Clinical Trial Protocol

Protocol Title:	Single Center, Randomized, Controlled, Single-Masked Clinical Trial to Evaluate the Chronic Efficacy of OC-01 Nasal Spray on Signs of Dry Eye Disease (The MYSTIC Study)
Protocol Number:	OPP-004
Study Phase:	2
Product Name:	OC-01 Nasal Spray
Indication:	Dry Eye Disease
Investigators:	Single Center
Sponsor:	Oyster Point Pharma, Inc. 700 Alexander Park Dr Suite 301 Princeton, NJ 08540

	Date
Original Protocol (Version 1):	12 April 2018
Amendment #1 (Version 2)	15 May 2018
Amendment #2 (Version 3)	11 July 2018
Amendment #3 (Version 4)	14 November 2018
Amendment #4 (Version 5)	07 March 2019

Confidentiality Statement

SPONSOR PERSONNEL

Chief Executive Officer	[redacted]
Clinical Development	[redacted]
Principal Investigator	[redacted]

SYNOPSIS

Protocol Title:	Single Center, Randomized, Controlled, Single-Masked Clinical Trial to Evaluate the Chronic Efficacy of OC-01 Nasal Spray on Signs of Dry Eye Disease
Protocol Number:	OPP-004
Investigational Product:	OC-01 Nasal Spray
Study Objective:	The objective of this study is to evaluate the chronic safety and effectiveness of OC-01 Nasal Spray as compared to placebo on signs of dry eye disease (DED)
Overall Study Design	
Structure:	A Phase 2, single-center, randomized, controlled, single-masked study
Duration:	Six study visits over approximately 3 months
Controls:	Placebo (OC-01 Vehicle Nasal Spray)
Dosing Regimen:	Intranasal Spray delivered BID
Summary of Visit Schedule:	• Visit 1 = Day 1, Screening, Randomization, and Treatment (Schirmer's Test Evaluation) • Visit 2 = Day 7 ± 2, Treatment (Schirmer's Test Evaluation) • Visit 3 = Day 14 ± 2, Treatment (Schirmer's Test Evaluation) • Visit 4 = Day 28 ± 2, Treatment (Schirmer's Test Evaluation) • Visit 5 = Day 56 ± 2, Treatment (Schirmer's Test Evaluation) • Visit 6 = Day 84 ± 2, Treatment (Schirmer's Test Evaluation)
Measures Taken to Reduce Bias:	This is a randomized, controlled, single-masked study
Study Population Characteristics	
Number of Subjects:	Approximately 120
Condition/Disease:	Dry Eye Disease
Inclusion Criteria:	**Subjects must:** 1. [redacted] 2. Have used and/or desired to us an artificial tear substitute for dry eye symptoms within 6 months prior to Visit 1

	3. [redacted] 4. [redacted] 5. [redacted] 6. [redacted] 7. [redacted] 8. [redacted] 9. [redacted] 10. [redacted]

[1] [redacted]

Exclusion Criteria:	**Subjects must not:** 1. [redacted] 6. Have had any intraocular surgery (such as cataract surgery), extraocular surgery (such as blepharoplasty) in either eye within three months or refractive surgery (e.g. laser-assisted in-situ keratomileusis, laser epithelial keratomileusis, photorefractive keratectomy or corneal implant) within twelve months of Visit 1 [redacted] 10. Have a history or presence of an ocular disorder or condition in either eye that would, in the opinion of the Investigator, likely interfere with the interpretation of the study results or participant safety such as significant corneal or conjunctival scarring; pterygium or nodular pinguecula; current ocular infection, conjunctivitis, or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; ocular herpetic infection; evidence of keratoconus; etc. Blepharitis not requiring treatment and mild meibomian gland disease that are typically associated with DED are allowed. [redacted]

	[redacted] 13. Have a known hypersensitivity to any of the procedural agents or study drug components [redacted]
Study Formulations:	OC-01 nasal solution delivered twice daily as a 50 microliter (µL)-intranasal spray in each nostril at the following formulations: • 40 subjects randomized to 0.1% varenicline tartrate • 40 subjects randomized to 0.2% varenicline tartrate • 40 subjects randomized to Placebo (OC-01 Vehicle Nasal Spray)
Evaluation Criteria	
Safety Measures:	• Adverse Event (AE) Query
Efficacy measures	• Schirmer's Test at Visit 6 (Day 84)
Other Measures:	• Urine pregnancy test (if applicable)
General Statistical Methods and Types of Analyses	

Analysis Populations:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized.
- Per Protocol Population – The per protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.
- Safety Population – The safety population includes all subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

Sample Size:

The sample size for this study is not based on statistical power considerations. It is expected that approximately 40 subjects will be enrolled in each arm, for a total of approximately 120 randomized subjects.

