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Title: Clinical Trial to Evaluate the Symptoms in Symptomatic Contact Lens Wearers Following Application of Intranasal Tear Neurostimulator Versus Control

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Protocol

RANDOMIZED, DOUBLE-ARM, CONTROLLED CLINICAL TRIAL TO EVALUATE SYMPTOMS IN SYMPTOMATIC CONTACT LENS WEARERS FOLLOWING APPLICATION OF INTRANASAL TEAR NEUROSTIMULATOR VERSUS CONTROL (CORIANDER)

Sponsor: Allergan Plc, Irvine, CA 92623 USA

Study number: P/580/16/A

[redacted]

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	Reviewed and approved (Print & sign)	Date DD/MMM/YYYY
Principal investigator		
Lead investigator		
Protocol author		
Quality assurance		
Sponsor		

Study Personnel

DOCUMENT CHANGE HISTORY

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Table of contents

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LIST OF ABBREVIATIONS

AE	Adverse event
ADE	Adverse device effect
CI	Confidence interval
CCLR	Centre for Contact Lens Research
CL	Contact lens
CLD	Contact lens dryness
CREC	Clinical Research Ethics Committee
CRF	Case report form
CWT	Comfortable wear time
DD	Daily disposible
FDA	Food and Drug Administration
GCP	Good clinical practice
HCVA	High contrast visual acuity
HIPAA	Health Information Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonisation
LLT	Lipid layer thickness
logMAR	Logarithm of the minimum angle of resolution
MGD	Meibomian gland disease
Mm	Millimeter
NITBUT	non-invasive tear break-up time
NSR	Non-significant risk
OTC	Over-the-counter
PP	Per protocol
SAE	Serious adverse event
SD	Standard deviation
SiHy	Silicone hydrogel
TFOS	Tear Film and Ocular Surface Society
TMH	Tear meniscus height
US	United States
WOCBP	Women of childbearing potential
WT	Wear time

1 INTRODUCTION

The worldwide contact lens (CL) market in 2016 was estimated to be $7.2 billion dollars in value.[1] Yet drop out from CL wear continues to be one of the major reasons for slow overall growth of this market with the most commonly cited reasons for drop out as 'discomfort and dryness'.[2,3]

In 2013, the Tear Film and Ocular Surface Society (TFOS) defined CL dryness (CLD) as: 'a condition characterized by episodic or persistent adverse ocular sensations related to CL wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of lens wear.'[4]

Given the progression of CLD from 'struggling with symptoms of discomfort', to 'reduced wear time' and finally 'discontinuation of CL wear', it is important for practitioners to have access to appropriate management strategies. CLD is multifactorial and some strategies involve CL-related modifiable factors such as material or wear modality.[4] Other areas of management address patient-related factors such as low tear volume or poor tear quality. Some studies have demonstrated reduction in dryness symptoms and increase in CL wear times via either intracanalicular[5] or inferior punctal occlusion.[6] These methods essentially increase the volume of tears in the eye. An alternative approach to increasing tear volume would be to stimulate tear production. The TrueTear device has been shown to do this.[7,8]

Rationale for TrueTear (Intranasal Neurostimulator Device)

The nasolacrimal reflex is a well-established pathway by which nasal stimuli promote both resting basal and bolus tear secretion.[9,10] 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.[11,12]

Reflex activation of the lacrimal glands is also one of the body's primary compensatory mechanisms for addressing ocular surface dryness.[13-17] 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 TrueTear application results in a statistically significant increase in tear production measured by the Schirmer test[7,8] and as such may provide a novel option for relief of CLD. This study is focused on quantifying the change in both comfortable wear time and total wear time following use of TrueTear for 30 days compared to a group using TrueTear sham control.

2 OBJECTIVES

The objective of this study is to evaluate the increase in comfort and comfortable CL wear time associated with application of TrueTear (active intranasal neurostimulation) compared with application of TrueTear sham control (intranasal application which is not electrically active) in symptomatic CL wearers.

The primary outcome variables for this study are:

- Contact Lens Dry Eye Questionnaire (CLDEQ-8)
- comfort ratings
- comfortable wear time (CWT)
- total wear time (total WT)

3 HYPOTHESIS

Improvements in CWT and comfort ratings in participants using TrueTear (active device) will be superior to those participants using the TrueTear sham control.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

4.1.1 OVERALL DESIGN

This is a prospective, double-masked, controlled, randomized by device (TrueTear vs TrueTear sham control), parallel arm study, with up to 6 study visits including a screening visit. Study participants (n=80) will be habitual, symptomatic wearers of daily disposable (DD) or reusable hydrogel and silicone hydrogel (SiHy) CLs. Symptomatic participants will be recruited, with a minimum average wear of 2 days/week and ≥3 hours of wear/day. It is expected that the majority of symptomatic wearers will be wearing the lenses on average 4-7 days/week. Wearers will be randomized to use the active device or the intranasal sham control.

Visit schedule:

There will be up to 6 study visits and cumulative total time commitment for the study is approximately 6 hours. [redacted] Permitted time interval between V1 and V2 is 7- 45 days.

[redacted]

[redacted]

4.1.2 TRUETEAR 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. The device is approved in Canada to increase tear production during stimulation. Use of the product to relieve CLD is investigational.

