Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

OC-01 (Varenicline Solution) Nasal Spray for the Treatment of Dry Eye Disease Signs and Symptoms in Subjects with Autoimmune Disease: Integrated Data from ONSET-1 and ONSET-2

Julie M Schallhorn[1], Selina McGee[2], Jeffrey Nau[3], Marian Macsai[3], Andrea Gibson[3], Gretchen Blemker[3], Laura H Hendrix[3], Mina Massaro-Giordano[4]

[1]Department of Ophthalmology and Francis I, Proctor Foundation, University of California, San Francisco, CA, USA; [2]BeSpoke Vision, Edmond, OK, USA; [3]Oyster Point Pharma, Princeton, NJ, USA; [4]Scheie Eye Institute, Penn Dry Eye and Ocular Surface Center, University of Pennsylvania Health System, Philadelphia, PA, USA

Correspondence: Mina Massaro-Giordano, Scheie Eye Institute, 51 N 39th Street, Philadelphia, PA, 19104, USA, Tel +1 216 662-9903, Email mina@pennmedicine.upenn.edu

Purpose: We evaluate the treatment effect of OC-01 (varenicline solution) nasal spray (VNS) in dry eye disease (DED) subjects from two randomized trials who self-reported autoimmune disease (AID).

Patients and Methods: Post hoc subgroup analysis of subjects reporting a history of AID from the integrated OC-01 VNS 0.03 or 0.06 mg and vehicle control (VC) treatment groups of the ONSET-1 and ONSET-2 trials. Mean change in Schirmer test with anesthesia score (STS, mm) and Eye Dryness Score (EDS) from baseline to 28 days was compared between OC-01 VNS and VC groups. Consistency of treatment effect in subjects with and without AID was evaluated using treatment–subgroup interaction terms in ANCOVA models for mean changes from baseline STS and EDS, and in a logistic regression model for proportion achieving ≥10 mm STS improvement.

Results: Of the 891 participants, 31 reported comorbid AID. In all models, the treatment–subgroup interaction terms were not significant ($p>0.05$), indicating consistency of therapeutic effect of OC-01 VNS in subjects with and without AID. In subjects with AID, the treatment difference for STS was 11.8 mm and −9.3 for EDS and difference for proportion of subjects with ≥10 mm STS improvement was 61.1%. The most common adverse event was sneeze (82–84%), graded as mild by 98% of subjects.

Conclusion: OC-01 VNS demonstrated consistency in improving both tear production and patient-reported symptoms in subjects with AID, consistent with pivotal ONSET-1 and 2 trial results. Further investigation is warranted, and results may further support use of OC-01 VNS for DED in AID patients.

Keywords: dry eye disease, autoimmune disease, Eye Dryness Score, nicotinic acetylcholine receptor, Schirmer test score, varenicline nasal spray, Tyrvaya

Introduction

Dry eye disease (DED) is among the most common ocular conditions worldwide.[1] DED has been defined as a multifactorial disease characterized by a persistently unstable and/or deficient tear film causing discomfort and/or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation, and neurosensory abnormalities.[2]

A number of autoimmune diseases have been associated with a worsening of the signs and symptoms of dry eye disease as a comorbidity.[3,4] Clinical signs of DED, including Schirmer test score (STS), tear break-up time (TBUT), and corneal fluorescein staining (CFS), as well as signs of ocular surface inflammation, present more severely in patients with autoimmune diseases than in patients without autoimmune comorbidity.[5]

Received: 7 January 2023
Accepted: 21 February 2023
Published: 3 March 2023

An unmet need in the management of autoimmune disease patient populations with DED is treatment that provides prolonged symptomatic relief and improves quality of life in patients suffering from these diseases. Mixed clinical results with this population have been found with topical anti-inflammatory treatment,[6–11] but the effects of a nasally administered cholinergic agent that stimulates the production of natural tear film have not been explored.

Varenicline solution nasal spray, a cholinergic agonist, is believed to activate the trigeminal parasympathetic pathway in the nasal cavity to produce basal tear film by stimulating the lacrimal functional unit.[12] Varenicline binds with high affinity and selectivity at human α4β2, α4α6β2, α3β4, α3α5β4, and α7 neuronal nicotinic acetylcholine receptors.[13] Formulated as a nasal spray that is administered once to each nostril twice daily, varenicline nasal spray 0.03 mg (TYRVAYA®; Oyster Point Pharma®) was approved in 2021 by the US Food and Drug Administration for the treatment of signs and symptoms of DED.[13] In phase 2b and 3 clinical trials, OC-01 (varenicline solution) nasal spray increased tear production and improved the signs and symptoms of DED significantly better than vehicle control over 4 weeks of therapy, with improvements in the proportion of subjects achieving ≥10 mm increase in STS, mean anesthetized STS, and Eye Dryness Score (EDS).[14–16]

This post hoc analysis of integrated data from the Phase 2b ONSET-1 and Phase 3 ONSET-2 trials evaluated the effect of OC-01 (varenicline solution) nasal spray on tear production and symptom score outcomes as compared to vehicle control in subjects with DED who self-reported a medical history of underlying autoimmune disease.

