Clinical Trial Protocol

Protocol Title:	Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET Study)-Long Term Safety Follow-up
Protocol Number:	OPP-002-01EXT
Study Phase:	2
Product Name:	OC-01 Nasal Spray
IND Number:	138645
Indication:	Dry Eye Disease
Investigators:	Multi-Center
Sponsor:	Oyster Point Pharma, Inc. 700 Alexander Park Suite 301 Princeton, NJ 08540
Contract Research Organization:	[redacted]
Institutional Review Board:	[redacted]

	Date
Original Protocol:	January 21, 2019

Confidentiality Statement

This protocol contains confidential, proprietary information of [redacted] Oyster Point Pharma, Inc. Further dissemination, distribution or copying of this protocol or its contents is strictly prohibited.

SPONSOR PERSONNEL

Chief Executive Officer:	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

SYNOPSIS

Protocol Title:	Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET Study)-Long Term Safety Follow-up
Protocol Number:	OPP-002-01
Investigational Product:	Subjects were previously treated in the OPP-002 study with one of the following formulations of OC-01 (varenicline tartrate) nasal spray: 0.02% (low dose), 0.1% (medium dose), 0.2% (high dose) or placebo
Study Objective:	The objective of this safety long-term follow-up study is to evaluate the safety of OC-01 Nasal Spray at 6 months and 12 months post treatment in the OPP-002 study.
Overall Study Design	
Structure:	A Phase 2 safety follow up extension study of the OPP-002 study.
Duration:	Two study visits over approximately 6 months
Control:	N/A
Dosing Regimen:	N/A
Summary of Visit Schedule:	• Visit 1 = Month 6 (± 7 days) • Visit 2 = Month 12 (± 7 days)
Study Population Characteristics	
Number of Subjects:	Approximately 180 subjects previously enrolled in the OPP-002 study
Condition/Disease:	Dry Eye Disease

Inclusion Criteria:	Subjects must: 1. Have been enrolled in the OPP-002 study 2. Have received at least one dose of the study drug/placebo in OPP-002 study 3. Completed the OPP-002 study to Visit 5 4. Have provided verbal and written informed consent

Exclusion Criteria:	**Subjects must not:** 1. Have discontinued prior to Visit 5 in the OPP-002 study.

Study Formulations:	Subjects were previously randomized 1:1:1:1 in the OPP-002 study and received treatment with OC-01 nasal solution delivered as a 50 microliter (µL)-intranasal spray in each nostril at the following formulations: • 0.02% OC-01 (varenicline tartrate) nasal spray [low dose] • 0.1% OC-01 (varenicline tartrate) nasal spray [medium dose] • 0.2% OC-01 (varenicline tartrate) [high dose] • Placebo nasal spray (OC-01 Vehicle Nasal Spray) No additional treatment will be administered during this long-term follow-up study.
Evaluation Criteria	
Safety Measures:	**Primary Safety Measures:** • Intranasal Exam at Months 6 and 12 • Slit Lamp Examination at Months 6 and 12 Adverse Events (AE) at Months 6 and 12
Summary of Known and Potential Risks and Benefits to Human Subjects	[redacted]

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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

[redacted]

2 STUDY OBJECTIVES

The objective of this long-term follow-up study is to evaluate the safety of OC-01 Nasal Spray at 6 months and 12 months from first treatment in the OPP-002 study.

3 CLINICAL HYPOTHESES

This study designed to collect data on the long-term follow up of subjects that were administered 28 days of BID treatment with OC-01 nasal spray.

4 OVERALL STUDY DESIGN

Protocol OPP-002-01 is a long-term follow-up study of those subjects that have previously participated in the OPP-002 study. The OPP-002 study was a Phase 2, multicenter, randomized, double-masked, placebo-controlled study designed to evaluate the safety and efficacy of OC-01 nasal spray in adult participants with DED.

[redacted]

5 STUDY POPULATION

5.1 Number of Subjects

Only subjects that previously participated in the OPP-002 study will be eligible to participate in this long-term follow-up extension study.

