

Randomized, Controlled, Double-Masked, Multicenter, Pilot Study Evaluating Safety and Efficacy of Intranasal Neurostimulation for Dry Eye Disease

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PURPOSE. We assess the safety and effectiveness of intranasal neurostimulation to promote tear production via the nasolacrimal pathway in subjects with dry eye disease.

METHODS. A multicenter, randomized, controlled, double-masked pilot study was conducted in adults with dry eye diagnosis and at least one eye with corneal fluorescein staining ≥ 2 in at least one region or a sum of all regions ≥ 5 (National Eye Institute grading), basal Schirmer test score ≤ 10 mm, a cotton-swab stimulated Schirmer score ≥ 7 mm higher, and an Ocular Surface Disease Index score ≥ 23 . Subjects were randomized to receive active intranasal neurostimulation or sham control intranasal stimulation 4 to 8 times per day. Assessments were scheduled before (unstimulated) and during (stimulated) device application at days 0, 7, 14, 30, and 90. The primary effectiveness endpoint was stimulation-induced change in Schirmer test (with anesthesia) score. Primary safety measure was incidence of device-related adverse events (AEs).

RESULTS. Fifty-eight subjects were randomized at nine sites in Australia and New Zealand; 56 completed the 90-day study. Stimulation-induced change in Schirmer score was significantly greater with active intranasal (mean \pm SEM, 9.0 ± 2.0) than sham control intranasal stimulation (0.4 ± 0.6 ; $P < 0.001$) at day 90. Similar results were observed at days 0, 7, 14, and 30 ($P < 0.001$). No serious device-related AEs were observed. Mild nosebleed, the most common device-related AE, was reported in five (16.7%) subjects.

CONCLUSIONS. Intranasal neurostimulation was effective in inducing acute tear production after 90 days of use and generally was well tolerated in subjects with dry eye disease.

Keywords: dry eye disease

Dry eye disease (DED) is a prevalent condition of the ocular surface estimated to affect up to 50% of the global population.¹ However, these estimates are anticipated to rise owing to environmental factors, such as air conditioning and with the increasing use of computers, tablets, and smartphones.^{2,3} DED is characterized by loss of homeostasis of the tear film, and is associated with varying degrees of ocular discomfort, visual disturbance, and reduction in quality of life.^{4,5} Dry eye often is progressive in nature, where insufficient tear coverage owing to diminished tear production from the lacrimal glands or excessive evaporation resulting from dysfunction of the meibomian glands, causes a hyperosmolar

environment that contributes to ocular surface inflammation leading to further damage and a worsening of symptoms.^{4,6}

Several treatment options currently are available for DED; however, most seek only to alleviate disease symptoms, failing to address the underlying etiology of or to effect an increase in tear production.^{7,8} In contrast to most available treatments that have only a modest capacity to repair the ocular surface, trophic natural factors in tears are profoundly healing.⁸ The nasolacrimal neural pathway is involved in transmitting signals from mechanical and chemical stimuli to promote natural tearing.^{9,10} The nasolacrimal pathway is believed to have an important role in basal and reflex-bolus tear production



involved in expelling irritants from the nose or eyes.^{9,11–13} Neurostimulation is a commonly used approach in medical therapeutics^{14,15} and intranasal neurostimulation has been identified as a potential option to increase tear production. Recently, a novel intranasal tear neurostimulator device (TrueTear; Allergan plc, Dublin, Ireland) received marketing authorization by the United States Food and Drug Administration for temporarily increasing tear production in adults.¹⁶

An initial open-label, nonrandomized pilot study tested a prototype of the intranasal tear neurostimulator in 40 subjects with DED and, with an average of 3.9 applications per day, showed significant increases in tearing over a 180-day study period.¹⁷ The current double-masked, randomized, controlled pilot study was conducted to further assess the safety of the prototype and its effectiveness in increasing tear production and reducing signs and symptoms of disease over 90 days of application in subjects with dry eye.

