Clinical Trial Protocol

Protocol Title:	Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-02 Nasal Spray on Signs and Symptoms of Dry Eye Disease
Protocol Number:	OPP-001
Study Phase:	2
Product Name:	OC-02 Nasal Spray
[redacted]	[redacted]
Indication:	Dry Eye Disease
Investigators:	Multi-Center
Sponsor:	Oyster Point Pharma, Inc. One Sansome Street, Suite #3630 San Francisco, CA 94104
Contract Research Organization:	[redacted]
Institutional Review Board:	Alpha IRB 1001 Avenida Pico Suite C, #497 San Clemente, CA 92673

	Date
Original Protocol:	11 October 2017
Amendment 1:	N/A

Confidentiality Statement

SPONSOR PERSONNEL

[redacted]

MEDICAL MONITOR

[redacted]

[redacted] PERSONNEL

[redacted]

SYNOPSIS

Protocol Title:	Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-02 Nasal Spray on Signs and Symptoms of Dry Eye Disease
Protocol Number:	OPP-001
Investigational Product:	OC-02 Nasal Spray
Study Objective:	The objective of this study is to evaluate the safety and effectiveness of OC-02 Nasal Spray as compared to placebo on signs and symptoms of dry eye disease (DED)
Overall Study Design	
Structure:	A Phase 2, multicenter, randomized, controlled, double-masked study
Duration:	Two study visits over approximately two weeks
Controls:	Placebo (OC-02 Vehicle Nasal Spray)
Dosing Regimen:	Treatment at Visit 1 and Visit 2
Summary of Visit Schedule:	• Visit 1 = Day 1, Screening and Treatment (Schirmer's Test Evaluation) • Visit 2 = Day 15 + 4, Treatment (Eye Dryness Score Evaluation)
Measures Taken to Reduce Bias:	This is a randomized, double-masked study
Study Population Characteristics	
Number of Subjects:	Approximately 160 (40 per arm)
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] 11. [redacted] 12. [redacted]

[1] The study eye will be defined as the eye that meets all inclusion 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.

Exclusion Criteria:	**Subjects must not:** 1. [redacted] 2. [redacted] 3. [redacted] 4. [redacted] 5. [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 7. [redacted] 8. [redacted] 9. [redacted] 10. Have a history or presence of any 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. 11. 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.) 12. Have a known hypersensitivity to any of the procedural agents or study drug components 13. [redacted] 14. [redacted] 15. [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 17. [redacted] 18. [redacted]
Study Formulations:	OC-02 nasal solution delivered as a 100 microliter (µL)-intranasal spray in each nostril at the following formulations: • 0.11% OC-02 (0.2% hemigalactarate salt) [low dose] • 0.55% OC-02 (1.0% hemigalactarate salt) [medium dose]

	• 1.1% OC-02 (2.0% hemigalactarate salt) [high dose] • Placebo (OC-02 Vehicle Nasal Spray)
Evaluation Criteria	
Efficacy Measures:	**Primary Efficacy Measures:** • Schirmer's Test at Visit 1 • Eye Dryness Score (EDS) at Visit 2
Safety Measures:	• Adverse Event (AE) Query
Other Measures:	• Ora Calibra® Ocular Discomfort Scale • 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. randomized.
- 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 of the four treatment arms, for a total of approximately 160 randomized subjects. Assuming a 5% drop out rate, approximately 38 subjects per group are expected to complete the study.

Multiplicity Consideration:

Adjustments for multiple testing will not be implemented for this early phase study.

Primary Efficacy Analyses:

Schirmer's Test and EDS 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 (ANCOVA) model will be used to compare results from Schirmer's Test concurrent with treatment between each dose of OC-02 Nasal Spray and placebo treatment groups. The ANCOVA 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-02 Nasal Spray and placebo will be calculated from this ANCOVA 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 change in EDS from pre- to post-treatment will be analyzed using an ANCOVA model with pre-treatment EDS as a covariate and with treatment and time point as fixed effects (accounting for repeated measures). LS means for each treatment, the corresponding 95% CIs, and the estimated treatment difference between each dose of OC-02 Nasal Spray and placebo will be calculated from this ANCOVA model. A study site by treatment interaction will also be explored in a separate model to evaluate how the treatment effect may differ across study sites.

