CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213978Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	NDA 213978 IND 138645
Priority or Standard	S
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Division/Office	OSM/DO
Reviewer Name(s)	Jennifer D. Harris, M.D.
Review Completion Date	
Established/Proper Name	varenicline tartrate
(Proposed) Trade Name	(b) (4)
Applicant	Oyster Point Pharma
Dosage Form(s)	(b) (4)
Applicant Proposed Dosing Regimen(s)	One spray in each nostril twice daily
Applicant Proposed Indication(s)/Population(s)	Treatment of signs and symptoms of dry eye disease
Recommendation on Regulatory Action	Recommend Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with dry eye disease

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

OC-01 (varenicline) is a small-molecule nicotinic acetylcholine receptor (nAChR) partial agonist being developed by Oyster Point Pharma, Inc. as a nasal spray for the treatment of signs and symptoms of dry eye disease (DED). The active ingredient in OC-01 nasal spray is currently marketed in the United States as an oral formulation with the trade name Chantix. It is indicated for use as an aid to smoking cessation treatment (approved in 2006).

Nicotinic acetylcholine receptors are believed to be involved in the nasolacrimal reflex which is supported by studies showing an increase in lacrimation when nicotine spray is applied directly to the nasal passages. The lacrimal glands produce the aqueous layer of the tear film, which comprises the bulk of tear volume and flow. OC-01 is believed to promote natural tear film production by stimulating the nAChR receptor and thereby improving the signs and symptoms of dry eye disease.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 213978 for OC-01 (varenicline) *is recommended for approval for the treatment of dry eye disease. Three trials (Onset-1, Onset-2 and Mystic) were submitted with this NDA to support the approval of OC-01. Each of the trials studied different endpoints to determine the clinical effectiveness of OC-1 in treating dry eye disease. This is an acceptable pathway for a dry eye indication. Acceptable endpoints for this indication that are applicable to this NDA submission are:*

- *Demonstrating efficacy for both an objective sign and a subjective symptom. These may be co-primary endpoints or may be tested separately as primary and secondary endpoints.*

or

- *Demonstrating and increase in Schirmer's score of at least 10mm*

The Onset-1 trial studied a change in Schirmer score (sign endpoint) for the primary efficacy endpoint. The trial then tested a primary secondary endpoint of eye dryness score (symptom endpoint).

Both the 0.6mg/mL and 1.2mg/mL doses of OC-01 met the primary efficacy endpoint for this clinical trial. However, only the 0.6mg/mL dose of OC-01 met the primary secondary endpoint. Since positive results of both the primary and secondary endpoints are required to demonstrate efficacy, the analyses only support the 0.6mg/mL dose for a dry eye indication. (b) (4)

(b) (4)

The Onset-2 trial studied the percentage of subjects that had at least a 10mm increase in Schirmer's score for the primary efficacy endpoint. Both the 0.6mg/mL and 1.2mg/mL doses of OC-01 met the primary efficacy endpoint for this clinical trial. Both showed statistically significant outcome at the <0.001.

The Mystic trial studied the percentage of subjects that had an increase in Schirmer's score for the primary efficacy endpoint. Both doses of OC-01 met the primary efficacy endpoint for the clinical trial. Since increase in Schirmer's score is not an acceptable endpoint to use on its own for the establishment of efficacy for dry eye trials, unless the increase is 10 mm or more, this study can only be used as supportive evidence.

The results of these three clinical trials support the use of the 0.6mg/mL (0.1%) dose of OC-01 for the treatment of dry eye disease. (b) (4)
(b) (4)

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The results of the clinical studies submitted in this NDA demonstrate that OC-01 (varenicline) 0.6mg/mL (0.1%) is both statistically and clinically superior compared to placebo in the treatment of the signs and symptoms of dry eye disease.

The safety of OC-01 was assessed in over 700 subjects dosed twice a day for 4 weeks with OC-01. The number of adverse event were similar between the 0.6mg/mL and 1.2 mg/mL dose although there was a higher percentage of discontinuations in the 1.2 mg/mL treatment group in each of the three clinical trials. The most common adverse events experienced with OC-01 were related to the nasal route of administration. The events that occurred at higher incidences in the with OC-01 compared with the placebo group include sneezing, cough, throat irritation and instillation site irritation. Over 80% of subjects treated with OC-01 experience sneezing as an adverse event. Although sneezing occurred at a rate of over 80%, there was only one subject in the 1.2 mg/mL group that discontinued the study due to this adverse event. The only ocular adverse event that occurred more frequently in the OC-01 than placebo at a rate > 1% was conjunctival hyperemia.

The benefits of treating dry eye disease outweigh the risks associated with the use of OC-01 (varenicline).

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Dry eye disease (DED) is a multifactorial, age-related, chronic, progressive disease of the ocular surface. • Chronic DED can cause severe pain, visual impairment, tear film hyperosmolarity and instability, and inflammation. Patients with DED are more susceptible than others to eye infections and damage to the surface of the eye (cornea).	The lacrimal glands produce the aqueous layer of the tear film, which comprises the bulk of tear volume and flow. OC-01 is believed to promote natural tear film production by stimulating the nAChR receptor in the lacrimal gland and thereby improving the signs and symptoms of dry eye disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Management of Dry Eye Disease may include: • Restasis (cyclosporine ophthalmic emulsion) 0.05% • Xiidra (lifitegrast ophthalmic solution) 5% • Cequa (cyclosporine ophthalmic solution) 0.09% • OTC solutions, gels and ointments	OC-01 would provide an alternate product for the treatment of DED by increasing tear production.
Benefit	• Demonstrating improvement in both a sign and symptom or increases of ≥ 10 mm from baseline in Schirmer's score in dry eye patients provide a clinically relevant benefit in patients with dry eye disease.	Onset-1, a multicenter, randomized, adequate and well-controlled clinical studies demonstrated efficacy for a sign and symptom for the 0.6 mg/mL dose of OC-01. Onset-2 a multicenter, randomized, adequate and well-controlled clinical studies demonstrated efficacy for increase in ≥ Schirmer's score for both the 0.6mg/mL and 1.2 mg/mL dose of OC-01.
Risk and Risk Management	• The most common adverse events experienced with OC-01 were related to the nasal route of administration. The events that occurred at higher incidences in the with OC-01 compared with the placebo group include sneezing, cough, throat irritation and instillation site irritation. The only ocular adverse event that occurred more frequently in the OC-01 than placebo at a rate > 1% was conjunctival hyperemia.	Treatment with OC-01 for the treatment of dry has an acceptable risk-benefit profile.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

√	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	√	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints
		√	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Dry eye disease (DED) is a multifactorial, age-related, chronic, progressive disease of the ocular surface resulting in pain, visual impairment, tear film hyperosmolarity and instability, and inflammation. Patients with DED are more susceptible than others to eye infections and damage to the surface of the eye (cornea). Dry eye disease is characterized by a reduction in tear volume, rapid breakup of the tear film, or an increase in the evaporative properties of the tear film layer.

This disease affects daily life activities including reading, driving, and the ability to tolerate contact lenses. While the prevalence of DED is difficult to report because of varying definitions and diagnostic criteria, it is estimated that approximately 16 million adults in the United States have been diagnosed with DED with a higher prevalence among women than men and increasing prevalence with age.

2.2. Analysis of Current Treatment Options

Summary of Treatment Armamentarium Relevant to Proposed Indication

NDA	Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration
	FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]			
50790	Restasis (cyclosporine (ophthalmic emulsion) 0.05%	Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca	2002	One drop twice a day in each eye approximately 12 hours apart
208073	Xiidra (lifitegrast ophthalmic solution) 5%	Indicated for the treatment of the signs and symptoms of dry eye disease (DED)	2016	One drop twice a day in each eye approximately 12 hours apart
210913	Cequa (cyclosporine ophthalmic solution) 0.09%	Indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye)	2018	One drop twice a day in each eye approximately 12 hours apart
	Multiple OTC demulcents			

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The active ingredient in OC-01 nasal spray is currently marketed in the United States as an oral formulation with the trade name Chantix as an aid to smoking cessation treatment (approved in 2006). The nasal formulation which is the subject of the application has not been approved for marketing.

3.2. Summary of Presubmission/Submission Regulatory Activity

Oyster Point submitted this application as a 505(b)(2) and cites NDA 021928 (Chantix) as the reference listed drug to supplement the nonclinical, clinical pharmacology, and clinical safety data.

The initial IND (138645) for this development program was submitted to the Agency in May 2018. An end-of-phase 2 meeting was held with the sponsor in February 2019 where the results of the phase 2 trial were discussed in addition to the design/endpoints of the proposed phase 3 trials. The following issues related to the design of their second safety and efficacy trial:

- The percentage of subjects demonstrating statistically significant increases of ≥ 10mm in Schirmer score compared to vehicle would be an acceptable endpoint.

- The Sponsor could also choose sign and symptom endpoints. The Agency did not have a preference between a co-primary endpoint and primary/secondary endpoints as long as there was control of potential Type I error.

- The ONSET-1 study could be submitted in support of an application for the safety and efficacy of the 0.1% (0.6mg/mL) OC-01 nasal spray for the signs and symptoms of dry eye disease. At least one additional study which strongly supports the safety and efficacy of the 0.1% of OC-01 would be expected to support an NDA filing for the indication considering there is weak support of a symptom in ONSET-1.

A pre-NDA meeting was held in July 2020 to discuss CMC issues only.

3.3. Foreign Regulatory Actions and Marketing History

OC-01 (varenicline) has not been approved for marketing in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

DSI inspections have been delayed due to COVID-19. The results of inspections are not available at the time of this review. Results will be addressed when they become available.

4.2. Product Quality

OC-01 (varenicline) nasal spray is a (b) (4) aqueous-based formulation consisting of the drug substance (b) (4) (b) (4). The OC-01 (varenicline) nasal spray is packaged in a 3.5-mL amber glass vial and capped with an Aptar 50 µL (b) (4) multidose nasal spray pump.

The study tested the following dose levels of OC-01 (varenicline) nasal spray delivered as a single 50 µL spray into each nostril:

- Placebo (vehicle) delivered as a 50 µL intranasal spray in each nostril BID
- OC-01 (varenicline) 0.6 mg/mL delivered as a 50 µL intranasal spray in each nostril BID
- OC-01 (varenicline) 1.2 mg/mL delivered as a 50 µL intranasal spray in each nostril BID

Formula for Varenicline Nasal Spray, 0.6 mg/mL and 1.2 mg/mL ((b) (4) mM (b) (4) Formulation)

Strength	0.6 mg/mL (Varenicline free base)		1.2 mg/mL (Varenicline free base)	
Ingredients	**Concentration (mg/ mL)**	**% w/v**	**Concentration (mg/ mL)**	**% w/v**
Varenicline tartrate	1.00	(b) (4)		(b) (4)
Sodium phosphate dibasic heptahydrate, USP	(b) (4)			
Monobasic Sodium Phosphate, Anhydrous, USP				
Sodium Chloride USP/ EP				
Hydrochloric Acid, NF/ EP	Adjust to pH 6.4	Adjust to pH 6.4		
Sodium Hydroxide, NF/ EP	(b) (4)	(b) (4)		
Water for Injection				

See Product Quality review for further details.

4.3. Clinical Microbiology

N/A – this is not an anti-infective product.

4.4. Nonclinical Pharmacology/Toxicology

Oyster Point Pharma has conducted nonclinical studies to evaluate the pharmacology, pharmacokinetics (PK), and toxicology of OC-01 (varenicline) for intranasal use. The nonclinical systemic toxicity profile of varenicline was characterized during the development of Chantix. The applicant is relying on FDA's findings of safety for Chantix with respect to the genotoxicity, carcinogenicity, and reproductive and developmental toxicity of varenicline for this 505(b)(2) application.
See pharmacology/toxicology review for further details.

4.5. Clinical Pharmacology

A Phase 1 open-label, randomized, 2-way crossover, clinical pharmacology/biopharmaceutics study was designed to evaluate the relative bioavailability of OC-01 (varenicline) nasal spray

(N=22) compared to varenicline administered orally as Chantix. The systemic exposure of varenicline in this study after an oral tablet dose of 1 mg Chantix was similar to previously published literature. No additional clinical pharmacology studies have been conducted by Oyster Point for the intended clinical route (intranasal) to support this application.

Summary of Pharmacokinetic Parameters for Varenicline-Pharmacokinetic Analysis Set

	Treatment B (Nasal)				Treatment A (Oral)			
Parameter (Unit)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
AUC_{0-t} (h*ng/mL)	16	4.49	3.42	76.2	16	98.74	25.49	25.8
AUC_{0-inf} (h*ng/mL)	16	8.30	4.09	49.3	16	102.53	26.82	26.2
C_{max} (ng/mL)	16	0.34	0.13	37.6	16	4.63	0.93	20.2
$T_{1/2\ el}$ (h)	16	18.93	9.899	52.3	16	19.59	10.385	53.0
K_{el} (/h)	16	0.044	0.015	35.4	16	0.042	0.015	35.4
Parameter (Unit)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
T_{max} (h)	16	2.00	0.3	3.0	16	3.00	1.0	6.0

N: Number of observations; SD: Standard Deviation; CV: Coefficient of variation; Min: Minimum; Max: Maximum.
Treatment A: Single oral dose of 1 mg varenicline (Chantix®) administered orally;
Treatment B: Intranasal dose of 0.12 mg OC-01 (varenicline)- delivered as a 50 µL (0.06 mg) spray into each nostril.
Ref. CSR OPP-100 page 54

4.6. Devices and Companion Diagnostic Issues

Not applicable to this application.

