CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL PRODUCT(S):		OC-01 (varenicline solution) Nasal Spray
STUDY NUMBER(S):	**IRB Number**	851655
	Other Protocol Identifiers	N/A
PROTOCOL(S) TITLE:		A **S**ingle-arm Investigator Initiated Study to **E**valuate the Efficacy of OC-01 (varenicline solution) **N**asal **S**pray on signs **a**nd symp**t**oms of Dry Eye D**i**sease in subjects with Sj**o**gren's Sy**n**drome
NUMBER:		NCT05700422
REGULATORY SPONSOR:		"[Insert Sponsor Name and Address Here]"
FUNDING SPONSOR(S):		Oyster Point Pharma
MEDICAL DIRECTOR		Mina Massaro-Giordano, MD
ORIGINAL PROTOCOL DATE:		February 16, 2023
VERSION NUMBER:		v.2
VERSION DATE:		April 27, 2023

PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	Oyster Point Pharma
STUDY TITLE:	A Single-arm Investigator Initiated Study to Evaluate the Efficacy of OC-01 (varenicline solution) Nasal Spray on signs and symptoms of Dry Eye Disease in subjects with moderate to severe Sjogren's Syndrome
STUDY ID	851655
PROTOCOL VERSION	v1.0

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name	Giacomina Massaro-Giordano, MD	Signature	
Affiliation:	Scheie Eye Institute	Date	

Abbreviations

AE	Adverse Event
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
SS	Sjogren's Syndrome

1 STUDY SUMMARY

1.1 Synopsis

Title:	A Single-arm Investigator Initiated Study to Evaluate the Efficacy of OC-01 (varenicline solution) Nasal Spray on signs and symptoms of Dry Eye Disease in subjects with moderate to severe Sjogren's Syndrome
Short Title:	The SENSation Study
Study Description:	Approximately 40 subjects at least 18 years of age with moderate to severe Sjogrens syndrome with confirmed diagnosis of dry eye disease (defined as Schirmers test score 10 mm) will receive an application of OC-01 (varenicline solution) 0.03 mg nasal spray twice daily (BID) for 28 days and will be compared to historical control. The study hypothesizes that SS patients treated with OC-01 will demonstrate significant improvement in their dry eye symptoms.
Objectives:	To evaluate the safety and effectiveness of OC-01 (varenicline solution) nasal spray among subjects with dry eye disease and moderate to severe Sjogren's Syndrome
Primary Endpoint:	• Mean change in cornea and conjunctival staining from baseline to Day 28 • Mean change in eye dryness score as measured by the Visual Analogue Scale (VAS) from baseline to Day 28
Secondary Endpoints:	• Mean change in best corrected visual acuity from baseline to Day 28 • Mean change in dry mouth and dry nose scale as measured by from baseline through Day 28 • Incidence and severity of adverse events
Study Population:	Sample size: n = 40 Gender: any

	Age: at least age 18yo Demographic group: any General health status: see specifics in Inclusion Criteria Geographic location: patients at Scheie Eye Institute in Philadelphia, PA
Phase:	Investigator-Initiated Clinical Trial
Description of Sites/Facilities	Scheie Eye Institute 51 N 39th St. Philadelphia, PA 19104
Enrolling Sites:	Scheie Eye Institute will be the only enrolling site.
Description of Study Intervention:	Study Drug: OC-01 (varenicline solution) 0.03 mg nasal spray Dose/Route/Schedule: Intranasal delivery of OC-01 nasal spray twice daily (BID): • 40 subjects will receive OC-01 (varenicline 0.03 mg) nasal spray for 28 days Schedule of visits: • Visit 1 - Screening – Day 1 • Visit 2 - Day 14 (Virtual visit) • Visit 3 - Day 28 OR possible early termination
Study Duration:	12 months
Participant Duration:	1 month

1.2 Key Roles and Study Governance

Sponsor	**Medical Director**
	Mina Massaro-Giordano, MD
Oyster Point Pharma, Inc.	Scheie Eye Institute
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1.3 Schema

Study Procedure	Screening/ Baseline (Visit 1)	15 minutes Post-administration	Visit 2	Visit 3	Early Termination
	Day -0	Day 0	Day 14 (Virtual)	Day 28	
Windows for Visits				+/- 2 days	+/- 7 days
Informed Consent	X				
Demographics	X				
Medical History and Concurrent Illnesses	X		X	X	X
Ocular History	X		X	X	X
Eligibility Criteria	X				
Urine Pregnancy Test*	X			X	X
Concomitant Medications	X		X	X	X
Intranasal Exam via history	X				
Eye Dryness Score (0-100) as measured by Visual Analogue Scale (VAS)	X		X	X	X
Nasal Dryness Score (0-100) as measured by VAS	X		X	X	X
Dry Mouth Score (0-100) as measured by VAS	X		X	X	X
QIDS-SR Questionnaire	X		X	X	X
Tear Film Imager (obtain tear film thickness)	X	X		X (15 mins post treatment)	X

Slit Lamp Biomicroscopy	X			X	X
Corneal Staining using NEI scale & Conjunctival Staining using Van Bijsterveld and Utrecht scale	X			X	X
Schirmer's Testwithout anesthesia	X			X	X
Tear sample Collection	X			X	X
Ophthalmic Examination (w/or w/o dilated fundus exam)	X				
Dispense Study Product	X				
Collect Study Product				X	X
Adverse Events	X		X	X	X
*For women of childbearing potential					

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Sjögren's syndrome (SS) is a common autoimmune disease affecting about four million Americans. It is a systemic condition that affects the entire body, with the most common symptoms being dry eyes, dry mouth, fatigue and pain in the joints. For Sjogren's patients, inflammation occurs to the tear secreting glands that are responsible for tear production, thus resulting in chronic dry eye. Many current treatments include artificial tears, punctal occlusion, and/or ophthalmic therapeutics. We hypothesize the use of OC-01 in patients who are diagnosed with Sjogren's Syndrome and have confirmed dry eye disease will show beneficial improvement in Schirmer's test score and corneal/conjunctival staining.

OC-01 (varenicline solution) nasal spray 0.03mg was developed by Oyster Point Pharma and FDA-approved on October 15, 2021 for the treatment of signs and symptoms of dry eye disease. OC-01 (varenicline solution) nasal spray is believed to activate the trigeminal parasympathetic pathway and stimulate natural tear production to bathe the cornea in a protective layer of tear film. This study is testing the hypothesis that OC-01 (varenicline solution) nasal spray 0.03mg will improve the signs and symptoms of dry eye disease in subjects with diagnosed Sjogren's syndrome.

2.2 Background

The administration of OC-01 0.03 mg and 0.06 mg (varenicline solution) Nasal Spray was safe, well tolerated, and efficacious as assessed in the ONSET-1 study of Dry Eye Disease. The ONSET-1 study was a multi-center, randomized, masked vehicle-controlled trial of BID OC-01 nasal spray administered for 28 days. OC-01 (varenicline) Nasal Spray was safe and well-tolerated at all concentrations assessed in the ONSET-1 clinical study. Most treatment-emergent AEs were mild to moderate in severity, with only 1 subject reporting a severe treatment-emergent AE. The most common AE in all treatment groups was sneezing which was temporally related to the administration of the study drug and resolved within a short period of time after administration. Sneezing AEs were characterized as mild to moderate, with no severe AEs reported.

