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

**Protocol Number:** OPP-001
**Version:** 1.0
**Date:** 10-May-2018

**Statistical Analysis Plan Approval**

**Prepared by:** [redacted] [redacted]
Date

**Reviewed by:** [redacted]
Date

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**Approved by:** [redacted]
Date

**Approved by:** [redacted]

[redacted]

[redacted]

# STATISTICAL ANALYSIS PLAN

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

Sponsor: Oyster Point Pharma, Inc.
700 Alexander Park Dr., Suite #301
Princeton, NJ 08540

Protocol Number: OPP-001

Author: [redacted]

Date: 10-May-2018

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**Prepared by:** [redacted]

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[redacted]

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[redacted]

## List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| ATC | Anatomical Therapeutic Chemical Classification |
| BCVA | Best Corrected Visual Acuity |
| CAE | Controlled Adverse Environment |
| CDVA | Corrected Distance Visual Acuity |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CS | Clinically Significant |
| CSR | Clinical Study Report |
| DED | Dry Eye Disease |
| eCRF | Electronic Case Report Form |
| EDS | Eye Dryness Score |
| ETDRS | Early Treatment of Diabetic Retinopathy Study |
| HIPAA | Health Information Portability and Accountability Act |
| ICH | International Conference on Harmonisation |
| IP | Investigational Product |
| ITT | Intent-to-Treat |
| logMAR | Logarithm of the Minimum Angle of Resolution |
| LS | Least Squares |
| MCMC | Markov Chain Monte Carlo |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple Imputation |
| MMRM | Mixed-effect Model Repeated Measures |
| NCS | Not Clinically Significant |
| NEI | National Eye Institute |
| PDF | Portable Document Format |
| PMM | Pattern Mixture Model |
| PP | Per Protocol |
| PT | Preferred Term |
| RTF | Rich Text Format |
| SAAS | Software-as-a-Service |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| [redacted] | [redacted] |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| TEAE | Treatment-Emergent Adverse Event |
| TE-SAE | Serious Treatment-Emergent Adverse Event |

| | |
|---|---|
| VA | Visual Acuity |
| WHO DDE | World Health Organization Drug Dictionary Enhanced |

## 1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol OPP-001, dated 11OCT2017.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the CSR.

## 2. Study Objectives

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

## 3. Study Variables

### 3.1 Efficacy Measures

The primary efficacy measures are:

- Schirmer's Test at Visit 1
- Eye Dryness Score (EDS) at Visit 2

An additional efficacy measure is the [redacted] Ocular Discomfort Scale at Visit 2.

### 3.2 Safety Measures

The safety measures include the following:

- Adverse Event (AE) query
- Visual Acuity
- Slit-lamp biomicroscopy
- Intranasal examination
- Pupil diameter

### 3.3 Other Measures

Other measures include the urine pregnancy test (if applicable).

### 3.4 Statistical Hypotheses

The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided.

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

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

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

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

A successful outcome will be one that rejects both null hypotheses ($H_{01}$ and $H_{02}$), although these hypotheses are exploratory as the study-wide Type I and II errors are not controlled.

## 4. Study Design and Procedures

### 4.1 General Study Design

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

OC-02 nasal solution is delivered as a 100 microliter (µL)-intranasal spray in each nostril. The subjects will be randomized to one of the following treatment arms:

- 0.11% OC-02 (0.2% hemigalactarate salt) [low dose]
- 0.55% OC-02 (1.0% hemigalactarate salt) [medium dose]
- 1.1% OC-02 (2.0% hemigalactarate salt) [high dose]
- Placebo (OC-02 Vehicle Nasal Spray)

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.

The Sponsor, Investigators, and study staff will be masked during the randomization process and throughout the study.

Study visits will be referred to in all tables and listings as the expected study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. The following table shows the scheduled study visits, their planned study day (note that there is no Day 0 and that Day 1 corresponds to the day of randomization), and the acceptable visit window for each study visit:

| Scheduled Visit | Planned Study Day | Visit Window |
|---|---|---|
| Visit 1 | Day 1 | NA |
| Visit 2 | Day 15 | + 4 |

### 4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.

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

| | | | | |
|---|---|---|---|---|
| Randomization | | X | | |
| Administer investigational drug / placebo | | $X_2$ | X | |
| AE Query | X | $X_1$ | X | X |
| Exit from study | | | | X |
| **$X_1$** = Post-treatment procedures; **$X_2$** = Concurrent with Schirmer's Test; **$X_3$** = For females of childbearing potential; **$X_4$** = Procedure started at time 0 and then conducted every 5 minutes thereafter during the 120 minute CAE® exposure; **$X_5$** = Procedure may be performed after CAE® exit at the Investigator's discretion as needed | | | | |

## 5. Study Treatments

### 5.1 Method of Assigning Subjects to Treatment Groups

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

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

### 5.2 Unmasking

All subjects, Investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the Investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), [redacted] and/or the Sponsor should be notified before unmasking study drug. Scratch off labels will be used to facilitate unmasking. The unmasked subject will be discontinued from the study.

