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Oyster Point Pharma, Inc.

Clinical Protocol: OPP-101:

A Phase 3, Multicenter, Randomized, Controlled, Double-Masked, Clinical Trial to Evaluate the Efficacy of OC-01 (varenicline)Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET-2 Study)

Statistical Analysis Plan
Version 3.0

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[redacted]

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1 Synopsis

Protocol Title:	A Phase 3, Multicenter, Randomized, Controlled, Double-Masked Clinical Trial to Evaluate the Efficacy of OC-01 (varenicline) Nasal Spray on Signs and Symptoms of Dry Eye Disease (The ONSET-2 Study)
Protocol Number:	OPP-101
Investigational Product:	OC-01 (varenicline) Nasal Spray: • 0.6 mg/mL • 1.2 mg/mL
Study Objective:	The objective of this study is to evaluate the safety and effectiveness of OC-01 (varenicline) Nasal Spray as compared to placebo on signs and symptoms of dry eye disease (DED)
Treatment Assignment	750 subjects will be randomized in a 1:1:1 into one of three treatment groups: • 0.6 mg/mL • 1.2 mg/mL • Placebo (vehicle)
Sample Size and Power	[redacted]
Randomization and Stratification	The randomization will be performed by a centralized IWRS system with three stratification factors: • Pre-procedure (Baseline) anesthetized Schirmer's score ($\leq$5, >5) measured at the screening/randomization visit. • Pre-procedure (Baseline) EDS (<60, $\geq$60) measured at the screening/randomization visit. • Study Site

Efficacy Endpoint	Primary Endpoint: • Percentage of subjects who achieve ≥10 mm improvement in Schirmer's Test Score from baseline at Visit 4 (Day 28) Secondary Endpoints • Mean change from Baseline in Eye Dryness Score (EDS) in the study eye at 5 minutes after threshold defined treatment administration in the Controlled Adverse Environment Chamber at Week 4 (Visit 4a) • Mean change from Baseline in Eye Dryness Score (EDS) in the study eye at Week 4 (Visit 4b) • Mean change from Baseline in Schirmer's Test Score (STS) in the study eye at Week 4 (Visit 4b) • Mean change from Baseline in Inferior Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b) • Mean change from Baseline in Eye Dryness Score (EDS) in the study eye at Week 2 (Visit 3) • Mean change from Baseline in Eye Dryness Score (EDS) in the study eye at Week 1 (Visit 2) • Mean change from Baseline in Nasal Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b) • Mean change from Baseline in Temporal Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b) • Mean change from Baseline in Central Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b) • Mean change from Baseline in Superior Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b) • Mean change from Baseline in Total Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b)

Statistical Analysis for Primary Endpoint	The primary efficacy endpoint will be analyzed on the ITT population using a [redacted] test comparing each of the treatment groups to placebo controlling for the randomization strata (study site, Baseline Schirmer's Test Score and Baseline EDS).
Multiplicity	[redacted]
Analysis Populations	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.

2 Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BCVA	best corrected visual acuity
BID	twice daily
CAE®	Controlled Adverse Environment®
CMH	Cochran-Mantel-Haenszel
CFR	Code of Federal Regulations
eCRF	Electronica case report form
CI	confidence interval
CRF	case report form
DED	dry eye disease
EDS	Eye Dryness Score
FDA	Food and Drug Administration
HIPAA	Health Information Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	institutional review board
ITT	intent-to-treat
logMAR	logarithm of the minimum angle of resolution
LS	least square
MAD	mucosal atomization device
MAR	missing at random
MCAR	missing completely at random
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
MMRM	mixed model for repeated measures
MNAR	missing not at random
µL	microliter
mm	millimeter
nAChR	nicotinic acetylcholine receptor
OSDI©	Ocular Surface Disease Index©
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan

SD	Standard deviation
STS	Schirmer's Test Score
TEAE	treatment-emergent adverse event
US	United States

3 Introduction

This statistical analysis plan (SAP), which is based on the original protocol of the study protocol dated [redacted] defines the methods and analyses that Oyster Point Pharma, Inc. (henceforth, Oyster Point) plans to use to analyze the data from Protocol OPP-101. This SAP complies with guidance promulgated by the International Conference on Harmonization (ICH) and the US Food and Drug Administration (FDA). If the protocol is subsequently amended, this SAP may be amended as well. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP prevails.