The device consists of four distinct parts (Figure 3):

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

TrueTear Base Unit with and without Cover

TrueTear Base Unit with Disposable Tips (Front and Back)

TrueTear System

Figure 3: TrueTear System Components

4.1.2.1 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.

4.1.2.2 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.

4.1.2.3 COVER

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

4.1.2.4 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.

4.1.3 TRUETEAR SHAM CONTROL

The comparator arm in this study is the TrueTear sham device, which is not electrically active, and will be applied intranasally. The sham device (Figure 4) consists of a Base Unit and Tip Assembly that have been modified so that the depth to which the probes are inserted into the nose is limited. All other parts of the device are identical. This sham device is also electrically nonfunctional; the device powers on, but no electrical stimulation energy is delivered through the Tip Assembly. Participants are to be instructed to place only the tips of the device into both nostrils simultaneously so that the nose stop on the device touches the participant's septum.

Figure 4: TrueTear Sham Control Base Unit with Disposable Tips

4.1.4 RANDOMIZATION

A randomization schedule will be generated using a web-based program: (www.randomization.com) with stratification by groups based on frequency of lens wear during the week. The final study randomization schedule will be generated [redacted] and provided to the research assistants for the study. Study investigators will remain masked to the randomization schedule until the study is completed and the database is locked.

4.1.5 MASKING

The study will be double-masked with both participant and site personnel interacting with the participant being masked. The participants will be aware that they will be randomized to an intranasal device with only one being electrically active. Neither participant or site personnel interacting with the participant will be told which device the participant is randomized too.

Researchers tasked with collecting study data will be masked throughout the study. The initial use of TrueTear or TrueTear sham control in V2-1 and reviewing the procedure for proper use of the device in V2-1, V2-2 and V3 will be conducted by either research assistants, unmasked investigators or study sponsor representatives.

4.2 STUDY POPULATION

4.2.1 SAMPLE SIZE CALCULATION

Due to the exploratory nature of this study, the planned sample size was determined empirically.

4.2.2 NUMBER OF PARTICIPANTS

[redacted] Up to 120 eligible participants will be dispensed / randomized with study products, with a target of 80 completing the study. Informed consent will be obtained for all participants prior to their enrolment in the study.

4.2.3 INCLUSION AND EXCLUSION CRITERIA

A person is eligible for inclusion in the study if he/she:

- [redacted]
- [redacted]
- [redacted]

4. In at least one eye, has a cotton swab nasal stimulation Schirmer test score at least 4 mm greater than 3 minute Schirmer with anesthesia basal score in the same eye at the Screening Visit
5. Is an adapted soft contact lens wearer and currently wears lenses an average of at least 2 days per week, with an average minimum wearing time of 3 hours each day over the past month, AND is able and willing to wear lenses for at least 6 hours on four study day visits.

- [redacted]

7. Has at least 20/40 visual acuity in both eyes with CL correction
8. Is symptomatic using Young's categorization as outlined in this protocol.

- [redacted]

A person will be excluded from the study if he/she:

- [redacted]
- [redacted]

[redacted]

9. Has undergone refractive error surgery;

[redacted]

12. 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;
13. Have had nasal or sinus surgery (including history of application of nasal cautery) or significant trauma to these areas;

[redacted]

15. Have a vascularized polyp, severely deviated septum or severe nasal airway obstruction as confirmed by intranasal examination performed at the Screening Visit;
16. Have an active implanted metallic or active implanted electronic device in the head, a cardiac demand pacemaker, or an implanted defibrillator.

[redacted]

4.2.4 REPEATED SCREENINGS

In some circumstances a repeated screening may need to be scheduled. Examples include, but are not limited to:

1. Incomplete information available at time of screening to determine eligibility (e.g. current lens brands worn, history from current eye care practitioner, etc.)
2. Study procedures unable to be completed in time scheduled for visit;
3. Study products not available at the time of the screening visit;
4. A transient health condition which may affect the eye(s) (e.g. a common cold, active allergies, fatigue, etc.)
5. Seven days after the final use of short term medications (e.g. antibiotics, antihistamines, etc.)
6. Reassessment of baseline ocular conditions (e.g. corneal and/or conjunctival staining, scars, etc.)

The maximum total number of repeated screenings permitted will be 1.

4.3 STUDY MATERIALS

4.3.1 LENSES

The participant will continue with their habitual CLs throughout the study. A one month supply of their current lenses will be dispensed to the participant at V2-1.

The participant must bring an unopened package of their current CLs to the screening visit. The specification of the CLs will be noted, and a one month supply of the lenses ordered by the CCLR. The CLs must be commercially available in Canada.

4.3.2 LENS CARE SYSTEM

A lens care system will be used when a participant habitually wears anything other than soft daily disposable CLs. They will continue with their habitual lens care system throughout the study. A one month supply of their lens care system will be dispensed to the participant at V2-1.

The participant must bring their lens care system with them to the screening visit. The type of system will be noted, and a one month supply ordered by the CCLR. The lens care system must be commercially available in Canada.

4.3.3 DEVICE (TRUETEAR AND TRUETEAR SHAM CONTROL)

Either a TrueTear or TrueTear sham control device will be dispensed at V2-1 along with a supply of tips. A second supply of tips will be dispensed at V4. Additional tips may be dispensed as required to allow participant access to a new tip every 24 hours as per usage guidelines. This may be required if the participant is seen at the end of each visit window for example.