Safety Variables:

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Frequencies and percentages of subjects with treatment-emergent AEs (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class, by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term and strongest relationship, and by system organ class, preferred term, maximal severity, and strongest relationship. Separate analyses will be performed for ocular specific and all AEs (including systemic).

Other safety endpoints including visual acuity, slit-lamp biomicroscopy and intranasal examination will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value for ocular safety assessments will be summarized.

Efficacy Analyses:

Schirmer's Test will be summarized by visit, time point (where appropriate) and treatment with descriptive statistics (n, mean, median, standard deviation, minimum and maximum).

An analysis of covariance ([redacted] model will be used to compare results from Schirmer's Test concurrent with treatment between each dose of OC-01 Nasal Spray and placebo treatment groups. The [redacted] model will include baseline Schirmer's Test (captured at Screening), treatment and study site as covariates. Least Squares Means (LS Means) for each treatment, the corresponding 95% confidence intervals (CIs), and the estimated treatment differences between each dose of OC-01 Nasal Spray and placebo will be calculated from this [redacted] model. In addition, the study site by treatment interaction will be explored in a separate model to evaluate how the treatment effect may differ across study sites.

The analyses will be performed on the ITT population on observed data. Two-sample t-tests and non-parametric Wilcoxon rank sum tests will be used to compare treatments as unadjusted sensitivity analyses. Sensitivity analyses will also be performed on the ITT population with multiple imputation (MI) to impute missing data, as well as the PP population with observed data only.
Summary of Known and Potential Risks and Benefits to Human Subjects There are no known risks with the instillation of OC-01 Nasal Spray.

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TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of covariance
BCVA	Best corrected visual acuity
BID	Two times a day
CAE®	Controlled adverse environment
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
EDS	Eye Dryness Score
DED	Dry eye disease
HIPAA	Health Information Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
logMAR	Logarithm of the minimum angle of resolution
LS	Least Square
MAD	Mucosal Atomization Device
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
µL	microliter
mm	Millimeter
nAChR	Nicotinic acetylcholine receptor
PP	Per Protocol
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
US	United States

3. INTRODUCTION

Dry eye disease (DED) is a multifactorial, age-related disorder of the ocular surface resulting in severe pain, visual impairment, tear film hyperosmolarity and instability, inflammation, and corneal wounding.

4. STUDY OBJECTIVE

The objective of this study is to evaluate the chronic safety and effectiveness of OC-01 Nasal Spray as compared to placebo on signs of dry eye disease (DED).

5. CLINICAL HYPOTHESES

The clinical hypothesis for this study is that OC-01 nasal spray is superior to placebo in treating the signs and symptoms of DED.

6. OVERALL STUDY DESIGN

This is a Phase 2, single-center, randomized, single-masked, placebo-controlled study designed to evaluate the safety and efficacy of OC-01 nasal spray in adult participants with DED. Approximately 120 subjects at least 22 years of age with a physicians' diagnosis of dry eye disease and meeting all other study eligibility criteria will be randomized to receive an application of OC-01 or placebo twice daily (BID) for 12 weeks.

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

7. STUDY POPULATION

7.1. Number of Subjects

It is estimated that approximately 120 participants will be enrolled at a single center in Mexico. Subjects will be randomized to receive one of the following three dose assignments:

- Placebo (vehicle) delivered as a 50 microliter (µL) intranasal spray in each nostril BID
- 0.1% OC-01 (varenicline tartrate) delivered as a 50 microliter (µL) intranasal spray in each nostril BID
- 0.2% OC-01 (varenicline tartrate) delivered as a 50 microliter (µL) intranasal spray in each nostril BID

7.2. Study Population Characteristics

All subjects must be at least 22 years of age, of either gender, and of any race, and must meet all inclusion criteria and none of the exclusion criteria.

