NCT 03827564

Study ID: 1919-802-019

Title: Goblet Cell Degranulation Produced by Nasal Neurostimulation: A Randomized, Controlled Study in Patients with Dry Eye Disease

Protocol Date: MARCH 4, 2019

Title Page

Protocol Title: Goblet Cell Degranulation Produced by Nasal Neurostimulation: A Randomized, Controlled Study in Patients with Dry Eye Disease

Protocol Number: 1919-802-019

Product: Intranasal Tear Neurostimulator (ITN) [TrueTear®]

Brief Protocol Title: Goblet Cell Degranulation Produced by ITN in DED

Development Phase: Post-Market

Sponsor Name: Allergan, Inc.

Legal Registered Address:
2525 Dupont Drive, Irvine, CA 92612, USA

Manufacturer: Allergan

Regulatory Agency Identifying Number: NCT to be added (in progress)

Serious Adverse Event Reporting:
[redacted]

Allergan Device Medical Safety Physician Contact Information:
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Allergan, Inc.

Refer to the final page of this protocol for electronic signature and date of approval.

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1. Protocol Summary

1.1. Synopsis

Structure: Single-center, prospective, randomized, parallel-group, open-label, controlled study

Duration: 30 to 60 days

Study Intervention Groups: Intranasal Tear Neurostimulator (ITN) [TrueTear®]

Control: ITN device applied extranasally

Dosage/Dose Regimen: Single intranasal or extranasal application of the ITN for approximately 3 minutes

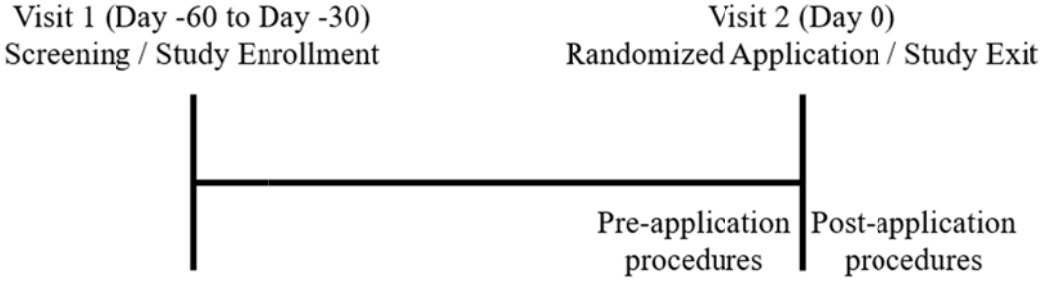
Randomization/Stratification: Randomization (2:1) to either intranasal or extranasal application of the ITN

Visit Schedule: This study consists of 2 visits, a Screening Visit and a randomized Application Visit/study exit (Day 0), separated by up to 60 days.

1.2. Schema

The study schema is provided in Figure 1-1.

Figure 1-1 Study Schema



1.3. Schedule of Activities

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2. Introduction

The Intranasal Tear Neurostimulator (ITN; TrueTear®), was granted a de novo petition by the US FDA on May 17, 2018 ([redacted]) with the following indications for use:

- The TrueTear ITN provides a temporary increase in tear production during neurostimulation to improve dry eye symptoms in adult patients with severe dry eye symptoms.

2.1. Study Rationale

The ITN delivers small electrical currents to the nasal cavity, stimulating the anterior ethmoidal branch of the trigeminal nerve, leading to activation of the nasolacrimal reflex pathway responsible for basal and bolus tear production. Numerous studies have been conducted to demonstrate that tear production is significantly increased during application of the ITN.

Tears are a complex aqueous fluid composed of proteins, lipids, and mucins. As the chemical composition of tears is essential for their optimized function, it was of interest to determine whether or not tears produced during application of the ITN were diluted (ie, reflex tears). Studies conducted to date have demonstrated equivalent lipid and protein concentrations in tears collected immediately following application of the ITN compared to baseline. In addition, mucin secretion stimulated by application of the ITN was suggested in a pilot study (OCUN-003). Specifically, a significantly higher ratio of degranulated to non-degranulated conjunctival goblet cells post-ITN stimulation was found, suggestive of mucin release.

This study aims to build on the data collected in the pilot study (OCUN-003) to verify that mucin secretion from goblet cells is stimulated with application of the ITN. These data would further support the conclusion that the tears stimulated with application of the ITN are representative of a complete basal tear as opposed to a diluted reflex fluid.

2.2. Background

DED is defined as a multifactorial disorder of the ocular surface characterized by loss of tear film homeostasis and ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (Craig 2017). An estimated 25 million Americans are reported to have DED, making DED one of the most common reasons patients seek care with their eye care professional (Behrens 2006, DEWS 2007).