4.3.4 ARTIFICIAL TEARS AND REWETTING DROPS

The use of artificial tears / rewetting drops is not permitted throughout the study. A participant must cease use of artificial tears / rewetting drops at least three days prior to visit 2, and must commit to not using any of these products throughout the duration of the study period.

4.3.5 ORDERING CONSUMABLES

The sponsor will provide TrueTear and TrueTear sham control devices (base units and associated tips). The CCLR will order CLs and CL care systems for each participant.

4.3.6 CONTACT LENS / LENS CARE PRODUCT ACCOUNTABILITY

Accountability logs will be kept to include the number of lenses and lens care system bottles received, dispensed, unused and returned to sponsor (where relevant). All products dispensed to participants will be recorded in the study binder.

4.3.6.1 TRUETEAR AND TRUETEAR SHAM CONTROL ACCOUNTABILITY

Each Base Unit of TrueTear and TrueTear sham control devices have 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 (for either TrueTear

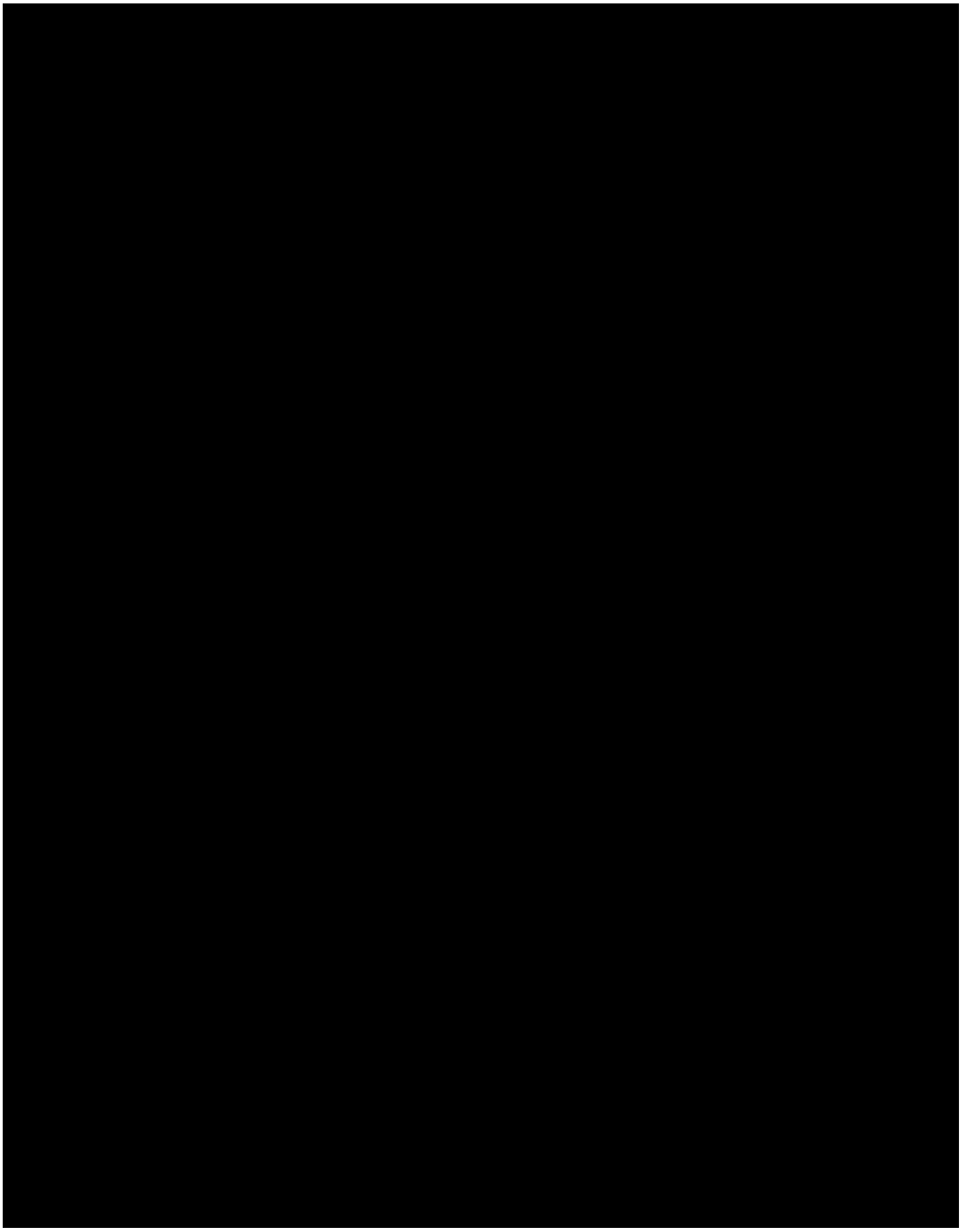
or TrueTear sham control), is provided in an air tight sealed pouch, which is labelled with the lot number and expiration date. The lot number of the Tips provided to a participant will also be recorded on the appropriate case report forms and on the device accountability log. Tips should not be used beyond the expiration date provided on the pouch.

4.4 SCHEDULED AND UNSCHEDULED VISITS

This study has a total of 6 study visits, including the screening visit.

4.4.1 SCREENING

The investigator will determine participant eligibility using the inclusion and exclusion criteria.



