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Original Research

Bilateral Effect of OC-01 (Varenicline Solution) Nasal Spray for Treatment of Signs and Symptoms in Individuals with Mild, Moderate, and Severe Dry Eye Disease

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ABSTRACT

Purpose: This study compares outcomes of therapy with OC-01 (varenicline solution) for dry eye disease in study eyes and nonstudy fellow eyes of participants in 2 pivotal clinical trials.

Methods: All 891 patients randomized to receive OC-01 (varenicline solution) 0.03 mg, OC-01 (varenicline solution) 0.06 mg, or vehicle control (VC) in each nostril twice daily for 28 days in the Phase IIb ONSET-1 (Evaluation of the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease) and Phase III ONSET-2 trials were included in this post hoc analysis. One eye was designated as the study eye. The mean change from baseline in anesthetized Schirmer test score (STS) and the percentage of eyes achieving a ≥10-mm STS improvement were compared between treatments in study and fellow eyes overall and by baseline Eye Dryness Score.

Findings: In the study eyes, the mean STS improvement from baseline to day 28 was 10.4 mm, 10.5 mm, and 4.9 mm in the 0.03 mg, 0.06 mg, and VC groups, respectively; comparable values in nonstudy fellow eyes were 8.7 mm, 8.8 mm, and 2.7 mm, respectively. The percentages of study eyes achieving a ≥10-mm STS improvement were 48.1%, 48.4%, and 25.9%, respectively, whereas the comparable values in nonstudy eyes were 42.9%, 43.9%, and 19.7%, respectively. No significant treatment-subgroup interactions were observed in study or fellow eye STS outcomes by baseline Eye Dryness Scores <40 and ≥40 ($p > 0.05$ for all).

Implications: OC-01 (varenicline solution) nasal spray had significant tear film production improvements compared with VC in both study and fellow eyes. These findings suggest efficacy across a broad spectrum of presenting disease severity. (*Clin Ther.* 2022;000:1–8.)

Keywords: dry eye disease, OC-01 (varenicline solution) nasal spray, pharmacologic neuroactivator, trigeminal parasympathetic pathway.

INTRODUCTION

Dry eye disease (DED) is among the most common ocular disorders, affecting up to half of the world's population by some estimates.[1] DED is characterized by an unstable and/or deficient precorneal tear film, resulting in ocular surface epitheliopathy, inflammation, and neurosensory abnormalities.[2] Symptoms include

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ocular discomfort and blurred vision, and signs include reduced tear production, reduced tear break-up time, and ocular surface staining with vital dyes.

Management of DED is largely supportive. Tear substitutes provide transient relief but do not address the underlying pathophysiology of DED because over-the-counter products (artificial tears) do not approximate the complexity of human tears, which contain >2000 distinct molecules.[3,4] Three approved prescription medications—cyclosporine A emulsion, cyclosporine A solution, and lifitegrast—block inflammation on the ocular surface but do not directly impact the underlying tear film stability/deficiency.[5,6] Numerous additional, highly focused therapies are available for DED associated with meibomian gland dysfunction (eg, vectored thermal pulsation, intense pulsed light) or corneal decompensation (eg, serum tears, amniotic membrane tissue and extract); however, these therapeutic measures are beyond the scope of this discussion.

The US Food and Drug Administration recently approved OC-01 (varenicline solution) nasal spray 0.03 mg* for the treatment of signs and symptoms of DED.[7] OC-01 (varenicline solution) nasal spray is a cholinergic agonist designed to address ocular surface disorders by activating the trigeminal parasympathetic pathway, resulting in increased basal tear production. OC-01 (varenicline solution) nasal spray binds to nicotinic acetylcholine receptors of the trigeminal nerve within the nasal mucosa, activating an action potential in the trigeminal nerve that stimulates the lacrimal functional unit to produce natural tears.[8] In numerous clinical trials, OC-01 (varenicline solution) nasal spray had clinically and statistically significant efficacy in improving the signs and symptoms of DED; compared with vehicle control, OC-01 (varenicline solution) nasal spray increased tear production during 4 weeks of therapy, with improvements in the mean anesthetized Schirmer test score (STS), the percentage of individuals achieving a ≥10-mm improvement in STS, and the Eye Dryness Score (EDS).[8–10] OC-01 (varenicline solution) nasal spray is unique among pharmacologic DED therapies in that it uses a neuroactivating molecule to stimulate the trigeminal-parasympathetic pathway via terminal branches of the anterior ethmoidal nerve in the nasal cavity. Animal models found that stimulation of this pathway results not only in increased ipsilateral tear production but also enhanced lacrimation in the contralateral eye.[11] Although unilateral (single nostril) stimulation can deliver a fellow eye response of approximately 50% in preclinical animal models,[12] OC-01 (varenicline solution) nasal spray was administered in individuals bilaterally (both nostrils, twice daily) in clinical trials to reflect the intended *real-world* administration. The goal of the present analysis was to explore whether the effect seen in the study eye was similar to the effect in the fellow eye by achieving maximal nasal receptor agonist activity via twice-daily dosing in each nostril.

*Trademark: Tyrvaya® (Oyster Point Pharma, Princeton, New Jersey).

In the Phase IIb ONSET-1 (Evaluation of the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease) trial and the Phase III ONSET-2 trial of OC-01 (varenicline solution) nasal spray for DED, patients were enrolled as long as 1 eye met the entry criteria (key eligibility criteria included anesthetized STS ≤10 mm and Ocular Surface Disease Index [OSDI] score ≥23).[8,10] Outcomes were only reported in 1 eye per patient, designated the study eye and selected as the only qualifying eye or the eye with worse DED at trial entry if both qualified. DED is almost always bilateral,[13,14] and to appropriately assess the impact of a DED therapy, holistic patient outcomes should be considered in terms of overall patient symptomatic outcomes and assessment of both study and fellow eye outcomes exposed to study treatment vs vehicle control. Most of the data presentations in dry eye clinical trials only present the data from the study eye and do not report fellow eye effects. Consistency of treatment improvements in both the study eye and fellow eye (typically the fellow eye is the less severe eye in clinical trials) may help support conclusions from the clinical trials and support bilateral (both nostril) dosing of OC-01 (varenicline solution) nasal spray in clinical practice. In this analysis, we evaluated DED outcomes from the integrated ONSET-1 and ONSET-2 data set in study and fellow eyes and explored outcomes by baseline EDS severity.

PARTICIPANTS AND METHODS

This was a post hoc analysis of the integrated data from 2 pivotal clinical trials evaluating the efficacy and safety of OC-01 (varenicline solution) nasal spray on the signs and symptoms of DED. The 2 trials—the Phase IIb ONSET-1 and the Phase III ONSET-2—have been reported previously.[8,9] Participants in both trials

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were randomly assigned to treatment with various formulations of OC-01 (varenicline solution) nasal spray versus vehicle control. Key end points included changes in STS and the percentage of eyes achieving a ≥10-mm improvement in STS from baseline to day 28 in the study eye. The study eye was defined identically in both trials as the qualifying eye; if both eyes qualified, the study eye was the worse eye (greater increase in tear production after stimulation by a cotton swab or, if similar, the eye with lower baseline STS) or, if similar, the right eye was assigned as the study eye. The purpose of this analysis was to evaluate key outcomes in the fellow, nonstudy eyes.

The data set for this analysis consisted of all individuals randomized to receive OC-01 (varenicline solution) nasal spray 0.03 mg, OC-01 (varenicline solution) nasal spray 0.06 mg, or vehicle control in each nostril twice daily (the intent-to-treat population) in each of the 2 trials. In both trials, the STS was performed with topical anesthesia in a standard fashion and assessed at 5 minutes. All study eyes were included in the study eye group, and all fellow eyes (including those that did not meet trial eligibility criteria) were included in the fellow eye group.

Key outcomes of this analysis were the mean change from baseline in STS at week 4 (the primary outcome of ONSET-1) and the percentage of patients achieving a ≥10-mm improvement in STS from baseline to week 4 (the primary outcome in ONSET-2) as well as the mean change from baseline in EDS. The least-squares (LS) mean changes from baseline in STS and EDS were evaluated using ANCOVA, with missing data imputed using the last observation carried forward approach. Study eyes and fellow eyes were modeled separately for each treatment group with study, site, treatment, baseline STS, and baseline EDS as covariates in all models. The percentage of eyes achieving a ≥10-mm improvement in STS was evaluated using the Cochran-Mantel-Haenszel test controlling for study site and baseline STS and EDS. A subgroup treatment-vehicle control interaction test was performed to evaluate outcomes in patients with mild DED (EDS <40 mm) compared with those with moderate to severe DED (EDS ≥40 mm).[15,16] 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 International Council for Harmonisation Good Clinical Practice. All patients provided written informed consent before participation. Correlation in mean change from baseline STS between the fellow and study eyes was evaluated using the Pearson correlation coefficient.

RESULTS

Disposition and Demographic Characteristics

All 891 individuals who received at least 1 dose of study medication were analyzed. Of these, 48, 44, and 43 individuals were drawn from the OC-01 (varenicline solution) nasal spray 0.03 mg, OC-01 (varenicline solution) nasal spray 0.06 mg, and vehicle control treatment groups of the Phase IIb ONSET-1 trial and 260, 245, and 251 individuals, respectively, from the Phase III ONSET-2 trial. Demographic characteristics and baseline ocular characteristics are provided in Table I. The mean baseline STS was similar across treatment groups in both study and fellow eyes; as expected, because of assignment of the worse eye as the study eye, the mean baseline STS was higher in fellow eyes by 2 to 3 mm. After cotton swab stimulation, both groups had the ability to produce similar absolute STSs (baseline plus change after cotton swab stimulation), indicating that both groups had similar gland potential. The OC-01 (varenicline solution) nasal spray and vehicle control groups were well matched on all patient-level and eye-level parameters.

Mean Improvement in STS

Mean baseline STS and LS mean change from baseline to day 28 in anesthetized STS in the study and fellow eyes for each treatment group are provided in Figure 1. The LS mean STS improvement was 10.4 to 10.5 mm in both OC-01 (varenicline solution) nasal spray dosing groups in study eyes and 8.7 to 8.8 mm in both dosing groups in fellow eyes. In both study and fellow eyes, improvements in OC-01–treated eyes were significantly greater than in vehicle control–treated eyes ($p < 0.0001$).

A greater improvement in mean change in STS from baseline was found in patients comparing those with mild DED (EDS <40, n = 200) versus those with moderate-severe DED (EDS ≥40, n = 691). The treatment groups had consistently greater improvement in mean change in STS from baseline with OC-01 (varenicline solution) nasal spray versus vehicle control in both study and fellow eyes (Figure 2). Mean

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Table I. Patient demographic and baseline ocular characteristics.

Characteristic	OC-01 0.03 mg (n = 308)	OC-01 0.06 mg (n = 289)	Vehicle Control (n = 294)
Age, mean (SD), y	60.7 (12.5)	59.8 (13.1)	59.2 (13.0)
Sex, No. (%)			
Male	80 (26)	74 (25.6)	61 (20.7)
Female	228 (74)	215 (74.4)	233 (79.3)
Ethnicity, No. (%)			
White	258 (83.8)	235 (81.3)	250 (85.0)
Black	31 (10.1)	40 (13.8)	29 (9.9)
Other	19 (6.2)	14 (4.8)	15 (6.0)
Eye Dryness Score, mean (SD), mm	59.3 (21.6)	58.4 (22.6)	59.1 (21.8)
Study eyes			
STS, mean (SD), mm	5.1 (2.9)	5.4 (2.9)	4.8 (2.9)
STS with cotton swab stimulation, mean (SD), mm	27.8 (8.2)	28.3 (8.2)	27.5 (8.0)
Corneal fluorescein staining score, mean (SD)	6.5 (2.2)	6.4 (2.2)	6.2 (2.1)
Fellow eyes			
STS, mean (SD), mm	7.2 (5.0)	8.3 (5.2)	7.4 (5.6)
STS with cotton swab stimulation, mean (SD), mm	24.3 (10.0)	25.2 (9.7)	23.4 (9.9)
Corneal fluorescein staining score, mean (SD)	6.4 (2.3)	6.2 (2.5)	6.1 (2.3)

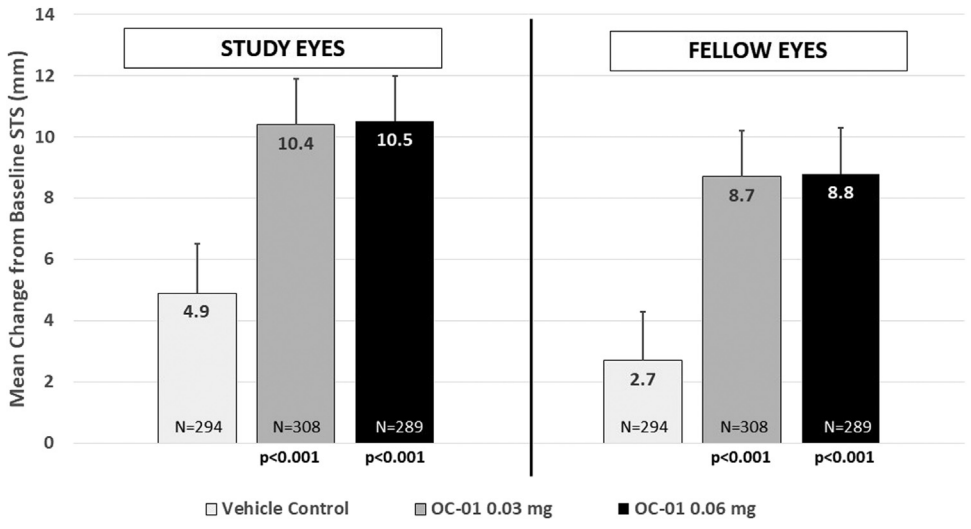

Figure 1. Baseline and change from baseline in Schirmer test score (STS) at week 4 in study and fellow eyes (integrated data). Error bars indicate SDs.

improvement in LS mean STS at day 28 in the OC-01–treated study eyes was 12.7 to 13.4 mm in eyes with mild DED and 11.4 mm in eyes with moderate-severe disease; in OC-01–treated fellow eyes, corresponding values were 8.7 to 11.0 mm and 9.2 to 9.9 mm, respectively. In all subgroups, improvements in OC-01–treated eyes were greater than in vehicle control–treated eyes.

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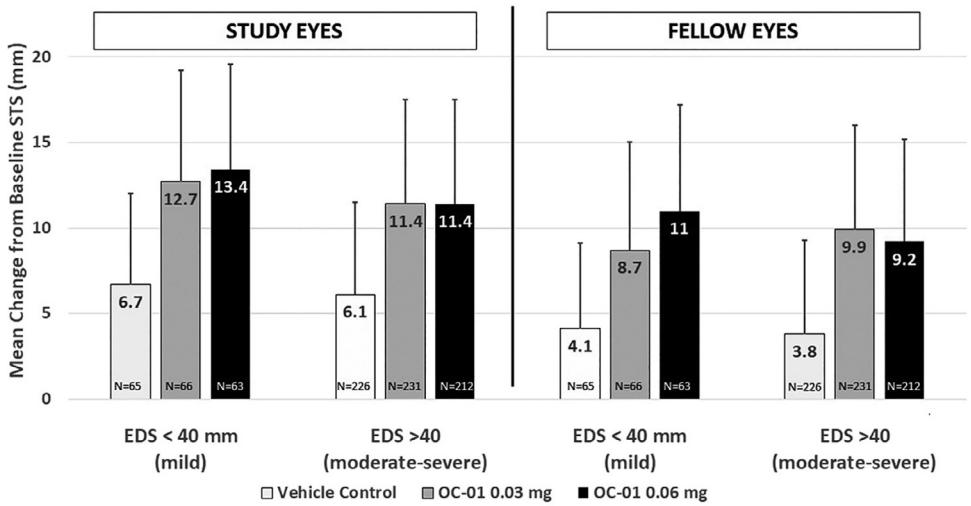

Figure 2. Mean change from baseline in Schirmer test score (STS) at week 4 in study and fellow eyes by baseline Eye Dryness Score (EDS) severity (integrated data). Error bars indicate SDs.

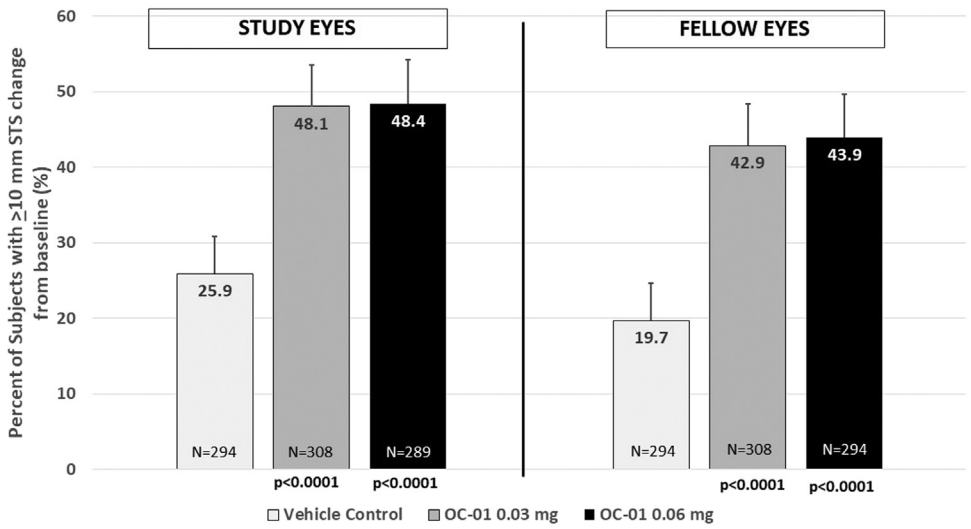

Figure 3. Percentage of patients with ≥10-mm change from baseline in Schirmer test score (STS) at week 4 in study and fellow eyes (integrated data). Error bars indicate SDs.

Percentage of Eyes With STS Improvement ≥10 mm

The percentages of study and fellow eyes achieving a ≥10-mm improvement in STS from baseline to week 4 by treatment are depicted in Figure 3. This outcome was achieved by 48.1% to 48.4% of OC-01–treated study eyes and 42.9% to 43.9% of OC-01–treated fellow eyes compared with only 25.9% of vehicle control–treated study eyes and 19.7% of vehicle control–treated fellow eyes ($p < 0.0001$ for all comparisons of OC-01 [varenicline solution] nasal spray groups vs vehicle control).

More OC-01–treated than vehicle control–treated study and fellow eyes achieved a ≥10-mm STS improvement among both the mild and moderate-severe DED subgroups (Figure 4). In study eyes, 50.0%

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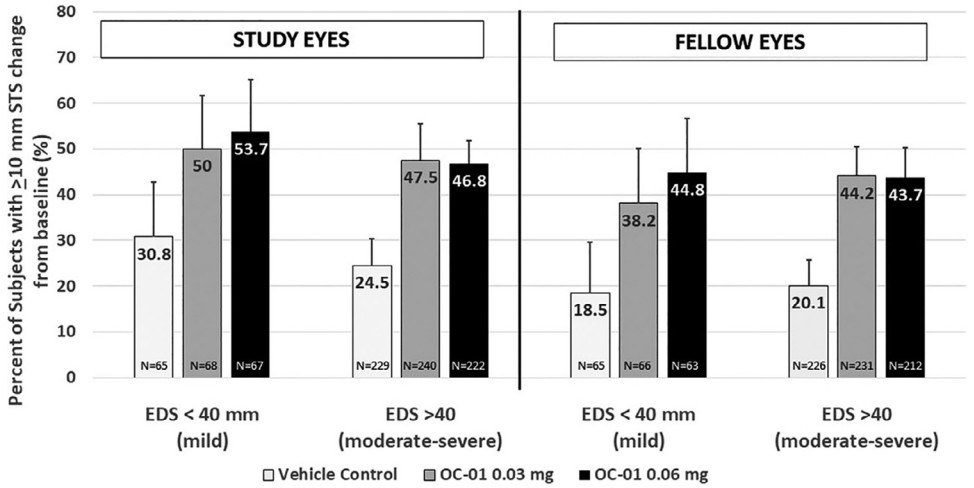

Figure 4. Percentage of patients with ≥10-mm change from baseline in Schirmer test score (STS) at week 4 by study and fellow eyes by baseline Eye Dryness Score (EDS) severity (integrated data). Error bars indicate SDs.

to 53.7% of eyes with mild DED and 46.8% to 47.5% of eyes with moderate-severe DED receiving OC-01 (varenicline solution) nasal spray achieved a ≥10-mm STS improvement versus only 24.5% to 30.8% of vehicle control–treated study eyes. In fellow eyes, 38.2% to 44.8% of OC-01–treated eyes with mild DED and 43.7% to 44.2% of OC-01–treated eyes with moderate-severe DED achieved this outcome versus only 18.5% to 20.1% of vehicle control–treated fellow eyes.

Overall Mean Change From Baseline Eye Dryness Score: Integrated Data

The LS mean change in EDS from baseline to week 4 was −9.0 mm in vehicle control–treated patients and improved significantly more in patients receiving OC-01 (varenicline solution) nasal spray 0.03 mg (−14.7 mm; $p = 0.0034$) and 0.06 mg (−16.2 mm; $p = 0.0003$). Because EDS is a holistic, subjective assessment that evaluates the overall discomfort score from both eyes (bilateral assessment), values are relevant to study and fellow eyes in combination. Mean changes from baseline STS among study and fellow eyes were highly correlated with a Pearson correlation coefficient of 0.7 ($p < 0.0001$).

Safety Outcomes

With regard to adverse events, sneeze was the most common, occurring in 82.2% to 83.9% of OC-01–treated patients and 22.4% of vehicle control–treated patients. Other commonly observed events included cough (15.8%–19.7% vs 1.5%), throat irritation (12.6%–16.1% vs 1.5%), and nasal site irritation (8.3%–13.3% vs 0.9%). More than 98% of individuals who reported treatment-emergent adverse events rated them as mild in severity.

DISCUSSION

This post hoc analysis of treatment outcomes in nonstudy fellow eyes of participants in 2 pivotal clinical trials found that pharmacologic neuroactivation of the trigeminal parasympathetic pathway with OC-01 (varenicline solution) nasal spray administered to each nostril twice daily improved bilateral basal tear production compared with vehicle control from baseline to week 4 in study and fellow eyes.

The ONSET-1 and ONSET-2 trials required that only 1 eye qualify for the patient to participate and, if both eyes qualified, the worse eye was designated the study eye. Consequently, baseline ocular characteristic differences between study and fellow eyes would be expected. The value of this analysis of outcomes in nonstudy fellow eyes is 2-fold: it has symmetry of bilateral therapeutic responses with bilateral (both nostril) nasal spray administration, and it characterizes outcomes in a sample with a milder baseline DED clinical presentation than the study eye sample that met all trial eligibility criteria.

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The symmetry of response to bilateral intranasal dosing of OC-01 (varenicline solution) nasal spray is of clinical significance in that the patient-level response requires satisfactory bilateral ocular response to therapy: patients' perception of DED is driven by the worse eye, and if either eye remains symptomatic, the patient remains symptomatic. This finding is evidenced in the current data set by the similarity of patient-level EDSs at baseline despite intereye differences in mean baseline STS of approximately 2.5 mm. We observed that STS outcomes had improvement consistency (no treatment-subgroup interaction) for both study and fellow eyes regardless of presenting baseline EDSs of <40 and ≥40. Previous clinical trials of DED therapies limited enrollment to patients with presenting EDSs of ≥40 mm, which may limit the ability to interpret symptomatic benefits in patients presenting with more mild symptomatic disease.[17,18] Despite intereye differences at baseline in the ONSET-1 and ONSET-2 trials, this post hoc analysis found that the magnitude of the treatment effect was consistent between study and fellow eyes with regard to mean STS improvement, mean EDS improvement, and percentage of eyes achieving ≥10-mm STS improvement. This finding was expected because OC-01 (varenicline solution) nasal spray therapy was applied bilaterally to both nostrils. Although laterality to treatment with respect to effect on both eyes with single nostril dosing is unknown, unilateral (single nostril) stimulation of the nasal mucosa can potentially trigger bilateral tear production.[13] As supported in our observed results in both study and fellow eyes, there was no expectation of differences in therapeutic response between eyes that would be related to differences in drug exposure with administration of nasal spray delivered to each nostril. The outcomes in this analysis (and overall ONSET-1 and ONSET-2 trials) were derived from twice daily bilateral (both nostril) dosing; the favorability of clinical signs and symptomatic outcome improvements further support this dosing regimen.

Generalizability of clinical trial outcomes is related to the stringency of trials' eligibility criteria. The more homogenous (strict) the eligibility criteria are, the less generalizable the results will be to the broader and more heterogeneous population of affected patients. In ONSET-1 and ONSET-2, study eyes were required to have a baseline STS ≤10 mm, indicative of moderate to severe DED. In the current analysis, baseline STS in study eyes ranged from 0 to 10 mm (the upper limit of eligibility), whereas in fellow eyes, baseline STS ranged from 0 to 28 mm, indicating the inclusion of fellow eyes with milder disease than was required in study eyes. This baseline difference in STS between study and fellow eyes provides an opportunity to generalize OC-01 (varenicline solution) nasal spray efficacy to eyes that may represent a broader population of patients with DED than do study eyes. The findings from this analysis—that response to treatment with OC-01 (varenicline solution) nasal spray was similar in study and fellow eyes with mild and moderate-severe DED at baseline—may further support use of OC-01 (varenicline solution) nasal spray for therapy in a broad population of patients with DED across the spectrum of presenting disease severity.

Strengths of this analysis include the use of robustly collected data from 2 well-designed and appropriately powered clinical trials. Selection bias was minimized by including all individuals randomly assigned to the included treatment groups. The outcomes of this analysis were the primary efficacy outcomes of the 2 trials from which the data were drawn (the percentage of patients with a ≥10-mm STS improvement in ONSET-1 and the mean change from baseline in STS in ONSET-2).[8,9] A key limitation is that this was an unplanned post hoc analysis, and the original study design aligned to US Food and Drug Administration guidance for clinical trials in DED requiring a declared study eye. The impact of these limitations on findings may be potentially mitigated by the strengths discussed above.

In conclusion, OC-01 (varenicline solution) nasal spray significantly improved tear production in the study eyes as well as in milder presenting nonstudy fellow eyes of ONSET-1 and ONSET-2 participants. The totality of these data supports the recommendation for bilateral nasal dosing with OC-01 (varenicline solution) nasal spray (both nostrils, twice daily) and further indicates improvements in tear production and symptomatic outcomes across a broad spectrum of patients with mild, moderate-severe DED.

DECLARATION OF INTEREST

The sponsor was involved in the study design, the interpretation of data, the writing of the manuscript, and the decision to submit the manuscript for publication. Laura M. Periman reports serving on the medical advisory board and speakers' bureau

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for Oyster Point Pharma Inc. Sathi Maiti reports receiving clinical research funding from Oyster Point Pharma Inc. Mandy Hemphill, Alan G. Kabat, Laura H. Hendrix, Puja Shah, and Andrea Gibson are employees and shareholders of Oyster Point Pharma Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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