4.7. Consumer Study Reviews

Not applicable to this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Studies Supporting Efficacy of OC-01 for Dry Eye Disease

	ONSET-2	ONSET-1	MYSTIC
Patient Population	Adults with dry eye disease	Adults with dry eye disease	Adults with dry eye disease
Study Design[a]	Multicenter, randomized, masked, placebo-controlled	Multicenter, randomized, masked, placebo-controlled	Single center, randomized, masked, placebo-controlled
Treatment (BID) with Number of Patients Randomized/Completed in the ITT Analysis Set	0.6 mg/mL OC-01 260/251 1.2 mg/mL OC-01 246/230 Placebo 252/242	0.12 mg/mL OC-01 47/47 0.6 mg/mL OC-01 48/46 1.2 mg/mL OC-01 44/40 Placebo 43/43	0.6 mg/mL OC-01 41/36 1.2 mg/mL OC-01 41/29 Placebo 41/32
Duration of Treatment	4 weeks	4 weeks	12 weeks
Efficacy Assessments	Schirmer's Test EDS (normal clinic and CAE® Chamber) CFS	Schirmer's Test EDS (normal clinic and CAE® Chamber) CFS	Schirmer's Test
Location	United States	United States	Mexico
Phase	3	2b	2

Abbreviations: BID = twice daily; CAE = Controlled Adverse Environment; CFS = corneal fluorescent staining; EDS = eye dryness score; ITT = Intent-to-Treat
[a] Whether described as single- or double-masked in the protocol titles, masking included subjects, Investigators, study site

Source section 2.5 Clinical Overview page 8

5.2. Review Strategy

Safety and efficacy for OC-1 was supported by three clinical studies Onset-1 (OPP-002), Onset-2 (OPP-101) and Mystic (OPP-004). The primary evidence of efficacy to support OP-01 for the treatment of dry eye disease was based on data from two (2) of the trials (Onset-1 and Onset-2) which evaluated efficacy endpoints that are considered clinically meaningful by the Division. The acceptable endpoints for dry eye trials which are applicable to this submission include:

- *Demonstrating a response for both an objective sign and subjective symptom (can be co-primary endpoint or can be evaluated separately as primary and secondary endpoints.*
- *Demonstrating an increase in Schirmer's score by at least 10mm.*

The third trial (Mystic) did not evaluate an acceptable efficacy endpoint so the results were only reviewed as supportive evidence.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Onset-1 (OPP-002)

6.1.1. Study Design

Overview and Objective

The objective of this study was to evaluate the safety and effectiveness of C-01 nasal spray as compared to placebo with respect to signs and symptoms of dry eye disease (DED).

Trial Design

This Phase 2b, multicenter, randomized, double-masked, placebo-controlled study was designed to evaluate the safety and efficacy of OC-01 nasal spray in adult subjects with DED. The study randomized 182 subjects, at least 22 years of age, who had a diagnosis of DED and met all other study eligibility criteria to receive an application of OC-01 or placebo twice daily (BID) for 4 weeks. The study randomized 182 subjects in a 1:1:1:1 ratio to receive 0.12 mg/mL OC-01 (varenicline) nasal spray (low dose; N=47), 0.6 mg/mL OC-01 (varenicline) nasal spray (medium dose; N=48), 1.2 mg/mL OC-01 nasal spray (high dose; N=44), or placebo (vehicle nasal spray; N=43).

- Placebo (OC-01 Vehicle nasal spray)
- 0.12 mg/mL OC-01 nasal spray
- 0.6 mg/mL OC-01 nasal spray
- 1.2 mg/mL OC-01 nasal spray

Schedule of Events

Procedure	Screen/ Visit 1		Visit 2		Visit 3		Visit 4 (Day 21 ±2)			Visit 5	
	Day 1	Days 2-6	Day 7 ±2	Days 8-13	Day 14 ±2	Days 15-20	Pre-CAE®	Post-CAE®	Days 22-27	Day 28 ±2	ET
Informed consent/HIPAA	X										
Demographics	X										
Medical history, prior medication(s), ocular history and updates	X										
Eligibility criteria	X										
Urine pregnancy test	X_4						X_4				X_4
OSDI© questionnaire	X										
Eye Dryness Score (EDS)	X						X	X_5		X_2	
Ora Calibra® Ocular Discomfort Scale	X						X	X_5			
BCVA	X_1		X_1		X_1			X_6		X_1	X
Slit lamp biomicroscopy	X_1		X_1		X_1			X_6		X_1	X
Corneal fluorescein staining	X									X_2	
Schirmer's test	X_1		X		X					X	
Schirmer's test with cotton swab stimulation	X										
Intranasal examination	X_1									X	X
Randomization	X										
Administer investigational drug / placebo	X_3	X	X_3	X	X_3	X	X		X	X_3	
Dispense investigational drug / placebo	X				X						
Concomitant medications	X		X		X		X			X	X
Adverse Event Query	X		X		X		X	X		X	X

X_1 = Pre- and Post-treatment procedures; X_2 = Post-treatment procedures X_3 = Concurrent with Schirmer's Test; X_4 = For females of childbearing potential; X_5 = Procedure started at time 0 and then conducted every 5 minutes thereafter during the 120-minute CAE® exposure; X_6 = Procedure may have been performed after CAE® exit at the Investigator's discretion as needed

Abbreviations: BCVA = Best corrected visual acuity; CAE = Controlled Adverse Environment; ET = Early Termination; HIPAA = Health Information Portability and Accountability Act; OSDI = Ocular Surface Disease Index

Source: CSR OPP-002 page 26

Inclusion Criteria

1. At least 22 years of age at the Screening Visit
2. Used and/or desired to use an artificial tear substitute for DED symptoms within 6 months prior to Visit 1
3. Had an Ocular Surface Disease Index (OSDI©) score of ≥23 with ≤3 responses of "Not Applicable" ("N/A") at the Screening Visit
4. Had ALL of the following in the study eye1 at the Screening Visit:
   - A corneal fluorescein staining score of ≥2 in at least one corneal region OR have a sum of ≥4 for all corneal regions
   - A baseline Schirmer's Test Score (STS; with topical anesthesia) of ≤10 mm/5 minutes with a cotton swab nasal stimulation STS at least 7 mm greater in the same eye
   - <20 mm difference from the study eye Schirmer's Test and the fellow eye Schirmer's Test
   - A diagnosis of DED
5. Had a baseline 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) in each eye at the Screening Visit

6. Had normal lid/lash anatomy, blinking function, and closure as determined by the Investigator
7. Not been familiar with (e.g., known the study drug was used to stimulate tear production) or had previously used the study drug
8. Been able to participate in the study for approximately four consecutive hours at Visit 4
9. Been able and willing to use the study drug and participate in all study assessments and visits
10. Provided verbal and written informed consent
11. If a female of childbearing potential who was not using an acceptable means of birth control (acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives, mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom, intrauterine device, or surgical sterilization of partner), had a negative urine pregnancy test on Day 1

Exclusion Criteria

1. Had clinically significant corneal epithelial defects at Day 1 prior to performing Schirmer's Test
2. Had chronic or recurrent epistaxis, coagulation disorders, or other conditions that, in the opinion of the Investigator, may have led to a clinically significant risk of increased bleeding
3. Had nasal or sinus surgery (including a history of application of nasal cautery) or significant trauma to these areas
4. Had a vascularized polyp, severely deviated septum, chronic recurrent nosebleeds, or severe nasal airway obstruction as confirmed by intranasal examination performed prior to Visit 1
5. Been currently treated with nasal continuous positive airway pressure (CPAP)
6. Had any intraocular surgery (such as cataract surgery), extraocular surgery (such as blepharoplasty) in either eye within three months or refractive surgery (e.g., laser epithelial keratomileusis, laser-assisted in-situ keratomileusis, photorefractive keratectomy, or corneal implant) within 12 months of Visit 1
7. Had a corneal transplant in either eye
8. Had used contact lenses within 7 days prior to Visit 1 or anticipated the use of contact lenses during the study period
9. Had any form of punctal or intracanalicular occlusion
10. Had a history or presence of any ocular disorder or condition in either eye that would, in the opinion of the Investigator, have likely interfered with the interpretation of the study results or subject safety such as significant corneal or conjunctival scarring; pterygium or nodular pinguecula; current ocular infection, conjunctivitis, or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; ocular herpetic infection; evidence of keratoconus; etc. Blepharitis not requiring treatment and mild meibomian gland diseases that are typically associated with DED were allowed.
11. Had a history of seizures or other factors that lowered the subject's seizure threshold.
12. Had a systemic condition or disease not stabilized or judged by the Investigator to be incompatible with participation in the study or with the lengthier assessments required by the study (e.g., current systemic infection, uncontrolled autoimmune disease, uncontrolled immunodeficiency disease, history of myocardial infarction or heart disease, etc.)
13. Had a known hypersensitivity to any of the procedural agents or study drug components

14. Had current concomitant use of snuff, chewing tobacco, or e-cigarettes or cigarettes/cigars during the study or within the previous 30 days
15. Had current concomitant use of a nicotinic acetylcholine receptor (nAChR) agonist (Nicoderm, Nicorette, Nicotrol NS [nicotine], Tabex, Desmoxan [cytisine], and Chantix [varenicline]) or within the previous 30 days
16. Had active or uncontrolled, severe:
    a. Systemic allergy
    b. Chronic seasonal allergies at risk of being active during the study
    c. Rhinitis or sinusitis requiring treatment such as antihistamines, decongestants, or oral or aerosol steroids at the Screening Visit
    d. Untreated nasal infection at Visit 1
17. Had any condition or history that, in the opinion of the Investigator, may have interfered with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject
18. Been a female who was pregnant, nursing an infant, or planning a pregnancy at Visit 1. Been a woman of childbearing potential who was not using an acceptable means of birth control; acceptable methods of birth control included: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device; or surgical sterilization of partner
19. Been currently enrolled in an investigational drug or device study or had used an investigational drug or device within 30 days prior to Visit 1.

Study Endpoints

Primary efficacy endpoint:
• Change in Schirmer's test score (STS) from baseline to Day 28 (Visit 5)

Secondary efficacy endpoints:
• Change in Eye Dryness Score (EDS) from baseline to Day 28 (Visit 5) (post treatment)
• EDS 5 minutes post treatment in a Controlled Adverse Environment (CAE) at Day 21 (Visit 4)

Exploratory efficacy endpoints:
• Change in EDS from baseline to Day 21 (Visit 4) (pre-CAE) assessment
• Time to qualifying treatment in CAE at Day 21 (Visit 4)
• Change in corneal fluorescein staining from baseline to Day 28 (Visit 5)
• Ora Calibra Ocular Discomfort Scale (ODS)
• Assessment of the above outcomes, including the primary and secondary outcome measures, on the fellow eye

Safety endpoints:
• Change in BCVA
• Slit-lamp biomicroscopy

- Intranasal examination
- Adverse events (AEs)

Statistical Analysis Plan

Primary Endpoint Analysis

The primary endpoint was the change in STS from baseline at Day 28 (Visit 5) in the study eye. The primary endpoint for each treatment group was summarized by visit with descriptive statistics. The primary efficacy analysis compared the treatment group differences in means of the medium and high dose against placebo using an analysis of covariance (ANCOVA) model that defined baseline STS, baseline STS with a cotton swab nasal stimulation, and study sites as covariates. The difference in the mean differences for each comparison was calculated and reported along with its Dunnett-corrected 95% confidence interval (CI). The study was to be considered to have shown that OC-01 is beneficial if either or both the medium and high doses of OC-01 (varenicline) nasal spray showed statistically significant evidence of superiority to placebo.

The comparison of low dose to placebo was performed descriptively, not as a formal statistical test.

Secondary Endpoint Analysis

The first secondary efficacy analysis compared the pairwise treatment group differences of medium and high doses of OC-01 (varenicline) nasal spray against placebo in mean change in EDS from baseline (Visit 1) to Day 28 (Visit 5) in the study eye, using an ANCOVA model that included baseline EDS and study sites as covariates. The difference in the mean difference for each comparison was calculated and reported along with its 95% CI.

The second secondary efficacy analysis compared the mean EDS at 5 minutes post treatment in the CAE® at Day 21 (Visit 4) in the study eye, using an ANCOVA model that included baseline EDS and study sites as covariates. The difference in the mean difference for each comparison was calculated and reported along with its 95% CI. Sensitivity analyses evaluated the mean EDS under CAE at Day 21 (Visit 4) at 10- and 15-minute time points using ANCOVA.

Protocol Amendments

Minimal changes were made to the protocol or planned analyses after the original draft of the protocol.

An inclusion criterion was added to the original protocol stating that there must be “<20 mm difference from the study eye Schirmer's Test and the fellow eye Schirmer's Test.” This criterion

was put in place to rule out possible neurological causes of unilateral DED indicated by a significant imbalance in the STS between oculus dexter (OD) and oculus sinister (OS).

An exclusion criterion clarification was added to the original protocol to add e-cigarettes to the list of excluded nicotine containing products.

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was performed in compliance with the ethical principles of the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice (GCP). In addition, all applicable local, state, and federal requirements relevant to the use of investigational agents in the country involved were followed.

Financial Disclosure

The sponsor of this NDA certified that they did not enter into any financial arrangement with the listed clinical investigators and that no investigators have disclosed financial interest with the company. See appendix 14.2.

Patient Disposition

All subjects received treatment as randomized and were therefore included in both the ITT and Safety Populations

	OC-01 0.12 mg/mL N=47 n (%)	OC-01 0.6 mg/mL N=48 n (%)	OC-01 1.2 mg/mL N=44 n (%)	Placebo N=43 n (%)
Analysis population				
Randomized (ITT Population)	47	48	44	43
Treated (Safety Population)	47	48	44	43
Study completion				
Completed study	47 (100)	46 (96)	40 (91)	43 (100)
Discontinued study (for reasons other than study completion)	0	2 (4)	4 (9)	0
Non-fatal adverse event	0	1 (2)	3 (7)	0
Withdraw by Investigator due to prohibited medication	0	0	1 (2)	0
Withdraw by subject	0	1 (2)	0	0
Died[a]	0	0	0	0

Source: CSR OPP-002 page 42

There were a lower number of subjects who completed the trial in the 1.2mg/mL group versus the 0.6mg/mL group (91% vs. 96%) and in the 1.2mg/mL group versus the placebo group (91%vs.100%). This appears to have been driven by the larger number of subjects who experienced non-fatal adverse events.