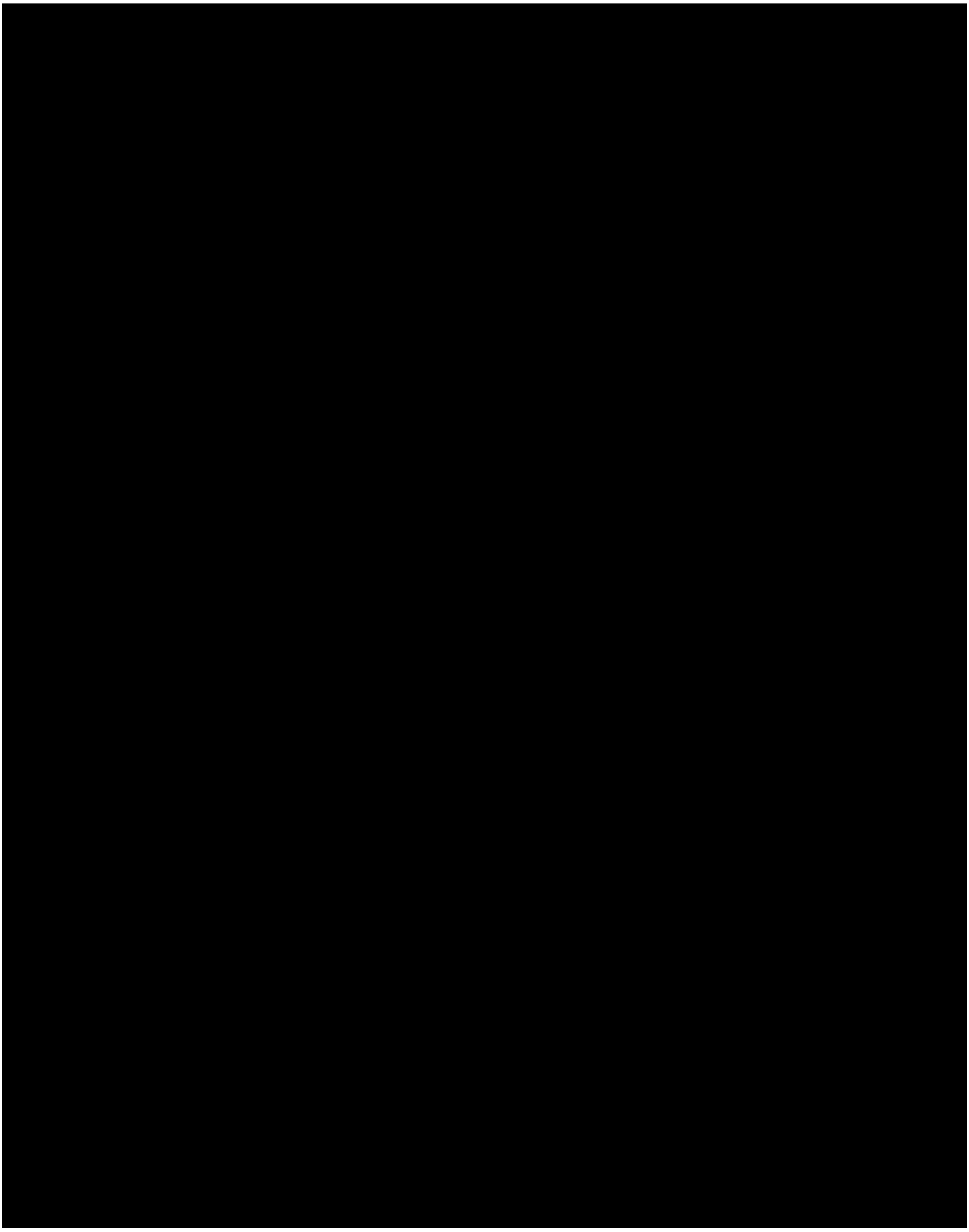
[redacted]

4.4.3 UNSCHEDULED VISITS

An unscheduled visit is defined as an interim visit requested by the participant or investigator due to an unanticipated problem. Data recorded at these visits will be entered into the database. Only relevant and applicable unscheduled visit information will be included in the final report as deemed necessary by the lead investigator.

4.5 STUDY PROCEDURES

[redacted]



[redacted]

STANDARD OPTOMETRIC PROCEDURES:

4.5.1 CASE HISTORY

Demographic information from the participant will be obtained, including age, gender, CL details, artificial tear use, and relevant health and medical information.

4.5.2 DETERMINATION OF SYMPTOMS

Patients will be considered symptomatic based on Young's catergorization.[4] This corresponds to the dark grey areas in Table 3 below:

Table 3: Young's categorization for contact lens dry eye score

Categorization grid for the Contact Lens Dry Eye score.

		Frequency of dryness				
		Never	Rarely	Sometimes	Frequently	Constantly
Intensity of late-day dryness	Never have it – 0	No	No	No	No	No
	Not at all intense – 1	No	No	No	No	No
	2	No	No	Marginal	Marginal	Marginal
	3	No	No	Yes	Yes	Yes
	4	No	No	Yes	Yes	Yes
	Very intense – 5	No	No	Yes	Yes	Yes

Note: Score derives from the combination of responses to frequency and intensity of dryness late in the day. Dark grey, Dry; light grey, Marginal; white, Not Dry.

4.5.3 VISUAL ACUITY

Visual acuity will be measured using high contrast computer-generated acuity charts. Participants will be asked to read letters that progressively decrease in size on a computer screen located at a distance of 6 meters.

