COVER PAGE

Clinical Protocol Title:
Assessing the Efficacy of Intranasal Neurostimulation in Ameliorating Symptoms of Neuropathic Corneal Pain

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Phase of clinical investigation: Pilot study

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Investigational device:
TrueTear® Intranasal Neurostimulator (Allergan)

Regulatory Sponsor:
Pedram Hamrah, MD

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Study Monitor

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Acronym List:

NCP- Neuropathic corneal pain
TG- Trigeminal ganglion
ITN- Intranasal Neurostimulator
NLR- Nasolacrimal reflex
IVCM-*In vivo* confocal microscopy
VAS- Visual analogue scale
CRF- Case report form
BVCA- Best correct visual acuity
TBUT- Tear break-up time
OSDI- Ocular surface disease index
OPAS- Ocular pain assessment survey
IDEEL- Impact of Dry Eye on Everyday Life
AE – Adverse Event
SAE- Serious adverse effect
UADE - Unanticipated Adverse Device Effect

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Assessing the Efficacy of Intranasal Neurostimulation in Ameliorating Symptoms of Neuropathic Corneal Pain

STUDY DESIGN SCHEMATIC

1. CLINICAL PROTOCOL

1.1. Background/ Rationale:

Neuropathic corneal pain, like neuropathic pain elsewhere in the body, is defined as pain resulting from a lesion/injury affecting the corneal somatosensory system on the ocular surface [1]. The increased numbers of patients with refractory corneal pain and discomfort following refractive surgery [2], and among patients with dry eye disease [3], has resulted in increased

interest by ophthalmologists and scientists to investigate the underlying mechanisms involved in NCP, and to search for new treatments to ameliorate neuropathic pain.

The cornea is highly innervated with sensory nerves, Aδ- and C- fibers that originate from the ophthalmic branch of the trigeminal nerve. These nerves end in the corneal epithelium as free terminals [4]. These free nerve endings are classified as different types of nociceptors, depending on their responses to stimuli [5, 6].

Corneal pain signals are transmitted to the primary afferent fibers in the trigeminal ganglion (TG). From there second-orders neurons join the contralateral spinothalamic tract to synapse with third-order neurons in the thalamus. These ascending signals are further modified by input from subcortical structures associated with emotions and memory before terminating in the somatosensory cortex where they are felt as pain [7].

Injury to corneal nerves, associated with inflammatory responses may result in peripheral sensitization, which involves a decrease in nociceptor threshold for excitation, resulting in pain responses to typically non-painful stimuli (hyperalgesia) or even in the absence of stimuli (allodynia). Persistent nerve injury leading to prolonged and continuous signaling through the afferent fibers may subsequently lead to central sensitization, in which nociceptors outside the site of the original lesion undergo a similar process and can be activated by sub-threshold stimuli or even spontaneously discharge independent of any peripheral signaling [8, 9].

Peripheral neuromodulation involves applying electrical currents to peripheral nerves for medical therapy. Its evolution and expansion has increased over the course of the last two decades for the management chronic pain [7, 10]. The “gate control theory” provides the understanding for this concept, by which activation of large myelinated nerve fibers inhibits transmission of pain impulses from the peripheral nervous system to the central nervous system. The antegrade stimulation of nociceptive Aδ nerve fibers leads to activation of interneurons in the TG. The same interneurons in the TG are also involved in the process of transmission of nociceptive signals from peripheral nerves. Non-painful stimuli from peripheral nerves, such as those conducted with the ITN, result in decreased excitability, increased electrical thresholds, transient slowing of conduction velocity, and result in inhibition of interneurons that leads to interruption of pain signal transmission from the territory innervated by the stimulated nerve [11, 12].

The TrueTear® ITN, recently approved by the FDA, is a portable neuromodulation device that delivers a small electrical current to the sensory nerves in the nasal cavity that stimulates the nasolacrimal reflex (NLR) [13]. The NLR afferent pathway emerges from the ethmoidal nerve, a subunit of the ophthalmic branch of the trigeminal nerve and ends at the interneurons in the TG.

2.0 STUDY OBJECTIVES

Hypothesis / Study Objective/ Purpose:

In our recent study using the TrueTear™ intranasal neurostimulator (ITN) in patients with dry eye disease (Dieckmann et al. ARVO 2017, unpublished observation) and concurrent neuropathic symptoms, some patients that suffered from neuropathic pain or photoallodynia, reported immediate relief of pain or photoallodynia after a single 3-minute use of ITN.

Thus, we hypothesize that the stimulation through the ethmoidal nerve in the nasal cavity may have an inhibitory effect on the primary TG interneurons and block the ocular pain signaling to the brain.

We propose a non-randomized, cross sectional, open-label, single arm pilot trial for treatment of neuropathic corneal pain (NCP) with ITN with the following specific aims:

Specific Aims:

1. To elucidate the efficacy of ITN in ameliorating pain among neuropathic corneal pain patients.
2. To elucidate the safety, efficacy, longevity of ITN in ameliorating pain among neuropathic corneal pain patients during a 90-day period with daily use.
3. To assess quality of life changes by treating neuropathic corneal pain with ITN during a 90-day period with daily use.

3.0 STUDY DESIGN

3.1. Study Design Description

This study is a prospective, interventional, open-label, single arm, non-randomized trial treating 45 patients with peripheral or mixed neuropathic corneal pain at their baseline exam and following 45 days and 90 days of daily use with the TrueTear™ ITN device.

3.2 Statistical analysis:

Two-tailed paired sample t-test and Pearson correlation will be performed for pain intensity, and to assess associations between different quality of life scores. Statistical comparisons of the mean values between different groups based will be performed using ANOVA.
The normality of continuous variables will be tested with the Shapiro-Wilk test. All tests will be two tailed and statistical significance will be considered for p values of less than 0.05.

4.0 SUBJECT SELECTION

4.1. Subject Inclusion Criteria:

1. Age ≥22.
2. Ability to consent to study.
3. Symptoms of neuropathic corneal pain for at least 3 months, such as burning, stinging, light sensitivity, discomfort or pain.
4. Positive in *vivo* confocal microscopy (IVCM) findings for NCP such as presence of microneuromas and decreased nerve density. The presence of positive IVCM findings serves in lieu of skin biopsies as proof of nerve injury.
5. Fifty percent or more relief of pain or discomfort after instillation of Proparacaine eye drops as measured by the Visual Analogue Scale (VAS).

