TrueTear® Intranasal Tear Neurostimulator Professional Information Guide

Rx Only—Federal law restricts this device to sale by or on the order of a physician or properly licensed practitioner.

Proper patient training on use of the device is required before home use.

1 INDICATIONS FOR USE

The TrueTear® Intranasal Tear Neurostimulator (TrueTear® device) provides a temporary increase in tear production during neurostimulation to improve dry eye symptoms in adult patients with severe dry eye symptoms.

2 CONTRAINDICATIONS

The patient should not be prescribed the device if they have any of the following (these contraindications are also provided in the patient labeling):

- A cardiac demand pacemaker, implanted or wearable defibrillator, or other implanted metallic or electronic device in the head or neck
- A known hypersensitivity to the hydrogel device material that contacts the nasal mucosa
- Chronic or recurrent nosebleeds, a bleeding disorder, or another condition that can lead to increased bleeding

3 WARNINGS

The patient should be warned of the following (these warnings are also provided in the patient labeling):

- Only apply stimulation in a manner consistent with the instructions in this document.
- Do not apply stimulation in the presence of electronic monitoring equipment (eg, cardiac monitors, ECG alarms), which may not operate properly when the electrical stimulation device is in use.
- Do not apply stimulation when in the bath or shower.
- Do not apply stimulation while driving, operating machinery, or during any activity in which sneezing or watery eyes may put the user at undue risk of injury.
- Do not apply the device to the neck, chest, or areas other than the nose.
- Persistent use of stimulation in the presence of irritation of the target nasal tissue may cause injury.
- Operation in close proximity (eg, 3 feet or less) to shortwave or microwave therapy equipment may produce instability in the output of the device.
- Do not use the device in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide as there is a remote possibility (comparable to the risk of a mobile phone) it could ignite the gas.
- The TrueTear® device is limited only to the improvement in dry eye symptoms as the safety and effectiveness in the treatment of dry eye disease has not been established.
- In the pivotal clinical study, the safety and effectiveness of intranasal electrical stimulation was characterized over a 6-month period of time. The safety and effectiveness of the device for longer periods of use has not been established. Periodic evaluation of the nasal cavity is recommended if the device is to be used over a longer period of time.
- The clinical studies were not designed to evaluate any changes in nerve sensitivity.
- The safety of intranasal electrical stimulation has not been established in the following conditions/patient populations:
    - Pregnancy
    - Pediatric patients (ie, under 22 years of age)
    - Nasal or sinus surgery (including history of application of nasal cautery) or significant trauma
    - Severe nasal airway obstruction (eg, severe septal deviation or inferior turbinate hypertrophy) or vascularized polyp
    - Active, severe:
        - Systemic allergy
        - Chronic seasonal allergies
        - Rhinitis or sinusitis requiring treatment such as antihistamines, decongestants, oral or aerosol steroids
        - Untreated nasal infection
    - Disabling arthritis, neuropathy, severe dexterity impairment, or limited motor coordination affecting self-handling of the TrueTear® device
- Use of accessories, transducers, and cables other than those specified or provided by the manufacturer of this equipment could result in increased electromagnetic emissions or decreased electromagnetic immunity of this equipment and result in improper operation. Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the TrueTear® device. Otherwise, degradation of the performance of this equipment could result.

4 PRECAUTIONS

The patient should also be advised of the following (these precautions are also provided in the patient labeling):

- Before operating the device, the patient should consult their healthcare provider for instructions.
- If the patient feels pain, discomfort, or numbness in their nose with higher levels of stimulation or a longer duration of stimulation, they should reduce the level or the number of times they stimulate the nose. If symptoms persist, they must discontinue use and contact their provider.
- For proper operation and good hygiene, the disposable tip must be disposed of every 48 hours and replaced with a new tip.
- Remove any studs, nose rings, or other piercings from the nose prior to using the device.
- Ophthalmic prescription eye medications (eye drops, gels, or ointments) should not be used within 30 minutes before or after applying stimulation.
- Nasal sprays should not be used within 30 minutes before or after applying stimulation.
- Patients with suspected or diagnosed heart disease should follow precautions recommended by their providers.
- Keep this device out of the reach of children.
- Patients with a severe phobia of placing objects in the nose may not be able to effectively utilize this device.
- Clean as directed.
- Failure to replace the tip as directed will cause the device to not work properly.

5 POTENTIAL COMPLICATIONS

- Nasal pain, discomfort, or burning sensation
- Transient electrical discomfort
- Nosebleeds
- Nasal congestion
- Excessive sneezing
- Nasal irritation or numbness
- Nasal infection, abrasion, ulceration or inflammation
- Irritation or sensitivity of the target nasal tissue
- Headache, lightheadedness
- Trace blood, dot heme in nostril
- Facial pain or pain around the eye, sinus pain, sore eye
- Increased salivation
- Sensation of teeth vibrating
- Excessive nose running
- Temporary aggravation of symptoms associated with nasal allergies
- Allergic reaction to contact materials
- Permanent nasal scarring with prolonged use

6 TRUETEAR® DEVICE OVERVIEW

The TrueTear® device consists of four distinct parts:

1. A **reusable base unit**, which produces the electrical stimulation
2. A **disposable tip** that inserts into the nasal cavity and stimulates the target intranasal tissue
3. A **reusable cover** to protect the disposable tip
4. A **charger**, which recharges the battery inside the base unit

The disposable tip connects to the base unit and contains a hydrogel (similar to the material used in contact lenses) that provides the contact for conducting the stimulation current, which is produced by the base unit, to the target site on the inside of the nose. Remove and replace the disposable tip every 48 hours; a separate cover can be used to protect the disposable tip between uses. With the disposable tip removed, the base unit can be inverted and placed onto the charger to replenish the base unit's battery. The base unit should be recharged every 48 hours or when you change the tip. All images show in this guide are for referencing only.

