Original Research

Efficacy and Safety of Single-Dose OC-02 (Simpinicline Solution) Nasal Spray on Signs and Symptoms of Dry Eye Disease: The PEARL Phase II Randomized Trial

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ABSTRACT

**Purpose:** Dry eye disease is a multifactorial disorder that affects the ocular surface, with symptoms including ocular irritation, impaired vision, and pain. Nicotinic acetylcholine receptor (nAChR) agonists are novel treatments for dry eye disease; this study investigates the nAChR agonist OC-02 (simpinicline solution) as an aqueous nasal spray.

**Methods:** PEARL (Clinical Trial to Evaluate the Efficacy of OC-02 Nasal Spray on Signs and Symptoms of Dry Eye Disease) was a Phase II study that evaluated the efficacy and safety of OC-02 (simpinicline solution) nasal spray (OC-02 SNS) in adult patients with dry eye disease. Patients ≥22 years of age were eligible if they had an Ocular Surface Disease Index score ≥23, corneal fluorescein staining score ≥2 in >1 region or ≥4 for all regions, or Schirmer test score (STS) ≤10 mm; there were no restrictions on eye dryness score (EDS). Patients (N = 165) were randomly assigned 1:1:1:1 to vehicle (control; n = 42) or OC-02 SNS (0.11 mg, 0.55 mg, or 1.1 mg; n = 41 per group) and received a single dose of study drug (100 μL using a nasal spray atomizer) at visit 1 and visit 2 (15–19 days after visit 1). Primary efficacy outcomes were change in the STS from baseline to immediately after treatment administration (visit 1) and change in the EDS from before to 5 minutes after treatment during controlled adverse environment exposure (visit 2).

**Findings:** Baseline demographic and ocular clinical characteristics were similar across all groups. Single-dose OC-02 SNS improved the signs and symptoms of dry eye disease. For the STS, statistically significant and dose-dependent improvements were found from before to after treatment with OC-02 SNS versus vehicle (least-squares mean change from baseline: vehicle, 3.0 mm; 0.11 mg OC-02 SNS, 9.0 mm; 0.55 mg, 17.5 mm; and 1.1 mg, 19.6 mm). For EDS, statistically significant and dose-dependent improvements were found from before to 5 minutes after treatment with higher doses of OC-02 SNS versus vehicle (least-squares mean change from baseline: vehicle, −6.5; 0.11 mg OC-02 SNS, −9.4; 0.55 mg, −17.4; and 1.1 mg, −20.7). OC-02 SNS was well tolerated: only 2 ocular adverse events were reported (eye pruritis and keratitis), and the most common nonocular events were cough and throat irritation.

**Implications:** Single-dose OC-02 SNS over a range of doses immediately and significantly increased tear production and improved eye dryness. Together with previous studies of OC-01 (varenicline solution) nasal spray, our findings suggest that agonist stimulation of nAChRs in the nasal cavity is a valid and effective mechanism to elicit natural tear production in patients with dry eye disease. ClinicalTrials.gov identifier: NCT03452397. (Clin Ther. 2022;000:1–9.) © 2022 The Authors. Published by Elsevier Inc.
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KEYWORDS: dry eye disease, nasal spray, nicotinic acetylcholine receptor, simpinicline.

INTRODUCTION
Dry eye disease is a multifactorial disorder that affects the ocular surface and results in tear film hyperosmolarity and instability.1 The prevalence of dry eye disease is high2 and is both age and sex related.3,4 Symptoms include ocular irritation (stinging, burning, and scratching sensations), impaired vision, and pain.5 Treatments such as artificial tears and agents that target inflammatory processes6-7 are available for dry eye disease, but these have limitations. For example, artificial tears are temporary, lack almost all components of natural tears,8 and may wash away beneficial endogenous proteins. Anti-inflammatories have a slow onset of action and adverse effects, such as burning and foreign body sensation.6

Given that electrical neurostimulation of the trigeminal nerve stimulates tear production,9 we postulated that pharmacologic neuroactivation of tear production could be achieved with a nasal spray that could depolarize the nerve. We developed OC-02 (simpinicline solution) nasal spray as an aqueous nasal spray candidate to treat the signs and symptoms of dry eye disease. Although previously studied for gastrointestinal conditions, the active component of OC-02 VNS, simpinicline, also binds to nicotinic acetylcholine receptors (nAChRs) on the trigeminal parasympathetic nerve in the nasal cavity10,11 to stimulate production of natural tears.12,13 Simpinicline is a strong agonist at the α3β4, α3α5β4, and α4β2 nAChR subtypes and a poor agonist at the α7-receptor subtype (company data on file). nAChRs are important ion channels that assist with chemical neurotransmission within the central nervous system.14 Each nAChR complex consists of various heteromeric or homomeric α and β subunits that combine to form pentameric ligand-gated ion channels composed of the subunits arranged around a central pore15,16; the ion fluxes through the channels generate transient changes in the membrane potential, allowing the dynamic control of the neuronal excitability.14 Given ubiquitous expression, nAChR agonists are in development as potential therapeutic options for conditions such as obesity, diabetes, and inflammation,17 skin disorders,18 and brain disorders,19 such as schizophrenia.20 The orally administered nAChR agonist varenicline is approved as an aid in smoking cessation.21

In addition, OC-01 (varenicline solution) nasal spray* is a recently approved treatment for the signs and symptoms of dry eye disease that overcomes some of the limitations of other treatments.22 We report the investigation of the single-dose efficacy and safety of the small-molecule nAChR agonist, OC-02 (simpinicline solution), as an aqueous nasal spray in patients with dry eye disease, a study that assisted with the development of OC-01 (varenicline solution) nasal spray.

PARTICIPANTS AND METHODS
PEARL (Clinical Trial to Evaluate the Efficacy of OC-02 Nasal Spray on Signs and Symptoms of Dry Eye Disease) was a Phase II, multicenter, randomized, double-masked, vehicle-controlled study to evaluate the efficacy and safety of OC-02 (simpinicline solution) nasal spray (OC-02 SNS) in adult patients with dry eye disease. The study was conducted at 3 sites in the United States between February and April 2018. Institutional review board/ethics committee approval was obtained from each study center, and the study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonisation Guideline for Good Clinical Practice. All patients provided written informed consent before participation.

Patients
Patients ≥22 years of age were eligible for enrollment if they had an Ocular Surface Disease Index score ≥23 and had used and/or desired to use an artificial tear substitute for symptoms within 6 months of study start. In addition, the following measures were required in the study eye at screening: a corneal fluorescein staining score ≥2 in ≥1 corneal region or a sum ≥4 for all corneal regions; a Schirmer test score (STS) with topical anesthesia of ≤10 mm and an STS ≥7 mm greater in the same eye after nasal stimulation with a cotton swab; a best-corrected visual acuity (BCVA) of 0.7 logarithm of the minimum angle of resolution (logMAR) or better (logMAR <0.7; Snellen equivalent score of 20/100 or better); and normal eyelid

* Trademark: Tyrvaya™ (Oyster Point Pharma Inc, Princeton, New Jersey).
or lash anatomy, blinking function, and closure, as determined by the investigator.

The study eye for each patient was defined as the eye that met all inclusion criteria. If both eyes qualified, then the eye with the greatest increase in tear production with stimulation by a cotton swab at the screening visit was selected as the study eye. If there was no difference, the eye with the lower basal STS at screening was selected, and where there was no difference for either measure, the right eye was used as the study eye.

Patients were excluded from participation in the study for a number of reasons, including the following: clinically significant corneal epithelial defects before performing the Schirmer test on study day 1; use of contact lenses within 7 days before visit 1 or anticipated use of contact lenses during the study period; any intraocular surgery (such as cataract surgery) or extracocular surgery (such as blepharoplasty) in either eye within 3 months or refractive surgery within 12 months of the study; or a corneal transplant in either eye. Chronic or recurrent epistaxis, coagulation disorders, or other conditions that, in the opinion of the investigator, may lead to a clinically significant risk of increased bleeding were also grounds for exclusion. Patients were excluded if they had any of the following: nasal or sinus surgery, including a history of application of nasal cautery, or significant trauma to these areas; a vascularized polyp, severely deviated septum, or chronic recurrent nosebleeds; current treatment with nasal continuous positive airway pressure; and any form of punctal or intracanalicular occlusion. Patients were considered ineligible for a known hypersensitivity to any of the procedural agents or study drug components or for current concomitant use of a nAChR agonist, snuff, chewing tobacco, or cigarettes or cigars during the study or within the previous 30 days.

Procedures

At screening, patients were randomly assigned (by assignment of a randomization number corresponding to a treatment group) 1:1:1:1 to vehicle (control) or OC-02 SNS 0.11 mg, 0.55 mg, or 1.1 mg. The randomization schedules were stratified to ensure randomization of an equal number of patients at each site to each study arm. Participants, investigators, and study personnel were masked with respect to the treatment assignments.

Patients received a single dose of study drug (100 μL using a nasal spray atomizer into each nostril) at Visit 1 and Visit 2 (15–19 days after visit 1). The excipients, viscosity, pH, and osmolality of each dose formulation were identical.

Efficacy Outcomes

The primary efficacy outcomes were the change in the STS from baseline to immediately after treatment administration (assessed at visit 1) and the change in the eye dryness score (EDS) from before treatment to 5 minutes after treatment during controlled adverse environment (CAE) exposure (assessed at visit 2). The secondary efficacy outcome was the pretreatment to posttreatment change in score on the Ocular Discomfort Scale (Ora Inc, Andover, Massachusetts) over time during CAE exposure; higher scores indicate increasing ocular discomfort (graded from 0 to 4). The post hoc outcome was the percentage of patients who achieved a ≥10-mm improvement in the STS. For this outcome, patients were also stratified by baseline dry eye disease severity by the EDS (mild-moderate, <60; severe, ≥60).

Safety Assessments

All adverse events and treatment-emergent adverse events (TEAEs) were recorded and coded using the Medical Dictionary for Regulatory Activities, version 20.1, and were graded as mild, moderate, or severe according to standard criteria. Changes from baseline in BCVA, slit-lamp biomicroscopic findings, pupil diameter for the study eye and fellow eye, and intranasal examination findings after study drug exposure were evaluated.

Statistical Analysis

A statistical power calculation was not used to determine sample size for the study. It was anticipated that if approximately 40 participants were enrolled in each study arm, an assumed dropout rate of 5% would result in approximately 38 patients per group completing the study.

Efficacy analyses were performed using an intent-to-treat population that included all randomized participants for analysis as randomized. Safety analyses were performed using all participants who received ≥1 dose of the study treatment. Efficacy analyses were performed using observed data only without imputation for missing data based on the small number.
of patients without data at the time of the assessment of the primary end point.

Changes from baseline in the STS and EDS were compared between each treatment dose and vehicle using an ANCOVA model with baseline test score, treatment, and study site as covariates.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 165 patients were enrolled and randomly assigned to vehicle (n = 42) or OC-02 SNS 0.11 mg (n = 41), 0.55 mg (n = 41), or 1.1 mg (n = 41) (Figure 1). Four patients discontinued participation in the study. There were 4 major protocol deviations, but none of these resulted in study discontinuation.

Baseline demographic characteristics were similar across all treatment groups (Table I), and most patients were female, with a higher percentage included in the vehicle group. Baseline ocular clinical characteristics related to dry eye disease were also similar across all treatment groups (Table I). The most common ocular medical history was cataracts (reported by 54 of 165 patients [32.7%]).

Primary Efficacy End Points

A single dose of OC-02 SNS improved the signs and symptoms of dry eye disease. For the STS, statistically significant and dose-dependent improvements were found from before to after treatment with OC-02 SNS compared with vehicle (Figure 2A). For the EDS, statistically significant and dose-dependent improvements were found from before to 5 minutes after treatment with the higher doses of OC-02 SNS compared with vehicle (Figure 2B).

Additional Efficacy End Points

Patients generally had less discomfort in the CAE after treatment with OC-02 SNS compared with vehicle (Table II). Change in Ocular Discomfort Scale scores from before treatment over time for the first 30 minutes that the patient was in the CAE was significantly improved with OC-02 SNS 1.1 mg.

The percentage of patients who achieved a ≥10-mm improvement in the STS was greater for the OC-02 SNS treatment groups compared with the vehicle group (Figure 3A). Similarly, a subset analysis of patients with a baseline EDS of <60 (mild-moderate dry eye disease) or ≥60 (severe dry eye disease) found that the percentage of patients who achieved a ≥10-mm improvement in the STS was greater for the OC-02 SNS treatment groups compared with the vehicle group, regardless of severity (Figure 3B and C).

Safety Outcomes

OC-02 SNS was well tolerated at the doses evaluated, and approximately half of patients receiving OC-02 SNS reported a TEAE (Table II). Most TEAEs were mild-moderate in severity, with only 1 patient reporting a severe TEAE of failure to thrive, which was considered unrelated to the study treatment but led to withdrawal from the study. No events resulting in death were reported. There were only 2 ocular
Table I. Baseline demographic and ocular clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vehicle (n = 42)</th>
<th>OC-02 SNS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.11 mg (n = 41)</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>64.4 (11.76)</td>
<td>64.4 (11.80)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>34 (81.0)</td>
<td>24 (58.5)</td>
</tr>
<tr>
<td>Race or ethnicity, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>39 (92.9)</td>
<td>37 (90.2)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3 (7.1)</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>39 (92.9)</td>
<td>41 (100)</td>
</tr>
<tr>
<td>STS (with anesthesia), mean (SD), mm</td>
<td>5.6 (2.80)</td>
<td>5.4 (2.61)</td>
</tr>
<tr>
<td>STS cotton swab, mean (SD), mm</td>
<td>30.5 (6.16)</td>
<td>29.4 (7.70)</td>
</tr>
<tr>
<td>EDS, mean (SD)</td>
<td>63.5 (19.69)</td>
<td>64.3 (19.83)</td>
</tr>
<tr>
<td>ODS score, mean (SD)</td>
<td>2.7 (1.11)</td>
<td>3.0 (0.79)</td>
</tr>
</tbody>
</table>

EDS = eye dryness score (scale 1–100, with 0 indicating no discomfort and 100 indicating maximal discomfort; OC-02 SNS = OC-02 (simpinicline solution) nasal spray; ODS = Ocular Discomfort Scale (grade 0–4, with 0 indicating no discomfort and 100 indicating maximal discomfort); STS = Schirmer test score.

Figure 2. Primary outcomes. Least-squares (LS) mean change from baseline in (A) Schirmer test score (STS) and (B) eye dryness score (EDS) after a single dose of OC-02 (simpinicline solution) nasal spray (OC-02 SNS). Samples sizes for the STS group are 42 for vehicle and 41 for 0.11 mg, 41 for 0.55 mg, and 41 for 1.1 mg OC-02 SNS. Sample sizes for EDS are 41 for vehicle and 37 for 0.11 mg, 41 for 0.55 mg, and 38 for 1.1 mg OC-02 SNS. *P < 0.01 versus vehicle. **P < 0.01 versus vehicle ***P < 0.001 versus vehicle.
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Table II. Ocular Discomfort Scale scores during controlled adverse environment exposure.

<table>
<thead>
<tr>
<th>Time</th>
<th>Least-Squares Pretreatment Change, Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle (n = 42)</td>
</tr>
<tr>
<td>At 10 min after treatment</td>
<td>-0.7 (-1.0 to -0.4)</td>
</tr>
<tr>
<td>At 20 min after treatment</td>
<td>-0.6 (-0.9 to -0.3)</td>
</tr>
<tr>
<td>At 30 min after treatment</td>
<td>-0.5 (-0.8 to -0.2)</td>
</tr>
<tr>
<td>At 40 min after treatment</td>
<td>-0.5 (-0.9 to -0.2)</td>
</tr>
<tr>
<td>At 50 min after treatment</td>
<td>-0.7 (-1.0 to -0.3)</td>
</tr>
<tr>
<td>At 60 min after treatment</td>
<td>-0.6 (-0.9 to -0.2)</td>
</tr>
</tbody>
</table>

OC-02 SNS = OC-02 (simpinicline solution) nasal spray.

* P < 0.05 compared with vehicle by ANCOVA.

ANCOVA = analysis of covariance; CAE = controlled adverse environment; LS = least squares; OC-02 SNS = OC-02 (simpinicline solution) nasal spray.

![Figure 3](image-url)  
**Figure 3.** Percentage of patients with ≥10-mm improvement in Schirmer test score (STS) after a single dose of OC-02 (simpinicline solution) nasal spray (OC-02 SNS) (A) overall, (B) with mild-moderate dry eye disease, and (C) with severe dry eye disease. Overall sample sizes are 42 for vehicle and 41 for 0.11 mg, 41 for 0.55 mg, and 41 for 1.1 mg OC-02 SNS. Sample sizes for mild-moderate dry eye disease are 18 for vehicle and 14 for 0.11 mg, 11 for 0.55 mg, and 18 for 1.1 mg OC-02 SNS. Sample sizes for severe dry eye disease are 24 for vehicle and 27 for 0.11 mg, 30 for 0.55 mg, and 23 for 1.1 mg OC-02 SNS. **P < 0.001 versus vehicle. ***P < 0.0001 versus vehicle.

TEAEs reported: eye pruritus and keratitis (Table II). The most common nonocular TEAEs were cough and throat irritation (Table III). There were no clinically significant changes from baseline in BCVA, slit-lamp biomicroscopic findings, intranasal examination findings, or pupil diameter during the study.

**DISCUSSION**

This was the first study to investigate and characterize an nAChR agonist nasal spray treatment for patients with dry eye disease. We found that a single dose of OC-02 (simpinicline solution) nasal spray over a range of doses immediately and significantly increased tear production and improved eye dryness. In addition, improvements in eye dryness and ocular discomfort with OC-02 (simpinicline solution) nasal spray were maintained for >1 hour in a CAE, and most patients treated with OC-02 nasal spray had a ≥10-mm improvement in STS, regardless of baseline dry eye disease severity. OC-02 (simpinicline solution) nasal
Table III. Adverse events.

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Patients Reporting TEAEs, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle (n = 42)</td>
</tr>
<tr>
<td>≥1 TEAE</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Ocular TEAEs</td>
<td>0</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>0</td>
</tr>
<tr>
<td>Keratitis</td>
<td>0</td>
</tr>
<tr>
<td>Nonocular TEAEs*</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>0</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Instillation site irritation</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related nonocular TEAEs*</td>
<td>2 (4.8)</td>
</tr>
</tbody>
</table>

OC-02 SNS = OC-02 (simpinicline solution) nasal spray; TEAE = treatment-emergent adverse event.
* For ≥5% of patients.

spray was well tolerated, with no changes in key optical parameters and few adverse events reported, and the safety profile was consistent with the newer OC-01 (varenicline solution) nasal spray. In agreement with published studies of OC-01 (varenicline solution) nasal spray, our findings suggest that agonist stimulation of nAChRs on the trigeminal parasympathetic nerve in the nasal cavity is a valid and effective mechanism to elicit natural tear production in patients with dry eye disease. Given the Phase II nature of this study, the data may be used to inform future clinical trials on nAChR agonists for dry eye disease and other ophthalmic diseases.

Physiologically, dry eye disease arises because of dysfunction of the lacrimal functional unit (composed of lacrimal glands, meibomian glands, conjunctival goblet cells, conjunctiva, cornea, lids, and their interconnecting innervation) rather than tear deficiency or evaporation. This dysfunction can result in abnormal tear film architecture of the mucous layer and/or the lipid layer. Therefore, stimulating natural tear production, such as via nAChRs, may be a viable treatment option, especially because activation of the lacrimal functional unit upregulates all layers of the tear film and produces tears that contain a complex mix of endogenously expressed anti-inflammatory and antimicrobial proteins.

Although this study investigated the effect of OC-02 (simpinicline solution) nasal spray after a single dose, in a Phase III clinical trial and in the real-world OC-02 would be administered twice daily over many months to help reestablish tear film homeostasis. From a pharmacologic perspective, delivery of an nAChR agonist into the nasal cavity would produce immediate activation of the receptors and subsequent smoldering activation to stimulate tear production, potentially over many hours after each dose. Although long-term administration of an nAChR agonist can acutely desensitize the receptors, the rate of recovery from desensitization is highly dependent on the length of agonist exposure and on the agonist used to induce the desensitization. Furthermore, the population of
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receptors on the trigeminal nerve would not all desensitize simultaneously, allowing for subsequent activation within a relatively short period. Therefore, we anticipate that OC-02 (simpinicline solution) nasal spray would be effective with repeated doses, similar to OC-01 (varenicline solution) nasal spray.25

The clinical implications of the study are limited by the single-dose assessments of OC-02 nasal spray, and a longer-term clinical trial will be needed to assess whether OC-02 (simpinicline solution) nasal spray is a suitable treatment for patients with dry eye disease in the real world. In addition, the trial was limited by study design because the order of assessments was not randomized. However, initial results reported here support continued development of OC-02 as a therapeutic option for the treatment of dry eye disease, likely with the 0.55 mg dose given the favorable risk-benefit ratio.

CONCLUSIONS
In conclusion, the PEARL study found that single-dose OC-02 (simpinicline solution) nasal spray was able to promote tear film production from the lacrimal functional unit and subsequently improve signs and symptoms of dry eye disease. In combination with previous studies of OC-01 (varenicline solution) nasal spray, our findings suggest that the pharmacologic activation of nACHRs in the nasal cavity is a physiologically relevant pathway that can improve the ocular surface and may be relevant in a range of ophthalmic disorders.

DECLARATION OF INTEREST
None.

ACKNOWLEDGMENTS
All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. Drs Torkildsen, Pattar, and Jenkins were study investigators. Ms Striffler completed the statistical analyses. Dr Nau was involved in the study design.

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