4.2. Subject Exclusion Criteria:

1. Clinically significant acute ocular surface diseases, such as active infectious keratitis or recent ocular surgery in the past 3 months.
2. Chronic or recurrent epistaxis, coagulation disorders.
3. Nasal or sinus surgery or significant trauma to the nose.
4. Severe nasal airway obstruction or vascularized nasal polyps.
5. Cardiac demand pacemaker, implanted or wearable defibrillator, or other implanted electronic device in the head or neck.
6. Chronic or recurrent nosebleeds
7. Bleeding disorder or another condition that can lead to increased bleeding
8. Known hypersensitivity (allergy) to the hydrogel material that contacts the nasal mucosa
9. Disabling arthritis, neuropathy, or limited motor coordination affecting self-handling of the device.
10. Allergic to benzalkonium chloride (the Co-Investigators who administer the eye drops ask all patients if they are allergic to any eye drop preservatives before proceeding with the eye drops)

5. STUDY DEVICE

5.1 Study Device Information

The ITN delivers small electrical currents to the inner cavity of the nose, gently activating nerves that stimulate the body's natural tear production system.

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

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

Figure 1: The TrueTear® Intranasal Neurostimulator (ITN) components.

1. Base Unit

When activated, the base unit provides electrical pulses to the Tip Assembly. The strength of these pulses is controlled by two buttons, with five different levels available, indicated by the number of illuminated LEDs on the base unit. The Base Unit can only be activated when a Tip Assembly is present. The base unit also records the use of the device, stimulation level and

duration, in internal memory. Upon return of the device, this information will be downloaded from the device and summarized as described in the Statistics section below.

2. Tip Assembly
The Tip Assembly is specially designed to allow the participant to easily apply stimulation to the target areas within the nose. The Tip Assembly connects to the Base Unit and contains a hydrogel (similar to the material used in contact lenses) that touches the inside of the nose to provide stimulation. The disposable Tip Assemblies are removed and replaced at least daily; a separate Cover can be used to protect the Tip Assembly when not in use.

3. Cover
The cover may be slipped over the top of the Base Unit and Tip Assembly between uses.

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

5. Device Accountability
The investigator will be responsible for maintaining a device accountability log(s) that will track device usage for all study participants. Information tracked will include date of device receipt, lot and/or serial number, date of device usage or return (if applicable), subject ID, the occurrence of any device malfunctions or failures.

6. Labeling, Packaging, Storage, and Return or Disposal of Study Devices
All devices will be stored and maintained in accordance with package directions. Non-disposable devices should be returned to the Sponsor at the conclusion of the study. Used disposable devices should be discarded after use; unused disposable devices should be returned to the Sponsor at the conclusion of the study.

5.2 Study Device Compliance/Adherence

Directed questioning using the (Ocular Tolerability and Compliance Questionnaire – Appendix VI) will be administerd by the investigator or research staff. Results on the participants' compliance and adherence to the study protocol and study device will be recorded on the paper case report form (CRF). During the study, all concomitant medication treatment regimens, ocular hygiene treatments (i.e., lid scrubs and warm compresses), or insertion of punctal plugs will be kept constant as permitted by accepted medical practice. If one of the aforementioned treatment regimens needs to be modified, the participant may be withdrawn based on the investigator's discretion.

Participants must be compliant with IVCM imaging on the study visit or they will be withdrawn. Subjects who are withdrawn may be replaced by new enrolled subjects to maintain the sample size.

5.3 Clinical procedures and training
Study procedure and device training

Device application using the ITN
Participants will be trained on how to use the ITN properly.
Shortly thereafter, participants will be instructed to place the tips of the ITN into both nostrils simultaneously (Figure 2). Participants will be asked to apply and control the intensity of stimulation by pressing the plus (+) or minus (-) buttons on the device. The level of intensity will be chosen and controlled by the participant. The level of intensity used may be between 2 and 5 out of a possible 5 levels. Each participant will be asked to apply application for 1 minute should no change in discomfort been noted after 1 minute and 3 minutes. Participants will also be told they can control the location of stimulation by the depth and angle of insertion until they feel a "tickle" sensation. Participants will be told they can cease stimulation by pressing the minus button on the Base Unit or by withdrawing the entire ITN device from the nostrils.

Patients will use the TrueTear® a minimum of at least twice a day. The patient is allowed to use it more often than twice a day if needed.

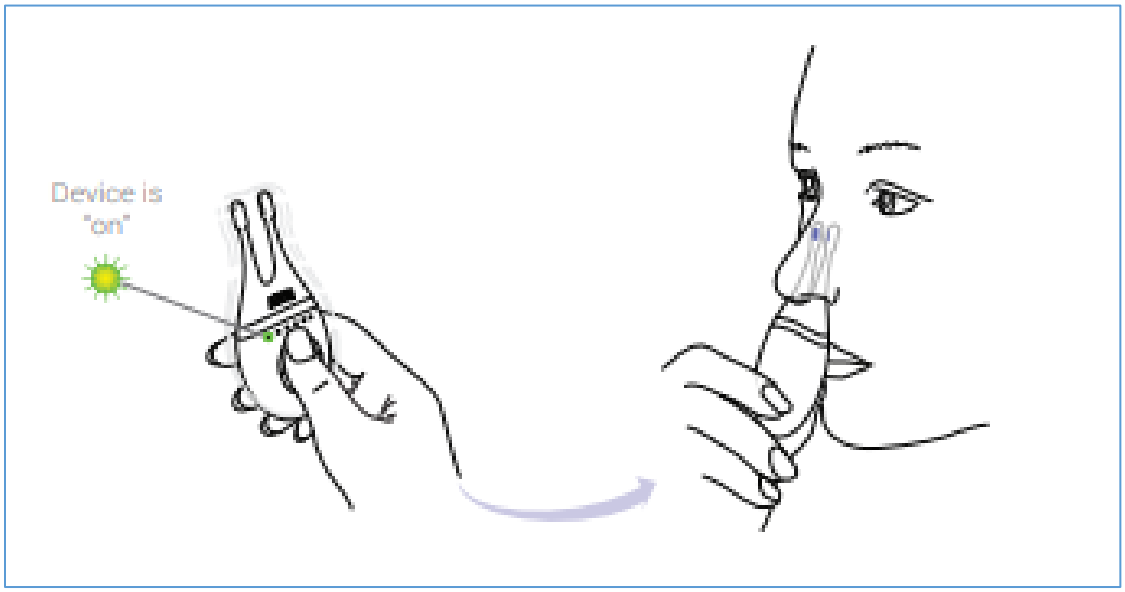

Figure 2: Use of the TrueTear® Intranasal Neurostimulator (ITN).
Turning on the device and placing it into the nose

5.4 Quality control and quality assurance

The collection of accurate, consistent, complete, and reliable data will be assured through the use of training sessions, monitoring of the investigator by qualified personnel, data verification, and cross-checking.