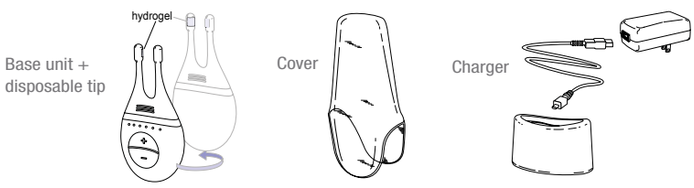

Figure 1. The TrueTear® device components.

7 CHARGING THE BATTERY

NOTE: Only use the provided AC adapter for attaching to charger.

1. Ensure the base unit is fully charged if using the device for the first time.
2. If the device has been fully charged and placed on the charger throughout the day (in between uses), it is not necessary to wait for the LED light to turn from a steady orange to green.
3. Connect the charger to the wall outlet (120-240V) using the micro USB wall adapter and cable (Figure 2). **CAUTION: The AC adapter provides protection from high voltages and should only be plugged into easily accessible outlets.**

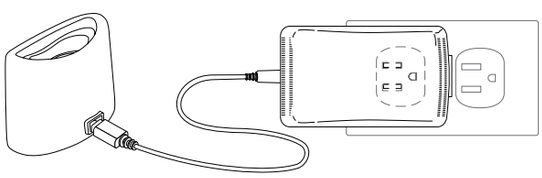

Figure 2. Connecting the charger.

4. Remove the disposable tip from the base unit by rocking the tip away from the buttons—the disposable tip should disconnect easily. Then place the base unit onto the charger. An LED light will turn to a steady orange to indicate that the base unit is correctly charging (Figure 3).

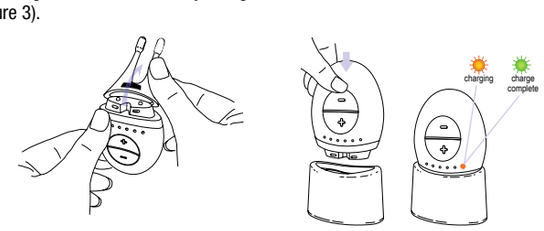

Figure 3. Placement of base unit on the charger.

5. Remember to charge the base unit every 48 hours. The charging process should take less than 4 hours to complete. An LED light will turn green to indicate that charging is complete. The base unit may be removed or left on the charger when charging is complete (Figure 4).

Figure 4. Upon completion of charge, remove base unit from charger.

8 ASSEMBLY INSTRUCTIONS

1. Ensure the base unit is fully charged if using the device for the first time (see CHARGING THE BATTERY).
2. Tear tip pouch at notch to open, and remove disposable tip from the pouch by grasping the base (as shown in Figure 5). Avoid touching the hydrogel.

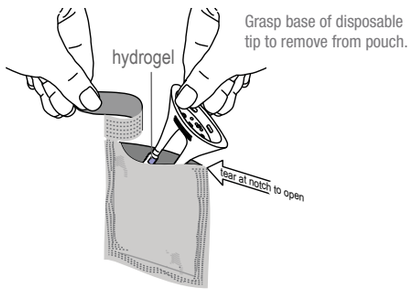

Figure 5. Remove the disposable tip from the pouch.

3. Connect the disposable tip to the base unit by aligning the tab on the underside of the disposable tip with the notch on the base unit, then rotate forward until the disposable tip snaps into place, as shown in Figure 6.

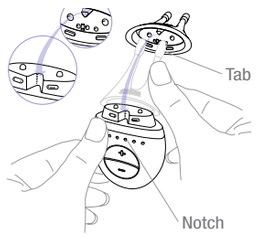

Figure 6. Align the tab to the notch for setup. The disposable tip only fits one way.

IMPORTANT: DO NOT USE A DISPOSABLE TIP FOR MORE THAN 48 HOURS. The disposable tip should be replaced every 48 hours. Failure to replace the disposable tip causes the hydrogel to dry out and may result in ineffective stimulation.

9 STIMULATION INSTRUCTIONS

The following set of instructions is provided to the patient in a separate document; however, the healthcare provider should confirm the patient's understanding of these instructions, including the patient's demonstration of stimulation and the tearing response, prior to prescribing the device and, if necessary, at subsequent visits:

1. With the device fully assembled, hold the + button for 5 seconds to turn on the device. The base unit LED lights will flash to indicate that it has been turned on; the green LED light will remain lit, as shown in Figure 7.

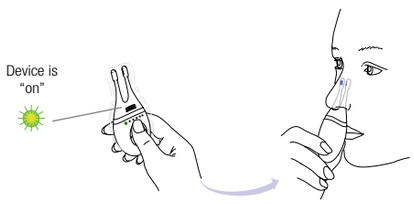

Figure 7. Turning on the device and placing it into the nasal cavity.

2. Press the + button to select a desired stimulation intensity level. Blue LED lights show the level selected.
3. Place thumb near buttons of the base unit, then insert the disposable tip into the nasal cavity with the buttons pointing towards your lips and face, as shown in Figure 7 above.
4. For effective stimulation, ensure tip is inserted all the way to the top and front of the nose, as shown in Figure 8.

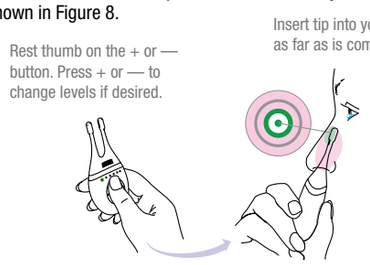

Figure 8. Target zone for correct insertion of disposable tip.

5. Gradually increase and adjust stimulation level (using the +/- buttons) until you feel a gentle tingling in your nose; this feeling is an indication that you are stimulating the correct tissue location and tears will start forming.
6. There are 5 stimulation intensity levels. The base unit vibrates briefly when a + button is pressed to indicate an increase or – button is pressed to indicate decrease in stimulation level. The blue LED light will be lit to indicate the stimulation level selected (Figure 9).