The primary 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.

Other Efficacy Analyses:

Change from pre to post-treatment in EDS will also be analyzed at each individual time point in a manner similar to the primary analysis for Schirmer's Test. These ANCOVA models will include pre-treatment EDS, treatment and study site as covariates.

Change from pre-to post-treatment in [redacted] Ocular Discomfort Scale results will be summarized by visit, time point (where appropriate) and treatment with quantitative descriptive statistics and will be analyzed at each individual time point in a manner similar to EDS.

The analyses will be performed for observed data only for the ITT and PP populations.

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 endoscopic 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.

Summary of Known and Potential Risks and Benefits to Human Subjects

There are no known risks with the instillation of OC-02 Nasal Spray.

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LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of covariance
BCVA	Best corrected visual acuity
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
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
OSDI©	Ocular Surface Disease Index©
PP	Per Protocol
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
US	United States

1 INTRODUCTION

Dry eye disease (DED) is a multifactorial, age-related disorder of the ocular surface resulting

[redacted]

2 STUDY OBJECTIVES

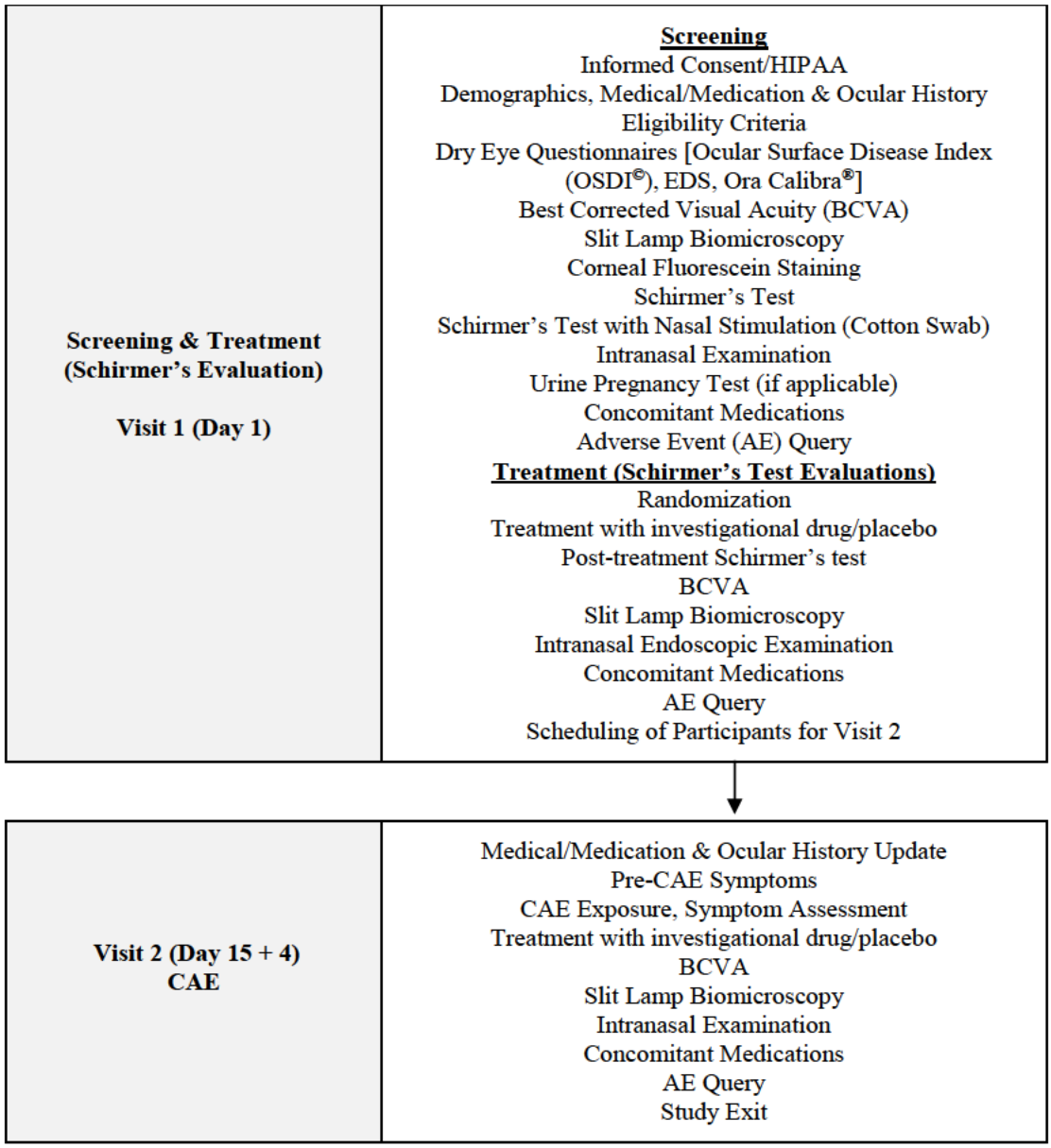
The objective of this study is to evaluate the safety and effectiveness of OC-02 Nasal Spray compared to placebo on signs and symptoms of DED.