6. BIOSPECIMEN COLLECTION (IF APPLICABLE)

6.1 Specimen preparation, handling, and shipping: N/A

6.2 Instruction for specimen preparation, handling and storage: N/A

6.3 Specimen shipment: N/A

6.4 Future use of stored specimens: N/A

7. STUDY PROCEDURES

7.1 Screening/Baseline Procedures

Prospective participants, as defined by the inclusion/exclusion criteria, will be considered for entry into this study. Concurrent enrollment of subjects who are participants in other studies will be allowed based on the investigator's discretion.

During the consent process, study design and treatment regimen will be discussed with each subject. Written informed consent will be obtained before any study specific procedures are performed. However, standard of care clinical information (such as: medical history, BCVA, TBUT, staining, and Schirmer's test) obtained during a subject's clinical visit within the previous 48 hours can be used during the screening visit to determine eligibility and as their baseline assessments.

The following evaluations and procedures will be performed for all subjects during the screening period:

- Written informed consent
- Record of current ocular and systemic medications
- Record of significant medical/surgical history in the past 5 years
- Record of demographic data, including date of birth, sex, and race/ethnicity
- Eye examination (best corrected visual acuity, slit-lamp biomicroscopy, introcular pressure)
- Corneal fluorescein staining
- Conjunctival lissamine green staining
- Tear break-up time (TBUT)
- Corneal *in vivo* confocal microscopy (IVCM)
- Ocular Surface Disease Index (OSDI) questionnaire
- Ocular Pain Assessment Survey (OPAS) questionnaire
- IDEEL QoL Questionnaire

- The following evaluations and procedures will be performed for all subjects during the Enrollment/Baseline procedures (once the patient is confirmed to be eligible):Visual Analogue Scale (VAS) questionnaire before and after each of the five tests (filter glasses response, hyperosmolar saline response, cold saline response, proparacaine challenge test)Schirmer's test II (with anesthesia)

The description of the procedures is as follows:
Ocular Surface Disease Index (OSDI) questionnaire: (Appendix I) 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning. The 12 items of the OSDI questionnaire are graded on a scale of 0 to 4, where 0 indicates none of the time; 1, some of the

time; 2, half of the time; 3, most of the time; and 4, all of the time. The total OSDI score is then calculated on the basis of the following formula: OSDI= [(sum of scores for all questions answered) x]/[(total number of questions answered) x 4].

Ocular Pain Assessment Survey (OPAS): OPAS Questionnaire (Appendix III): 27-item quantitative questionnaire designed to provide an assessment of the symptoms and quality of life effect of ocular pain. The 27 items of the OPAS questionnaire are graded on a scale of 0 to 10, or 10 to 100, where 0 indicates none and 10 or 100 indicate maximum. This questionnaire should take approximately 2-3 minutes to complete.

Visual Analogue Questionnaire: (Appendix IV) Symptoms of ocular comfort and dryness will be graded for each eye on a scale of 0-100, where 0=extremely uncomfortable, extremely dry and 100=excellent comfort, no dryness. An average rating will be provided for the morning, afternoon and evening. This questionnaire should take approximately 2-3 minutes to complete.

IDEEL QoL Questionnaire (Appendix V): This is a 27-item questionnaire, designed specifically for DED and is divided into three parts. It assesses the quality of life in three aspects of life for the previous 2 weeks: daily activities, work and feelings. The quality of life is assessed on a scale of 0-5, with zero being inability to do the activity. The score is calculated between 0 – 100 with higher scores indicating a better quality of life. This questionnaire should take about 5-10 minutes complete.

Filter glasses: This test will be done in a dimly lit room, about 50 lumens of light intensity (approximately 50-75 square feet room with 10 lumens per square feet), room temperature, pressure and humidity. Each eye will be assessed separately. The other eye will be covered with an occluder to eliminate exposure to the light. The study eye will be covered using a 100% opaque filter and then the opacity of the filters will be reduced in decrements of 10%. Ten graded filters have been developed for this purpose; each of these filters decrease light opacity by 10%. Light will be shone at a distance of approximately 10 cm from the eye, using a mussel light (halogen fiber-optic transilluminator). Starting at the 100% opaque filter, the filter at which the patient starts to feel pain/photophobia will be noted. That light level will be used to assess threshold and a pain/photophobia for each filter will be noted on a scale of 1-10. Using pilot studies we have seen that the pain/burning can increase with an increase in light in patients with NCP.

Cold Response Test: One drop of cold 0.9% preservative-free saline eye drops will be topically applied onto the patient's eyes. The level of discomfort/pain will be assessed by the VAS questionnaire before and after the drops are applied.

Hyperosmolatity Response: One drop of 5% sodium chloride (Muro 128® 5%) drop will be topically applied on the conjunctival fornix of both eyes. The level of discomfort will be measured the VAS questionnaire before and after application of a 5% sodium chloride drop.

Proparacaine Challenge Test: One drop of Proparacaine Hydrochloride Ophthalmic Solution 0.5% will be topically applied in both eyes to differentiate between the peripheral versus central

component of the patient's pain or discomfort. The level of discomfort/pain will be assessed by the VAS questionnaire.

Schirmer's (II) Test with Anesthesia: The Schirmer's test will be performed 3 minutes after a drop of topical anesthesia with 0.5% proparacaine (Alcon Inc., Ft Worth TX) is applied to the eye. The Schirmer test is performed by placing a narrow filter-paper strip (5 x 35 mm strip of Whatman #41 filter paper) in the inferior cul-de-sac. This test is to be conducted in a dimly lit room. The subject should gently close their eyes until five minutes have elapsed and the strips are removed. Since the tear front will continue advancing a few millimeters after it has been removed from the eyes, it is important to mark the tear front with a ball-point pen at precisely five minutes. Aqueous tear production will be measured by the length in millimeters that the strip wets during 5 minutes. This procedure should take approximately 10 minutes to complete.

Tear Break-Up Time (TBUT): The standard TBUT measurement will be performed by dropping a fluorescein drop to the inferior tarsal conjunctiva. After several blinks, the tear film will be examined using a broad beam of the slit lamp with a blue filter. The time lapse between the last blink and the appearance of the first randomly distributed dark discontinuity in the fluorescein stained tear film will be measured three times and the mean value of the measurements will be calculated. The tear break-up time will be evaluated prior to the instillation of any eye drops and before the eyelids are manipulated in any way. Break-up times less than 10 seconds are considered abnormal. A positive change from baseline indicates improvement. This procedure should take approximately 10 minutes total to complete.