Approximately 180 participants (approximately 40 per arm) were enrolled in the OPP-002 main study at three sites in the US. Subjects were randomized 1:1:1:1 to receive one of the following four dose assignments. All doses were delivered as a 50 microliter (µL) intranasal spray in each nostril BID for a total of 4 weeks:

- Placebo (vehicle) [control]
- 0.02% OC-01 (varenicline tartrate) nasal spray [low dose]
- 0.1% OC-01 (varenicline tartrate) nasal spray [medium dose]
- 0.2% OC-01 (varenicline tartrate) nasal spray [high dose]

No additional treatment will be administered in this long-term follow-up study.

5.2 Study Population Characteristics

Only subjects that previously participated in the OPP-002 study will be eligible to participate in this long-term follow-up study.

5.3 Inclusion Criteria

Subjects must:

1. Have been enrolled in the OPP-002 study
2. Have received at least one dose of the study drug/placebo in OPP-002 study
3. Completed the OPP-002 study to Visit 5
4. Have provided verbal and written informed consent

5.4 Exclusion Criteria

Subjects must not:

1. Have discontinued prior to Visit 5 in the OPP-002 study

5.5 Withdrawal Criteria

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 Primary Safety Measure

- Intranasal Exam at Months 6 and 12
- Slit Lamp Examination at Months 6 and 12
- Adverse Events (AE) at Months 6 and 12

7 STUDY METHODS AND PROCEDURES

7.1 Participant Entry Procedures

7.1.1 Overview

Participants as defined by the criteria in Sections 5.2, 5.3, and 5.4 will be considered for entry into this study. Only subjects that were previously enrolled in the OPP-002 study will be eligible for participation in this long-term follow-up study.

7.1.2 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.

7.1.3 Washout Intervals

There are no washout intervals required for this study.

7.1.4 Procedures for Final Study Entry

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

7.1.5 Subject Enrollment

Each subject who agrees to participate in 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. [redacted]

7.2 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.

7.1.6 Prohibited Medications/Treatments

There are no disallowed medications/treatments during the study.

7.1.7 Escape Medications

No escape medication is required for this study.

7.1.8 Special Diet or Activities

No special diets or activity is required for this study.

7.2 Examination Procedures

7.2.1 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 (Month 6 ±7 days)

- Informed consent/Health Information Portability and Accountability Act (HIPAA) consent
- Eligibility Criteria
- Slit lamp biomicroscopy
- Intranasal examination
- Concomitant Medications
- AE Query

Visit 2 (Month 12 ±7 days)

- Slit lamp biomicroscopy
- Intranasal examination
- Concomitant Medications
- AE Query
- Study Exit

Early Termination (if applicable)

- Slit lamp biomicroscopy
- Intranasal examination

- Concomitant Medications
- AE Query

7.3 Schedule of Visits, Measurements and Dosing

7.3.1 Scheduled Visits

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

7.3.2 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;
- Intranasal Examination;
- Assessment of AEs;
- Assessment of concurrent medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

7.4 Subject Disposition

7.4.1 Completed Subjects

A completed subject is one who has completed all study visits (Visit 1 and Visit 2).

7.4.2 Discontinued Subjects

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;
- 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 from study involvement from 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 [redacted] Sponsor and will be clearly documented on the eCRF.

Discontinued subjects will not be replaced.

7.5 Study Termination

The study may be stopped at any time by the Investigator [redacted] after consultation with the Sponsor, with appropriate notification.

7.6 Study Duration

An individual subject's participation will involve 2 visits over approximately 6 months.

7.7 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess 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 quality assurance, [redacted] 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.

8 SAFETY DEFINITIONS, SAFETY MONITORING AND REPORTING

8.1 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.

8.1.1 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.

8.1.2 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.

8.1.3 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.

8.2 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 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.

8.3 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.

8.3.1 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.