4 Study objective

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

5 Study Design

This is a Phase 3, multicenter, randomized, controlled, double- masked study designed to evaluate the safety and efficacy of OC-01 (varenicline) Nasal Spray in adult participants with DED. Approximately 750 subjects at least 22 years of age with a physician's diagnosis of dry eye disease and meeting all other study eligibility criteria will be randomized to receive an application of OC-01 (varenicline) Nasal Spray or placebo twice daily (BID) for 28 days with three additional long-term follow-up visits at 6 weeks, 6 months and 12 months.

The three treatments are:

- Placebo (vehicle) [control]
- OC-01 (varenicline) Nasal Spray, 0.6 mg/mL
- OC-01 (varenicline) Nasal Spray, 1.2 mg/mL

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

Appendix 1 describes the detailed study visits, measurements, and dosing information.

6 Primary and Secondary Endpoints

6.1 Primary Efficacy Endpoint

The primary endpoint is percentage of subjects who achieve ≥ 10 mm improvement in the study eye on Schirmer's Test Score (STS) from baseline at Visit 4 (Day 28).

[redacted]

6.2 Secondary Efficacy Endpoints

There are 11 secondary efficacy endpoints:

1. Mean change from Baseline in Eye Dryness Score (EDS) in the study eye at 5 minutes after threshold defined treatment administration in the Controlled Adverse Environment Chamber at Week 4 (Visit 4a)
2. Mean change from Baseline in Eye Dryness Score (EDS) in the study eye at Week 4 (Visit 4b)
3. Mean change from Baseline in Schirmer's Test Score (STS) in the study eye at Week 4 (Visit 4b)
4. Mean change from Baseline in Inferior Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b).
5. Mean change from Baseline in Eye Dryness Score (EDS) at Week 2 (Visit 3)
6. Mean change from Baseline in Eye Dryness Score (EDS) at Week 1 (Visit 2)
7. Mean change from Baseline in Nasal Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b)
8. Mean change from Baseline in Temporal Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b)
9. Mean change from Baseline in Central Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b)
10. Mean change from Baseline in Superior Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b)
11. Mean change from Baseline in Total Corneal Fluorescein Staining in the study eye at Week 4 (Visit 4b)

6.3 Other Efficacy Endpoints

- The listed primary and secondary endpoints in the fellow eye
- The listed primary and secondary endpoints combining data from both study and fellow eyes

7 Sample Size Determination and Power Calculation

Approximately 750 subjects will be randomized into a 1:1:1 ratio to the three treatment groups. Approximately 250 subjects in each treatment group are expected to complete their assigned treatment and have endpoint assessments at Visit 4.

[redacted]

8 Statistical Hypothesis Testing

The null hypothesis for the primary endpoint is to test equality of the percentage of subjects who have ≥ 10mm change from baseline to Visit 4 in STS between the active drug-treated subjects and the placebo-treated subjects.

H_0: Pl - Pp = 0 vs. H_1: P1 - Pp ≠ 0

or

H_0: Ph - Pp = 0 vs. H_1: Ph - Pp ≠ 0

where Pl, Ph, and Pp denote the percentage of subjects in each group (low dose, high dose, and placebo, respectively) who have ≥ 10mm change from baseline to Visit 4 in STS.

9 Statistical Analysis

9.1 General Consideration

Descriptive and inferential statistics will be used to summarize results of Protocol OPP-101. Continuous variables will be summarized using the number of subjects (n), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Categorical variables will be summarized using frequency counts and percentages. Baseline measures will be defined as the last measure prior to the initiation of study treatment, usually at Visit 1 screening.

All summaries for safety data and efficacy data will be presented by treatment group. For the baseline characteristics, all summaries will be presented by treatment group and overall. All collected data will be presented in listings which will be sorted by treatment, subject ID, and visit when it is appropriate. Summaries, data listings, and statistical analyses will be generated using SAS® Version 9.4 or higher.