Corneal Fluorescein Staining: (Appendix II) Corneal fluorescein staining will be performed after 3 minutes of application of a fluorescein drop. The entire cornea will be then examined using slit-lamp evaluation with cobalt blue illumination. Staining will be graded using the NEI grading scheme, with a total range of 0-15.

Conjunctival Lissamine Green Staining: (Appendix II) Grading of conjunctival lissamine green staining will be performed after 2 minutes of application of a lissamine green drop. The nasal and temporal conjunctiva will be examined using slit-lamp evaluation with white light. Staining will be graded using the NEI grading scheme, with a total range of 0-18. This procedure should take approximately 2 minutes to complete.

***In Vivo* Confocal Microscopy (IVCM):** *In vivo* confocal microscopy (IVCM) is a new imaging method, which allows visualization of the corneal structures at the cellular level. With a magnification of 800 times, it makes it possible to detect and quantify changes in the epithelial layers and sub-basal nerve plexus.

7.2 Study Visit

The study will be performed in four visits. During the baseline visit, all patients will be evaluated using the flowchart (page 2). The first visit will include in-office testing of ITN and response to ITN. After 45 days (6 weeks ± 1 week) and 90 days (3 months ± 2 weeks) of using the ITN on a daily basis, the patients will return for follow-up visits. The same flowchart as for screening visit will be followed in these two visits (with the exception confocal microscopy on visit 2). Additionally, evaluation of diary for daily use (Appendix VII) and questionnaires regarding

tolerability and safety of device and any reduction in the use of concomitant pain medications will be assessed on these visits.

7.3 Standard of Care Procedures
The following procedures are the standard of care:

- Ocular Surface Disease Index Questionnaire (OSDI)
- OPAS
- VAS
- Eye examination (best corrected visual acuity, bio-microscopy, intraocular pressure measurement)
- Schirmer's II test (may be study specific)
- Tear break-up time (TBUT)
- Corneal fluorescein staining
- Conjunctival lissamine green staining
- Central corneal *in vivo* confocal microscopy

7.4 Study Specific Procedures:
At the study visit, the following procedures will be performed for study specific purposes in addition to standard of care procedures:

- Questionnaires: OPAS, VAS after ITN, IDEEL, Safety and tolerability questionnaires
- ITN response at 1 minute and 3 minutes to assess pain and light sensitivity
- Diary to keep readings (Appendix VII)
- Schirmer's test with anesthesia (may be standard of care)
- Filter glasses test
- Cold saline solution response
- Hypertonic saline solution response
- Proparacaine challenge test (may be standard of care)

7.4 Follow-up Procedures
Subjects will come back for a 1st visit after the screening visit; 2nd visit at 45 days (± 1 week) following the first visit, and 3rd visit following 90 days after the first visit (± 2 weeks). All of the procedures done at the baseline visit will be done in the 2nd and 3rd visits (see flowchart).

In addition, subjects will be asked about their usage of the ITN. Ocular safety and tolerability questionnaire (appendix VI) will be administered in the 2nd and 3rd visit. The subject will be asked to complete a diary every day to record any pain symptoms (Appendix VII). The subject will be asked to send their pain diary weekly to the study coordinator, in however method works for the subject to ensure compliance with the ITN. They will also need to bring the diary to each study visit, to ensure compliance.

Ocular Tolerability Questionnaire (Appendix VI): This questionnaire assesses tolerability of the ITN device. It assesses symptoms of discomfort in each eye after ITN use.

7.5 Unscheduled Visits

If the subject reports to the Cornea Department for a visit that is not related to the study, only a review of adverse assessments will be required per the study.

7.6 Early Termination

If a subject withdraws or is withdrawn from the study prior to completion of all study visits, there will be no additional procedures performed

8. SAFETY AND EFFECTIVENESS ASSESSMENTS

8.1 Safety Assessments

The primary safety variable monitored will be the occurrence of adverse events. The severity of each adverse event observed will be evaluated as serious or not serious and the occurrence will be evaluated as expected or unexpected. The relationship of the event to the study medication will be assessed by the investigator as possibly, probably, or definitely related. Safety variables will be evaluated at all study visits. If adverse events occur, the first concern will be the safety of the study participants. Any serious adverse event occurring during the study period will be immediately reported to TUFTS IRB. At each visit throughout the study, the investigator will begin querying for adverse events by asking each subject a general, non-directed question such as "How have you been feeling since the last visit?" or "How have your eyes been since the last visit?"

A comprehensive eye examination including best-corrected visual acuity, evaluation of the condition of conjunctiva, cornea, anterior chamber, iris/pupil, lens, will be performed.

Withdrawal from the study will happen if any of the following occurs:

- Investigator determination that it is not in the best interest of the subject to continue participation.
- Subject's wish to withdraw for any reason.

After being withdrawn, subjects will be followed according to each case until the adverse event is resolved.

9. ADVERSE EVENT RECORDING AND REPORTING

9.1 Recording Requirements

Adverse Events (AEs)
An adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution.

Serious Adverse Events (SAEs)
A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

Unanticipated Problems
According to the Office of Human Research Protections (OHRP), unanticipated problems includes "any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated Adverse Device Effect (UADE)
Unanticipated adverse device effect means 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 application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Research subjects will be routinely questioned about adverse events at study visits. All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study device(s) will be recorded in the subjects' case histories (source data, case report form). For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and; 2) an assessment of the causal relationship between the adverse event and the study device.

Adverse events or abnormal test findings thought to be associated with the study device (ITN) will be followed until the event (or its sequel) or the abnormal test finding resolves or stabilizes at a level acceptable to the Investigator.
An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
- The test finding is considered an adverse event by the Investigator. Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

The Investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study device; and 3) if the adverse event meets the criteria for a serious adverse event.
If the Investigator's final determination of causality is "unknown and of questionable relationship to the study device", the adverse event will be classified as associated with the use of the study device for reporting purposes. If the Investigator's final determination of causality is "unknown but not related to the study device", this determination and the rationale for the determination will be documented in the respective subject's case history (source data or case report form).

9.2 REPORTING PROCEDURES

- **REPORTING OF ADVERSE EVENTS TO FDA**

Unanticipated Adverse Device Effect (UADE) will be reported to the sponsor and the IRB within 5 business days after investigators first learns of the event.

Reporting Adverse Events to Other External Entities

Therefore no reports on adverse events will be submitted to external entities.

- **Reporting Adverse Events to the Human Studies Committee**

  TUFTS policy for "REPORTING ADVERSE EVENTS AND UNANTICIPATED PROBLEMS" will be followed.