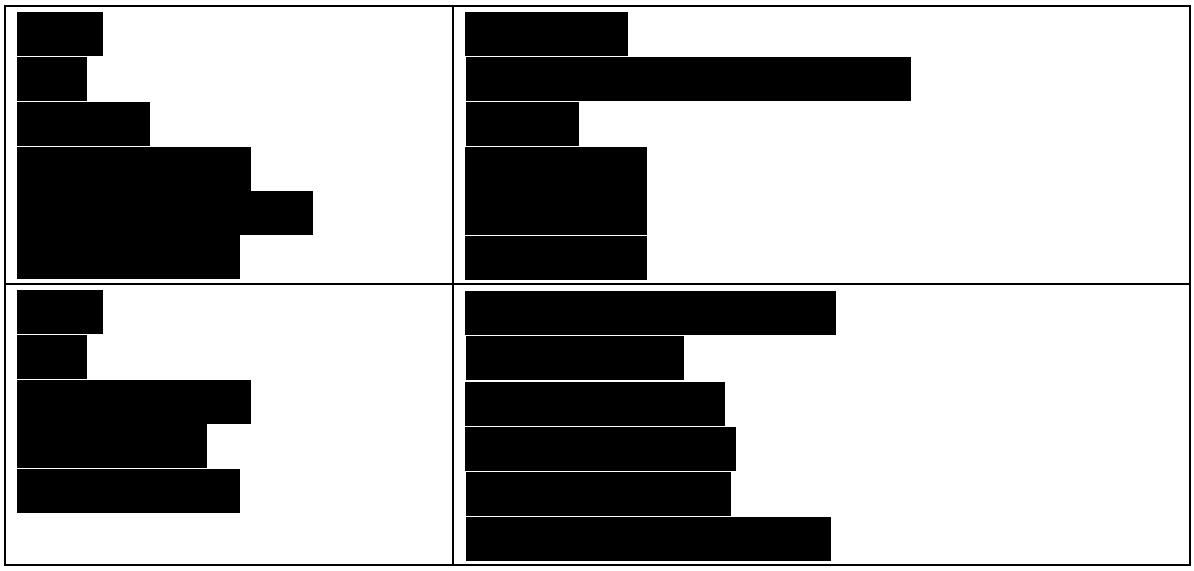
8.3.2 Reporting a Serious Adverse Event

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] 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:



8.4 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), [redacted] the Sponsor 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.

8.5 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 [redacted] 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.

8.6 Compliance with Protocol

Subjects will be instructed on the necessity to attend Visit 1 and Visit 2 to be examined and to have their adverse event information collected.

8.7 Subject Disposition

8.7.1 Completed Subjects

A completed subject is one who has completed both study visits (Visit 1 and Visit 2).

8.7.2 Discontinued Subjects

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

- AEs;
- protocol violations;
- sponsor termination of study;
- non-compliance
- withdraw by subject
- other

Note: In addition, any subject may be discontinued from from study involvement from 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 [redacted] Sponsor and will be clearly documented on the eCRF.

Discontinued subjects will not be replaced.

8.8 Study Termination

The study may be stopped at any time by the Investigator [redacted] after consultation with the Sponsor, with appropriate notification.

8.9 Study Duration

An individual subject's participation will involve 2 study visits over approximately 6 months

8.10 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review

protocol compliance, 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 quality assurance, [redacted] 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 STATISTICAL ANALYSIS

Statistical considerations and methods of analyses for this study are have been detailed in the OPP-002 study and the OPP-002 Statistical Analysis Plan (SAP).

9.1 Analysis Populations

9.1.1 Safety Population

[redacted]

9.2 Statistical Analysis

This section briefly outlines the planned efficacy analyses. The SAP describes the methods to be used in detail. If the SAP and the protocol disagree, the details and methods of the SAP will prevail.

9.2.1 General Considerations

Quantitative variables will be summarized using the number of subjects (n), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Qualitative variables will be summarized using counts and percentages.