All AEs that were suspected to be related to the study drug with the exception of AEs with each of the following terms; nasal dryness, nasal congestion and throat irritation were reported to be recovered/or resolved before study completion. Eleven ocular treatment-emergent AEs were reported, 7 of which were reported in the placebo group; all other AEs were classified as non-ocular. The Investigators considered 3 of the 7 ocular TEAEs (visual acuity reduced, conjunctival hemorrhage, and eyelid oedema) to be possibly related to study drug, all resolved, and none was categorized as severe. One treatment emergent SAE (anemia) was reported and was considered to be unrelated to study drug. No treatment-related treatment-emergent SAEs were observed. No deaths occurred during the study. Visual acuity, slit-lamp biomicroscopy,

intranasal examination, and pupil diameter did not indicate clinically significant changes from baseline.

The administration of OC-01 (varenicline solution) nasal spray, 0.03 mg and 0.06 mg was safe, well tolerated, and efficacious as assessed in the ONSET-2 study of Dry Eye Disease. The ONSET-2 study was a multi-center, randomized, masked vehicle-controlled trial of BID OC-01 nasal spray administered for 28 days. In the ONSET-2 study, the most commonly reported ocular treatment-emergent AE by PT was conjunctival hyperemia (4.6% and 4.5% of subjects in the 0.006 mg/mL and 0.06 mg OC-01 groups, respectively, and 2.8% of subjects in the placebo group). The incidences of other commonly reported ocular treatment-emergent AEs by PT were similar across the 0.03 mg OC-01, the 0.06 mg OC 01, and the placebo groups: visual acuity reduced (3.5%, 3.7%, and 4.4% of subjects, respectively), blepharitis (1.2%, 0.4%, and 0.4% of subjects, respectively), and eye irritation (0.4%, 0.4% and 1.2% of subjects, respectively).

The incidences of the most commonly reported non-ocular treatment-emergent AEs were higher in the 0.03 mg and the 0.06 mg OC 01 groups compared with the placebo group: sneezing (95.0% and 96.7% vs. 29.1% of subjects, respectively), cough (18.8% and 22.0% vs. 2.0% of subjects, respectively), and throat irritation (13.5% and 18.0% vs. 2.0% of subjects, respectively). The most common treatment-emergent AE in both the OC-01 and placebo groups, sneezing, was likely caused by stimulation of the trigeminal nerve (and to some extent, due to the mechanical administration of the nasal spray, as demonstrated by the sneezing in the placebo group). With the exception of one instance of cough considered not related to study drug by the Investigator in the 0.06 mg OC-01 group, all instances of sneezing, cough, and throat irritation were considered related to study drug, and all instances of sneezing, cough, and throat irritation were mild and non-serious.

Most treatment-emergent AEs were mild in severity. The incidence of subjects with severe treatment-emergent AEs was low across all treatment groups: 2 (0.8%), 3 (1.2%), and 2 (0.8%) subjects in the 0.03 mg OC-01, 0.06 mg OC 01, and placebo groups, respectively; none were classified as ocular treatment-emergent AEs.

No deaths were reported during the ONSET-2 study. Overall, 10 subjects (1.3%) overall reported serious treatment-emergent AEs: 2 (0.8%), 5 (2.0%), and 3 (1.2%) subjects in the 0.03 mg OC-01, 0.06 mg OC-01, and placebo groups, respectively. All serious treatment-emergent AEs were either moderate or severe in intensity; none were considered related to study drug, and none were fatal.

Sneezing data collected from subject diaries showed that almost all sneezing instances were mild among the treatment groups (no intervention was needed). In the OC-01 groups, approximately 50% of administrations caused any sneezing; approximately 80% of administrations caused 0 to 2 sneezes, approximately 20% of administrations caused 3 to 5 sneezes, and ≤5% of administrations caused ≥6 sneezes. Among subjects who sneezed after administration, the majority of sneezing was experienced within the first minute and stopped within the first 5 minutes in the OC 01 groups.

Visual acuity, slit lamp biomicroscopy, intranasal examination, and pupil diameter did not indicate any clinically relevant changes from baseline.

These data from the ONSET-1 and ONSET-2 study suggest that 28 days of BID delivery of OC-01 (varenicline solution) Nasal Spray is safe and efficacious in subjects with DED.

The MYSTIC study was designed to provide efficacy and safety data on chronic dosing of OC-01 (varenicline solution) nasal spray for up to 84 days of BID treatment. OC-01 nasal spray was shown to be safe and well tolerated at both concentrations assessed in this clinical study. The only ocular treatment-emergent AE reported in more than 1 subject was visual acuity reduced, with similar frequencies in the placebo (7.3%) and OC-01 groups (0.03 mg [9.8%] and 0.06 mg [7.3%]).

Most treatment-emergent AEs were mild in severity; no severe treatment-emergent AEs were reported. All treatment-emergent AEs assessed as related to the study drug by the Investigator were reported to be recovered or resolved before study completion with the exception of two cases each of visual acuity reduced and sneezing in subjects treated with OC-01 and eyelid edema in 1 subject treated with placebo. No SAEs or deaths were reported.

2.2.1 Pharmacokinetics, Pharmacodynamics and Toxicology

TYRVAYA nasal spray contains varenicline which is a partial nicotinic acetylcholine receptor agonist of α4β2, α4α6β2, α3β4, and α3α5β4 receptors and a full α7 receptor agonist. Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid whose chemical name is 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361.35 Daltons and a molecular formula of $C_{13}H_{13}N_3 \cdot C_4H_6O_6$.

TYRVAYA (varenicline solution) nasal spray is formulated for intranasal use as a clear 0.6 mg/mL strength solution, at pH 6.4. After priming, each actuation delivers a 0.05 mL spray containing 0.03 mg varenicline free base, equivalent to 0.05 mg of varenicline tartrate. The formulation also contains the following inactive ingredients:
sodium phosphate dibasic heptahydrate, monobasic sodium phosphate anhydrous, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

The efficacy of TYRVAYA in dry eye disease is believed to be the result of varenicline's activity at heteromeric sub-type(s) of the nicotinic acetylcholine (nACh) receptor where its binding produces agonist activity and activates the trigeminal parasympathetic pathway resulting in increased production of basal tear film as a treatment for dry eye disease. Varenicline binds with high affinity and selectivity at human α4β2, α4α6β2, α3β4, α3α5β4 and α7 neuronal nicotinic acetylcholine receptors. The exact mechanism of action is unknown at this time.

Following administration of 0.12 mg (0.06 mg per 50-µL spray in each nostril), a strength of varenicline that is higher than the labeled concentration, varenicline can be detected in plasma by

5 minutes, generally achieves peak concentration within 2 hours, with a mean C_{max} of 0.34 ng/mL, and has an $AUC_{0\text{-}inf}$ of 7.46 h*ng/mL. The systemic exposure ($AUC_{0\text{-}inf}$) following this intranasal dose was approximately 7.5% of the exposure observed following a 1 mg oral dose of varenicline.

The mean ± SD elimination half-life of varenicline after intranasal administration is approximately 19 ± 10 hours. Varenicline undergoes minimal metabolism with 92% excreted as unchanged drug in the urine.

NONCLINICAL TOXICOLOGY
Carcinogenesis
Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (810 times the maximum recommended human dose [MRHD], on a mg/m^2 basis). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 405 times the MRHD on a mg/m^2 basis) and maximum dose (2 tumors, 15 mg/kg/day, 1216 times the MRHD on a mg/m^2 basis). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.
Mutagenesis
Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations in vivo in rat bone marrow and in vitro in human lymphocytes.
Impairment of Fertility
There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (1216 times the MRHD on a mg/m^2 basis). Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day. A decrease in fertility was noted in the offspring of pregnant rats administered varenicline succinate at an oral dose of 15 mg/kg/day. The decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (243 times the MRHD, on a mg/m^2 basis).

2.2.2 Assessment for Potential Study Products Drug-Drug, Drug-Device, Device-Device Interactions

There are no known drug interactions for TYRVAYA varenicline solution) nasal spray.

