Clinical Trial Protocol

Protocol Title:	A Single-Center, Randomized, Controlled, Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Goblet Cell and Meibomian Gland Stimulation (The IMPERIAL Study)
Protocol Number:	OPP-005
Study Phase:	2
Product Name:	OC-01 Nasal Spray
[redacted]	[redacted]
Indication:	Dry Eye Disease
Investigators:	Single Center
Sponsor:	Oyster Point Pharma, Inc. 700 Alexander Park Suite 301 Princeton, NJ 08540

	Date
Original Protocol:	June 14, 2018
Amendment 1:	July 11, 2018
Amendment 2:	October 23, 2018
Amendment 3:	January 21, 2019
Amendment 4:	March 26, 2019

Confidentiality Statement

SPONSOR PERSONNEL

Chief Executive Officer:	[redacted]

SYNOPSIS

Protocol Title:	A Single-Center, Randomized, Controlled, Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Goblet Cell and Meibomian Gland Stimulation (The IMPERIAL Study)
Protocol Number:	OPP-005
Investigational Product:	0.2% OC-01 (varenicline tartrate) nasal spray
Study Objective:	The objective of this study is to evaluate the safety and effectiveness of OC-01 Nasal Spray as compared to placebo in simulating Goblet Cell and Meibomian Gland function in adult subjects with DED.
Overall Study Design	
Structure:	A Phase 2, single-center, randomized, controlled, masked study
Duration:	A single study visit
Control:	Placebo (OC-01 Vehicle Nasal Spray)
Dosing Regimen:	Intranasal delivery of OC-01 at a single visit
Summary of Visit Schedule:	• Screening • Visit 1 (Meibomian Gland and Goblet Cell Evaluation)
Measures Taken to Reduce Bias:	This is a randomized, masked study
Study Population Characteristics	
Number of Subjects:	Approximately 45 (30 subjects in the OC-01 nasal spray arm; and 15 subjects in the placebo (vehicle) nasal spray arm)
Condition/Disease:	Dry Eye Disease
Inclusion Criteria:	Subjects must: 1. [redacted]

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

	[redacted]

Exclusion Criteria:	**Subjects must not:** 1. [redacted] 5. 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] 8. 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. [redacted] d. 10. 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.) 11. Have a known hypersensitivity to any of the procedural agents or study drug components [redacted] [redacted] 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]
Study Formulations:	Subjects will be randomized 2:1 to be treated with OC-01 nasal solution delivered as a 50 microliter (µL)-intranasal spray in each nostril at the following formulations: • 0.2% OC-01 (varenicline tartrate) nasal spray • Placebo nasal spray (OC-01 Vehicle Nasal Spray)
Evaluation Criteria	
Efficacy Measures:	**<u>Primary Efficacy Measures:</u>** • Change in Pre- vs, Post-Treatment Goblet cell area at Visit 2 • Change in Pre- vs, Post-Treatment Goblet cell perimeter at Visit 2

	• Change in Pre- vs, Post-Treatment Meibomian gland area lower lids at Visit 2
Safety Measures:	• Adverse Event (AE) Query
Summary of Known and Potential Risks and Benefits to Human Subjects There are no known risks with the instillation of OC-01 (varenicline tartrate) nasal spray.	