METHODS

Study Design and Subjects

This prospective, randomized, controlled, double-masked, parallel arm, multicenter, pilot study was conducted at nine centers in Australia and New Zealand (Supplementary Table) between December 12, 2013 and October 7, 2014 (Australian New Zealand Clinical Trials Registry #ACTRN12613001110774). Site personnel were carefully trained in proper examination technique and in appropriate collection of data by qualified sponsor and contract research organization personnel to prepare and standardize performance of the investigators. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and International Council for Harmonisation guidelines, and complied with all local laws. The protocol and all amendments were approved by the local ethics committees (Bellberry Human Research Ethics Committee, Eastwood, SA, Australia and Central Health and Disability Ethics Committee, Thorndon, Wellington, New Zealand) and all subjects provided written informed consent before any study procedure was performed.

Subjects 18 years or older with dry eye were eligible for the study. In at least one eye, subjects were required to demonstrate corneal fluorescein staining ≥ 2 in one region or sum ≥ 5 in all regions (using the National Eye Institute [NEI; Bethesda, MD, USA] grading scale of 0 to 3 in each of 5 regions), a basal Schirmer (with topical anesthesia) score ≤ 10 mm/5 minutes, and an intranasal cotton swab stimulation Schirmer score ≥ 7 mm higher in the same eye, an Ocular Surface Disease Index (OSDI) score of ≥ 23 (with no more than three responses of “not applicable”), and normal eyelid function. Prospective subjects with any condition or disease judged by the investigator to potentially interfere with participation in the study, including severe nasal airway obstruction; active, severe allergy; history of recurrent nosebleed; bleeding disorder; recent ocular/nasal surgery/trauma; or corneal transplant, were excluded. Individuals with an implanted electronic or metallic device, or a diagnosis of epilepsy with seizures within 5 years were ineligible to participate. Contact lens wear was not permitted within 7 days before screening or for the duration of the study.

Study Visits and Assessments

Subject eligibility was assessed at a first screening visit, 3 to 30 days before randomization. At the second screening visit/first study visit (day 0), eligibility was reconfirmed and the eye that met the screening criteria was identified as the study eye; if

both eyes qualified then the worse eye (lowest tear production at screening determined by the average of the basal Schirmer score on both screening days) was designated as the study eye. Subjects were randomized (1:1) using a computer-generated randomization schedule stratified by site to receive the active neurostimulator or the sham control device intranasally. An independent, unmasked, individual dispensed the devices and provided user training.

At four follow-up visits on days 7 (± 3), 14 (± 3), 30 (± 7), and 90 (± 14), study assessments were conducted before and during application of the assigned active or sham control device by the subject. Subjects and study personnel performing the assessments were masked with respect to the treatment application and the masked assessor was not present when the subject was applying the device. Before device application, corneal fluorescein staining, conjunctival lissamine green staining (nasal and temporal regions) and tear breakup time (TBUT) also were performed. Dry eye symptoms (12-item OSDI questionnaire and ocular symptoms of pain, dryness, sticky feeling, burning/stinging, foreign body sensation, itching, blurred vision, photophobia, and severity of dry eye symptoms rated on a visual analog scale [VAS] of 0, no discomfort to 100, maximal discomfort) were assessed at each study visit before device application. Schirmer testing (with topical anesthesia) was performed before (unstimulated) and during (stimulated) application of the active intranasal tear neurostimulator or sham control device. Adverse events (AEs) were recorded at each visit. Additional safety measures included corrected distance visual acuity (CDVA), IOP, slit-lamp biomicroscopy (eyelids, tear film, conjunctiva, anterior chamber, lens), indirect ophthalmoscopy, nasal endoscopy and the University of Pennsylvania Smell Identification Test (UPSIT).

Subjects were requested to discontinue use of their current artificial tears or lubricant drops at the first screening visit and for the duration of the study, and were provided with unit dose unpreserved artificial tears to be instilled if their dry eye symptoms became intolerable. The amount of artificial tear use was recorded at each follow-up visit.