2.2.3 Clinical Adverse Event Profile

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In three clinical studies of dry eye disease conducted with varenicline solution nasal spray, 349 patients received at least 1 dose of TYRVAYA. The majority of patients had 31 days of treatment exposure, with a maximum exposure of 105 days.
The most common adverse reactions reported in 82% of TYRVAYA treated patients was sneezing. Other common adverse reactions that were reported in >5% of patients include cough (16%), throat irritation (13%), and instillation-site (nose) irritation (8%).

2.2.4 Dosing Rationale

These data from the ONSET-1 and ONSET-2 study suggest that 28 days of BID delivery of OC-01 (varenicline solution) Nasal Spray is safe and efficacious in subjects with DED.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

In 3 clinical studies conducted with OC-01 (varenicline) nasal spray, the most common side effects reported in ≥2% of treated subjects at a frequency greater than placebo:

- sneezing (84%)
- coughing (19%)
- throat irritation (16%)
- instillation site irritation (13%)
- conjunctival hyperemia (eye redness) (3%)
- headache (2.4%)
- rhinorrhea (runny nose) (2.4%)
- reduced visual acuity (2.1%)

2.3.2 Known Potential Benefits

You may or may not directly benefit medically from taking part in this study. You may gain information about your health from the different tests (e.g., eye exams, etc.) that are done. It is possible that if you have dry eye disease from Sjogren's Syndrome, your signs and/or symptoms of dry eye disease may get better, stay the same, or get worse. Information from this study may help doctors learn things about OC-01 (varenicline solution) nasal spray that could help others with dry eye disease due to Sjogren's.

2.3.3 Assessment of Potential Risks and Benefits

Based on clinical trial data, most treatment-emergent AEs were mild in severity; no severe treatment-emergent AEs were reported.

Benefits include possible improvement in dry eye symptoms.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Evaluate the safety and effectiveness of OC-01 (varenicline solution) nasal spray among subjects with dry eye disease and moderate to severe Sjogren's Syndrome	Mean change in cornea and conjunctival staining from baseline to Day 28 Mean change in eye dryness score as measured by the Visual Analogue Scale (VAS) from baseline to Day 28	
Secondary		
	Mean change in best corrected visual acuity from baseline to Day 28 Mean change in dry mouth and dry nose scale as measured by from baseline through Day 28 Incidence and severity of adverse events	To assess secondary endpoints such as visual acuity, safety, dry mouth/nose.

4 STUDY PLAN

4.1 Study Design

This is a single-center, single-arm study to assess the efficacy of OC-01 (varenicline solution) nasal spray in signs and symptoms of dry eye disease for subjects with diagnosed Sjogren's syndrome.

Approximately 40 subjects at least 18 years of age with moderate to severe Sjogren's syndrome with confirmed diagnosis of dry eye disease (defined as Schirmer's test score ≤10 mm and meeting all other study eligibility criteria. 40 subjects will receive an application of OC-01 (varenicline solution) 0.03 mg nasal spray twice daily (BID) and will be compared to age-matched historical control.

Subjects who terminate early during the application period will be asked to complete safety assessments (if subjects agree) prior to study exit. Subjects who are terminated early from the study will not be replaced.

4.2 Scientific Rationale for Study Design

This study is a single center, single-arm, investigator-initiated study to investigate the efficacy of OC-01 on signs and symptoms of dry eye disease with moderate to severe Sjogren's syndrome.

4.3 Justification for Dose

The dosing and schedule is as was used in previous clinical trials of this drug.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit.

Study Population

4.5 Inclusion Criteria

Subjects must:

- Provide signed written consent prior to study-related procedures
- Be at least 18 years of age at the screening visit
- Have diagnosed moderate to severe Sjogrens Syndrome via blood work or biopsy Category 2 staining score for Conjunctiva based on the Van Bjisterveld and Utrect scale and 3 staining score for cornea based on the NEI scale
- Have continuous use of all topical ocular medication for > 3 months and willingness to continue until completion of the study
- Be literate and able to complete questionnaires independently
- Be able and willing to use the study drug and participate in all study assessments and visits
- Have sufficient hand strength, in the opinion of the Investigator, to be able to independently administer the study drug
- Have provided verbal and written informed consent
- If a female is of childbearing potential, they must: use 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, IUD, or surgical sterilization of partner), and have a negative urine pregnancy test on Day 1

4.6 Exclusion Criteria

Subjects must not:

- Have undergone previous ocular surgery (e.g., intraocular, oculoplastic, corneal or refractive surgical procedure) in the past 1 year
- Have had thermal pulsation or IPL in prior 3 months
- Have used topical ophthalmic corticosteroid therapy in prior 4 weeks
- Have had cataract surgery in the last 6 months
- Have clinically significant ocular trauma.
- Have active ocular Herpes simplex or Herpes Zoster infection
- Have ocular inflammation (uveitis, iritis, scleritis, episcleritis, keratitis, conjunctivitis) at the discretion of the investigator.
- Have ocular infection (e.g., viral, bacterial, mycobacterial, protozoan or fungal infection or the cornea, conjunctiva, lacrimal gland, lacrimal sac or eyelids including hordeolum/stye).
- Have retinal pathology that can limit visual potential and refractive outcomes in the opinion of the investigator

- Have severe (Grade 3 or 4) inflammation of the eyelid (e.g., blepharochalasis, staphylococcal blepharitis or seborrheic blepharitis)
- Have eyelid abnormalities that significantly affect the lid function (e.g., entropion, ectropion, tumor, edema, blepharospasm, lagophthalmos, severe trichiasis, severe ptosis).
- Have ocular surface abnormality that may compromise the corneal integrity (e.g., prior chemical burn, recurrent corneal erosion, corneal epithelial defect, Grade 3 corneal fluorescein staining, map dot fingerprint dystrophy, or the effect of any other ophthalmic medication that might in the opinion of the investigator compromise the ocular surface integrity).
- Have 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.)
- Have chronic or recurrent epistaxis, coagulation disorders or other conditions that, in the opinion of the Investigator, may lead to clinically significant risk of increased bleeding.
- Have had nasal or sinus surgery (including history of application of nasal cautery) or significant trauma to these areas
- Be currently treated with nasal continuous positive airway pressure
- Have any untreated nasal infection at Visit 1
- Have a vascularized polyp, severely deviated septum, chronic recurrent nosebleeds, or severe nasal obstruction as confirmed by intranasal examination performed at Visit 1.
- Have a known hypersensitivity to any of the procedural agents or study drug components
- Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days prior to Visit 1 and during the treatment period.
- Be a female who is pregnant, nursing, or planning a pregnancy at Visit 1. Be a woman of childbearing potential who is 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; IUD; or surgical sterilization of partner. The risks of OC-01 among pregnant patients are not known.

4.7 Lifestyle Considerations

During this study, patients will be asked to refrain from activities as listed above in the exclusion criteria. If they are unable to do so, then they will be excluded from the study.

4.8 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not eligible to entered in the study. A minimal set of screen failure information is required to

ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

4.9 Strategies for Recruitment and Retention

Subjects will be recruited in the outpatient clinic setting from dry eye patients who are seen at Scheie Eye Institute. ***

5 STUDY INTERVENTION

5.1 Study Intervention(s) Administration

5.1.1 Study Intervention Description

Package Insert Patient information:

Patient Information
TYRVAYA™ (Teer-vye-ah)
(varenicline solution)
nasal spray, for intranasal use

What is TYRVAYA?
TYRVAYA is a prescription nasal spray used to treat the signs and symptoms of dry eye disease.

Before you use TYRVAYA, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if TYRVAYA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TYRVAYA passes into your breast milk. You and your healthcare provider should decide if you will use TYRVAYA if you plan to breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use TYRVAYA?