9.3 Withdrawal of Subjects due to Adverse Events

Withdrawal from the study will happen if any of the following occurs:

- Investigator determines that is not in the best interest of the subject to continue participation.
- Subject's wishing to withdraw for any reason.

After being withdrawn, subjects will be followed according to each case until the adverse event is resolved.

10. STATISTICAL METHODS/DATA ANALYSIS

10.1 Primary endpoint(s) or outcome measure(s)

- Change to overall pain by the Visual Analogue Scale (VAS) after ITN stimulation

10.2 Secondary Outcome Measures:

- Change to overall pain by the Visual Analogue Scale (VAS) after daily ITN stimulation over 45-day period.
- Change to overall pain by the Visual Analogue Scale (VAS) after daily ITN stimulation over 90-day period.
- Change in quality of life as measured daily with OPAS and IDEEL
- Safety
- Tolerability
- Change in response to hypertonic solution
- Change in response to proparacaine challenge test
- Change in the intraocular pressure (IOP) measured in each visit.
- Reduction on other concomitant pain therapy

10.3 Sample Size Determination:

There is no existing systematic epidemiological study regarding the neuropathic corneal pain and there are no studies available to determine the population sample needed to detect differences between patients before and after the neuro stimulation for neuropathic corneal pain. However, based on a recent preliminary observations in 5 patients with concurrent NCP and dry eye disease, and the decrease in pain levels immediately after the use of ITN, we would achieve 80% power with an alpha error of 0.05 for pain scale intensity of 1-10, and assumption of 50% decrease in pain levels, for a sample size of 25 patients. The enrollment of 30 patients with NCP would compensate for potential dropouts.

10.4 Analysis Population

N/A

10.5 Effectiveness Analysis

Effectiveness will be assessed through pain and quality of life questionnaires (VAS/ OPAS/ IDEEL) Questionnaires regarding changes or reduction in the current systemic medications will be applied and used as a clinical effective parameter.

10.6 Safety Analysis

The primary safety variable monitored will be the occurrence of adverse events. The severity of each adverse event observed will be evaluated as serious or not serious as defined by the Tufts

HSC and the occurrence will be evaluated as expected or unexpected. The relationship of the event to the study medication will be assessed by the investigator as possibly, probably, or definitely related. Safety variables will be evaluated at screening and at all study visits. If adverse events occur, the first concern will be the safety of the study participants. Any serious adverse event occurring during the study period will be immediately reported to Tufts IRB. Directed questioning will be done to assess tolerability. Additional steps taken to assess safety will be followed as outlined in section 8.1 of this SUPP M form.

10.7 Interim Analysis

N/A

11. DATA AND SAFETY MONITORING

11.1 Data and Safety Monitoring Plan

The PI, research fellows, research coordinators, and technicians involved with this protocol will be required to read the protocol, participate in a group meeting to discuss roles before the protocol is approved, and participate in weekly clinical research meetings. The pharmacy and the clinical fellows on the protocol will be required to read the protocol and separate meetings will be created to discuss roles as they relate to the protocol.

A copy of the approved protocol and study related materials will be placed on a shared network drive accessible to authorized research staff involved in this study and on IRBnet.org.
The primary safety variable monitored will be the occurrence of adverse events. The severity of each adverse event observed will be evaluated as outlined in section 10.6 by the treating investigator. The PI will be made aware of all AEs within one week. The ocular surface exam and IVCM imaging will only be performed by a research technician, fellow, or investigator to ensure adherence to the required tests and accurate assessments.

The study coordinator will be responsible for monitoring each visit to ensure that the procedures are performed as outlined in the protocol and documented appropriately.

Raw data collected for this study will be entered into a master database by the study coordinator, research technician, or fellow and uploaded for access to the principal investigator and all authorized research staff members on the U-Drive of password-protected computers located in the Cornea Research Department.

12. DATA HANDLING, RECORD-KEEPING AND MONITORING

12.1 Data Recording, Record-Keeping and Monitoring

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The Investigator will review, approve and sign/date each completed CRF; the Investigator's signature serving as attestation of the responsibility for ensuring that all clinical data entered on the CRF are complete, accurate and authentic.

The LMR will be considered Source Data and will contain the clinical findings and observations, and other information collected during the visit. Subject consents will be maintained within the Department of Ophthalmology Clinical Research Office.

All data will be stored on in the G-drive located on encrypted, password protected computers in the Cornea Research Department. Only the PI and researchers specific to this study who have been granted access to the data by the PI will be able to view the data in the TUFTS network protected folder. When data is sent out to be analyzed the data will be de-identified. The data will contain subject identification numbers, which are linked to identifiers on a separately secured spreadsheet. The data will be coded by assigning each participant a subject identification number and removing any identifiable information. The code will be secured by the PI and Study Coordinator in in the U-drive located on encrypted, password protected computers in the Cornea Research Department. The code that links information that can identify the participant to the data collected for this research will be kept separate from their health information, which will be destroyed once this study is complete and the manuscript has been published.

Study data are boxed and logged when the study is terminated and housed in on-site locked room until the 7 year requirement is met, and then transferred to off-site storage.

13. STUDY DISCONTINUATION CRITERIA

13.1 Discontinuation of Individual Research Subjects

Please see sections 9.3.

13.2 Investigator Discontinuation of the Clinical Research Study

References:

1. Goyal S, Hamrah P. Understanding neuropathic corneal pain--gaps and current therapeutic approaches. Semin Ophthalmol. 2016;31:59-70.

2. Theophanous C, Jacobs DS, Hamrah P. Corneal Neuralgia after LASIK. Optom Vis Sci. 2015;92:e233-40.

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8. Rosenthal P, Borsook D. Ocular neuropathic pain. Br J Ophthalmol. 2016;100:128-34.

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10. Goroszeniuk T, Pang D. Peripheral neuromodulation: a review. Curr Pain Headache Rep. 2014;18:412.

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12. Wall PD. The gate control theory of pain mechanisms. A re-examination and re-statement. Brain. 1978;101:1-18.

13. Friedman NJ, Butron K, Robledo N, Loudin J, Baba SN, Chayet A. A nonrandomized, open-label study to evaluate the effect of nasal stimulation on tear production in subjects with dry eye disease. Clin Ophthalmol. 2016;10:795-804.