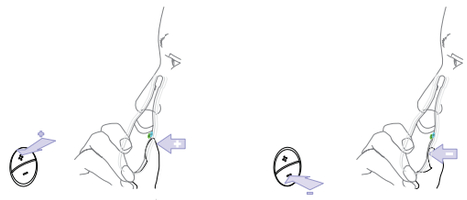

Figure 9. Adjust stimulation by pressing the + or - buttons.

7. Tip may be repositioned along the inside surface of the nose to achieve the desired stimulation. At its maximum, the sensation should be mild.
8. If you do not feel any sensation at all, replace the tip with a new tip and try again.
9. If you feel uncomfortable during stimulation, remove the device from your nose.
10. The device automatically turns off after one minute of stimulation. Alternatively, the device may also be turned off by holding down the - button for 2 seconds. The device will vibrate and the LED lights will turn off to indicate that the power has been switched off.
11. If you prefer a longer stimulation time, restart the device after it turns off.
12. When finished, clean system with tissue or an alcohol wipe (see CARING FOR DEVICE) prior to attaching the cover to protect the disposable tip between uses (Figure 10).

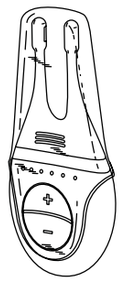

Figure 10. Cover attached to base unit to protect diposable tip.

10 RECOMMENDED STIMULATION SCHEDULE

The patient is to perform intranasal tear stimulation at least twice a day, as needed. For each instance, stimulation longer than 3 minutes (3 sequential cycles) is not recommended and the patient should wait for at least 60 minutes before proceeding to the next application.

The device is capable of single-day stimulation up to a limit of 30 minutes, for all stimulation levels combined. Once the daily limit has been reached, the device will turn on and then off immediately and will no longer deliver stimulation.

11 CARING FOR THE THE TRUETEAR® DEVICE

The following set of instructions is provided to the patient in a separate document; however, the healthcare provider should confirm the patient's understanding of these instructions prior to prescribing the device and, if necessary, at subsequent visits:

1. Use alcohol wipes to clean the cover, disposable tip, and device between uses. Avoid damaging the hydrogel.
2. Use alcohol wipes to clean the durable parts of the device including the base, charger, and cover (including the interior of the cover). Clean the inside of the cover weekly or more often if needed to ensure proper hygiene.

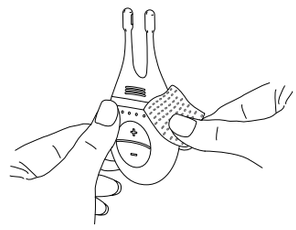

Figure 11. Cleaning with alcohol wipes.

3. Do NOT submerge or immerse the base unit, electrical plug, or charger in water or other liquid.

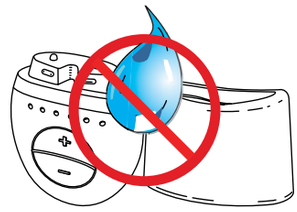

Figure 12. Do not rinse base unit or charger in water or any other liquid.

4. Handle with care. Store the TrueTear® device system in a clean, cool, and dry location. Avoid exposure to extreme temperatures and humidity.

   CAUTION: Exposure to direct heat can cause the hydrogel in the disposable tip to dry out and may result in ineffective stimulation. Avoid touching the metal contacts of the base unit or charger if either unit is exposed to high temperature extremes (eg, sitting in a hot car).

12 SUMMARY OF PIVOTAL CLINICAL STUDIES

Two pivotal clinical studies have been conducted with the TrueTear® device. Both studies evaluated the TrueTear® device's safety and effectiveness in dry eye patients. Both pivotal studies (OCUN-009 and OCUN-010) demonstrated the device's capability to temporarily increase tear production during stimulation.

Study OCUN-010 demonstrated the device's capability to improve dry eye symptoms as a result of stimulation. The next section summarizes both pivotal studies.

Acute Tear Production Pivotal Clinical Trial (OCUN-009)

This pivotal trial, "A Randomized, Controlled, Double-Masked, Multicenter Trial Designed to Evaluate Acute Tear Production During Neurostimulation With the TrueTear® Device Compared to Two Control Applications in Patients With Aqueous Deficient Dry Eye," evaluated the effectiveness and safety of the TrueTear® device during stimulation.

Potential subjects were required to meet the following main inclusion criteria at screening:

- 22 years of age or older
- Baseline Ocular Surface Disease Index© (OSDI©) score of at least 13 with no more than three responses of "not applicable"
- In at least one eye, a baseline Jones Schirmer test with anesthetic of ≤ 10 mm/5 minutes and a cotton swab nasal stimulation Jones Schirmer test at least 7 mm higher in the same eye

Potential subjects were excluded if they met any of the following criteria:

- Clinically significant corneal epithelial defects at study day (visit 2) prior to performing the Jones Schirmer tests
- Chronic or recurrent epistaxis, coagulation disorders or conditions
- Nasal or sinus surgery or significant trauma
- Severe nasal airway obstruction or vascularized nasal polyp
- Cardiac demand pacemaker, implanted defibrillator, or other implanted electronic device
- Disabling arthritis, neuropathy, or limited motor coordination affecting self-handling of the device

In this 2-visit study, potential subjects underwent a screening (visit 1) to determine eligibility prior to device use on the study day (visit 2). On the study day, each subject underwent 3 applications, 1 active and 2 control applications, administered in random order. These applications consisted of the following:

- Active intranasal stimulation (active)
- Active extranasal (off-target) device application (control)
- Sham device intranasal application (control)

The primary effectiveness endpoint was the difference between the Schirmer test score during active stimulation and during each of the 2 control applications. A crossover linear model was fit with Schirmer test result as the response variable; sequence, application, period, and the application by period interaction as fixed effects; and participant (sequence) as a random effect to account for correlation among observations within a participant. Pairwise comparisons between the active device and each of the controls were formed using least-square mean results from the crossover model. The direct clinical benefit of temporarily increasing tear production as a therapy for patients with dry eye disease was not assessed as part of this clinical trial.