9.2 Analysis Populations

9.2.1 Intention-to-treat (ITT) population

The ITT population will include all randomized subjects. Analyses using the ITT population will group subjects according to the treatment to which they were randomized.

9.2.2 Per-protocol (PP) population

The PP population will include all subjects in the ITT population with post-baseline (Visit 1) data, excluding subjects who have major protocol deviations. Major protocol deviations will be identified prior to database lock by the sponor. Analyses using the PP population will group subjects according to the treatment to which they were treated.

9.2.3 Safety population

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

9.3 Unit of Analysis

For efficacy endpoints, the unit of analysis will be the study eye as defined as the eye that meets all inclusion and exclusion criteria. If both eyes qualify, then the study eye will be the eye with the greatest increase in tear production with stimulation by a cotton swab at the Screening Visit. If there is no difference in stimulated tear production, the study eye will be the eye with the lower Schirmer's Test Score at screening. If there is no difference for either measure, the right eye will be used as the study eye.

For safety endpoints, both eyes will be analyzed.

9.4 Definition of Study Day or Dosing Day

Study and dosing days are defined as follows:

Study Day = [Event date – Randomization date + 1] if after randomization
[Event date – Randomization date] if before randomization

Dosing Day= [Event date – First dosing date + 1] if after first dosing date
[Event date – First dosing date] if before first dosing date.

Note that with the definition above, days of "0" will not be used.

For subjects whose reference date is missing, the study day will also be categorized as missing.

9.5 Missing and Partial Data

[redacted]

[redacted]

[redacted]

9.6 Protocol Deviations

[redacted]

9.7 Data Handling with Mis-stratified Subjects

Subjects are randomized through an IWRS system with 3 stratification factors:

1. Pre-procedure (Baseline) anesthetized Schirmer's score (<5, >5) measured at the screening/randomization visit.

2. Pre-procedure (Baseline) EDS (<60, >60) measured at the screening/randomization visit.
3. Study Site.

Subjects may be mis-stratified for the baseline STS or baseline EDS in the IWRS. The analyses using the ITT and PP populations will follow the stratification factor to which each subject was categorized in the IWRS system. A sensitivity analysis using the corrected stratification factor may be performed as a related analysis.

9.8 Subject Disposition

The number and percentage of subjects randomized and included in each analysis population will be summarized by treatment and overall. Reasons for excluding subjects from the analysis populations will be presented in a by-subject listing.

The number of randomized subjects who completed the study, discontinued early from study drug, and reasons for discontinuation will be summarized by treatment group and overall. The Case Report Form (CRF) lists the following reasons why subjects may discontinue treatment before completing of the study:

- Non-fatal adverse event (AE)
- Protocol violation
- Lost to follow-up
- Pregnancy
- Physician decision
- Subject non-compliance
- Death
- Study terminated by sponsor
- Withdrawal by subject
- Other reasons

9.9 Demographics and Baseline Characteristics

Continuous variables will be summarized using the number of subjects (n), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Categorical variables will be summarized using counts and percentages. Summary data will be presented by treatment group and overall.

The following demographic and baseline characteristics will be summarized: age, gender, ethnicity, race, and ocular history.

Age in years will be calculated as the integer portion of the following:
[(Date of informed consent - Date of birth) + 1] / 365.25.

Other baseline measurements, such as baseline visual acuity, will be summarized by treatment group.

9.10 Medical, Ocular and Dry Eye History

Medical history terms and ocular history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and the number and percent of subjects with medical history will be summarized by (SOC) and Preferred Term (PT) for each treatment group based on the safety population.

In addition, the duration of ocular history and dry eye history will be summarized by treatment group and overall.

9.11 Treatment Exposure

Each randomized subject will receive an application of OC-01 (varenicline) Nasal Spray or placebo twice daily (BID) for 28 days. Duration of exposure to study treatment, in days, will be summarized for all randomized subjects. Summary statistics for duration of exposure will be presented by visit and treatment group.

10 Ocular Assessments

Ocular assessments will occur at baseline and post-baseline study visits. The results, grade, clinical significance, and relatedness to administration procedure and study drug, will be listed, summarized in tables, and presented in figures as appropriate.