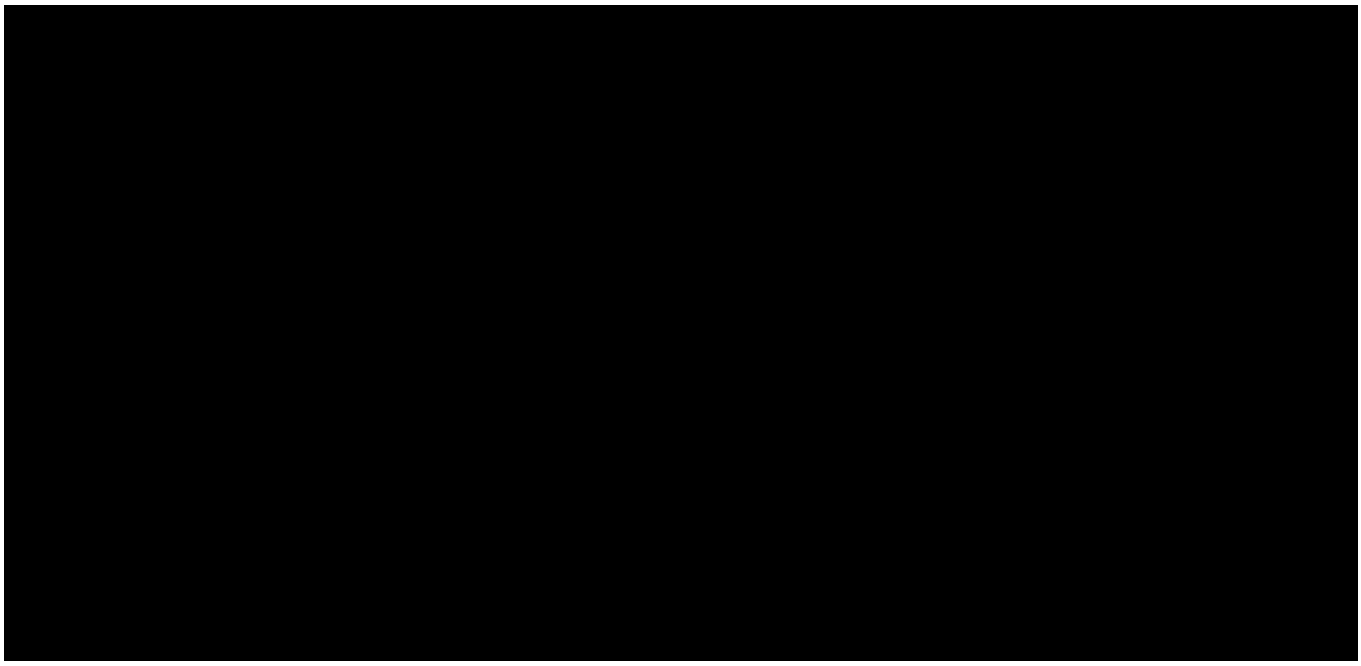
All summaries will be presented by treatment group. Summaries will be provided for demographics, medical history, concomitant medications, and subject disposition.

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

Baseline measures are defined in the OPP-002 protocol as the last measure prior to the initiation of study treatment, usually at Visit 1 screening.

9.2.2 Unit of Analysis

For safety endpoints, both eyes will be analyzed.



10 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.

10.1 Protection of Human Subjects

10.1.1 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] Sponsor and provided in writing by [redacted] Sponsor prior to the consent process.

10.1.2 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.

10.2 Ethical Conduct of Study

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

10.3 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.

10.4 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.

10.4.1 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.

10.5 Recording of Data on Source Documents and Electronic Case Report 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 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.

10.6 Handling of Biological Specimens

Not applicable.

10.7 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 the Sponsor completes 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.