3 CLINICAL HYPOTHESES

The clinical hypothesis for this study is that OC-02 nasal spray is superior to placebo in treating the signs and symptoms of DED.

4 OVERALL STUDY DESIGN

This is a Phase 2, multicenter, randomized, double-masked, placebo-controlled study designed to evaluate the safety and efficacy of OC-02 nasal spray in adult participants with DED. Approximately 160 subjects at least 22 years of age with a subject-reported history of dry eye and meeting all other study eligibility criteria will be randomized to receive an application of OC-02 or placebo at Visit 1 and Visit 2.



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.

5 STUDY POPULATION

5.1 Number of Subjects

It is estimated that approximately 160 participants (approximately 40 per arm) will be enrolled at up to 3 sites in the US. Subjects will be randomized to receive one of the following four dose assignments:

- Placebo (vehicle) delivered as a 100 microliter (µL) intranasal spray in each nostril
- 0.11% OC-02 (0.2% hemigalactarate salt) delivered as a 100 µL intranasal spray in each nostril
- 0.55% OC-02 (1.0% hemigalactarate salt) delivered as a 100 µL intranasal spray in each nostril
- 1.1% OC-02 (2.0% hemigalactarate salt) delivered as a 100 µL intranasal spray in each nostril

Subjects will be administered OC-02/Placebo at Visit 1 and Visit 2.

5.2 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.

5.3 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]

[redacted]

s

2 The study eye will be defined as the eye that meets all inclusion 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.

- [redacted]

5. [redacted]
6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]

5.4 Exclusion Criteria

Subjects must not:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [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 epithelial keratomileusis, laser-assisted in-situ keratomileusis, photorefractive keratectomy or corneal implant) within twelve months of Visit 1
7. [redacted]

8. [redacted]od
9. [redacted]
10. Have a history or presence of any 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.
11. 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.)
12. Have a known hypersensitivity to any of the procedural agents or study drug components
13. [redacted]
14. [redacted]
15. [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [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
17. [redacted]
18. [redacted]

5.5 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 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 8.6.2).

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measures

The following primary endpoints will be tested:

- Schirmer's Test at Visit 1
- EDS at Visit 2

6.2 Safety Measure

- AEs

6.3 Other Measures

- [redacted] Ocular Discomfort Scale
- Urine pregnancy test (Day 1)

7 STUDY MATERIALS

7.1 Study Drug(s)

7.1.1 Formulations

- Placebo (OC-02 Vehicle Nasal Spray)
- 0.11% OC-02 (0.2% hemigalactarate salt)
- 0.55% OC-02 (1.0% hemigalactarate salt)
- 1.1% OC-02 (2.0% hemigalactarate salt)