The primary safety measure was the proportion of subjects reporting 1 or more adverse events (AEs) in addition to the proportion of subjects reporting device-related AEs. Additional safety measures included an intranasal speculum examination, slit lamp biomicroscopy, fluorescein staining, corrected distance visual acuity (CDVA), heart rate (HR), oxygen saturation (SpO_2), blood pressure (BP), and a cardiovascular and pulmonary symptom assessment.

The study was conducted at 2 sites in the United States and enrolled 48 subjects. The mean age of the total study population was 56.9 ± 13.2 years. Thirty-nine (81.3%) subjects were female and 9 (18.8%) were male. The majority (n = 45, 93.8%) of subjects were white, 2 (4.2%) subjects were African-American, and 1 (2.1%) subject was Asian.

The TrueTear® device stimulated a large increase in tear production, and the study met its primary effectiveness endpoint of increased tear production relative to each of the 2 control applications. An average Schirmer score of 25.3 mm ± 10.7 was observed during active neurostimulation, compared with only 9.2 mm ± 7.3 for the sham control application ($P < .0001$), and 9.5 mm ± 8.2 for the extranasal control application ($P < 0.0001$) (Figure 13). The mean difference between Schirmer score with active stimulation versus sham control application and versus extranasal control application was 16.1 mm and 15.8 mm, respectively.

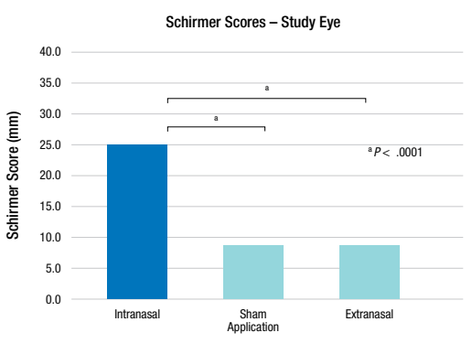

Figure 13. Schirmer test scores of study eye by device application group.

The TrueTear® device presented an acceptable safety profile in this study, with no serious adverse events (SAEs) and no AEs that led to discontinuation from the study. Two AEs were deemed related to or possibly related to the device. These included transient lightheadedness (asked of patients on the cardiopulmonary questionnaire, and considered possibly related) and intermittent nose itching (related). Both AEs resolved without sequelae.

Heart rate and BP were slightly increased during stimulation with the neurostimulator device applied intranasally and returned to prestimulation levels approximately two minutes following stimulation. Minimal[2] change was observed in SpO_2 between the prestimulation, stimulated, and poststimulation values for the device intranasal or control applications. None of the changes in vital signs were considered a "dive response" by the masked Clinical Events Committee, and none were considered device-related AEs. No relevant changes were observed in intranasal speculum examination, slit lamp biomicroscopy, fluorescein staining, or CDVA.

In conclusion, there was a clinically and statistically significantly higher degree of tear production during stimulation with the TrueTear® device than with either of the 2 control applications. Safety during the study was acceptable, and there were no relevant changes in any cardiopulmonary measures.

Six-Month Pivotal Clinical Trial (OCUN-010)

This pivotal trial, "Single-Arm, Multicenter, Open-Label Study to Evaluate the Safety and Effectiveness of the TrueTear® device in Subjects With Aqueous Tear Deficient Dry Eye," evaluated the safety and effectiveness of the TrueTear® device at multiple time points during the study (7, 30, 90, and 180 days) for subjects with aqueous tear deficient (ATD) dry eye.

Potential subjects were required to meet the following main inclusion criteria at screening:

- 22 years of age or older
- Baseline OSDI© score of at least 23 with no more than three responses of "not applicable"
- In at least one eye, a baseline Jones Schirmer test with anesthetic of ≤ 10 mm/5 minutes and a cotton swab nasal stimulation Jones Schirmer test at least 7 mm higher in the same eye
- Corneal fluorescein staining score of 2 or more in at least one corneal region and a sum of 4 or more for all corneal regions in the same eye
- No contact lens wear for at least 7 days prior to screening and willingness to forego contact lens wear for the study duration

Potential subjects were excluded if they met any of the following criteria:

- Change in ophthalmic cyclosporine preparation dosage within 30 days prior to day 0 or anticipated change during study
- Chronic or recurrent epistaxis, coagulation disorders or conditions
- Nasal or sinus surgery or significant trauma
- Cardiac demand pacemaker, implanted defibrillator, or other implanted electronic device
- Severe nasal airway obstruction or vascularized polyp
- Disabling arthritis, neuropathy, or limited motor coordination affecting self-handling of the device

Prior to the start of the study, one eye was qualified as the Study eye, and the other eye as the Qualified Fellow Eye, for which data were also collected to further corroborate device performance.

Subjects were enrolled at day 0 and were provided with a device for home use. Participants were instructed to perform intranasal neurostimulation at least 2 times a day and as often as 10 times per day, as needed, and no more than 3 minutes per use. Participants were followed for 180 days and were seen for follow-up exams at days 7, 30, 90, and 180.

The primary effectiveness measure was the Schirmer test as an assessment of the increase in acute stimulated tear production in the study eye at day 180 (primary endpoint) and days 0, 7, 30, and 90 (secondary endpoints). Symptoms were assessed with the Ocular Surface Disease Index [OSDI] at the Screening Visit and days 0, 7 and 30. Analyses were conducted for the entire eligible population and as well as stratified by dry eye severity subgroup. Dry eye severity subgroups were determined by the Screening Visit OSDI score where moderate dry eye was defined as an OSDI total score of 13 to 22 and a severe dry eye was defined as an OSDI total score of 33 or more. The primary safety assessment was the proportion of subjects who experienced 1 or more device-related AEs. Additional safety measures included CDVA, slit lamp biomicroscopy findings, nasal endoscopy, and sensitivity of olfaction (UPSIT) at study exit compared to baseline.