7.3. Inclusion Criteria

Subjects must:

1. [redacted]
2. Have used and/or desired to us an artificial tear substitute for dry eye symptoms within 6 months prior to Visit 1
3. [redacted]
4. [redacted]
5. [redacted]

[redacted]

[redacted]

10. [redacted]

7.4. Exclusion Criteria

Subjects must not:

[redacted]

6. Have had any intraocular surgery (such as cataract surgery), extraocular surgery (such as blepharoplasty) in either eye within three months or refractive surgery (e.g. laser-assisted in-situ keratomileusis, laser epithelial keratomileusis, photorefractive keratectomy or corneal implant) within twelve months of Visit 1

[redacted]

10. Have a history or presence of an ocular disorder or condition in either eye that would, in the opinion of the Investigator, likely interfere with the interpretation of the study results or participant safety such as significant corneal or conjunctival scarring; pterygium or nodular pinguecula; current ocular infection, conjunctivitis, or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; ocular herpetic infection; evidence of keratoconus; etc. Blepharitis not requiring treatment and mild meibomian gland disease that are typically associated with DED are allowed.

[redacted]

12. 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.)
13. Have a known hypersensitivity to any of the procedural agents or study drug components

[redacted]

16. Have any condition or history that, in the opinion of the investigator, may interfere with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject

[redacted]

7.5. Withdrawal Criteria

If at any time during the study the Investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study.

Subjects may withdraw from treatment at any time, but will be asked to return for follow -up visits.

Subjects may withdraw consent from the study at any time.

Sponsor and/or Investigator may discontinue any subject for non-compliance or any valid medical reason during the course of the study (see Section 10.6.2).

8. STUDY PARAMETERS

8.1. Safety Measures

- Adverse Events

8.2. Efficacy Measures

The following endpoints will be tested:Schirmer's Test at Visit 6 (Day 84)

- Schirmer's Test at Visit 6 (Day 84)

8.3. Other Measures

Urine pregnancy test (Visit 1 and Visit 6/ET) (if applicable)

9. STUDY MATERIALS

9.1. Study Drug(s)

9.1.1. Formulations

- Placebo (vehicle) delivered as a 50 microliter (µL) intranasal spray in each nostril BID
- 0.1% OC-01 (varenicline tartrate) delivered as a 50 microliter (µL) intranasal spray in each nostril BID
- 0.2% OC-01 (varenicline tartrate) delivered as a 50 microliter (µL) intranasal spray in each nostril BID

9.1.2. Dispensation Schedule

- At Visit 1, qualified subjects will be randomized and the first dose of study drug will be administered in office.
- At Visit 2, Visit 3, Visit 4, Visit 5, and Visit 6 the first daily dose of study drug will be administered in office concurrent with Schirmer's testing.
- At study Days 2-6, 8-13, 15-27, 29-55, and 57-83 subjects will self-administer OC-01 BID as a 50 µL intranasal spray in each nostril.

