NCT03274999

Study ID: OCUN-020

Title: Randomized, Controlled, Single-Center, Cross-Over Clinical Study to Evaluate Tear Characteristics Following Acute TrueTear™ Use

Protocol Date: 09Aug2017

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Randomized, Controlled, Single-Center, Cross-Over Clinical Study to Evaluate Tear Characteristics Following Acute TrueTear™ Use

Protocol Number: OCUN-020

Protocol Date: May 22, 2017

Device Name: TrueTear™

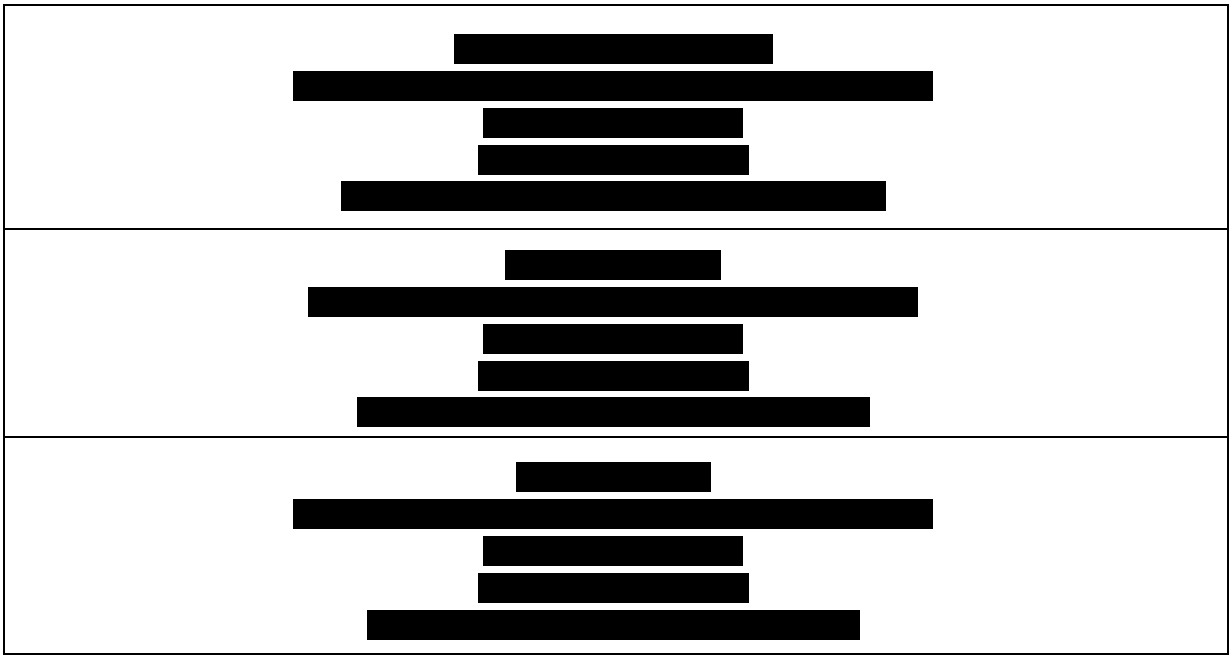
Sponsor: Allergan (North America)
[redacted]

Site: [redacted]