4.5.4 BASELINE OCULAR MEASURES

4.5.4.1 PRE-LENS NON-INVASIVE TEAR BREAK UP TIME

Pre-lens non-invasive tear breakup time (NITBUT) will be assessed using a placido-disc device. The rings of the disc will be projected onto the tear film and the time to first disruption of that image in between blinks will be noted. An average result will be calculated from three measures in each eye.

4.5.4.2 TEAR MENISCUS HEIGHT (TMH)

An image of the tear meniscus in both eyes will be taken using the Oculus Keratograph 5M instrument. TMH will be calculated as an average of two measures taken using the on-screen calipers.

4.5.5 CONTACT LENS ASSESSMENT

Contact lens wettability and deposition will be graded using a 0-4 scale (0.25 steps), 0 = excellent, 4 = poor

4.5.6 THREE-MINUTE BASAL SCHIRMER TEST WITH TOPICAL ANESTHESIA

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

1. One drop of topical anesthetic drops 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 three minutes have elapsed or both strips have reached maximum score.
7. After three minutes, strips will be removed from both eyes and the amount of wetting will be recorded. The strips should be taped to the CRF.
8. Following this test, a three-minute Schirmer test with cotton swab nasal stimulation will be performed (see Section 4.6.2).

4.5.7 DETERMINATION OF REFRACTION

Participants will have a measure of their ocular prescription taken using an autorefractor. A full subjective refraction will only be conducted where it is not possible to correct either eye to better than 0.20 logMAR with their habitual contact lenses.

4.5.8 BIOMICROSCOPY / OCULAR HEALTH EVALUATION

The participant will sit behind a slit lamp and the following will be assessed.

4.5.8.1 BULBAR AND LIMBAL HYPEREMIA

The redness of the bulbar and limbal conjunctiva of both eyes will be assessed using the EFRON Grading scale (0 to 4, 0 = no redness).

4.5.8.2 CORNEAL AND CONJUNCTIVAL STAINING

A sodium fluorescein strip, wetted with a few drops of saline, will be applied to the superior bulbar conjunctiva of both eyes. Staining will be graded using the CCLR scale (0 to 100, 0 = no staining) while viewing with cobalt blue light through a Wratten no. 12 barrier filter.

4.5.8.3 PALPEBRAL CONJUNCTIVAL HYPEREMIA AND ROUGHNESS

The redness and roughness of the upper and lower eyelids (tarsal plate zone 2) will be assessed using the CCLR scale (0 to 100, 0 = no redness/roughness).

4.5.9 COMFORT RATINGS

Participants will be asked to complete subjective ratings at the study visits and at home on certain study days. They will record their responses on an online database [redacted] Responses will be captured at screening, on study day 0 (at V2-1, V2-2), and subsequently at days 3, 6, 8, 12, 15, 18, 21, and 24 where comfort will be recorded after lens insertion, after 2 hours of lens wear and prior to lens removal at the end of the wearing day. Comfort will be assessed on a 100 point scale with a score of 0 indicating “Extremely uncomfortable” and a score of 100 indicating “Extremely comfortable.” Verbal instructions on how to complete the diary will be provided and email reminders will be send to the participant for each rating. The CLDEQ-8 questionnaires will also be completed at Visit 1, 4 and 5 using the [redacted] on the participant’s phone. The individual assessments on the CLDEQ-8 questionnaire will be summarized to provide a score of 1 to 37.

4.5.10 ASSESSMENT OF COMPLIANCE

Participants will be asked to declare the number of days of contact lens wear and the number of times the intranasal device has been used.

4.6 NON-STANDARD OPTOMETRIC PROCEDURES:

4.6.1 INTRANASAL EXAMINATION

The intranasal examination can be completed without topical anesthesia using a nasal speculum. The speculum is gently inserted into the lower end of each of the nares. A light should be utilized to enhance visualization. The speculum is opened to expand the nares such that the the nasal cavity can be 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.

4.6.2 THREE-MINUTE SCHIRMER TEST WITH 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 Section 4.5.6 above.

1. With new strips in place, the participant should be instructed to hold the cotton swabs and gently probe both nasal turbinates simultaneously, resting intermittently before probing again if necessary. The examiner should continuously coach the participant on how to perform this test properly.
2. The Schirmer strips should remain in place until three minutes have elapsed or both strips have reached maximum score or until both eyes have responded with minimal inclusion criteria of at least an increase of 4 mm compared to Basal Schirmer Scores.

Both Schirmer scores will be recorded and verified that they meet the inclusion criteria.

5 PARTICIPANT TRAINING, DISPENSING AND HOME USE OF TRUETEAR

On Day 0, participants randomized to the TrueTear group will be provided a TrueTear device and disposable tips to take home with them and use daily. Participants will be instructed to use the device as described in the Patient Guide. They will receive training to perform intranasal neurostimulation and will receive a copy of the Patient Guide.

For TrueTear application, participants 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. They will be instructed to fully insert the tips of the TrueTear into both nostrils simultaneously towards the top and front of the nose (as in Figure 5). 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 Tips with a new one if they do not feel any sensation.

For the initial in-office device application at Day 0, each participant will be trained on the device consistent with instructions in the patient guide. At Day 0 follow up and 1 week, 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.

Figure 5: 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.