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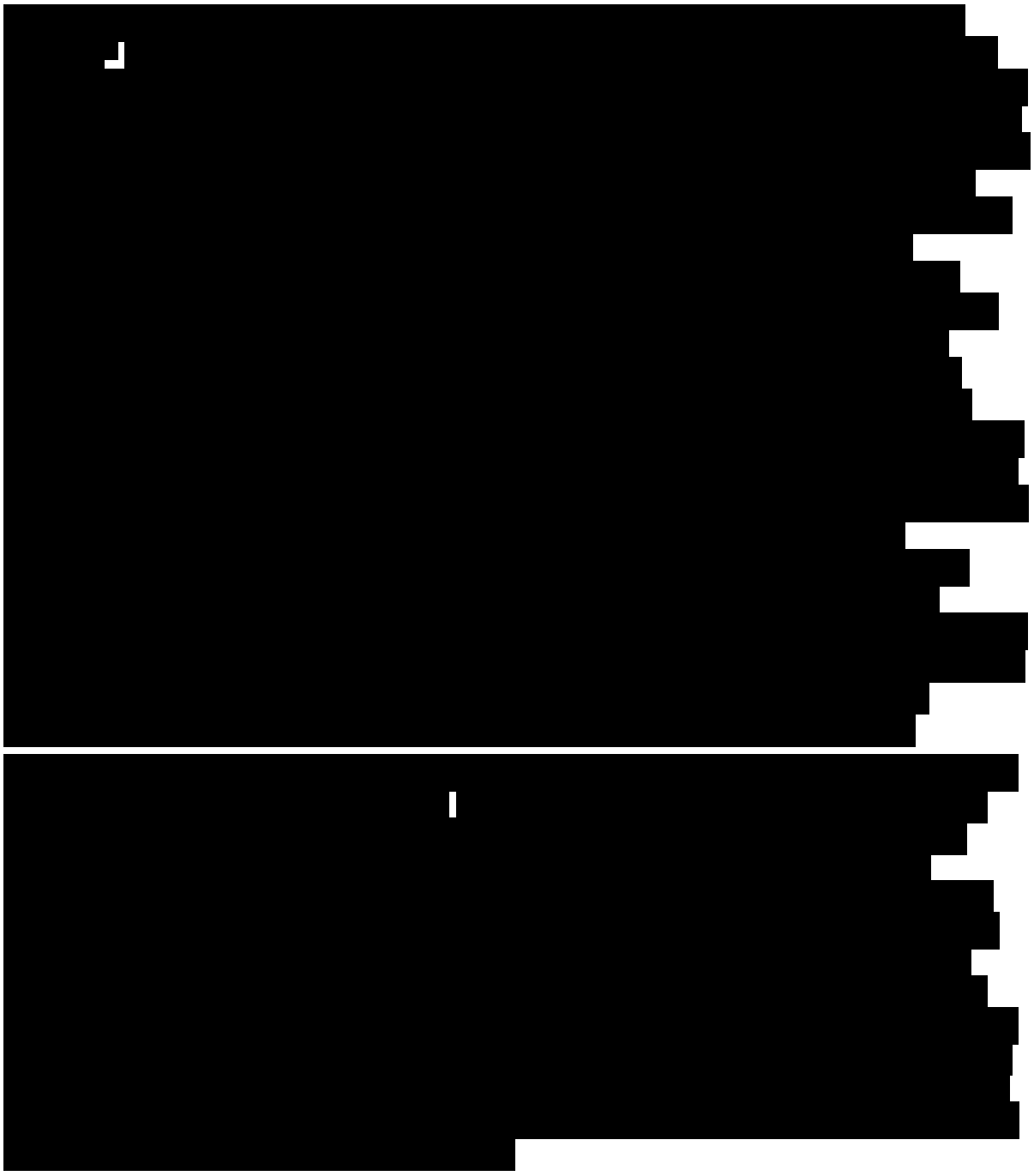
LIST OF ABBREVIATIONS

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
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
SAP	Statistical Analysis Plan
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 in severe pain, visual impairment, tear film hyperosmolarity and instability, inflammation, and corneal wounding.



2 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and effectiveness of OC-01 Nasal Spray as compared to placebo in simulating goblet cell and meibomian gland function in adult participants with DED.

3 CLINICAL HYPOTHESES

This study is testing the hypothesis that OC-01 nasal spray is superior to placebo in stimulating goblet cell and meibomian gland function as assessed by pre- vs. post-treatment change in goblet cell area, pre- vs. post-treatment change in goblet cell perimeter, and pre- vs. post-treatment change in meibomian gland area within the region of the lower lids.

4 OVERALL STUDY DESIGN

Protocol OPP-005 is a Phase 2, single-center, randomized, masked, placebo-controlled study designed to evaluate the safety and effectiveness of OC-01 Nasal Spray as compared to placebo in simulating goblet cell and meibomian gland function in adult participants with DED. Approximately 45 subjects at least 18 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 at a single visit and have pre- and post-treatment images acquired.

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

Approximately 45 subjects will be enrolled at a single center in the US. Subjects will be randomized 2:1 to receive one of the two dose assignments. All doses will be delivered as a 50 microliter (µL) intranasal spray in each nostril at a single visit.

- 30 subjects- 0.2% OC-01 (varenicline tartrate) nasal spray
- 15 subjects- Placebo (vehicle) nasal spray [control]

5.2 Study Population Characteristics

All subjects must be at least 18 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 use an artificial tear substitute for dry eye symptoms within 6 months prior to Visit 1
3. [redacted]

[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.