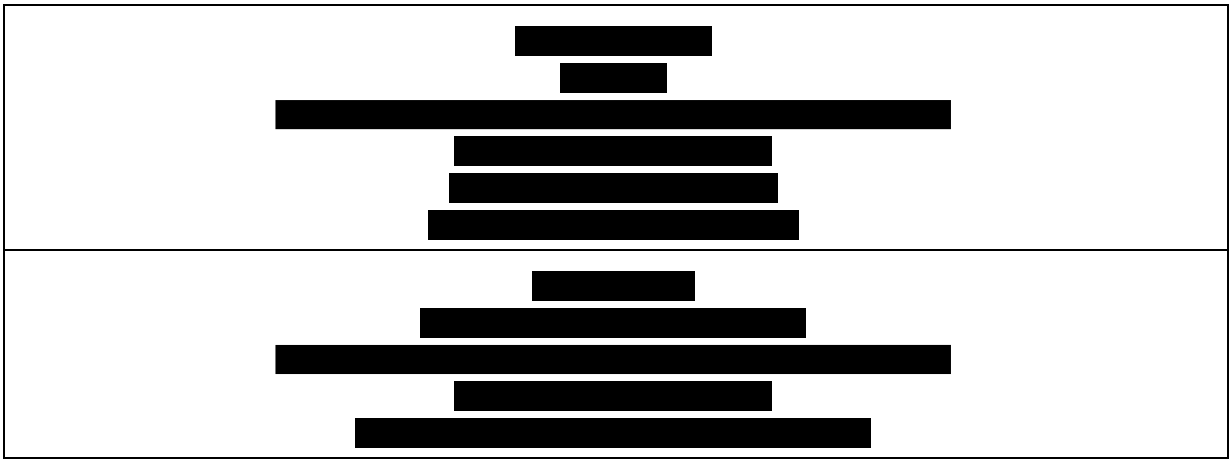
STUDY ADMINISTRATION

MEDICAL MONITOR

SPONSOR PERSONNEL



SITE PERSONNEL



STUDY SYNOPSIS

Protocol Title:	Randomized, Controlled, Single-Center, Cross-Over Clinical Study to Evaluate Tear Characteristics Following Acute TrueTear™ Use
Protocol Number:	OCUN-020
Study Device(s):	TrueTear™ (Intranasal Tear Neurostimulator) CE marked and to be used as per its intended use.
Study Objective:	The primary objective of this study is to compare the change in tear meniscus height (TMH) (immediately post versus pre-application) produced by intranasal stimulation with TrueTear versus the same device applied extranasally (control). In addition, this study will also: • Compare the duration of change in TMH (post versus pre-application) produced by intranasal versus extranasal (control) application of TrueTear • Compare the change and duration of change (post versus pre-application) in lipid layer thickness (LLT) produced by intranasal versus extranasal (control) application of TrueTear • Compare the change and duration of change (post versus pre-application) in non-invasive tear film break-up time (NITBUT), protective index and exposed area produced by intranasal versus extranasal (control) application of TrueTear
Overall Study Design	
Structure:	Prospective, randomized, single-center, cross-over design comparing the effect of intranasal versus extranasal (control) stimulation with TrueTear
Duration:	Participation is expected to last up to 50 days for each participant
Control:	Extranasal stimulation
Device Regimen:	There are two applications of TrueTear planned, one intranasal (test) and one extranasal (control). Participants will receive both applications, in random sequence, one at each of the two application days (Visit 2 and Visit 3). The two applications consist of: • Active intranasal device application for a duration of approximately 3 minutes • Active but extranasal device application (control) for a duration of approximately 3 minutes

Visit Schedule:	Visit 1: Screening (Day -14 (±11days)) Visit 2: First application (Day 0) Visit 3: Second application / Exit (Day 14 (±11 days))
Study Population Characteristics	
Number of Participants:	Approximately 35 participants with dry eye will be enrolled at one site in the UK in two groups: an initial 10 participants and a second group of 25 participants to be enrolled following an interim analysis.
Condition/Disease:	Dry Eye Disease (DED)
Evaluation Criteria	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

General Statistical Methods and Types of Analyses

Sample Size

Approximately 35 completed participants will be enrolled. This is an exploratory study and no formal sample size calculation was performed.

[redacted]

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
ADE	Adverse device effect
BCVA	Best corrected distance visual acuity
CI	Confidence interval
DED	Dry eye disease
CRF	Case report form
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EMS	Electro-neuromuscular stimulation
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good clinical practice
HIPAA	Health Information Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonisation
LED	Light-emitting diode
LFU	Lacrimal functional unit
LLT	Lipid layer thickness
logMAR	Logarithm of the minimum angle of resolution
Mm	Millimeter
NITBUT	Non-invasive tear film break-up time
OSDI©	Ocular Surface Disease Index©
OTC	Over-the-counter
PP	Per protocol
SAE	Serious adverse event
TENS	Transcutaneous electrical nerve stimulation
TMH	Tear meniscus height
US	United States
WOCBP	Women of childbearing potential

1. 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] DED 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]

DED is recognized as a disturbance of the Lacrimal Functional Unit (LFU), an integrated system comprised of the lacrimal glands, ocular surface (cornea, conjunctiva) and lids (meibomian glands), 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 DED 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 DED 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 DED 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 driving[8] as well as daily activities, social and physical functioning, workplace productivity, and quality of life.[5]

Treatment for DED 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.

1.2. RATIONALE

The nasolacrimal reflex is a well-established pathway by which nasal stimuli promote both resting basal[10] 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.

Studies have demonstrated that intranasal stimulation via use of the TrueTear device results in a statistically significant increase in tear production measured by the Schirmer test[11,12] and as such may provide a novel option for the treatment of DED. However, to date, the duration of increased tear secretion post TrueTear use has not been quantified. Thus this study is aimed at quantifying both the acute change and duration of change of tear secretion post-use of TrueTear. In addition, the quality of the secreted tears will be characterized through measures of lipid layer thickness and break-up time. Altogether, this study should provide significant insight into the nature and duration of acute tear secretion associated with TrueTear application.