6 PARTICIPANT TRAINING, DISPENSING AND HOME USE OF TRUETEAR SHAM CONTROL

On Day 0, participants randomized to the TrueTear sham control group will be provided a TrueTear sham control device and disposable tips to take home with them and use daily. Participants will be instructed to use the device as described in the Patient Guide. They will receive training to perform intranasal neurostimulation and will receive a copy of the Patient Guide.

For TrueTear sham control application, participants will be instructed to fully insert the tips of the sham device into both nostrils. Participants will be told to apply and control the intensity of stimulation by pressing the plus (+) or minus (-) buttons on the device. When using the device, participants will be told the LEDs on the device are illuminated when stimulation is being delivered, even if they do not feel a “tickle” sensation. Participants will be told they can cease stimulation by pressing the minus button on the device or by withdrawing the device from the nostrils.

For the initial in-office device application at Day 0, each participant will be trained on the device, consistent with instructions in the patient guide. At Day 0 follow up and 1 week, 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.

7 MONITORING PROTOCOL ADHERENCE

Guidelines to be included on adherence to visit windows and windows around other data collection points (i.e. subjective ratings). Procedures for monitoring and reporting deviations from the windows are described in the protocol.

8 POTENTIAL RISKS AND BENEFITS TO HUMAN PARTICIPANTS

This is a non-significant risk (NSR) device study because of the use of marketed products and standard optometric assessments. This device has been granted marketing authorization by the US Food and Drug Administration (FDA) for the purpose of temporarily increasing tear production during stimulation.

Contact lenses in this study will be worn on a daily wear basis, with the participant continuing with their normal lenses and solutions, and with lenses being worn in accordance with their normal wear schedule. Adverse events and/ or complications in daily wear of soft contact lenses can occur (e.g.: inflammation and infection). When contact lenses are worn on a daily wear basis there is a small risk of an adverse event compared to not wearing contact lenses.

Anticipated risks from use of TrueTear may include: an increase in nasal secretions, uncomfortable sensations, epistaxis and other nasal irritations. The full list of potential adverse events from the use of the device is detailed in section 9 (Adverse Events) below.

Anticipated benefits may be a reduction in CL discomfort symptoms and longer comfortable wearing time of CLs over the course of the study.

9 ADVERSE EVENTS

See CCLR SOP012 for a description of adverse event definitions, adverse event management and reporting.

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 applicable 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 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.

9.2.1 SEVERITY/INTENSITY

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

9.2.2 RELATIONSHIP 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.

9.2.3 ANTICIPATED ADVERSE EVENTS

The following is a list of potential AEs associated with the use of TrueTear or TrueTear sham control:

- 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

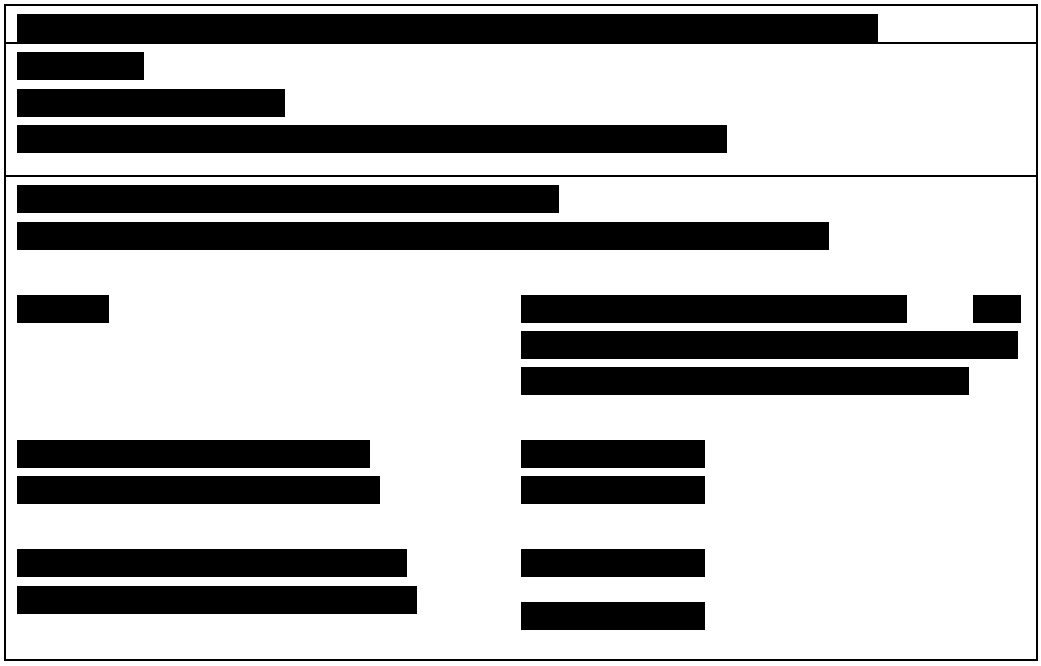
9.3 ADVERSE EVENT REPORTING

As per CCLR SOP012, all SAEs (Serious Adverse Events) must be reported by the Investigator to Allergan 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.

[redacted]



10 DISCONTINUATION FROM THE STUDY

Participants discontinued from the study will be reimbursed [redacted] for their active involvement in the study (including the initial screening visit). Participants may be discontinued at the discretion of the investigator, sponsor or participant. The following is a list of possible reasons for discontinuation from the study:

- Screening failure: Participants will be discontinued if they do not meet the inclusion and exclusion criteria outlined in section 4.2.3.