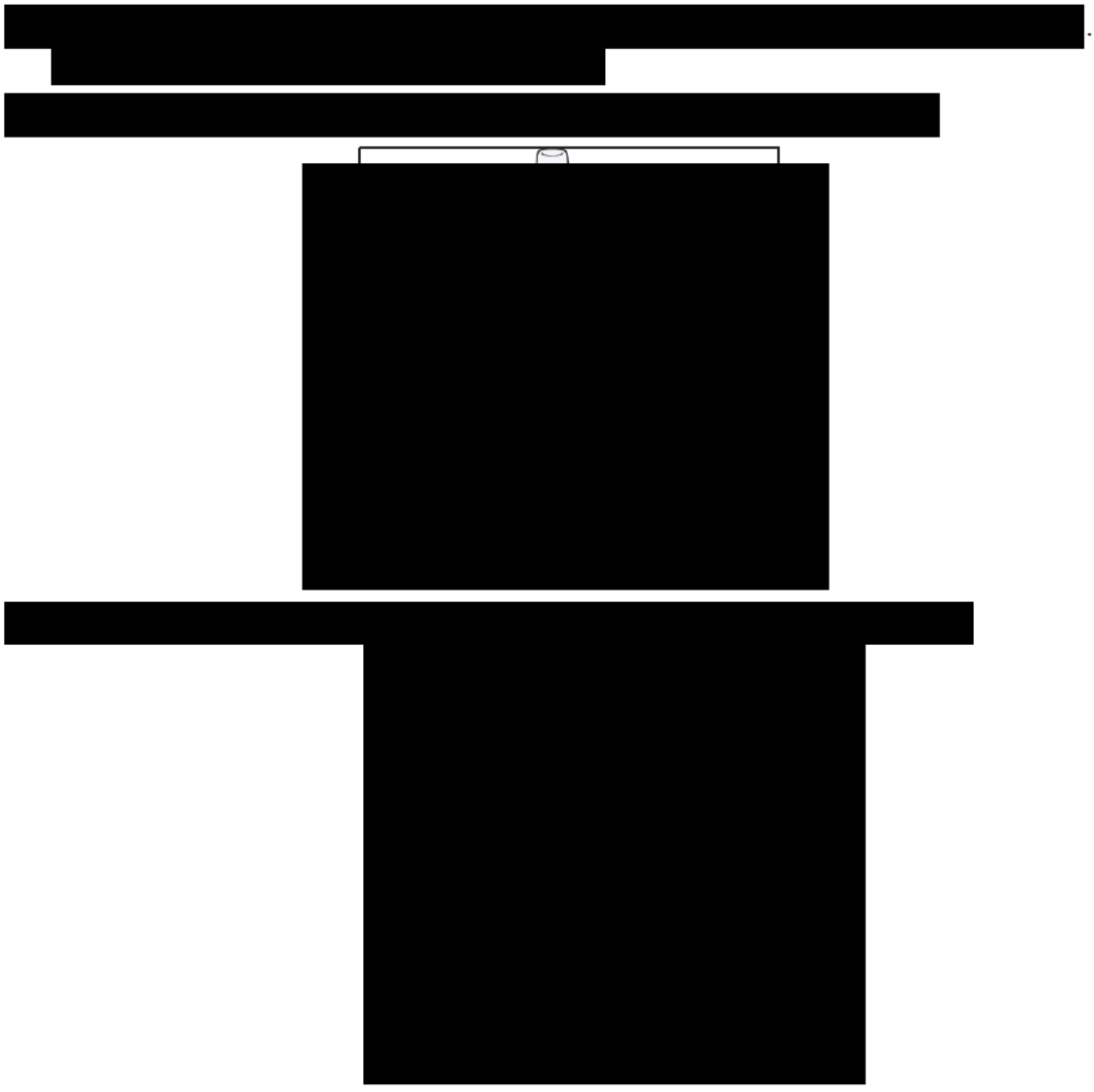
9.1.3. Instructions for Use

General Appearance

- OC-01/Placebo will be formulated at the desired concentration depending upon dose group assignment in phosphate buffered saline as a sterile 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 particles are present.
- OC-01 solution must be administered without dilution.

Preparation



4.

[redacted]

Administration

1. [redacted]

[redacted]

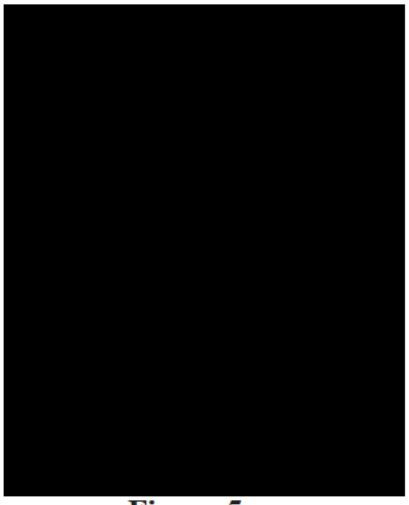


Figure 5

2. 

Figure 6

3. 

[redacted]

[redacted]

10. STUDY METHODS AND PROCEDURES

10.1. Participant Entry Procedures

10.1.1. Overview

Participants as defined by the criteria in Section 7.3 and Section 7.4 will be considered for entry into this study.

10.1.2. Informed Consent

Prior to a participant's participation in the trial (i.e., prior to study-related procedures), the study will be discussed with each potential participant and participants wishing to participate must be administered and provide written informed consent using an Institutional Review Board (IRB) or Independent Ethics Committee (IEC)-approved informed consent form (ICF). The ICF must be the most recent version that has received approval by a properly constituted IRB/IEC.

10.1.3. Washout Intervals

Prohibited medications, treatments, and activities are outlined in the Exclusion Criteria (Section 7.4).