Investigational Device and Application

The prototype intranasal neurostimulator was designed to deliver microcurrents to the intranasal mucosa to stimulate the nasolacrimal pathway and induce tearing. A transcutaneous electrical neurostimulation (TENS) unit, serving as a source of neuromuscular stimulation, was connected to a handheld base with two intranasal posts. Disposable polymer sleeves with hydrogel tips covered the posts and were the only parts of the unit to contact the nasal mucosa. The sham control device was nonfunctional and had a stop to limit the depth of intranasal insertion, but was otherwise identical to the active neurostimulator device. Active and sham devices created a buzzing noise during use and subjects were informed that this indicated that the unit was functional. Additionally, subjects were advised that the absence or presence of sensation did not necessarily influence the effectiveness of the treatment.

During the 3-month study phase, subjects were instructed to use the assigned device at least 4 times per day or as needed up to 8 times per day, for a minimum of 30 seconds and up to 3 minutes each use. The location of the application could be adjusted during use, and the stimulation intensity regulated using an activation dial.

Statistical Methods and Analysis

The primary effectiveness endpoint was the amount of stimulation-induced change in Schirmer score as measured by the difference in pre- and post-stimulation Schirmer scores

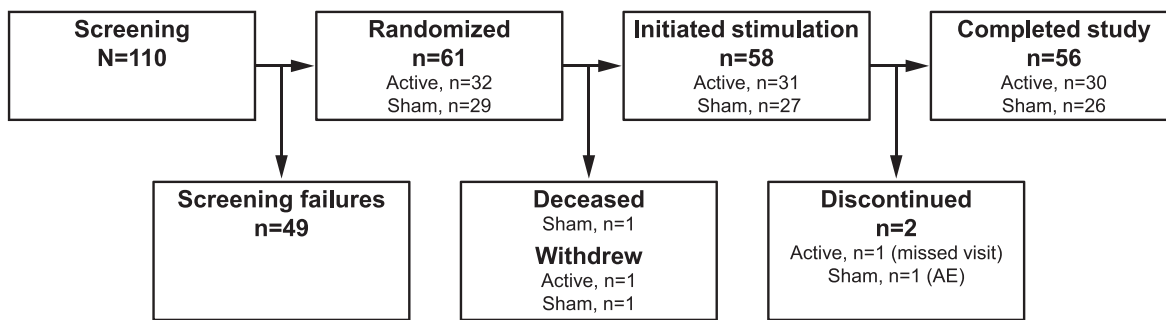


FIGURE 1. Subject accountability. Active, active intranasal stimulation; Sham, sham control intranasal stimulation.

(i.e., acute tear production). Efficacy summaries and analyses were performed with all available data at each visit. No exclusions were applied and missing values were not imputed. Continuous variables were summarized by descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum), and categorical variables, by frequencies and percentages. Data were tested for normality, and for effectiveness endpoints, and differences between active and sham applications were assessed using a two-sample *t*-test or the Wilcoxon Rank Sum (WRS) test, as appropriate. Demographic and clinical characteristics were compared between treatment arms using Fisher's exact test for categorical response variables and the WRS for continuous or ordered categorical variables. The change in Schirmer score with stimulation at each visit was compared between treatment arms using a 2-sample *t*-test. A 2-tailed $P < 0.05$ indicated statistical significance. Since this is a pilot study, no adjustment was made for multiple comparisons.

The primary safety endpoint was the incidence of AEs and relatedness to the study device. Safety summaries included all available data for subjects who applied either the active or the sham control intranasal device. AEs were summarized by presenting the number and percentage of subjects disclosing any AE and other information (such as severity or relationship to study device) was recorded as appropriate.

Sample size and power calculations were based on data from a previous study of the prototype neurostimulator.¹⁷ The previous study demonstrated a mean change over 30 days in the poststimulation Schirmer score of 3.2 mm with a standard deviation of 2.3 mm. To show a difference in the change between active and control groups of 2 mm as statistically significant (2-tailed, $\alpha = 0.05$) with 90% power required 30 subjects per randomized group. For this study, it was determined that 50 subjects (25 per randomized group) were

required to show a difference in a change in Schirmer score, between active and sham application, of 2 mm as statistically significant (2-tailed, $\alpha = 0.05$) with 85% power.

RESULTS

Subjects Disposition and Baseline Characteristics

Of 61 subjects enrolled in the study, 32 were randomized to active and 29 to sham control intranasal stimulation (Fig. 1). Of the 58 subjects who initiated active ($n = 31$) or sham ($n = 27$) stimulation on day 0, only two did not complete the 3-month study (one in each group). Subject demographics and clinical characteristics were comparable at screening between the active and sham control intranasal stimulation groups (Table 1). The study population was predominantly female (79%) and Caucasian (97%), with a mean age of 63 years (range, 37–82 years).

Primary Effectiveness Endpoint: Change in Acute Tear Production With Neurostimulation

At day 0, and at all subsequent follow-up visits, significantly greater increases in stimulated tear production from unstimulated levels were observed during active intranasal compared with sham control intranasal stimulation ($P < 0.001$; Fig. 2, Table 2). In the active and sham control groups, little change was observed across study visits in basal (unstimulated) tear production. Mean Schirmer scores following sham control intranasal stimulation were consistent across study visits, while mean stimulated Schirmer score for subjects in the active intranasal stimulation group showed a trend of being highest during the first application (day 0), declined slightly over the next two weeks, and remained consistent thereafter (Table 2).

TABLE 1. Subjects Demographics and Clinical Characteristics Did Not Differ Between the Active and Sham Groups at Screening

	Active Intranasal Stimulation, $n = 32$	Sham Control Intranasal Stimulation, $n = 29$	<i>P</i> Value
Age, mean years (range)	58.8 (37, 79)	66.8 (47, 82)	0.014*
Female, n (%)	27 (84)	21 (72)	0.351†
Caucasian	31 (97)	28 (97)	0.944†
Schirmer score in the study eye, mean mm (SD)			
Unstimulated	5.7 (3.1)	5.8 (2.4)	0.908*
Intranasal cotton swab stimulation	25.8 (9.2)	23.9 (10.3)	0.461*
Corneal staining score in the study eye, mean (SD)	4.7 (3.3)	5.2 (2.4)*‡	0.994*
Conjunctival staining score in the study eye, mean (SD)	4.6 (4.9)	3.8 (2.9)*‡	0.378*
OSDI score, mean (SD)	52.0 (20.5)	55.1 (16.3)	0.647*

* Wilcoxon rank-sum test.

† Fisher's exact test.

‡ $n = 28$.

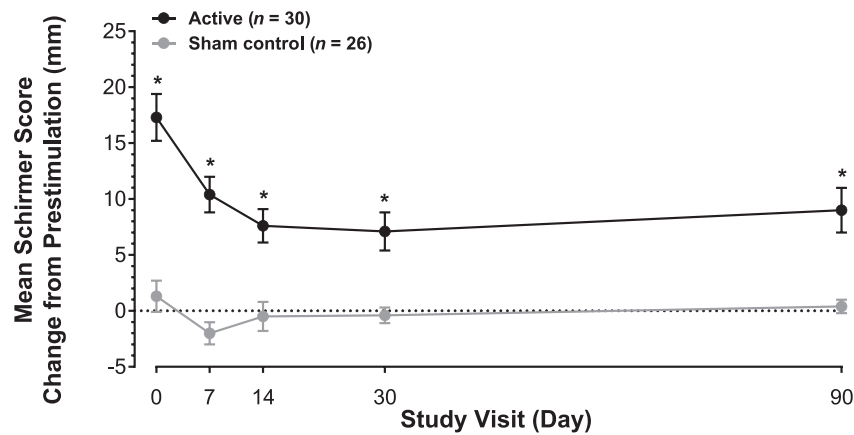


FIGURE 2. Mean Schirmer test score change from prestimulation in study eyes for active and sham control intranasal stimulation groups. Error bars: SEM. * $P < 0.001$ for active compared with sham by 2-sample t -test (2-tailed test). n represents the number of subjects assessed at day 90.