5.4 Exclusion Criteria

Subjects must not:

1. [redacted]

5. 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

[redacted]

8. 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.

[redacted]

10. 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.)
11. Have a known hypersensitivity to any of the procedural agents or study drug components

[redacted]

[redacted]

14. 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]

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 treatment.

Subjects may withdraw consent from the study at any time.

Sponsor or designee and/or Investigator may discontinue any subject from study treatment for non-compliance or any valid medical reason during the course of the study (see Section 8.5.2).

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

The following efficacy measures will be tested:

- Change in Pre- vs, Post-Treatment Goblet cell area at Visit 2
- Change in Pre- vs, Post-Treatment Goblet cell perimeter at Visit 2
- Change in Pre- vs, Post-Treatment Meibomian gland area lower lids at Visit 2

6.2 Safety Measure

- Adverse Events

7 STUDY MATERIALS

7.1 Study Drug(s)

7.1.1 Regimens

The study drug will be delivered as a 50 microliter (µL) intranasal spray in each nostril at Visit 2::

- Placebo (vehicle)
- 0.2% OC-01 (varenicline tartrate) nasal spray

7.1.2 Dispensation Schedule

Qualified subjects will be randomized and the first dose of study drug will be administered in office at Visit 2.

7.1.3 Instructions for Use

General Appearance

[redacted]

Preparation

[redacted]

Figure 1

3. 

Figure 2

4. [redacted]

Figure 3

[redacted]

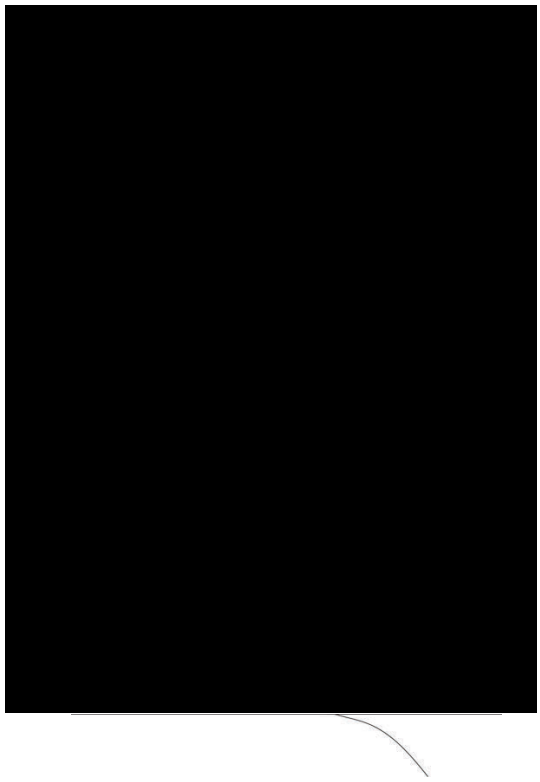
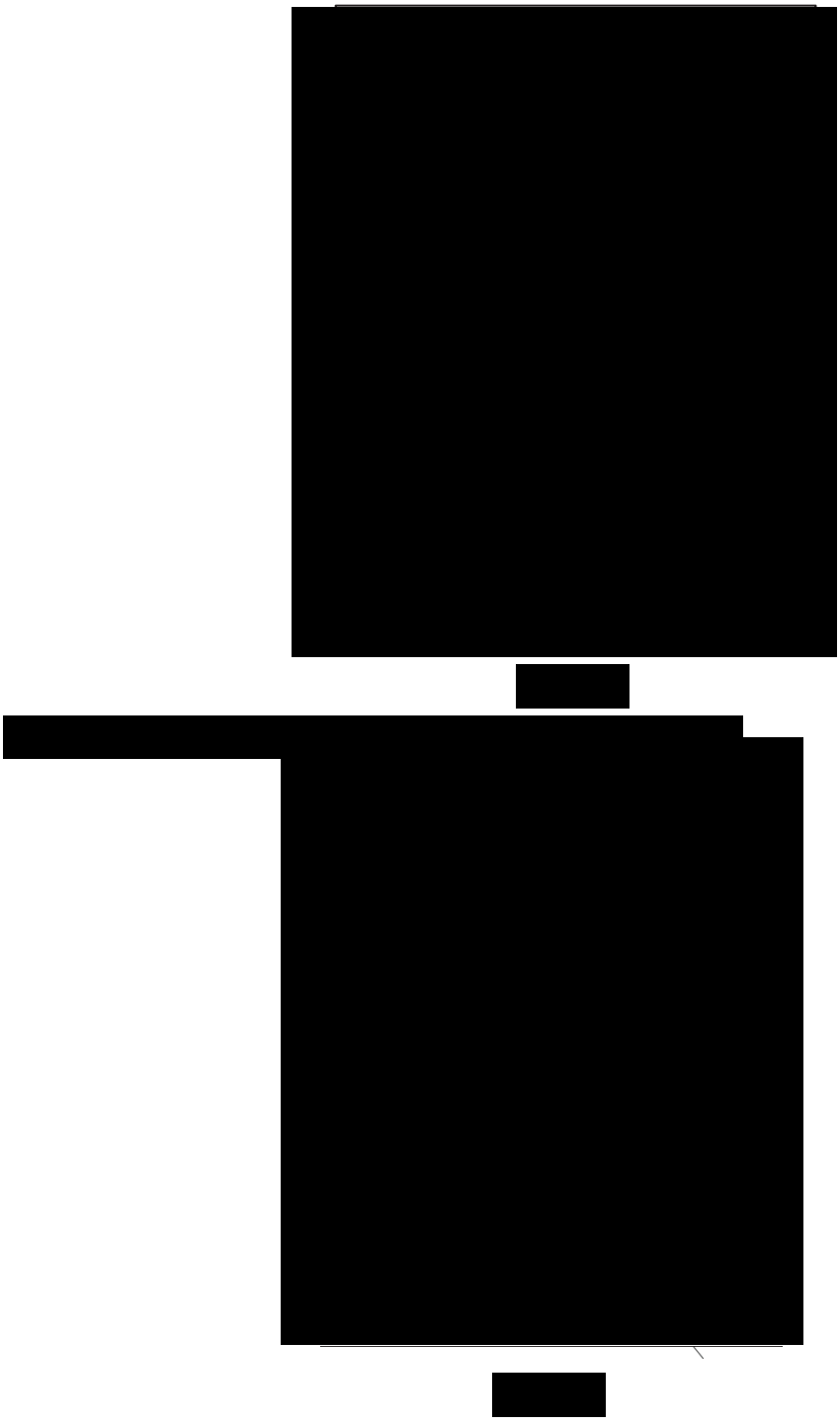