2. STUDY OBJECTIVES

The primary objective of this study is to compare the change in tear meniscus height (TMH) (immediately post versus pre-application) produced by intranasal application of TrueTear (test) versus the same device applied extranasally (control). In addition, this study will also:

- Compare the duration of change in TMH (post versus pre-application) produced by intranasal (test) versus extranasal (control) application of TrueTear
- Compare the change and duration of change (post versus pre-application) in lipid layer thickness (LLT) produced by intranasal (test) versus extranasal (control) application of TrueTear
- Compare the change and duration of change (post versus pre-application) in non-invasive tear film break-up time (NITBUT), protective index and exposed area produced by intranasal (test) versus extranasal (control) application of TrueTear

3. CLINICAL HYPOTHESES

The clinical hypothesis for this study is that the difference in TMH measured pre-application and immediately post-application in the study eye between the two applications (intranasal vs extranasal control) will be statistically significantly greater in favor of intranasal stimulation.

Additionally, the difference in the change of the lipid layer thickness measured pre-application and immediately post-application in the study eye between the two applications (intranasal vs extranasal control) will be statistically significantly greater in favor of intranasal stimulation.

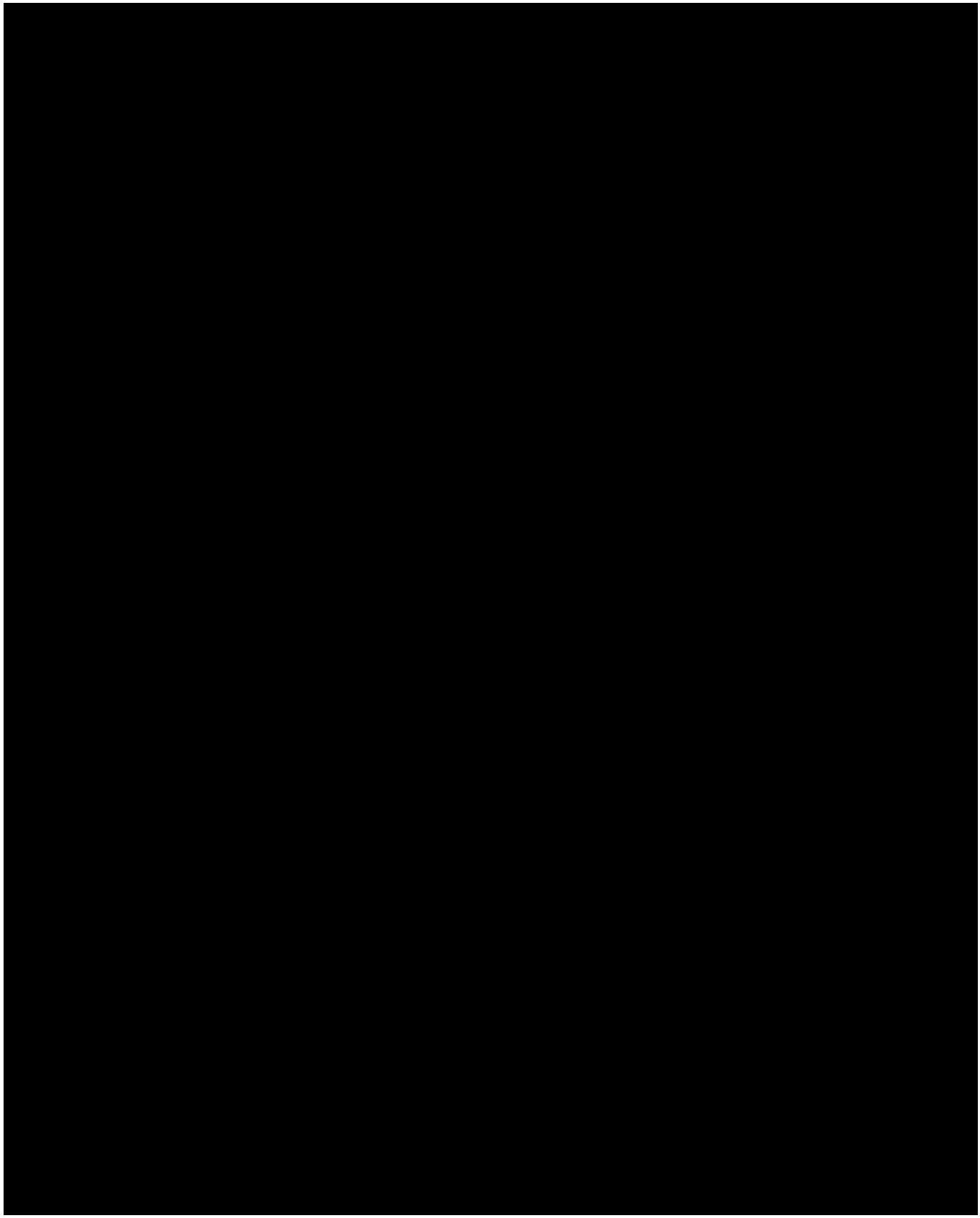
4. OVERALL STUDY DESIGN

This is a prospective, randomized (order of the test and control applications), cross-over design comparing the effect of intranasal (test) versus extranasal (control) stimulation with TrueTear on change in tear meniscus height (TMH) and duration of this change. Additionally, the change and duration of change in the lipid layer thickness (LLT), non-invasive tear film break-up time (NITBUT), protective index and exposed area caused by intranasal versus extranasal (control) stimulation with TrueTear will be evaluated.