## 6. Sample Size and Power Considerations

[redacted]

[redacted]

## 7. Data Preparation

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

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

## 8. Analysis Populations

Analysis populations include the intent-to-treat (ITT) population, the per-protocol (PP) population, and the Safety population. The statistical analysis of safety data will be performed for the safety population. The analysis of baseline and efficacy data will be performed for the ITT population. Efficacy analyses will also be performed for the PP population as sensitivity analyses.

### 8.1 Intent-to-Treat

The ITT population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized.

### 8.2 Per Protocol

The PP population includes subjects in the ITT population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.

[redacted]

### 8.3 Safety

The Safety population includes all randomized subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

## 9. General Statistical Considerations

### 9.1 Unit of Analysis

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

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

### 9.2 Missing or Inconclusive Data Handling

[redacted]

### 9.3 Definition of Baseline

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

### 9.4 Data Analysis Conventions

All data analysis will be performed by Statistics & Data Corporation (SDC) after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in RTF (Rich Text Format) for tables and PDF (Portable Document Format) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, and visit (as applicable) based on all enrolled subjects unless otherwise specified.

All summaries will be presented by treatment group. Summaries will be provided for demographics, medical history, concomitant medications, and subject disposition. For the purpose of summarization, medical history, concomitant medications, and AEs will be coded to Medical Dictionary for Regulatory Activities (MedDRA) 20.1 and World Health Organization (WHO) Drug Global Dictionary (Enhanced B3, September 2017), as appropriate.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%).

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence levels where appropriate. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999".

### 9.5 Adjustments for Multiplicity

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

## 10. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, completed the study, and discontinued from the study. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and for all subjects.

The number of randomized subjects in each of the analysis populations (ITT, PP and Safety) will be displayed by treatment. The ITT population uses treatment as randomized; PP and Safety populations use treatment as treated. Percentages are based on the total number of subjects randomized in each treatment group.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all randomized subjects. The reasons for study discontinuation that will be summarized include: AE, protocol violations, administrative reasons (e.g., inability to continue, lost to follow up), sponsor termination of study, subject choice, and other. In addition, any subject may be discontinued for any sound medical reason at the discretion of the Investigator (after consultation with the Sponsor) or Sponsor. A subject listing will be provided that includes the date of and reason for premature study discontinuation.

The number and percentage of subjects with any, major, and minor protocol deviations will be summarized by treatment group for all randomized subjects. The number and percentage of subjects with any protocol deviation will also be summarized for the following categories: Informed Consent, Inclusion / Exclusion and Randomization, Test Article / Study Drug Instillation and Assignment at Site, Improper Protocol Procedures at Site, Site's Failure to Report SAE / AE, Visit Out of Window, Subject's Non-compliance with Test Article, Subject's Use of Prohibited Concomitant Medication, Subject's Failure to Follow Instructions, and Other. A subject listing will be provided that includes the date and description of each deviation.

In addition, subject listings will be provided that include randomization and treatment; whether inclusion and exclusion criteria were met; and inclusion in the ITT, Safety, and PP populations.

## 11. Demographic and Pretreatment Variables

### 11.1 Demographic Variables

The demographic variables collected in this study include age, sex, race, ethnicity and iris color. Demographic variables will be summarized, overall and by treatment group, for the ITT and Safety populations, separately.

Age (years) will be summarized using continuous descriptive statistics. Age will also be categorized as follows: <65 years and ≥65 years. Age will be reported in years and calculated using the following formula:

Age = (informed consent date – date of birth) / 365.25 truncated as an integer

The number and percentage of subjects will be presented for age category, sex, race, ethnicity and iris color. Iris color will be summarized for the right eye (OD) and left eye (OS) separately.

A subject listing that includes all demographic variables for all randomized subjects will be provided.