Figure 4

Administration

7. [redacted]



11. [redacted]

Figure 9

[redacted]

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 enrollment in the trial (i.e., prior to any 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 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 2 treatment groups.

8.2 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.

8.2.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 5.4)

8.2.2 Escape Medications

No escape medication is required for this study.

8.2.3 Special Diet or Activities

No special diets or activity is required for this study.

8.3 Examination Procedures

8.3.1 Imaging Procedures

Imaging procedures will begin first prior to bilateral intranasal delivery of drug/placebo. Meibography will be performed first followed by in vivo confocal goblet cell imaging. Approximately 10 minutes after the delivery of bilateral intranasal drug/placebo delivery, imaging procedures will be repeated. Meibography will be performed first followed by in vivo confocal goblet cell imaging.

8.3.1.1 Meibomian Gland Imaging

Meibomian glands will be imaged by the keratography 5M® and Meibomian gland area will be assessed using the MeiboScan digital measurement software.

8.3.1.2 Goblet Cells Imaging

Goblet cells will be imaged by In vivo confocal microscopy (Heidelberg Retinal Tomograph 3/Rostock cornea module; Heidelberg Engineering).

8.3.2 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): Screening

- 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)
- OSDI© questionnaire
- EDS (visual analog scale)
- Slit-lamp biomicroscopy
- Corneal fluorescein staining

- Schirmer's Test[3] (pre-treatment)
- Schirmer's Test with nasal stimulation (cotton swab) [pre-treatment][4]
- Intranasal examination
- Concomitant Medications
- AE Query

Treatment and Imaging Visit (Visit 2) [Meibomian Gland and Goblet Cell Evaluation]

Pre-treatment Assessments (prior to administration of study drug/placebo)

- Concomitant Medications
- AE Query
- Slit-lamp biomicroscopy
- Randomization
- Dispense study drug/placebo intranasal applicator
- Imaging of conjunctival inferonasal goblet cells with Heidelberg Retinal Tomograph 3®/Rostock cornea module
- Meibography assessment by infrared imaging with Oculus Keratograph 5M®

ADMINISTRATION OF STUDY DRUG/PLACEBO

Post-treatment Assessments (after administration of study drug/placebo)

- Imaging of conjunctival inferonasal goblet cells with Heidelberg Retinal Tomograph 3®/Rostock cornea module
- Meibography assessment by infrared imaging with Oculus Keratograph 5M®
- AE Query

8.4 Compliance with Protocol

As subjects will be treated at a single visit at the clinic, it is expected that compliance with the protocol will be excellent.