Signs of dry eye include ocular surface damage, reduced tear volume, delayed tear clearance, abnormal tear osmolarity and decreased tear film break-up time. Accompanying symptoms can include dryness, grittiness, burning, stinging, discomfort, photophobia and blurry or fluctuating vision. These symptoms are typically worse later in the day and can be triggered or exacerbated by environmental conditions such as low humidity or wind.

While progress continues to further our understanding of the underlying pathology of DED and corresponding potential targets for treatment intervention, to date treatment of DED remains a large unmet medical need (Bielory 2016, Wolffsohn 2017).

Neuromodulation represents a therapeutic strategy for directly stimulating peripheral neuronal connections to attenuate neuronal dysfunction and alleviate symptoms in treating DED. The ITN acts via stimulation of the nasociliary nerve (peripheral branch of the trigeminal nerve), activating the nasolacrimal reflex through a parallel pathway, acting directly on multiple components of the LFU such as lacrimal glands, goblet cells, and meibomian glands (LeDoux 2001, Dartt 2009, Bron 2017). Therefore, not only is aqueous production stimulated, but also secretion of protein, mucin, and meibum.

It was recently demonstrated that application of the ITN can trigger both an increase in tear volume and goblet cell degranulation in patients with DED (Gumus 2017). Moreover, Dieckmann et al demonstrated a significant reduction in the area and size of goblet cells immediately after stimulation with ITN, suggesting an increase in mucin secretion (Dieckmann 2017). Data reported by Green 2017 and Woodward 2017 have concluded that protein and lipid concentration of tears collected post-application of the ITN is equivalent to that of tears collected pre-stimulation, suggesting that the ITN promotes release of proteins from secretory granules in the lacrimal gland and meibum (lipid) from Meibomian glands. Lastly, Pondelis 2017 demonstrated a decrease in the area and perimeter of meibomian glands immediately after 3-minute application of the ITN, reinforcing the suggestion that the ITN can stimulate lipid secretion. These studies to date demonstrate a clear effect of neurostimulation with ITN on all major components of tear film, thus offering a promising new approach for treatment of DED.

2.2.1. Device Description

The ITN is a non-surgical device intended for the application of low level electrical stimulation to sensory neurons of the nasal cavities to increase tear production and improve dry eye symptoms.

The device consists of four distinct non-sterile subassemblies, as listed below and shown in Figure 2-1:

1. A reusable base unit which produces the electrical stimulation waveform.
2. A disposable tip that provides the contact surface for the stimulation to the intranasal skin and mucosa.
3. A reusable charger which recharges the sealed battery inside the base unit.
4. A reusable cover to protect the disposable tip.

Figure 2-1 Intranasal Tear Neurostimulator System Components

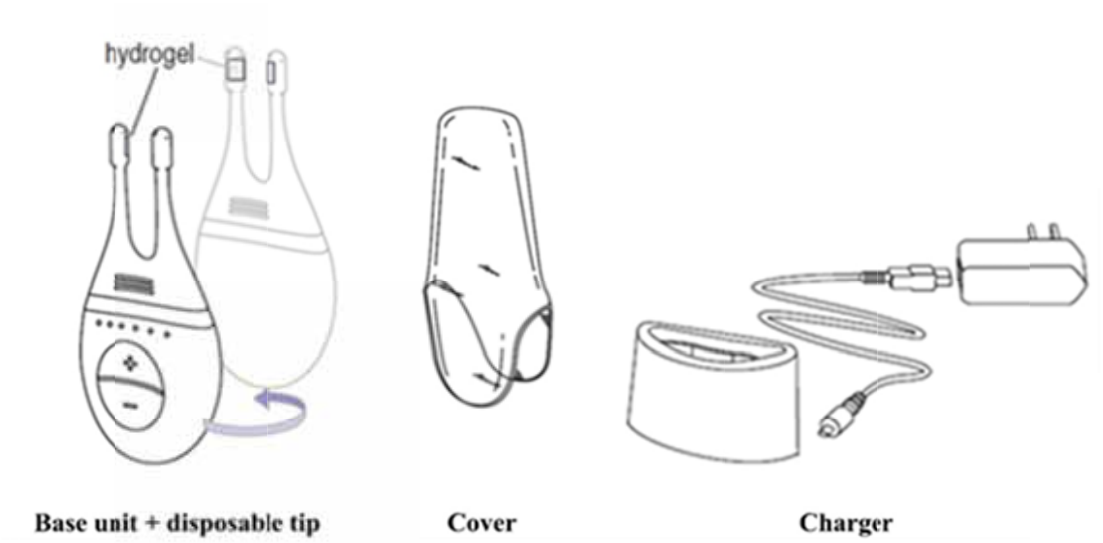


Figure 2-2 shows the correct application of the device.