Other Effectiveness Outcomes

At the last visit (day 90), mean corneal staining decreases from baseline (day 0) were observed in the active and sham control stimulation groups. The decrease in the absolute level of corneal staining was numerically greater in the active intranasal stimulation group, but the difference between applications failed to reach statistical significance ($P = 0.075$; Fig. 3A). Conjunctival staining showed improvement in the active and sham control intranasal stimulation groups from baseline, with a trend towards slightly greater improvement observed with active than sham control intranasal stimulation ($P = 0.145$; Fig. 3B). Small increases in mean TBUT were observed at day 90 in

the study eyes of subjects in the active and sham control stimulation groups, but there were no significant differences between the two groups at any time point during the 90-day study ($P = 0.470$; Fig. 3C). Improvement in the mean OSDI score change from baseline in the active and sham control intranasal stimulation groups were measured with no significant differences between the groups ($P = 0.608$; Fig. 3D).

Analysis of the mean change from baseline in dry eye symptom category scores at day 90 indicated that there was a significant decrease in pain in the active compared with the sham control intranasal stimulation groups (-19.8 vs. -4.5 ; $P = 0.047$). No statistically significant differences were observed in other symptoms scores assessed using the VAS ($P \geq 0.368$; Fig. 4).

TABLE 2. Acute Tear Production in the Study Eye at Each Study Visit

Study Visit	Mean Schirmer Score (SEM)		P Value*
	Active Intranasal Stimulation	Sham Control Intranasal Stimulation	
Day 0			
n	30	27	<0.001
Unstimulated	6.8 (0.9)	6.8 (0.8)	
Stimulated	24.2 (2.0)	8.0 (1.3)	
Change with stimulation	17.3 (2.1)	1.3 (1.4)	
Day 7			
n	31	25	<0.001
Unstimulated	6.6 (0.8)	8.7 (1.0)	
Stimulated	17.0 (1.8)	6.8 (0.8)	
Change with stimulation	10.4 (1.6)	-2.0 (1.0)	
Day 14			
n	31	25	<0.001
Unstimulated	7.3 (1.2)	7.9 (0.9)	
Stimulated	14.9 (1.7)	7.4 (1.2)	
Change with stimulation	7.6 (1.5)	-0.5 (1.3)	
Day 30			
n	31	26	<0.001
Unstimulated	7.6 (1.1)	7.3 (0.8)	
Stimulated	14.7 (1.8)	6.9 (0.8)	
Change with stimulation	7.1 (1.7)	-0.4 (0.7)	
Day 90			
n	30	26	<0.001
Unstimulated	7.0 (1.2)	7.2 (0.6)	
Stimulated	16.2 (2.1)	7.5 (0.8)	
Change with stimulation	9.0 (2.0)	0.4 (0.6)	

* P value based on 2-sample t -test (2-tailed test).

Safety

No serious device-related AEs were reported among the 58 subjects who were enrolled and applied active or sham control intranasal stimulation. One subject, randomized to the sham control intranasal stimulation group, died before receiving the study device. A total of 19 device-related AEs were reported by 13 subjects in the nasal stimulation group and 14 device-related events were reported by nine subjects in the sham group (Table 3). The most frequent device-related AEs reported in the active intranasal stimulation group included nosebleed in five (16.7%) subjects, trace bleeding in four (13.3%), and intranasal jolt or stinging sensation in three (10.0%) subjects. Trace bleeding, nose discomfort (irritation, soreness), eye discomfort (painful, red, sore, swelling), and headache, each reported in two (7.1%) subjects, were the most common device-related AEs in the sham device group. All device-related events reported by both groups were mild or moderate in intensity.

