened and approximately 60 participants may be enrolled to meet this goal.</p>	
<u>Primary Effectiveness Analysis</u>	
<p>The primary effectiveness analysis will be acute symptom relief at Day 45 defined as the difference in the pre-application and post-application values, assessed using the EDS in the CAE. The test will be one-sided and evaluated at an α of 0.025 in the Full Analysis Set (FAS) population.</p>	
<u>Exploratory Effectiveness Analyses</u>	
<p>[REDACTED]</p>	
<u>Safety Analyses</u>	
<p>[REDACTED]</p>	

TABLE OF CONTENTS

SYNOPSIS.....	4
TABLE OF CONTENTS.....	6
TABLE OF FIGURES.....	8
LIST OF ABBREVIATIONS.....	9
1.0 INTRODUCTION.....	10
1.1 Background.....	10
1.2 Current Treatment Options for Dry Eye Disease.....	10
1.3 Rationale.....	11
1.4 Controlled Adverse Environment Model.....	12
1.5 Proposed Indication.....	12
2.0 STUDY OBJECTIVES.....	12
3.0 CLINICAL HYPOTHESES.....	12
4.0 OVERALL STUDY DESIGN.....	12
5.0 STUDY POPULATION.....	13
5.1 Number of Participants.....	13
5.2 Study Population Characteristics.....	13
5.3 Inclusion Criteria.....	14
5.4 Exclusion Criteria.....	14
5.5 Inclusion/Exclusion Exceptions.....	15
5.6 Discontinuation Criteria (if applicable).....	15
6.0 STUDY PARAMETERS.....	16
6.1 Effectiveness Measures.....	16
6.1.1 Primary Effectiveness Measure.....	16
[REDACTED]	
[REDACTED]	
[REDACTED]	
7.0 DEVICE DESCRIPTION.....	17
7.1.1 Base Unit.....	19
7.1.2 Disposable Tip.....	19
7.1.3 Cover.....	19
7.1.4 Charger.....	19
7.2 Device Accountability.....	19
7.3 Other Study Supplies.....	19
8.0 STUDY METHODS AND PROCEDURES.....	20
8.1 Participant Entry Procedures.....	20
8.1.1 Overview.....	20
8.1.2 Informed Consent.....	20

8.1.3	Washout Intervals and Prohibited Treatments	20
8.1.4	Procedures for Final Study Entry.....	20
8.1.5	Methods for Assignment of Participant Number	20
8.2	Participant Training, Device Dispensing, and Home Use	21
8.3	Concurrent Therapies.....	22
8.4	Examination Procedures	22
8.4.1	Procedures to be Performed at the Screening Visit (Visit 1; Day -21 ± 20).....	22
8.4.2	Procedures to be Performed on the Day 0 CAE Visit (Visit 2; Day 0)	23
8.4.3	Procedures to be Performed on Tear Production Assessment Visit (Visit 3; Day 7 ± 2)	24
8.4.4	Procedures to be Performed on Day 45 CAE Visit (Visit 4; Day 45 ± 7)	24
8.4.1	Early Termination/Discontinuation	25
8.5	Schedule of Visits	25
8.5.1	Scheduled Visits.....	25
8.5.2	Unscheduled Visits	26
8.6	Completed Participants	26
8.7	Study Termination	26
8.8	Study Duration	26
8.9	Monitoring and Quality Assurance.....	26
8.9.1	Study Monitoring.....	26
8.9.1	Recording of Data.....	27
9.0	ADVERSE EVENTS.....	27
9.1	Adverse Event Recording	27
9.2	Adverse Event Evaluation.....	27
9.3	Relationship of the AE to the investigational device.....	28
9.4	Serious and Unanticipated Adverse Device Effects	28
9.5	Adverse Event Reporting.....	29
9.6	Anticipated Adverse Events.....	30
10.0	PREGNANCY	30
11.0	STATISTICAL HYPOTHESIS AND METHODS OF ANALYSES.....	31
11.1	Power Calculation and Determination of Sample Size.....	31
11.2	Statistical Hypotheses and Level of Significance.....	31
11.3	Randomization	32
11.4	Evaluability of Data	32
11.5	General Statistical Considerations	32
11.6	Participant Accountability and Missing Data	32
11.7	Participant Demographic and Baseline Characteristics	32
11.8	Effectiveness Analyses	32

11.9 Safety Analyses.....33

12.0 FINAL CLINICAL STUDY REPORT33

13.0 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES.....33

13.1 Protection of Human Participants.....33

13.1.1 Participant Informed Consent33

13.1.2 Institutional Review Board (IRB) Approval.....34

13.1.3 Ethical Conduct of the Study34

13.1.4 Participant Confidentiality34

13.2 Documentation.....34

13.2.1 Retention of Documentation.....34

13.3 Regulatory Status35

13.4 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Device35

13.5 Recording of Data on Source Documents and Case Report Forms (CRFs)35

13.6 Amendments to the Protocol.....35

13.7 Publications.....35

14.0 REFERENCES36

15.0 APPENDICES38

15.1 Appendix 1: Schedule of Visits and Measurements39

15.2 Appendix 2: Examination Procedures, Tests, Equipment, and Techniques40

15.2.1 Visual Acuity Procedures40

15.2.2 Slit Lamp Biomicroscopy41

15.2.2.1 Corneal Fluorescein Staining.....42

15.2.3 Intranasal Examination43

15.2.4 Basal Schirmer Test with Topical Anesthesia43

15.2.5 Dry Eye Questionnaires45

15.3 Appendix 3: Sponsor and [REDACTED] Approvals49

15.4 Appendix 4: Investigator’s Signature50

TABLE OF FIGURES

Figure 1 The TrueTear system components 18

Figure 2 Use of the TrueTear 22

Figure 3 Target area of cotton swab nasal stimulation..... 44

LIST OF ABBREVIATIONS

AE	Adverse event
ADE	Adverse device effect
CAE [®]	Controlled adverse environment
CDVA	Corrected distance visual acuity
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
DED	Dry eye disease
DEWS	Dry eye workshop
DHHS	Department of Health and Human Services
EDS	Eye Dryness Score
EMS	Electro-neuromuscular stimulation
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FAS	Full Analysis Set
GCP	Good clinical practice
HIPAA	Health Information Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFU	Instructions for use
IRB	Institutional/independent review board
LASEK	Laser assisted sub-epithelial keratectomy
LASIK	Laser-assisted in situ keratomileusis
LED	Light-emitting diode
LFU	Lacrimal functional unit
logMAR	Logarithm of the minimum angle of resolution
MGD	Meibomian gland dysfunction
mm	Millimeter
NEI	National Eye Institute
OSDI [®]	Ocular Surface Disease Index [®]
OTC	Over-the-counter
PP	Per protocol
PRK	Photorefractive keratectomy
PROSE	Prosthetic replacement of the ocular surface ecosystem
SAE	Serious adverse event
SOP	Standard operating procedure
TENS	Transcutaneous electrical nerve stimulation
UADE	Unanticipated adverse device effect
US	United States
VAS	Visual analog scale
WOCBP	Women of childbearing potential

1.0 INTRODUCTION

1.1 Background

The 2007 National Eye Institute (NEI)/Industry Dry Eye Workshop defined dry eye disease (DED) as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.¹ Dry eye disease has a complex pathophysiology and a multifactorial etiology related to an inadequacy of one or more layers of the tear film. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.¹ An estimated 25 million Americans are reported to have DED, one of the most common reasons patients seek care with their eye care professional.^{1,2}

Dry eye is recognized as a disturbance of the Lacrimal Functional Unit (LFU), an integrated system comprised of the lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands) and lids, and the sensory and motor nerves that connect them.³ This functional unit controls the major components of the tear film in a regulated fashion and is responsive to environmental, endocrinological, and cortical influences. Its general function is to preserve tear film integrity, corneal transparency, and the image quality projected onto the retina.⁴⁻⁶

Signs of dry eye include reduced tear volume, delayed tear clearance, abnormal tear osmolarity, decreased tear film break-up time, punctate keratitis and distorted mires on keratometry or corneal topography. Symptoms can include dryness, grittiness, burning, stinging, discomfort, photophobia, redness, tearing, reduced ability for prolonged reading or computer work and fluctuating vision. These symptoms are typically worse later in the day and can be triggered or exacerbated by environmental conditions such as low humidity or wind.

The severity and prevalence of dry eye in the general population increases with age and is particularly common in post-menopausal women and in those 65 and older. While patients with mild to moderate DED experience a range of complaints, as described above, patients with severe dry eye are at risk for more serious ocular findings, such as punctate keratopathy evidenced by significant fluorescein staining of the cornea and epithelial defects. More severely affected patients can experience a quality of life deficiency comparable to that of moderate to severe angina.⁷

Studies suggest that dry eye can be associated with significant impact on visual function, including reading and driving⁴ as well as daily activities, social and physical functioning, workplace productivity, and quality of life.⁵

1.2 Current Treatment Options for Dry Eye Disease

Treatment for dry eye is generally palliative in nature and intended to supplement patients' natural tears or to improve the residence time of a limited volume of tears. Depending on the severity of disease and the underlying etiology of the DED, treatment options include artificial tear substitutes (solutions, ointments, and gels), punctal plugs, warm compresses, environmental

modification, omega-3 fatty acid supplements, and moisture chamber goggles.^{8,9} For patients with an inflammatory component to their DED, topical cyclosporine (RESTASIS[®]; Allergan) or lifitegrast (Xiidra[®]; Shire) are treatment options and an eyelid thermal pulsation system (Lipiflow Thermal Pulsation System; TearScience, Inc.) can be used by patients with evaporative dry eye or lipid deficient dry eye. Patients with more severe disease may be treated with punctal cautery, systemic cholinergic agonists, systemic anti-inflammatory agents, mucolytic agents, autologous serum tears, Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE) scleral contact lenses and tarsorrhaphy.

The most commonly used treatment for DED, artificial tear substitutes, have significant limitations as therapeutic modalities for this condition. Many artificial tear formulations contain preservatives such as benzalkonium chloride, which have been shown to be toxic to the corneal epithelium. While preservative-free DED products are commercially available, the risk of microbial contamination if improperly stored and the limited time after opening before disposal is required make this option less than ideal.

Punctal plugs are associated with poor retention and complications. A study focused on the time course of retention showed that 29% of plugs were lost within the first month of use¹⁰ and another showed that 56% of silicone plugs were retained after two years.¹¹ Complications include plug migration, biofilm formation and infection.¹² Punctal plugs that are displaced into the lacrimal system may pass through the system, and blockage and secondary infection have been reported.

Given the limitations of the most commonly available therapies for dry eye (artificial tears and punctal plugs), it is not surprising that DED continues to be considered one of the most poorly treated diseases in ophthalmology.

1.3 Rationale

The nasolacrimal reflex is a well-established pathway by which nasal stimuli promote both resting basal¹³ and bolus tear secretion. The reflex plays a functional role in expelling foreign bodies or irritants from the nose by secreting tears into the nasal cavity via the nasolacrimal duct upon stimulation by the irritant.

Reflex activation of the lacrimal glands is also one of the body's primary compensatory mechanisms for addressing ocular surface dryness. Unfortunately, over time, an arid environment and resulting inflammation results in damage to the afferent nerves innervating the cornea, compromising the reflex response and ultimately leading to an even drier ocular surface.

The application of electrical stimulation to sensory neurons of the nasal cavities to acutely increase natural tear production in DED is a promising alternative to replenishment and symptom reduction with artificial tears and ointment.

1.4 Controlled Adverse Environment Model

The signs and symptoms of dry eye are known to respond to environmental conditions such as temperature, relative humidity, air flow, allergens and pollutants.¹⁴ Variations in these environmental conditions can make the testing of investigational products for the treatment of dry eye challenging. In response, models have been developed to control ocular exposure to temperature, relative humidity and air flow. By controlling these factors, clinical testing can be performed under a more uniform set of conditions. This study utilizes the controlled adverse environment (██) model to assess symptoms of dry eye.¹⁵ The CAE is a room that standardizes environmental conditions by regulating humidity, temperature, airflow, lighting conditions and visual tasking. The CAE represents everyday situations¹⁶ that induce discomfort for dry eye patients such as forced air heating systems, airplane travel and computer use and allows for the standardization of these influential factors. As such, the CAE has been used in several studies of pharmaceuticals for dry eye.¹⁷⁻¹⁹ In this study, dry eye participants are exposed to the CAE for up to two hours while symptoms are evaluated before and after application of the investigational device.

1.5 Proposed Indication

The TrueTear provides a temporary improvement in dry eye symptoms during neurostimulation in adult patients.

2.0 STUDY OBJECTIVES

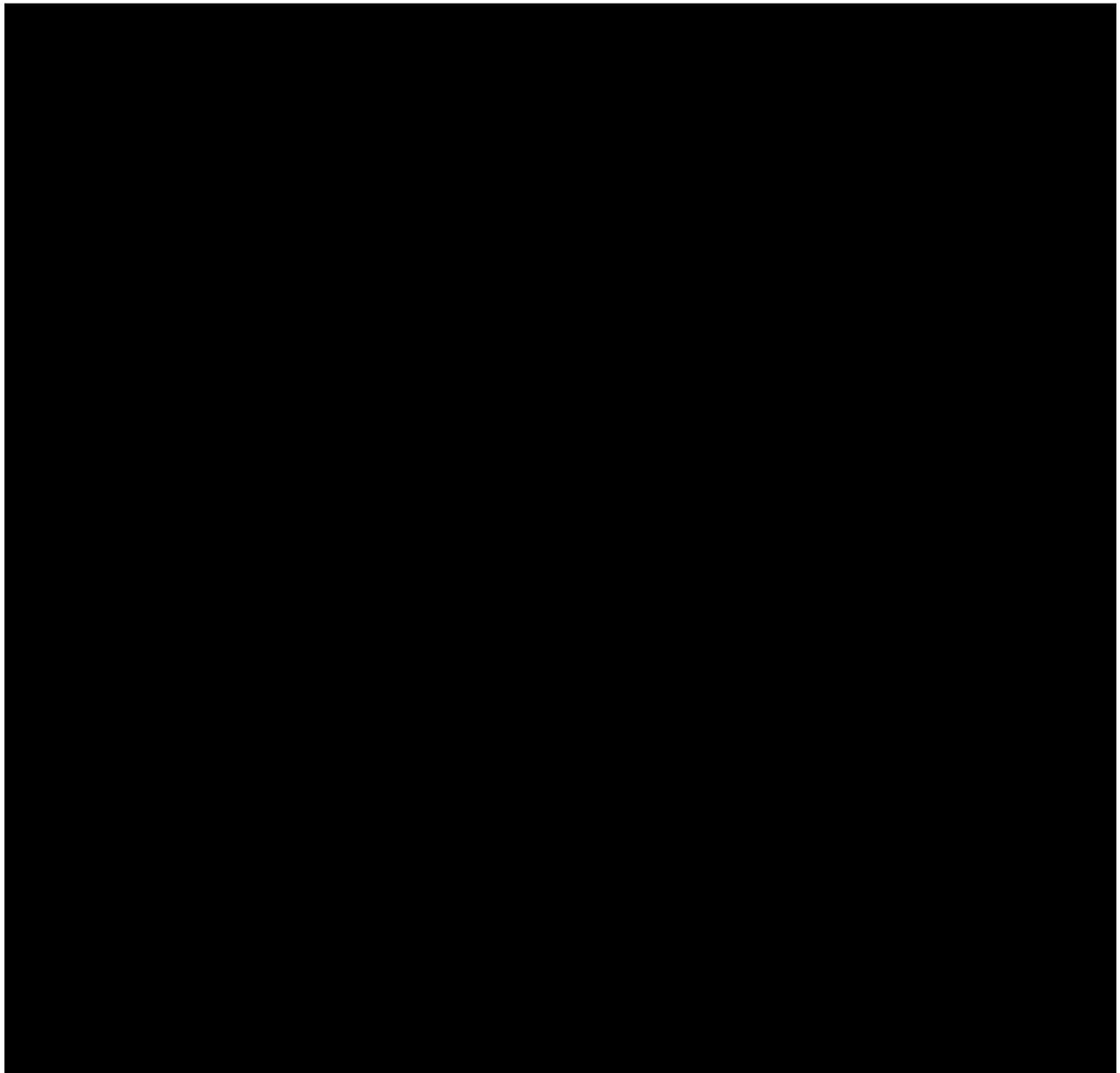
The objective of this study is to characterize acute dry eye symptom relief assessed during exposure to a Controlled Adverse Environment (CAE) following use of TrueTear for 45 days.

3.0 CLINICAL HYPOTHESES

After 45 days of TrueTear use, neurostimulation continues to result in a statistically significant reduction in eye dryness as exacerbated by exposure to the CAE.

4.0 OVERALL STUDY DESIGN

This is a prospective, single-arm, open-label study conducted at up to two sites in the US, designed to characterize acute dry eye symptom relief following 45 days of use of the TrueTear device in adult participants with DED. Approximately 60 male and female participants at least 22 years of age with a participant-reported history of dry eye in both eyes and meeting all other study eligibility criteria will use the TrueTear on a daily basis and during CAE exposure.



5.0 STUDY POPULATION

5.1 Number of Participants

It is estimated that approximately 125 participants will be screened at up to two sites in the US to achieve approximately 60 qualified participants.

5.2 Study Population Characteristics

All participants should meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Participants should:

1. Be at least 22 years of age at the Screening Visit
2. Have used and/or desired to use an artificial tear substitute for dry eye symptoms within 6 months prior to the Screening Visit
3. [REDACTED]
4. [REDACTED]
[REDACTED]
5. [REDACTED]
[REDACTED]
6. Be literate, able to speak English, and able to complete questionnaires independently
7. [REDACTED]
8. [REDACTED]

5.4 Exclusion Criteria

Participants should not:

1. [REDACTED]
2. Have chronic or recurrent epistaxis, coagulation disorders or other conditions that, in the opinion of the Investigator, may lead to clinically significant risk of increased bleeding
3. Have had nasal or sinus surgery (including history of application of nasal cautery) or significant trauma to these areas
4. [REDACTED]
5. [REDACTED]
6. Have had a corneal transplant in either or both eyes
7. Have used contact lenses within 7 days prior to the Screening Visit or anticipate the use of contact lenses at any time during the study

8. [REDACTED]

9. [REDACTED]

meibomian gland disease that are typically associated with dry eye disease are allowed.

10. Have a cardiac demand pacemaker, implanted defibrillator, or other active implanted metallic or active implanted electronic device in the head

11. [REDACTED]

12. [REDACTED]

13. [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

14. Be a female who is pregnant, nursing an infant, or planning a pregnancy during the duration of the study

15. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days prior to the Screening Visit

5.5 Inclusion/Exclusion Exceptions

The investigator has the right to exclude a potential participant’s enrollment in the study if s/he deems it in the best interest of the participant. Reasons for exclusion on this basis will be recorded.

5.6 Discontinuation Criteria (if applicable)

Participants are free to discontinue their participation in this study at any time and for any reason, specified or unspecified, without prejudice. In addition, the Investigator may decide to

discontinue a participant from the study for safety reasons or when it is in the best interest of the participant. No constraints will be placed on ordinary patient management.

Reasons for participant withdrawal may include but are not limited to the following:

- Either at the Investigator's request, for safety reasons (e.g., serious or severe AE), or at the participant's request
- Non-compliance (e.g., failure to follow application instructions, missing visits, using prohibited medications)
- When a concomitant therapy likely to interfere with the results of the study is reported or required by the participant (the Investigator will report all such information on the source documents/ case report forms (CRFs) and decide, in accordance with the Sponsor, whether the participant is to be withdrawn)
- A confirmed positive pregnancy test at any time during the study
- When a participant is lost to follow-up. The Investigator (or designee) will attempt three times to reach the participant by telephone, and will send a follow-up letter by certified mail before considering the participant as lost to follow-up. These actions will be documented and recorded on the End of Study CRF and a copy of the follow-up letter maintained in the Investigator's file.
- When a participant is erroneously admitted into the study or does not meet the eligibility criteria

In addition, the Sponsor also reserves the right to discontinue the study at any time for clinical or administrative reasons.

All early discontinuations and their reasons should be carefully documented by the Investigator on the End of Study CRF and, if applicable, on the Adverse Event (AE) CRF. Notification of a participant's discontinuation and the reason for discontinuation will be made to [REDACTED] and/or Sponsor. No participant who has entered the CAE at Day 0 can be replaced by another participant if the participant is discontinued prematurely for any reason. Participants who terminate early will be asked to complete safety assessments (if the participant agrees) prior to study exit.

6.0 STUDY PARAMETERS

6.1 Effectiveness Measures

6.1.1 Primary Effectiveness Measure

The visual analog scale (VAS) has frequently been used for the collection of patient-reported outcomes and has been commonly used to assess dry eye symptoms in clinical studies.²⁰⁻²⁹ As such, the 2007 report of the International Dry Eye WorkShop (DEWS) listed the Visual Analog Scale as a well-defined symptom assessment methodology suitable for use in dry eye clinical trials.³⁰ Patient-reported outcomes assessed using the Eye Dryness Score (EDS) VAS have been used in other dry eye studies and were recently used as the primary symptom endpoint for FDA approval of lifitegrast (Xiidra®)

for the treatment of the signs and symptoms of dry eye disease.^{31,32,33} Based on this information, the EDS visual analog scale was selected as the primary effectiveness variable to provide a direct assessment of the participant’s perception of their current eye dryness symptoms.

The primary effectiveness measure will be the change in dry eye symptom severity score during CAE exposure at Study Day 45 assessed using the EDS. The EDS will be assessed using a self-administered VAS every five minutes during CAE exposure. The analysis variable will be the change in EDS values from the last time point prior to application administration to the subsequent time point following administration. The primary effectiveness analysis will compare the change in EDS between the pre-application and post-application scores to an expected change of 0. The test will be one-sided and evaluated at an α of 0.025 in the Full Analysis Set (FAS) population.

6.1.1 [REDACTED]

[REDACTED]

[REDACTED]

6.2 Safety Measures

[REDACTED]

6.3 Other Measures

- [REDACTED]
- [REDACTED]
- [REDACTED]

7.0 DEVICE DESCRIPTION

The TrueTear device delivers small electrical currents to the inner cavity of the nose, activating nerves that stimulate the body’s natural tear production system.

The device consists of four distinct parts (Figure 1):

1. A reusable Base Unit which produces the electrical stimulation waveform.
2. A disposable Tip that inserts into the nasal cavity and stimulates the target intranasal tissue.
3. A reusable Cover to protect the Tip.
4. A Charger which recharges the battery inside the Base Unit.



Base Unit with Cover



Base Unit with Disposable Tips (Front and Back)



TrueTear System

Figure 1 The TrueTear system components

7.1.1 Base Unit

When activated, the Base Unit provides electrical pulses to the Tip. The strength of these pulses is controlled by two buttons, with five different intensity levels available, indicated by the number of illuminated LEDs on the Base Unit. The device internally records the time and duration of device use.

7.1.2 Disposable Tip

The disposable Tip is specially designed to allow the participant to easily apply stimulation to the target areas within the nose. The Tip attaches to the Base Unit and contains hydrogel (similar to the material used in contact lenses) that contacts the inside of the nose to provide stimulation. Each tip may be used up to 24 hours. After 24 hours, the used tip should be discarded and a fresh tip should be attached. A separate Cover can be used to protect the Tip and Base Unit when the device is not in use.

7.1.3 Cover

The Cover may be placed over the top of the Tip attached to the Base Unit for protection in between uses.

7.1.4 Charger

The Base Unit may be recharged by removing the Tip and placing the Base Unit onto the Charger. Charging typically takes under 4 hours, and a green LED indicates that the process has completed.

7.2 Device Accountability

Each Base Unit has a unique serial number and the serial number of the Base Unit used by each participant will be recorded on the appropriate case report form and device accountability log. The disposable Tip is provided in a sealed pouch, which is labeled with a lot number and expiration date. The lot number of the Tips provided to a participant will also be recorded on the appropriate case report forms and on the device accountability log. Tips should not be used beyond the expiration date provided on the pouch.

7.3 Other Study Supplies

The following will be provided by the Investigator:

- Urine pregnancy test kits
- Schirmer test strips
- Fluorescein sodium solution or fluorescein strips
- Proparacaine

8.0 STUDY METHODS AND PROCEDURES

8.1 Participant Entry Procedures

8.1.1 Overview

Participants as defined by the criteria in [section 5.2](#), [5.3](#), and [5.4](#) will be considered for entry into this study.

8.1.2 Informed Consent

Prior to a participant's participation in the trial (i.e., prior to study-related procedures), the study will be discussed with each potential participant and participants wishing to participate should give written informed consent using an IRB approved informed consent form (ICF). The ICF should be the most recent version that has received approval by a properly constituted Institutional Review Board (IRB).

8.1.3 Washout Intervals and Prohibited Treatments

Prohibited treatments and activities are outlined in the Exclusion Criteria and include:

- Contact lenses – 7 days prior to the Screening Visit and throughout study duration
- Punctal or intracanalicular plugs – Throughout study duration

Medications or dry eye products prohibited as follows:

- Ophthalmic prescription or OTC eye medications (eye drops, gels, or ointments) or dry eye products on the day of and for duration of Visit 1, Visit 2, Visit 3 and Visit 4. Participants may use such products as needed at the completion of each study visit.
- Nasal sprays within 4 hours of and for the duration of Visit 1, Visit 2, Visit 3 and Visit 4
- Use of TrueTear on the day of Visit 2, Visit 3 and Visit 4 (application of TrueTear at Visit 2 and Visit 4 will be performed in the CAE) after which participants may perform additional applications as needed

8.1.4 Procedures for Final Study Entry

Participants should meet all inclusion and none of the exclusion criteria.

8.1.5 Methods for Assignment of Participant Number

At the Screening Visit, participants who provide written informed consent will be assigned a unique 5-digit screening number, which includes the 2-digit site number plus a unique 3-digit screening number beginning with 001 (e.g., 11001, 11002, 11003, etc.). Screening

numbers should be assigned in ascending consecutive order. Participants who meet all of the eligibility criteria will be scheduled to return for the Day 0 Visit.

8.2 Participant Training, Device Dispensing, and Home Use

On Day 0, participants will be provided with a TrueTear and disposable tips to take home with them and use daily per the Instructions for Use (IFU). Participants will receive training to perform intranasal neurostimulation and will receive a user guide. Following device training and prior to entering the CAE, devices for home use will be dispensed to participants. The serial number of the unit and the lot number of disposable tips will be documented in the participant's CRF.

Participants will undergo stimulation for the first time on Day 0 during the CAE session where they will be instructed to apply stimulation for approximately three minutes. Training will include instruction on the following points:

- Between study visits, participants will be asked to perform neurostimulation at least two times per day up to as many as 10 times per day, as needed. Each stimulation should last no longer than three minutes. Participants should be instructed that the device has a single-day stimulation limit of 30 minutes at which point the device will time-out.
- Participants will be asked to fully charge the device before first use and to re-charge daily.
- After using the device, participants will be instructed to clean the system with tissue or an alcohol pad if necessary prior to placing the cover to protect the tip between uses.
- Participants should be instructed to replace the disposable tip daily according to the IFU and that the used tip should be discarded in trash.

For the device application, participants will be instructed to place the tips of the TrueTear into both nostrils simultaneously towards the top and front of the nose (as in [Figure 2](#)). They will be told to turn on the unit by holding down the + button for approximately two seconds. There are five stimulation intensity levels and participants may adjust the level by pressing the + or – buttons to obtain a gentle tingling sensation. Participants will be told they can cease stimulation by holding down the – button for approximately two seconds on the base unit or by withdrawing the tips from the nostrils. Participants will be instructed to replace the Tip if they do not feel any sensation.



Figure 2 Use of the TrueTear

(L) Starting position and (R) Correct application position by inserting the disposable tips fully into the nasal cavity and to the front of the nose.

At Visit 3 (Day 7), prior to in-office application and evaluation of tear secretion, trained clinical personnel will review procedures for the proper use of the device (e.g., correct positioning intranasally, frequency and duration of use, daily replacement and disposal of tips, etc.) with participants.

Note: A Sponsor representative may be present at visits to assist in training participants on the use of the device.

8.3 Concurrent Therapies

The use of any concurrent medication, prescription or OTC, is to be recorded on the participant’s CRF along with the reason the medication was taken. Concomitant medications that are considered necessary for the participant’s welfare, but will not interfere with study assessments and evaluations, will be allowed during the study at the Investigator’s discretion.

Concurrent enrollment in another investigational drug or device study is not permitted.

8.4 Examination Procedures

The following procedures will be performed (see [Appendix 2](#) for description):

8.4.1 Procedures to be Performed at the Screening Visit (Visit 1; Day -21 ± 20)

Review of qualification criteria should take place with each test that relates to eligibility.

- [REDACTED]
- [REDACTED]
- [REDACTED]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

8.4.2 Procedures to be Performed on the Day 0 CAE Visit (Visit 2; Day 0)

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

- Approximately 120 minutes of CAE exposure

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

8.4.3 Procedures to be Performed on Tear Production Assessment Visit (Visit 3; Day 7 ± 2)

- [Redacted]

8.4.4 Procedures to be Performed on Day 45 CAE Visit (Visit 4; Day 45 ± 7)

- [Redacted]
- [Redacted]
 - [Redacted]
 - [Redacted]
 - [Redacted]

[REDACTED]

8.4.1 Early Termination/Discontinuation

If a participant is discontinued from the study prior to Visit 4, then all safety evaluations and Pre-CAE evaluations that are to be performed should be completed on the day of discontinuation (early termination) with the participant's agreement.

8.5 Schedule of Visits

8.5.1 Scheduled Visits

Participants will remain in the study for approximately 66 days and will be seen at the following intervals:

Visit 1	Screening Visit (Day -21 ± 20)
Visit 2	Day 0 CAE Visit (Day 0)
Visit 3	Tear Production Assessment Visit (Day 7 ± 2)
Visit 4	Day 45 CAE Visit (Day 45 ± 7)

The schedule of exams and procedures performed at these visits can be found in [Appendix 1](#). Descriptions of exams and procedures performed during these visits can be found in [Appendix 2](#).

Participants who are exited from the study due to unanticipated adverse device effects (UADEs) will be followed until their medical outcome is determined. The Investigator should provide written reports about the status of UADEs to the study Sponsor.

8.5.2 Unscheduled Visits

These visits may be performed in order to ensure participant safety. For participants reporting for an unscheduled visit, assessments performed are at the discretion of the Investigator. At minimum, AEs should be assessed. All procedures performed at an unscheduled visit will be recorded on the Unscheduled Visit CRF. Any procedure indicated in the CRF that is not performed should be indicated as “Not done.”

8.6 Completed Participants

A completed participant is one who has not been discontinued from the study and has successfully completed Visit 4.

8.7 Study Termination

The study may be stopped at any time by the Investigator, the Sponsor, and/or [REDACTED] with appropriate notification.

8.8 Study Duration

An individual participant’s participation will involve up to four visits over an approximate 66 day period.

8.9 Monitoring and Quality Assurance

8.9.1 Study Monitoring

Allergan personnel (or designees) will monitor this study in a manner consistent with applicable health authority regulations and the procedures adopted by the SOPs of the Sponsor, Allergan. Prior to the start of the study, member(s) of Allergan and/or [REDACTED] (or designees) will review the protocol, CRFs, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Principal Investigator/Sub-Investigator(s) and pertinent study staff. Monitoring visits will occur as necessary during the course of the investigation to verify:

- The rights and well-being of participants are protected
- The conduct of the investigation is in compliance with the currently approved protocol/amendment, GCP and IRB/IEC requirements
- The integrity of the data
- Study device accountability
- Adequate study documentation

During the course of the study, if the Sponsor (or designee) determines that the Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor (or designee) will take written action to correct the non-compliance and to secure compliance. In addition, the Sponsor (or designee) may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the Sponsor's actions. This termination will be documented in a memo or follow-up letter to the Principal Investigator.

8.9.1 Recording of Data

Participant data recorded on CRFs during the study will be documented in an anonymous fashion. The participant will only be identified by the participant number. If, as an exception, it is necessary for safety or regulatory reasons to identify the participant, the Sponsor or its representatives, and the Investigator, are bound to keep this information confidential.

9.0 ADVERSE EVENTS

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding) symptom, or disease temporally associated with the use of an investigational product but not necessarily related to the investigational product. An AE may also be called a complication. The capture of AEs will begin with the participant's entry into the CAE.

9.1 Adverse Event Recording

All AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate pages of the CRF. Any clinically relevant deterioration in clinical finding is considered an AE and should be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

9.2 Adverse Event Evaluation

The Investigator should evaluate if each AE is serious, related to the investigational device and anticipated using the following definitions.

A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- It results in death (i.e., the AE actually causes or leads to death);
- It is life threatening (i.e., the AE places the participant at immediate risk of death);
- It requires or prolongs inpatient hospitalization. If a participant is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event. For example, if a participant is hospitalized to undergo coronary bypass surgery, the heart condition that necessitated the bypass should be recorded. Hospitalizations for diagnostic or elective surgical procedures or

hospitalizations required to allow outcome measurement for the study should not be recorded as SAEs:

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the participant's ability to conduct normal life functions);
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational device;
- It is considered a significant medical event by the investigator based on medical judgment (e.g. may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above);
- It is considered sight-threatening by the Investigator.

9.3 Relationship of the AE to the investigational device

<i>Definite</i>	A clear cut causal relationship with the study device and no other possible cause
<i>Probable</i>	A causal relationship with the study device is likely although alternate etiologies are also possible
<i>Possible</i>	A causal relationship with study device is not definite, alternate etiologies are also possible
<i>Not related</i>	The AE has no causal relationship to study device and/or there is evidence of alternative etiology such as concurrent medication or illness.
<i>Not applicable</i>	The participant has not been exposed to the study device.

The AE will be determined to be device-related, making it an adverse device effect (ADE), if it is identified to have had a definite, probable or possible causal relationship to the investigational device.

An AE is unanticipated if the nature, severity, or frequency of the event is not consistent with either the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, user manuals and the current IRB-approved informed consent document, and (b) other relevant sources of information such as product labeling and package inserts; or the expected natural progression of any underlying disease, disorder, or condition of the participant(s) experiencing the AE and the participant's predisposing risk factor profile for the AE.

9.4 Serious and Unanticipated Adverse Device Effects

A serious and unanticipated adverse device effect is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device

if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants.”

9.5 Adverse Event Reporting

All AEs that occur during the course of the study should be reported on the Adverse Event CRF. The Investigator should determine the intensity of the event.

<i>Mild</i>	Awareness of sign or symptom, but easily tolerated
<i>Moderate</i>	Discomfort enough to cause interference with normal daily activities
<i>Severe</i>	Inability to perform normal daily activities

All SAEs and ADEs should be reported by the Investigator to [REDACTED] and the Sponsor in writing within 24 hours from the point in time when the Investigator becomes aware of the event. It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB) of all unanticipated SAEs and unanticipated problems, per the IRBs reporting requirements.

Throughout the course of the proposed study, all efforts will be made to remain alert to possible adverse experiences or untoward findings. If adverse experiences occur, the first concern will be the safety and welfare of the participant. Appropriate medical intervention will be made.

[REDACTED] and the Sponsor will immediately conduct an evaluation of any UADE. The results of the evaluation will be reported to the IRB within 10 days of [REDACTED] and/or the Sponsor becoming aware of the event. If it is determined by [REDACTED] and the Sponsor to present an unreasonable risk to study participants, all investigations or parts of the investigation presenting that risk will be terminated as soon as possible. Termination will occur not later than five working days after [REDACTED] and the Sponsor makes this determination, and not later than 15 working days after first receiving notice of the event. [REDACTED] and the Sponsor will not resume an investigation terminated under these conditions without an additional IRB approval.

Contact information for reporting Serious Adverse Events:

[REDACTED]	[REDACTED]
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Sponsor Contact Information	
[REDACTED]	[REDACTED]

Office Facsimile:	650-737-0200
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9.6 Anticipated Adverse Events

The following is a list of potential AEs associated with the use of the device:

- Nasal discomfort or pain
- Epistaxis
- Excessive sneezing
- Nasal irritation, paresthesia or numbness post-stimulation
- Nasal infection, abrasion or inflammation
- Skin irritation or hypersensitivity
- Headache (e.g., tension, migraine, etc.)
- Facial pain
- Excessive salivation
- Sensation of teeth vibrating
- Excessive rhinorrhea
- Temporary aggravation of nasal allergies
- Allergic reaction to contact materials

The following is a list of potential AEs associated with the testing procedures at Screening or with CAE exposure:

- Ocular discomfort
- Moderate or severe conjunctival injection
- Clinically significant decrease in visual acuity
- Clinically significant increase in corneal or conjunctival epithelial defects
- With use of proparacaine, temporary burning, stinging and conjunctival redness of the eyes
- With use of proparacaine, a rare hyperallergic corneal reaction characterized by epithelial keratitis, sloughing of epithelium, corneal filaments and iritis
- With the Schirmer test, corneal irritation and abrasion
- Allergic reaction to contact materials

10.0 PREGNANCY

Women of Childbearing Potential (WOCBP) include any females who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or are not postmenopausal at least 12 months since last

menses. WOCBP will be required to use designated methods of birth control during the course of the study. All women who are pregnant, nursing an infant, or planning a pregnancy during the duration of this study will be excluded from participation.

If a participant or Investigator suspects that the participant may be pregnant prior to study device administration, the study device should be withheld until the results of pregnancy testing are available. If pregnancy is confirmed, the participant should not administer the study device and should not be enrolled in the study.

If a female participant becomes pregnant during the study, the Investigator will notify Allergan (or designee) immediately after the pregnancy is confirmed. The Investigator will (1) obtain a consent from the female participant for pregnancy follow-up and (2) follow the progress of the pregnancy to term. The Investigator should document the outcome of the pregnancy and provide a copy of the documentation to Allergan (or designee).

11.0 STATISTICAL HYPOTHESIS AND METHODS OF ANALYSES

11.1 Power Calculation and Determination of Sample Size

In a previous controlled study assessing the change in EDS while in the CAE at Day 0, the observed mean (SD) treatment difference for the TrueTear device compared to the control was -13.4 (23.9). It is unknown what, if any, effect on the change in EDS while in the CAE will be with the TrueTear device application after 45 days of use. Using an estimated standard deviation of 25, 45 participants will provide over 90% power to detect a EDS reduction of 13 based on a one-sided test at an α of 0.025.

In the previous study, approximately 10% of the participants did not reach the application threshold during the CAE session. In order to allow for participants that discontinue the study before Day 45 or do not reach the application threshold in the CAE, approximately 60 qualified participants will be identified to initiate the study to ensure Day 45 results for 45 participants.

11.2 Statistical Hypotheses and Level of Significance

The null hypothesis is, after 45 days of TrueTear use, neurostimulation fails to result in a statistically significant reduction in EDS exacerbated by exposure to the CAE.

The alternative hypothesis is, after 45 days of TrueTear use, neurostimulation will result in a statistically significant reduction in EDS exacerbated by exposure to the CAE.

The hypothesis can be expressed as:

$$H_0: \Delta \leq 0 \text{ mm}$$

$$H_A: \Delta > 0 \text{ mm}$$

where Δ represents the change in EDS score, symptom relief, from the TrueTear application. Statistical tests for the primary and exploratory effectiveness variables will be one-sided and evaluated at an α of 0.025.

11.3 Randomization

This study is not randomized.

11.4 Evaluability of Data

All participants who initiated at least one study application will be eligible for inclusion in the analyses. Participation in the study will be summarized by presenting the number of participants who were enrolled, the number of participants who completed the study, and the number of participants who did not complete the study due to not reaching the threshold or by reason of early discontinuation.

Full Analysis Set Population (FAS): The FAS population will include all participants who initiated at least one application of the TrueTear device at any point during the study.

Per protocol population (PP): The PP population is a subset of the FAS population, which did not have a major protocol deviation likely to seriously affect the primary outcome of the study. This population will be the secondary population for the effectiveness analyses and will also be used to summarize the primary and exploratory effectiveness variables. If the PP and FAS populations are exactly the same, then additional efficacy analyses on the PP population will not be performed.

Safety Population: The safety population will be the same as the FAS population.

11.5 General Statistical Considerations

Statistical analyses will use a two-tailed test and will be evaluated at an α of 0.05 unless otherwise specified. The mean, standard deviation (SD), median, minimum and maximum will be presented for continuous variables such as participant age. For categorical variables, such as sex, the number for each category, the total number evaluated, and the percentage will be presented.

11.6 Participant Accountability and Missing Data

Participants who withdraw from the study will be tabulated with the reasons for the withdrawal. A sensitivity analysis of the FAS population will only be conducted if $\geq 5\%$ of the primary effectiveness results are missing. The imputation method is described below in the Effectiveness Analyses section. Missing data will not be imputed for the PP or Safety populations.

11.7 Participant Demographic and Baseline Characteristics

The demographic and baseline characteristics of the study population observed will be presented descriptively.

11.8 Effectiveness Analyses

The primary effectiveness variable will be the change in EDS between the time point preceding application and the subsequent time point following application. The primary effectiveness endpoint will be the analysis of the primary effectiveness variable for the FAS population at Day

45 without imputation. The analysis will use a paired *t*-test or Wilcoxon signed-rank test, as appropriate, and will be evaluated at a one-sided α of 0.025. If $\geq 5\%$ of the FAS population is missing the primary effectiveness variable at Day 45, a sensitivity analysis of EDS difference at Day 45 will be performed by imputing the missing EDS difference as zero. Study participants with a missing Day 45 result will be imputed one at a time and the analysis will be repeated. This process will continue until either the result is no longer statistically significant or all participants with missing results have been imputed. As an additional sensitivity analysis, missing values will be imputed using a random selection process from the available Day 45 results and the analysis will be repeated. This process will be performed 10 times and a single combined p-value for the 10 imputations will be obtained by a method described in Rubin³⁸ and in the SAS manual for PROC MIANALYZE.³⁹ If the study includes more than one site, summaries of the primary effectiveness endpoint without imputation will be presented by site.

The primary effectiveness analysis will be repeated in the PP population as a sensitivity analysis.

The exploratory effectiveness variables will be the difference in EDS at Day 0, the difference in dry eye discomfort using the [REDACTED] Calibra scale in the FAS population at Day 0 and Day 45 and the difference in Schirmer test results at Day 7. The analysis will be performed using the same method as the primary effectiveness variable. Statistical significance will be determined using a one-sided test at an α of 0.025.

11.9 Safety Analyses

The safety analyses will be performed for the Safety population. The primary safety endpoint will be the proportion of participants who experience one or more device-related AEs for each application and overall. The proportion and exact 95% confidence interval will be computed. Any changes in corrected distance visual acuity or slit lamp biomicroscopy findings will be summarized.

12.0 FINAL CLINICAL STUDY REPORT

A final clinical study report will be prepared after completion of the study.

13.0 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

13.1 Protection of Human Participants

13.1.1 Participant Informed Consent

Informed consent should take place before any study-specific procedures are initiated. Signed and dated written informed consent should be obtained from each participant and/or from the participant's parent or legal guardian prior to enrollment into the study.

All ICFs should be approved for use by the Sponsor and receive approval/favorable opinion from an IRB prior to use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Sponsor and [REDACTED] prior to submission to

the governing IRB and that it is read, signed and dated by all participants subsequently enrolled in the study as well as those currently enrolled in the study if required by the governing IRB.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed should be determined by [REDACTED] and/or study Sponsor and provided in writing by [REDACTED] and/or study Sponsor prior to the consent process.

13.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 Code of Federal Regulations [CFR] Part 56.103). The Investigator should obtain appropriate IRB approval before initiating the study and re-approval at least annually.

13.1.3 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including the International Conference on Harmonisation (ICH) Guidelines, and the ethical principles that originated with the Declaration of Helsinki.

13.1.4 Participant Confidentiality

All personal study participant data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of [REDACTED] the Sponsor, the IRB approving this study, the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and other domestic government agencies, will be granted direct access to the study participant's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study device may ultimately be marketed, but the participant's identity will not be disclosed in these documents.

13.2 Documentation

Source documents may include a participant's medical records, hospital charts, clinic charts, the Investigator's study participant files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiographs. The Investigator's copy of the CRFs serves as the Investigator's record of a participant's study-related data.

13.2.1 Retention of Documentation

All study-related correspondence, participant records, consent forms, record of the distribution and use of all study device and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until

at least two years have elapsed since the formal discontinuation of clinical development of the study device. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody should be transferred to a person who will accept the responsibility. The Sponsor should be notified in writing of the name and address of the new custodian.

13.3 Regulatory Status

A previous version of the TrueTear (formerly known as the Oculeve Intranasal Lacrimal Neurostimulator) received CE Mark on December 22, 2014 (CE 615662). It has been approved for marketing in Canada and Australia as well. It is an investigational device in the US.

13.4 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Device

All investigational devices will be clearly labeled “For Investigational Use Only.” A device accountability log recording the distribution and return of all devices will be maintained by the site and will be filed in the Trial Master File. Used disposable tips should be discarded after use; unused disposable tips should be returned to the Sponsor at the conclusion of the study.

13.5 Recording of Data on Source Documents and Case Report Forms (CRFs)

All participant data will be captured in the participant CRFs (i.e. source document). The Investigator is responsible for ensuring that study data is completely and accurately recorded on each participant’s CRF and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

13.6 Amendments to the Protocol

Any amendment containing major modifications (particularly if it may involve an increased risk to the participants) should be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the Sponsor.

13.7 Publications

Information collected during this clinical study concerning TrueTear and results of the data obtained are proprietary and strictly confidential. The Sponsor reserves all rights to any such information. Authorship and manuscript composition will reflect cooperation among all parties

involved in the study. Authorship will be established before writing the manuscript. Sponsor and [REDACTED] will have the final decision regarding the manuscript and publication.

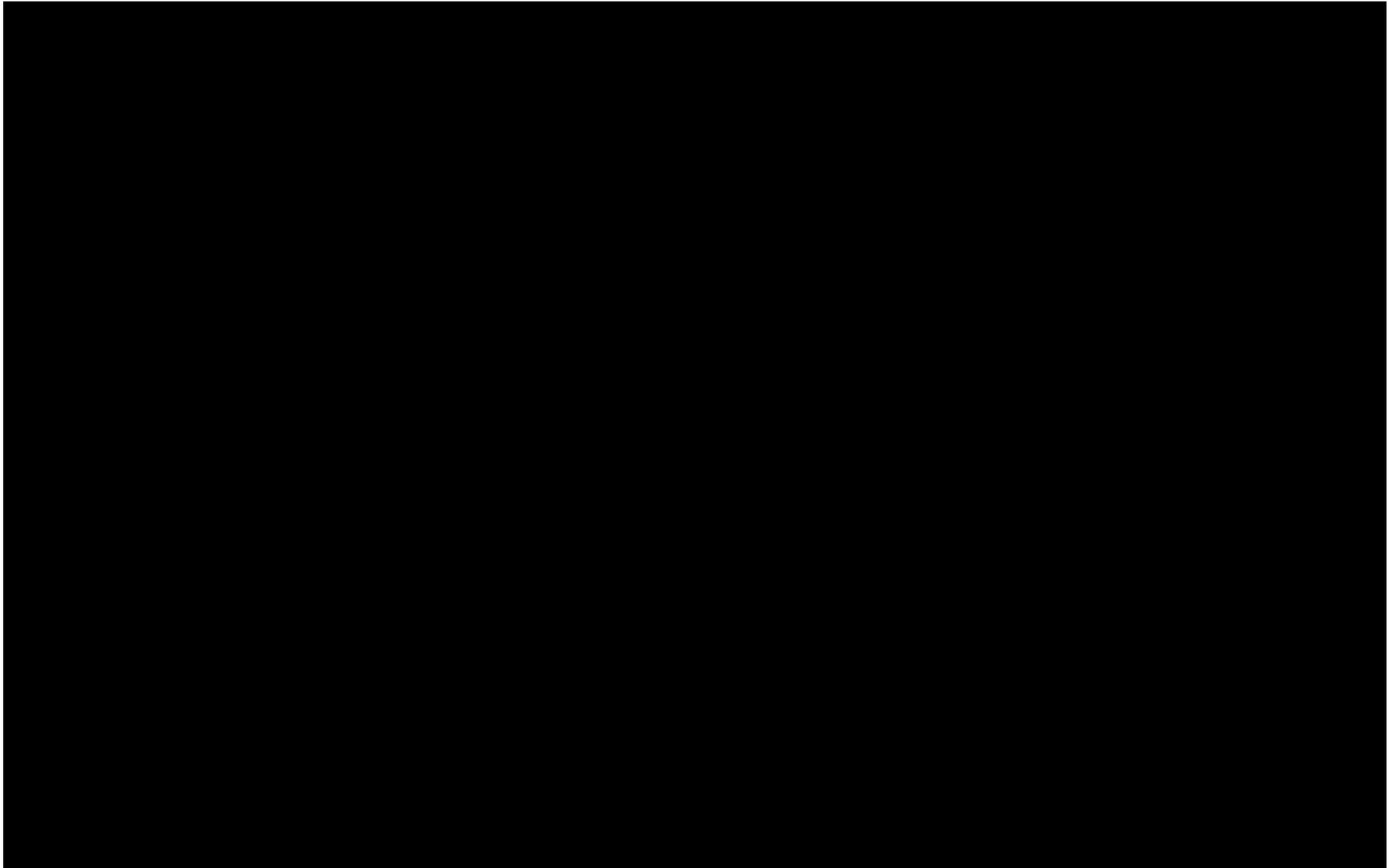
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15.0 APPENDICES



15.2 Appendix 2: Examination Procedures, Tests, Equipment, and Techniques

15.2.1 Visual Acuity Procedures

LogMAR visual acuity should be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual acuity should be evaluated at the beginning of each visit in the study (i.e., prior to slit lamp examination). Participants should use the most recent correction to attain their corrected distance visual acuity (CDVA); if they forget their spectacles, this prescription can be placed in a trial frame.

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the participant viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites should use only ETDRS Series 2000 Chart 1 & 2, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and be well illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The participant should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The participant should be told that the chart has letters only, no numbers. If the participant reads a number, s/he should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The participant should be asked to read slowly, so as to achieve the best identification of each letter. S/he is not to proceed to the next letter until s/he has given a definite response.

If the participant changes a response (e.g., 'that was a "C" not an "O"') before s/he has read aloud the next letter, then the change should be accepted. If the participant changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the participant says s/he cannot read a letter, s/he should be encouraged to guess. If the participant identifies a letter as one of two letters, s/he should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number " $N \times 0.02$ " where 'N' represents the total number of letters

missed up to and including the last line read. This total sum represents the logMAR visual acuity for that eye.

Example: Participant correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
$N \times T$ ($T=0.02$)	= 0.08
Base logMAR + ($N \times T$)	= 0.1 + 0.08
logMAR visual acuity	= 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site should be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (i.e., a participant broke his/her glasses), the reason for the change in correction should be documented.

Note: A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from the Screening Visit (Visit 1) should be evaluated by the Investigator as a potential AE.

15.2.2 Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed during the study. Observations will be graded as *Normal* or *Abnormal*. Abnormal findings, which are clinically significant, will be described. The following will be examined at each visit:

- Cornea
- Conjunctiva
- Anterior Chamber
- Lid

15.2.2.1 Corneal Fluorescein Staining

The examiner should instill 5 μ L of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. Alternatively, corneal staining can be assessed using 1.0 mg sodium fluorescein strips. After moistening the tip of the strip with sterile buffered saline, the excess is shaken into a waste bin with a sharp flick. The lower lid is then pulled down and the flat end of the tip should be gently applied to the inferior tarsal conjunctiva with the intent of not inducing reflex tearing and instilling a very small volume of dye.

The participant will be instructed to blink naturally several times without forced closure of the eyelid to distribute the fluorescein. In order to achieve maximum fluorescence, the examiner should wait at least two minutes after instillation before evaluating corneal fluorescein staining. A Wratten #12 yellow filter will be used to enhance the ability to grade fluorescein staining. The staining will be graded with the NEI Scale. The upper eyelid is lifted slightly to grade the entire corneal surface.

NEI/Industry Workshop Scale

Score each of five areas on the cornea of each eye.

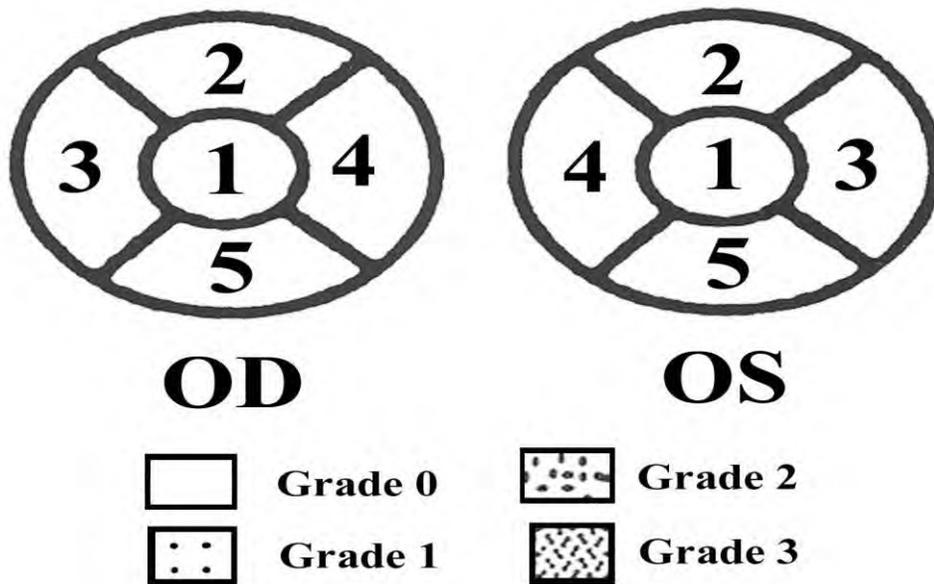


Diagram of the division of the corneal surface for measuring fluorescein uptake. A standardized grading system of 0-3 is used for each of the five areas on each cornea. Grade 0 will be specified when no staining is present. The maximum score is 15.

15.2.3 Intranasal Examination

The intranasal examination can be completed without topical anesthesia using nasal endoscopy or a nasal speculum. If using endoscopy, the endoscope is gently inserted into each of the nares and the nasal cavity is carefully inspected. If using a nasal speculum, the speculum is gently inserted into each of the nares. A light should be utilized to enhance visualization. The speculum is opened to expand the nares and the nasal cavity is carefully inspected. With the intranasal examination, still images or video may be captured.

The nasal cavity is inspected for vascularized polyp, severely deviated septum, severe nasal airway obstruction or evidence of prior surgery/cautery. Any other gross abnormalities or irregularities should be documented accordingly.

15.2.4 Basal Schirmer Test with Topical Anesthesia

The Schirmer test with topical anesthesia will be used to assess tear production using the following steps:

1. One drop of topical anesthetic such as 0.5% proparacaine hydrochloride or equivalent should be instilled in each eye of the participant.
2. The participant will be instructed to keep the eyes gently closed for one minute.
3. After opening the eyes and allowing the eyes to recover for approximately one additional minute, excess moisture in the inferior fornix is gently removed with a spear.
4. Schirmer strips (35 mm x 5 mm size filter paper strip) will be placed in each eye at the junction of the middle and lateral thirds of the lower eye lid.
5. Under ambient light, the participant will be instructed to look forward and to blink normally during the course of the test. The test should be performed in a room with no direct air on the participant's face.
6. The Schirmer strips should remain in place until five minutes have elapsed or both strips have reached maximum score.
7. After five minutes, strips will be removed from both eyes and the amount of wetting will be recorded. The strips should be taped to the CRF.

Schirmer test using cotton swab nasal stimulation

At the Screening Visit, the Schirmer test should be performed using cotton swab nasal stimulation. New anesthetic drops should be instilled following the same procedure specified in steps #1 to #3 in the Basal Schirmer Test section.

1. With new strips in place, the examiner should insert cotton swabs in the participant's two nostrils simultaneously and gently probe both nasal middle turbinates for approximately 30 seconds. After this, the examiner can simply hold the swabs in place, applying gentle pressure, and repeat probing intermittently as necessary.

2. Alternatively, the participant can be instructed to hold the cotton swabs and gently probe both nasal turbinates simultaneously, resting intermittently before probing again. The examiner should continuously coach the participant on how to perform this test properly.
3. The Schirmer strips should remain in place until five minutes have elapsed or both strips have reached maximum score.

Both Schirmer scores will be recorded and it should be verified that the inclusion criteria have been met.

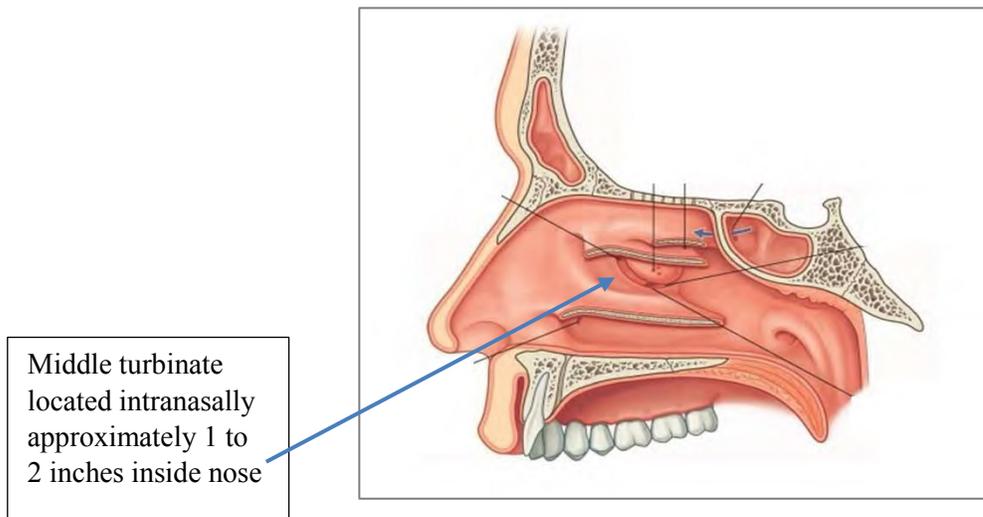


Figure 3 Target area of cotton swab nasal stimulation

Schirmer test during device application

At Visit 3, the Schirmer test should be performed using the device. New anesthetic drops should be instilled following the same procedure specified in the Basal Schirmer Test section.

1. With new strips in place, the examiner should instruct the participant to fully insert the device in the nasal cavity and use the device for approximately 3 minutes. As needed, the examiner should continuously coach the participant on how to use the device properly.
2. The Schirmer strips should remain in place until five minutes have elapsed or both strips have reached maximum score.

15.2.5 Dry Eye Questionnaires

15.2.5.1 Ocular Surface Disease Index© (OSDI©)

To minimize bias, participants will be asked to complete the OSDI questionnaire independently and in private after instructions have been provided by site personnel.

The OSDI is a 12-item questionnaire generated by the Outcomes Research Group at Allergan (Irvine, CA),⁴⁰ which asks participants to describe the nature and frequency of their irritation symptoms. The participant will answer the 12 questions by circling the number that best represents each answer: 4 (all of the time), 3 (most of the time), 2 (half of the time), 1 (some of the time), or 0 (none of the time). The final score for the questionnaire is calculated as follows:

Add subtotals from Sections I, II, and III = A

Determine total number of questions answered from Sections I, II, and III (do not include N/A) = B

Final OSDI score = A x 25 divided by B

An example of the questionnaire is as follows:

Ocular Surface Disease Index[®] (OSDI[®])²

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following <i>during the last week</i> ?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? ..	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following <i>during the last week</i> ?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations <i>during the last week</i> ?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned? ...	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

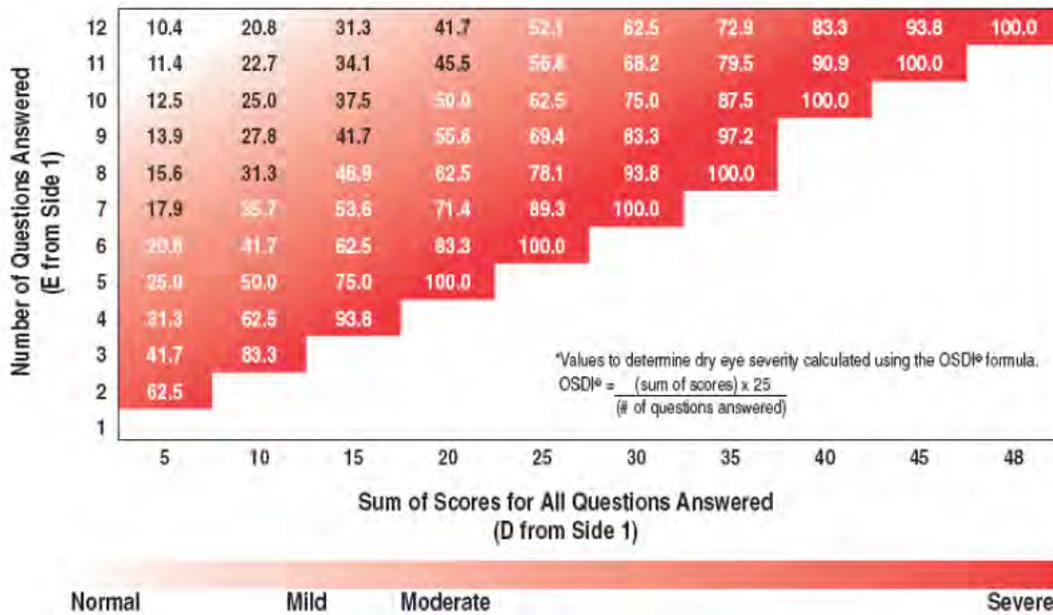
Please turn over the questionnaire to calculate the patient's final OSDI[®] score.

Evaluating the OSDI® Score¹

The OSDI® is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI® is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient’s Dry Eye Disease^{1,2}

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below. * Find where your patient’s score would fall. Match the corresponding shade of red to the key below to determine whether your patient’s score indicates normal mild, moderate, or severe dry eye disease.

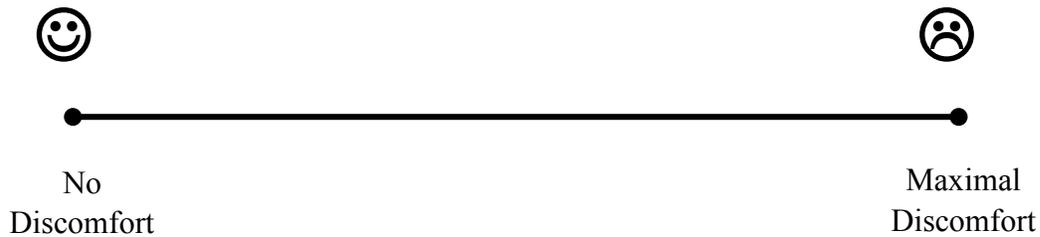


1. Data on file, Allergan, Inc.
 2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

15.2.5.2 Eye Dryness Score (EDS) Visual Analog Scale (VAS)

Participants will be asked the following question regarding eye dryness as specified in the protocol. On the CAE visit days, EDS will be collected upon entering the CAE and every 5 minutes during CAE exposure. The participants will be asked to rate their current eye dryness (both eyes simultaneously) by placing a vertical mark on the horizontal line to indicate the level of eye dryness; 0 corresponds to “no discomfort” and 100 corresponds to “maximal discomfort.” The assessment line length of the scale will be 100 mm and will be similar to the following depiction:

Please rate your current eye dryness by drawing a vertical line on the line below:



15.2.5.1 [REDACTED] Calibra™ Ocular Discomfort Scale



15.3 Appendix 3: Sponsor and [REDACTED] Approvals

Protocol Title: Prospective, Single-Arm Clinical Trial to Evaluate Acute Dry Eye Symptom Relief Assessed During Exposure to a Controlled Adverse Environment (CAE®) Following a 45 Day Period with Application of TrueTear™

Protocol Number: OCUN-029

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.



Signed: _____
[REDACTED]

Date: _____

15.3 Appendix 3: Sponsor and [REDACTED] Approvals

Protocol Title: Prospective, Single-Arm Clinical Trial to Evaluate Acute Dry Eye Symptom Relief Assessed During Exposure to a Controlled Adverse Environment (CAE[®]) Following a 45 Day Period with Application of TrueTear[™]

Protocol Number: OCUN-029

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

Signed: _____ Date: _____
[REDACTED]

15.3 Appendix 3: Sponsor and Ora Approvals

Protocol Title: Prospective, Single-Arm Clinical Trial to Evaluate Acute Dry Eye Symptom Relief Assessed During Exposure to a Controlled Adverse Environment (CAE[®]) Following a 45 Day Period with Application of TrueTear[™]

Protocol Number: OCUN-029

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

Signed: _____ Date: _____

[Redacted Signature]

Signed: _____ [Redacted Signature]

[Redacted Signature]

[Redacted Signature] Date: _____

15.3 Appendix 3: Sponsor and Ora Approvals

Protocol Title: Prospective, Single-Arm Clinical Trial to Evaluate Acute Dry Eye Symptom Relief Assessed During Exposure to a Controlled Adverse Environment (CAE[®]) Following a 45 Day Period with Application of TrueTear[™]

Protocol Number: OCUN-029

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

Signed: _____ Date: _____

[Redacted Signature]

15.4 Appendix 4: Investigator's Signature

Protocol Title: Prospective, Single-Arm Clinical Trial to Evaluate Acute Dry Eye Symptom Relief Assessed During Exposure to a Controlled Adverse Environment (CAE[®]) Following a 45 Day Period with Application of TrueTear[™]

Protocol Number: OCUN-029

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by [redacted] and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed: _____ Date: _____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____