[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

8.5 Subject Disposition

8.5.1 Completed Subjects

A completed subject is one who has completed Visit 2, been administered investigational therapy, and completed all imaging exams.

8.5.2 Discontinued Subjects

As subjects will be treated at a single visit at the clinic, it is expected that a minimal amount of subjects will be discontinued from the study.

Subjects may be discontinued from treatment, or from involvement in the study 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

Notification of a subject discontinuation and the reason for discontinuation will be made to Sponsor or designee and will be clearly documented on the CRF.

Discontinued subjects will not be replaced.

8.6 Study Termination

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

8.7 Study Duration

An individual subject's participation will involve 2 visits.

8.8 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, subject safety, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. A monitoring plan will outline further details of the study monitoring.

Regulatory authorities of domestic and foreign agencies, Sponsor or designee quality assurance and or its designees may carry out on-site inspections and/or audits, which may

include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 SAFETY DEFINITIONS, SAFETY MONITORING AND REPORTING

9.1 Adverse Event

An adverse event (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

- *Possible:* 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 or designee, 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 in an offspring of a study subject.

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 the Sponsor or designee, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate CRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to the Sponsor or designee 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 the Sponsor or designee 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 or designee 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 the Sponsor or designee 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:	[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 regimen has been assigned to a subject. When possible (i.e., in non-emergent situations), the Sponsor or designee should be notified before unmasking study drug. The unmasked subject will continue the study if warranted by the Investigator in consultation with the Medical Monitor.

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/email to Sponsor or designee 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 ANALYSIS

Statistical considerations and methods of analyses for this study are provided below.

10.1 Sample Size and Power Considerations

The sample size for this study is not based on statistical power considerations. The study will randomize approximately 45 subjects in a 2:1 ratio to the two treatment groups. It is expected that approximately 30 subjects will be enrolled in the investigational treatment arm

and 15 subjects will be enrolled in the placebo arm. It is expected that all 45 subjects will be enrolled.

10.2 Analysis Populations

10.2.1 Intention-To-Treat Population

The intent-to-treat (ITT) population will include all randomized subjects. Analyses using the ITT population will group subjects according to the treatment to which they were randomized.

10.2.2 Safety Population

The safety population will include all randomized subjects who received at least one dose of the study drug. Analysis on the safety population will group subjects according to the treatment actually received.

10.3 Statistical Hypotheses

Meibomian Gland Area

The mean change in meibomian gland area from Pre-Treatment to Post-Treatment is denoted as μ_p, μ_v for placebo and 0.2% OC-01, respectively.

H_{01}: $\mu_p = \mu_v$

H_{11}: $\mu_p \neq \mu_v$

Goblet Cell Area

The mean change in goblet cell area from Pre-Treatment to Post-Treatment is denoted as μ_p, μ_v for placebo and 0.2% OC-01, respectively.

H_{01}: $\mu_p = \mu_v$

H_{11}: $\mu_p \neq \mu_v$

Goblet Cell Perimeter

The mean change in goblet cell perimeter from Pre-Treatment to Post-Treatment is denoted as μ_p, μ_v for placebo and 0.2% OC-01, respectively.

H_{01}: $\mu_p = \mu_v$

H_{11}: $\mu_p \neq \mu_v$

A successful outcome will be one that rejects the null hypothesis.

10.4 Statistical Analysis

This section briefly outlines the planned efficacy analyses.

10.4.1 General Considerations

[redacted]

10.4.2 Unit of Analysis

[redacted]

10.4.3 Subject Demographics and Baseline Characteristics

Continuous summary statistics will be generated for age in years by treatment group and for all subjects. Discrete summary statistics will be generated for the following qualitative demographic variables: age category, gender, ethnicity, race, and other baseline intranasal examination results, tabulated by treatment group and for all subjects. Individual subject data listings will support the Summary tables.

10.4.4 Efficacy Analysis

The efficacy endpoints will be the mean change in meibomian cell area, goblet cell area, and goblet cell perimeter from Pre-Treatment to Post-Treatment.