### 11.2 Baseline Variables

Baseline disease characteristics will be summarized by treatment group for the study eye (where applicable) using continuous descriptive statistics for basal Schirmer's test, Schirmer's test with cotton swab stimulation, EDS, ocular discomfort score, total OSDI© score, corneal fluorescein staining, BCVA and pupil diameter. The scales for OSDI, corneal fluorescein staining and Schirmer's test with cotton swab stimulation are described below. The scales for the efficacy endpoints of Schirmer's test, EDS, and ocular discomfort score are provided in the respective subsections in Section 14 of this SAP. The scales for the safety endpoints of BCVA and pupil diameter are provided in the respective subsections in Section 15 of this SAP.

[redacted]

#### 11.2.1 OCULAR SURFACE DISEASE INDEX©

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The OSDI© asks the following 12 questions at the subject level:

Have you experienced any of the following during the last week:

1) Eyes that are sensitive to light?
2) Eyes that feel gritty?
3) Painful or sore eyes?
4) Blurred vision?
5) Poor vision?

Have problems with your eyes limited you in performing any of the following during the last week:

6) Reading?
7) Driving at night?
8) Working with a computer or bank machine (ATM)?
9) Watching TV?

Have your eyes felt uncomfortable in any of the following situations during the last week:

10) Windy conditions?
11) Places or areas with low humidity (very dry)?
12) Areas that are air conditioned?

OSDI© will be collected for both eyes pre- treatment at Visit 1. The 5-unit scale for responses to the OSDI© is given by the following: 0=None of the time, 1=Some of the time, 2=Half of the time, 3=Most of the time and 4=All of the time. The total OSDI© score is calculated by the following:

$$\text{OSDI©} = \frac{(\text{sum of scores}) \times 25}{\#\text{ of questions answered}}$$

Note that the number of questions answered in the denominator should exclude those questions with a response of “N/A”.

#### 11.2.2 CORNEAL FLUORESCEIN STAINING

Corneal fluorescein staining will be performed on both eyes and graded using the National Eye Institute (NEI)/Industry Workshop Scale. The scale will grade the cornea by five regions: inferior, superior, central, temporal, and nasal. The scale ranges from 0 to 3. Grade 0 indicates no staining is present. The maximum total score is 15.

Fluorescein staining scores will be summarized by region (5 regions, plus total score) for the study eye using quantitative summary statistics.

#### 11.2.3 SCHIRMER'S TEST WITH COTTON SWAB STIMULATION

Schirmer's test with cotton swab stimulation will be performed on both eyes. Schirmer's scores are between 0 mm and 35 mm, inclusive. The result will be summarized for the study eye using quantitative summary statistics.

## 12. Medical History and Concomitant Medications

### 12.1 Medical History

Medical history will be coded using MedDRA Version 20.1.

Ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. Non-ocular medical history will be similarly summarized at the subject and event level. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

Listings of medical history will be generated separately for ocular and non-ocular data.

### 12.2 Prior and Concomitant Medications

Concomitant medications are defined as those medications listed as having been taken 1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or 2) at any time following the first administration of study drug.

Concomitant medications will be coded using WHO Drug Global B3 Dictionary September 2017 and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (eg, multivitamins) then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of "Uncoded."

Concomitant medications will be summarized using the ITT population. Prior medications will be provided in subject listings, but will not be summarized. Ocular and non-ocular medications will be summarized separately. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than 1 medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant medications will be generated separately for ocular and non-ocular data.

[redacted]

## 13. Treatment Exposure

### 13.1 Treatment Exposure

Percent exposure (%) will be assessed by calculating the volume of dose administered and comparing that to the volume expected as follows:

$$\text{Percent Exposure (\%)} = \frac{\text{Volume Administered (µL)}}{\text{Volume Expected (µL)}} \times 100\%$$

The volume administered will be calculated by adding the volume administered in the left and right nostrils in µL Visits 1 and 2. The volume expected at each visit is 200 µL (100 µL in each nostril) and hence the volume expected is 400 µL for subjects that complete the study and 200 µL for subjects that discontinue prior to Visit 2.

Volume of study drug administered and volume expected for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group, using the Safety population. The number and percentage of subjects with percent exposure ≤ 80% and > 80% will also be summarized by treatment group. A subject listing of percent exposure, volume administered, and volume expected will also be produced.