Figure 2-2 Correct Application of the Intranasal Tear Neurostimulator

[redacted]

the material used in contact lenses) that contacts the inside of the nose to provide stimulation. Each tip may be used up to 48 hours. After 48 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.

[redacted]

2.2.2. Extranasal Control Description

The comparator arm in this study is an identical, active ITN device which will be applied extranasally as shown in Figure 2-3. Participants will be instructed to place the tips of the device on the tip of the nose, hydrogel side down.

Figure 2-3 Schematic Showing Location of Tips for Extranasal Control Application

2.3. Benefit/Risk Assessment

The treatment of DED remains a large unmet medical need. Patients with DED generally present with ocular surface epithelial damage attributed to either or both inadequate tear production and tear film instability. These pathophysiological changes are generally accompanied by patient reported symptoms of ocular surface discomfort, often described as dryness, burning, pain, grittiness and blurred vision.

The benefit of the ITN is the replenishment of endogenous tears leading to subsequent improvement in ocular surface health and dry eye symptoms, thus providing a valuable treatment option for patients with DED.

To date, application of the ITN is safe and well-tolerated and there were no unexpected safety concerns. No SADEs have been observed. The most frequently reported ADEs were all related to nasal findings consisting of: nasal pain/discomfort (reported as aching, burning, discomfort, pain, or soreness), transient intranasal electrical discomfort, nosebleed, and nasal congestion.

3. Objectives and Endpoints

Objectives	Endpoints
Primary: To evaluate the change in goblet cell degranulation following randomized application of device • Immunofluorescence staining of cells obtained via impression cytology	• Mean change in goblet cell degranulation post-intranasal application of the ITN at the Application Visit compared to without-intranasal application of the ITN at the Screening Visit.
[redacted]	

[redacted]

4. Study Design

4.1. Overall Design

This is a prospective, randomized, controlled, parallel-group, open-label, single-center study in participants with DED.

This study consists of 2 visits: Screening and the Application Visit (Day 0). A study schema is located in Section 1.2 and the Schedule of Visits and Procedures is located in Section 1.3.

Participants will be randomized (in a 2:1 ratio) at Screening to either intranasal or extranasal acute (single) application of the ITN, which they will apply accordingly for approximately 3 minutes during the Application Visit. Approximately 36 participants with DED will be enrolled at a single site in the United States.

At Screening, and prior to any testing, participants will be provided with an IRB-approved ICF which they will have the opportunity to review and ask questions about before written consent is obtained. The Screening Visit should occur 30 to 60 days prior to the Application Visit.

The Application Visit will be separated into pre-ITN application and post-ITN application assessments. CDVA, slit-lamp examination, TMH measurement via OCT, and tear collection will occur at least 45-minutes prior to ITN application, and will be performed again following ITN application. Impression cytology will be performed following these procedures after ITN application.

Safety measures will be assessed before and after ITN application at the Application Visit, including CDVA and slit-lamp biomicroscopy. AEs will be queried prior to study exit.

4.1.1. Clinical Hypotheses

Post-application of the ITN, a greater percentage of goblet cells will be degranulated relative to pre-application of the ITN as measured by immunofluorescence staining of cells collected by impression cytology.

4.2. Scientific Rationale for Study Design

The ITN stimulates the anterior ethmoidal branch of the trigeminal nerve in the upper nasal cavity, leading to an increase in tear production with concomitant increases in proteins and lipids. In addition, evidence suggests degranulation of conjunctival goblet cells occurs post-application of the ITN.

Data from Study OCUN-014 demonstrated that tera film protein and lipid concentrations post-ITN application were equivalent to those collected prior to ITN application. In a pilot study (OCUN-003), participants with DED were assigned to both intranasal and extranasal application of the ITN for 3 minutes in random sequence. Results suggested that goblet cell degranulation post-intranasal application of the ITN was greater than prior to intranasal application, and that intranasal application demonstrated significantly greater goblet cell degranulation relative to

extranasal application. In both OCUN-003 and OCUN-014, ITN application demonstrated a statistically significant increase in tear production as measured by TMH. While these and other studies have provided support for the ITN's putative mechanisms of action, the effect of stimulation on ocular surface pro-inflammatory cytokines has not been clearly established.

The rationale for this study is to confirm the ITN's effect on goblet cell release of mucin and to explore its effect on tear film cytokine concentration.

4.3. Justification for Treatment Administration

The ITN will be applied in accordance with the instructions for use.

4.4. End of Study Definition

The end of study is defined as the date of the Application Visit for the last participant in the study, or the AE query on this day for the last participant in the study.

A participant is considered to have completed the study if he/she has completed both the Screening Visit and Application Visit or exited early from the study.