[redacted]

[redacted]

10.4.5 Safety Analysis

[redacted]

10.4.6 Interim Analysis

[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 or designee or designee 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 Sponsor or designee 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 Sponsor or designee and provided in writing by 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 the Sponsor or designee, 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 or designee 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 multi-use intranasal applicator that will be assigned at randomization.

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 for destruction.

11.6 Recording of Data on Source Documents and Electronic Case Reports Forms

If applicable, 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, electronic 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

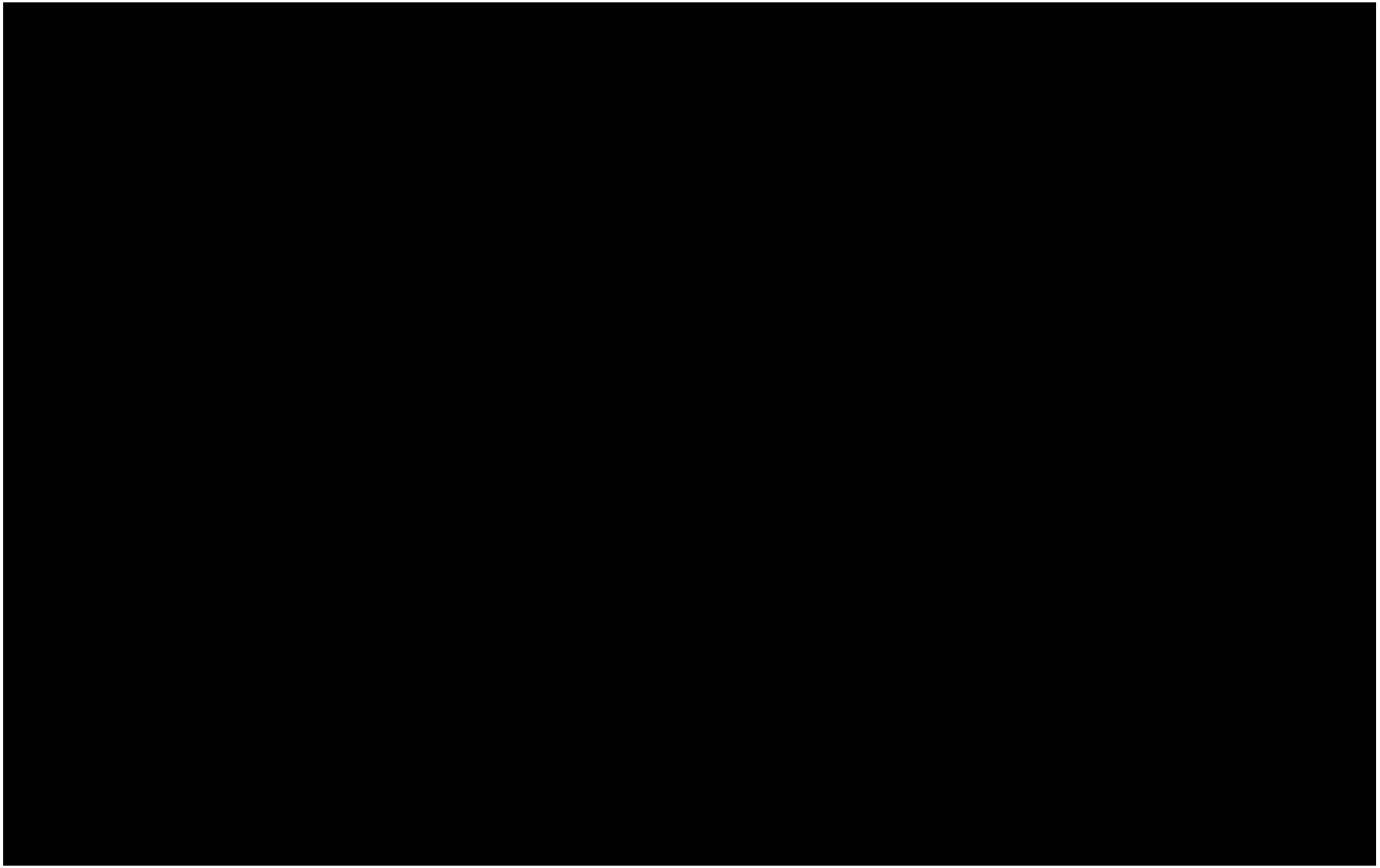
Not applicable.