10.1.4. Procedures for Final Study Entry

Subjects must meet all inclusion criteria and none of the exclusion criteria.

10.1.5. Methods for Assignment to Treatment Groups

Each subject who enters the screening period for the study (defined as the point at which the subject signs the informed consent form (ICF) receives a unique subject identification number before any study-related activities/procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study. This number will not necessarily be the same as the randomization number.

Subjects who meet the eligibility requirements will be randomly assigned to 1 of 3 treatment groups.

10.2. Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or device study is not permitted.

10.2.1. Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 7.4)

10.2.2. Escape Medications

No escape medications are required for this study.

10.2.3. Special Diet or Activities

No special diets or activities are required for this study.

10.3. Examination Procedures

10.3.1. Procedures to be Performed at Each Study Visit with Regard to Study Objectives(s)

The following procedures will be performed (see Appendix 2 for description).

Screening/Visit 1 (Day 1): Screening and Schirmer's Test Evaluation

- Informed consent/Health Information Portability and Accountability Act (HIPAA) consent
- Demographic data, medical history, prior medication (s), and ocular history
- Eligibility Criteria
- Urine pregnancy test (if applicable)
- BCVA (pre-and post-treatment)
- Slit lamp biomicroscopy (pre-and post-treatment)
- Corneal fluorescein staining
- Schirmer's Test[3]
- Schirmer's Test with nasal stimulation (cotton swab)[4]
- Intranasal examination
- Randomization
- Dispense new study drug/placebo intranasal applicator
- Administration of study drug/placebo
- Concomitant Medications

[3] Procedure will occur prior to treatment and after corneal fluorescein staining and post treatment

[4] Schirmer's test with nasal stimulation will occur 10 minutes after the first Schirmer's test

- AE Query

Visit 2 (Day 7 ±2): Schirmer's Test Evaluation

- BCVA (pre-and post-treatment)
- Slit lamp biomicroscopy (pre-and post-treatment)
- Administration of study drug/placebo
- Schirmer's Test (concurrent with treatment)
- Concomitant Medications
- AE Query

Visit 3 (Day 14 ±2): Schirmer's Test Evaluation

- BCVA (pre-and post-treatment)
- Slit lamp biomicroscopy (pre-and post-treatment)
- Administration of study drug/placebo
- Schirmer's Test (concurrent with treatment)
- Dispense new study drug/placebo intranasal applicator
- Concomitant Medications
- AE Query

Visit 4 (Day 28 ±2): Schirmer's Test Evaluation

- BCVA (pre-and post-treatment)
- Slit lamp biomicroscopy (pre-and post-treatment)
- Administration of study drug/placebo
- Schirmer's Test (concurrent with treatment)
- Dispense new study drug/placebo intranasal applicator
- Concomitant Medications
- AE Query

Visit 5 (Day 56 ±2): Schirmer's Test Evaluation

- BCVA (pre-and post-treatment)
- Slit lamp biomicroscopy (pre-and post-treatment)
- Administration of study drug/placebo
- Corneal fluorescein staining
- Schirmer's Test (concurrent with treatment)

- Dispense new study drug/placebo intranasal applicator
- Concomitant Medications
- AE Query

Visit 6 (Day 84 ±2): Schirmer's Test Evaluation

- Urine pregnancy test (if applicable)
- Intranasal examination
- BCVA (pre-and post-treatment)
- Slit lamp biomicroscopy (pre-and post-treatment)
- Administration of study drug/placebo
- Schirmer's Test (concurrent with treatment)
- Concomitant Medications
- AE Query

10.4. Schedule of Visits, Measurements and Dosing

10.4.1. Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

10.4.2. Unscheduled Visits

These visits may be performed in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

- Slit-lamp Biomicroscopy;
- Visual Acuity;
- Intranasal Examination;
- Urine Pregnancy Test (if applicable);
- Assessment of AEs;
- Assessment of concurrent medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

10.5. Compliance with Protocol

Subjects will be instructed on how study drug will be administered at all visits and provided detailed written instructions to review on how to self-administer study medication via intranasal pump.

10.6. Subject Disposition

10.6.1. Completed Subjects

A completed subject is one who has not be discontinued from the study.