7.1.2 Dispensation Schedule

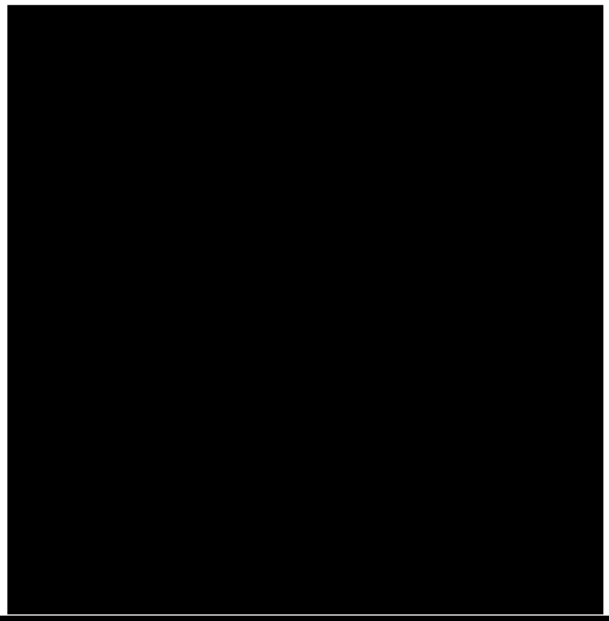
- At Visit 1, qualified subjects will be randomized and the first dose of study drug will be administered in office.
- At Visit 2, subjects will receive their second dose of study drug during CAE® exposure.

7.1.3 Instructions for Use

[redacted]

Preparation

[redacted]



4. [redacted]

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Administration

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- [redacted]
- [redacted]
- [redacted]

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- [redacted]

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- [redacted]

[redacted]

7.2 Other Study Supplies

- Urine pregnancy test kits
- Fluorescein sodium solution or fluorescein strips
- Schirmer's test strips
- Proparacaine

8 STUDY METHODS AND PROCEDURES

8.1 Participant Entry Procedures

8.1.1 Overview

Participants as defined by the criteria in Sections 5.2, 5.3, and 5.4 will be considered for entry into this study.

8.1.2 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)-approved informed consent form (ICF). The ICF must be the most recent version that has received approval by a properly constituted IRB.

8.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the Exclusion Criteria (Section 5.4).

8.1.4 Procedures for Final Study Entry

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

8.1.5 Methods for Assignment to Treatment Groups

Each subject who qualifies will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. If all inclusion and exclusion criteria are met at Visit 1, each qualifying subject will then be assigned a randomization number.

A randomization schedule will be provided to each investigational site. The randomization schedule will be stratified by site, such that there will be an approximate equal number of subjects assigned to each of the four treatment arms at each site. The site staff will dispense to the patient the study kit labeled with the corresponding randomization number. The randomization number will be recorded on the patient's source document and electronic case report form (eCRF). The Sponsor, Investigators, and study staff will be masked during the randomization process and throughout the study.

8.2 Concurrent Therapies

[redacted]

8.3 Examination Procedures

8.3.1 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).

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

Screening

- Informed consent/Health Information Portability and Accountability Act (HIPAA) consent
- Demographic data, medical/medication, and ocular history
- Eligibility Criteria
- OSDI©
- EDS (visual analog scale)
- [redacted]Ocular Discomfort Scale
- BCVA
- Slit lamp biomicroscopy
- Corneal fluorescein staining
- Schirmer's Test[3]
- Schirmer's Test with nasal stimulation (cotton swab)[4]
- Intranasal examination
- Urine Pregnancy Test (if applicable)
- Concomitant Medications
- AE Query

Treatment (Schirmer's Test Evaluation)

Pre-Treatment Procedures:

- Randomization: Qualified participants will be assigned to one of the following treatment groups:
    - Placebo (vehicle) delivered as a 100 µL intranasal spray in each nostril
    - 0.11% OC-02 (0.2% hemigalactarate salt) delivered as a 100 µL intranasal spray in each nostril

[3] Procedure will occur after corneal fluorescein staining

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

- 0.55% OC-02 (1.0% hemigalactarate salt) delivered as a 100 µL intranasal spray in each nostril
- 1.1% OC-02 (2.0% hemigalactarate salt) delivered as a 100 µL intranasal spray in each nostril

Treatment Procedures:

- Instruct subjects on investigational drug / placebo administration
- Treatment with investigational drug/placebo

Post-Treatment Procedures:

- Post-treatment Schirmer's test (performed immediately after investigational drug administration)
- BCVA
- Slit lamp biomicroscopy
- Intranasal endoscopic examination
- Concomitant Medications
- AE Query
- Schedule participant for Visit 2