## 14. Efficacy Analyses

### 14.1 Primary Analysis

The two primary endpoints are:

- Schirmer's Test results at Visit 1
- Eye Dryness Score during Controlled Adverse Environment® (CAE®) at Visit 2

For both primary endpoints, treatment comparisons between active and placebo will be calculated as active – placebo. For Schirmer's Test, a positive difference indicates a better score for the active treatment. For EDS, a negative difference indicates a better score for the active treatment.

#### 14.1.1 SCHIRMER'S TEST

Schirmer's test with topical anesthesia will be performed pre- and post-treatment at Visit 1. Schirmer's test result will be summarized by time point (pre- and post-treatment at Visit 1), and treatment with quantitative descriptive statistics (n, mean, median, standard deviation, minimum and maximum).

[redacted] model will be used to compare the change in Schirmer's Test pre- to post-treatment in the study eye between each dose of OC-02 Nasal Spray and placebo treatment groups. The [redacted] model will include baseline Schirmer's Test (captured at Screening) and study

site as covariates. Least Squares Means (LS Means) for each treatment, the corresponding 95% confidence intervals (CI), and the estimated treatment differences between each dose of OC-02 Nasal Spray and placebo will be calculated from this [redacted] model. In addition, the study site by treatment interaction will be explored in a separate model to evaluate how the treatment effect may differ across study sites. In the case of a significant interaction at the 0.05 level, analyses will be performed by site to understand how the treatment effect differs across sites. The differences in means, two-sided 95% CIs for the difference in means and p-values will be reported. Pairwise t-tests from the ANCOVA model will be used to compare treatment and placebo groups.

The primary analyses will be performed on the ITT population on observed data only. The SAS code for the analysis is:

[redacted]

[redacted] analysis estimates of pre- to post-treatment changes will be displayed in a bar chart with standard error bars by treatment group. Two sample t-tests and non-parametric Wilcoxon rank sum tests will be used to compare treatments as unadjusted sensitivity analyses. The number and percentage of subjects with a greater than 10 mm and greater than 20 mm increases relative to baseline will also be reported by treatment group. The percentage of subjects in each treatment group will be compared using Fisher's Exact Test. Sensitivity analyses will also be performed on the ITT population with multiple imputation (MI) to impute missing data, as well as the PP population with observed data only.

The multiple imputation sensitivity analysis will use MCMC imputation to have a full accounting of the ITT population at Visit 1. The MCMC method will be performed using the SAS procedure PROC MI. The SAS code for obtaining multiple imputation data is:

[redacted]

After obtaining twenty complete data sets and calculating changes from baseline, the following SAS code will be used to run the [redacted] model on each data set and combine the results from the twenty analyses:

[redacted]

[redacted]

Schirmer's test will also be analyzed in the fellow eye using the ITT and PP populations with observed data only.

Stratified analyses of Schirmer's test will include [redacted] analysis, t-tests and Wilcoxon rank sum tests using the ITT population with observed data only, in the study eye and fellow eye, separately. The following strata will be used:

- Inferior corneal staining < 1.5
- Inferior corneal staining ≥ 1.5
- Baseline EDS < 60
- Baseline EDS ≥ 60

#### 14.1.2 Eye Dryness Score as the Primary Analysis

Eye dryness will be assessed pre-treatment at Visit 1, pre-CAE at Visit 2, and every 5 minutes during CAE® exposure at Visit 2. For each assessment, the participant will be asked to rate their ocular symptoms (both eyes simultaneously) due to eye dryness by placing a vertical mark on a 100 mm horizontal line to indicate the level of discomfort; 0 corresponds to "no discomfort" and 100 corresponds to "maximal discomfort".

Treatment with study drug will be administered upon the participant reporting an Ocular Discomfort ([redacted]Scale) score ≥ 3 at two or more consecutive timepoints in at least one eye during CAE® exposure. If a participant has an Ocular Discomfort rating of 3 at time = 0 for an eye, s/he must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye. Participant will resume symptom assessments 1 minute after the application ends every five minutes.

The primary analysis will be a one-timepoint analysis in which the pre-treatment EDS will be the EDS at the timepoint that the subject first qualifies for study drug administration during the CAE® and post-treatment EDS will be the EDS at the first timepoint following qualification. If a participant fails to qualify

for study drug administration, the timepoint of qualification and the pre-treatment and post-treatment EDS will be missing.

Eye dryness score will be summarized by visit, timepoint, and treatment with quantitative descriptive statistics (n, mean, median, standard deviation, minimum and maximum).