5. Study Population

The study population will consist of adult male and female participants with objective and subjective evidence of DED. The study will be conducted at a single site and will enroll up to 36 participants who have provided written informed consent and have met the eligibility criteria below.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participants must be at least 22 years of age, at the time of signing informed consent
[redacted]	
3.	**Sex**
3.01	Male and female
4.	**Informed Consent**
4.01	Capable of giving verbal and signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
4.02	Written informed consent from the participant or legally authorized representative has been obtained prior to any study-related procedures
4.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable. (eg, Written Authorization for Use and Release of Health and Research Study Information for the United States)
5.	**Other**

5.01	Have not worn contact lenses for at least 7 days prior to the Screening Visit and are willing to forego the use of contact lenses for the duration of the study
5.02	The participants should be literate, able to speak English, and able to complete questionnaires independently

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	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
1.02	Have had nasal or sinus surgery (including history of application of nasal cautery) or significant trauma to these areas
[redacted]	
1.04	Have had a corneal transplant in either or both eyes
[redacted]	
1.06	Have a cardiac demand pacemaker, implanted defibrillator, or other active implanted metallic or active implanted electronic device in the head
1.07	Have a systemic condition or disease not stabilized or judged by the investigator to be incompatible with participation in the study
2.	**Prior/Concomitant Therapy**

[redacted]

2.02	Have used contact lenses within 7 days prior to the Screening Visit or anticipate the use of contact lenses at any time during the duration of the study

[redacted]

3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study

[redacted]

[redacted]

5.	**Other**
5.01	Females who are pregnant, nursing an infant, or planning a pregnancy during the study. WOCBP who do not agree to use a reliable form of contraception throughout the study.

[redacted]

5.3. Lifestyle Considerations

No lifestyle consideration restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo(s), or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Study Intervention	**TrueTear Intranasal Tear Neurostimulator (ITN)** – Intranasal Application	**TrueTear Intranasal Tear Neurostimulator (ITN)** – Extranasal Application (Control)
Number and Timing of Interventions	Single application at Application Visit	Single application at Application Visit
Manufacturer	Allergan	Allergan

6.1.1. Instructions for Use and Administration

Intranasal Application

At the Application Visit, participants will be trained on the application of the ITN based on approved instructions for use and instructed to administer a single stimulation for approximately 3 minutes. A sponsor representative may be present for training purposes.

[redacted]

6.2. Preparation/Handling/Storage/Accountability

[redacted]

6.3. Measures to Minimize Bias: Randomization and Blinding

At the time of randomization at the Screening Visit, qualified participants will be randomly assigned in a 2:1 ratio to receive either intranasal ITN or extranasal (control) ITN stimulation at the Application Visit. Electronic randomization methods will be used to create a randomization scheme prior to study start.

6.4. Concomitant Therapy

The use of any concomitant medication, prescription or OTC, is to be recorded on the participant's CRF at each visit along with the reason the medication is taken.

At both visits, site staff will question each participant specifically on the use of concomitant medications. Site staff must notify the sponsor immediately if a participant consumes any concomitant medications not permitted by the protocol. Participants who use(d) prohibited concomitant medications may be discontinued from the study at the discretion of the investigator or the sponsor.

6.4.1. Washout Before the Study

Contact lens wear must be discontinued at least 7 days prior to the Screening Visit.

6.4.2. Rescue Medicine

Rescue medicine is not applicable.

6.4.3. Prohibited Interventions During the Study

The decision to administer a prohibited intervention is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited intervention is administered. Use of the following interventions is prohibited during the study:

- Contact lens wear within 7 days prior to the Screening Visit
- Punctal or intracanalicular plugs throughout study duration
- Initiation or change in dosing of any ophthalmic cyclosporine preparations (eg, RESTASIS) or lifitegrast 5% ophthalmic solution (Xiidra), any topical ocular glaucoma drop, any topical ocular antihistamine drop, or any artificial tear or lubricant ≥ 1 month prior to the Screening Visit, or anticipated change during the study. Drops continuing at stable dosing (defined as having a start date ≥ 30 days prior to Screening) may continue to be used. **However, drops should not be used within 2 hours of either study visit.**

- Initiation or anticipated change in dosing of any systemic medication (OTC, herbal, prescription, or nutritional supplements), which may affect dry eye or vision, ≤ 1 month prior to the Screening Visit. Such medications may include, but are not limited to, the following: Flax seed oil, fish oil, omega-3 supplements, cyclosporine, antihistamines, cholinergic agents, anticholinergics, antimuscarinics, beta blocking agents, tricyclic antidepressants, phenothiazines, estrogen, progesterone, and other estrogen derivatives.
- Use of lid-heating therapy (ie, LipiFlow, iLUX, etc.), meibomian gland probing, or therapeutic meibomian gland expression in either eye within 3 months prior to the Screening Visit.