Appendix I: Ocular Surface Disease Index (OSDI)

Have you experienced any of the following during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Have problems with your eyes limited you in performing any of the following during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Have your eyes felt uncomfortable in any of the following situations during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Total score for answers 1 to 12: ____

Total number of questions answered: ____

(Do not include questions answered N/A)

OSDI = (sum of scores) x 25/(# of questions answered): ____

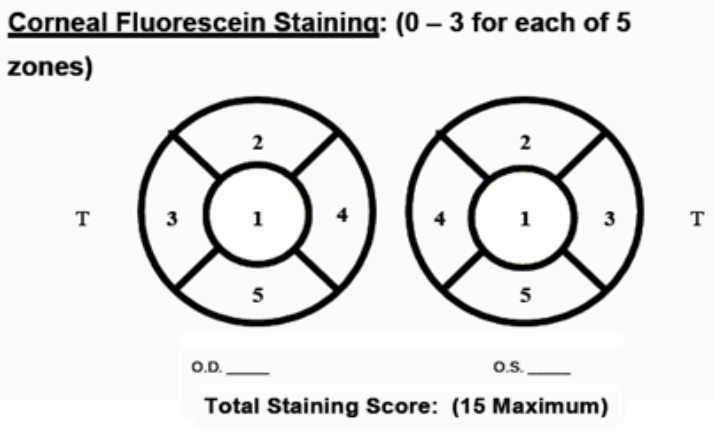
Appendix II: Cornea Fluorescein Staining

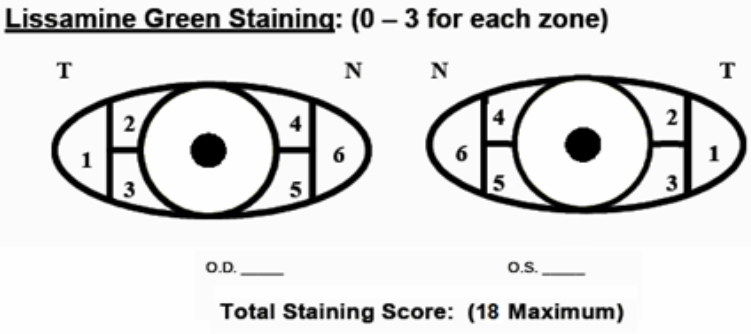
Fluorescein instillation:

Fluorescein strip wetted with buffered saline. Drop instilled on inferior palpebral conjunctiva. The participant is asked to blink several times.

Staining:

5 corneal regions (shown below) will be graded with a staining scale of 0-3. The "total scores" of the cornea and each region will be measured.





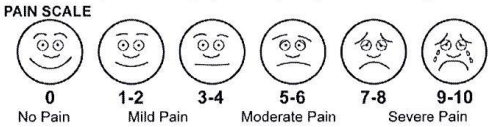
Appendix III: Ocular Pain Assessment Scale (OPAS) questionnaire

Ocular Pain Assessment Survey (OPAS) © 2013 Massachusetts Eye and Ear Infirmary

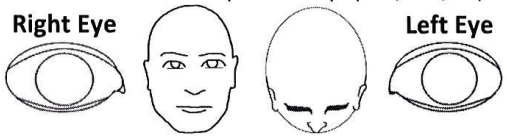
Please fill this form **only if** you HAVE EYE/FACIAL PAIN today or HAVE FILLED THIS FORM BEFORE

[Patient information sticker]

1. Please rate the overall severity of your pain today: (0= no pain, 10= worst pain ever)



2. On the diagram below, please shade the area where you have eye pain, and/or pain in the face and head region.



3. Do you have any longstanding pain elsewhere in your body? ☐ NO If yes, please state where:_____

ALL QUESTIONS REFER TO PAIN IN YOUR WORSE EYE. Please circle the **level** of your **eye** pain for the following:

EYE PAIN INTENSITY 24 HOURS

Level of eye pain when it is **MOST** painful:

4. in the past 24 hours — 0 1 2 3 4 5 6 7 8 9 10 — No pain / Severe pain

Level of eye pain when it is **LEAST** painful:

5. in the past 24 hours — 0 1 2 3 4 5 6 7 8 9 10 — No pain / Severe pain

Level of eye pain on **AVERAGE**:

6. in the past 24 hours — 0 1 2 3 4 5 6 7 8 9 10 — No pain / Severe pain

EYE PAIN INTENSITY 2 WEEKS

7. in the past 2 weeks — 0 1 2 3 4 5 6 7 8 9 10 — No pain / Severe pain

8. in the past 2 weeks — 0 1 2 3 4 5 6 7 8 9 10 — No pain / Severe pain

9. in the past 2 weeks — 0 1 2 3 4 5 6 7 8 9 10 — No pain / Severe pain

NON-EYE PAIN

Please circle the **level** of your **worst non-eye pain** (pain at temples, back of head, cheek area):

10. in the past 24 hours — 0 1 2 3 4 5 6 7 8 9 10 — No pain / Severe pain

11. in the past 2 weeks — 0 1 2 3 4 5 6 7 8 9 10 — No pain / Severe pain

Please circle the percentage of time you spend thinking about your **non-eye pain (face/head)**:

12. **Not at all** — 0% — 50% — 100% — **All the time**

Ocular Pain Assessment Survey (OPAS) © 2013 Massachusetts Eye and Ear Infirmary

QUALITY OF LIFE (QOL)

Please circle one number that describes how much your pain has interfered with/affected the following:

Reading and/or Computer use

13. Not at all 0 1 2 3 4 5 6 7 8 9 10 Completely ☐ N/A

Driving and/or Watching TV

14. Not at all 0 1 2 3 4 5 6 7 8 9 10 Completely ☐ N/A

General activity (walking, doing house chores)

15. Not at all 0 1 2 3 4 5 6 7 8 9 10 Completely ☐ N/A

Mood

16. Not at all 0 1 2 3 4 5 6 7 8 9 10 Completely ☐ N/A

Sleep

17. Not at all 0 1 2 3 4 5 6 7 8 9 10 Completely ☐ N/A

Enjoying life/Relations with other people

18. Not at all 0 1 2 3 4 5 6 7 8 9 10 Completely ☐ N/A

Please circle the percentage of time you spend thinking about your **eye pain**:

19. Not at all 0% 50% 100% All the time

AGGRAVATING FACTORS

Please circle how much your **pain is increased** when exposed to:

Wind, dry air, heat, air conditioning

20. No change 0% 50% 100% Severe increase

Volatile chemicals (cleaning agents, fumes, cosmetic fragrances)

21. No change 0% 50% 100% Severe increase

ASSOCIATED FACTORS

Please circle **how often** your eye pain is accompanied by the following symptoms:

Redness

22. Never 0% 50% 100% All the time

Burning

23. Never 0% 50% 100% All the time

Sensitivity to light

24. Never 0% 50% 100% All the time

Tearing

25. Never 0% 50% 100% All the time

SYMPTOM RELIEF

Please circle **how much pain relief** you have experienced since the last visit:

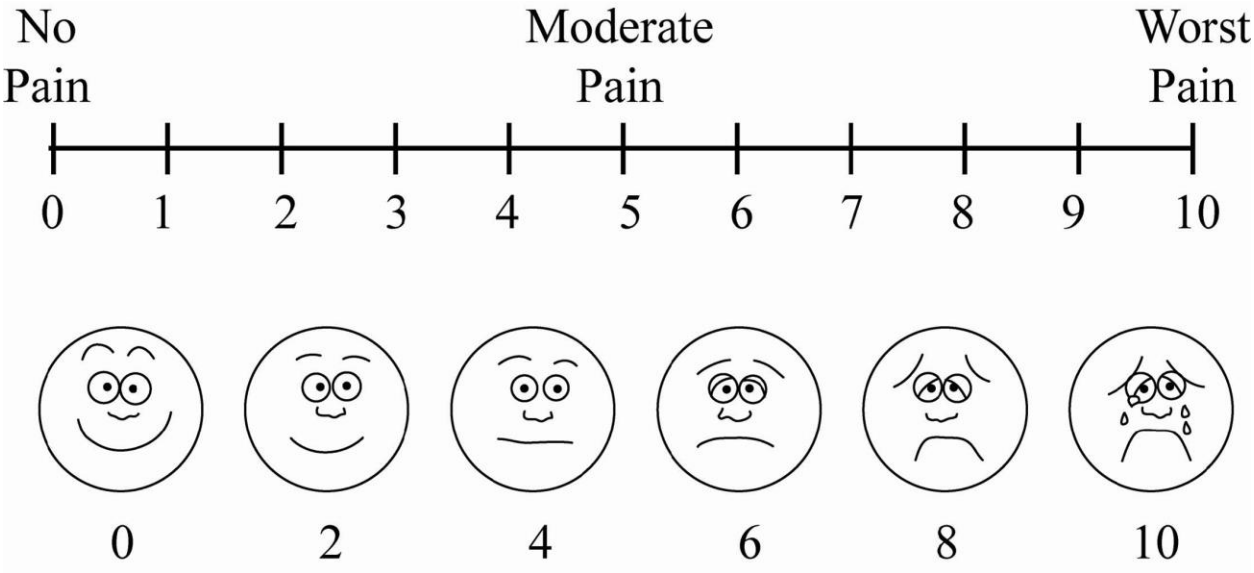
Eye pain

26. No relief 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete relief ☐ N/A

Non-eye pain (face/head)

27. No relief 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete relief ☐ N/A

Appendix IV: Visual Analogue Scale questionnaire



Appendix V: IDEEL QoL questionnaire

Daily Activities

- The following is a list of day-to-day activities that you may or may not have participated in OVER **THE LAST TWO WEEKS.**
- If you participated in the activity, please choose how often you were **limited in or stopped doing** the activity **BECAUSE OF YOUR DRY EYES**.
- Choose 'I did not perform this activity due to reasons OTHER than dry eye' if you did not take part in the activity for reasons other than your dry eyes.
- Please choose only one box per question.

OVER THE LAST TWO WEEKS, how limited were you in doing the following activities **BECAUSE OF YOUR DRY EYES**?	I did not do this activity for reasons **OTHER** than my dry eyes/Not applicable (5)	**OVER THE LAST TWO WEEKS I was limited BECAUSE OF MY DRY EYES:**					
		None of the time (5)	A little of the time (4)	Some of the time (3)	Most of the time (2)	All of the time (1)	I can **no longer** do this activity **due to my dry eyes** (0)
1. Doing close work in the **morning or afternoon** (such as crossword puzzles, reading, looking at a computer, and/or sewing)	☐	☐	☐	☐	☐	☐	☐
2. Doing close work in the **evening or at night**	☐	☐	☐	☐	☐	☐	☐
3. Driving	☐	☐	☐	☐	☐	☐	☐
4. Being around and/or using scented products (such as cologne or hairspray)	☐	☐	☐	☐	☐	☐	☐
5. Working on a computer	☐	☐	☐	☐	☐	☐	☐
6. Going somewhere where there is tobacco smoke	☐	☐	☐	☐	☐	☐	☐

OVER THE LAST TWO WEEKS, how limited were you in doing the following activities **BECAUSE OF YOUR DRY EYES**?	I did not do this activity for reasons **OTHER** than my dry eyes/Not applicable (5)	**OVER THE LAST TWO WEEKS I was limited BECAUSE OF MY DRY EYES:** None of the time (5)	A little of the time (4)	Some of the time (3)	Most of the time (2)	All of the time (1)	I can **no longer** do this activity **due to my dry eyes** (0)
or being around someone who smokes							
7. Wearing contact lenses	☐	☐	☐	☐	☐	☐	☐
8. Wearing make-up near or on my eyes	☐	☐	☐	☐	☐	☐	☐
9. Flying on an airplane	☐	☐	☐	☐	☐	☐	☐

Feelings

The following questions ask about how dry eye affected your mood and social life **OVER THE LAST TWO WEEKS**. Please choose how **often** you experienced each **feeling BECAUSE OF YOUR DRY EYES**. Please choose only one box per question.

OVER THE LAST TWO WEEKS, how often do you have each of the following feelings **BECAUSE OF YOUR DRY EYES**?	**OVER THE LAST TWO WEEKS**, I experienced this feeling **BECAUSE OF MY DRY EYES**: None of the time (4)	A little of the time (3)	Some of the time (2)	Most of the time (1)	All of the time (0)

OVER THE LAST TWO WEEKS, how often do you have each of the following feelings **BECAUSE OF YOUR DRY EYES**?	**OVER THE LAST TWO WEEKS**, I experienced this feeling **BECAUSE OF MY DRY EYES**:				
	None of the time (4)	A little of the time (3)	Some of the time (2)	Most of the time (1)	All of the time (0)
10. Irritability	☐	☐	☐	☐	☐
11. Impatience	☐	☐	☐	☐	☐
12. Feeling sad	☐	☐	☐	☐	☐
13. Worry that my dry eyes will get worse	☐	☐	☐	☐	☐
14. Feeling annoyed	☐	☐	☐	☐	☐
15. Feeling like my eyes do not look nice	☐	☐	☐	☐	☐
16. Feeling like I have to make adjustments to my life	☐	☐	☐	☐	☐
17. Feeling different from other people because of my dry eyes	☐	☐	☐	☐	☐
18. Feeling like I am always aware of my eyes	☐	☐	☐	☐	☐
19. Feeling older than I really am	☐	☐	☐	☐	☐
20. Feeling like people look at me and think I am fine when I'm not	☐	☐	☐	☐	☐
21. Feeling like there is nothing I can do for my dry eyes	☐	☐	☐	☐	☐

Work

22. Are you currently working?

☐ Yes If "Yes," please read the instructions below.