12 REFERENCES

[redacted]

[redacted]

13 APPENDICES



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

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

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 an intranasal 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 intranasal exam 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 intranasal exam). Still images or video may be captured. The procedure used for the intranasal exam can be conducted either by endoscopic examination or nasal specula.

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.

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.

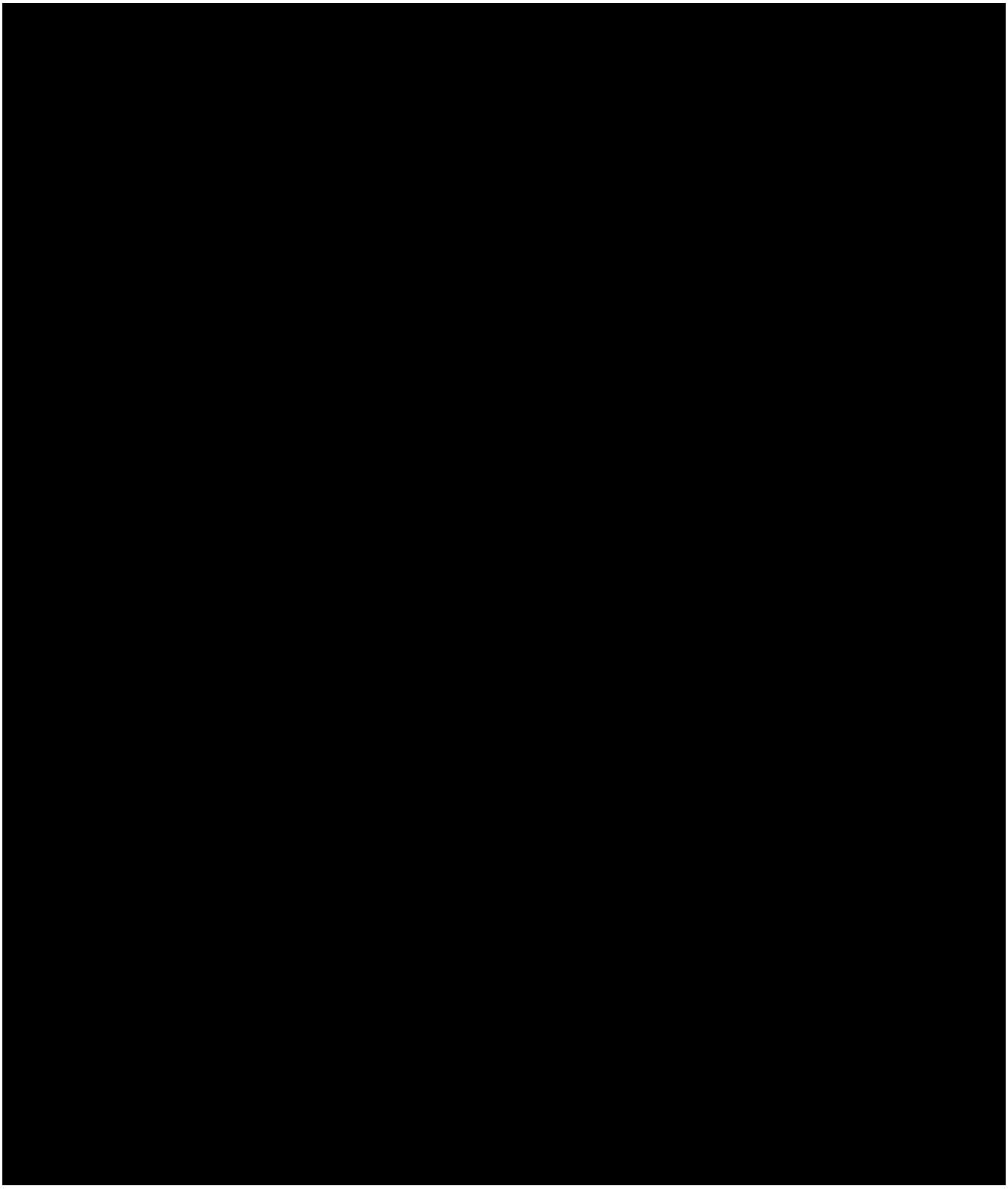
The OSDI is a 12-item questionnaire generated by the Outcomes Research Group at Allergan (Irvine, CA),(Walt JG 1997) which asks participants to describe the severity and the nature of their irritation symptoms. The participant will answer the 12 questions by circling the number that best represents each 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:

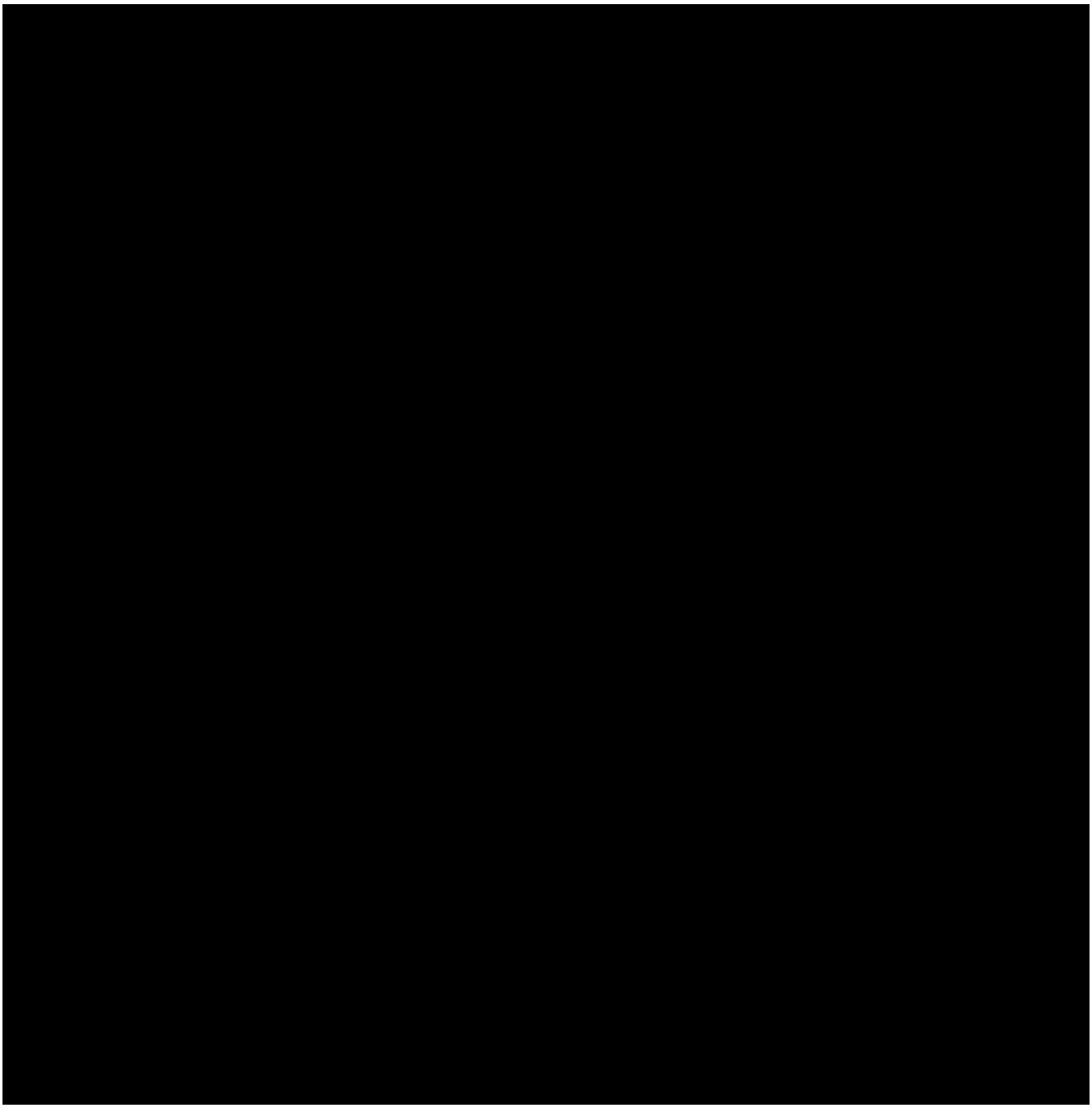
Add subtotals from Sections I, II, and III = A

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.





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

APPENDIX 3: SPONSOR AND APPROVALS

Protocol Title: A Single-Center, Randomized, Controlled, Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Goblet Cell and Meibomian Gland Stimulation (The IMPERIAL Study)

Protocol Number: OPP-005

[redacted]

3/28/2019

Date:

APPENDIX 4: INVESTIGATOR'S SIGNATURE

Protocol Title: A Single-Center, Randomized, Controlled, Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Goblet Cell and Meibomian Gland Stimulation (The IMPERIAL Study)

Protocol Number: OPP-005

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 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: _____