- See the Instructions for Use at the end of this Patient Information leaflet for information about the right way to use TYRVAYA.
- TYRVAYA increases tear production in the eye after being sprayed in the nose.
- Use TYRVAYA exactly as your healthcare provider tells you to use it.
- Do not shake the bottles.
- Spray TYRVAYA 1 time in each nostril, 2 times daily (about 12 hours apart).
- A 1-month supply of TYRVAYA consists of 2 nasal spray bottles. Finish 1 bottle before opening the second. TYRVAYA comes in glass bottles with a white nasal pump and blue dust cover.
- If you miss a dose of TYRVAYA, skip that dose and take your next dose at your regular scheduled time. Do not take an extra dose to make up for a missed dose.

What are the possible side effects of TYRVAYA?
The most common side effects of TYRVAYA include sneezing, cough, and throat and nose irritation.
These are not the only possible side effects of TYRVAYA. Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088.

How should I store TYRVAYA?

- Store TYRVAYA at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze.
- Throw away (discard) TYRVAYA nasal spray bottle 30 days after first use.

Keep TYRVAYA and all medicines out of the reach of children.

General information about the safe and effective use of TYRVAYA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TYRVAYA for a condition for which it was not prescribed. Do not give TYRVAYA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TYRVAYA that is written for health professionals.

What are the ingredients in TYRVAYA?
Active ingredient: varenicline tartrate
Inactive ingredients: sodium phosphate dibasic heptahydrate, monobasic sodium phosphate, anhydrous, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

TYRVAYA™ is a trademark of Oyster Point Pharma, Inc.
TYRVAYA™ and/or the use of TYRVAYA™ in a method may be covered by one or more patents or patent applications, available at www.oysterpointrx.com/patent-notices.
Manufactured for: Oyster Point Pharma, Inc., 202 Carnegie Center, Suite 109, Princeton, NJ 08540

This Patient Information has been approved by the U.S. Food and Drug Administration Issued: 10/2021

5.1.2 Dosing and Administration

Spray TYRVAYA once in each nostril twice daily (approximately 12 hours apart). If a dose is missed, resume regular dosing at the next scheduled dose time.

Priming Instructions
Priming: Prime TYRVAYA before initial use by pumping seven (7) actuations into the air away from the face. When TYRVAYA has not been used for more than 5 days, re-prime with 1 spray into the air. Do not shake.

DOSAGE FORMS AND STRENGTHS

Nasal spray delivering 0.03 mg of varenicline in each spray (0.05 mL).

5.2 Preparation/Handling/Storage/Accountability

5.2.1 Acquisition and accountability

Oyster Point Pharma will provide sufficient drug for the study in its commercially available form.

5.2.2 Formulation, Appearance, Packaging, and Labeling

Investigational drug will be provided in multi-use intranasal applicator.

The investigational drug must be stored in accordance with the pharmacy manual for this study, which contains detailed information regarding the storage and administration

The study drug will be delivered as a 50 microliter (µL) intranasal spray in each nostril BID:

- OC-01 (varenicline solution) nasal spray, 0.03 mg

General Appearance

- OC-01 (varenicline solution) will be formulated at the desired concentration in sodium phosphate buffers and sodium chloride as an aqueous solution and presented in a multi-use preservative-free nasal pump.
- The product is preservative-free and intended for intranasal use only. The product should not be used if cloudy or if particulate matter is present.
- OC-01 (varenicline solution) must be administered without dilution.

5.2.3 Product Storage and Stability

Store TYRVAYA nasal spray at 20°C to 25°C (68°F to 77°F). Do not freeze.

Discard TYRVAYA nasal spray bottle 30 days after opening bottle.

5.2.4 Preparation

Preparation

1. Tear off removable portion of vial label and place on appropriate source document. Ensure that subject ID is noted on vial label.
2. Remove plastic safety clip and cap from the nasal pump (see Figure 1).

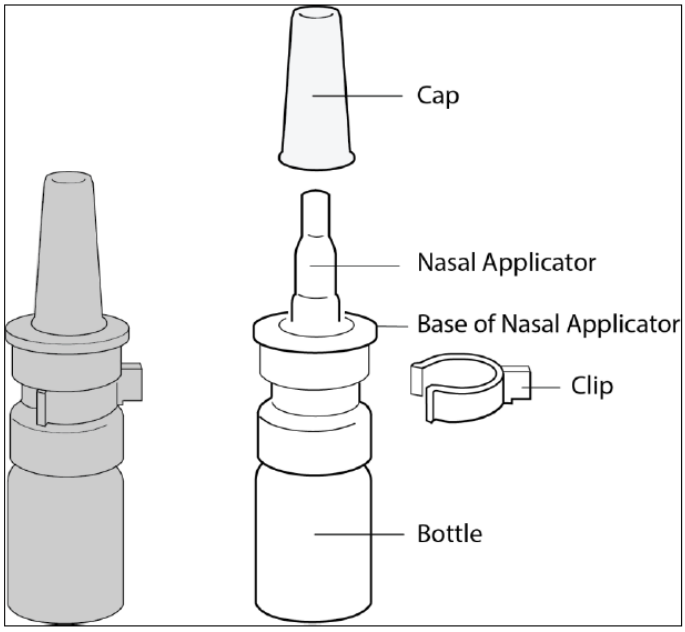

Figure 1

3. Discard the plastic safety clip and remove and set the cap aside (Figure 2).

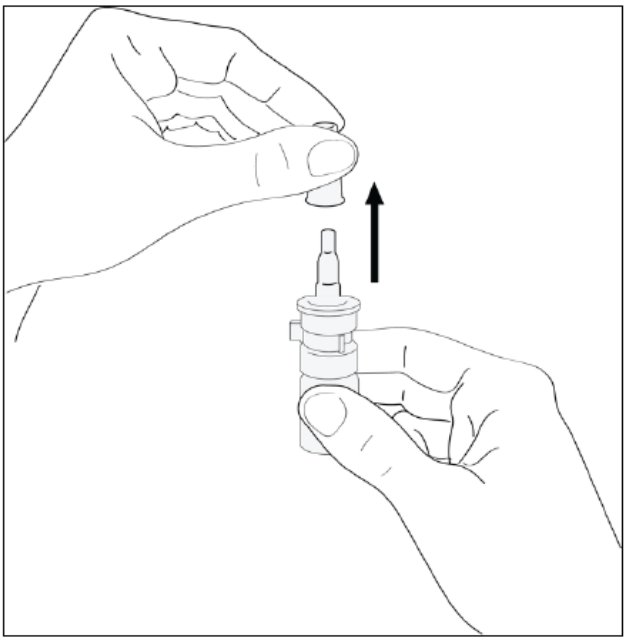

Figure 2

4. Hold the nasal pump upright and away from your face. Place one finger on each side of the base of the nasal applicator and your thumb underneath the bottle (see Figure 3).