- Unacceptable performance with products to be used in study: Participants may be discontinued if they are unable to achieve acceptable comfort and /or vision with the study products, or if they are unable or unwilling to use the intranasal device as instructed.
- Positive slit lamp finding: Participants may be permanently discontinued from the study depending on the severity of the condition and on the judgement of the investigator.
- Adverse event: If a participant experiences an adverse event during the study, they may be discontinued based on the clinical judgement of the investigator or at the participant's request.
- Symptoms: If the participant has persistent symptoms, they may be discontinued based on the clinical judgement of the investigator.
- Disinterest, relocation or illness: The participant may choose to discontinue due to reasons within or beyond their control.
- Violation of protocol or non-compliance: The participant will be discontinued if they are unable or unwilling to follow the protocol specified visit schedules and/or study procedures.
- Instillation of topical ocular medication: The participant will be discontinued if they elect / are required to use a topical ocular medication during the study.
- A confirmed positive pregnancy test at any time during the study.
- Lost to follow-up: The participant will be discontinued if they cannot be contacted and do not return for a final exit visit, and if the investigator has made a reasonable effort to contact the participant for a final study visit.
- Premature termination of the study by the sponsor, the CCLR or the Office of Research Ethics at the University of Waterloo.

A discontinuation form will be completed, which requires the signatures of both the participant and the investigator except where the participant is lost to follow-up in which case only the signature of the investigator is required.

11 STUDY COMPLETION AND REMUNERATION

At the last scheduled protocol visit, a study completion form will be completed, which requires the signatures of both the participant and the investigator. The participants will also be provided with a letter of appreciation.

This study involves partial deception which must be explained to the participant at their last study visit (or study exit if discontinued earlier). Each participant will receive an information letter at their last visit which explains the nature of the partial deception and why the study had to be designed in such a way. Each participant will be given time to read, understand and ask questions.

Once their involvement in the study is complete, participants will be informed about receiving feedback following study completion in the Letter of Appreciation.

[redacted]

12 STATISTICAL ANALYSIS AND DATA MANAGEMENT

12.1 STATISTICAL ANALYSIS

[redacted] Descriptive statistics will be provided on information regarding baseline variables (age, gender, refractive error distribution, etc.).

Approximately 80 participants will be enrolled and randomized. 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.

Analysis of variables will be conducted separately on each eye, and data will not be pooled. The study eye will be defined as the qualified eye with the greatest increase in tear production with stimulation by a cotton swab at the Screening Visit (V1). If both eyes qualify and have the same increase in tear production with stimulation by a cotton swab, then the right eye will be designated as the study eye. Table 4 lists the exploratory outcome variables and anticipated statistical procedures.

Table 4: Statistical procedures

Variable	Analysis	Statistical test
Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8), Comfort (scored immediately after insertion, after 2 hours and immediately before lens removal), Comfortable wear time and Total wear time	Descriptive statistics	Mean, Standard Deviation, Min, Max, Count by visit
	Effect of application by visit (comparison of change from baseline between application groups)	*t*-test / Wilcoxon rank-sum test (as appropriate)
	Stratified analyses by visit (comparison of change from baseline between application groups stratified by CL freq strata and CL type)	*t*-test / Wilcoxon rank-sum test (as appropriate)
Pre-lens non-invasive tear breakup time (NITBUT) and Tear meniscus height (TMH)	Descriptive statistics	Mean, Standard Deviation, Min, Max, Count by visit
	Effect of application by visit (comparison of change from baseline between application groups)	*t*-test / Wilcoxon -rank-sum test (as appropriate)

All data will be tested for normality of distribution using Shapiro-Wilk tests. The appropriate test will be selected based on tests of normality.

The critical alpha level for statistical significance will be set at $p \leq 0.05$, with no adjustments for multiple comparisons. All participants who were evaluated will be used in the analysis. In the event of missing data, individual data points will be excluded in the analysis and not extrapolated from the collected data. As this is a proof of concept, additional statistical analysis may be conducted.

Dependent on the outcome of the study, analysis may be conducted on the contact lenses that have been collected. If the decision is made to not analyse the contact lenses then they will be destroyed according to University guidelines.

Additional analyses may be performed to examine the results observed relative to the device usage recorded by the device itself.

Safety assessments include adverse events, visual acuity and slit lamp biomicroscopy. Summaries by application will be prepared of the number and percentage of subjects reporting one or more adverse events, the number and percentage of subjects reporting one or more device-

related adverse events, the number and percentage of eyes with a clinically significant change in visual acuity at each follow-up exam and the number and percentage of eyes with a clinically significant change in slit lamp biomicroscopy at each visit. A clinically significant change in visual acuity is defined as a change of more than 2 lines (logMAR score change greater than 0.2). A clinically significant change in the slit lamp biomicroscopy parameters will be a change of 2 or more grades.

12.2 DATA MANAGEMENT

Data from this study will be retained by the CCLR for a minimum of 25 years on a password-protected server. After 25 years, data will be disposed of in accordance with the guidelines laid out by the University of Waterloo.