Adverse Events Leading to Discontinuation

Treatment Arm	Subject ID	Reason for Discontinuation
0.6 mg/mL	(b) (6)	dizziness
1.2 mg/mL	(b) (6)	sneezing, throat irritation
	(b) (6)	nasopharyngitis
	(b) (6)	tinnitus, headache, eyelid edema

Protocol Violations/Deviations

Protocol deviations were assessed and classified prior to database lock and unmasking. A total of 74 protocol deviations were reported in 51 subjects. Three subjects had deviations that were classified as major; the remaining subjects had minor deviations.

Of the three major deviations, one was related to an exclusion criterion and two were related to the EDS assessment:

- Subject (b) (6) (placebo group) met exclusion criterion 9 (subject had punctal plugs

oculus uterque [OU]) at baseline (Visit 1) but was randomized in error

- Subject (b) (6) (0.6 mg/mL OC-01 group) was not exposed to CAE® for two minutes of designated exposure
- Subject (b) (6) (0.12 mg/mL OC-01 group) did not have the EDS captured at the 45-, 50-, and 55-minute time points in the CAE®

Table of Demographic Characteristics

	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43
Age (years) at randomization				
Mean (SD)	64.2 (12.7)	66.5 (9.4)	67.4 (10.6)	64.0 (10.3)
Range (min, max)	24, 89	49, 88	22, 84	32, 89
Quartiles (25th, median, 75th)	58, 65, 73	60, 65, 73	64, 68, 73	57, 63, 71
Male, n (%)	**11 (23)**	**14 (29)**	**9 (20)**	**11 (26)**
Race, n (%)				
White	42 (89)	39 (81)	36 (82)	40 (93)
Black or African-American	2 (4)	4 (8)	6 (14)	2 (5)
Asian	3 (6)	4 (8)	0	1 (2)
American Indian or Alaska Native	0	1 (2)	1 (2)	0
Native Hawaiian or other Pacific Islander	0	0	1 (2)	0
Ethnicity, n (%)				
Not Hispanic or Latino	39 (83)	45 (94)	42 (95)	38 (88)
Hispanic or Latino	8 (17)	3 (6)	2 (5)	5 (12)
Iris color (OD and OS), n (%)[a]				
Brown	23 (49)	25 (52)	18 (41)	17 (40)
Blue	7 (15)	12 (25)	17 (39)	17 (40)
Hazel	10 (21)	7 (15)	3 (7)	6 (14)
Green	7 (15)	3 (6)	6 (14)	3 (7)
Gray	0	1 (2)	0	0
Different iris color OD and OS, n (%)	**0**	**0**	**0**	**0**

The overall age and sex characteristics of the subjects enrolled in this study is consistent with the demographics of dry eye disease.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline Disease Characteristics

Baseline assessment	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43
Schirmer's test (mm)				
Mean (SD)	5.2 (3.1)	4.8 (2.7)	5.5 (3.0)	4.5 (2.9)
Range (min, max)	0, 10	1, 10	0, 10	0, 10
Quartiles (25th, median, 75th)	3, 5, 8	2, 5, 7	4, 5, 8	2, 4, 7
Cotton swab Schirmer's test (mm)				
Mean (SD)	28.2 (7.3)	29.2 (7.8)	29.6 (7.5)	25.9 (7.0)
Range (min, max)	14, 35	10, 35	10, 35	15, 35
Quartiles (25th, median, 75th)	20, 30, 35	22, 34, 35	24, 34, 35	20, 25, 35
Eye Dryness Score (mm)[a]				
Mean (SD)	65.6 (20.1)	63.7 (18.4)	53.5 (22.4)	65.2 (17.7)
Range (min, max)	10, 100	27, 98	5, 96	33, 98
Quartiles (25th, median, 75th)	51, 68, 83	52, 66, 80	33, 56, 72	51, 66, 80
Ora Calibra Ocular Discomfort Scale (grade)				
Mean (SD)	2.8 (0.9)	2.7 (0.9)	2.5 (1.0)	2.7 (0.9)
Range (min, max)	1, 4	0, 4	1, 4	1, 4
Quartiles (25th, median, 75th)	2, 3, 4	2, 3, 3	2, 3, 3	2, 3, 3
Visual acuity (logMAR)				
Mean (SD)	0.12 (0.13)	0.11 (0.16)	0.13 (0.17)	0.09 (0.12)
Range (min, max)	-0.1, 0.4	-0.2, 0.5	-0.2, 0.6	-0.2, 0.4
Quartiles (25th, median, 75th)	0.0, 0.1, 0.2	0.0, 0.1, 0.2	0.0, 0.1, 0.2	0.0, 0.1, 0.2
Ocular Surface Disease Index (grade)[a]				
Mean (SD)	53.8 (17.0)	49.7 (15.7)	45.5 (15.0)	51.7 (16.6)
Range (min, max)	25, 100	25, 79	25, 75	25, 83
Quartiles (25th, median, 75th)	42, 50, 63	35, 51, 61	33, 42, 57	35, 53, 67

Baseline assessment	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43
Corneal fluorescein staining (grade)				
Mean (SD)	5.9 (1.6)	6.7 (2.1)	6.9 (2.4)	6.7 (2.4)
Range (min, max)	4, 10	4, 12	4, 14	4, 14
Quartiles (25th, median, 75th)	5, 6, 7	5, 6, 9	5, 7, 8	5, 6, 8

Column header counts are the number of randomized subjects. No baseline observations were missing for any variable in this table. Unless otherwise noted, results are presented for the study eye only.
Abbreviations: logMAR = logarithm of the minimum angle of resolution; max = maximum; min = minimum; SD = standard deviation a Assessment relates to both eyes

Baseline ocular assessment results were generally similar across all treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study visit treatment exposure was captured at each study visit. Compliance with BID dosing at home was based on assessments of used/unused study drug at each clinic visit.

The use of medications such as antihistamines and nasal decongestants that are known to cause dry eye and could interfere with the interpretation of the trial results was prohibited.

Study compliance was similar across treatment groups.

Efficacy Results – Primary Endpoint

The primary endpoint of the ONSET-1(OPP-002) study was the mean change from baseline to Day 28 (Visit 5) in STS (with anesthesia) in the designated study eye. This endpoint was analyzed using an ANCOVA model that specified baseline STS, baseline STS with a cotton swab nasal stimulation, and study sites as covariates

Schirmer's Test Score in Study Eye at Day 28 (Visit 5) (Primary Endpoint)

At Day 28 (Visit 5) (Study eye)	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43
Mean change from baseline (mm)				
N	47	46	40	43
Mean (SD)	10.0 (9.5)	11.8 (8.9)	11.4 (9.3)	3.2 (5.6)
Range (min, max)	-5, 34	-2, 29	-3, 31	-4, 26
Quartiles (25th, median, 75th)	3, 7, 15	5, 10, 15	5, 8, 19	0, 2, 5
LS mean change from baseline (mm)				
LS mean (SE)	10.1 (1.2)	11.4 (1.3)	11.1 (1.3)	3.7 (1.3)
95% CI	7.7, 12.5	8.9, 13.9	8.5, 13.7	1.1, 6.2
LS mean difference (mm)				
LS mean difference (SE)	6.4 (1.8)	7.7 (1.8)	7.5 (1.9)	--
95% CI[a]	--	3.8, 11.7	3.4, 11.6	--
p-value[b]	--	<0.001	<0.001	--

Column header counts are the number of randomized subjects. All comparisons are made to placebo group.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error; STS = Schirmer's Test Score
[a] Dunnett corrected 95% CIs.
[b] ANCOVA p-value was calculated using a model with baseline STS (study eye), baseline STS with cotton swab nasal stimulation (study eye), and study sites, as covariates.

Both the 0.6mg/mL and 1.2mg/mL doses of OC-01 met the primary efficacy endpoint for this clinical trial. One of the acceptable pathways to establish efficacy for dry eye trials is to demonstrate a response for both an objective sign and subjective symptom. Since an increase in Schirmer's score is not an acceptable endpoint to use on its own, the evaluation of the pre-specified secondary endpoint of eye dryness score was required to determine the outcome of this trial. See secondary efficacy endpoints results below.

Data Quality and Integrity

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

The ONSET-1 study had two pre-specified secondary endpoints which were analyzed hierarchically. The first secondary endpoint was the mean change from baseline to Day 28 in EDS (both eyes). This endpoint was analyzed using an ANCOVA with baseline EDS and study sites as covariates.

Eye Dryness Score at Day 28 (Visit 5) (Secondary Endpoint)

At Day 28 (Visit 5)	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43
Mean change from baseline (scale)				
N	**47**	**46**	**40**	**43**
Mean (SD)	**-13.7 (25.5)**	**-19.5 (33.6)**	**-8.3 (27.8)**	**-7.8 (24.8)**
Range (min, max)	**-69, 55**	**-79, 48**	**-74, 49**	**-58, 51**
Quartiles (25th, median, 75th)	**-32, -14, 1**	**-47, -23, 5**	**-23, -3, 7**	**-24, -9, 3**
LS mean change from baseline (scale)				
LS mean (SE)	**-11.4 (3.6)**	**-19.0 (3.7)**	**-15.4 (4.0)**	**-5.6 (3.8)**
95% CI	**-18.6, -4.2**	**-26.2, -11.7**	**-23.3, -7.5**	**-13.1, 1.8**
LS mean difference (scale)				
LS mean difference (SE)	**-5.8 (5.2)**	**-13.3 (5.2)**	**-9.8 (5.5)**	**--**
95% CI[a]	**--**	**-25.0, -1.7**	**-21.8, 2.2**	**--**
p-value[b]	**--**	**0.021**	**0.13**	**--**

Column header counts are the number of randomized subjects. All comparisons made are in reference to placebo group.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EDS = Eye Dryness Score; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error
[a] Dunnett corrected 95% CIs.
[b] ANCOVA p-value is calculated using a model with baseline EDS, study sites, and treatment as covariates.

Only the 0.6mg/mL dose of OC-01 met the primary secondary endpoint for this clinical trial. This endpoint in conjunction with the statistically significant result from the primary endpoint analysis is acceptable to support efficacy for a dry eye indication. (b) (4)

(b) (4)

The second secondary efficacy endpoint was the change from baseline to Day 21 (Visit 4) in EDS at 5 minutes post treatment in the CAE®. This endpoint was analyzed using an ANCOVA model that included baseline EDS and study sites as covariates.

Eye Dryness Score During CAE at Day 21 (Visit 4) at 5 minutes Post treatment (Secondary

Endpoint

At Day 21 (Visit 4) - 5 minutes post treatment	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43
Mean EDS (scale)				
N	**44**	**45**	**38**	**42**
Mean (SD)	**55.0 (17.7)**	**46.9 (19.3)**	**40.8 (19.3)**	**58.2 (18.9)**
Range (min, max)	**19, 97**	**1, 85**	**7, 85**	**22, 96**
Quartiles (25th, median, 75th)	**44, 52, 71**	**39, 48, 60**	**26, 40, 56**	**45, 60, 73**
LS mean EDS (scale)				
LS mean (SE)	**53.2 (2.7)**	**45.4 (2.7)**	**42.9 (3.0)**	**56.9 (2.8)**
95% CI	**47.8, 58.6**	**40.0, 50.7**	**37.0, 48.8**	**51.4, 62.4**
LS mean difference (scale)				
LS mean difference (SE)	**-3.7 (3.8)**	**-11.6 (3.8)**	**-14.0 (4.1)**	**--**
95% CI[a]	**--**	**-20.1, -3.0**	**-22.9, -5.1**	**--**
p-value[b]	**--**	**0.006**	**not formally calculated[c]**	**--**

Column header counts are the number of randomized subjects. All comparisons made are in reference to placebo group.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EDS = Eye Dryness Score; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error
[a] Dunnett corrected 95% CIs.
[b] ANCOVA p-value is calculated using a model with baseline EDS, study sites, and treatment as covariates.
[c] The nominal p-value is 0.001.

The analysis of the second prespecified secondary endpoint further supports the use of the 0.6mg/mL dose for the treatment of dry eye.

Dose/Dose Response

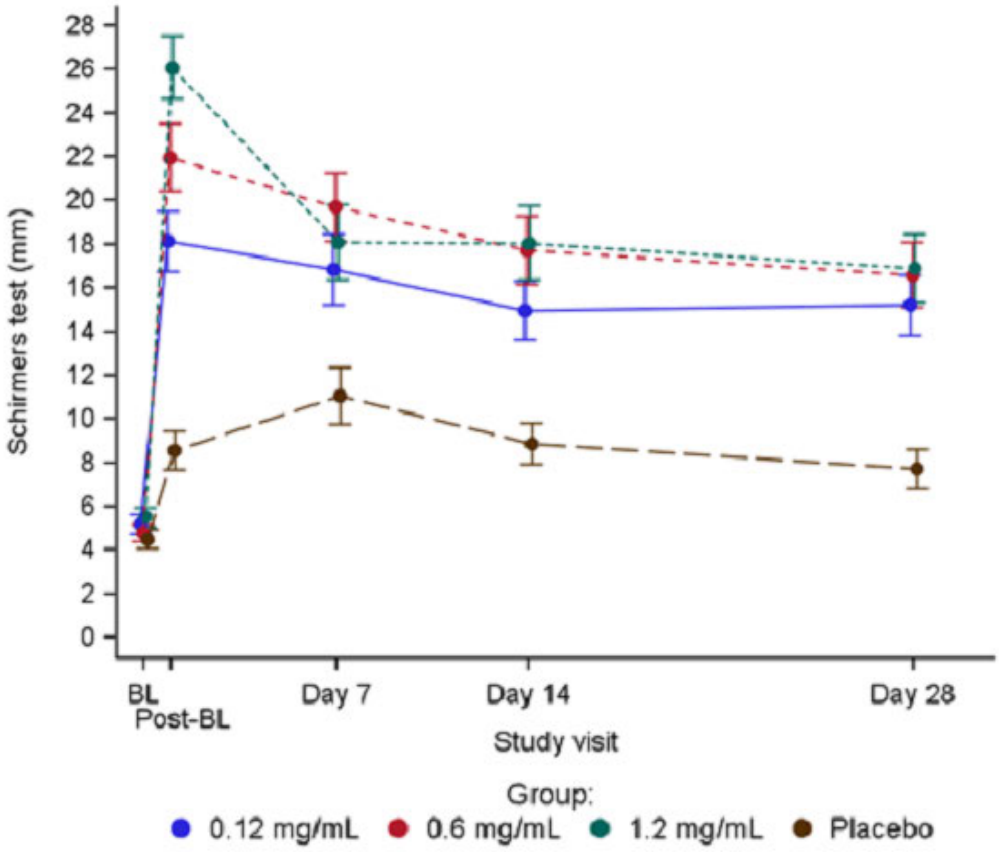
Dose response was not evaluated in this development program; however, both of the higher doses (0.6mg/mL and 1.2mg/mL) had similar responses in the ability to increase Schirmer's score. The 0.12mg/mL was somewhat lower, but a dose response could not be determined.