At day 90, one eye (1/31, 3.2%) in the active intranasal stimulation group and four (4/26, 15.4%) in the sham control group had a decrease in logMAR CDVA from baseline (day 0) of 2 or more lines. Slit-lamp biomicroscopy findings revealed that one subject in the nasal stimulation group had superior conjunctival limbal inflammation in both eyes and one in the sham group had conjunctivochalasis of the right eye. No clinically significant retinal or optic nerve changes from screening were found on ophthalmoscopy at day 90 in the active intranasal stimulation group. In the sham control intranasal stimulation group, clinically significant retinal findings were reported in the left eye of one subject, bilateral optic nerve findings in another subject, and bilateral vitreous floaters in a third subject. No significant between-group differences were observed in IOP change from baseline (day

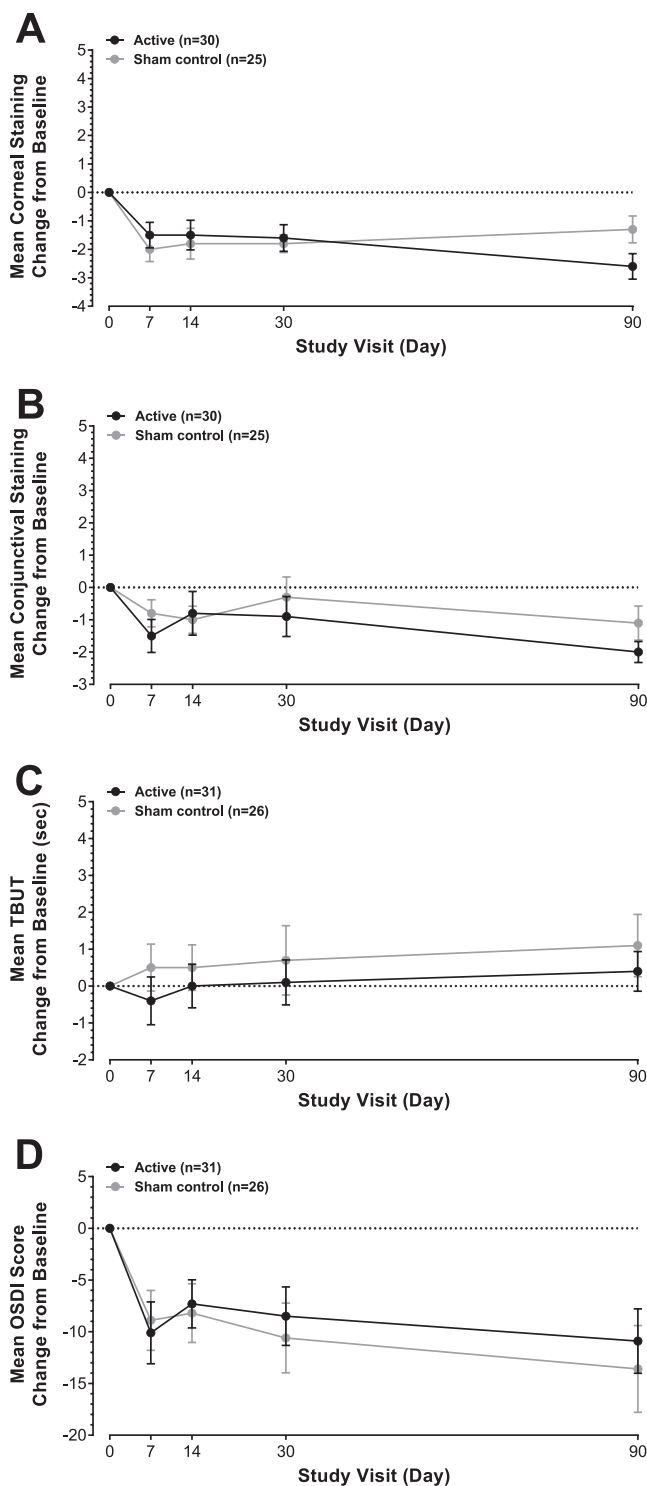


FIGURE 3. Mean change from baseline in (A) corneal staining, (B) conjunctival staining, (C) TBUT, and (D) OSDI in active intranasal stimulated and sham control intranasal stimulation groups. Error bars: SEM. *n* represents the number of subjects assessed at day 90.

0) to days 30 and 90 during the study. On nasal endoscopy, one subject in the active intranasal stimulation group had a large, right, inferior turbinate at day 90 that had not been reported at screening. There were no significant differences between the active intranasal stimulation groups and sham control intranasal stimulation groups in UPSIT smell test score change relative to baseline (day 0) at day 90.

DISCUSSION

In subjects with DED, the intranasal tear neurostimulator produced a statistically significant increase in acute tear production compared to sham stimulation at all time points through day 90 ($P < 0.001$). In the active intranasal stimulation group, acute tear production appeared greatest during the first 2 weeks after initiating neurostimulation. It is hypothesized that the initial tear production may have resulted from a combination of mechanical stimulation and neurostimulation with the subject somewhat adapting to the mechanical component. After the initial 2-week period, the subject response to neurostimulation appeared to remain constant across all time points to day 90.

The active and sham control intranasal stimulation groups showed trends towards a reduction in corneal and conjunctival staining, an increase in TBUT, and reductions in OSDI score and dry eye symptoms assessed by VAS. The nonsignificant difference in ocular staining and TBUT between active and sham control intranasal stimulation may be related to artificial tears supplied during the study. Use of noninvasive TBUT (NIBUT) measurements that are more sensitive and discriminative,¹⁸ may have demonstrated a difference between treatment groups. The artificial tears may have contributed to improved ocular surface staining and tear film integrity in the sham control intranasal stimulation group. At day 90, only the active intranasal stimulation group reported a statistically significant reduction in the dry eye symptom of pain and demonstrated a clear trend towards a decrease in corneal staining compared with the sham control intranasal stimulation group. The significant improvement in ocular pain reported by subjects in this study is of interest and merits further evaluation.

The intranasal tear neurostimulator was generally well tolerated; all AEs considered to be related to study device were mild-to-moderate in intensity, with nosebleeds and trace blood, not unexpectedly being the most frequently reported AEs in the active and sham control stimulation groups, given the delivery mode. Such isolated events did not deter subjects from continuing in the study. As expected, since the sham control device was inert, the stinging or tingling sensation was reported only in the active nasal neurostimulation group. Except for changes in CDVA that occurred predominantly in the sham control group, there were no clinically significant differences between the two cohorts in changes in slit-lamp biomicroscopy findings, indirect ophthalmoscopy, IOP, nasal endoscopy examinations, or smell test during the study. At day 90, one subject in the active intranasal stimulation group had a large, right, inferior turbinate on nasal endoscopy, which may have been attributable to an allergy or cold at follow-up.

The findings from this study support results of a previous open-label, nonrandomized pilot study with a prototype intranasal tear neurostimulator in 40 subjects with dry eye disease.¹⁷ At each clinic visit over the previous 180-day study, mean Schirmer score was significantly higher during intranasal stimulation than immediately before intranasal stimulation. It appears that under these conditions, the phenomenon of stimulation-induced exocrine gland exhaustion described in preclinical models is not significant.¹⁹ Trends toward improvement in corneal and conjunctival staining were noted during the course of the study, with the conjunctival staining score showing a significant reduction relative to baseline after day 30. From day 7, individual symptom scores and the overall OSDI score were significantly reduced compared to baseline values at all study visits. In the study by Friedman et al.,¹⁷ no serious device-related AEs were reported and patient satisfaction with the intranasal tear neurostimulator was high, with 83% of patients stating that they would recommend the device

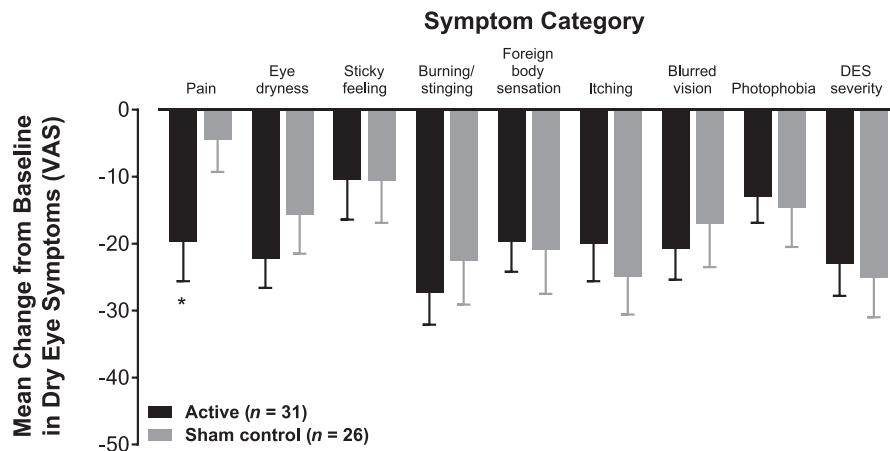


FIGURE 4. Mean change from baseline in dry eye symptoms assessed using a VAS in active and sham control intranasal stimulation groups at day 90. Error bars: SEM. *P < 0.05 for active compared with sham by 2-sample t-test (2-tailed test).

to friends or family members with dry eye. Subjects in the current study showed slightly smaller magnitude improvements in OSDI and dry eye symptoms to those reported by Friedman et al.,¹⁷ which may be due to differences in study design, subject populations, and the shorter study duration.

Limitations of the present study included the small number of patients and the duration of device application. Studies enrolling a greater number of subjects and conducted over a longer term could provide more detailed safety and effectiveness information. Additionally, there were no evaluations of tear composition during neurostimulation, which is the focus of ongoing studies.

In conclusion, for at least 3 months, use of the prototype intranasal neurostimulator device was associated with significantly more endogenous tear production and a significant reduction in dry eye-associated pain, compared with a sham control device. Intranasal neurostimulation appeared to be safe, with minor nosebleeds being the most frequently

reported device-related AE and no serious AEs observed. These results suggest that intranasal neurostimulation may be an effective and safe long-term option to increase natural tears in patients with DED.

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TABLE 3. Device-Related Adverse Events Reported in at Least One Subject in Either the Active Intranasal Stimulation or Sham Control Intranasal Stimulation Group

Adverse Event, n (%)	Active Intranasal Stimulation, n = 30	Sham Control Intranasal Stimulation, n = 28	P Value*
Nosebleed	5 (16.7%)	1 (3.6%)	0.195
Trace blood	4 (13.3%)	2 (7.1%)	0.671
Electric jolt/sting sensation in nose	3 (10.0%)	0 (0%)	0.238
Nose discomfort (irritation, soreness)	2 (6.7%)	2 (7.1%)	1.000
Eye discomfort (pain, red, sore, swelling)	1 (3.3%)	2 (7.1%)	0.605
Headache	1 (3.3%)	2 (7.1%)	0.605
Eyelid irritation	1 (3.3%)	0 (0%)	1.000
Runny nose	1 (3.3%)	0 (0%)	1.000
Sensitive teeth	1 (3.3%)	0 (0%)	1.000
Ear discomfort	0 (0%)	1 (3.6%)	0.483
Dry mouth	0 (0%)	1 (3.6%)	0.483
Itchy eye	0 (0%)	1 (3.6%)	0.483
Keratitis	0 (0%)	1 (3.6%)	0.483
Sticky eye(s)	0 (0%)	1 (3.6%)	0.483

* Fisher's exact test.

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