The change in EDS from pre- to post-treatment will be analyzed using an [redacted] model with pre-treatment EDS and timepoint of qualification for study drug administration as covariates and with treatment as a fixed effect. LS means for each treatment, the corresponding 95% CIs, and the estimated treatment difference between each dose of OC-02 Nasal Spray and placebo will be calculated from this [redacted] model. A study site by treatment interaction will also be explored in a separate model to evaluate how the treatment effect may differ across study sites. In the case of a significant interaction at the 0.05 level, analyses will be performed by site to understand how the treatment effect differs across sites. The differences in means, two-sided 95% confidence intervals (CI) for the difference in means and p-values will be reported. Pairwise t-tests from the [redacted] model will be used to compare treatment and placebo groups.

The primary analyses will be performed on the ITT population on observed data only. SAS code for the [redacted] analysis will resemble the SAS code for Schirmer's test. [redacted] analysis estimates of pre- to post-treatment changes will be displayed in a bar chart with standard error bars by treatment group. Two sample t-tests and non-parametric Wilcoxon rank sum tests will be used to compare treatments as unadjusted sensitivity analyses. Sensitivity analyses will also be performed on the ITT population using MCMC to impute missing data, as well as the PP population with observed data only.

[redacted]

[redacted]

[redacted]

[redacted]

### 14.2 Other Efficacy Analyses

The continuous variables for the other efficacy analyses will be summarized descriptively (n, mean, standard deviation, median, min and max) at the pre-treatment at Visit 1 and by timepoint during the CAE® exposure at Visit 2. Changes from pre- to post-treatment will also be summarized descriptively by timepoint (based on the change in timepoint from the pre-treatment assessment to the respective post-treatment assessment) at Visit 2 and treatment group. No imputation will be performed for secondary efficacy variables. Analyses will be performed on the ITT and PP populations with observed data only. All exploratory measures will also be presented in subject listings.

The following secondary efficacy endpoints will be tested:

- Eye Dryness Score throughout CAE®
- Ora Calibra® Ocular Discomfort Scale;

#### 14.2.1 Eye Dryness Score

Change from pre- to post-treatment in EDS will be analyzed at each individual timepoint (based on the timepoint from the pre-treatment assessment to the respective post-treatment assessment) in a manner similar to the primary analysis for EDS given in section 14.1.2. ANCOVA models will be used that include pre-treatment EDS, timepoint of qualification, treatment and study site as covariates. ANCOVA analysis estimates of pre- to post-treatment changes will be displayed graphically by timepoint in a line plot by treatment group. Two sample t-tests and non-parametric Wilcoxon rank sum tests will be used to compare treatments as unadjusted sensitivity analyses.

The change from pre- to post-treatment in EDS will also be analyzed in a three-timepoint analysis by subtracting for each subject the average EDS at the three timepoints following the timepoint of qualification (post-treatment average) from the average EDS at the three most recent timepoints at or prior to the timepoint of qualification (per-treatment average). This pre- to post-treatment average change in EDS will be analyzed using an ANCOVA model with pre-treatment average EDS and timepoint of qualification for study drug administration as covariates and with treatment as a fixed effect. LS means for each treatment, the corresponding 95% CIs, and the estimated treatment difference between each dose of OC-02 Nasal Spray and placebo will be calculated from this ANCOVA model. ANCOVA analysis estimates of pre- to post-treatment average change will be displayed in a bar chart with standard error bars by treatment group. The differences in means, two-sided 95% confidence

intervals (CI) for the difference in means and p-values will be reported. Pairwise t-tests from the [redacted] model will be used to compare treatment and placebo groups.

A [redacted] model will also be used as an additional analysis of change from pre- to post-treatment in EDS. This model will include site, treatment, timepoint, and the interaction between treatment and timepoint as fixed effects, and subject as a random effect. This model will also include a fixed effect for the duration between a post-treatment timepoint and the timepoint of qualification, and the interaction of this duration variable with treatment. The duration variable will be defined as zero for all pre-treatment timepoints and durations greater than 60 minutes will be pooled together. Thus the variable will be treated as discrete, with possible values 0 minutes, 5 minutes, …, 60 minutes, and 60+ minutes. An unstructured covariance matrix will initially be used to model the covariance among repeated measures; however, if the model fails to converge using this covariance structure, either heterogeneous TOEPLITZ, homogeneous TOEPLITZ, or compound symmetry will be implemented according to the Akaike information criterion with a correction for finite sample sizes (AICc).