The study will be carried out in two phases: an initial phase involving 10 participants who have provided informed consent and have met the eligibility criteria and a second phase following an Interim Data Analysis involving the remainder of the population of up to a total of 25 additional participants who have met the same criteria.

At the completion of the initial phase, an interim analysis will be carried out to obtain a first indication of the duration of the changes that are being measured. The test visit protocol sets the follow-up visits post application at six hours, based upon information obtained during previous clinical studies. However, the exact duration of the effect is unknown and this exploratory study may demonstrate that the effect is of a shorter or longer duration. Hence, to avoid unnecessary burden to participants, if the effect is of shorter duration than six hours or to optimize the scientific validity of the study if the effect is of a longer duration, the follow-up period will be reviewed and potentially modified. There is no plan to stop this study based on the results of the Interim Data Analysis.

The two-phase approach optimizes the protocol and allows for any potential change to receive ethics approval before implementation. At the completion of the initial phase, the Ethics Committee will be either informed that the follow-up period remains unchanged and the study continues under the current protocol or that a change to the protocol will be submitted for review that will be limited to the duration of the follow-up period and timing of the post application measurements.; The corresponding information to participants and consent forms will also be submitted for approval.



Participants who terminate early during the application period will be asked to complete safety assessments (if the participants agree) prior to study exit. Participants who are terminated early from the study will not be replaced.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

1. Eighteen (18) years of age or older
2. Baseline OSDI© score of at least 23 with no more than three responses of "not applicable"
3. In at least one eye, a baseline Schirmer test of ≤ 10 mm/5 minutes AND a cotton swab nasal stimulation Schirmer test of at least 7 mm higher in the same eye

[redacted]

5.2. EXCLUSION CRITERIA

Participants must not:

1. 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
2. Have had nasal or sinus surgery (including history of application of nasal cautery) or significant trauma to these areas
3. Have a vascularized polyp, severely deviated septum or severe nasal airway obstruction as confirmed by intranasal examination performed at the Screening Visit
4. Have had any intraocular surgery (such as cataract surgery), extraocular surgery (such as blepharoplasty) in either eye within three months or refractive surgery (e.g. LASIK, LASEK, PRK or corneal implant) within twelve months of the Screening Visit

[redacted]

[redacted]

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

[redacted]

5.3. 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.

5.4. 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 make every attempt to reach the participant by telephone and/or letter before considering the participant as lost to follow-up.
- 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 must be carefully documented by the Investigator on the End of Study CRF and, if applicable, on the Adverse Event (AE) CRF. No participant who has been randomized can be replaced by another participant if the participant is discontinued prematurely for any reason.

6. STUDY PARAMETERS

[redacted]

7. DEVICE DESCRIPTION

7.1. STUDY DEVICE

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 is CE marked and will be used in this study as per its intended use.

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 the Disposable Tips (Front and Back)

TrueTear System

Figure 1 TrueTear 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 removable disposable Tip is provided in an air tight sealed pouch, which is labeled with the lot number and expiration date. The lot number of the Tip 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. COMPARATOR APPLICATION ARMS

The comparator (control) will consist of the use of TrueTear applied externally to the nose where the participant may feel some stimulation.

7.4. OTHER STUDY SUPPLIES

The following will be provided by Allergan:

- Urine pregnancy test kits
- Schirmer test strips

The following will be provided by the investigator:

- Proxymetacaine

8. STUDY METHODS AND PROCEDURES

8.1. PARTICIPANT ENTRY PROCEDURE

8.1.1. Overview

Participants who meet all inclusion and exclusion criteria 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 must give written informed consent using an Ethics Committee approved informed consent form (ICF).

The prospective participants will be selected from the existing clinical population of the [redacted] or recruited my means of an advertisement if necessary. The participants fulfilling the criteria for inclusion and none of the exclusion criteria, will be invited in a random fashion to participate in the study until the test population is achieved.

The prospective participants will initially be contacted by telephone, the investigation will be explained in detail and if interested a screening / enrolment visit will be scheduled. The prospective participants will be sent a copy of the Participant Information Sheet and Informed Consent by email prior to the visit and will be asked to read and the Informed Consent to sign prior to any evaluation.

[redacted]

- [redacted]

8.1.4. Procedures for Final Study Entry

Participants must meet all inclusion and none of the exclusion criteria to qualify for enrollment

8.1.5. Methods for Assignment to the Order of Use of the Test and Control Applications

Each participant who qualifies for entry at Visit 1 will be assigned a screening number. All screening numbers will be a three-digit number starting with [redacted] assigned in strict numerical sequence at the site and no numbers will be skipped or omitted. The site number will precede the screening number in the fashion of [redacted].