10.1 Schirmer's Test

The Schirmer's Test with topical anesthetic will be performed to assess tear production at the Screening Visit (Visit 1). This first Schirmer's Test, which should be performed after corneal fluorescein staining, will be used as the baseline Schirmer's Test score. A second anesthetized Schirmer's Test with nasal stimulation using cotton swab will occur 10 minutes after the first anesthetized Schirmer's Test. Additional Schirmer's Tests with topical anesthetic will be assessed after the first treatment at Visit 1. At Week 2 (Visit 3), Week 4 (Visit 4b), the Schirmer's Tests will be performed concurrent with treatment.

10.2 Eye Dryness Score (EDS)

The Eye Dryness Score (EDS) will be assessed using a Visual Analog Scale (VAS). Subjects score EDS at Screening (Visit 1), Day 7 (Visit 2), Week 2 (Visit 3), Week 4 (Visit 4; pre-CAE®), Week 4 in the CAE® chamber (Visit 4a; pre-treatment followed by post-treatment

every 5 minutes within the CAE® for a total of 120 minutes), Week 4 (Visit 4b), and Early Termination (if necessary). At Visit 4, EDS from multiple time points and change in EDS from pre- to post-treatment will be collected and summarized by CAE exposure period and by treatment group. Participants will be asked to rate their ocular symptoms (both eyes simultaneously).

Some subjects did not meet the criterion of receiving a study drug during CAE® exposure (Ocular Discomfort score ≥ 3 at two or more consecutive time points in at least one eye during CAE® exposure). For such subjects, the EDS collected during CAE® exposure will be treated as missing and the EDS prior to entering CAE® will be carried forward to impute the missing EDS during CAE® exposure.

10.3 BCVA

Best corrected visual acuity (BCVA) will be performed and collected at Screening (Visit 1), Day7 (Visit 2), Week 2 (Visit 3), Week 4 (Visits 4a (pre-CAE) and 4b), and Early Termination (if necessary). Visual function of the study and fellow eye will be assessed starting at 10 feet using the best corrected ETDRS protocol. Visual acuity examiners must be certified to ensure consistent measurement of BCVA. 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 performed consistently using the same lighting conditions and same correction, if possible, during the entire study. If the same correction cannot be used (e.g., a subject broke his/her glasses), the reason for the change in correction should be documented. BCVA will be summarized by visit and by treatment group for both study and fellow eyes.

10.4 [redacted] Ocular Discomfort Scale

The [redacted] Ocular Discomfort Scale (ODS) will be collected at Screening (Visit 1) and Week 4 (Visit 4a; pre-CAE and post-CAE). Subjects will grade themselves on the ODS with scores from 0 to 4 to indicate the level of discomfort: 0 corresponds to "No discomfort", 1 to "Intermittent awareness", 2 to "Constant awareness", 3 to "Intermittent discomfort", and 4 to "Constant discomfort". The ODS collected at Visit 4a will be used to determine treatment administration. Treatment of study drug will be administered when a participant reports an ODS ≥ 3 at two or more consecutive time points in at least one eye during CAE exposure (subjects with an ODS of 3 at time 0 for an eye must report an ODS of 4 for two consecutive measurements for that eye) using the Ora Calibra Scale. ODS will be summarized by visit, pre-CAE and every 5 minutes in CAE at Visit 4, and treatment group for both study and fellow eyes.

10.5 Ocular Surface Disease Index (OSDI)

The OSDI will be collected at screening. The protocol provides the questionnaire, calculation, and details of categorization. The OSDI score will be summarized by treatment

with quantitative descriptive statistics (n, mean, median, standard deviation, 25th quartile, 75th quartile, minimum, and maximum).