Durability of Response

Durability of the clinical effect on was not evaluated in this development program. However, the

onset of improvement in Schirmer's score begins on the first day of treatment, decreases somewhat during the first week and remains stable with continued dosing throughout the study period.

Schirmer's Test Score Mean by Visit



Abbreviation: BL=baseline.
Intervals are +/- 1 standard error. Means based on study eye.

Persistence of Effect

Persistence of clinical effect was not evaluated in this development program.

Additional Analyses Conducted on the Individual Trial

An additional analysis was conducted to determine the percentage of subjects that improved ≥ 10mm in Schirmer's score (STS). Since this is an endpoint that is accepted to be used alone by the Division for demonstrating efficacy of dry eye products, it has been included in this section for comparison . It should be noted that the Sponsor conducted this as one of multiple secondary endpoints. There was no correction made for multiplicity in the statistical analysis plan. The p-values are not applicable and cannot be used to assess the outcome of the trial; however, all doses of OC-01 were superior to placebo for this endpoint.

Percent of Subjects Who Achieved at Least 10 mm Improvement on STS at Week 4

At Day 28 (Visit 5) (Study eye)	OC-01 0.12 mg/mL N=47	OC-01 0.6 mg/mL N=48	OC-01 1.2 mg/mL N=44	Placebo N=43
n (%)	21 (44.7)	25 (52.1)	19 (43.2)	6 (14.0)
Proportion Difference (95% CI)	30.7 (13.14, 48.31)	38.1 (20.61, 55.65)	29.2 (11.30, 47.16)	—

Column header counts are the number of randomized subjects. All comparisons are made to placebo group.
Source: OPP-002 CSR Addendum page 6

6.2. Onset-2 (OPP-101)

6.2.1. Study Design

Overview and Objective

The objective of this study was to evaluate the safety and effectiveness of OC-01 (varenicline) nasal spray as compared to placebo on the signs and symptoms of dry eye disease (DED).

Trial Design

This was a Phase 3, multicenter, randomized, controlled, double-masked (including subjects, Investigators, study site personnel, and Sponsor personnel) study designed to evaluate the safety and efficacy of OC-01 (varenicline) nasal spray 0.6 mg/mL and 1.2 mg/mL in adult participants with DED. The study randomized 758 subjects at least 22 years of age with a diagnosis of DED and meeting all other study eligibility criteria to receive OC-01 (varenicline) nasal spray (one spray in each nostril) or placebo twice daily (BID) for 28 days with three additional long-term follow-up visits at 6 weeks, 6 months, and 12 months.

Schedule of Events

Procedure	Screen/Visit 1 Day 1	Day 2-6	Visit 2 Day 7±2	Day 8-13	Visit 3 Week 2 Day 14±3	Day 15-27	Visit 4 Week 4 Day 28±4			Visit 5 Week 6 Day 42 ± 3	Visit 6 Week 24 Day 168 ±7	Visit 7 Week 48 Day 336 ±7	ET
							Visit 4a		Visit 4b (+3 days of 4a)				
							Pre-CAE	Peri-CAE	Schirmer's Test Evaluation				
Informed consent/HIPAA	X												
Demographics	X												
Medical history, prior medication(s), ocular history and updates	X												
Eligibility criteria	X												
Urine pregnancy test	X[1]						X[1]					X[1]	X[1]
OSDI© questionnaire	X												
Eye Dryness Score (EDS)	X		X		X		X	X[4]	X[6]				X
Ora Calibra® Ocular Discomfort Scale	X						X	X[4]					
BCVA	X[2]		X		X[2]		X		X[2]				X
Slit-lamp biomicroscopy	X[2]		X		X[2]				X[2]	X	X	X	X
Corneal fluorescein staining	X								X[6]				X
Schirmer's Test	X[2]				X				X[5]				
Schirmer's Test with cotton swab stimulation	X												
Intranasal examination	X[2]		X						X[2]	X	X	X	X

Procedure	Screen/Visit 1 Day 1	Day 2-6	Visit 2 Day 7±2	Day 8-13	Visit 3 Week 2 Day 14±3	Day 15-27	Visit 4 Week 4 Day 28±4			Visit 5 Week 6 Day 42 ± 3	Visit 6 Week 24 Day 168 ±7	Visit 7 Week 48 Day 336 ±7	ET
							Visit 4a		Visit 4b (+3 days of 4a)				
							Pre-CAE	Peri-CAE	Schirmer's Test Evaluation				
Randomization	X												
Administer OC-01/placebo	X[3]	X		X	X[3]	X		X	X[3]				
Diary Completion		X		X		X							
Dispense OC-01/placebo	X				X		X						
Concomitant medications	X		X		X		X		X	X	X	X	X
AE Query	X		X		X		X		X	X	X	X	X

ET = Early Termination
X[1] = For females of childbearing potential; X[2] = Pre- and Post-treatment procedures; X[3] = Concurrent with Schirmer's Test; X[4] = Procedure started at time 0 and was then conducted every 5 minutes thereafter during the 120-minute CAE® exposure; X[5] = At Visit 4, Schirmer's Test Evaluation and CAE® procedures were performed on different days within the visit window. The Schirmer's Test Evaluation and all assessments were performed after the CAE® visit assessment.
X[6] = Post-Treatment Procedures

Inclusion Criteria

1. At least 22 years of age at the Screening Visit
2. Used and/or desired to use an artificial tear substitute for dry eye symptoms within 6 months prior to Visit 1
3. Had an Ocular Surface Disease Index (OSDI) score of ≥23 with ≤3 responses of "Not Applicable") at the Screening Visit
4. Had ALL of the following in the study eye1 at the Screening Visit:
   a. A corneal fluorescein staining (CFS) score of ≥2 in at least one corneal region OR a sum of ≥4 for all corneal regions
   b. A baseline Schirmer's Test Score (STS; with topical anesthesia) of ≤10 mm/5 minutes with a cotton swab nasal stimulation STS at least 7 mm greater in the same eye
   c. <20 mm difference from the study eye STS and the fellow eye STS at baseline
   d. A physician's diagnosis of DED
5. Had 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) in each eye at the Screening Visit
6. Had normal lid/lash anatomy, blinking function, and closure as determined by the Investigator
7. Not been familiar with (e.g., known the study drug was used to stimulate tear production) or had previously used the study drug
8. Been literate and able to complete questionnaires independently
9. Been able to participate in the study for approximately four consecutive hours at Visit 4a
10. Been able and willing to use the study drug and participate in all study assessments and visits
11. Had sufficient hand strength, in the opinion of the Investigator, to be able to independently administer the study drug
12. Provided verbal and written informed consent
13. If a female of childbearing potential, used an acceptable means of birth control (acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives, mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom, intrauterine device, or surgical sterilization of partner), and had a negative urine pregnancy test on Day 1

Exclusion Criteria

1. Had clinically significant corneal epithelial defects at Visit 1 prior to performing Schirmer's Test
2. Had chronic or recurrent epistaxis, coagulation disorders, or other conditions that, in the opinion of the Investigator, that may have led to a clinically significant risk of increased bleeding
3. Had nasal or sinus surgery (including a history of application of nasal cautery) or significant trauma to these areas
4. Had a vascularized polyp, severely deviated septum, chronic recurrent nosebleeds, or severe nasal airway obstruction as confirmed by intranasal examination performed prior to Visit 1
5. Been currently treated with nasal continuous positive airway pressure
6. Had any intraocular surgery (such as cataract surgery), extraocular surgery in either eye within 3 months or refractive surgery (e.g., laser-assisted in-situ keratomileusis, laser

epithelial keratomileusis, photorefractive keratectomy or corneal implant) within 12 months of Visit 1
7. Had blepharoplasty in either eye
8. Had a corneal transplant in either eye
9. Used Restasis or Xiidra in the past 60 days
10. Used contact lenses within 7 days prior to Visit 1 or anticipated the use of contact lenses during the study treatment period
11. Had any form of punctal or intracanalicular occlusion
12. Had a history or presence of any ocular disorder or condition in either eye that would have, in the opinion of the Investigator, likely interfered with the interpretation of the study results or participant safety such as significant corneal or conjunctival scarring; pterygium or nodular pinguecula; current ocular infection, conjunctivitis, or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; ocular herpetic infection; evidence of keratoconus; etc. Blepharitis not requiring treatment and mild Meibomian gland disease that are typically associated with DED were allowed.
13. Had a history of seizures or other factors that lowered the subject's seizure threshold.
14. Had a systemic condition or disease not stabilized or judged by the Investigator to be incompatible with participation in the study or with the lengthier assessments required by the study (e.g., current systemic infection, uncontrolled autoimmune disease, uncontrolled immunodeficiency disease, history of myocardial infarction or heart disease, etc.)
15. Had a known hypersensitivity to any of the procedural agents or study drug components
16. Had current concomitant use of a nicotinic acetylcholine receptor agonist (Nicoderm, Nicorette, Nicotrol Nasal Spray [nicotine], Tabex, Desmoxan [cytisine], and Chantix [varenicline]) within the previous 30 days of Visit 1 and during the treatment period
17. Had active or uncontrolled, severe:
    a. Systemic allergy
    b. Chronic seasonal allergies at risk of being active during the study treatment period
    c. Rhinitis or sinusitis requiring treatment such as antihistamines, decongestants, or oral or aerosol steroids at the Screening Visit or to been expected to require treatment during the treatment period of the study
    d. Untreated nasal infection at Visit 1
18. Had any condition or history that, in the opinion of the Investigator, may have interfered with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject
19. Been a female who was pregnant, nursing an infant, or planning a pregnancy at Visit
20. Been a woman of childbearing potential who was not using an acceptable means of birth control; acceptable methods of birth control included: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device; or surgical sterilization of partner
21. Been currently enrolled in an investigational drug or device study or had used an investigational drug or device within 30 days prior to Visit 1 and during treatment period

Study Endpoints

Primary efficacy endpoint

- Percent of subjects who achieved ≥10 mm improvement in the study eye on STS from baseline at Week 4 (Visit 4b)

Secondary efficacy endpoints

- Change from baseline in Eye Dryness Score (EDS)* at 5 minutes after threshold-defined treatment administration in the Controlled Adverse Environment (CAE) Chamber at Week 4 (Visit 4a)
- Change from baseline in EDS at Week 4 (Visit 4b)
- Change from baseline in STS in the study eye at Week 4 (Visit 4b)
- Change from baseline in Inferior CFS in the study eye at Week 4 (Visit 4b)
- Change from baseline in EDS at Week 2 (Visit 3)
- Change from baseline in EDS at Week 1 (Visit 2)
- Change from baseline in Nasal CFS in the study eye at Week 4 (Visit 4b)
- Change from baseline in Temporal CFS in the study eye at Week 4 (Visit 4b)
- Change from baseline in Central CFS in the study eye at Week 4 (Visit 4b)
- Change from baseline in Superior CFS in the study eye at Week 4 (Visit 4b)
- Change from baseline in Total CFS in the study eye at Week 4 (Visit 4b)

*EDS score was rated based on both eyes simultaneously

Other efficacy endpoints

- The listed primary and secondary endpoints in the fellow eye
- The listed primary and secondary endpoints combining data from both study and fellow eyes

Safety endpoints

- Adverse events (AEs)
- Intranasal examination
- Slit-lamp biomicroscopy
- Change in BCVA

Statistical Analysis Plan

Primary Efficacy Analyses

The primary endpoint, percentage of subjects who achieved ≥10 mm in STS from baseline to Week 4 (Visit 4b), was analyzed on the ITT Population using a Cochran-Mantel-Haenszel test comparing each treatment group to placebo controlling for the randomization strata (study site, baseline STS [≤5, >5] and baseline EDS [<60, ≥60]).

Because there were two comparisons, low dose (0.6 mg/mL) vs. placebo and high dose (1.2 mg/mL) vs. placebo, the overall familywise error rate was protected using Hochberg's approach.

Specifically, if the p-value for both comparisons was <0.05, the null hypotheses were rejected for both treatment groups to conclude that both low dose and high dose of OC-01 (varenicline) were superior to placebo. If not, the smaller of the two p-values was tested at the 0.025 level; if the null hypothesis was rejected, the dose of OC-01 (varenicline) with p<0.025 would be shown superior to placebo

Secondary Efficacy Analyses
A hierarchical procedure (closed testing procedure) was used to test the primary and the 11 secondary efficacy endpoints to control overall familywise error rate for the 0.6 mg/mL dose and 1.2 mg/mL dose of OC-01 (varenicline) against placebo

If the null hypothesis for the primary endpoint for a given dose was rejected, the secondary endpoints in the order specified above were to be tested to maintain the overall two-sided type I error of 0.05. If the p-value from a test for both comparisons were <0.05 for the first secondary endpoint, both doses would be claimed superior to placebo and the testing would progress to the next comparison in the above sequence. In the case where one dose group was concluded to be superior to placebo for the primary endpoint, the secondary endpoints were to be tested in the order specified above using the type I error of 0.025 for that dose only.

Protocol Amendments

The original protocol was amended once to reflect the following changes to the study:

- Eligibility criteria were updated to reflect that all females of childbearing potential were required to use an acceptable means of birth control, to exclude subjects who were nursing, and to exclude those with active or uncontrolled, severe allergies during the treatment period of the study rather than for the entire study period.
- The amendment clarified that dosing of study drug on the day of Visit 2 was to be self-administered following the subject's routine schedule.
- Instructions for Visit 1 were clarified to reflect that Schirmer's Test with nasal stimulation was to occur >10 minutes after the baseline Schirmer's Test.

6.2.2. Study Results

Compliance with Good Clinical Practices

The study was performed in compliance with the ethical principles of the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice. In addition, all applicable local, state, and federal requirements relevant to the use of investigational agents in the country involved were followed.

Financial Disclosure

The sponsor of this NDA certified that they did not enter into any financial arrangement with the listed clinical investigators and that no investigators have disclosed financial interest with the company. See appendix 14.2.

Patient Disposition

Category	OC-01 0.6 mg/mL N=260 n (%)	OC-01 1.2 mg/mL N=246 n (%)	Placebo N=252 n (%)
Randomized	260	246	252
ITT Population[a]	260 (100.0)	246 (100.0)	252 (100.0)
Safety Population[b]	260 (100.0)	245 (99.6)	251 (99.6)
Per-protocol Population[c]	252 (96.9)	240 (97.6)	248 (98.4)
mITT-1 Population[d]	227 (87.3)	216 (87.8)	220 (87.3)
mITT-2 Population[e]	235 (90.4)	221 (89.8)	228 (90.5)
mITT-3 Population[f]	248 (95.4)	238 (96.7)	242 (96.0)
ITT-COVID-19 Population[g]	37 (14.2)	33 (13.4)	34 (13.5)
Subjects completed treatment	251 (96.5)	230 (93.5)	242 (96.0)
Subjects discontinued treatment (for reasons other than treatment completion)	9 (3.5)	16 (6.5)	10 (4.0)
Non-fatal adverse event	5 (1.9)	8 (3.3)	4 (1.6)
Protocol violation	0	0	1 (0.4)
Lost to follow up	2 (0.8)	1 (0.4)	2 (0.8)
Pregnancy	0	0	0
Physician decision	1 (0.4)	0	0
Subject non-compliance	0	1 (0.4)	1 (0.4)
Death	0	0	0
Study terminated by Sponsor	0	0	0
Withdraw by subject	1 (0.4)	6 (2.4)	2 (0.8)
Other	0	0	0
Subjects completed study	23 (8.8)	24 (9.8)	24 (9.5)
Ongoing subjects	222 (85.4)	199 (80.9)	216 (85.7)
Subjects discontinued from study (for reasons other than study completion)	15 (5.8)	23 (9.3)	12 (4.8)
Non-fatal adverse event	4 (1.5)	1 (0.4)	0
Protocol violation	0	0	1 (0.4)
Lost to follow up	6 (2.3)	12 (4.9)	6 (2.4)
Pregnancy	0	0	0
Physician decision	2 (0.8)	0	0

Category	OC-01 0.6 mg/mL N=260 n (%)	OC-01 1.2 mg/mL N=246 n (%)	Placebo N=252 n (%)
Subject non-compliance	0	1 (0.4)	0
Death	0	0	1 (0.4)
Study terminated by Sponsor	0	0	0
Withdraw by subject	3 (1.2)	9 (3.7)	3 (1.2)
Other	0	0	1 (0.4)

Percentages were calculated based on all randomized subjects.
Abbreviation: COVID-19 = Coronavirus disease-2019; ITT = intent-to-treat; mITT = modified intent-to-treat
[a] The ITT Population included all randomized subjects.
[b] The Safety Population included all randomized subjects who received at least one dose of study drug.
[c] The Per Protocol Population included all subjects in the ITT Population with post-baseline (Visit 1) data, excluding subjects who had major protocol deviations.
[d] The mITT-1 Population was defined as randomized subjects excluding Sites 48 and 51.
[e] The mITT-2 Population was defined as randomized subjects excluding Sites 45 and 48.
[f] The mITT-3 Population was defined as randomized subjects excluding Site 51.
[g] The ITT-COVID-19 Population was defined as randomized subjects of Sites 45, 48, and 51 who were impacted by COVID-19.

The number of subjects that completed the study was similar between the treatment groups.

Analysis Populations

In the ONSET-2 study, most subjects had completed the treatment period prior to the COVID-19 pandemic outbreak. Follow-up visits and enrollment were impacted at four clinical centers. This study randomized 758 subjects. One hundred and four (104) subjects at three of the 22 clinical centers (Center 45, 9 subjects; Center 48, 65 subjects, Center 51, 30 subjects) had some missing data for select efficacy endpoints due to the pandemic therefore, the following analysis groups were identified:

- Intent-to-Treat (ITT) Population – The ITT Population included all randomized subjects. Subjects in the ITT Population were analyzed as randomized.
- modified ITT (mITT): Three mITT populations were defined by centers excluded because of being impacted by COVID-19, based on the center's ability to collect specific study data, as follows:
    - mITT-1 excluded Sites 48 and 51
    - mITT-2 excluded Sites 45 and 48
    - mITT-3 excluded Site 51
- The ITT-COVID-19 Population was defined as randomized subjects at Sites 45, 48, and 51 who were impacted by COVID-19.
- Per Protocol (PP) Population – The PP Population included all subjects in the ITT Population with post-baseline (Visit 1) data, excluding subjects who had major protocol deviations. Protocol deviations were assessed prior to database lock and unmasking.

Subjects in the PP Population were analyzed as treated.

- Safety Population – The Safety Population included all randomized subjects who received at least one dose of the study drug.

Protocol Violations/Deviations

Eight (8) subjects had deviations that were classified as major during the trial. The following major violations occurred:

- 3 subjects (1.2%) in the 0.6 mg/mL OC-01 group and 1 subject (0.4%) in the placebo group had deviations related to inclusion/exclusion criteria and inadvertent randomization.

- 1 subject (0.4%) in the 0.6 mg/mL OC-01 group and 3 subjects (1.2%) in the 1.2 mg/mL OC-01 group had deviations related to improper procedures at the site.

Deviations occurred in only approximately 1 % of subjects enrolled.

Table of Demographic Characteristics

Category Statistic	OC-01 0.6 mg/mL N=260	OC-01 1.2 mg/mL N=246	Placebo N=252
Age (Years)[a]			
Mean (SD)	59.6 (12.76)	58.4 (13.03)	58.4 (13.29)
Range (min, max)	22, 91	22, 91	23, 95
Quartiles (25^{th}, median, 75^{th})	52.0, 61.0, 69.0	50.0, 59.0, 68.0	51.0, 59.0, 68.0
Female, n (%)	194 (74.6)	181 (73.6)	201 (79.8)
Race, n (%)			
American Indian or Alaska Native	1 (0.4)	2 (0.8)	6 (2.4)
Asian	11 (4.2)	7 (2.8)	5 (2.0)
Black or African American	27 (10.4)	35 (14.2)	29 (11.5)
Native Hawaiian or other Pacific Islander	2 (0.8)	0	1 (0.4)
White	219 (84.2)	200 (81.3)	211 (83.7)
Other	0	2 (0.8)	0
Ethnicity, Hispanic or Latino, n (%)	27 (10.4)	37 (15.0)	36 (14.3)

*The overall age and sex characteristics of the subjects enrolled in this study is consistent with the demographics of dry eye disease.***Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Baseline Ocular Assessments (Safety Population)

Baseline Assessment Category Statistic	OC-01 0.6 mg/mL N=260	OC-01 1.2 mg/mL N=245	Placebo N=251
Schirmer's Test Score (mm)[a]			
Mean (SD)	5.1 (2.95)	5.4 (2.93)	4.9 (2.89)
Range (min, max)	0, 10	0, 10	0, 10
Quartiles (25th, median, 75th)	3.0, 5.0, 7.0	3.0, 5.0, 8.0	2.0, 5.0, 7.0
Schirmer's Test Score with cotton swab stimulation (mm)[a]			
n	257	239	248
Mean (SD)	27.6 (8.27)	28.1 (8.33)	27.8 (8.16)
Range (min, max)	8, 35	7, 35	8, 35
Quartiles (25th, median, 75th)	21.0, 30.0, 35.0	21.0, 33.0, 35.0	22.0, 31.0, 35.0
Eye Dryness Score (mm)[b]			
Mean (SD)	58.5 (22.05)	59.3 (22.61)	58.1 (22.35)
Range (min, max)	2, 100	4, 99	3, 100
Quartiles (25th, median, 75th)	42.0, 63.0, 75.5	43.0, 64.0, 76.0	42.0, 62.0, 77.0
Best corrected visual acuity (logMAR)[a]			
Mean (SD)	0.113 (0.1421)	0.130 (0.1538)	0.129 (0.1581)
Range (min, max)	-0.3, 0.52	-0.2, 0.6	-0.18, 0.62
Quartiles (25th, median, 75th)	0.000, 0.100, 0.200	0.020, 0.120, 0.240	0.020, 0.100, 0.220
Ora Calibra Ocular Discomfort Scale (grade)[a]			
Mean (SD)	2.8 (0.88)	2.8 (1.05)	2.8 (0.97)
Range (min, max)	0, 4	0, 4	0, 4
Quartiles (25th, median, 75th)	2.0, 3.0, 3.0	2.0, 3.0, 4.0	2.0, 3.0, 3.0
Ocular Surface Disease Index[b]			
Mean (SD)	51.31 (19.458)	52.43 (18.755)	50.94 (18.856)
Range (min, max)	18.8, 100	25, 100	25, 100
Quartiles (25th, median, 75th)	34.55, 50.00, 66.70	37.50, 50.00, 66.70	35.40, 47.90, 63.60
Corneal fluorescein staining (score)[a]			
Mean (SD)	6.4 (2.16)	6.3 (2.19)	6.2 (2.05)
Range (min, max)	2, 14	2, 15	2, 13
Quartiles (25th, median, 75th)	5.0, 6.0, 8.0	5.0, 6.0, 7.0	5.0, 6.0, 8.0

Baseline ocular assessment results were generally similar across all treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study visit treatment exposure was captured at each study visit. Compliance with BID dosing at home was not monitored but was based on assessments of used/unused study drug at each clinic visit. Study compliance was similar across treatment groups.

Efficacy Results – Primary Endpoint

Primary Endpoint, ITT Population, Observed: Percent of Subjects who Achieved at Least 10 mm Improvement on STS from Baseline to Visit 4b in Study Eye

Subjects Who Achieved ≥10 mm Improvement From Baseline at Visit 4b	OC-01 0.6 mg/mL N=260	OC-01 1.2 mg/mL N=246	Placebo N=252
n (%)	100 (38.5)	103 (41.9)	56 (22.2)
Proportion difference (95% CI)[a]	16.2 (8.41, 24.07)	19.6 (11.63, 27.67)	
Odds ratio (95% CI)[a]	2.50 (1.623, 3.848)	2.56 (1.707, 3.854)	
p-value[b]	<0.0001	<0.0001	

Column header counts are the number of randomized subjects. All comparisons are made to placebo group.
The ITT Population included all randomized subjects.
Subjects who early terminated before or were missing at Visit 4b were considered NOT to have achieved ≥10 mm improvement.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EDS = Eye Dryness Score; ITT = intent-to-treat; STS = Schirmer's Test Score
[a] The CMH test compared each of the treatment groups to placebo controlling for study site, baseline STS (≤5, >5), and baseline EDS (<60, ≥60).

Both the 0.6mg/mL and 1.2mg/mL doses of OC-01 met the primary efficacy endpoint for this clinical trial. Both showed statistically significant outcome at the <0.001 level for the clinically meaningful increase in Schirmer's score.

A sensitivity analysis using LOCF to impute missing data was conducted on the primary analysis. The results of the primary analysis for the primary endpoint in the ITT Population were supported by results obtained with a sensitivity analysis using LOCF to impute missing data.

Primary Endpoint, ITT Population, LOCF: Percent of Subjects who Achieved at Least 10 mm Improvement on STS from Baseline to Visit 4b in Study Eye

Subjects Who Achieved ≥10 mm Improvement From Baseline at Visit 4b	OC-01 0.6 mg/mL N=260	OC-01 1.2 mg/mL N=246	Placebo N=252
n (%)	123 (47.3)	121 (49.2)	70 (27.8)
Proportion difference (95% CI)[a]	19.5 (11.32, 27.74)	21.4 (13.07, 29.75)	
Odds ratio (95% CI)[a]	2.55 (1.716, 3.792)	2.48 (1.695, 3.626)	
p-value[b]	<0.0001	<0.0001	

Column header counts are the number of randomized subjects. All comparisons are made to placebo group.
The ITT Population included all randomized subjects.
When the LOCF imputation approach was used, if a subject had a Visit 3 value but was missing the Visit 4b value, the Visit 3 value was carried forward to Visit 4b. If the subject had neither Visit 3 nor Visit 4b values, the Visit 1 value was not carried forward and the subject was not considered to have achieved ≥10 mm improvement.
Subjects who early terminated before or were missing at Visit 4b were considered NOT to have achieved ≥10 mm improvement.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EDS = Eye Dryness Score; ITT = intent-to-treat; LOCF = last observation carried forward; STS = Schirmer's Test Score
[a] The CMH test compared each of the treatment groups to placebo controlling for study site, baseline STS (≤5, >5), and baseline EDS (<60, ≥60).

Data Quality and Integrity

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

The first of the secondary efficacy endpoints was the change from baseline in EDS at 5 minutes after threshold-defined treatment administration in the CAE Chamber at Week 4 (Visit 4a). This endpoint was analyzed using observed data that was actually measured when subjects were in the CAE chamber. Due to the impact of COVID-19, the data was not collected on any of the subjects at sites 45 and 48; therefore, the MITT-2 population was used for analysis.