The primary effectiveness endpoint was the increase in tear production in the study eye during use of the TrueTear® device compared to the unstimulated tear production as assessed by the Schirmer test at day 180. Secondary effectiveness endpoints were the increase in tear production in the study eye during use of the device at the other study visits. The analysis used a paired t test or Wilcoxon signed-rank test, as appropriate, and was evaluated at a one-sided α of 0.025. Symptoms were assessed by analyses of the mean OSDI change from baseline and proportion of subjects that improved or worsened in symptoms by a clinically important difference as measured with OSDI. The minimal clinically important difference (MCID) thresholds for the analyses were based on those characterized by Miller et al (Arch Ophthalmol. 2010;128(1):94-101). Safety was assessed by an analysis of adverse events in addition to several specific safety measures, including olfaction sensitivity as measured using the UPSIT, nasal endoscopic exam, assessment of corneal edema, CDVA, and slit lamp biomicroscopy.

Ninety-seven adult subjects were enrolled at 3 sites in the United States, and 89 subjects were followed to day 180. The mean age of the total study population was 61.1 ± 10.0 years. Seventy-seven (79.4%) subjects were female and 20 (20.6%) subjects were male. Seventy-eight subjects (80.4 %) were white, 16 (16.5%) subjects were African-American, and 3 (3.1%) subjects were Asian. Eight of the subjects (8.3%) were Hispanic or Latino.

Subject accountability is shown in Table 1.

Table 1: Subject accountability

Enrolled = 97	Day 0	Day 7	Day 30	Day 90	Day 180
Available for analysis	97 (100%)	95 (98%)	91 (94%)	89 (92%)	89 (92%)
Missing	0	0	2 (2%)	0	0
Discontinued	0	2 (2%)	6 (6%)	8 (8%)	8 (8%)
Subject choice	0	1 (1%)	3 (3%)	4 (4%)	4 (4%)
Adverse event	0	0	0	3 (3%)	3 (3%)
Other	0	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Percentages are based on the total number of subjects enrolled.					

The study met its primary effectiveness endpoint and each of its secondary effectiveness endpoints. Mean acute stimulated tear production in the study eye was statistically significantly better than the mean unstimulated tear production on day 180 ($P < .0001$, one-sided paired *t* test). In comparing the stimulated vs unstimulated tear production during the study, following the initial stimulation, there was a trend toward decreased effectiveness (tear production) with time with the use of the TrueTear® device; this trend appeared to plateau toward the end of the study. The mechanism for this decrease has not been identified and was not analyzed as part of this study. The mean difference in Schirmer score (stimulated versus unstimulated) was 18.0 mm on day 0, 13.1 mm on day 7, 8.1 mm on day 30, 8.3 mm on day 90, and 9.4 mm on day 180.

Statistical significance was also seen at day 180 for the qualified fellow eye. The mean (SD) difference between stimulated and unstimulated tear production at day 180 was 9.4 mm (10.9) and 10.2 mm (9.9) for the study eye and qualified fellow eye, respectively (Table 2).

Table 2: Acute tear production at day 180

	All Subjects (N = 97)	
	Stimulated Schirmer Test	**Unstimulated Schirmer Test**
Study Eye		
n	89	89
Mean (SD)	17.28 (11.948)	7.92 (6.386)
Median	13.00	6.00
Min-Max	0.0, 35.0	0.0, 28.0
Mean Difference (SD), Stimulated vs Unstimulated	9.36 (10.902)	---
95% CI for the Mean Difference	(7.06, 11.66)	---
P value, paired *t* test	< .0001	---
P value, Wilcoxon signed-rank test	< .0001	---
Qualified Fellow Eye		
n	40	40
Mean (SD)	16.73 (11.071)	6.55 (5.514)
Median	14.00	5.00
Min-Max	0.0, 35.0	0.0, 23.0
Mean Difference (SD), Stimulated vs Unstimulated	10.18 (9.884)	---
95% CI for the Mean Difference	(7.01, 13.34)	---
P value, paired *t* test	< .0001	---
P value, Wilcoxon signed-rank test	< .0001	---
Abbreviations: CI: confidence intervals; Min: minimum; Max: maximum; N: total number of subjects; n: number of subjects in given subgroup; SD: standard deviation.		

The primary study endpoint outcomes at day 180 were stratified by age, sex, race, and baseline Schirmer score. The outcomes were statistically significant for all age strata except those subjects over age 70, which was composed of only 16 subjects. The results were also statistically significant for both males and females, as well as white and nonwhite races.

Subjects with a baseline Schirmer score of 0 to 5 mm experienced a mean (SD) increase in stimulated Schirmer score of 8.9 (11.4) mm, and subjects with a baseline Schirmer score of 6 to 10 mm experienced a mean increase of 9.8 (10.5) mm. The results were statistically significant for both the 0- to 5-mm group and the 6- to 10-mm group.

Secondary effectiveness endpoints included the acute stimulated tear production in the study eye on days 0, 7, 30, and 90. Mean acute stimulated tear production in the study eye following device application was statistically significantly better than the mean unstimulated tear production on days 0, 7, 30, and 90 overall (Table 3). Overall, mean (SD) differences in tear production in the study eye compared to baseline ranged from 8.1 mm (11.2) to 18.0 mm (9.6) at the 5 study time points.

Table 3: Acute tear production in the study eye by visit.