Materials and Methods

Study Designs

This was a post hoc subgroup analysis of integrated data from the Phase 2b ONSET-1 trial (ClinicalTrials.gov, NCT03636061)[14] and the Phase 3 ONSET-2 trial (ClinicalTrials.gov, NCT04036292),[15] the randomized controlled pivotal trials reported previously that supported the FDA approval of the efficacy and safety of OC-01 (varenicline solution) nasal spray versus vehicle for the treatment of the signs and symptoms of DED. For both studies, institutional review board (Alpha IRB, San Clemente, CA) approval was obtained, and the study was conducted in compliance with the ethical principles of the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice. All subjects provided written informed consent before participation.

Methods and safety and efficacy results from these clinical trials have been previously reported.[14,15] Briefly, subjects with DED (anesthetized STS ≤10 mm, Ocular Surface Disease Index [OSDI®] score ≥23) were randomized to receive OC-01 (varenicline solution) nasal spray in various concentrations or vehicle control once to each nostril twice daily. Inclusion criteria included subjects who demonstrated an increase of 7 mm or greater on cotton swab nasal stimulation at screening. One eye of each subject was included in the primary analysis. The study eye was the qualifying eye or, if both qualified, the worse eye at baseline. Key endpoints of the ONSET studies included mean changes from baseline in STS and EDS, as well as the proportion of eyes achieving a ≥10mm improvement from baseline in STS, all assessed at day 28. In both ONSET trials, STS was performed with anesthesia in a standard fashion and assessed at 5 minutes. EDS was obtained by asking subjects to rate their eye dryness symptoms on a 100-mm visual analog scale (0=no discomfort, 100=maximal discomfort).

The study population consisted of all subjects randomized who received at least one dose of study medication: OC-01 (varenicline solution) nasal spray 0.03 mg/0.06 mg, or vehicle control once to each nostril twice daily in ONSET-1 and ONSET-2 trials. Subjects with autoimmune disease were selected from this population. Autoimmune disease status was determined by subject self-report at baseline of a comorbid autoimmune disease (Table 1). For this analysis, the OC-01 (varenicline solution) nasal spray 0.03 mg (n=9) and 0.06 mg (n=11) treatment groups were combined (n=20) and compared to the vehicle control group (n=11). Among the subjects who received 0.06 mg treatment in the ONSET-1 study, no subjects self-reported a medical history of autoimmune disease, and therefore this dose group was not included.

Statistical Analysis

To evaluate consistency of treatment effect among subjects with and without autoimmune disease, treatment–subgroup interaction tests were performed for each endpoint using the complete integrated ONSET-1 and ONSET-2 dataset. Analysis of covariance (ANCOVA) models were used to test for treatment–subgroup interaction for mean changes in

Table 1 Subject Demographics, Comorbid Autoimmune Diseases, and Baseline Ocular Characteristics by Subgroup and Treatment

	Patient-Reported Autoimmune Disease		No Patient-Reported Autoimmune Disease	
	OC-01 VNS (n=20)	Vehicle Control (n=11)	OC-01 VNS (n=577)	Vehicle Control (n=283)
Age (yr),				
Mean (SD)	57.5 (12.3)	63.6 (9.4)	60.4 (12.8)	59.0 (13.1)
Median (range)	57.5 (38.0–78.0)	64.0 (45.0–80.0)	62.0 (22.0–91.0)	60.0 (23.0–95.0)
Gender, n (%)				
Male	2 (10)	1 (9.1)	152 (26.3)	60 (21.2)
Female	18 (90)	10 (90.9)	425 (73.7)	223 (78.8)
Race, n (%)				
White	16 (80)	10 (90.9)	477 (82.7)	240 (84.8)
Other	4 (20)	1 (9.1)	100 (17.3)	43 (15.2)
Comorbid autoimmune disease, n (%)				
Rheumatoid arthritis	7 (35)	7 (63.6)	-	-
Sjögren's syndrome	2 (10)	2 (18.2)	-	-
Autoimmune thyroiditis (Hashimoto)	2 (10)	0 (0)	-	-
Colitis	1 (5)	1 (9.1)	-	-
Crohn's disease	2 (10)	0 (0)	-	-
Multiple sclerosis	2 (10)	1 (9.1)	-	-
Psoriasis	2 (10)	0 (0)	-	-
Systemic lupus erythematosus	2 (10)	0 (0)	-	-
STS (mm)				
Mean (SD)	5.6 (2.8)	4.2 (3.4)	5.2 (2.9)	4.96 (2.9)
Median (range)	6.0 (1.0–10.0)	4.0 (0.0–10.0)	5.0 (0.0–10.0)	5.0 (0.0–10.0)
EDS				
Mean (SD)	59.2 (26.1)	52.7 (24.4)	58.9 (21.7)	59.4 (21.7)
Median (range)	60.5 (14.0–98.0)	64.0 (13.0–80.0)	63.0 (2.0–100.0)	63.0 (3.0–100.0)

Abbreviations: EDS, Eye Dryness Score; SD, standard deviation; STS, Schirmer test score; VNS, varenicline nasal spray.

baseline STS and EDS. Logistic regression was used to test for treatment–subgroup interaction for the proportion of subjects achieving a ≥10 mm improvement in STS. All models included covariates baseline EDS, baseline STS, study, and site, and a treatment–subgroup interaction term. In accordance with published guidelines regarding post hoc subgroup analyses, heterogeneity of treatment effect among subgroups was evaluated with treatment-by-subgroup interaction tests.[17] Per these guidelines, only effect sizes and 95% confidence intervals are reported, as significance testing is inappropriate for post hoc derived subgroup analyses. The level of significance for interaction is $p>0.05$. If no interaction was observed, estimates and 95% confidence intervals for each endpoint and OC-01 (varenicline solution) nasal spray-vehicle control differences were calculated. The outcome measures assessed in these analyses were identical

to those in the original pivotal studies and included the proportion of eyes achieving a ≥10 mm improvement in STS from baseline to Day 28 in STS and mean change in STS and EDS from baseline to Day 28.

Results

Demographic and Baseline Clinical Characteristics

In ONSET-1, 182 subjects were randomized 1:1:1:1 to receive 0.006 mg, 0.03 mg, or 0.06 mg OC-01 (varenicline solution) nasal spray or vehicle control. In ONSET-2, 758 subjects were randomized 1:1:1 to receive 0.03 mg or 0.06 mg OC-01 (varenicline solution) nasal spray or vehicle control. Of the 891 subjects from both studies, 31 subjects who received either 0.03 mg or 0.06 mg OC-01 (varenicline solution) nasal spray or vehicle control self-reported a comorbid autoimmune disease.

The demographic data and baseline ocular characteristics of these subjects, as well as the nature and frequency of autoimmune diseases included in the autoimmune subgroup, are provided in Table 1. Baseline characteristics of subjects with and without autoimmune disease were similar; both were predominantly White and female with a mean age of approximately 60 years. The most common autoimmune diseases were rheumatoid arthritis (45.2%) and Sjögren's syndrome (12.9%). During the study period, 30% of the treated and 57% of the vehicle control groups reported use of artificial tears at some point during the clinical trial as a concomitant medication. There were no significant treatment–subgroup interactions observed ($p>0.05$) for all studied endpoints, demonstrating consistency of OC-01 (varenicline solution) nasal spray treatment effect in evaluated measures among subjects with and without autoimmune disease (Table 2).

Improvements in Mean Schirmer Test Score After OC-01 (Varenicline Solution) Nasal Spray Administration

In subjects with and without autoimmune disease, the mean baseline STS was 5.6 mm and 5.2 mm in OC-01 (varenicline solution) nasal spray-treated subjects and 4.2 mm and 4.9 mm in vehicle control-treated subjects, respectively. Following 28 days of treatment in subjects with and without autoimmune disease, the mean STS change from baseline was 13.6 mm and 11.7 mm in OC-01 (varenicline solution) nasal spray subjects and 1.8 mm and 6.4 mm in vehicle control subjects, respectively. In subjects with autoimmune disease, a treatment difference of 11.8 mm (95% confidence interval [CI]: 6.5, 17.1) was observed as compared to 5.3 mm (95% CI: 4.1, 6.5), in subjects without autoimmune disease (Table 2). In the subgroup with autoimmune disease, the mean change from baseline STS was 13.6 mm in OC-01 (varenicline solution) nasal spray-treated subjects and 1.8 mm in vehicle control group (Figure 1).

Improvements in Categorical (Proportion with ≥10 mm Increase) in Schirmer Test Score After OC-01 (Varenicline Solution) Nasal Spray Administration

Following 28 days of treatment, 61.1% and 50.0% of subjects with and without autoimmune disease who received OC-01 (varenicline solution) nasal spray achieved a ≥10 mm improvement in STS compared to 0% and 27.1% of subjects who

Table 2 Treatment Effect (Treatment – Vehicle Difference) Outcomes by Subgroup

	Patient-Reported Autoimmune Disease Subgroup			No Patient-Reported Autoimmune Disease Subgroup			No Interaction (p>0.05) Demonstrates Treatment Effect (Benefit) is Consistent Between Subgroups
	OC-01 VNS	Vehicle Control	Treatment – Vehicle Difference	OC-01 VNS	Vehicle Control	Treatment – Vehicle Difference	
Mean CFB STS (mm)	13.6	1.8	11.8 (95% CI]: 6.5, 17.1)	11.7	6.4	5.3 (95% CI: 4.1, 6.5),	p> 0.05
Proportion of ≥10 mm STS from baseline	61.1%	0%	61.1% (95% CI: 46.0%, 76.2%)	50.0%	27.1%	22.9% (95% CI: 18.2%, 27.5%)	p>0.05
Mean CFB EDS (mm)	−19.6	−10.3	−9.3 (95% CI: −26.6, 8.2)	−20.0	−14.0	−6.0 (95% CI: −9.9, −2.1)	p> 0.05

Abbreviations: CFB, change from baseline, CI, confidence interval, EDS, Eye Dryness Score; mm, millimeters, SD, standard deviation; STS, Schirmer test score; VNS, varenicline nasal spray.

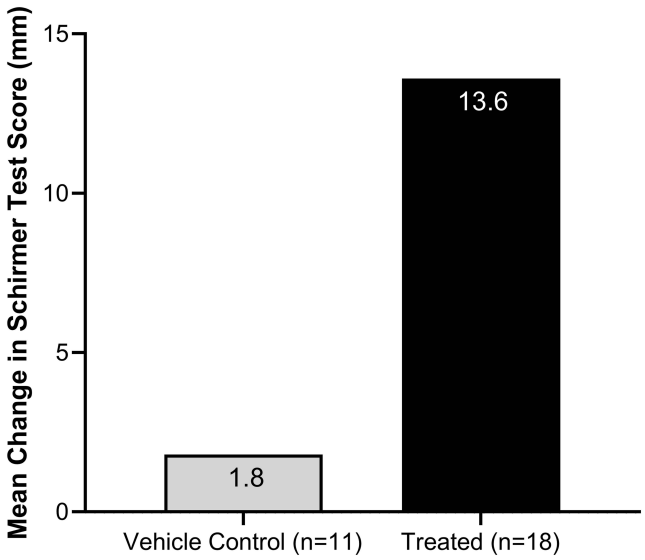

Figure 1 Mean change in Schirmer test score by autoimmune disease subgroup and treatment group.

received vehicle control, respectively. Treatment differences were 61.1% (95% CI: 46.0%, 76.2%) in subjects with autoimmune disease and 22.9% (95% CI: 18.2%, 27.5%) in subjects without autoimmune disease for the proportion of subjects with a ≥10 mm STS improvement (Table 2). Following 28 days of treatment, 61% of subjects who received OC-01 (varenicline solution) nasal spray achieved a ≥10 mm improvement in STS compared to 0% of subjects who received vehicle control in the subgroup with autoimmune disease (Figure 2).

Improvements in Eye Dryness Score After OC-01 (Varenicline Solution) Nasal Spray Administration

In subjects with and without autoimmune disease, the mean baseline EDS was 59.2 and 58.9 in OC-01 (varenicline solution) nasal spray-treated subjects and 52.7 and 59.4 in vehicle control-treated subjects, respectively. Following 28 days of treatment in subjects with and without autoimmune disease, the mean EDS change from baseline was −19.6 and

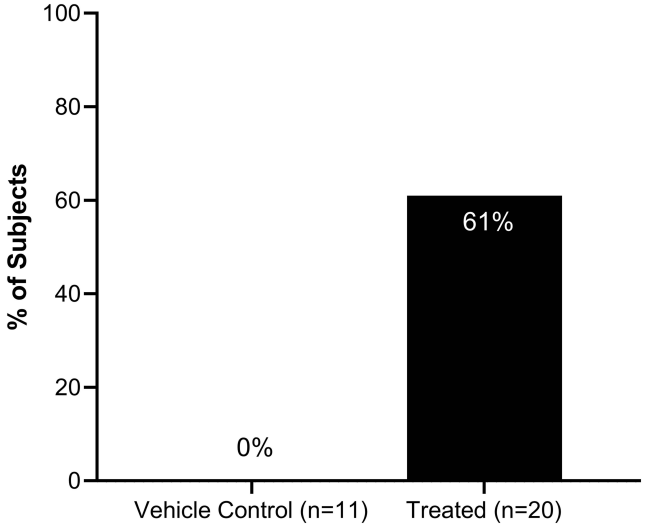

Figure 2 Categorical (proportion of subjects achieving a ≥10 mm) improvement in Schirmer test score at day 28 by autoimmune disease subgroup and treatment group.

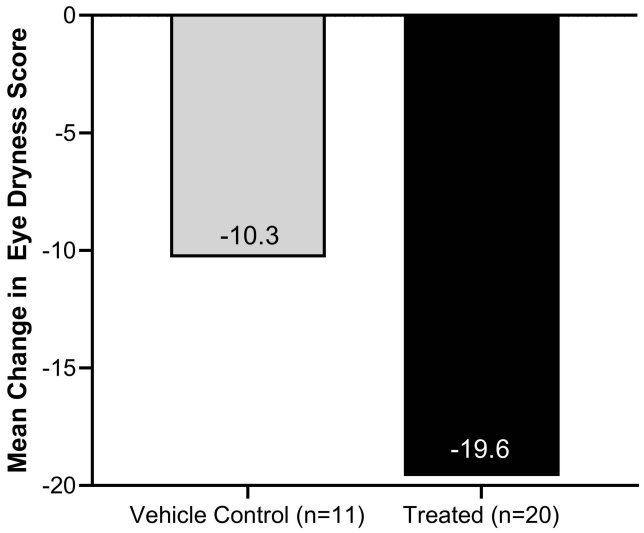

Figure 3 Mean change in Eye Dryness Score by autoimmune disease subgroup and treatment group.

−20.0 in OC-01 (varenicline solution) nasal spray subjects and −10.3 and −14.0 in vehicle control subjects, a treatment difference for EDS change from baseline of −9.3 (95% CI: −26.6, 8.2) and −6.0 (95% CI: −9.9, −2.1), respectively (Table 2). Following 28 days of treatment, the mean EDS change from baseline was −19.6 in OC-01 (varenicline solution) nasal spray subjects and −10.3 in vehicle control subjects in the subgroup with autoimmune disease (Figure 3).

Discussion

DED is common in patients with autoimmune disease, and pathophysiology is likely related to the underlying mechanisms of autoimmunity. Autoimmunity can directly involve tissues of the lacrimal functional unit, leading to tear film deficiency and instability and clinical signs and symptoms of DED.[18,19] It remains unclear as to the exact pathophysiology of how autoimmunity can impact basal tear production whether by an inflammatory process, via interaction with receptors in the nervous system responsible for gland stimulation, or by direct damage to nerves responsible for stimulating gland secretion.

Interestingly, the vehicle control group data from this study illustrate the limited tear film production in this patient population as demonstrated by a minimal mean change from baseline in Schirmer's test score (1.8 mm). This level of tear production is lower than observed in the overall integrated ONSET-1 and ONSET-2 dry eye disease vehicle control group population (4.9 mm).[20] This low level of basal tear production is likely a cause of desiccating stress on the corneal and conjunctival epithelium in these patients, increasing the amount of corneal fluorescein staining and inflammatory cell markers, similar to what has been shown in botulinum toxin induced dry eye animal models.[21] In addition, it has been shown from impression cytology that the percentage of conjunctival epithelial cells undergoing apoptosis is higher in patients with autoimmune disease and dry eye symptoms.[22,23] Despite the lack of increase in basal tear production in the vehicle control group, the OC-01 (varenicline solution) nasal spray-treated group illustrates a robust mean change from baseline following treatment (13.6 mm). Based on these findings, it is likely that autoimmune patients may have functional gland structures with residual gland volume and these patients produced tear film at levels consistent with the broader dry eye disease population seen in the ONSET-1 and ONSET-2 trials.[14,15]

Recently, Jin et al showed that interruption of neural stimuli to the lacrimal gland by denervation of parasympathetic postganglionic nerves immediately and chronically decreased tear secretion, causing lacrimal gland atrophy.[24] These atrophic changes resulted in infiltration of inflammatory cells, further questioning whether inflammation is the instigating factor of dry eye disease or a sequelae of the lack of neural input to the gland. Additionally, in their study, infusion of the nicotinic and muscarinic agonist carbachol maintained the lacrimal gland weight and morphology in context of postganglionic denervation of the gland, whereas the muscarinic antagonist scopolamine reduced tear secretion and

gland weight and increased gland atrophy.[24] Results may suggest that the underlying pathophysiology of autoimmune disease effect on the lacrimal gland does not have a major impact on the parasympathetic nervous system's ability to maintain lacrimal gland structure and function, but may potentially implicate an interaction with receptor(s), including muscarinic (M3) receptors located on the gland. This hypothesis is supported by the numerous studies indicating that anti-muscarinic acetylcholine receptor antibodies are present in patients with Sjögren's syndrome.[25–28] There are a number of other muscarinic receptor classes including M2, and M4 located on the lacrimal gland structures and innervating nerves that could potentially be implicated to play a role. Autoimmune patients, including those with Sjögren's syndrome, have been shown to have autoantibodies against the ganglionic acetylcholine receptor (gAChR), which has been associated with systemic dysautonomic symptoms. These autoantibodies induce the internalization of cell-surface nicotinic gAChRs and subsequent impairment in synaptic transmission within the autonomic nervous system. While it is not known exactly how autoimmune disease negatively impacts lacrimal gland function, it is likely either through the blocking of receptors or may involve impairment of the nerve impulses to the gland.

In this analysis of subjects with autoimmune disease, downstream activation of the trigeminal nerve in the nasal cavity with the nicotinic agonist OC-01 (varenicline solution) nasal spray activated robust tear production consistent with results from treated subjects in the pivotal studies,[14,15] overcoming whatever mechanism was limiting tear production in vehicle control treated subjects. This might suggest that not only is the pathway for activation of the gland intact in autoimmune disease patients, but it may be harnessed by cholinergic activation with OC-01 (varenicline solution) nasal spray to produce basal tear film. It has been suggested that anti-muscarinic antibodies (M3) circulate at low levels in patients with Sjögren's syndrome;[29] perhaps their impact on compromised gland functioning may potentially be overcome with downstream nicotinic receptor agonist activation resulting in lacrimal functional unit secretion. Dartt et al demonstrated that M3AChR and P2X7 receptors use different pathways to stimulate protein secretion.[30] One mechanism by which cholinergic agonists stimulate lacrimal gland protein secretion is to activate P2X7 receptors. In the presence of M3 anti–muscarinic antibodies, stimulation of this alternate pathway with cholinergic agonist treatment may activate lacrimal gland secretion.[30] The presence of M3 autoantibodies does not necessarily mean that the entire population of M3 receptors on the lacrimal gland are blocked, as receptor populations are often in dynamic states of activation at any one point in time. It is possible that some portion of the M3 receptor population is still functional and available to be bound, as illustrated by the decreased, but not absent, tear production commonly seen in Sjögren's patients treated with pilocarpine (a muscarinic agonist) (Figure 4.) Therefore, it could be further hypothesized that persistent activation of the parasympathetic pathway may potentially improve tear secretion and prevent future gland atrophy. Future studies are needed to explore this further.

In this analysis, study subjects who self-reported autoimmune disease and were treated with OC-01 (varenicline solution) nasal spray demonstrated directionally greater improvements from baseline in mean changes in STS, EDS, and achievement of ≥10 mm increase in STS compared to vehicle control as evidenced by the treatment–subgroup interaction terms in all relevant models ($p>0.05$). Consistency of treatment benefit was demonstrated among subjects with and without autoimmune disease. Given the likelihood of greater severity of DED signs and symptoms in patients with comorbid autoimmune disease, these findings may further inform support for use of OC-01 (varenicline solution) nasal spray for DED treatment in these patients.

Overall, the OC-01 (varenicline solution) nasal spray compared to vehicle control safety outcomes have been characterized in previously reported pivotal clinical studies.[14–16] It is inappropriate to perform safety analyses in subpopulations as it could lead to erroneous conclusions, including under- or over-reporting adverse event rates.

OC-01 (varenicline solution) nasal spray represents a novel first-in-class drug therapy for DED sufferers, including those with associated autoimmune disease. The drug is delivered via nasal rather than via topical ophthalmic administration. The intranasal route has the benefit of preventing disruption of the tear film or ocular surface at the time of dosing, an important consideration given that tear film instability and deficiency is a fundamental component of the pathophysiology of DED.[2] Once in the nasal passage, OC-01 (varenicline solution) nasal spray binds nicotinic acetylcholine receptors on the anterior ethmoid nerve of the trigeminal parasympathetic pathway to produce endogenous tearing, thereby bolstering the natural tear film. Many patients with autoimmune disease retain functional gland morphology and

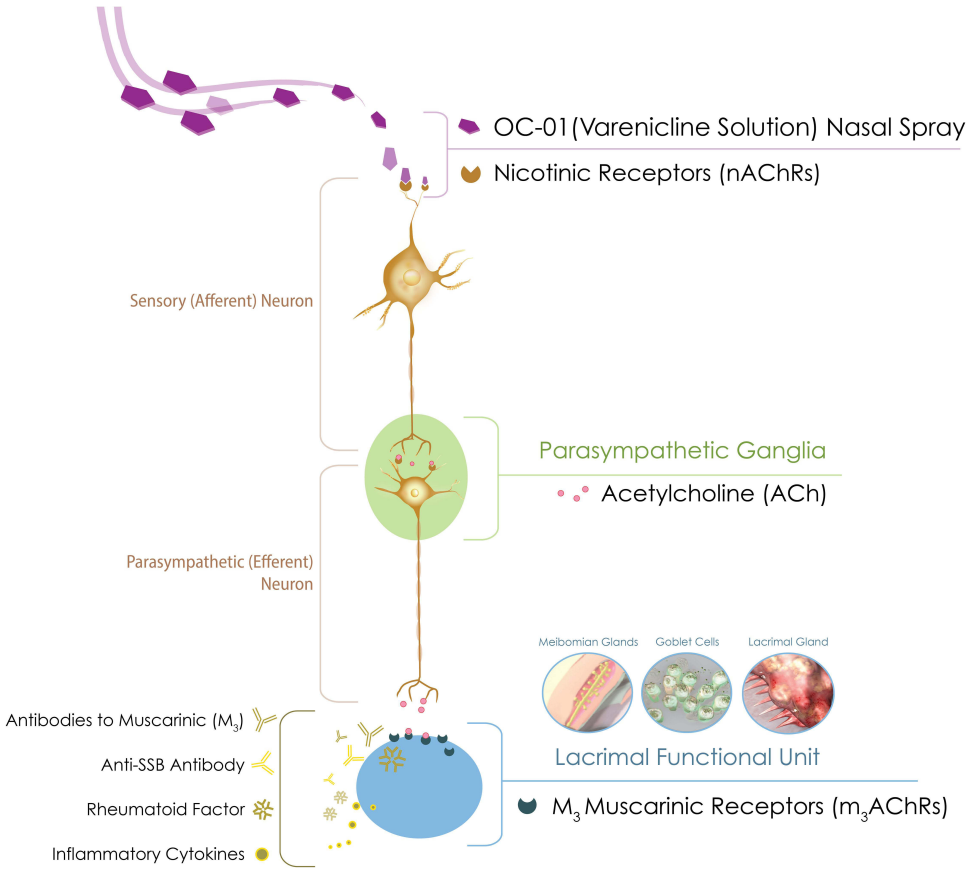

Figure 4 Nicotinic acetylcholine receptor agonist activation of trigeminal parasympathetic pathway and depiction of anti-muscarinic acetylcholine receptor antibodies present in Sjögren's syndrome. For illustrative purposes only.

residual lacrimal gland volume despite likely immunological effects at the cellular and glandular levels, thereby making them potential candidates for treatment.

This analysis is strengthened by the utilization of robust data collected from two prospective, randomized, controlled clinical trials. The outcomes of this analysis are the same as the primary efficacy outcomes of the two studies from which the clinical data were drawn, and appropriate statistical guidelines for treatment effect interaction testing (not significance testing) for post hoc derived subgroups were followed.[17] A key limitation of the study is its post hoc subgroup nature: neither ONSET-1 nor ONSET-2 was designed to evaluate OC-01 (varenicline solution) nasal spray efficacy and safety specifically in patients with autoimmune comorbidities. Additionally, due to the post hoc subgroup analysis structure, the two groups being analyzed were not protected by randomization to treatment group at baseline. Nonetheless, this is an important population of dry eye disease patients to study, as they may represent a group with distinct underlying pathophysiology that is not well understood. Lastly, the autoimmune disease subgroup in this analysis was based on study subjects' self-reported autoimmune diagnoses unconfirmed by a physician, therefore primary versus secondary Sjögren's syndromes were not captured, and subjects in both groups reported artificial tear use with a higher proportion of utilization within the vehicle control group.

Conclusion

In conclusion, OC-01 (varenicline solution) nasal spray directionally demonstrated improved tear production (measured by STS) and patient-reported symptoms (measured by EDS) in subjects with self-reported autoimmune diseases, consistent with pivotal ONSET-1 and ONSET-2 trial results. While future prospective studies with larger samples of subjects with autoimmune disease are warranted to confirm these findings, the results of this analysis may further support the use of OC-01 (varenicline solution) nasal spray for DED treatment in this patient population.

Abbreviations

ANCOVA, analysis of covariance; CI, confidence interval; EDS, eye dryness score; gAChR, ganglionic acetylcholine receptors; M2, M3, M4, muscarinic receptors 2, 3, 4; M3AChR, muscarinic acetylcholine receptor 3; P2X7, purinoreceptor 7SD, standard deviation; STS, Schirmer Test Score; VC, vehicle control; VNS, varenicline solution nasal spray.

Data Sharing Statement

The data used to support the primary findings of this study are available at ClinicalTrials.gov (NCT03636061 and NCT04036292).

Ethics Approval and Informed Consent

This study was conducted in accordance with the principles of Declaration of Helsinki and in compliance with the ICH E6 GCP Consolidated Guideline, ISO 14155:2011, and the applicable US FDA 21 CFR Regulations. Before clinical study initiation, the protocol and all amendments, the informed consent form, any other written information given to subjects, and any advertisements planned for subject recruitment was approved by an IRB/IEC (Alpha IRB, San Clemente, CA).

Acknowledgments

Medical writing assistance was provided by Tony Realini, MD, MPH of Hypotony L.L.C. and was funded by Oyster Point Pharma, Inc. Portions of these data were presented at the Association for Research in Vision and Ophthalmology Annual 2022 Meeting; May 1–5; Denver, Colorado, and Women in Ophthalmology 2022 Summer Symposium; August 25–28; Monterey, California.

Author Contributions

All authors made significant contributions to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was sponsored by Oyster Point Pharma, Inc., manufacturer/licensee of OC-01 (varenicline solution) nasal spray.

Disclosure

J.M.S. is an investigator and advisor for Oyster Point Pharma, Inc. She reports personal fees from Zeiss, Allergan, and Forsight V6; equities from Journey 1, Neurotrigger, and Novus Vision, outside the submitted work. M.M.G. is an advisor of Oyster Point Pharma, Inc. She reports that she has invested $300 in stocks of Kala; advisory board member for Claris Bio and Dompe. S.M. is a speaker, advisor and advisory board member for Oyster Point Pharma, Inc. She is also a speaker of and/or advisory board member for Allergan, Bausch & Lomb, Bruder, Cynosure, Dompe, Eyevance, Horizon, Lumenis, Ocuphire, RVL, Novartis, Science Based Health, Sun, and Tarsus, outside the submitted work. J.N. is an employee and shareholder of Oyster Point Pharma, Inc. He reports patents (9504644, 9504645, 9532944, 9597284, 10456396, and 11224598) issued to Oyster Point Pharma, Inc. M.M. is an employee and shareholder of Oyster Point Pharma, Inc. A.G. is an employee and shareholder of Oyster Point Pharma, Inc. G.B. is an employee and shareholder of Oyster Point Pharma, Inc. L.H.H. is an employee and shareholder of Oyster Point Pharma, Inc. The authors report no other conflicts of interest in this work.

References

1. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. 2017;15(3):334–365. doi:10.1016/j.jtos.2017.05.003
2. Tsubota K, Pflugfelder SC, Liu Z, et al. Defining dry eye from a clinical perspective. *Int J Mol Sci*. 2020;21(23):9271. doi:10.3390/ijms21239271
3. Nguyen CQ, Peck AB. Unraveling the pathophysiology of Sjogren syndrome-associated dry eye disease. *Ocul Surf*. 2009;7(1):11–27. doi:10.1016/S1542-0124(12)70289-6

4. Yu K, Bunya V, Maguire M, et al. Systemic conditions associated with severity of dry eye signs and symptoms in the dry eye assessment and management study. *Ophthalmology*. 2021;128(10):1384–1392. doi:10.1016/j.ophtha.2021.03.030
5. Wang H, Wang PB, Chen T, et al. Analysis of clinical characteristics of immune-related dry eye. *J Ophthalmol*. 2017;2017:8532397. doi:10.1155/2017/8532397
6. Moscovici BK, Holzchuh R, Sakassegawa-Naves FE, et al. Treatment of Sjogren's syndrome dry eye using 0.03% tacrolimus eye drop: prospective double-blind randomized study. *Cont Lens Anterior Eye*. 2015;38(5):373–378. doi:10.1016/j.clae.2015.04.004
7. Moawad P, Shamma R, Hassanein D, Ragab G, El Zawahry O. Evaluation of the effect of topical tacrolimus 0.03% versus cyclosporine 0.05% in the treatment of dry eye secondary to Sjogren syndrome. *Eur J Ophthalmol*. 2022;32(1):673–679. doi:10.1177/1120672121992680
8. Deveci H, Kobak S. The efficacy of topical 0.05 % cyclosporine A in patients with dry eye disease associated with Sjögren's syndrome. *Int Ophthalmol*. 2014;34(5):1043–1048. doi:10.1007/s10792-014-9901-4
9. Kang MJ, Kim YH, Chou M, et al. Evaluation of the efficacy and safety of a novel 0.05% cyclosporin A topical nanoemulsion in primary Sjögren's syndrome dry eye. *Ocul Immunol Inflamm*. 2020;28(3):370–378. doi:10.1080/09273948.2019.1587470
10. Cubuk MO, Ucgul AY, Ozgur A, Ozulken K, Yuksel E. Topical cyclosporine a (0.05%) treatment in dry eye patients: a comparison study of Sjogren's syndrome versus non-Sjogren's syndrome. *Int Ophthal*. 2021;41(4):1479–1485. doi:10.1007/s10792-021-01708-1
11. de Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine A therapy for dry eye syndrome. *Cochrane Database Syst Rev*. 2019;9:CD010051. doi:10.1002/14651858.CD010051.pub2
12. Nau J, Wyatt DJ, Rollema H, Crean CS. A Phase I, open-label, randomized, 2-Way crossover study to evaluate the relative bioavailability of intranasal and oral varenicline. *Clin Ther*. 2021;43(9):1595–1607. doi:10.1016/j.clinthera.2021.07.020
13. Tyrvaya™ (varenicline solution) nasal spray [package insert]. Princeton, NJ: Oyster Point Pharma, Inc; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213978s000lbl.pdf. Accessed February 22, 2023.
14. Wirta D, Torkildsen G, Boehmer B, et al. ONSET-1 phase 2b randomized trial to evaluate the safety and efficacy of OC-01 (varenicline solution) nasal spray on signs and symptoms of dry eye disease. *Cornea*. 2022;41(10):1207–1216. doi:10.1097/ICO.0000000000002941
15. Wirta D, Vollmer P, Paauw J, et al. Efficacy and safety of OC-01 (varenicline) nasal spray on signs and symptoms of dry eye disease: the ONSET-2 phase 3, randomized trial. *Ophthalmology*. 2022;129(4):379–387. doi:10.1016/j.ophtha.2021.11.004
16. Quiroz-Mercado H, Hernandez-Quintela E, Chiu KH, Henry E, Nau JA. A Phase II randomized trial to evaluate the long-term (12-week) efficacy and safety of OC-01 (varenicline solution) nasal spray for dry eye disease: the MYSTIC study. *Ocul Surf*. 2021;24:15–21. doi:10.1016/j.jtos.2021.12.007
17. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357(21):2189–2194. doi:10.1056/NEJMsr077003
18. Meadows JF, Dionne K, Nichols KK. Differential profiling of T-Cell cytokines as measured by protein microarray across dry eye subgroups. *Cornea*. 2016;35(3):329–335. doi:10.1097/ICO.0000000000000721
19. Gao Y, Min K, Zhang Y, Su J, Greenwood M, Gronert K. Female-specific downregulation of tissue polymorphonuclear neutrophils drives impaired regulatory T Cell and amplified effector T Cell responses in autoimmune dry eye disease. *J Immunol*. 2015;195(7):3086–3099. doi:10.4049/jimmunol.1500610
20. Sheppard JD, O'Dell LE, Karpecki PM, et al. Does dry eye disease severity impact efficacy of varenicline solution nasal spray on sign & symptom treatment outcomes? *Optom Vis Sci*. 2022;2012:1.
21. Zhu L, Shen J, Zhang C, et al. Inflammatory cytokine expression on the ocular surface in the Botulinum toxin B induced murine dry eye model. *Mol Vis*. 2009;15:250–258.
22. Guannan H, Long S, Xia H, Dong W, Shaozhen Z. Clinical characterisation and cytological study of dry eye in patients with autoimmune disease. *J Pak Med Assoc*. 2018;68(3):353–358.
23. Perzynska-Mazan J, Maslinska M, Gasik R. Neurophysiological features of peripheral nervous system involvement and immunological profile of patients with primary Sjögren syndrome. *J Rheumatol*. 2020;47(11):1661–1667. doi:10.3899/jrheum.181464
24. Jin K, Imada T, Hisamura R, et al. Identification of lacrimal gland postganglionic innervation and its regulation of tear secretion. *Am J Pathol*. 2020;190(5):1068–1079. doi:10.1016/j.ajpath.2020.01.007
25. Sumida T, Tsuboi H, Iizuka M, Asashima H, Matsumoto I. Anti-M3 muscarinic acetylcholine receptor antibodies in patients with Sjögren's syndrome. *Mod Rheumatol*. 2013;23(5):841–845. doi:10.3109/s10165-012-0788-5
26. Tsuboi H, Matsumoto I, Wakamatsu E, et al. New epitopes and function of anti-M3 muscarinic acetylcholine receptor antibodies in patients with Sjögren's syndrome. *Clin Exp Immunol*. 2010;162(1):53–61. doi:10.1111/j.1365-2249.2010.04188.x
27. Waterman SA, Gordon TP, Rischmueller M. Inhibitory effects of muscarinic receptor autoantibodies on parasympathetic neurotransmission in Sjögren's syndrome. *Arthritis Rheum*. 2000;43(7):1647–1654. doi:10.1002/1529-0131(200007)43:7<1647::AID-ANR31>3.0.CO;2-P
28. Musayeva A, Jiang S, Ruan Y, et al. Aged mice devoid of the M3 muscarinic acetylcholine receptor develop mild dry eye disease. *Int J Mol Sci*. 2021;22(11):6133. doi:10.3390/ijms22116133
29. Dawson LJ, Allison HE, Stanbury J, Fitzgerald D, Smith PM. Putative anti-muscarinic antibodies cannot be detected in patients with primary Sjogren's syndrome using conventional immunological approaches. *Rheumatology*. 2004;43(12):1488–1495. doi:10.1093/rheumatology/keh389
30. Dartt DA, Hodges RR. Cholinergic agonists activate P2X7 receptors to stimulate protein secretion by the rat lacrimal gland. *Invest Ophthalmol Vis Sci*. 2011;52(6):3381–3390. doi:10.1167/iovs.11-7210