[redacted]

RU

Estimates of pre- to post-treatment changes will be displayed graphically by duration in a line plot by treatment group.

#### 14.2.2 [redacted] Ocular Discomfort Scale

Ocular discomfort scores will be subjectively graded by the subjects using the [redacted] Ocular Discomfort Scale at pre-treatment Visit 1 and at various timepoints during the CAE® exposure at Visit 2, immediately upon entering the chamber and every 5 minutes thereafter for the duration of the 120 minute exposure. The ocular discomfort scale ranges from 0 to 4 where 0 = no discomfort, 1 = intermittent awareness, 2 = constant awareness, 3 = intermittent discomfort, and 4 = constant discomfort.

[redacted] Ocular Discomfort Scale results will be summarized by timepoint at Visit 2 and treatment with quantitative descriptive statistics. Change from pre- to post-treatment in [redacted] Ocular Discomfort Scale results will also be summarized by timepoint (based on the timepoint from the pre-treatment assessment to the respective post-treatment assessment) at Visit 2 and treatment group with quantitative descriptive statistics in a manner similar to EDS. [redacted] models will be used that include pre-treatment ocular discomfort, timepoint of qualification, treatment and study site as covariates. [redacted] analysis estimates of pre- to post-treatment changes will be displayed graphically by timepoint

in a line plot by treatment group. Two sample t-tests and non-parametric Wilcoxon rank sum tests will be used to compare treatments as unadjusted sensitivity analyses.

## 15. Safety Analyses

All safety analyses will be conducted using the Safety population.

### 15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (eg, 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. All AEs will be coded using MedDRA Version 20.1.

Treatment-emergent adverse events (TEAEs) are defined as any AE that occurs or worsens after the first dose of study treatment. AEs recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

An overall summary will be presented that includes the number of AEs, TEAEs, serious AEs (SAE), and serious TEAEs (TE-SAE). The summary will also include the number and percentage of subjects withdrawn due to an AE, the number and percentage of subjects with an AE resulting in death, and the number and percentage of subjects who experienced at least one AE, TEAE, SAE and TE-SAE, by treatment group and for all subjects. This summary will include breakdowns of AEs further categorized as ocular or non-ocular.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by SOC and PT. Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject and event level as well as for study and fellow eyes separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in order of descending frequency for all subjects; PTs will be listed in order of descending frequency for all subjects within each SOC. The occurrence of non-ocular and ocular TEAEs will also be tabulated by SOC, PT, and maximal severity.

The relationship of each adverse event 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.

All possible, probable, and definite TEAEs are considered as treatment-related TEAEs.

Separate summaries will be provided for the following categories of AEs:

- Ocular TEAEs
- Non-ocular TEAEs
- Treatment-related ocular TEAEs
- Treatment-related non-ocular TEAEs
- SAEs

Severity of an adverse event is defined as a qualitative assessment of the degree of intensity of an adverse event 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.

Summaries of TEAEs by maximal severity will be presented for ocular AEs and non-ocular AEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximal severity.

All AEs will be presented in a subject listing that classifies each AE as ocular or non-ocular and indicates whether it is a TEAE. Separate listings will be produced for AEs leading to study discontinuation, AEs leading to death and SAEs.

### 15.2 Best-Corrected Visual Acuity (BCVA)

The visual acuity procedure will be performed at pre- and post-treatment at Visit 1 and may be performed post-CAE® at Visit 2 at the Investigator's discretion as needed. The logarithm of the minimum angle of resolution (logMAR) VA must be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Subjects should use their most recent correction to attain their corrected distance visual acuity (CDVA).

The observed and change from baseline visual acuity will be summarized for each eye (study eye and fellow eye) using continuous descriptive statistics by visit for each treatment group. A subject listing of visual acuity will also be produced. This listing will also include values used in the calculation of BCVA including base logMAR, which is the last line in which a letter is read correctly, N, which is the number of letters missed up to and including the last line read, and T, which is a multiplier equal to 0.02.

### 15.3 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, lid, motility and pupil will be performed at pre- and post-treatment at Visit 1 and may be performed post-CAE® at Visit 2 at the Investigator's discretion as needed. The results will be graded as Normal, Abnormal Not Clinically Significant (NCS) or Abnormal Clinically Significant (CS). Abnormal findings will be described.

The results will be summarized using counts and percentages for each treatment group at each visit for each eye (study eye and fellow eye). