CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213978Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader and Division Director Review of NDA 213978

Date	October 14, 2021
From	William M. Boyd, M.D., Wiley A. Chambers, M.D.
Subject	Cross-Discipline Team Leader and Division Director, Review
NDA #	213978
Applicant	Oyster Point Pharma
Date of Submission	December 17, 2020
PDUFA Goal Date	October 17, 2021
Proprietary Name	TYRVAYA
Established or Proper Name	varenicline solution
Dosage Form(s)	Nasal Spray
Dosing Regimen(s)	One spray in each nostril twice daily (approximately 12 hours apart)
Regulatory Action	Approval
Indication(s)/Population(s)	Treatment of signs and symptoms of dry eye disease

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Dheera Semidey
Medical Officer Review	Jennifer Harris
Statistical Review	Yushuf Sharker
Pharmacology Toxicology Review	Aling Dong
OPQ Review	Chunchun Zhang, Anne Marie Russell, Daniel Schu
Clinical Pharmacology Review	Amer Al-Khouja
OPDP	Carrie Newcomer
DMPP	Maria Nguyen
OSI	Ling Yang
CDTL Review	William M. Boyd
OSE/DMEPA	Nasim Roosta, Jason Flint, Valerie Vaughan, Mishale Mistry

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Summary

Varenicline, also referred to as OC-01 in this review, is a small-molecule nicotinic acetylcholine receptor (nAChR) partial agonist 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). This a 505(b)(2) application which identifies the listed drug product Chantix in support of systemic safety.

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.

NDA 213978 for OC-01 (varenicline) will be approved 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. 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. The most common adverse reaction reported in > 80% of patients was sneezing. Events that were reported in 5-15% of patients were cough, throat irritation, and instillation-site irritation.

2. Benefit-Risk Assessment

BLA 761094 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 experienced 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 benefits of treating dry eye disease outweigh the risks associated with the use of OC-01 (varenicline).

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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.
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 alternative product for the treatment of DED by increasing tear production.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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.	Treatment with OC-01 for the treatment of dry has an acceptable risk-benefit profile.

3. Background

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 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.

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			
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			

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.

4. Product Quality

Drug Substance

Specifications for varenicline tartrate are provided in the following table.

Specifications for Varenicline Tartrate

Test	Acceptance Criteria	Analytical Method
Description	White to off-white to slightly yellow powder	Visual
Identification -Test A (IR)	(b) (4)	USP <197K>
Identification -Test B (HPLC)		House method [a]
Specific Optical rotation		USP <781S>
Loss on drying		USP <731>
Residue on ignition		USP <281>
(b) (4)		House method
Assay		House method [a]
Residual solvents		House method
(b) (4)		House method
		House method

(b) (4)

Source: Module 3.2.S.4.1

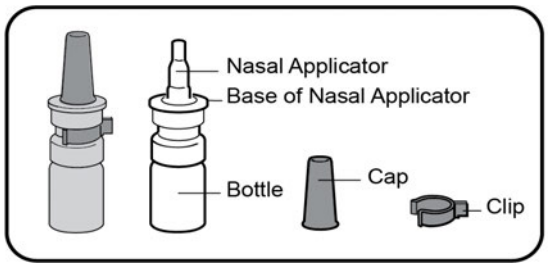
The applicant's specification includes a limit of (b) (4) ppm for (b) (4), a (b) (4) process impurity, which was found by OGD/Division of Clinical Review to be acceptable in DMF (b) (4) for all referencing applications based on a lifetime exposure as per ICH M7. The proposed limit was found acceptable by the Division of Ophthalmology P/T review team on Aug 3, 2021.

Drug Product

TYRVAYA (varenicline solution) Nasal Spray is a non-sterile, (b) (4) aqueous solution for multiple dose nasal administration. The proposed commercial concentration is 0.6 mg/mL. The daily dose is 0.12 mg, administered as a single 50 µL spray into each nostril, twice daily for 15 days.

The formulated drug product solution is presented in a 3.5 mL amber glass Type I bottle fitted with a snap-on multidose nasal spray pump. The bottle is from (b) (4) and has a (b) mL brimful capacity. The pump design from is Aptar Pharma. It is their Cartridge Pump System (CPS) (b) (4) multidose dispensing spray pump with a blue colored dust cap and white clip.

The bottle is filled with a target quantity of (b) (4) mL ((b) (4) g) intended to deliver 60 effective doses (one 50 µL spray in each nostril, twice a day for 15 days = 3.0 mL / bottle) in addition to the initial priming and any necessary re-priming sprays. Each 50 µL spray delivers approximately 30 µg of varenicline. The composition of the drug product, provided in the following table, includes phosphate (b) (4) and sodium chloride for (b) (4).



Source: Module 1.14.1.3

Drawing of Aptar Cartridge Pump System (CPS) Nasal Spray Pump and Material of Construction

Source: OPQ Integrated Review NDA 213978 08/27/2021, page 206

Composition of Drug Product

Unit Composition, Pharmaceutical Function, Quality Standards and Ingredients of Varenicline Nasal Spray 0.6 mg/mL (free base)

	1.0 mg mL tartrate salt which is equivalent to 0.6 mg/mL free base			Pharmaceutical Function	Quality Standards
	Quantity (mg) per Bottle	% w/v	mg/ 50 µL spray		
Active Ingredient					
Varenicline tartrate	(b) (4) mg of tartrate salt which is equivalent to (b) (4) mg of free base	(b) (4)% tartrate salt (b) (4)% free base	0.05 mg of tartrate salt is equivalent to 0.03 mg of free base	Active	Non-compendial[1] See Section 3.2.S.4.1 Specification
Inactive Ingredients					
Sodium Phosphate dibasic heptahydrate	(b) (4)			(b) (4)	USP
Monobasic sodium phosphate, anhydrous					USP
Sodium Chloride					USP
Sodium Hydroxide				pH adjuster	NF

Hydrochloric Acid	(b) (4)			pH adjuster	NF
Water for Injection				(b) (4)	USP
Total	(b) (4)	100%			

[1] Varenicline tartrate is tested at (b) (4) for identity and assay as outlined in Section 3.2.S.2.1 Manufacturers. **Source: Module 3.2.P.1**

Drug Product Specification

The quality control specifications for varenicline nasal spray are provided in the following table.

Quality Control Specifications

Test		Acceptance Criteria	Test Method
Appearance		Clear, colorless solution, essentially free of visible particulates in a 3.5 mL amber glass bottle fitted with a white nasal applicator with a white clip and blue dust cover	Visual Examination Method # (b) (4)
Identification by UV Spectrum:		(b) (4	(b) (4)
Identification by Retention Time:			
Assay			
Impurities	Unspecified Individual Impurity		
	Total Unspecified and Specified Impurities		
pH			USP <791>
Osmolality			USP <785>
Particulate Matter			USP <788>

Test	Acceptance Criteria	Test Method
Pump Delivery (PD)	(b) (4)	(b) (4)
Delivered Dose Uniformity (DDU)		
Spray Pattern (b) (4) cm		
Droplet Size Distribution (b) (4) cm		
Actuation Force		
Sterility		USP<71>
Net Contents		(b) (4)

[1] performed as in-process (b) (4) check

HPLC = High Performance Liquid Chromatography, mOsm/kg = milliosmole per kilogram, NMT = Not more than, USP = United States Pharmacopoeia, UV = ultraviolet

Source: Module 3.2.P.5.1

Drug Product Container Closure

The primary container closure system consists of the following:

- 3.5 mL amber Type I (b) (4) glass bottle with a (b) mL brimful capacity from (b) (4) (b) (4)
- 50 µL Cartridge Pump System (CPS) (b) (4) multidose dispensing spray pump with a white clip and a blue colored dust cap from Aptar Pharma.

Primary Packaging Components for Varenicline Nasal Spray

Packaging Component	Component Manufacturer	DMF Number
Amber Type I glass bottle, (b) (4) mL	(b) (4)	
50 µL, Cartridge Pump System (CPS) (b) (4) multidose dispensing pump, with a white clip and a blue colored dust cap		

Source: Module 3.2.P.7

Microbiology

Varenicline nasal spray, 0.6 mg/mL will not be labeled as a sterile product. However, it will be manufactured using an (b) (4) and sterility testing (USP <71>) will be conducted on the product at the time of release and on stability. This application is recommended for approval by Product Quality Microbiology.

OPQ CDRH

CDRH assessed biocompatibility of non-drug contacting components, and Dr. Kathleen Fitzgerald found it acceptable on 7/15/2021. Additionally, Dr. Alan Stevens from CDRH reviewed the device performance data including pump activation force, pump delivery volume and the device EPR Control Strategy and found it adequate with one PMC (PMC# 4139-1) on 8/20/2021. CDRH review are located in the finalized OPQ Integrated Review NDA 213978 dated 08/27/2021.

Establishment Information

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on 8/11/2021.

Facility name and address	FEI	Responsibilities and profile code(s)	Status
[redacted] (b) (4)			Approve - Based on Previous History
[redacted]			Approve - Based on Previous History
[redacted]			Approve - Based on Previous History
[redacted]			Approve - Based on Previous History
[redacted]			Approve - Based on Previous History
Oyster Point Pharma, Inc.	80478750	Final Approval and Release of the Product to the Market || 356h Status: Active	No Evaluation Necessary
[redacted] (b) (4)			
[redacted]			Approve - Based on Previous History

Office of Product Quality Recommendation

NDA 213978, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product varenicline nasal spray, 0.6 mg/mL. All information requests and review issues have been addressed. Therefore, NDA 213978 is recommended for approval from Product Quality perspective with Post Marketing Commitments (PMCs).

CMC Post-Marketing Commitments

The applicant concurred with following PMCs on Aug 25, 2021, and these PMCs should be included in the planned Action Letter:

1. Post Marketing Commitment # 4139-1: Provide a release test method and verification data for actuation force.

Final protocol submission date: Dec 27, 2021
Study completion: Feb 27, 2022
Final report submission: Apr 27, 2022.

2. Post Marketing Commitment # 4139-2: Develop and validate a new analytical method that is sufficiently sensitive to measure (b) (4) in the drug product at the Acceptable Intake (AI) limits in the FDA guidance. Generally, sensitive methods with limits of quantitation (LOQ) in the parts per- billion (ppb) range are needed to meet the low AI recommended for (b) (4). The (b) (4) should include those identified in the submitted (b) (4) Risk Assessment (b) (4) and those in the FDA guidance (b) (4) Submit data from confirmatory testing using the new method. Confirmatory testing should include aged samples of the three drug product registration lots. Propose a (b) (4) control strategy for your commercial drug product quality program based on the results of confirmatory testing. This may include routine release and stability testing for (b) (4) until sufficient data are available to support discontinuation. Submit new method, data and (b) (4) control strategy in a Prior-Approval supplement.

Final protocol submission date: Sep 27, 2021
Study completion: Dec 27, 2021
Final report submission: Jan 27, 2022.

3. Post Marketing Commitment # 4139-3: Improve Pump Delivery (PD) and Delivered Dose Uniformity (DDU) performance in varenicline nasal spray consistent with FDA[1] and USP[2] guidelines. This includes determining the root cause of low dose failures, reported in release, stability, dosing orientation and freeze/thaw studies submitted in the NDA, and implementing corrective actions to analytical methods or container closure system. Depending on the root cause, additional one-time studies such as In-Use Testing may be needed to demonstrate PD and DDU performance through end of life of the unit (15 days/60 doses) at expiry. The manufacturer's Certificate of Analysis for the pump (CPS) specifies a dose volume acceptance criteria of mean (b) (4)% and single values (b) (4)%, which do not meet FDA guidelines for pump delivery. The actuation method, (b) (4), also does not meet guidelines for PD and DDU performance. PD and DDU method validation studies should be submitted along with data from confirmatory testing consistent with the guidelines. Confirmatory testing should include aged samples of the three drug product registration lots. Method validations, additional studies and data should be submitted in a Prior-Approval supplement. ([1]Guidance for Industry "Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation" (2002). [2]USP <601> Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers.)

Final protocol submission date: Dec 27, 2021
Study completion: Feb 27, 2022
Final report submission: Apr 27, 2022.

5. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 8/8/2021:

This NDA provides original nonclinical data in support of the ocular (and nasal) safety of OC-01 and relies on the FDA's previous findings of safety and effectiveness for Chantix

(varenicline tartrate) Tablet, EQ 0.5 mg base, EQ 1 mg base, as the listed drug (LD), to support the systemic safety.

In order to bridge OC-01 to Chantix, the Applicant has conducted a comparative bioavailability study in humans (Study #192007). In the clinical study #192007, 22 healthy volunteers between 18-65 years of age were administered either a single 1 mg (MRHD) oral dose of Chantix in Treatment A, or an intranasal dose of 0.12 mg OC-01 (50 µL 1.2 mg/mL OC-01 nasal spray, equivalent to 0.06 mg into each nostril) in Treatment B (7 days between Treatments A and B). Varenicline C_{max} and AUC_{inf} values were 0.34 ng/mL and 8.30 ng•h/mL following OC-01, compared to 4.63 ng/mL and 102.53 pg•h/mL following Chantix. Thus, the systemic exposure to varenicline from OC-01 at a dose (0.12 mg; (b) (4) (b) (4),) higher than the currently proposed commercial clinical dose (0.06 mg, with the currently proposed commercial concentration 0.6 mg/mL) was less than the exposure from Chantix at the MRHD, (note that the two OC-01 formulations are same, except for the API concentration, and both have been administered in clinical trials throughout the OC-01 development). As such, reliance on the LD Chantix to support the systemic safety of OC-01 is scientifically justified.

The Applicant also submitted original nonclinical studies, including two (2) pivotal 28-day toxicity studies in rats and rabbits and one (1) 6- month rabbit study which all used the complete clinical formulation of OC-01 nasal spray and included ocular (and nasal) toxicity evaluation, and by relied on previous findings of safety and efficacy of the LD for systemic safety, including genotoxicity, carcinogenicity, reproductive and developmental toxicity findings. Exposure margins comparing NOAELs of 6-month pivotal nonclinical study and the maximum proposed clinical dose provide chronic safety support for intended clinical dosing regimen.

The P/T reviewer verified that the recommendations described in the current version of FDA Guidance for Industry "Control of (b) (4) Impurities in Human Drugs" (published (b) (4)), have been met. The impurity (b) (4) specification in these tested lots were within the proposed limit of (b) (4) ppm, per the Applicant-submitted batch analysis in Module 3.2.S.4.4 dated 5/28/2021. Approval of the application is recommended.

6. Clinical Pharmacology

From the original Clinical Pharmacology review dated 8/13/2021:

For the nasal spray product, the Applicant initially proposed (b) (4) (b) (4) (b) (4) the proposed commercial strength and regimen have been updated to 0.6 mg/mL, given as one spray in each nostril BID. Each actuation of the 0.6 mg/mL spray delivers 0.05 mL containing 0.03 mg varenicline free base.

The clinical pharmacology submission includes one study, Study OPP-100 (ZEN), a phase 1, open-label, single-center, single-dose, randomized, two-way crossover study in healthy volunteers comparing the relative bioavailability of 0.12 mg intranasal varenicline (0.06 mg per

nostril) using the 1.2 mg/mL strength, and 1 mg oral varenicline (Chantix oral tablets) in the fasted state. Results from this study demonstrated that there is lower varenicline exposure following administration of 0.12 mg intranasal varenicline relative to 1 mg oral varenicline. Based on this data from OPP-100, a PK bridge has been established between the proposed intranasal spray product and the listed drug (Chantix oral tablets). The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) found the application acceptable to support approval from a clinical pharmacology perspective.

Clinical/Statistical- Efficacy

From the original Medical Officer Review dated 8/20/2021:

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 (STS) by at least 10mm.

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

Onset-1 (OPP-002) 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.

Efficacy Results – Secondary and other relevant endpoints

The ONSET-1 study had two pre-specified secondary endpoints which were analyzed hierarchically.

1) 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 (25^{th}, median, 75^{th})	**-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.

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.

2) 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 also supports the use of the 0.6mg/mL dose for the treatment of dry eye.

Onset-2 (OPP-101) Efficacy Results – Primary Endpoint

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 Eye Dryness Score (EDS) [<60, ≥60]).

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.

Mystic (OPP-004)

Efficacy Results – Primary Endpoint

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.

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 (25^{th}, median, 75^{th})	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.

Both doses of OC-01 met the primary efficacy endpoint for the clinical trial. However, they did not demonstrate that the amount of change was clinically significant. This study was only used as supportive evidence.

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 applicant conducted this as one of multiple secondary endpoints. Adjustments for multiple testing were not implemented for this study. 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

Efficacy Summary Statement

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 Onset-1 trial studied a change in Schirmer score (sign endpoint) for the primary efficacy endpoint. The amount of change was considered clinically significant because the primary secondary endpoint of eye dryness score (symptom endpoint) also demonstrated significance. 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. 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 the increase in Schirmer's score was not demonstrated to be clinically significant, this study was 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.

7. Safety

From the original Medical Officer Review dated 8/20/2021:

Safety Database

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

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.

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.

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

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.

Safety Summary Statement

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. Treatment with TYRVAYA (varenicline solution) Nasal Spray for the treatment of dry has an acceptable risk-benefit profile.

8. Advisory Committee Meeting

The application did not raise any new efficacy or safety issues. There were no issues that were thought to benefit from a discussion at an advisory committee meeting. An Advisory Committee Meeting was not held for the NDA.

9. Pediatrics

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.

The product triggers PREA as a new indication was presented at the Pediatric Review Committee (PeRC) on August 3, 2021. The PeRC agreed with granting full waiver for dry eye disease.

10. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the original Biostatistics review dated 10/08/2021:

ONSET-2 and ONSET-1 each demonstrated independent evidence for efficacy but on different endpoints, and MYSTIC is supportive, thus the data from the OC-01 (varenicline solution) nasal spray clinical development program provided substantial evidence of efficacy. There was consistent evidence by the Schirmer's score, either in the proportion with more than 10mm increase or in the changes from baseline in all three studies. However, for symptoms only ONSET-1 study showed statistically significant reduction in mean EDS from baseline to Day 28 compared to that of placebo. This symptom endpoint is not statistically significant in ONSET-2 and therefore not confirmed.

FINANCIAL DISCLOSURE
The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There were no investigators with disclosable financial interests/arrangements (Form FDA 3455). There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the Applicant for covered studies [i.e., Onset-1 (OPP-002), Onset-2 (OPP-101) and Mystic (OPP-004)].

OSI
A routine Office of Scientific Investigations (OSI) audit was requested. Per the OSI review dated 9/13/2021:
Clinical data from Studies ONSET-1 (OPP-002) and ONSET-2 (OPP-101) were submitted to the Agency in support of this New Drug Application (NDA) 213978 for varenicline solution nasal spray for the proposed indication of treatment of dry eye disease.

Two clinical investigators (CIs): Dr. David Wirta (Site #82 for Study OPP-002 and Site #30 for Study OPP-101), and Dr. Blair Boehmer (Site #81 for Study OPP-002 and Site #49 for Study OPP-101) were selected for clinical inspections. The inspections verified the sponsor Oyster Point Pharma, Inc. (Oyster) submitted clinical data with source records at the CI sites.

Based on the results of these CI inspections, Studies ONSET-1 (OPP-002) and ONSET-2 (OPP-101) appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the proposed proprietary name, TYRVAYA, and granted conditional acceptance on 10/1/2021. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

DMEPA had previously finalized a review of the proposed proprietary name, (b) (4), and granted conditional acceptance on 10/1/2021. The applicant requested that (b) (4) be withdrawn, and this was acknowledged in a letter from DMPEA dated 9/16/21.

DMEPA completed a Human Factors Study Report and Labels and Labeling Review of the originally submitted USPI, Instructions for Use (IFU), Patient Package Insert/Patient Leaflet (PPI) and carton/container labeling on 8/9/2021.

DMEPA completed a review on 10/8/2021 of the revised Prescribing Information, Patient Information, Instructions for Use, container labels, and carton labeling received on October 5, 2021. DO did not agree with the following labeling recommendations in that review:

Regarding the Package Insert:

- Revise the title of subsection 2.2 to state: "Important Administration and Priming Instructions" and include a statement to refer end-users to the Instructions for Use for detailed preparation and administration instructions.
- Recommend removing dosage information from Section 16.

DO did not agree with these specific recommendations regarding the PI because Section 2.2 and Section 16 are currently clear and understandable for the end-user as written. Section 17 refers the end-user to the FDA-approved patient labeling (Patient Information and Instructions for Use) and specifically details the need for priming the bottle.

Regarding the Patient Information and Instructions for Use:

- Revise the phrase "1 time" within the image to state, "Spray 1 time".
- Recommend bolding the phrase "**Repeat Steps 5 and 6 to deliver a second spray in the other nostril**" or using another method (e.g., different color font) to increase the prominence of this important information to the end user.

DO did not agree with these specific recommendations regarding the Patient Information and Instructions for Use because these sections are currently clear and understandable for the end-user as written.

Regarding Container Label(s) and Carton Labeling:

- Consider revising the proprietary name, TYRVAYA, such that all letters appear in one font color.

DO did not agree with these specific recommendations regarding the Container Label(s) and Carton Labeling. The proprietary name is easily legible and of equal prominence to the established name.

DMPP and OPDP

The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) completed a joint review dated 9/1/2021 of the Package Insert (PI), Patient Package Insert (PPI) and Instructions for Use (IFU). In a separate review dated 9/7/2021, OPDP also provided comments for the USPI and the carton and container labeling.

DMPP informally reviewed the revised Prescribing Information, Patient Information, Instructions for Use, container labels, and carton labeling received on October 5, 2021. DO did not agree with the following labeling recommendations in that review:

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

(b) (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 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.			

11. Labeling

The labeling submitted by the applicant on 10/12/2021 and 10/13/2021 (carton and container), is acceptable and is attached at the end of this review in an Appendix. The application for NDA 213978 TYRVAYA (varenicline solution) Nasal Spray for the treatment of dry eye will be approved with the attached labeling.

12. Regulatory Action

NDA 213978 TYRVAYA (varenicline solution) Nasal Spray will be approved for the treatment of dry eye. There are no recommended post-marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of the drug product.

The following post-marketing commitments, agreed to by the applicant, will be included in the approval letter:

1. Post Marketing Commitment # 4139-1: Provide a release test method and verification data for actuation force.

Final protocol submission date: Dec 27, 2021
Study completion: Feb 27, 2022
Final report submission: Apr 27, 2022.

2. Post Marketing Commitment # 4139-2: Develop and validate a new analytical method that is sufficiently sensitive to measure (b) (4) in the drug product at the Acceptable Intake (AI) limits in the FDA guidance. Generally, sensitive methods with limits of quantitation (LOQ) in the parts per- billion (ppb) range are needed to meet the low AI recommended for (b) (4). The (b) (4) should include those identified in the submitted (b) (4) Risk Assessment (b) (4) and those in the FDA guidance (b) (4) Submit data from confirmatory testing using the new method. Confirmatory testing should include aged samples of the three drug product registration lots. Propose a (b) (4) control strategy for your commercial drug product quality program based on the results of confirmatory testing. This may include routine release and stability testing for (b) (4) until sufficient data are available to support discontinuation. Submit new method, data and (b) (4) control strategy in a Prior-Approval supplement.

Final protocol submission date: Sep 27, 2021
Study completion: Dec 27, 2021
Final report submission: Jan 27, 2022.

3. Post Marketing Commitment # 4139-3: Improve Pump Delivery (PD) and Delivered Dose Uniformity (DDU) performance in varenicline nasal spray to meet FDA[1] and USP[2] guidelines. This includes determining the root cause of low dose failures, reported in release, stability, dosing orientation and freeze/thaw studies submitted in your NDA, and implementing corrective actions to your analytical methods or container closure system. Depending on the root cause, additional one-time studies such as In-Use Testing may be needed to demonstrate PD and DDU performance through end of life of the unit (15 days/60 doses) at expiry. The manufacturer's Certificate of Analysis for your model pump (CPS) specifies a dose volume acceptance criteria of mean (b) (4)% and single values (b) (4)%, which do not meet FDA guidelines for pump delivery. We also note that your actuation method, (b) (4), does not meet guidelines

for PD and DDU performance. Submit PD and DDU method validation studies and data from confirmatory testing which meet guidelines. Confirmatory testing should include aged samples of the three drug product registration lots. Submit method validations, additional studies and data in a Prior-Approval supplement. ([1]Guidance for Industry "Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation" (2002). [2] USP <601> Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers.)

Final protocol submission date: Dec 27, 2021
Study completion: Feb 27, 2022
Final report submission: Apr 27, 2022.

Appendix

Following is the Applicant's final agreed-upon labeling (i.e., package insert, patient information and instructions for use, carton and container labeling) submitted on 10/12/2021 and 10/13/2021.

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
10/14/2021 06:49:32 AM

WILEY A CHAMBERS
10/15/2021 10:58:06 AM