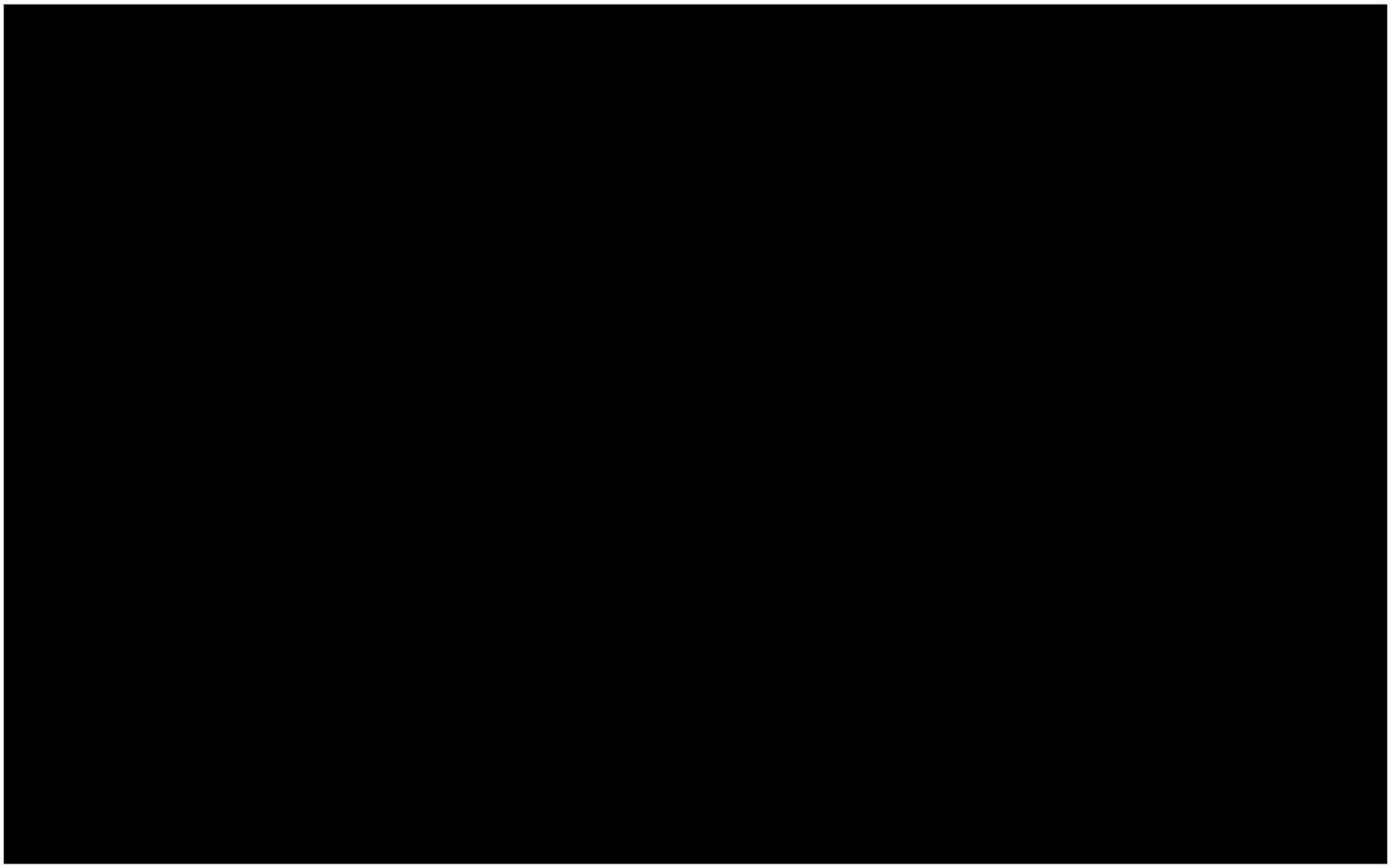
11 REFERENCES

[redacted]

[redacted]

12 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS



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

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

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.

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.

APPENDIX 3: SPONSOR AND [redacted] APPROVALS

Protocol Title: Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET study) – Long Term Safety Follow-up

[redacted]

APPENDIX 4: INVESTIGATOR'S SIGNATURE

Protocol Title: Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET Study) – Long Term Safety Follow-up

Protocol Number: OPP-002-01

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] 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: _____