Observed: EDS in CAE at Week 4 (Visit 4a) at 5 Minutes Post-Treatment (Secondary Endpoint) (mITT-2 Population)

At Week 4 (Visit 4a) - 5 Minutes Post-treatment	OC-01 0.6 mg/mL N=235	OC-01 1.2 mg/mL N=221	Placebo N=228
Mean change from baseline			
n	187	171	169
Mean (SD)	-10.3 (26.18)	-9.3 (25.78)	-6.5 (24.23)
Range (min, max)	-81, 62	-75, 54	-78, 78
Quartiles (25^{th}, median, 75^{th})	-28.0, -9.0, 4.0	-25.0, -8.0, 9.0	-20.0, -7.0, 9.0
LS mean change from baseline			
LS mean (SE)[a]	-10.3 (1.62)	-9.0 (1.75)	-7.4 (1.74)
95% CI	-13.49, -7.15	-12.48, -5.61	-10.84, -4.00
Treatment comparison			
LS mean difference (SE)[b]	-2.9 (2.27)	-1.6 (2.32)	
95% CI	-7.35, 1.55	-6.19, 2.92	
p-value	0.2008	0.4818	

The mITT-2 Population was defined as randomized subjects excluding Sites 45 and 48.
Abbreviations: ANCOVA = analysis of covariance; CAE = controlled adverse environment; CI = confidence interval; EDS = Eye Dryness Score; LS = least squares; max = maximum; min = minimum; mITT = modified intent-to-treat; SD = standard deviation; SE = standard error; STS = Schirmer's Test Score
[a] The LS means were derived from an ANCOVA model with treatment, site, baseline STS, and baseline EDS as covariates.
[b] All comparisons made are in reference to placebo group.

Neither dose level of OC-01 showed statistical significance for improving eye dryness score (EDS). In accordance with the statistical analysis plan, no further hierarchical testing was done on the remaining secondary endpoints.

Dose/Dose Response

Dose response was not evaluated in this development program; however, both of the doses studied (0.6mg/mL and 1/2mg/mL) had similar responses in the ability to increase Schirmer's score by a clinically meaningful amount (i.e. > 10mm).

Persistence of Effect

Persistence of clinical effect was not evaluated in this development program.

6.3. Mystic (OPP-004)

6.3.1. Study Design

Overview and Objective

The objective of this study was to evaluate the safety and effectiveness of OC-01 nasal spray as compared to placebo on signs of dry eye disease (DED).

Trial Design

This was a Phase 2, single-center, randomized, masked (including subjects, Investigators, and study site personnel), placebo-controlled study designed to evaluate the safety and efficacy of OC-01 (varenicline) nasal spray in adult subjects with DED. Approximately 120 subjects at least 22 years of age with a physicians' diagnosis of DED and meeting all other study eligibility criteria were randomized to receive an application of OC-01 or placebo twice daily for 12 weeks.

Inclusion Criteria

1. At least 22 years of age at the Screening Visit
2. Used and/or desired to use an artificial tear substitute for dry eye symptoms within 6 months prior to Visit 1
3. Had diagnosis of dry eye and ALL of the following in the study eye at the Screening Visit
    a. A corneal fluorescein staining (CFS) score of ≥2 in at least one corneal region OR have a sum of ≥4 for all corneal regions
    b. A baseline Schirmer's Test (with topical anesthesia) score of ≤10 mm/5 minutes with a cotton swab nasal stimulation Schirmer's Test score (STS) at least 7 mm greater in the same eye
4. Had 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) in each eye at the Screening Visit
5. Had normal lid/lash anatomy, blinking function, and closure as determined by the Investigator
6. Not been familiar with (e.g., know the study drug is used to stimulate tear production) or have previously used the study drug
7. Been literate, able to speak Spanish/English, and able to complete questionnaires independently
8. Been able and willing to use the study drug and participate in all study assessments and visits
9. Provided verbal and written informed consent
10. Had a negative urine pregnancy test on Visit 1, if a female of childbearing potential

Exclusion Criteria

1. Had chronic or recurrent epistaxis, coagulation disorders or other conditions that, in the opinion of the Investigator, might have led to clinically significant risk of increased bleeding
2. Had nasal or sinus surgery (including history of application of nasal cautery) or significant

trauma to these areas
3. Had a vascularized polyp, severely deviated septum, chronic recurrent nosebleeds, or severe nasal airway obstruction as confirmed by intranasal examination performed prior to Visit 1
4. Been currently treated with nasal continuous positive airway pressure
5. Had any intraocular surgery (such as cataract surgery), extraocular surgery (such as blepharoplasty) in either eye within 3 months or refractive surgery (e.g., laser-assisted in-situ keratomileusis, laser epithelial keratomileusis, photorefractive keratectomy, or corneal implant) within 12 months of Visit 1
6. Had a corneal transplant
7. Used contact lenses within 7 days prior to Visit 1 or anticipated the use of contact lenses during the study period
8. Had punctal or intracanalicular occlusion
9. Had a history or presence of an ocular disorder or condition in either eye that would, in the opinion of the Investigator, likely interfere with the interpretation of the study results or subject safety such as significant corneal or conjunctival scarring; pterygium or nodular pinguecula; current ocular infection, conjunctivitis, or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; ocular herpetic infection; evidence of keratoconus; etc. Blepharitis not requiring treatment and mild meibomian gland disease that are typically associated with DED were allowed.
10. Had a history of seizures or other factors that lowered the subject's seizure threshold
11. Had a systemic condition or disease not stabilized or judged by the Investigator to be incompatible with participation in the study or with the lengthier assessments required by the study (e.g., current systemic infection, uncontrolled autoimmune disease, uncontrolled immunodeficiency disease, history of myocardial infarction or heart disease, etc.)
12. Had a known hypersensitivity to any of the procedural agents or study drug components
13. Had current concomitant use of a nicotinic acetylcholine receptor (nAChR) agonist [Nicoderm, Nicorette, Nicotrol NS (nicotine), Tabex, Desmoxan (cytisine), and Chantix (varenicline)] or within the previous 30 days
14. Had active or uncontrolled, severe:
    a. Systemic allergy
    b. Chronic seasonal allergies at risk of being active during the study
    c. Rhinitis or sinusitis requiring treatment such as antihistamines, decongestants, oral or aerosol steroids at Visit 1
    d. Untreated nasal infection at Visit 1
15. Had any condition or history that, in the opinion of the Investigator, might have interfered with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject
16. A female who was pregnant, nursing an infant, or planning a pregnancy, at Visit 1
17. Currently enrolled in an investigational drug or device study or had used an investigational drug or device within 30 days prior to Visit 1

Study Schedule

Procedure	Screen/ Visit 1		Visit 2 (Day 7 ±2)		Visit 3 (Day 14 ±2)		Visit 4 (Day 28 ±2)		Visit 5 (Day 56 ±2)		Visit 6/ET (Day 84 ±2)
	Day 1	Days 2-6		Days 8-13		Days 15-27		Days 29-55		Days 57-83	
Informed consent/HIPAA	X										
Demographics	X										
Medical history, prior medications, ocular history and updates	X										
Eligibility criteria	X										
Urine pregnancy test	X_4										X_4
Best corrected visual acuity (BCVA)	X_2		X_2		X_2		X_2		X_2		X_2
Slit lamp biomicroscopy	X_2		X_2		X_2		X_2		X_2		X_2
Corneal fluorescein staining	X								X		
Schirmer's Test	X_2		X_1		X_1		X_1		X_1		X_1
Schirmer's Test with cotton swab stimulation	X										
Intranasal examination	X										X
Randomization	X										
Administer investigational drug / placebo	X_3	X	X_3	X	X_3	X	X_3	X	X_3	X	X_3
Dispense investigational drug/placebo	X				X		X		X		
Adverse event query	X		X_1		X_1		X_1		X_1		X_1
Concomitant medications	X		X_1		X_1		X_1		X_1		X_1
Exit from study											X

Abbreviations: ET =early termination; HIPAA = Health Insurance Portability and Accountability Act
X_1 = Post-treatment procedures; X_2 = Pre- and post-treatment; X_3 = Concurrent with Schirmer's Test; X4 = For females of childbearing potential

Study Endpoints

Primary efficacy endpoint:

- Change from baseline in the study eye on Schirmer's Test at Day 84 (Visit 6).

Other efficacy endpoints:

- The percent of subjects who achieved ≥10 mm improvement in STS from baseline at Day 84 (Visit 6).
- The percent of subjects who achieved ≥10 mm improvement in STS from baseline at Day 28 (Visit 4).
- Change from baseline in the fellow eye on Schirmer's Test at Day 84 (Visit 6).
- Change from baseline in the study eye on Schirmer's Test at Day 28 (Visit 4).
- Change from baseline in the fellow eye on Schirmer's Test at Day 28 (Visit 4).
- Change from baseline in CFS at Day 56 (Visit 5).
    - Change from baseline in Inferior CFS at Day 56 (Visit 5)
    - Change from baseline in Nasal CFS at Day 56 (Visit 5)
    - Change from baseline in Temporal CFS at Day 56 (Visit 5)
    - Change from baseline in Central CFS at Day 56 (Visit 5)
    - Change from baseline in Superior CFS at Day 56 (Visit 5)
    - Change from baseline in Total CFS at Day 56 (Visit 5)

Safety endpoints:

- Adverse events (AEs)
- Change in BCVA
- Slit-lamp biomicroscopy

- Intranasal examination

Statistical Analysis Plan

The primary efficacy endpoint was mean change from baseline in the study eye on Schirmer's Test at Day 84 (Visit 6). The analysis of covariance (ANCOVA) model was used to compare between each dose of OC-01 (varenicline) nasal spray and placebo group on the ITT Population.

Adjustments for multiple testing of the secondary endpoints were not implemented for this study.

Protocol Amendments

The original protocol for this study was finalized on 12 April 2018. The protocol was subsequently amended four times. The amendments revised the inclusion/exclusion criteria, safety evaluations and increased the number of subjects from 100 to 120.

The amendments made to the protocol do not raise any issues with the evaluation of the study outcome.

6.3.2. Study Results

Compliance with Good Clinical Practices

The sponsor of this NDA certified that the study was performed in compliance with the ethical principles of the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice. In addition, all applicable local, state, and federal requirements relevant to the use of investigational agents in Mexico were followed.

Financial Disclosure

The sponsor of this NDA certified that they did not enter into any financial arrangement with the listed clinical investigators and that no investigators have disclosed financial interest with the company. See appendix 14.2.

Patient Disposition

The study randomized 123 subjects in a 1:1:1 ratio between treatment groups. All subjects received treatment as randomized and were therefore included in both the ITT and Safety Populations.

	OC-01 0.6 mg/mL N=41 n (%)	OC-01 1.2 mg/mL N=41 n (%)	Placebo N=41 n (%)
Analysis Population			
ITT Population (Randomized)	41 (100.0)	41 (100.0)	41 (100.0)
Safety Population (Treated)	41 (100.0)	41 (100.0)	41 (100.0)
Per-protocol Population	35 (85.4)	33 (80.5)	34 (82.9)
Study completion			
Subjects completed study	36 (87.8)	29 (70.7)	32 (78.0)
Subjects discontinued study (for reasons other than study completion)	5 (12.2)	12 (29.3)	9 (22.0)
Non-Fatal Adverse Event	1 (2.4)	3 (7.3)	3 (7.3)
Protocol Violation	0	0	0
Lost to Follow up	4 (9.8)	4 (9.8)	5 (12.2)
Pregnancy	0	0	0
Physician Decision	0	0	0
Subject Non-compliance	0	1 (2.4)	0
Death	0	0	0
Study Terminated by Sponsor	0	0	0
Withdraw by Subject	0	4 (9.8)	1 (2.4)
Other	0	0	0

Percentages are calculated based on all randomized subjects.
Abbreviations: ITT = intent-to-treat

Source: OPP-004 CSR page 37

There was approximately a three-fold increase in the number of subjects that discontinued from this study compared to Onset-1 or Onset-2. There was a lower number of subjects who completed the trial in the 1.2mg/mL group versus the 0.6mg/mL group (71%vs.88%) and in the 1.2mg/mL group versus the placebo group (71%vs.78%). This appears to have been driven by the larger number of subjects who made the decision to withdraw from the study or did not follow-up.

Protocol Violations/Deviations

A total of 3 subjects had a protocol deviation classified as "major".

- Subject (b) (6) (0.6 mg/mL OC-01 group) did not receive study drug prior to the Schirmer's Test at the final visit because the subject ran out of study drug in the nasal pump 2 days prior.
- Subject (b) (6) (0.6 mg/mL OC-01 group) did not receive study drug on Study Day 129 (Visit 6, was scheduled per protocol for Day 84±2 days) because the subject ran out of study drug in the nasal pump.
- Subject (b) (6) (1.2 mg/mL OC-01 group) met exclusion criterion #2 (subject had Parkinson's disease) and was randomized in error.

These three protocol deviations out of 150 subjects enrolled in the study do not raise any concerns about the integrity of the study.

Table of Demographic Characteristics

Category Statistic	OC-01 0.6 mg/mL N=41	OC-01 1.2 mg/mL N=41	Placebo N=41
Age (Years)[a]			
Mean (SD)	51.4 (13.18)	54.2 (11.77)	55.8 (13.17)
Range (min, max)	28, 74	28, 74	26, 77
Quartiles (25^{th}, median, 75^{th})	42.0, 51.0, 62.0	48.0, 56.0, 61.0	48.0, 57.0, 65.0
Male, n (%)	9 (22.0)	6 (14.6)	8 (19.5)
Race, n (%)			
Other[b]	41 (100.0)	41 (100.0)	41 (100.0)
Ethnicity, n (%)			
Hispanic or Latino	41 (100.0)	41 (100.0)	41 (100.0)
Significant ocular history, n (%)			
Yes	16 (39.0)	17 (41.5)	17 (41.5)

Source: OPP-004 CSR page 39

The overall age and sex characteristics of the subjects enrolled in this study is consistent with the demographics of dry eye disease.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline Ocular Assessments

Baseline Assessment Category Statistic	OC-01 0.6 mg/mL N=41	OC-01 1.2 mg/mL N=41	Placebo N=41
Schirmer's Test score (mm)			
Mean (SD)	5.5 (2.46)	5.4 (2.47)	5.3 (2.04)
Range (min, max)	0, 9	0, 9	0, 9
Quartiles (25th, median, 75th)	4.0, 5.0, 8.0	4.0, 6.0, 7.0	4.0, 6.0, 7.0
Cotton swab Schirmer's Test score (mm)			
Mean (SD)	20.3 (7.53)	19.6 (7.27)	19.5 (8.07)
Range (min, max)	10, 35	9, 35	9, 35
Quartiles (25th, median, 75th)	16.0, 18.0, 25.0	15.0, 17.0, 22.0	14.0, 17.0, 25.0
Best corrected visual acuity score (logMAR)	n=24	n=24	n=18
Mean (SD)	0.184 (0.2009)	0.183 (0.1596)	0.236 (0.2046)
Range (min, max)	-0.18, 0.64	-0.10, 0.62	-0.06, 0.56
Quartiles (25th, median, 75th)	0.030, 0.160, 0.270	0.040, 0.200, 0.280	0.120, 0.180, 0.420
Corneal fluorescein staining – total score (grade)			
Mean (SD)	4.6 (1.92)	6.0 (3.34)	5.8 (3.78)
Range (min, max)	2, 10	2, 15	2, 15
Quartiles (25th, median, 75th)	3.0, 4.0, 6.0	4.0, 5.0, 8.0	3.0, 4.0, 6.0

Abbreviations: logMAR = logarithm of the minimum angle of resolution; max = maximum; min = minimum; SD = standard deviation
Source: OPP-004 CSR page 39

Baseline ocular assessment results were generally similar across all treatment groups with except for a lower mean CFS score in the 0.6mg/mL group. However, baseline Schirmer's score was consistent and is the basis for the measurement of the primary efficacy endpoint.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study visit treatment exposure was captured at each study visit. Compliance was calculated at each visit based on the number of non-missing doses divided by the number of expected doses. Compliance ranged from 70.7% to 85.4% by treatment group. The compliance rate was highest

in the 0.6 mg/mL OC-01 group (82.9% to 85.4%) and lowest in the 1.2 mg/mL group (70.7% to 80.5%).