Visit 2 (Day 15+4): CAE

- Medical/medication and ocular history updates
- EDS
- Ora Calibra® Ocular Discomfort Scale
- Approximately 120 minutes of CAE® Exposure
- EDS collected upon entering the CAE® and every 5 minutes thereafter.
- [redacted] Ocular Discomfort Scale upon entering the CAE® and every 5 minutes thereafter.
- Instruct subjects on investigational drug/placebo administration
- Treatment with investigational drug/placebo
    - Treatment with Investigational drug/placebo will be administered upon participant reporting an Ocular Discomfort score ≥ 3 at two or more consecutive time points in at least one eye during CAE® exposure (if a participant has an Ocular Discomfort rating of 3 at time = 0 for an eye, s/he must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye) using the [redacted] Scale. Participant will resume symptom assessments 1 minute after the application ends every 5 minutes.
- BCVA
- Slit lamp biomicroscopy

- Intranasal Examination
- Urine Pregnancy Test (if applicable)
- Concomitant Medications
- AE Query
- Study exit

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

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

8.4.2 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.

8.5 Compliance with Protocol

Subjects will be instructed on how study drug will be administered at Visits 1 and 2 and provided detailed written instructions to review.

Dosing compliance will be based on used/unused study drug at Visits 1 and 2.

8.6 Subject Disposition

8.6.1 Completed Subjects

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

8.6.2 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 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 Ora and/or Sponsor and will be clearly documented on the eCRF.

Discontinued subjects will not be replaced.

8.7 Study Termination

The study may be stopped at any time by the investigator, the Sponsor, and/or Ora with appropriate notification.

8.8 Study Duration

An individual subject's participation will involve 2 visits over approximately 2-weeks (14 days)

8.9 Monitoring and Quality Assurance

[redacted]

9 ADVERSE EVENTS

9.1 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.

9.1.1 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.

9.1.2 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.

9.1.3 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.

9.2 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.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to [redacted] 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.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

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

9.3.2 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 [redacted] and/or 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 [redacted] and 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 [redacted] and the 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 of the SAE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:

Name: Title: Company: Office Telephone: Alternative Telephone: Office Facsimile:	[redacted]
Name: Title: Office Telephone: Mobile Phone: Office Facsimile:	[redacted]

9.4 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), [redacted] and/or the Sponsor should be notified before unmasking study drug. The unmasked subject will be discontinued from the study.

9.5 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 faxed to Ora 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.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis populations will be considered:

- 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.

The statistical analysis of safety data will be performed for the safety population. The analysis of baseline and efficacy data will be performed for the ITT population. Efficacy analyses will also be performed for the PP population as sensitivity analyses.

10.2 Statistical Hypotheses

H_{01}: There is no difference between OC-02 Nasal Spray (Low Dose, Medium Dose, or High Dose), and placebo in the change from baseline in Schirmer's Test results.

H_{11}: There is a difference between OC-02 Nasal Spray (Low Dose, Medium Dose, or High Dose) and placebo in the change from baseline in Schirmer's Test results.

H_{02}: There is no difference between OC-02 Nasal Spray (Low Dose, Medium Dose, or High Dose) and placebo in the change from pre- to post-treatment in EDS.

H_{12}: There is a difference between OC-02 Nasal Spray (Low Dose, Medium Dose, or High Dose) and placebo in the change from pre- to post-treatment in EDS.

A successful outcome will be one that rejects both null hypotheses (H_{01} and H_{02}).

10.3 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 four treatment arms, for a total of approximately 160 randomized subjects. Assuming a 5% drop out rate, approximately 38 subjects per group are expected to complete the study.

10.4 Statistical Analysis

10.4.3 Missing Data

The primary analyses will be performed using observed data (without imputing missing data). Sensitivity analyses for the primary efficacy analysis will be performed using Markov Chain Monte Carlo multiple imputation methodology to impute missing data. The rate of missing data is expected to be low; however, if the missing data rate exceeds 5%, additional missing data imputation methods (such as tipping point analyses) will be employed to understand the potential impact of missing data on the primary outcomes.

Other efficacy analyses will be performed using observed data only.

10.4.4 Multiplicity Consideration

Adjustments for multiple testing will not be implemented for this early phase study.

10.4.5 Primary Efficacy Analyses

10.4.6 Other Efficacy Analyses

[redacted]

10.4.7 Safety Variables

[redacted]

10.4.8 Interim Analyses

[redacted]

11 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.

11.1 Protection of Human Subjects

11.1.1 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 and receive approval/favorable opinion from an IRB 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 [redacted] prior to submission to the governing IRB 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 [redacted] and/or Sponsor and provided in writing by [redacted] and/or Sponsor prior to the consent process.

11.1.2 Institutional Review Board Approval

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

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

11.2 Ethical Conduct of Study

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

11.3 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 [redacted] the Sponsor, the IRB approving this study, the Food and Drug Administration, 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.

11.4 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.

11.4.1 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 investigator/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.

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

11.5.1 Labeling/Packaging

Investigational drug will be provided in single-use vials and assigned prior to each treatment at Visit 1 and Visit 2.

11.5.2 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.

11.5.3 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.

11.5.4 Return or Disposal of Study Drug

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

11.6 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, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

11.7 Handling of Biological Specimens

Not applicable.

11.8 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.

12 REFERENCES

[redacted]

[redacted]

13 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

Procedure	Visit 1 (Day 1)		Visit 2 (Day 15 + 4)	
	Screening	Schirmer's Test Evaluation	Pre-CAE®	Post-CAE®
Informed consent/HIPAA	X			
Demographics	X			
Medical/Medication, ocular history and updates	X		X	
Eligibility criteria	X			
Urine pregnancy test	X_3		X_3	
OSDI© questionnaire	X			
Eye Dryness Score (EDS)	X		X_4	X_4
[redacted] Ocular Discomfort Scale	X		X_4	X_4
BCVA	X	X_1		X_5
Slit lamp biomicroscopy	X	X_1		X_5
Corneal fluorescein staining	X			
Schirmer's test	X	X_1		
Schirmer's test with cotton swab stimulation	X			
Intranasal examination	X	X_1		X
Concomitant medications	X	X_1		X
Randomization		X		
Administer investigational drug / placebo		X_2	X	
AE Query	X	X_1	X	X
Exit from study				X

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

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. The following will be examined at each visit:

- Cornea
- Conjunctiva
- Anterior Chamber
- Lid

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

Score each of five areas on the cornea of each eye.

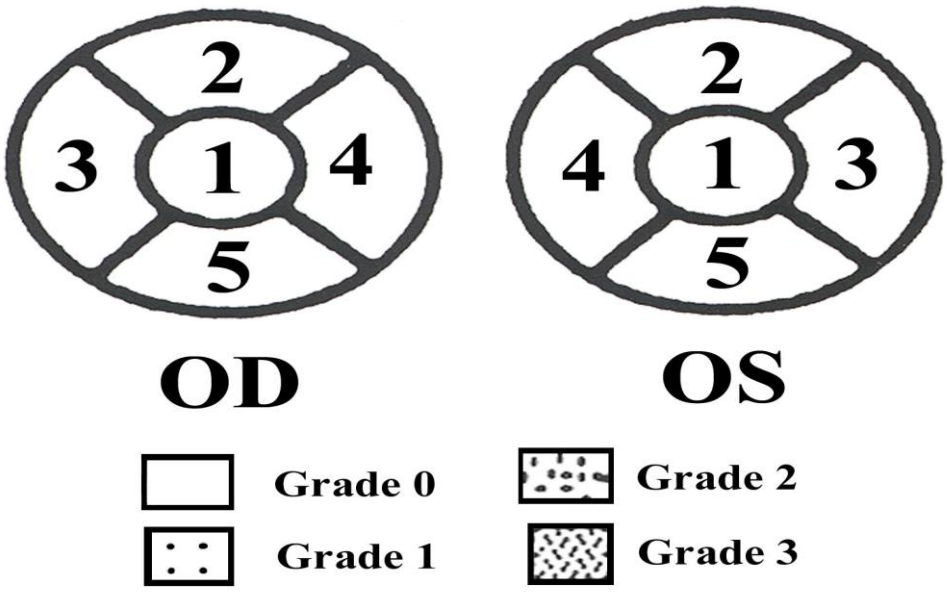


Diagram of the division of the corneal surface for measuring fluorescein uptake. A standardized grading system of 0-3 is used for each of the five areas on each cornea. Grade 0 will be specified when no staining is present. The maximum score is 15.

Intranasal Examination

Qualified participants for the study must undergo a nasal endoscopy 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 an endoscopic camera 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 endoscopy). Still images or video may be captured. Participants should be instructed not to perform nasal stimulation on the day nasal endoscopy 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.

Schirmer's test using cotton swab nasal stimulation

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.

Ocular Surface Disease Index©

To minimize bias, participants will be asked to complete the OSDI questionnaire independently and in private after instructions have been provided by site personnel.

The OSDI is a 12-item questionnaire generated by the Outcomes Research Group at Allergan (Irvine, CA),(Walt JG 1997) which asks participants to describe the severity and the nature of their irritation symptoms. The participant will answer the 12 questions by circling the number that best represents each answer: 4 (all of the time), 3 (most of the time), 2 (half of the time), 1 (some of the time), or 0 (none of the time). The final score for the questionnaire is calculated as follows:

Add subtotals from Sections I, II, and III = A

Determine total number of questions answered from Sections I, II, and III (do not include N/A) = B

Final OSDI score = A x 25 divided by B

An example of the questionnaire follows.

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?.	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?.	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?.	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?. . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

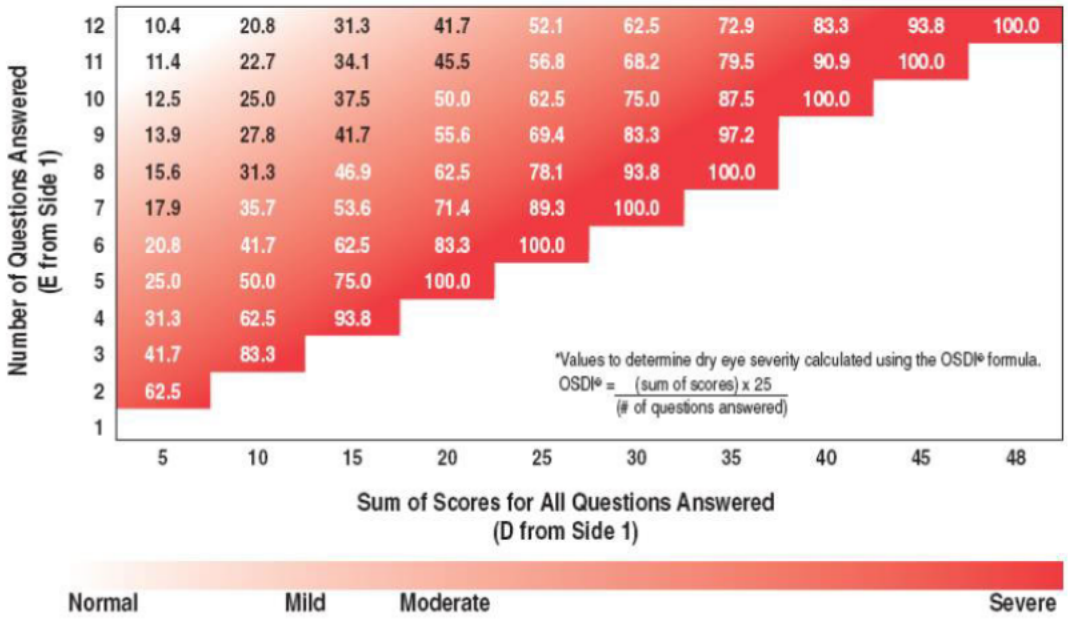
Please turn over the questionnaire to calculate the patient's final OSDI® score.

Evaluating the OSDI© Score[1]

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI© is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



[redacted]

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

Participants will be asked the following question regarding eye dryness every 5 minutes during CAE® exposure.

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

[redacted]

[redacted] Ocular Discomfort Scale

Ocular discomfort scores will be subjectively graded by the participants according to the following scale, rating each eye separately.

0 = No discomfort

1 = Intermittent awareness

2 = Constant awareness

3 = Intermittent discomfort

4 = Constant discomfort

APPENDIX 3: SPONSOR AND [redacted] APPROVALS

Protocol Title: Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-02 Nasal Spray on Signs and Symptoms of Dry Eye Disease

Protocol Number: OPP-001

Signed:____ Date:____

Signed:____ Date:____

Signed:____ Date:____

Signed:____ Date:____

Signed:____ Date:____

APPENDIX 4: INVESTIGATOR'S SIGNATURE

Protocol Title: Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-02 Nasal Spray on Signs and Symptoms of Dry Eye Disease

Protocol Number: OPP-001

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 [redacted] and the Sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB) 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: _____