If all inclusion and exclusion criteria are met at Visit 1, each qualifying participant will be assigned an enrollment randomization number at Visit 1. Enrollment randomization numbers will be a 4-digit site specific number assigned in sequential order [redacted] A computer-generated block randomization schedule will be prepared with the application sequences to correspond to each randomization number.

8.2. MASKING AND DISPENSING

On Day 0, participants will receive training by trained clinical staff on the use of TrueTear consistent with their randomized assignment (intranasal or extranasal application). The serial number of the unit will be documented in the participant's CRF and device accountability log. The lot number of the tip provided to a participant will also be recorded on the appropriate case record form and device accountability log. Participants will remain masked as to which application is the active and which is the control.

8.3. PARTICIPANT TRAINING AND DISPENSING OF DEVICE

Participants will receive training to perform nasal neurostimulation and will undergo stimulation for the first time on Day 0. On Day 0, participants will be provided with a TrueTear device and a disposable tip.

For the intranasal application, participants will be instructed to place the tips of 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 asked to apply stimulation for approximately three minutes.

Figure 2 Use of TrueTear (L) Starting position and (R) Correct treatment position by inserting the tips fully into the nasal cavity

For the control (extranasal) application, participants will be instructed to place the tips of the TrueTear on the lower part of the nose (one tip on each side as in Figure 3). 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 the best 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 removing contact with the nose. Participants will be asked to apply stimulation for approximately three minutes.

Figure 3 Schematic showing location of Tip Assembly application for control (extranasal) application of TrueTear

8.4. 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.

8.5. EXAMINATION PROCEDURES

[redacted]

[redacted]

8.5.4. Early Termination/Discontinuation

If a participant is discontinued from the study prior to Day 0, then all safety evaluations that are to be performed on Day 0 should be performed on the day of discontinuation (early termination) at the discretion of the Investigator. Participants who are terminated early from the study will not be replaced.

8.6. SCHEDULE OF VISITS

8.6.1. Scheduled Visit

Participants will remain in the study for up to 50 days and will be seen at the following intervals:

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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 will be followed until their medical outcome is determined. The Investigator must provide written reports to the study Sponsor.

8.6.2. 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 pages. Any procedure indicated in the CRF that is not performed should be indicated as "Not done."

8.7. PARTICIPANT ACCOUNTABILITY

8.7.1. Completed Participants

A completed participant is one who has not been discontinued from the study and has successfully completed Visits 1 through 3.

8.7.2. Discontinued Participants

Participants may be discontinued prior to their completion of the study due to:

- AE
- Protocol deviation
- Administrative reasons (e.g., inability to continue)
- Lost to follow-up
- Pregnancy
- Sponsor termination of study
- Other

Note: In addition, any participant may be discontinued for any sound medical reason.

Notification of a participant discontinuation and the reason for discontinuation will be made to the Sponsor and will be clearly documented on the participant's CRF.

8.8. STUDY TERMINATION

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

8.9. STUDY DURATION

An individual participant's participation will involve up to three visits over a maximum of 50 days.

8.10. MONITORING AND QUALITY ASSURANCE

8.10.1. Study Monitoring

[redacted] (or designees) will monitor this study in a manner consistent with applicable health authority regulations and the procedures adopted by the SOPs of [redacted]. Prior to the start of the study, member(s) of Allergan, Inc. (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 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.

8.10.2. Recording of Data and Retention of Documents

Participant data recorded on eCRFs 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.

The Investigator must retain essential documents for at least two years after the approval of the device and for as long as it is required in the UK in compliance with the Data protection regulations. Investigator agrees to adhere to the document retention procedures when signing the Protocol Investigator's Signature page.

9. 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 a product but not necessarily related to the product. An AE may also be called a complication. The capture of AEs will begin with the participant's entry into the study.

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 eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must 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 study 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 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 STUDY DEVICE

Definite	A clear cut causal relationship with the study device and no other possible cause
Probable	A causal relationship with the study device is likely although alternate etiologies are also possible
Possible	A causal relationship with study device is not definite, alternate etiologies are also possible
Not related	The AE has no causal relationship to study device and/or there is evidence of alternative etiology such as concurrent medication or illness.
Not applicable	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 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 EC-approved research protocol, user manuals and the current EC-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 subjects."

9.5. ADVERSE EVENT REPORTING

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

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

All SAEs and adverse device effects (ADEs) must be reported by the Investigator to Allergan 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 Ethics Committee (EC) of all SAEs and unanticipated problems, per the ECs 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.