At the completion of the study the CCLR will provide a copy of the study data to the sponsor when requested. Data will typically be sent using a secure file share system operated by the University of Waterloo called [redacted] which uses 128bit (or 256bit) SSL encryption. This system provides a secure way to transfer files when email is not appropriate, whether because of file size, file type or concerns over security. [redacted] includes features such as password protection, a restricted time period for download, IP logging and email notification of download. Files may be encrypted prior to transmission at the request of the sponsor. Using this method means that data files are only stored on University of Waterloo servers.

12.3 COMMENTS ON SOURCE DOCUMENTS

Data analysis will not be conducted on comments which have been recorded in the source documents. Only highlighted comments will be entered into the study database. Only relevant and applicable comments will be included in the final report as deemed necessary by the lead investigator.

13 PROTOCOL TRAINING

All study personnel will be required to complete training prior to their involvement in the study. A series of training modules will be developed for the study and records of training will be kept at the CCLR.

14 STUDY MONITORING

Status reports will be provided to the study sponsor by email on a regular basis.

Status reports will include:

- The number of participants screened, enrolled, and randomized (i.e. assigned a study ID number), discontinued and completed.
- Details of protocol deviations.
- Reports of unintended events.

Study monitoring visits may be conducted throughout the study and will be scheduled by the study sponsor in conjunction with the lead investigator. In addition study records may be inspected at the CCLR by the sponsor, the sponsor's designate, the Office of Research Ethics at the University of Waterloo, and by regulatory authorities in Canada and the United States, namely Health Canada and the United States Food and Drug Administration (FDA); however, no records containing identifiable/personal information will be permitted to leave the custody of the CCLR.

15 STUDY MANAGEMENT

15.1 STATEMENT OF COMPLIANCE

This clinical study is designed to be in compliance with the ethical principles in the Declaration of Helsinki, with the ICH guidelines for Good Clinical Practice (GCP), GCP principles described in ISO 14155, the University of Waterloo's Guidelines for Research with Human Participants and with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 2nd Edition.

- Declaration of Helsinki
- ICH E6 - International Conference on Harmonisation; Good Clinical Practice
- ISO 14155 Clinical investigation of medical devices for human subjects – Good clinical practice
- http://iris.uwaterloo.ca/ethics/human/guidelines/index.htm
- http://iris.uwaterloo.ca/ethics/human/ethicsReview/UWStatement.htm
- http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/

15.2 ETHICS REVIEW

This protocol will be submitted to and reviewed through the Office of Research Ethics (ORE) at the University of Waterloo. Notification of ethics clearance of the application is required prior to the commencement of the study.

15.3 PROTOCOL DEVIATIONS

Protocol deviations are unanticipated or unintentional changes to a study after it has received prior sponsor approval and ethics clearance. Protocol deviations can be major or minor.

15.3.1 MAJOR PROTOCOL DEVIATIONS

Major protocol deviations may impact the research protocol, information consent document or other study materials, usually cannot be anticipated ahead of time and are often necessary to ensure the safety and welfare of the participants.

The following are examples of protocol deviations that must be reported to the ORE:

- Changes in procedures initiated to eliminate immediate risks/hazards to participants;
- Enrollment of participants outside the protocol inclusion/exclusion criteria whether agreed to or not by the sponsor;
- Medication / device / intervention errors (i.e. incorrect device / incorrect contact lens(es) dispensed / incorrect care system dispensed);
- Inadvertent deviation in specific research intervention procedures or timing of the research intervention which could impact upon the safety or efficacy of the study-related intervention or upon the experimental design;
- Information consent documentation violations: no documentation of informed consent; incorrect version of, or incomplete, informed consent documentation used.

15.3.2 MINOR PROTOCOL DEVIATIONS

Protocol deviations caused by or which originate with research participants are considered minor, and normally are not reported to the ORE unless they result in increased risk to the participant(s). The following are examples of protocol deviations that are considered minor and do not require reporting to the ORE:

- Logistical or administrative aspects of the study (e.g., study participant missed appointment, change in appointment date);
- Inadvertent deviation in specific research intervention procedures or timing of the research intervention which would not impact upon the safety or efficacy of the study-related intervention or upon the experimental design (i.e., missing a measurement during a session that is not considered critical for the study).

15.3.3 REPORTING AND DOCUMENTING PROTOCOL DEVIATIONS

Major protocol deviations must be reported to the ORE within 7 days of the deviation occurring (or its discovery) using the Protocol Deviation Report Form 107 (PDRF). Information from the PDRF is provided to the Clinical Research Ethics Committee (CREC) at the next monthly meeting.

All protocol deviations (major and minor) occurring during the study will be documented and included in the final report.

15.4 PREMATURE TERMINATION OF THE STUDY

The sponsor, the CCLR or the Office of Research Ethics at the University of Waterloo may terminate the study at any time for any reason.

15.5 STUDY PARTICIPANT RECORDS

Study participant records will be completed to comply with GCP guidelines. Records will contain:

- Unique study acronym and/or code;
- Participant ID;
- Date enrolled;
- Confirmation by lead investigator that participant met eligibility criteria;
- Confirmation that participant received a signed and dated copy of informed consent;
- Exit date;
- Lead investigators signature confirming study exit.

15.6 RETENTION OF STUDY RECORDS AND DATA

Records and data from this study will be retained for a minimum of 25 years. Details regarding storage procedures are given in CCLR SOP 6.3.

16 REPORT

A report will be sent to the sponsor according to terms described in the study contract.

17 REFERENCES

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