	All Subjects (N = 97)	
	Stimulated Schirmer Test	**Unstimulated Schirmer Test**
Day 0 (Baseline)		
n	97	97
Mean (SD)	26.20 (10.583)	8.19 (6.621)
Median	33.00	7.00
Min-Max	3.0, 35.0	0.0, 30.0
Mean Difference (SD), Stimulated vs Unstimulated	18.01 (9.588)	---
95% CI for the Mean Difference	(16.08, 19.94)	---
P value, paired *t* test	< .0001	---
P value, Wilcoxon signed-rank test	< .0001	---
Day 7		
n	95	95
Mean (SD)	19.73 (11.142)	6.63 (6.316)
Median	19.00	5.00
Min-Max	2.0, 35.0	0.0, 33.0
Mean Difference (SD), Stimulated vs Unstimulated	13.09 (9.702)	---
95% CI for the Mean Difference	(11.12, 15.07)	---
P value, paired *t* test	< .0001	---
P value, Wilcoxon signed-rank test	< .0001	---
Day 30		
n	91	91
Mean (SD)	17.40 (10.742)	9.34 (6.665)
Median	14.00	9.00
Min-Max	1.0, 35.0	0.0, 34.0
Mean Difference (SD), Stimulated vs Unstimulated	8.05 (11.150)	---
95% CI for the Mean Difference	(5.73, 10.38)	---
P value, paired *t* test	< .0001	---
P value, Wilcoxon signed-rank test	< .0001	---
Day 90		
n	89	89
Mean (SD)	16.22 (11.206)	7.92 (6.567)
Median	12.00	6.00
Min-Max	2.0, 35.0	0.0, 26.0
Mean Difference (SD), Stimulated vs Unstimulated	8.26 (10.437)	---
95% CI for the Mean Difference	(6.06, 10.46)	---
P value, paired *t* test	< .0001	---
P value, Wilcoxon signed-rank test	< .0001	---

Table 3: Acute tear production in the study eye by visit.(Continued)

	All Subjects (N = 97)	
	Stimulated Schirmer Test	**Unstimulated Schirmer Test**
Day 180		
n	89	89
Mean (SD)	17.28 (11.948)	7.92 (6.386)
Median	13.00	6.00
Min-Max	0.0, 35.0	0.0, 28.0
Mean Difference (SD), Stimulated vs Unstimulated	9.36 (10.902)	---
95% CI for the Mean Difference	(7.06, 11.66)	---
P value, paired *t* test	< .0001	---
P value, Wilcoxon signed-rank test	< .0001	---
Abbreviations: CI: confidence intervals; Min: minimum; Max: maximum; N: total number of subjects; n: number of subjects in given subgroup; SD: standard deviation.		

Tear production at each follow-up visit including 180 days (6 months) is shown in Figure 14.

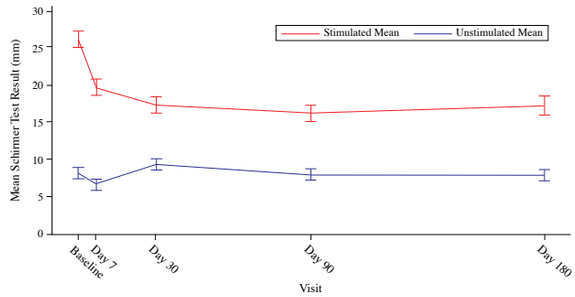

Figure 14: Acute tear production, study eye.

Symptom assessment was based on the 12-item OSDI questionnaire at Screening, day 0, day 7, and day 30. The OSDI uses a 5-unit scale (0 = none of the time, 4 = all of the time) for question responses. Subjects were stratified into moderate and severe dry eye subgroups based on Screening Visit OSDI total score. The proportion of subjects with a clinically important change in OSDI at follow-up days 7 and 30 for all available subjects stratified by dry eye severity subgroup and by the upper and lower limit of the MCID was analyzed. Of the 97 subjects that were enrolled, 77 had severe dry eye symptoms at the start of the study and were seen following treatment. Of these subjects, between 18 (23%) and 33 (43%) were shown to have a clinically meaningful improvement in their symptoms (Table 4). There were more subjects with severe dry eye symptoms that had a meaningful improvement in symptoms from baseline as measured with the OSDI than the number with meaningful worsening of symptoms at day 7 and at day 30. The sample size of the moderate dry eye group was too small to make meaningful inferences regarding the results.

Table 4: Proportion of Subjects With Severe Dry Eye Symptoms at Screening with Clinically Important Change in the OSDI* From Baseline at Days 7 and 30.

Cohort	MCID**	Change	Day 7	Day 30
Severe Dry Eye Subgroup	7.3	Improved	42.86% (33/77)	38.67% (29/75)
		Worsened	12.99% (10/77)	12.00% (9/75)
	13.4	Improved	23.38% (18/77)	25.33% (19/75)
		Worsened	5.19% (4/77)	6.67% (5/75)
*OSDI: Ocular Surface Disease Index ** MCID: Minimal Clinically Important Difference				

The safety profile of the TrueTear® device was acceptable in this study, with no device-related SAEs, and only mild device-related AEs that were largely nasal in nature (Table 4). All device-related AEs (mostly mild discomfort or epistaxis) were evident to the patients and therefore self-limiting (with the exception of one case of chapped skin around the nostrils that resolved with over-the-counter Neosporin®) since patients could remove the device and discontinue stimulation at any time. The incidence of device-related AEs decreased over the course of the study, with the highest number (22, 61%) occurring in the first month, followed by 6 (17%) mild AEs that occurred between days 31 and 90, and 8 (22%) mild AEs occurring in the final 3 months of the study. These 36 device-related mild AEs occurred in 97 subjects with 27,338 cumulative stimulations.

Table 5: Proportion of subjects experiencing adverse event–related or possibly related to the TrueTear® device–safety population

Adverse Event Description	Number of Subjects (N = 97)	Percentage
Nasal pain, discomfort, or burning	10	10.3%
Transient electrical discomfort	5	5.2%
Nosebleed	5	5.2%
Nasal congestion	3	3.1%
Headaches	2	2.1%
Trace blood, dot heme in nostril	2	2.1%
Facial pain	2	2.1%
Sore eye	1	1.0%
Sinus pain	1	1.0%
Periorbital pain	1	1.0%
Runny nose	1	1.0%
Nasal ulcers	1	1.0%
Lightheadedness	1	1.0%
Total Subjects	**30***	**30.9%**
*Some subjects had more than one adverse event.		

No relevant changes were observed in olfaction, endoscopic exam, corneal edema, CDVA, or slit lamp findings over the 180-day study period. Seven serious adverse events were reported; however, none of these events were device related, and all were nonocular and nonnasal in nature.

The device was applied for an average of 1.7±1.5 times per day with an average daily application time of 130±159 seconds/day (2.16±2.66 minutes/day). Subjects applied the device a total of 27,338 times during the study, and the total device application time for the study was 34,726 minutes. The majority of application time was at Level 2 (≈ 37%), Level 3 (≈ 37%), and Level 4 (≈ 19%), with less application time at Level 1 (≈ 3%) and Level 5 (≈ 5%).

The circuitry within the device adjusts the voltage, up to a maximum of 13V, in order to achieve the consistent peak current level. As the impedance rises above the maximum value, less than the targeted peak current will be provided. Table 5 also shows, for each user-selected stimulation level, the percentage of impedance measurements in the OCUN-010 trial that were less than or equal to the maximum load impedance, and reflects the proportion of applications that resulted in full peak current delivery.

Table 6: Impedance summary, OCUN-010 study

Level	Peak Current (mA)	Maximum Impedance for Full Peak Current Delivery (kOhms)	% of Impedance Measurements Less Than Maximum for Each Level
1	0.7	18.6	100.0% (48,180/48,180)
2	1.5	8.7	96.2% (450,223/468,209)
3	2.5	5.2	82.7% (327,092/395,508)
4	3.7	3.5	76.4% (158,221/206,976)
5	5.0	2.6	66.9% (32,322/48,304)
All			87.1% (1,016,038/1,167,177)

The mean number of device applications per subject over the study period was 288 (SD: 154 applications, range: 12-685). The mean duration of the TrueTear® device use per subject was 21,932 seconds or 365.5 minutes (SD: 18,582 seconds, range: 1,745-128,659).

In conclusion, a clinically and statistically significant increase in tear production during stimulation in the study eye at day 180 and all other visits was observed. The device also exhibited an acceptable safety profile, with no device-related SAEs and a decrease over time in the incidence of AEs, largely mild and self-limiting, for subjects with 27,338 cumulative stimulation events.

13 COMPLAINT REPORTING

If your patient reports a problem with the device, please contact the manufacturer at 1-866-502-8327.

14 ELECTRICAL SPECIFICATIONS

Base unit output	Max current	5mA
	Max voltage	13V AC
	Max pulse width	300 µs
	Frequency	30-60 Hz
Charger	Input	5V DC
	Output	6V AC
AC adapter	Input current	0.3A
	Input voltage	120-240V AC
	Output current	1.0A
	Output voltage	5.0V DC

14.1 ELECTROMAGNETIC COMPATIBILITY

The TrueTear® device has been tested for immunity to electrostatic discharge, radio frequency interference, proximity RF fields from wireless equipment, and power frequency magnetic fields, as specified in the tables below. Emissions of energy are not likely to cause interference with nearby electrical equipment.

Guidance and Manufacturer's Declaration – Emissions
Medical Equipment and Medical Systems

The TrueTear® device is intended for use in the electromagnetic environment specified below. The customer or user of the TrueTear® device should ensure that it is used in such an environment.

Emissions Test	Compliance	Electromagnetic Environment – Guidance
RF Emissions CISPR 11	Group 1	The TrueTear® device uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.
RF Emissions	Class B	The TrueTear® device is suitable for use in all establishments, including domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.
Harmonics EN 61000-3-2	Class A	
Flicker EN 61000-3-3	Complies	

Guidance and Manufacturer's Declaration – Emissions
Medical Equipment and Medical Systems

The TrueTear® device contains a fully certified *Bluetooth®* transmitter module. This device complies with Part 15 of the FCC Rules. Operation of the Bluetooth transceiver is subject to the following two conditions: (1) this device may not cause harmful interference, and (2) this device must accept any interference received.

Specification	Description
Standard	Bluetooth 4.1
ISM Frequency Band	2.4 ~ 2.48 GHz
Channels	0-39
Transmit Power	+7.5 dBm
Modulation Method	GFSK
Max Data Rate	1 Mbps

Guidance and Manufacturer's Declaration – Immunity
Medical Equipment and Medical Systems

The TrueTear® device is intended for use in the electromagnetic environment specified below. The customer or user of the TrueTear® device should ensure that it is used in such an environment.

Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment – Guidance
ESD IEC 61000-4-2	±8kV Contact ±15kV Air	±8kV Contact ±15kV Air	Floors should be wood, concrete or ceramic tile. If floors are synthetic, the r/h should be at least 30%.
EFT IEC 61000-4-4	±2kV Mains ±1kV I/Os	±2kV Mains ±1kV I/Os	Mains power quality should be that of a typical commercial or hospital environment.
Surge IEC 61000-4-5	±1kV Differential ±2kV Common	±1kV Differential ±2kV Common	Mains power quality should be that of a typical commercial or hospital environment.
Voltage Dips/ Dropout IEC 61000-4-11	>95% Dip for 0.5 Cycle >95% Dip for 1 Cycle 30% Dip for 25/30 Cycles >95% Dip for 250/300 Cycles	>95% Dip for 0.5 Cycle >95% Dip for 1 Cycle 30% Dip for 25/30 Cycles >95% Dip for 250/300 Cycles	Mains power quality should be that of a typical commercial or hospital environment. If the user of the TrueTear® device requires continued operation during power mains interruptions, it is recommended that the TrueTear® device be powered from an uninterruptible power supply or battery.
Power Frequency 50/60Hz Magnetic Field IEC 61000-4-8	30A/m	30A/m	Power frequency magnetic fields should be that of a typical commercial or hospital environment.
Conducted RF IEC 61000-4-6	3 V 0.15 MHz-80 MHz 6 V in ISM and amateur radio bands between 0.15 MHz and 80 MHz 80 % AM at 1 kHz	3 V 0.15 MHz-80 MHz 6 V in ISM and amateur radio bands between 0.15 MHz and 80 MHz 80 % AM at 1 kHz	Home Healthcare Environment
Radiated RF IEC 61000-4-3	10 V/m 80 MHz – 2.7 GHz 80 % AM at 1 kHz	10 V/m 80 MHz – 2.7 GHz 80 % AM at 1 kHz	Home Healthcare Environment

Guidance and Manufacturer's Declaration –
Immunity to RF wireless communications equipment
ME Equipment and ME Systems

The TrueTear® device is intended for use in the electromagnetic environment specified below. The customer or user of the TrueTear® device should ensure that it is used in such an environment.

Test	Band[1]	Service[1]	Modulation[2]	Maximum Power	Distance	Immunity Test Level
MHz	MHz			W	Meters	(V/m)
385	380 - 390	TETRA 400	Pulse modulation[2] 18 Hz	1.8	0.3	27
450	430 - 470	GMRS 460, FRS 460	FM[3] ± 5 kHz deviation 1 kHz sine	2	0.3	28
710 745 780	704 - 787	LTE Band 13, 17	Pulse modulation[2] 217 Hz	0.2	0.3	9
810 870 930	800 - 960	GSM 800/900, TETRA 800, iDEN 820, CDMA 850, LTE Band 5	Pulse modulation[2] 18 Hz	2	0.3	28
1720 1845 1970	1700 - 1900	GSM 1800; CDMA 1900; GSM 1900; DECT; LTE Band 1, 3, 4, 25; UMTS	Pulse modulation[2] 217 Hz	2	0.3	28
2450	2400 - 2570	Bluetooth, WLAN, 802.11 b/g/n, RFID 2450, LTE Band 7	Pulse modulation[2] 217 Hz	2	0.3	28
5240 5500 5785	5100 - 5800	WLAN 802.11a/n	Pulse modulation[2] 217 Hz	0.2	0.3	9

NOTE: If necessary to achieve the IMMUNITY TEST LEVEL, the distance between the transmitting antenna and the ME EQUIPMENT or ME SYSTEM may be reduced to 1 m. The 1 m test distance is permitted by IEC 61000-4-3.
[1] For some services, only the uplink frequencies are included.
[2] The carrier shall be modulated using a 50% duty cycle square wave signal.
[3] As an alternative to FM modulation, 50% pulse modulation at 18 Hz may be used because while it does not represent actual modulation, it would be worst case.

15 EXPECTED SERVICE LIFE

Base unit, charger: 3 years from date of original purchase.

Tip assemblies: expiration date provided on product labeling.

16 DISPOSAL & REPLACEMENT

The base unit, charger, and AC adapter should be returned to the local distributor for recycling and disposal in accordance with any applicable local, state, and national regulations for disposal of electronic equipment.

Tip assemblies may be discarded with regular trash. The patient is instructed to contact their doctor if any portion of the system is not operating properly or if they need additional supplies.

17 Bluetooth®

This device includes *Bluetooth® Smart* wireless technology. This feature allows patients to download their TrueTear® device data so they can view and track their usage on their smartphone via the TrueTear® mobile app. The *Bluetooth®* feature does not have to be on for patients to use the TrueTear® device. For more information on using *Bluetooth®* and the TrueTear® mobile app, please visit www.truetear.com/app.

The *Bluetooth®* word mark and logos are registered trademarks owned by Bluetooth SIG, Inc. and any use of such marks by Allergan is under license. Other trademarks and trade names are those of respective owners.

18 FCC COMPLIANCE

This device contains FCC ID: T9JRN4020. This device complies with Part 15 of the FCC Rules.

Operation is subject to the following two conditions: (1) this device may not cause harmful interference, and (2) this device must accept any interference received, including interference that may cause undesired operation.

This equipment has been tested and found to comply with the limits for a Class B digital device, pursuant to part 15 of the FCC Rules. These limits are designed to provide reasonable protection against harmful interference in a residential installation. This equipment generates, uses and can radiate radio frequency energy, and if not installed and used in accordance with the instructions, may cause harmful interference to radio communications. However, there is no guarantee that interference will not occur in a particular installation. If this equipment does cause harmful interference to radio or television reception, which can be determined by turning the equipment off and on, the user is encouraged to try to correct the interference by one or more of the following measures:

- Reorient or relocate the receiving antenna
- Increase the separation between the equipment and receiver
- Connect the equipment into an outlet on a circuit different from that to which the receiver is connected

Consult the dealer or an experienced radio/TV technician for help.

19 ENVIRONMENTAL OPERATING CONDITIONS

Ambient temperature range: 5°C to 40°C
Relative humidity range: 20% to 90%

20 SYMBOLS & MARKINGS

Symbol	Description	Symbol	Description
	Type BF applied part		Federal law restricts this device to sale by or on the order of a physician or properly licensed practitioner.
	Base unit is protected against solid foreign objects of 12.5 mm Ø and greater. Protection against vertically falling water drops when enclosure tilted up to 15°.		Charger is protected against solid foreign objects of 12.5 mm Ø and greater. Protection against vertically falling water drops.
	Nonionizing electromagnetic radiation		*Bluetooth®* / *Bluetooth®* Smart mark

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