Efficacy Results – Primary Endpoint

Schirmer's Test Score in Study Eye at Day 84 (Visit 6) (ITT Population)

At Day 84 (Visit 6) (Study Eye)	OC-01 0.6 mg/mL N=41	OC-01 1.2 mg/mL N=41	Placebo N=41
Change from baseline (mm)			
n	35	29	32
Mean (SD)	10.6 (9.58)	11.0 (8.37)	6.3 (6.05)
Range (min, max)	-3, 31	-5, 31	-1, 24
Quartiles (25th, median, 75th)	4.0, 7.0, 14.0	5.0, 10.0, 16.0	2.0, 4.0, 10.0
LS mean change from baseline (mm)			
LS mean (SE)[a]	10.6 (1.39)	11.0 (1.53)	6.2 (1.45)
95% CI	7.87, 13.39	7.93, 13.99	3.34, 9.11
Treatment comparison (mm)			
LS mean difference (SE)[b]	4.4 (2.02)	4.7 (2.11)	—
95% CI	0.41, 8.41	0.55, 8.92	—
p-value	0.0313	0.0270	—

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LS = least squares; max = maximum; min = minimum; SD = standard deviation; SE = standard error; STS = Schirmer's Test Score
[a] LS means were derived from ANCOVA model with treatment and baseline STS as covariates.
[b] All comparisons were made to placebo group.

A sensitivity analysis using LOCF to impute missing data in the ITT Population and the PP Population supported the results of the primary analysis.

Both doses of OC-01 met the primary efficacy endpoint for the clinical trial. Since increase in Schirmer's score is not an acceptable endpoint to use on its own for the establishment of efficacy for dry eye trials, this study can only be used as supportive evidence.

Data Quality and Integrity

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

There were twelve (12) secondary endpoints analyzed for this clinical study. One of the secondary analyses was to determine the percentage of subjects that improved ≥ 10mm in Schirmer's score (STS). This endpoint is an accepted endpoint by the Division for demonstrating efficacy of dry eye products. The Sponsor conducted this as one of multiple secondary endpoints. Adjustments for multiple testing were not implemented for this study. Therefore, the analysis is only being presented for review. The p-values are not applicable and cannot be used to assess the outcome of the trial; however, both the 0.6mg/mL dose and 1.2mg/mL dose were numerically superior to placebo for this endpoint. Further exploration of the secondary endpoints is not warranted since this study is only supportive.

Percent of Subjects Who Achieved at Least 10 mm Improvement on STS from Baseline to Day 84 (Visit 6) (ITT Population)

At Day 84 (Visit 6), Eye Statistic	OC-01 0.6 mg/mL N=41	OC-01 1.2 mg/mL N=41	Placebo N=41
Study Eye			
n (%)	12 (29.3)	16 (39.0)	8 (19.5)
Difference in Proportions (95% CI)	9.8 (-8.71, 28.23)	19.5 (0.27, 38.75)	—
Odds Ratio (95% CI)[a]	1.72 (0.621, 4.784)	2.65 (0.979, 7.179)	—

Source OPP-004 CSR page 47

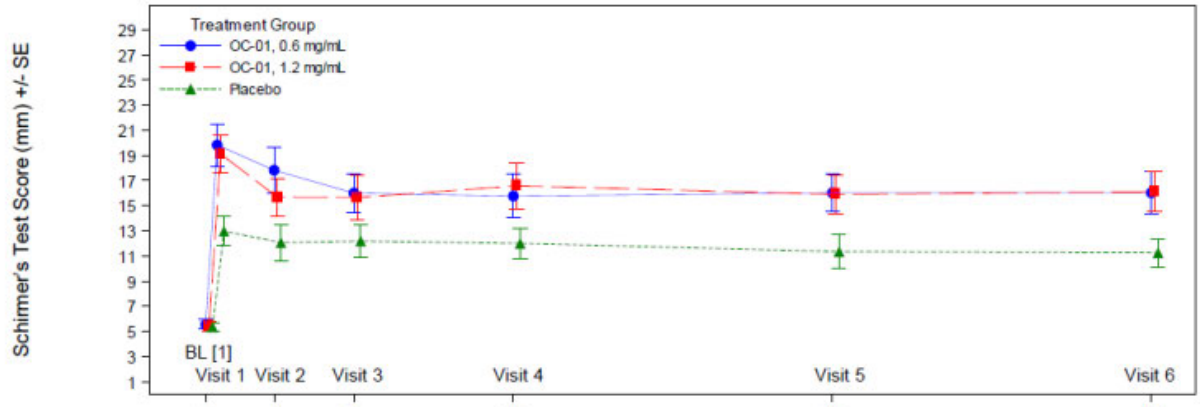
Dose/Dose Response

This trial studied two doses of OC-01: 0.6mg/mL and 1.2mg/mL). Both had similar responses in the ability to increase Schirmer's score. (See efficacy results above).

Durability of Response

Durability of the clinical effect on was not evaluated in this development program. However, the onset of improvement in Schirmer's score begins on the first day of treatment, decreases somewhat during the first week and remains stable with continued dosing throughout the study period.

Schirmer's Test Mean Scores and Changes from Baseline in Study Eye by Visit (ITT Population)



OC-01, 0.6 mg/mL	41	34	35	34	35	35
OC-01, 1.2 mg/mL	41	33	31	31	30	29
Placebo	41	31	33	31	32	32

Source: OPP-004 CSR

Persistence of Effect

Persistence of clinical effect was not evaluated in this development program.

Additional Analyses Conducted on the Individual Trial

N/A

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Three trials (Onset-1, Onset-2 and Mystic) were submitted with this NDA to support the approval of the (b) (4) *OC-01 for the treatment of dry eye disease. Each of the trials studied different endpoints to determine the clinical effectiveness of OC-1 in treating dry eye disease. This is an acceptable pathway for a dry eye indication. Acceptable endpoints for this indication that are applicable to this NDA submission are:*

- *Demonstrating efficacy for both an objective sign and a subjective symptom. These may be co-primary endpoints or may be tested separately as primary and secondary endpoints.*

or

- *Demonstrating and increase in Schirmer's score of at least 10mm*

The Onset-1 trial studied a change in Schirmer score (sign endpoint) for the primary efficacy endpoint. The trial then tested a primary secondary endpoint of eye dryness score (symptom endpoint). Both the 0.6mg/mL and 1.2mg/mL doses of OC-01 met the primary efficacy endpoint for this clinical trial. However, only the 0.6mg/mL dose of OC-01 met the primary secondary endpoint. Since positive results of both the primary and secondary endpoints are required to demonstrate efficacy, the analyses only support the 0.6mg/mL dose for a dry eye indication. (b) (4) (b) (4)

The Onset-2 trial studied the percentage of subjects that had at least a 10mm increase in Schirmer's score for the primary efficacy endpoint. Both the 0.6mg/mL and 1.2mg/mL doses of OC-01 met the primary efficacy endpoint for this clinical trial. Both showed statistically significant outcome at the <0.001.

The Mystic trial studied the percentage of subjects that had an increase in Schirmer's score for the primary efficacy endpoint. Both doses of OC-01 met the primary efficacy endpoint for the clinical trial. Since increase in Schirmer's score is not an acceptable endpoint to use on its own for the establishment of efficacy for dry eye trials, this study can only be used as supportive evidence.

The results of these three clinical trials support the use of the 0.6mg/mL (0.1%) dose of OC-01 for the treatment of dry eye disease. (b) (4) (b) (4)

7.2. Additional Efficacy Considerations

N/A

8. Review of Safety

8.1. Safety Review Approach

The primary source for safety data for OC-01 was from the three multidose studies used for the efficacy analysis: ONSET-1 (OPP-002), ONSET-2 (OPP-101), and MYSTIC (OPP-004) See section 5.1. In addition, the sponsor conducted two earlier phase single dose studies. The result of these studies are not integrated into the pooled data since they are not representative of the dose or duration as proposed for marketing.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

OC-01 Exposures in All Studies Contributing to the Safety of OC-01

Study	OC-01 Dose	Number of Subjects Treated with OC-01
Single-dose studies		
OPP-100 (ZEN)	1.2 mg/mL (0.12 mg delivered as a 50-µL [0.06 mg] spray into each nostril)	22
OPP-005 (IMPERIAL)	1.2 mg/mL	12
Multiple-dose studies		
OPP-002 (ONSET-1)	0.12 mg/mL BID for 4 weeks	47
	0.6 mg/mL BID for 4 weeks	48
	1.2 mg/mL BID for 4 weeks	44
OPP-101 (ONSET-2)	0.6 mg/mL BID for 4 weeks	260
	1.2 mg/mL BID for 4 weeks	245
OPP-004 (MYSTIC)	0.6 mg/mL BID for 12 weeks	41
	1.2 mg/mL BID for 12 weeks	41
	Total	760

Abbreviation: BID = twice daily

Source: Summary of Clinical Safety p.31

A total of 726 subjects were exposed to OC-01 twice a day at the or above the 0.6 mg/mL which is the dose proposed for approval based on this review.

Duration of Exposure

Category Statistic	OC-01				Placebo
	0.12 mg/mL N=47	0.6 mg/mL N=349	1.2 mg/mL N=349	Overall N=726	N=335
Duration of exposure (days)					
n	47	349	330	726	335
Mean (SD)	29.6 (2.03)	33.8 (18.09)	32.3 (18.25)	32.9 (17.60)	33.8 (17.86)
Range (min, max)	27, 36	1, 105	1, 108	1, 108	1, 113
Quartiles (25th, median, 75th)	28.0, 29.0, 30.0	28.0, 30.0, 31.0	28.0, 29.0, 31.0	28.0, 29.5, 31.0	28.0, 29.0, 31.0

Duration of exposure = Last dose date – First dose date + 1.
Abbreviations: max = maximum; min = minimum; SD = standard deviation
Source: Summary of Clinical Safety p.32

8.2.2. Relevant characteristics of the safety population:

Baseline Demographics (Safety Population)

Category Statistic	OC-01			Placebo
	0.12 mg/mL N=47	0.6 mg/mL N=349	1.2 mg/mL N=349	N=335
Age (Year)[a]				
N	47	349	330	335
Mean (SD)	64.2 (12.69)	59.6 (12.94)	59.1 (13.03)	58.8 (13.08)
Range (min, max)	24, 89	22, 91	22, 91	23, 95
Female, n (%)	36 (76.6)	260 (74.5)	250 (75.8)	266 (79.4)
Ethnicity, n (%)				
Hispanic or Latino	8 (17.0)	71 (20.3)	80 (24.2)	82 (24.5)
Not Hispanic or Latino	39 (83.0)	278 (79.7)	250 (75.8)	253 (75.5)
Race, n (%)				
American Indian or Alaska Native	0	1 (0.3)	2 (0.6)	3 (0.9)
Asian	3 (6.4)	13 (3.7)	7 (2.1)	6 (1.8)
Black or African American	2 (4.3)	31 (8.9)	40 (12.1)	29 (8.7)

Native Hawaiian or other Pacific Islander	0	1 (0.3)	1 (0.3)	0
White	42 (89.4)	258 (73.9)	235 (71.2)	250 (74.6)
Multiple	0	4 (1.1)	2 (0.6)	6 (1.8)
Other	0	41 (11.7)	43 (13.0)	41 (12.2)

Abbreviations: max = maximum; min = minimum; SD = standard deviation
Source: Summary of Clinical Safety p.38

The overall age and sex characteristics of the subjects enrolled in the safety database are consistent with the demographics of dry eye disease.

8.2.3. Adequacy of the safety database:

The overall exposure to OC-01 dosed twice per day for at least 4 weeks was 726 subjects. The size of this database and the clinical evaluations conducted during development were adequate to assess the safety profile of this drug product.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This NDA submission was of sufficient quality to perform a substantive review of this product.

8.3.2. Categorization of Adverse Events

Adverse events for all studies were coded according to the MedDRA Version 22.0. A treatment emergent adverse event (TEAE) was defined as any AE that was new or worsened in severity after the first dose of study drug. Treatment-emergent AEs were categorized by system organ class (SOC) and preferred term (PT), seriousness, severity, and relationship to study drug. Ocular and non-ocular TEAEs were summarized separately.

8.3.3. Routine Clinical Tests

The routine clinical testing required to evaluate the safety concerns associated with the treatment of ophthalmic conditions (i.e. biomicroscopy, fundoscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the trials for this product. In addition, an intranasal exam was conducted due to the route of administration. There were no clinically relevant changes from baseline in visual acuity, slit-lamp biomicroscopy, pupil diameter, or intranasal examination.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in any of the clinical trials during the treatment period. One subject died during the Onset-1 extension period: Subject (b) (6) randomized to placebo died due to a car accident. One subject died during the post-treatment follow-up period of the Onset-2 study: Subject (b) (6) randomized to the placebo group died due to pneumonia.