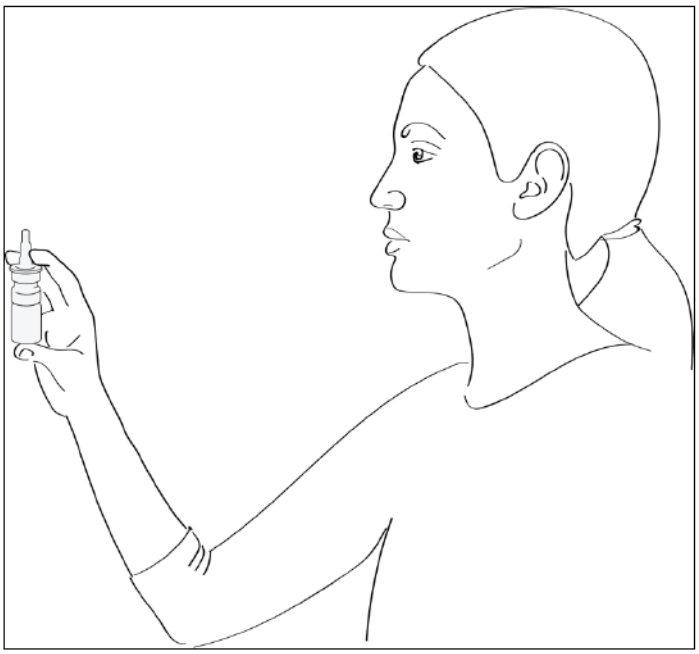

Figure 3

5. Completely press (pump) the nasal pump 7 times by squeezing your thumbs and fingers together. This will prime the pump for use (see Figure 4).

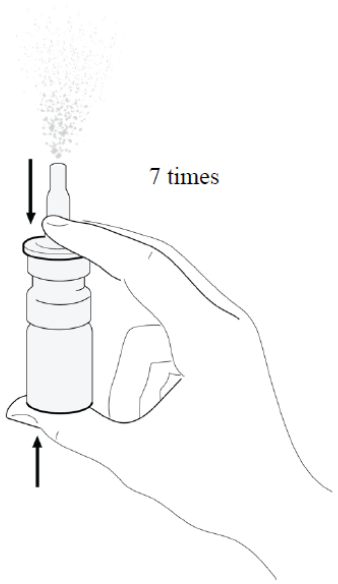

Figure 4

6. OC-01 is now ready to administer.

Administration

7. Instruct the subject to blow their nose to clear their nostrils (see Figure 5).

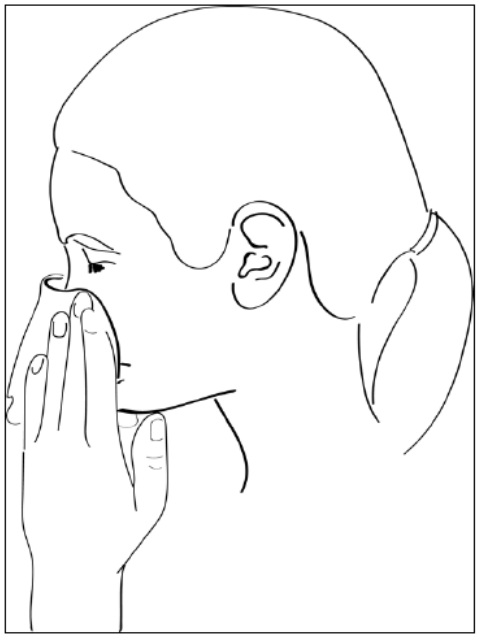

Figure 5

8. Have the subject hold the bottle upright (see Figure 6).

Figure 6

9. Have the subject tilt their head back slightly (see Figure 7).

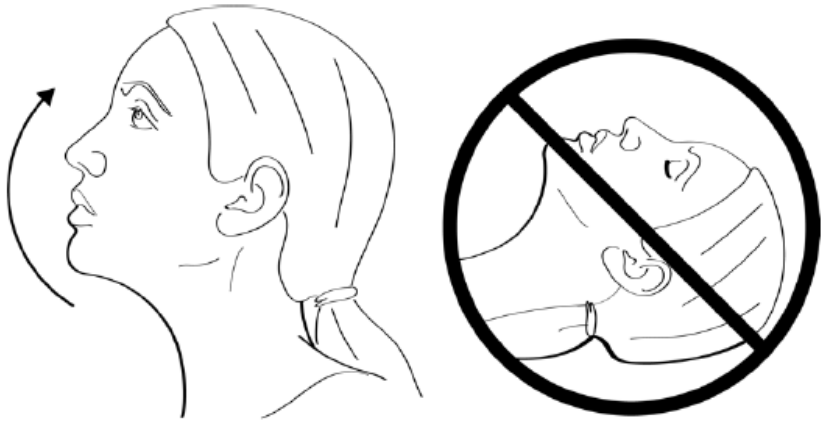

Figure 7

NOTE: Nasal applicator MUST be held in an upright position to deliver the correct dose. Do not instruct the subject to lie down or tilt their head too far back while OC-01 is being administered.

10. Instruct the subject to insert the intranasal applicator into the left or right nostril. Have the subject keep the intranasal applicator in the **opposite** hand from the nostril which they are administering spray info. Have them place the tip into the nasal cavity far enough to avoid nasal hairs. Have them aim the tip of the nasal spray pump to the top of their ear on the **same** side as the nostril (see Figure 8).

Figure 8

11. Instruct the subject to place their tongue to the roof of their mouth (closing the soft palate to minimize drug into the throat) and have them breathe in (inhale) gently while they pump the intranasal applicator one time, aiming outward toward the top of the ear on the same side (see Figure 9).

Figure 9

12. Have the subject gently breathe in through the nose and out through the mouth several times.
13. Have the subject repeat this administration with the other nostril.
14. Instruct the subject to wipe the intranasal applicator with a clean tissue (see Figure 10).
15.

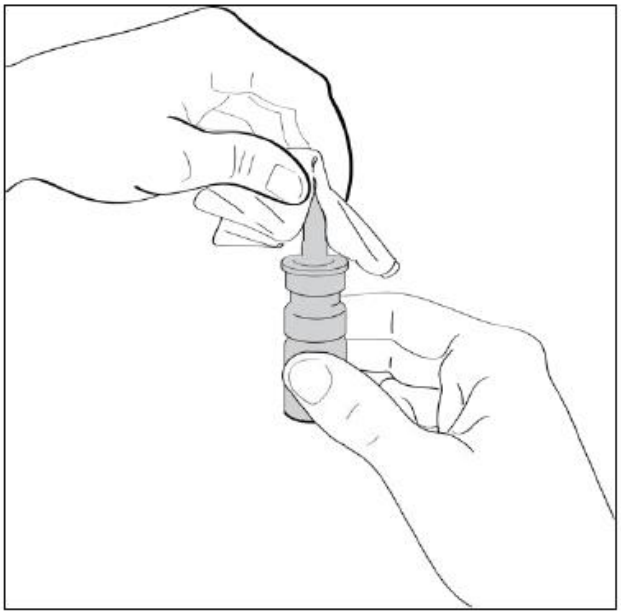

Figure 10

16. Replace plastic safety cap (see Figure 11).

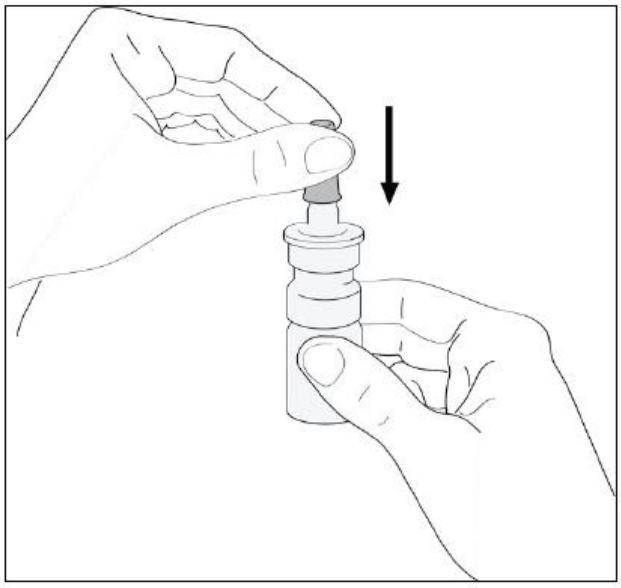

Figure 11

5.3 Measures to Minimize Bias: Randomization and Blinding

This is a single-arm study which does not involve randomization or blinding.