10.6 Corneal Fluorescein Staining

Corneal fluorescein staining will be performed and data will be collected at Screening (Visit 1), Week 4 (Visit 4b), and Early Termination (if necessary). Corneal fluorescein staining will be assessed for both the study and fellow eye. Staining will be graded using the National Eye Institute (NEI)/Industry Workshop Scale. Examiners will score each of five areas on the cornea of each eye: 1 – Central; 2 – Superior; 3 – Temporal; 4 – Nasal; 5 – Inferior. A standardized grading system of 0-3 will be used for each of the five areas. The corneal fluorescein staining score will be described by visit, treatment, study eye, and fellow eye with summary statistics. Specifically, scores will be presented by each of the five cornea areas and total scores for all corneal areas.

10.7 Slit Lamp Biomicroscopy

The slit lamp biomicroscopy will be performed at Screening (Visit 1, pre-and post-treatment procedures), Day 7 (Visit 2), Week 2 (Visit 3), Week 4 (Visit 4b, pre-and post-treatment procedures), Week 6 (Visit 5), Week 24 (Visit 6), Week 48 (Visit 7), and Early Termination (if necessary). A slit lamp will be used for external examination and biomicroscopy. The eyelids, cornea, conjunctiva, anterior chamber, iris, and lens will be examined at each visit. Slit lamp biomicroscopy results will be summarized for each treatment group for the study and fellow eye by visit using discrete summary statistics. Abnormal clinically significant findings will be described. Shifts from baseline including normal to abnormal (not clinically significant), and normal to abnormal (clinically significant) will be presented using counts and percentages

11 Intranasal Examination

Intranasal assessments collected at Screening (Visit 1), Day 7 (Visit 2), Week 4 (Visit 4b), and Early Termination (if necessary) will be summarized by treatment group with counts and percentages. Shifts from baseline of normal to abnormal (not clinically significant) and normal to abnormal (clinically significant) will be presented using counts and percentages.

[redacted]

12 Efficacy Analysis

[redacted]

Table 1. Hierarchical order of hypothesis testing

OC-01 Nasal Spray, 0.6 mg/mL vs. placebo	OC-01 Nasal Spray, 1.2 mg/mL vs. placebo
Primary endpoint	
[redacted]	[redacted]
Secondary endpoints	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
…..	…..
[redacted]	[redacted]

Footnote:

1. [redacted]

[redacted]

12.1 Primary Endpoint

[redacted]

12.2 Secondary Efficacy Endpoints

[redacted]

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[redacted]

[redacted]

Table 2 Closed Testing Procedure Example

[redacted]

[redacted]

12.3 Exploratory Analyses

[redacted]

12.4 Handling Missing Efficacy Data

[redacted]

[redacted]

13 Safety Analysis

The safety population will be used for all safety analyses. All recorded safety parameters will be listed by treatment, subject ID and visit or visit date.

13.1 Adverse Events

The investigator will promptly review each Adverse Event (AE) for accuracy and completeness, and classify each AE according to its intensity, its relationship to study drug or administration procedure, and its seriousness. AEs will be coded using version 22.0 of the MedDRA dictionary. AEs will be monitored throughout the study and documented on the appropriate AE form. AEs will be categorized as ocular and non-ocular events as well as by system organ class (SOC) and preferred term (PT), seriousness, severity, and relation to study medications.

All treatment-emergent adverse events (TEAEs) will be summarized. A TEAE is defined as an AE that is new or worsened in severity compared to the first dose of study drug. All AEs will be presented in data listing with a flag indicating the event is a TEAE.

TEAEs will be summarized by subject. In addition, the number of TEAE episodes that occurred during the study will be provided in the overall summary of AE table.

The following presentations of TEAEs will be generated:

- Overall adverse events summary (including any TEAEs, ocular TEAEs, resolved ocular TEAEs, non-ocular TEAEs, ocular TEAEs, non-ocular TEAEs, SAEs, treatment- emergent SAEs, treatment-related treatment emergent SAEs, TEAEs by maximum severity, TEAEs by relationship to study drug, AEs leading to treatment/study discontinuation);
- Serious adverse events (SAE) by SOC and PT;
- All ocular TEAEs by SOC and PT;
- All non-ocular TEAEs by SOC and PT;
- TEAEs leading to treatment discontinuation.
- TEAEs leading to study discontinuation.

13.2 Prior and Concomitant Medications

[redacted]

Table 3 describes the classification of prior and concomitant medications.

Table 3 Classification of prior and concomitant medications

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

14 Subgroup Analyses

[redacted]

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[redacted]

Appendix 1 Schedule of Visits and Measurements

Procedure	Screen/ Visit 1 Day 1	Day 2-6	Visit 2 Day 7 ±2	Day 8-13	Visit 3 Week 2 Day 14 ±3	Day 15-27	Visit 4 Week 4 Day 28 ±4			Visit 5 Week 6 Day 42 ± 3	Visit 6 Week 24 Day 168 ±7	Visit 7 Week 48 Day 336 ±7	ET
							Visit 4a		Visit 4b (+3 days of 4a)				
							Pre-CAE®	Peri-CAE®	Schirmer's Test Evaluation				
Informed consent/HIPAA	X												
Demographics	X												
Medical history, prior medication(s), ocular history and updates	X												
Eligibility criteria	X												
Urine pregnancy test	X[1]						X[1]					X[1]	X[1]
OSDI© questionnaire	X												
Eye Dryness Score (EDS)	X		X		X		X	X[4]	X[6]				X
[redacted] Ocular Discomfort Scale	X						X	X[4]					
BCVA	X[2]		X		X[2]		X		X[2]				X
Slit lamp biomicroscopy	X[2]		X		X[2]				X[2]	X	X	X	X
Corneal fluorescein staining	X								X[6]				X
Schirmer's test	X[2]				X				X[5]				
Schirmer's test with cotton swab Stimulation	X												
Intranasal examination	X[2]		X						X[2]	X	X	X	X
Randomization	X												
Administer investigational drug / Placebo	X[3]	X		X	X[3]	X		X	X[3]				
Diary Completion		X		X		X							

[redacted]

Dispense investigational drug / placebo	X				X		X						
Concomitant medications	X		X		X		X		X	X	X	X	X
AE Query	X		X		X		X		X	X	X	X	X

X^1 = For females of childbearing potential; X^2 = Pre- and Post-treatment procedures; X^3 = Concurrent with Schirmer's Test; X^4 = Procedure started at time 0 and then conducted every 5 minutes thereafter during the 120 minute CAE® exposure; X^5= At Visit 4, Schirmer's Test Evaluation and CAE® procedures should be performed on different days within the visit window. The Schirmer's Test Evaluation and all assessments should be performed after the CAE® visit assessment. X^6- Post Treatment Procedures. ET=Early Termination

[redacted]

Appendix 2 Analysis for secondary efficacy endpoints with multiple imputation

[redacted]

1. **Exhibit 1. Sample SAS code for assessing missing data patterns**

[redacted]

[redacted]

Study OPP-101 SAP Addendum for Efficacy Analysis Based on Impact from COVID-19

The ONSET-2 study has randomized 758 subjects in all. The final group of 103 subjects at three of the 22 clinical centers in the ONSET-2 study (Center 45, 8 subjects; Center 48, 65 subjects, Center 51, 30 subjects) had some missing data for select efficacy endpoints due to the COVID-19 pandemic. These missing data are, from a statistical point of view, "missing at random" because of the COVID-19 pandemic, not the status of their dry eye disease, led to their missing data. We intend to use all available data for the statistical analyses; specifically, we will use data from all of centers for each primary and secondary endpoint where COVID-19 did not impact study visits.

The pandemic had different effects on the three centers: Center 45 was not able to complete Visit 4a; Center 48 was not able to complete Visits 4a and 4b (although was able to collect Corneal Fluorescein Staining as well as EDS symptom data captured remotely); Center 51 was not able to complete Visit 4b (although was able to collect EDS symptom data remotely). Therefore, in Addendum Table 1 below, we display all primary and secondary efficacy endpoints, and for each, its relevant modified ITT population (original ITT population or modified ITT [mITT] population, mITT-1, mITT-2, or mITT-3).

Each of these three modified ITT populations is defined by which centers are excluded because COVID-19 impacted them.

[redacted]

Addendum Table 1: Summary of Efficacy Endpoints and Relevant ITT Population

Endpoint	Endpoints impacted by COVID-19	ITT Population	Site(s) excluded from the population
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]