6.5. Intervention after the End of the Study

No interventions after the end of the study are planned.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

7.1. Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- Participants will be discontinued if they use any prohibited intervention described in Section 6.4.3.
- For participants who discontinue from the study early, every effort should be made to have these participants return to the clinical center for completion of the exit visit. AEs leading to participant early discontinuation must be followed-up as appropriate.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- See the Schedule of Visits and Procedures (Section 1.3) for data to be collected at the time of study discontinuation (early exit).

7.2.1. Reasons for Discontinuation: Acceptable Terms

A premature discontinuation will occur if a participant who signs the ICF and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Completed	Failure to meet randomization criteria
Lost to follow-up	Progressive disease
Non-compliance	Recovery
Other	Technical problems
Physician decision	Withdrawal by parent/guardian
Pregnancy	
Protocol deviation	
Screen failure	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

8. Study Assessments and Procedures

Please see the schedule of activities (Section 1.3) for the Schedule of Visits and Procedures (Table 1–1). The overall study design is illustrated in Figure 1-1. The visit schedule includes 2 visits: Screening and Application Visits. Study procedures must be performed in sequence as described in the Schedule of Visits and Procedures.

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Visits and Procedures, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The study will be discussed with the participant and a participant wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The participants must also give authorization and other written documentation in accordance with local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.
- Each participant who provides informed consent will be assigned a participant number that will be used on participant documentation throughout the study.
- WOCBP must have a negative pregnancy test result prior to entry into the study, and prior to ITN device application at the Application Visit.
- A participant is considered to have entered the study at the time of randomization during the Screening Visit (Day -60 to -30). See Section 6.3 for the method for assignment to study intervention groups/randomization.

8.1. Visit 1 – Screening (Days -60 to -30)

[redacted]

8.2. Visit 2 – Application Visit (Day 0)

[redacted]

[redacted]

8.3. Effectiveness Assessments

Effectiveness assessments are goblet cell degranulation, TMH, and tear film cytokine concentration.

Timing and measurement details are provided in Table 8–1.

Table 8–1 Effectiveness Assessments

Assessment	Timing	Measurement
Goblet cell degranulation	• Screening Visit • Application Visit after randomized ITN application	Impression cytology followed by immunofluorescence staining
[redacted]		

[redacted]

[redacted]

8.4. Safety Assessments

8.4.1. Corrected Distance Visual Acuity

CDVA is performed at the Screening Visit and Application Visit. At the Application Visit, it is performed both prior to and after ITN stimulation. Any changes from baseline should be evaluated for possible reporting as an AE.

[redacted]

[redacted]

[redacted]

8.5. Other Assessments

8.5.1. Urine Pregnancy Test

WOCBP will have a urine pregnancy test performed at Screening and the Application Visit. Additional details are provided in Appendix 6.

[redacted]

[redacted]

[redacted]

[redacted]

8.5.5. Intranasal Exam (Screening Visit Only)

[redacted]

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

8.6. Adverse Events/Adverse Device Effects and Serious Adverse Events/Serious Adverse Device Effects

The definitions of an AE/ADE or SAE/SADE can be found in Appendix 2.

AEs/ADEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE/ADE or SAE/SADE and remain responsible for following up AEs/ADEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

8.6.1. Time Period and Frequency for Collecting Adverse Event/Adverse Device Effect and Serious Adverse Event/Serious Adverse Device Effect Information

All SAEs/SADEs from the signing of the ICF will be collected at the timepoints specified in the Schedule of Visits and Procedures (Section 1.3), and as observed or reported spontaneously by study participants.

All AEs/ADEs from the signing of the ICF will be collected at the timepoints specified in the Schedule of Visits and Procedures (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent, will be recorded in the AE section of the CRF.

All SAEs/SADEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE/SADE data to the sponsor within 24 hours of it being available.

The investigator is not obligated to actively seek AE/ADE or SAE/SADE information after conclusion of study participation. However, if the investigator learns of any SAE/SADE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs/ADEs and SAE/SADEs and the procedures for completing and transmitting SAE/SADE reports are provided in Appendix 2.

8.6.2. Method of Detecting Adverse Events/Adverse Device Effects and Serious Adverse Events/Serious Adverse Device Effects

Care will be taken not to introduce bias when detecting AEs/ADEs and/or SAEs/SADEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE/ADE occurrences.

8.6.3. Follow-up of Adverse Events/Adverse Device Effects and Serious Adverse Events/Serious Adverse Device Effects

After the initial AE/ADE/SAE/SADE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/ADEs/SAEs/SADEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Allergan to elucidate the nature and/or causality of the AE/ADE or SAE/SADE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study, the investigator will provide Allergan with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE/SADE data to Allergan within 24 hours of receipt of the information.

8.6.4. Regulatory Reporting Requirements for Serious Adverse Events/Serious Adverse Device Effects

- Prompt notification by the investigator to the sponsor of an SAE/SADE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to the investigator as necessary.
- An investigator who receives an investigator safety report describing an SAE/SADE or other specific safety information (eg, summary or listing of SAEs/SADEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.6.5. Pregnancy

- If a female study participant becomes pregnant, the investigator should inform Allergan within 24 hours of confirming the pregnancy [redacted] Best practices are to be followed to ensure the welfare of the participant and the fetus.
- Once the pregnancy has reached term, the second page of the Pregnancy Surveillance Form concerning outcome is to be completed by the investigator and submitted to the sponsor. The sponsor will contact the investigator to obtain information about the pregnancy outcome.

- Hospitalization for a normal delivery or elective abortion of a normal fetus does not constitute an SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious.

Additional details are provided in Appendix 6.

8.6.6. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes of evaluating goblet cell degranulation produced by nasal neurostimulation. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident, deficiency, or malfunction that occur during the study with such devices, using the Device Deficiency Form.

The definitions of a medical device incident and a device deficiency can be found in Appendix 7.

Incidents fulfilling the definition of an AE/ADE/SAE/SADE will also follow the processes outlined in Section 8.6.3 and Appendix 2 of the protocol.

8.6.6.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents, deficiencies, or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device incidents is provided in Appendix 7.

8.6.6.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE/SAE will be followed and reported in the same manner as other AEs (see Section 8.6.3). This applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.6.6.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.

- The Medical Device Incident Report Form will be sent to the sponsor by email. If email is unavailable, then fax should be used.
- The same individual will be the contact for the receipt of medical device reports and SAEs.

8.6.6.4. Regulatory Reporting Requirements for Medical Device Incidents and Deficiencies

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8.6.7. Adverse Events of Special Interest

AEs related specifically to impression cytology, including:

- Conjunctival hyperemia
- Chemosis (swelling)
- Discomfort (foreign body sensation, pain)
- Allergic reaction

8.6.8. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study intervention
- Wrong dose (including dosing regimen, strength, form, concentration, or amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

8.7. Treatment of Overdose

Treatment of overdose is not applicable to this ophthalmology device study.

8.8. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.9. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

[redacted]

8.11. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

For the primary effectiveness analysis of mean change in goblet cell degranulation post-intranasal application of the ITN compared to without-intranasal application of the ITN, the null and alternative hypotheses are as follows:

- Null hypothesis: Intranasal application of the ITN is equally effective in improving mucin secretion, as measured by the mean change in goblet cell degranulation, post-ITN application at the Application Visit versus without-ITN application at the Screening Visit.
- Alternative hypothesis: Intranasal application of the ITN is not equally effective in improving mucin secretion, as measured by the mean change in goblet cell degranulation, post-ITN application at the Application Visit versus without-ITN application at the Screening Visit.

9.2. Sample Size Determination

Approximately 36 participants are required to apply randomized device and complete the Application Visit, in which 24 participants will be in the intranasal ITN application group and 12 will be in the extranasal ITN application group. Approximately 50 participants may be enrolled to meet this goal.

It is assumed that the standard deviation of the change in goblet cell degranulation post-ITN application versus pre-ITN application is 4.52. With 24 participants in the intranasal ITN application group, it is estimated that the accuracy of a half width of the 95% CI is approximately 1.8.

9.3. Populations for Analyses

The analysis populations will consist of participants as defined below:

- The ITT population includes all randomized participants. Participants will be summarized according to the randomized study intervention.
- The safety population includes all treated participants who receive ≥ 1 administration of study intervention. Participants will be summarized according to the study intervention they actually receive.

[redacted]

9.4.1. Effectiveness Analyses

The effectiveness analyses will be based on the ITT population. The ITT population is considered as the primary analysis population.

9.4.1.1. Primary Effectiveness Endpoint

- The mean change in goblet cell degranulation post-intranasal application of the ITN at the Application Visit compared to without-intranasal application of the ITN at the Screening Visit.

[redacted]

9.4.1.3. Primary Effectiveness Analyses

The primary effectiveness variable will be the number of goblet cells degranulated in the study eye. The study eye will be the eye with the lower tear meniscus height prior to the application or, if both eyes are equal, the right eye.

The primary effectiveness endpoint will be the mean change in goblet cell degranulation post-intranasal application of the ITN at the Application Visit compared to without-intranasal application of the ITN at the Screening Visit. Summary statistics of count, mean, median, minimum, and maximum will be provided to evaluate the change in the number of degranulated goblet cells and a 95% CI will also be provided.

9.4.1.4. Analyses on Exploratory Effectiveness Endpoints

The other exploratory effectiveness variables will be descriptively summarized by ITN application groups. The continuous variables will be summarized with count, mean, standard deviation, median, minimum, and maximum. The categorical variables will be presented with the count and percentage in each category.

The details of the statistical analyses and summary methods on each exploratory endpoint will be provided in the SAP.

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population. The numbers and percentage of participants reporting AEs will be tabulated regardless of causality. Frequency of device and procedure related AEs, as well as AESIs will be summarized.

9.4.2.1. Adverse Events

An AE or ADE will be considered a TEAE/TEADE if:

- The AE or ADE began on or after the date of the first application of study intervention; or
- The AE or ADE was present before the date of the first dose of study intervention, but increased in severity or became serious on or after the date of the first application of study intervention

An AE or ADE that occurs more than 30 days after the last dose of study intervention will not be counted as a TEAE or TEADE.

A SAE or SADE will be considered a TESAE or TESADE if it is a TEAE that additionally meets any SAE criteria or if it is a TEADE and meets SADE criteria.

Throughout the course of the study, all AEs will be reported and monitored on an AE CRF, including event name, duration, seriousness, relatedness, severity, action taken, and outcome. If AEs occur, the first concern will be the safety of the study participants.

All events and device deficiencies are to be recorded on the corresponding CRF for the participant upon the site becoming aware of said event.

TEAEs and TEADEs will be coded with the MedDRA. The number of participants with TEAEs and TEADEs will be summarized by study intervention group for SOC and PT. TEAEs and TEADEs will also be summarized based on intensity and relationship to study intervention.

TESAEs and TESADEs will also be summarized by study intervention group for SOC and PT.

A listing of AEs, ADEs, and pregnancy test results will be also presented.

The definitions of AE/ADE and SAE/SADE can be found in Appendix 2.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH/ISO GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Posting Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the United States National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.
- The investigator must maintain accurate documentation (source data).
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, GCP: Consolidated Guidance and records must be attributable, legible, contemporaneous, original, and accurate.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study site will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between investigators and Allergan personnel. Authorship will be established prior to the writing of the manuscript.
- The sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
- For devices, an AE is defined in accordance with ISO 14155 as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.
- For devices, disease signs and symptoms that existed prior to the study intervention are not considered AEs.

Adverse Device Effect

- An ADE is defined in accordance with ISO 14155 as an AE related to the use of a medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error (per ISO 62366) or from intentional misuse of the medical device.

AE of Special Interest

An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

There are no AESIs identified for the study interventions. AESIs pertaining specifically to impression cytology are identified in Section 8.6.7.

Events Meeting the AE/ADE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease); for example: o The test result is associated with accompanying symptoms, and/or o The test result requires additional diagnostic testing or medical/surgical intervention, and/or o The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or o The test result is considered to be an AE by the investigator or sponsor. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/ADE or SAE/SADE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of effectiveness or failure of expected pharmacological action per se will not be reported as an AE/ADE or SAE/SADE. Such instances will be captured in the effectiveness assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AEs/ADEs or SAEs/SADEs if they fulfil the definition of an AE/ADE or SAE/SADE.

Events NOT Meeting the AE/ADE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE/ADE. Any abnormal test result that is determined to be an error does not require recording as an AE/ADE. • The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE/ADE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined in accordance with ISO 14155 as an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury, or 2. A permanent impairment of a body structure or a body function, or 3. Inpatient or prolonged hospitalization, or 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect
Serious Adverse Device Effect: A SADE is defined in accordance with ISO 14155 as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Adverse Device Effect:

An UADE is defined in accordance with 21 CFR 812.3 as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or 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 participants.

Recording and Follow-Up of AEs/ADEs and/or SAEs/SADEs

AE and SAE Recording

- When an AE/ADE or SAE/SADE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/ADE or SAE/SADE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Allergan in lieu of completion of the AE/ADE or SAE/SADE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Allergan. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Allergan.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE/SADE, NOT when it is rated as severe.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the device and/or study procedure. Causality should be assessed using the categories presented below:

- Not related: Clinical event of which the relationship to the device and/or procedure can be excluded, such as if the event is incompatible time relationship to study procedure and/or use of the device, involves a body part or organ not expected to be affected by the device or procedure, could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study device, and is not due to use error.
- Unlikely: Clinical event whose time relationship to use of the device and/or study procedure makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
- Possible: Clinical event with a reasonable time relationship to the use of the device and/or study procedure, but that could also be explained by concurrent disease or other drugs or chemicals. Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- Probable: Clinical event with a reasonable time relationship to the use of the device and/or study procedure, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Causal relationship: Clinical event with plausible time relationship to the use of the device and/or study procedure, is a known side effect of the product category the device belongs to or of similar devices and procedures; follows a known response pattern to the medical device; involves a body-site or organ that the device or procedures are applied to and/or influence; harm is due to error in use, and that cannot be explained by concurrent disease or other drugs or chemicals.

Reporting of SAEs/SADEs

SAE/SADE Reporting to Allergan
• All SAEs/SADEs that occur from the time the ICF is signed through to their final study visit must be entered into the CRF and reported to the sponsor. • Notify the sponsor immediately (within 24 hours) by fax using the Serious Adverse Event/Adverse Event of Special Interest Form for Devices. [redacted]

10.3. Appendix 3: Abbreviations

Abbreviation/Term	Definition
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
CAM	Cornea-Anterior Module
CDISC	Clinical Data Interchange Standards Consortium
CDVA	corrected distance visual acuity
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
DED	dry eye disease
ECG	electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	independent ethics committee
IRB	institutional review board
ISO	International Organization for Standardization
ITN	intranasal tear neurostimulator
ITT	intent-to-treat
LED	light-emitting diode
LFU	lacrimal functional unit
logMAR	logarithmic minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NEI	National Eye Institute
OCT	optical coherence tomography
OSDI	Ocular Surface Disease Index
OTC	over-the-counter

Abbreviation/Term	Definition
PT	preferred term
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEADE	treatment-emergent adverse device event
TEAE	treatment-emergent adverse event
TESADE	treatment-emergent serious adverse device advent
TESAE	treatment-emergent serious adverse event
TMH	tear meniscus height
UADE	unanticipated adverse device effect
WOCBP	women of childbearing potential

10.4. Appendix 4: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Progressive disease	A disease process that is increasing in extent or severity (NCI)

CDISC Submission Value	CDISC Definition
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.5. Appendix 5: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	Goblet Cell Degranulation Produced by Nasal Neurostimulation: A Randomized, Controlled Study in Patients with Dry Eye Disease
	Clinical Study Sponsor	Allergan, Inc.
	Trial Phase Classification	Post-market
	Trial Indication	Dry eye disease
	Trial Indication Type	Exploratory
	Trial Type	Efficacy Safety
	Trial Length	1 day, plus the Screening Visit 30 to 60 days prior to Day 0
	Planned Country of Investigational Site	United States
	Planned Number of Participants	36
	FDA-Regulated Device Study	Yes
	FDA-Regulated Drug Study	No
	Pediatric Study	No
Participant information	Diagnosis Group	Dry eye disease
	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	22
	Planned Maximum Age of Participants	N/A
	Sex of Participants	Male or female
	Stable Disease Minimum Duration	Not specified

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	Intranasal Tear Neurostimulator (ITN)
	Intervention Type	Device
	Pharmacological Class of Invest. Therapy	N/A
	Dose per Administration	3 minutes
	Dose Units	N/A
	Dosing Frequency	Once
	Route of Administration	Intranasal application of ITN
	Current Therapy or Treatment	No
	Added on to Existing Treatments	No
	Control Type	Extranasal application of ITN
	Comparative Treatment Name	ITN
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2
	Trial is Randomized	Yes
	Randomization Quotient	2:1 (intranasal to extranasal)
	Trial Blinding Schema	Open-label
	Stratification Factors	N/A
	Adaptive Design	No
	Study Stop Rules	None

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

WOCBP

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   [redacted]
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10–1.

Table 10–1 Highly Effective Contraceptive Methods

[redacted]

Female participants of childbearing potential are eligible to participate if they agree to use an acceptable method of contraception consistently and correctly.

Acceptable birth control methods that result in a failure of more than 1% per year include:

[redacted]

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test at Screening and also a negative test on Day 0.

Collection of Pregnancy Information:

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to Allergan within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to Allergan. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. [redacted]
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. [redacted] Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to Allergan as described in Section 8.6.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1 for the list of sponsor medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of Incidents

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate intervention.
- A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF.
- For incidents fulfilling the definition of an AE/ADE or an SAE/SADE, the appropriate AE/ADE or SAE/SADE CRF page will be completed as described in Appendix 2.
- The CRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE/ADE or SAE/SADE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

Device Deficiency

A device deficiency is defined in accordance with ISO 14155 as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

If a device deficiency occurs, the investigator will notify the sponsor using the fax number or email on the front page of the protocol. Device deficiencies shall be documented throughout the study and appropriately managed by the sponsor. The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SADE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

11. References

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Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
04-Mar-2019 15:23 GMT-080	[redacted]	Clinical Development Approval