10.6.2. Discontinued Subjects

Subjects may be discontinued at any time prior to their completion of the study due to:

- AEs;
- unmasking when medically necessary;
- protocol violations;
- administrative reasons (e.g., inability to continue, lost to follow up);
- Sponsor/Investigator termination of study;
- subject choice (e.g. withdrawal of consent); and
- other

Note: In addition, any subject may be discontinued for any sound medical reason at the discretion of the investigator (after consultation with the Sponsor) or Sponsor.

Notification of a subject discontinuation and the reason for discontinuation will be made to Investigator and/or Sponsor and will be clearly documented on the eCRF.

Discontinued subjects will not be replaced.

10.7. Study Termination

The study may be stopped at any time by the Investigator or the Sponsor with appropriate notification.

10.8. Study Duration

An individual subject's participation will involve 6 study visits over approximately 12 weeks (3 months).

10.9. Monitoring and Quality Assurance

[redacted]

11. ADVERSE EVENTS

11.1. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the study drug, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the study drug will also be considered a new AE.

Study drug includes the investigational drug under evaluation and placebo.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the Investigator or reported by the subject upon indirect questioning.

11.1.1. Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

11.1.2. Relationship to Study Drug

The relationship of each AE to the investigational product should be determined by the investigator (in a blinded manner) using these explanations:

- *Definite:* When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product and AE

- *Probable:* When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable
- P*ossible:* When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example; due to missing data or insufficient evidence.
- *None:* When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.
- *Unclassified:* When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

11.1.3. Expectedness

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- *Unexpected:* An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- *Expected:* An AE that is listed in the IB at the specificity and severity that has been observed.
- *Not Applicable:* Any AE that is unrelated to the study drug.

AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

11.2. Serious Adverse Events

An AE is considered serious (SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE

Note: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization

Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay

units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

Note: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.3. Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to the Sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

11.3.1. Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to the Sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

11.3.2. Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the study drug, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate CRFs. The investigator is obligated to pursue and obtain information requested by the Sponsor in addition to that information reported on the CRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the Investigator must notify the Sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; and inform the IRB/IEC of the SAE within their guidelines for reporting SAEs.

11.4. Procedures for Unmasking of Study Drug

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), the Sponsor should be notified before unmasking study drug. The unmasked subject will be discontinued from the study.

11.5. Type and Duration of the Follow-up of Subjects after Adverse Events

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the patient is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the patient via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the Investigator becomes aware of any new information regarding an existing SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and submitted within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

12. STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

12.1. Analysis Populations

[redacted]

12.2. Statistical Hypotheses

H_{01}: There is no difference between OC-01 Nasal Spray (0.1% or 0.2%), and placebo in the change from baseline in Schirmer's Test results.

H_{11}: There is a difference between OC-01 Nasal Spray (0.1% or 0.2%) and placebo in the change from baseline in Schirmer's Test results.

A successful outcome will be one that rejects the null hypotheses (H_{01}).

12.3. Sample Size

The sample size for this study is not based on statistical power considerations. It is expected that approximately 40 subjects will be enrolled in each of the arms, for a total of approximately 120 randomized subjects.

12.4. Statistical Analysis

12.4.1. General Considerations

Quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. Qualitative variables will be summarized using counts and percentages.

All summaries will be presented by treatment group. Summaries will be provided for demographics, medical history, concomitant medications, and subject disposition.

For the purpose of summarization, medical history, concomitant medications, and AEs will be coded to MedDRA and World Health Organization Drug dictionaries, as appropriate.

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 1 screening.

12.4.2. Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the study eye as defined by the following:

The study eye is defined as the eye that meets all inclusion/exclusion criteria; if both eyes qualify then the eye with the greatest increase in tear production with stimulation by a cotton swab at the Screening Visit or, if there is no difference in stimulated tear production, the eye with the lower basal Schirmer's score at screening. If there is no difference for either measure, the right eye will be used as the study eye.

12.4.3. Missing Data

[redacted]

[redacted]

12.4.4. Multiplicity Consideration

[redacted]

12.4.5. Efficacy Analyses

Efficacy analyses will be conducted on Schirmer's Test data.

[redacted]

12.4.6. Safety Variables

[redacted]

13. COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, Good Clinical Practices, including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drugs in the countries involved will be adhered to.

13.1. Protection of Human Subjects

13.1.1. Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent forms must be approved for use by the Sponsor/Investigator and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by the Sponsor prior to submission to the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by the Sponsorand provided in writing by the Sponsor prior to the consent process.

13.1.2. Institutional Review Board Approval

This study is to be conducted in accordance with IRB/IEC regulations [U.S. 21 Code of Federal regulations (CFR) Part 56.103]. The investigator must obtain appropriate IRB/EC approval before initiating the study and re-approval at least annually.

Only an IRB/IEC-approved version of the informed consent form will be used.

13.2. Ethical Conduct of Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

13.3. Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Oyster Point Pharma, the IRB/IEC approving this study, the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), the Food and Drug Administration (FDA), the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

13.4. Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the CRFs serves as the investigator's record of a subject's study-related data.

13.4.1. Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all study drug and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

13.5. Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug

13.5.1. Labeling/Packaging

Investigational drug will be provided in multi-use intranasal applicator that will be assigned at randomization for use during the first 14 days of study. A second multi-use intranasal applicator will be provided at Visit 3 (Day 14) for use during days 14-27, multi-use intranasal applicators three and four will be provided at Visit 4 (Day 28) for use during days 28-55, multi-use intranasal applicators five and six will be provided at Visit 5 (Day 56) for use during days 56-84.

13.5.2. Storage of Investigational Drug / Placebo

The investigational drug / placebo must be stored in a secure area accessible only to the investigator and his/her designee(s). Study drug(s) must be refrigerated (2-8°C, Do Not Freeze), protected from light, and secured at the investigational site in a locked container.

13.5.3. Accountability of Study Drug

The investigational drug / placebo is only prescribed by the principal investigator or his/her named sub investigator(s),and is to only be used in accordance with this protocol. The study drugs must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drugs by maintaining a detailed inventory. This includes the amount of study drugs received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

13.5.4. Return or Disposal of Study Drug

All study drugs will be returned to the Sponsor or their designee for destruction.

13.6. Recording of Data on Source Documents and Electronic Case Reports Forms

All subject data will be captured in the subject source documents which will be transcribed in the eCRFs. The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements, and will be performed only by staff who have been trained on the system and have access to the system. Data will not be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

13.7. Handling of Biological Specimens

Not applicable for this study.

13.8. Publications

The study will be documented in a final report, which will contain appropriate statistical analysis and medical overview. No individual site or Investigator may publish or present any results from the study until a joint, multi-center publication of the trial results is made by Sponsor in

conjunction with various participating Investigators and appropriate sites contributing data and comments. Subsequently, individual Investigators may request to publish or present results from the trial; however, approval will be at the sole discretion of the Sponsor. Should the foregoing language be in conflict with the language addressing publication in the clinical trial agreement, the language in the Clinical Trial Agreement will prevail.

14. REFERENCES

[redacted]

[redacted]

15. APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

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

X_1 = Post-treatment procedures; X_2= Pre- and Post-treatment; X3 = Concurrent with Schirmer's Test; X_4 = For females of childbearing potential

APPENDIX 2: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

The following examination procedures, tests, equipment and techniques are listed in this Appendix:

Visual Acuity Procedures

LogMAR visual acuity must be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual acuity should be evaluated at the beginning of each visit in the study (i.e., prior to slit lamp examination). Participants should use the most recent correction to attain their corrected distance visual acuity (CDVA); if they forget their spectacles, this prescription can be placed in a trial frame.

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the participant viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only ETDRS Series 2000 Chart 1 & 2, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and be well illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The participant should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The participant should be told that the chart has letters only, no numbers. If the participant reads a number, s/he should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The participant should be asked to read slowly, so as to achieve the best identification of each letter. S/he is not to proceed to the next letter until s/he has given a definite response.

If the participant changes a response (e.g., 'that was a "C" not an "O"') before s/he has read aloud the next letter, then the change must be accepted. If the participant changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the participant says s/he cannot read a letter, s/he should be encouraged to guess. If the participant identifies a letter as one of two letters, s/he should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and including the last line read. This total sum represents the logMAR visual acuity for that eye.

Example: Participant correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR visual acuity	= 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (i.e., a participant broke his/her glasses), the reason for the change in correction should be documented.

Note: A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from the Screening Visit (Visit 1) should be evaluated by the Investigator as a potential AE.

Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed during the study. Observations will be graded as *Normal* or *Abnormal*. Abnormal findings, which are clinically significant, will be described.

Corneal Fluorescein Staining

The examiner should instill 5 μL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. Alternatively, corneal staining can be assessed using 1.0 mg sodium fluorescein strips. After moistening the tip of the strip with sterile buffered saline, the excess is shaken into a waste bin with a sharp flick. The lower lid is then pulled down and the flat end of the tip should be gently applied to the inferior tarsal conjunctiva with the intent of not inducing reflex tearing and instilling a very small volume of dye.

The participant will be instructed to blink naturally several times without forced closure of the eyelid to distribute the fluorescein. In order to achieve maximum fluorescence, the examiner should wait at least two minutes after instillation before evaluating corneal fluorescein staining.

A Wratten #12 yellow filter will be used to enhance the ability to grade fluorescein staining. The staining will be graded with the NEI Scale. The upper eyelid is lifted slightly to grade the entire corneal surface.

NEI/Industry Workshop Scale

Diagram of the division of the corneal surface for measuring fluorescein uptake. A standardized grading system of 0-3 is used for each of the five areas on each cornea. Grade 0 will be specified when no staining is present. The maximum score is 15.

Intranasal Examination

Qualified participants for the study must undergo a nasal exam to make the final eligibility determination (e.g. severe nasal airway obstruction such as, severe septal deviation or inferior turbinate hypertrophy, or vascularized polyp seen on examination are reasons for exclusion). To monitor nasal mucosal integrity during the study for participant safety, an examination of the nasal cavities via a speculum will be performed at the Screening Visit (after all other screening procedures have been completed). This examination will be performed by an Ear Nose and Throat (ENT) specialist, otolaryngologist or other suitably qualified medical practitioner (i.e. one who has been trained to perform nasal exams). Participants should be instructed not to perform nasal stimulation on the day nasal exam will be performed.

Schirmer's Test with Topical Anesthesia

At the Screening Visit, one basal Schirmer's test will be performed followed by a Schirmer's test with cotton swab nasal stimulation. The Schirmer's test with topical anesthetic will be used to assess tear production using the following steps:

1. Topical anesthetic drops such as 0.5% proparacaine hydrochloride or equivalent should be instilled in both eyes of the participant.
2. The participant will be instructed 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, excess moisture in the inferior fornix is gently removed with a spear.
4. Schirmer's strips (35 mm x 5 mm size filter paper strip) will be placed in each eye at the junction of the middle and lateral thirds of the lower eye lid.
5. Under ambient light, the participant will be instructed 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 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, strips will be removed from both eyes and the amount of wetting will be recorded. The strips should be taped to the CRF.

<u>Schirmer's test using cotton swab nasal stimulation</u>

At the Screening Visit, the Schirmer's test should be performed using cotton swab nasal stimulation. New anesthetic drops should be instilled following the same procedure specified in steps #1 to 3 above.

1. With new strips in place, the examiner should insert cotton swabs in the participant's two nostrils simultaneously and gently probe both nasal middle turbinates for approximately 30 seconds. After this, the examiner can simply hold the swabs in place, applying gentle pressure, and repeat probing intermittently as necessary.
2. Alternatively, the participant can be instructed to hold the cotton swabs and gently probe both nasal turbinates simultaneously, resting intermittently before probing again. The examiner should continuously coach the participant on how to perform this test properly.
3. The Schirmer's strips should remain in place until five minutes have elapsed or both strips have reached maximum score.

Both Schirmer's scores will be recorded and verified that they meet the inclusion criteria.

APPENDIX 3: SPONSOR APPROVALS

Protocol Title: Single Center, Randomized, Controlled, Single-Masked Clinical Trial to Evaluate the Chronic Efficacy of OC-01 Nasal Spray on Signs of Dry Eye Disease (The MYSTIC Study)

Protocol Numb [redacted]

Signed: [redacted] Date: 3/11/2019

[redacted]

APPENDIX 4: INVESTIGATOR'S SIGNATURE

Protocol Title: Single Center, Randomized, Controlled, Single-Masked Clinical Trial to Evaluate the Chronic Efficacy of OC-01 Nasal Spray on Signs of Dry Eye Disease (The MYSTIC Study)

Protocol Number: OPP-004

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by Oyster Point Pharma in confidence and, when this information is submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____