☐ No

The following questions ask about how often your dry eyes affected your work life **OVER THE LAST TWO WEEKS**. Please choose how **often** you experienced the following situations **at work BECAUSE OF YOUR DRY EYES**. Please choose only one box per question.

	OVER THE LAST TWO WEEKS I experienced the following situation at work **BECAUSE OF MY DRY EYES:**				
OVER THE LAST TWO WEEKS, how often did you experience the following situations at work **BECAUSE OF YOUR DRY EYES**?	None of the time (4)	A little of the time (3)	Some of the time (2)	Most of the time (1)	All of the time (0)
23. Feeling distracted	☐	☐	☐	☐	☐
24. Feeling like I couldn't concentrate	☐	☐	☐	☐	☐
25. Having to take a break from work	☐	☐	☐	☐	☐
26. Having to change the way I work (such as the way I read, look at a computer, or work outside)	☐	☐	☐	☐	☐
27. Having to change my work environment (such as how close I am to an air conditioning or heating vent)	☐	☐	☐	☐	☐

Thank you for finishing this questionnaire.
Please make sure that you answered every question.

Appendix VI: Ocular Tolerability and Compliance Questionnaire

After you used the TrueTear® neurostimulation, how intensely have you experienced the following symptoms?

Itching

Right Eye: None Trace Mild Moderate Severe

Left Eye: None Trace Mild Moderate Severe

Burning Sensation

Right Eye: None Trace Mild Moderate Severe

Left Eye: None Trace Mild Moderate Severe

Foreign Body Sensation

Right Eye: None Trace Mild Moderate Severe

Left Eye: None Trace Mild Moderate Severe

Have you experienced any other symptoms after undergoing the study tests?

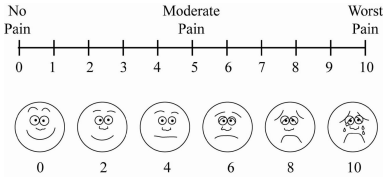
YES NO

If yes, which one(s)_____
_____

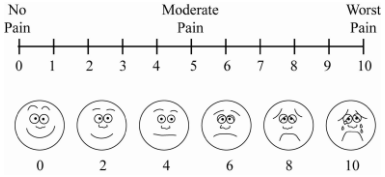
Appendix VII: Diary Recording (Sample Pages):
(Page 1):
(may be replicated for each ITN use)

Date: **Time:**

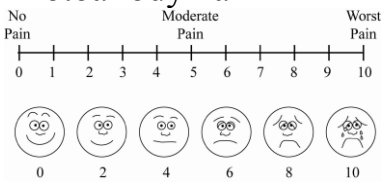
1. Before ITN use:
   Discomfort



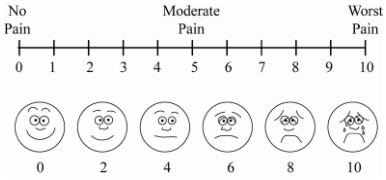
   Pain



   Photosensitivity/
   Photoallodynia

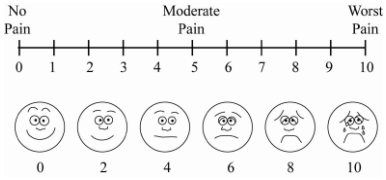


2. After ITN use:
   a. Discomfort



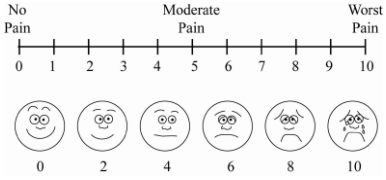
   after ____ mins of use

   Pain



   after ____ mins of use

   Photosensitivity/
   Photoallodynia



   after ____ mins of use

3. Duration of ITN use needed:_____ minutes
4. Number of times ITN use was needed/day: _____
5. Duration of symptom-free period after ITN: _____

(Page 2)
(to be filled out for each day of the study)

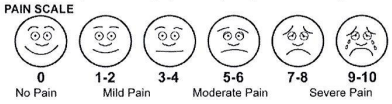
Date:

Ocular Pain Assessment Survey (OPAS) © 2013 Massachusetts Eye and Ear Infirmary

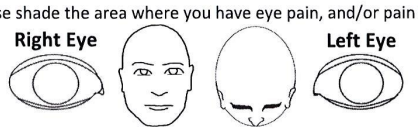
Please fill this form **only if** you HAVE EYE/FACIAL PAIN today or HAVE FILLED THIS FORM BEFORE

[Patient information sticker]

1. Please rate the overall severity of your pain today: (0= no pain, 10= worst pain ever)



2. On the diagram below, please shade the area where you have eye pain, and/or pain in the face and head region.



3. Do you have any longstanding pain elsewhere in your body? ☐ NO If yes, please state where:_____

QUALITY OF LIFE (QOL)

Please circle one number that describes how much your pain has interfered with/affected the following:

13.	Reading and/or Computer use: Not at all	0	1	2	3	4	5	6	7	8	9	10	Completely ☐ N/A
14.	Driving and/or Watching TV: Not at all	0	1	2	3	4	5	6	7	8	9	10	Completely ☐ N/A
15.	General activity (walking, doing house chores): Not at all	0	1	2	3	4	5	6	7	8	9	10	Completely ☐ N/A
16.	Mood: Not at all	0	1	2	3	4	5	6	7	8	9	10	Completely ☐ N/A
17.	Sleep: Not at all	0	1	2	3	4	5	6	7	8	9	10	Completely ☐ N/A
18.	Enjoying life/Relations with other people: Not at all	0	1	2	3	4	5	6	7	8	9	10	Completely ☐ N/A

Please circle the percentage of time you spend thinking about your **eye pain**:

19. Not at all — 0% — 50% — 100% — All the time

AGGRAVATING FACTORS

Please circle how much your **pain is increased** when exposed to:

20. Wind, dry air, heat, air conditioning: No change — 0% — 50% — 100% — Severe increase

21. Volatile chemicals (cleaning agents, fumes, cosmetic fragrances): No change — 0% — 50% — 100% — Severe increase

ASSOCIATED FACTORS

Please circle **how often** your eye pain is accompanied by the following symptoms:

22. Redness: Never — 0% — 50% — 100% — All the time

23. Burning: Never — 0% — 50% — 100% — All the time

24. Sensitivity to light: Never — 0% — 50% — 100% — All the time

25. Tearing: Never — 0% — 50% — 100% — All the time