5.4 Study Intervention Compliance

Adherence to protocol will be documented in the electronic medical record and use of the drug will be self-reported by patients.

5.5 Concomitant Therapy

At the discretion of their physician, patients may continue to receive all medications and standard treatments administered for other conditions.

5.5.1 Rescue Medicine

Not applicable.

6 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 Discontinuation of Study Intervention

Discontinuation from use of the study drug does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation (i.e. Early Termination visit) will include the following:

- Record of any changes in medical/surgical history
- Collection of current ocular and systemic medications
- Eye/Nasal/Mouth Dryness Score as measured by Visual Analogue Scale
- QIDS-SR Questionnaire
- Tear Film Imager (5 mins post treatment administration)
- Subjective Refraction
- Best-corrected visual acuity
- Slit lamp biomicroscopy
- Corneal and Conjunctival Staining
- Schirmer's Test without Anesthesia
- Collect Schirmer's test strips
- Adverse Events (AEs): Documentation of monitoring of AEs
- Collect Study Product

6.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant drug non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the drug

- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive drug for 1 day

6.3 Lost To Follow-Up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 STUDY ASSESSMENT AND PROCEDURES

7.1 Efficacy Assessments

- Eye Dryness Score as measured by Visual Analogue Scale (VAS): Symptoms of ocular comfort and dryness will be graded for each eye on a scale of 0-100, where 0=no discomfort and 100=maximum discomfort. An average rating will be provided for the morning, afternoon and evening (See Appendix I)
- Nasal Dryness Score as measured by VAS: Symptoms of nasal dryness will be graded for each nostril on a scale of 0-100, where 0=no discomfort and 100=maximum discomfort. An average rating will be provided for the morning, afternoon and evening (see Appendix I)
- Mouth Dryness Score as measured by VAS: Symptoms of mouth dryness will be graded on a scale of 0-100, where 0=no discomfort and 100=maximum discomfort. An average rating will be provided for the morning, afternoon and evening (see Appendix I)
- The Quick Inventory of Depressive Symptomatology Self report (QIDS-SR): It is a self-report tool of 16 questions designed to screen for depression and measure changes in severity of symptoms. (See Appendix II)
- The Tear Film Imager quantifies the dynamic properties of the tear film inner layers (muco-aqueous layer and lipid layer) using a single non-contact measurement. The Tear Film Imager's measurement features the natural behavior of the tears while allowing the patient to blink naturally (See Appendix III)
- Eye Examination
- Best-corrected visual acuity - routine visual acuity (not standardized or by certified technician)
- Slit lamp biomicroscopy: assessment of eyelids, conjunctiva, cornea, lens, iris, and anterior chamber. Observations will be graded as *Normal* or *Abnormal*. Abnormal findings, which are clinically significant, will be described.
- Corneal Staining/Conjunctival Staining: The appearance of tissue disruption or other pathophysiological changes in the anterior eye. These changes are typically seen with the use of fluorescein dye. The NEI scale is the method that will be used to measure corneal staining using fluorescein strips. It divides the corneal and conjunctival surfaces to help measure fluorescein uptake. The Van Bijsterveld and Utrecht scale is the method that will be used to measure conjunctival staining while using lissamine green dye (See Appendix IV)
- Schirmer's Test without anesthesia: A filter paper inside the lower lid of the eye to determine whether the eye produces enough tears. The paper is removed after 5-minutes and the moisture is measured
- Collection of Schirmer's test strips: Place Schirmer's strips into tubes for further study. Place tubes into a -20 to -80 degree freezer until shipped onto dry ice to lab. (See Appendix V)

- Dilated Fundus Exam: assessment of posterior retina, lens, and vitreous.

7.2 Safety and Other Assessments

- Collection of current ocular and systemic medications
- Eye/Nasal/Mouth Dryness Score as measured by Visual Analogue Scale
- QIDS-SR Questionnaire
- Tear Film Imager (5 mins post treatment administration)
- Subjective Refraction
- Best-corrected visual acuity
- Slit lamp biomicroscopy
- Corneal and Conjunctival Staining
- Schirmer's Test without Anesthesia
- Collect Schirmer's test strips
- Urine Pregnancy Test
- Adverse Events (AEs): Documentation of monitoring of AEs

7.3 Adverse Events and Serious Adverse Events

7.3.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.

7.3.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of either the investigator or the sponsor, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect

- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
- required intervention to prevent permanent impairment or damage (for devices only)

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

7.3.3 Unanticipated Adverse Device Effect (UADE)

Unanticipated Adverse Device Effect (UADE)

A UADE is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Classification of an Adverse Event

7.3.3.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

7.3.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to the drug assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be considered.

- Related – The AE is known to occur with the drug, there is a reasonable possibility that the drug caused the AE, or there is a temporal relationship between the drug and event.

Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.

- Not Related – There is not a reasonable possibility that the administration of the drug caused the event, there is no temporal relationship between the drug and event onset, or an alternate etiology has been established.

7.3.3.3 Expectedness

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the drug.

7.3.4 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by monitoring and recording potential adverse effects at each study visit. Participants will be monitored by medical histories and physical examinations. If grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the subject, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (CTCAE Grade 1-5)
2. Duration (start and end dates)
3. Relationship to the study treatment or process – [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment or process – [Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol].
5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

7.3.5 Adverse Event Reporting

Reporting Period

Adverse events will be reported from the time of informed consent until study completion.

Investigator Reporting: Notifying the Study Sponsor

Every SAE, regardless of suspected causality (e.g., relationship to study product(s) or study procedure(s) or disease progression) must be reported to the sponsor within **24 hours** of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported to the Sponsor as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

Send the SAE report to the PI.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

7.3.6 Serious Adverse Event Reporting

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the

participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The SAE reports to the Sponsor should be sent to : the study sponsor.

The study sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction per applicable regulations. In addition, the sponsor must notify FDA, as applicable and all participating investigators of potential serious risks, from clinical trials or any other source, as per the applicable regulation.

7.3.7 Reporting Events to Participants

AEs, SAs, and study-related results will be reported to participants on an aggregate level.

7.3.8 Events of Special Interest

Not applicable.

7.3.9 Reporting of Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug or process may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject, and the fetus is exposed to study drug and/or process (maternally or paternally), the following procedures should be followed to ensure subject safety:

Stopping the drug.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

7.4 Unanticipated Problems

7.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.4.2 Unanticipated Problem Reporting

Unanticipated problems (UPs) such as:

- Post-marketing withdrawal of a drug, device, or biologic used in a research protocol due to safety concerns.
- FDA ban of a drug, device, or biologic used in a research protocol due to safety concerns.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study
- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.)

should be reported by the investigator to the Sponsor, reviewing Institutional Review Board (IRB) and to the lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported as any other SAE.

- Any other UP will be reported to the <Sponsor, IRB and to the DCC/study sponsor within <insert timeline in accordance with SOP and policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within appropriate timeline of the IRB's receipt of the report of the problem from the investigator.

7.4.3 Reporting Unanticipated Problems To Participants

Unanticipated problems will be reported to participants on an aggregate level.

7.5 Device Reporting

Safety reporting for the device(s) will be according to 21 CFR 812.150.

8 STATISTICAL CONSIDERATIONS

8.1 Statistical Hypotheses

No formal sample size calculation will be made in this small directional signal seeking study. Demographic and baseline characteristics will be summarized descriptively. Continuous variables will be summarized with mean, median, and standard deviation. Categorical variables will be summarized with frequency and percentage. Independent t tests will compare between the two groups and paired t tests to compare data before and after treatment within groups

8.2 Sample Size Determination

No formal sample size calculation will be made in this small directional signal seeking study.

8.3 Populations for Analyses

All participants will be included in the analysis.

8.4 Statistical Analyses

8.4.1 General Approach

Demographic and baseline characteristics will be summarized descriptively. Continuous variables will be summarized with mean, median, and standard deviation. Categorical variables will be summarized with frequency and percentage. Independent t tests will compare between the two groups and paired t tests to compare data before and after treatment within groups.

8.4.2 Analysis of the Primary Efficacy Endpoint(s)

Mean change in cornea and conjunctival staining from baseline to Day 28

Mean change in eye dryness score as measured by the Visual Analogue Scale (VAS) from baseline to Day 28

8.4.3 Analysis of the Secondary Endpoint(s)

Mean change in best corrected visual acuity from baseline to Day 28

Mean change in dry mouth and dry nose scale as measured by from baseline through Day 28

Incidence and severity of adverse events

8.4.4 Safety Analyses

Summary statistics of adverse events will be presented in a table.

8.4.5 Baseline Descriptive Statistics

Demographic and baseline characteristics will be summarized descriptively.

8.4.6 Planned Interim Analyses

Not applicable.

8.4.7 Sub-Group Analyses

Due to small sample size, sub-group analyses will not be performed.

8.4.8 Tabulation of Individual Participant Data

Individual participant data will not be tabulated.

8.4.9 Exploratory Analyses

Mean change in Muco-Aqueous layer thickness (MALT) and Lipid Map Uniformity (LMU) values from baseline to 15 minutes post treatment as measured by the Tear Film Imager masked reading center evaluation

Mean change in Muco-Aqueous layer thickness (MALT) and Lipid Map Uniformity (LMU) values from baseline to Day 28 as measured by the Tear Film Imager masked reading center evaluation[Insert Text Here]

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 Regulatory, Ethical, and Study Oversight Considerations

9.1.1 Informed Consent Process

9.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the drug, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering drug. The following consent materials are submitted with this protocol: consent form.

9.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the Sponsor or the PI at any site if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator and participants. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

9.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by <specify name of Data Coordinating Center> research staff will be secured and password protected. At the end

of the study, all study databases will be de-identified and archived at the <specify name of Data Coordinating Center>.

9.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the <specify name of Data Coordinating Center >. After the study is completed, the de-identified, archived data will be transmitted to and stored at the <specify name of Data Repository>, for use by other researchers including those outside of the study. Permission to transmit data to the <specify name of Data Repository> will be included in the informed consent.

There will be no biological samples stored.

9.1.5 Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor.

9.1.6 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

9.1.7 Quality Assurance and Quality Control

All monitoring and audits are to be performed according to ICH GCP E6(R2).

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, and specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on

Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.1.8 Data Handling and Record Keeping

9.1.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data and follow ALCOAC standards (attributable, legible, contemporaneous, original, accurate, and complete).

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>, a 21 CFR Part 11-compliant data capture system provided by the <specify Data Coordinating Center>. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.]

If using the Penn CTMS, the following text may be included:

[Clinical and laboratory data will be entered into a 21 CFR Part 11-compliant electronic data capture system (EDC) that includes individual user account level password protection. This EDC (Velos version 9) supports programmable data entry validation rules and edit checks to identify data entry errors.]

9.1.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the drug. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the

responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.1.9 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect subject safety; OR
- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the subject's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

9.1.10 Publication and Data Sharing Policy

This study will comply with the data sharing agreement.

The Sponsor must approve all sharing of information/data prior to its occurrence.

9.1.11 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to

have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 Additional Considerations

Not applicable.

9.3 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
V.2	24Apr2023	Inclusion/Exclusion and Procedure Changes	Error in previous protocol

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11 APPENDIX

11.1 Schedule of Activities (SoA)

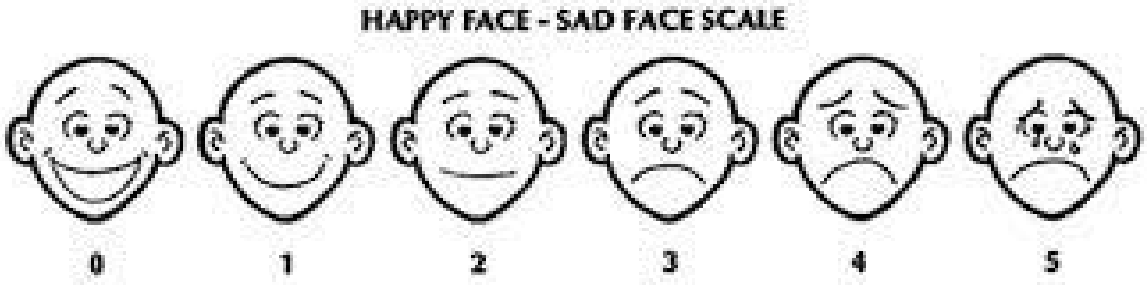
Study Procedure	Screening/ Baseline (Visit 1)	15 minutes Post-administration	Visit 2	Visit 3	Early Termination
	Day -0	Day 0	Day 14 (Virtual)	Day 28	

Windows for Visits				**+/- 2 days**	**+/- 7 days**
Informed Consent	X				
Demographics	X				
Medical History and Concurrent Illnesses	X		X	X	X
Ocular History	X		X	X	X
Eligibility Criteria	X				
Urine Pregnancy Test*	X			X	X
Concomitant Medications	X		X	X	X
Intranasal Exam via history	X				
Eye Dryness Score (0-100) as measured by Visual Analogue Scale (VAS)	X		X	X	X
Nasal Dryness Score (0-100) as measured by VAS	X		X	X	X
Dry Mouth Score (0-100) as measured by VAS	X		X	X	X
QIDS-SR Questionnaire	X		X	X	X
Tear Film Imager (obtain tear film thickness)	X	X		X (15 mins post treatment)	X
Slit Lamp Biomicroscopy	X			X	X
Corneal Staining using NEI scale & Conjunctival Staining using Van Bijsterveld and Utrecht scale	X			X	X
Schirmer's Test without anesthesia	X			X	X
Tear sample Collection	X			X	X

Ophthalmic Examination (w/or w/o dilated fundus exam)	X				
Dispense Study Product	X				
Collect Study Product				X	X
Adverse Events	X		X	X	X
*For women of childbearing potential					

APPENDICES

Appendix I: Visual Analogue Scale



Eye Dryness Score (EDS) Using a Visual Analog Scale (VAS)

The participant will be asked to rate their ocular symptoms (both eyes simultaneously) due to eye dryness by placing a vertical mark on the horizontal line to indicate the level of discomfort; 0 corresponds to "no discomfort" and 100 corresponds to "maximal discomfort." The assessment line length of the scale will be 100 mm.

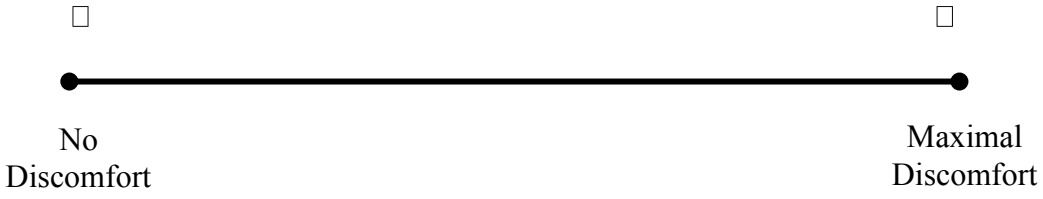
Please rate your current eye dryness by drawing a vertical line on the line below:

No Discomfort — Maximal Discomfort

The EDS is an instrument that has been used in other studies.(Sheppard, Torkildsen et al. 2014, Tauber, Karpecki et al. 2015)

Please rate your current nose dryness by drawing a vertical line on the line below:

No Discomfort · **current mouth dryness by drawing a vertical lin** Maximal Discomfort **ow:**



Appendix II: QIDS-SR Questionnaire

The Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR16)

Name or ID:_____ Date: _____

CHECK THE ONE RESPONSE TO EACH ITEM THAT BEST DESCRIBES YOU FOR THE PAST SEVEN DAYS.

During the past seven days...

1. Falling Asleep:

☐ 0 I never take longer than 30 minutes to fall asleep.

☐ 1 I take at least 30 minutes to fall asleep, less than half the time.

☐ 2 I take at least 30 minutes to fall asleep, more than half the time.

☐ 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night

☐ 0 I do not wake up at night.

☐ 1 I have a restless, light sleep with a few brief awakenings each night.

☐ 2 I wake up at least once a night, but I go back to sleep easily.

☐ 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:

☐ 0 Most of the time, I awaken no more than 30 minutes before I need to get up.

☐ 1 More than half the time, I awaken more than 30 minutes before I need to get up.

☐ 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.

☐ 3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:

☐ 0 I sleep no longer than 7-8 hours/night, without napping during the day.

☐ 1 I sleep no longer than 10 hours in a 24-hour period including naps.

☐ 2 I sleep no longer than 12 hours in a 24-hour period including naps.

☐ 3 I sleep longer than 12 hours in a 24-hour period including naps.

During the past seven days...

5. Feeling Sad:

☐ 0 I do not feel sad.

☐ 1 I feel sad less than half the time.

☐ 2 I feel sad more than half the time.

☐ 3 I feel sad nearly all of the time.

Please complete either 6 or 7 (not both)

6. Decreased Appetite:

☐ 0 There is no change in my usual appetite.

☐ 1 I eat somewhat less often or lesser amounts of food than usual.

☐ 2 I eat much less than usual and only with personal effort.

☐ 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

- OR -

7. Increased Appetite:

☐ 0 There is no change from my usual appetite.

☐ 1 I feel a need to eat more frequently than usual.

☐ 2 I regularly eat more often and/or greater amounts of food than usual.

☐ 3 I feel driven to overeat both at mealtime and between meals.

Please complete either 8 or 9 (not both)

8. Decreased Weight (Within the Last Two Weeks):

☐ 0 I have not had a change in my weight.

☐ 1 I feel as if I have had a slight weight loss.

☐ 2 I have lost 2 pounds or more.

☐ 3 I have lost 5 pounds or more.

- OR -

9. Increased Weight (Within the Last Two Weeks):

☐ 0 I have not had a change in my weight.

☐ 1 I feel as if I have had a slight weight gain.

☐ 2 I have gained 2 pounds or more.

☐ 3 I have gained 5 pounds or more.

During the past seven days...

10. Concentration / Decision Making:

☐ 0 There is no change in my usual capacity to concentrate or make decisions.

☐ 1 I occasionally feel indecisive or find that my attention wanders.

☐ 2 Most of the time, I struggle to focus my attention or to make decisions.

☐ 3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:

☐ 0 I see myself as equally worthwhile and deserving as other people.

☐ 1 I am more self-blaming than usual.

☐ 2 I largely believe that I cause problems for others.

☐ 3 I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:

☐ 0 I do not think of suicide or death.

☐ 1 I feel that life is empty or wonder if it's worth living.

☐ 2 I think of suicide or death several times a week for several minutes.

☐ 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest

☐ 0 There is no change from usual in how interested I am in other people or activities.

☐ 1 I notice that I am less interested in people or activities.

☐ 2 I find I have interest in only one or two of my formerly pursued activities.

☐ 3 I have virtually no interest in formerly pursued activities.

During the past seven days...

14. Energy Level:

☐ 0 There is no change in my usual level of energy.

☐ 1 I get tired more easily than usual.

☐ 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking, or going to work).

☐ 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:

☐ 0 I think, speak, and move at my usual rate of speed.

☐ 1 I find that my thinking is slowed down or my voice sounds dull or flat.

☐ 2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.

☐ 3 I am often unable to respond to questions without extreme effort.

16. Feeling Restless:

☐ 0 I do not feel restless.

☐ 1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.

☐ 2 I have impulses to move about and am quite restless.

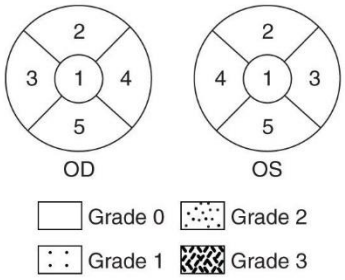
☐ 3 At times, I am unable to stay seated and need to pace around.

Appendix III: Tear Film Imager

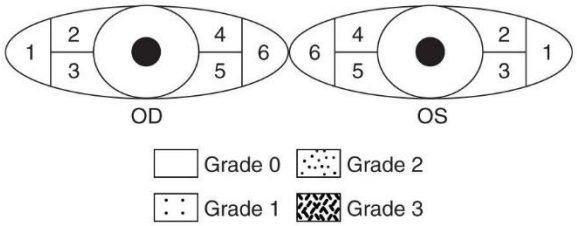
TFI quantifies the dynamic properties of the tear film inner layers (muco-aqueous and lipid) using a single non-contact measurement

Appendix IV: NEI Scale

Score each of 5 areas of the cornea and total score:

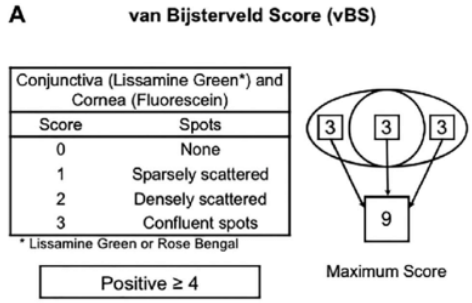


Score each of 6 areas of the conjunctiva and total score:



Add cornea and conjunctival scores for total score

Appendix IV: Van Bijsterveld and Utercht Scale



Appendix VI: Schirmer's Test without Topical Anesthesia and Tear Collection

Schirmer's Strips without Topical Anesthesia:

2. Instruct the participant to keep the eyes gently closed for one minute.
3. After opening the eyes and allowing the eyes to recover for approximately one additional minute, remove the excess moisture in the inferior fornix with a spear.
4. Place Schirmer's strips (35 mm x 5 mm size filter paper strip) in each eye at the junction of the middle and lateral thirds of the lower eye lid.
5. Under ambient light, instruct the participant to look forward and to blink normally during the course of the test. The test should be performed in a room with no direct air or sunlight on the participant's face.
6. The Schirmer's strips should remain in place until five minutes have elapsed or both strips have reached maximum score.
7. After five minutes, remove the Schirmer strips from both eyes and record the amount of wetting.
8. Use forceps to hold the strip and cut 2-3mm above the tear migration line (dye line) and place into the collection tube.
9. Place one strip into each of the collection tubes that were provided. On the label, please indicate if it is Right or Left eye (R = right and L = left) next to the subject ID (ex: 115-001-R; 115-001-L). Place the label on the applicable collection tube.

Kit Content:

- **2 Collection Tubes (Eppendorf Tubes)**
- **2 Schirmer's Strips**
- **2 Labels (one for each tube)**

Schirmer's test and collection

Once both strips have been placed into their own labeled vial, insert both vials back into the labeled collection kit box and store at -20C until further instructions for shipment.

Samples may be batch shipped. Ship all samples overnight on Dry Ice

END OF DOCUMENT