The Sponsor will immediately conduct an evaluation of any unanticipated adverse device effect. If it is determined by 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 the Sponsor makes this determination, and not later than 15 working days after first receiving notice of the event. The Sponsor will not resume an investigation terminated under these conditions without an additional EC approval.

Contact information for reporting Serious Adverse Events:

Sponsor Contact Information for reporting Serious Adverse Events
Allergan: [redacted]
ADDITIONALLY please send a copy to: [redacted]

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:

- 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 proxytacaine, temporary burning, stinging and conjunctival redness of the eyes
- With use of proxytacaine, 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. 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 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 must be withheld until the results of pregnancy testing are available. If pregnancy is confirmed, the participant must not administer the study device and must not be enrolled in the study.

11. STATISTICAL HYPOTHESIS AND METHODS OF ANALYSES

11.1. POWER CALCULATION AND DETERMINATION OF SAMPLE SIZE

Approximately 35 completed participants will be enrolled. This is an exploratory study and no formal sample size calculation was performed. The results from this study may be used to determine the appropriate time points and power for future studies.

11.2. STATISTICAL HYPOTHESES AND LEVEL OF SIGNIFICANCE

The null hypothesis for each of the exploratory parameters is the difference in the change from the pre-application value at each post-application time point between the intranasal (test) and extranasal (control) applications are zero.

The alternative hypothesis for each of the exploratory parameters is the difference in the change from the pre-application value at each post-application time point between the intranasal (test) and extranasal (control) applications are not zero.

The hypothesis can be expressed as:

H_0: $\Delta = 0$

H_A: $\Delta \neq 0$ mm

where Δ represents the difference between applications for the change from the pre-application value and each post-application time point. Statistical tests will be two-sided and evaluated at an α of 0.05.

11.3. RANDOMIZATION

Each participant will be treated with the active and control applications. The sequence of the applications will be randomly assigned using a computer-generated randomization schedule. Participants will be randomly assigned to one of two application sequences:

A. Intranasal: Extranasal
B. Extranasal: Intranasal

11.4. EVALUABILITY OF DATA

Full Analysis Set Population (FAS): The FAS population will include all participants who completed both applications.

Per protocol population (PP): The PP population is a subset of the FAS population, which did not have a major protocol deviation likely to significantly affect the primary outcome of the study. If the PP and FAS populations are exactly the same, then additional exploratory analyses on the PP population will not be performed.

Safety Population: The safety population will include all participants that initiated at least one application.

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.

The study being exploratory no correction for multiplicity will be made to the statistical comparisons.

11.6. PARTICIPANT ACCOUNTABILITY AND MISSING DATA

Participation in the study will be summarized by presenting the number of participants who were enrolled, the number of participants who only completed the first application and the number of participants who completed both applications. No imputation for missing values will be performed.

11.7. PARTICIPANT DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

[redacted]

12. FINAL CLINICAL STUDY REPORT

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

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

13.1. PROTECTION OF HUMAN PARTICIPANTS

13.1.1. Participant Informed Consent

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

All ICFs must be approved for use by the sponsor and receive approval/favorable opinion from an Ethics Committee (EC) prior to their 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 EC 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 informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must 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. Ethics Committee (EC) Approval

This study is to be conducted in accordance with the harmonized EC standard *Clinical investigation of medical devices for human subjects – Good clinical practice* (EN ISO 14155). The Investigator must obtain appropriate EC 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 EC approving this study and the regulatory authorities 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. On site and off site storage facilities are allocated which ensure that all stored records are identifiable and retrievable, and the storage areas are free from damp and other agents which could cause premature deterioration. All records are retained for the minimum legal requirements. For clinical records the minimum requirement is of 7 years; requirements vary for records relative to the execution of individual customer contracts.

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

13.3. REGULATORY STATUS

The Allergan TrueTear device received CE Mark on December 22, 2014 (CE 615662). It has been approved for marketing in Canada and Australia as well. This device has been granted marketing authorization by the US Food and Drug Administration (FDA).

13.4. LABELING, PACKAGING, STORAGE, ACCOUNTABILITY, AND RETURN OR DISPOSAL OF STUDY DEVICE

All devices will be stored and maintained in accordance with the corresponding Instructions for Use. Used disposable devices should be discarded after use; unused disposable devices should be returned to the Sponsor at the conclusion of the study. A device accountability log will be maintained by the site and will be filed in the Trial Master File.

13.5. RECORDING OF DATA ON SOURCE DOCUMENTS AND CASE REPORT FORMS (ECRFS)

The EDC system, EntryPoint i4 is CFR21 Part 11 compliant; all participant data will be captured in the participant eCRFs (i.e. source document). The Investigator is responsible for ensuring that study data is completely and accurately recorded on each participant's eCRF and all study-related materials. EntryPoint i4 has a full data audit trail and access to the eCRF is password controlled for individual user accounts; the combined procedures ensure that all changes are time stamps and the individual who made the change identified.

13.6. AMENDMENTS TO THE PROTOCOL

Any amendment containing major modifications (particularly if it may involve an increased risk to the participants) must be approved by the EC 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 will have the final decision regarding the manuscript and publication.

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15. 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 best corrected distance visual acuity (BCVA); 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 must 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 must 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 x 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 x T (T=0.02)	= 0.08
Base logMAR + (N x 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 must 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 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

Sodium fluorescein may be used at Investigator's discretion only for the post-application slit lamp biomicroscopy exam.

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.

The nasal cavity is inspected for gross ulceration, mass lesions, severe septal deviations or evidence of prior surgery/cautery. Any other gross abnormalities or irregularities should be documented accordingly.

15.2.4. Schirmer Test with Topical Anesthesia

At the Screening Visit, one basal Schirmer test will be performed followed by a Schirmer test with cotton swab nasal stimulation. The Schirmer test with topical anesthesia will be used to assess tear production using the following steps:

1. Topical anesthetic drops such as 0.5% proparacaine hydrochloride or equivalent should be instilled in both eyes 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 above.

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 verified that they meet the inclusion criteria.

15.2.5. Dry Eye Questionnaires

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.

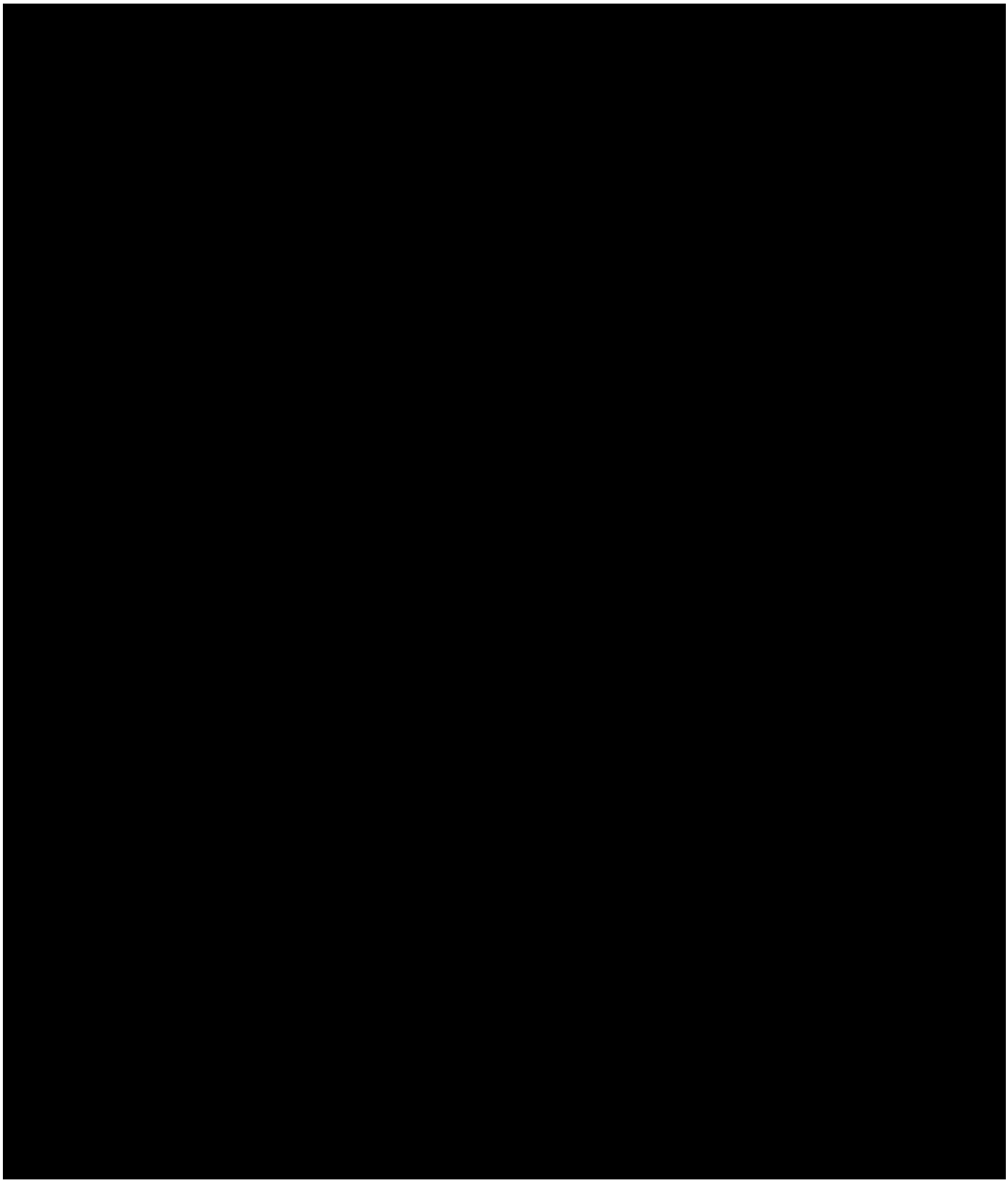
The OSDI is a 12-item questionnaire generated by the Outcomes Research Group at Allergan (Irvine, CA),[13] which asks participants to describes the nature and frequency of their irritation symptoms. The participant will answer the 12 questions by circling the number that best represents each answer: 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:

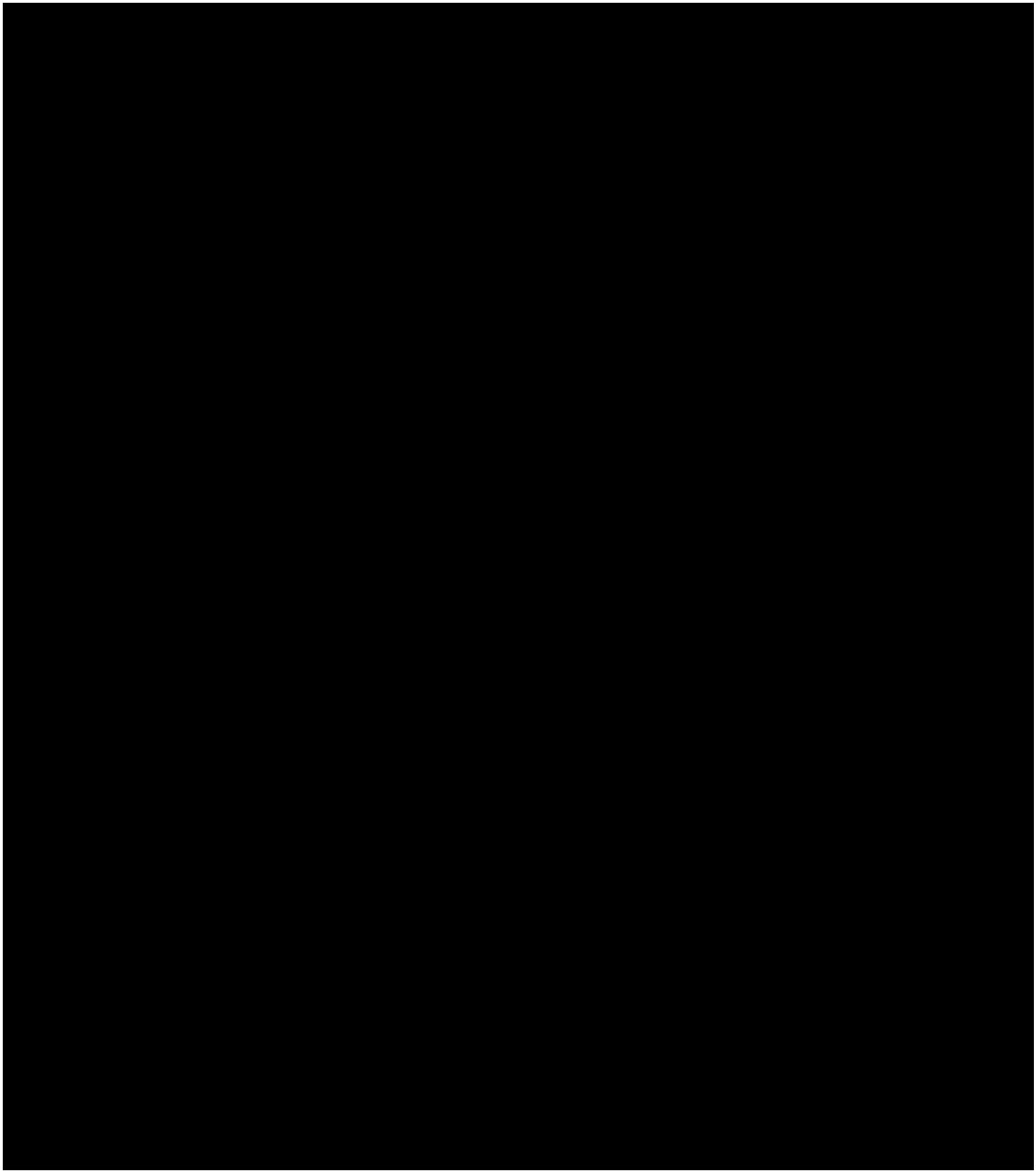
Add subtotals from Sections I, II, and III = A

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:





15.4. APPENDIX 4: INVESTIGATOR'S SIGNATURE

Protocol Title:	Randomized, Controlled, Single-Center, Cross-Over Clinical Study to Evaluate Tear Characteristics Following Acute TrueTear™ Use
Protocol Number:	OCUN-020

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 the sponsor in confidence and, when this information is submitted to an Ethics Committee (EC) 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: _____