8.4.2. Serious Adverse Events

Treatment group Subject ID/gender/age (years)/ race	TEAE preferred term	TEAE Start-End (Study Days)	Reason for Serious AE	Study	Outcome
OC-01 0.6 mg/mL					
(b) (6)/F/76/I	Anemia	Day 15-Day 16	Hospitalization	ONSET-1	Resolved
(b) (6)/F/75/W	Back pain	Day 268-Day 290	Hospitalization	ONSET-1 EXT	Resolved
(b) (6)/F/68/W	Ankle fracture	Day 334-Day 337	Hospitalization	ONSET-1 EXT	Resolved
(b) (6)/M/54/W	Sepsis	Day 7-ongoing	Hospitalization	ONSET-2	Ongoing
(b) (6)/F/70/W	Lumbar spinal stenosis	Day 14-Day 36	Hospitalization	ONSET-2	Resolved
(b) (6)/F/69/W	Osteomyelitis	Day 41-Day 76	Hospitalization	ONSET-2	Resolved
OC-01 1.2 mg/mL					
(b) (6)/F/57/B	Bradycardia	Day 3-Day 7	Hospitalization	ONSET-2	Resolved
(b) (6)/M/51/O	Coronary artery disease	Day 174-Day 178	Hospitalization	ONSET-2	Resolved with sequelae
(b) (6)/F/39/W	Cholecystitis acute	Day 32-Day 37	Hospitalization	ONSET-2	Resolved
(b) (6)/F/58/W	Humerus fracture	Day 38-Day 112	Hospitalization	ONSET-2	Resolved

Treatment group Subject ID/gender/age (years)/ race	TEAE preferred term	TEAE Start-End (Study Days)	Reason for Serious AE	Study	Outcome
(b) (6)/F/56/W	Deep vein thrombosis	Day 47-Day 53	Hospitalization	ONSET-2	Resolved with sequelae

(b) (6) /F/63/W	Diabetic gangrene	Day 102-Day 124	Hospitalization	ONSET-2	Resolved with sequelae
(b) (6) /M/64/O	Gangrene	Day 92-Day 130	Hospitalization	ONSET-2	Resolved
	Gangrene	Day 159-Day 169	Hospitalization		Resolved
(b) (6) /M/59/W	Myocardial infarction	Day 281	Hospitalization	ONSET-2	No further information available
	Transient Ischemic attack	Day 281	Hospitalization		
Placebo					
(b) (6) /F/59/W	Breast cancer	Day 284-ongoing	Unknown	ONSET-1 EXT	Not resolved
	Road traffic accident	Day 351	Death		Fatal
(b) (6) /F/74/W	Atrial fibrillation	Day 153-Day 159	Hospitalization	ONSET-2	Resolved
(b) (6) /F/63/W	Pneumonia bacterial	Day 11-Day 52	Hospitalization	ONSET-2	Resolved
(b) (6) /F/76/W	Lung neoplasm malignant	Day 28-ongoing	Hospitalization	ONSET-2	No further information available

Treatment group Subject ID/gender/age (years)/ race	**TEAE preferred term**	**TEAE Start-End (Study Days)**	**Reason for Serious AE**	**Study**	**Outcome**
(b) (6) /F/69/W	Pneumonia	Day 183	Hospitalization	ONSET-2	Fatal

Abbreviations: B = Black/African American; I = American Indian/Alaska native; W = White; F = female; M = male; O = Other; TEAE = treatment-emergent adverse event
Source: Summary of Clinical Safety p.71

The number of subjects that discontinued across the treatment group were similar. None of the adverse events appear to be related to the treatment drug.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Thirteen (13) subjects (1.8%) in the overall OC-01 group and 3 subjects (0.9%) in the placebo group discontinued the study due to an adverse event. The number of subjects that discontinued in each of the OC-01 treatment groups were similar.

Treatment group Subject ID/gender/age (years)/ race	TEAE preferred term	TEAE Start-End (Study Days)	Study	Outcome
0.6 mg/mL OC-01				
(b) (6) /F/65/Mz	Headache	Day 1-Day 1	MYSTIC	Resolved
(b) (6) /M/50/W	Dizziness	Day 1-Day 1	ONSET-1	Resolved
(b) (6) /F/76/W	Vertigo	Day 6-Day 7	ONSET-2	Resolved
	Nausea	Day 6-Day 7	ONSET-2	Resolved
(b) (6) /M/42/W	Tachycardia	Day 1-Day 14	ONSET-2	Resolved
	Throat irritation	Day 1-Day 14	ONSET-2	Resolved
(b) (6) /F/60/W	Oropharyngeal pain	Day 1-Day 5	ONSET-2	Resolved
(b) (6) /F/53/W	Instillation site	Day 1-Day 7	ONSET-2	Resolved
	Nasopharyngitis	Day 5-ongoing	ONSET-2	Ongoing
1.2 mg/mL OC-01				
(b) (6) /F/59/Mz	Nausea	Day 1-Day 13	MYSTIC	Resolved
(b) (6) /F/55/Mz	Headache	Day 4-Day 9	MYSTIC	Resolved
(b) (6) /F/31/Mz	Eye irritation	Day 1-Day 2	MYSTIC	Resolved
	Headache	Day 1-Day 2		Resolved
(b) (6) /F/67/W	Sneezing	Day 1-Day 1	ONSET-1	Resolved
	Throat irritation	Day 1 - ongoing		Ongoing
(b) (6) /F/82/W	Nasopharyngitis	Day 2-Day 16	ONSET-1	Resolved
(b) (6) /F/84/W	Tinnitus	Day 2-ongoing	ONSET-1	Ongoing
	Headache	Day 2-ongoing		Ongoing
	Eyelid edema	Day 2-Day 4		Resolved
(b) (6) /M/70/W	Rash	Day 5-ongoing	ONSET-2	Resolved
Placebo				
(b) (6) /M/74/Mz	Depression	Day 30-ongoing	MYSTIC	Resolving
(b) (6) /F/38/Mz	Nausea	Day 1-Day 1	MYSTIC	Resolved
	Dizziness	Day 1-Day 1		Resolved

	Nasal discomfort	Day 1-Day 1		Resolved
(b) (6)/F/56/Mz	Chest pain	Day 1-Day 6	MYSTIC	Resolved
	Dyspnea	Day 1-Day 6		Resolved

Abbreviations: AE = adverse event; F = female; M = male; Mz = Mestizo; TEAE = treatment-emergent adverse event; W = White
Source: Summary of Clinical Safety p.75
Sources: OPP-101 CSR page 122, OPP-002 CSR page 78, OPP-004 CSR page 64

8.4.4. Significant Adverse Events

See section 8.4.3 for significant events that lead to either study drug discontinuation or subject withdrawal from the study.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Non-ocular TEAEs Occurring in >1 Subject in Any Individual Treatment Group

System Organ Class Preferred term	OC-01		Placebo
	0.6 mg/mL N=349 n (%)	1.2 mg/mL N=330 n (%)	N=335 n (%)
Subjects with any non-ocular TEAE	**303 (86.8)**	**290 (87.9)**	**153 (45.7)**
Respiratory, thoracic, and mediastinal disorders			
Sneezing	287 (82.2)	277 (83.9)	75 (22.4)
Cough	55 (15.8)	65 (19.7)	5 (1.5)
Throat irritation	44 (12.6)	53 (16.1)	5 (1.5)
Nasal mucosal disorder	9 (2.6)	7 (2.1)	9 (2.7)
Epistaxis	9 (2.6)	6 (1.8)	4 (1.2)
Rhinorrhea	7 (2.0)	8 (2.4)	6 (1.8)
Nasal discomfort	8 (2.3)	5 (1.5)	7 (2.1)
Dysesthesia pharynx	4 (1.1)	3 (0.9)	0
Nasal congestion	8 (2.3)	3 (0.9)	11 (3.3)
Nasal dryness	1 (0.3)	1 (0.3)	5 (1.5)
General disorders and administration site conditions			
Instillation site irritation	27 (7.7)	43 (13.0)	3 (0.9)
Infections and infestations			
Nasopharyngitis	10 (2.9)	18 (5.5)	14 (4.2)

Upper respiratory tract infection	5 (1.4)	4 (1.2)	0
Sinusitis	0	4 (1.2)	2 (0.6)
Nervous system disorders			
Headache	10 (2.9)	12 (3.6)	4 (1.2)
Dysgeusia	4 (1.1)	6 (1.8)	0
Dizziness	4 (1.1)	1 (0.3)	1 (0.3)
Gastrointestinal disorders			
Nausea	1 (0.3)	6 (1.8)	3 (0.9)

Source: Summary of Clinical Safety p.60

Ocular TEAEs Occurring in >1 Subject in Any Individual Treatment Group

System Organ Class Preferred term	OC-01		Placebo
	0.6 mg/mL N=349 n (%)	1.2 mg/mL N=330 n (%)	N=335 n (%)
Eye disorders			
Visual acuity reduced	13 (3.7)	12 (3.6)	17 (5.1)
Conjunctival hyperemia	13 (3.7)	11 (3.3)	8 (2.4)

Source: Summary of Clinical Safety p.56

The highlighted adverse events are those that occurred more frequently in either of the treatment groups at of rate of > 1%. The most common adverse events experienced with OC-01 were related to the nasal route of administration. The events that occurred at higher incidences in the with OC-01 compared with the placebo group include sneezing, cough, throat irritation and instillation site irritation. The only ocular adverse event that occurred more frequently in the OC-01 than placebo at a rate > 1% was conjunctival hyperemia.

8.4.6. Laboratory Findings

There were no clinical laboratory evaluations, vital signs or electrocardiograms performed in Onset-1, Onset-2 or Mystic. Clinical laboratory parameters were evaluated in ZEN which was an open label study to compare the bioavailability and, clinical and laboratory safety of varenicline administered orally and intranasally in healthy volunteers. See biopharmaceutics review for details.

8.4.7. Immunogenicity

N/A – not assessed during this development program.

8.5. Analysis of Submission-Specific Safety Issues

There are no submission specific safety issues requiring additional analysis.

8.6. Safety Analyses by Demographic Subgroups

The demographic subgroups analyzed included age, gender, race and ethnicity. Age subgroups were divided into ≤ 55, 56 to 65 and > 65 years of age. Race was divided into American Indian or Alaska Native or Other, Asian or Native Hawaiian or Other Pacific Islander, Black or African American, and White. Ethnicity was divided into Hispanic/Latino and not Hispanic/Latino.

There were no clinically meaningful safety issues raised in any of the subgroup analyses.

8.7. Specific Safety Studies/Clinical Trials

There were no safety trials conducted to address a specific safety concern related to OC-01.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The nonclinical systemic toxicity profile of varenicline was characterized during the development of Chantix. The applicant is relying on FDA's findings of safety for Chantix with respect to the genotoxicity, carcinogenicity, and reproductive and developmental toxicity of varenicline for this 505(b)(2) application.

8.8.2. Human Reproduction and Pregnancy

No adequate and well-controlled trials of OC-01 have been conducted in pregnant or lactating women.

8.8.3. Pediatrics and Assessment of Effects on Growth

Dry eye disease is rare in the pediatric population. The applicant has requested a full product specific waiver for all pediatric age groups (i.e. birth to < 18 years) on the grounds that studies would be impossible or highly impractical due to the very limited number of pediatric patients.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was no evidence seen during the clinical studies that the use of OC-01 is associated with drug abuse or drug dependence. No formal studies have been conducted to assess the effects of rapid withdrawal of OC-01.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

OC-01 (varenicline) nasal spray is not approved or marketed in any country.

8.9.2. Expectations on Safety in the Postmarket Setting

There are no expected potential safety issues of concern. There are no recommended Post-marketing Requirements or Phase 4 Commitments.

8.9.3. Additional Safety Issues From Other Disciplines

N/A – all safety issues have adequately been addressed in this review.

8.10. Integrated Assessment of Safety

Safety was assessed in over 700 subjects dosed twice a day for 4 weeks with OC-01. The number of adverse event were similar between the 0.6mg/mL and 1.2 mg/mL dose although there was a higher percentage of discontinuations in the 1.2 mg/mL treatment group in each of the three clinical trials. The most common adverse events experienced with OC-01 were related to the nasal route of administration. . The events that occurred at higher incidences in the with OC-01 compared with the placebo group include sneezing, cough, throat irritation and instillation site irritation. Over 80% of subjects treated with OC-01 experience sneezing as an adverse event. Although sneezing occurred at a rate of over 80%, there was only one subject in the 1.2 mg/mL group that discontinued the study due to this adverse event. The only ocular adverse event that occurred more frequently in the OC-01 than placebo at a rate > 1% was conjunctival hyperemia.

A 120 day safety update for this NDA was submitted to the Agency in April 2021. No new subjects were exposed to OC-01 since the original cut-off data of 8/28/2020. The update includes long term follow up out to month 12 in subjects enrolled on the Onset-2 trial. There were no new safety issues identified and the adverse events were consistent the data submitted in the original NDA.

9. Advisory Committee Meeting and Other External Consultations

N/A – an Advisory Committee Meeting was not held for the NDA.

10. Labeling Recommendations

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

11. Risk Evaluation and Mitigation Strategies (REMS)

There are no Risk Evaluation or Mitigation strategies recommended for this NDA.

12. Post-marketing Requirements and Commitments

There are no Post-marketing Requirements or Commitments recommended for this NDA.

13. Appendices

13.1. References

N/A

13.2. Financial Disclosure

Covered Clinical Studies [Onset-1 (OPP-002), Onset-2 (OPP-101) and Mystic (OPP-004)]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 25		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A		

Significant equity interest held by investigator in S Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. List of Clinical Investigators

Clinical Investigator		
Name	Address	Study Participation
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James Paauw, MD	116 Nationwide Drive Lynchburg, VA 24502	OPP-101
Yen Nieman, MD	5717 Balcones Drive Austin, TX 78731	OPP-101

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/s/

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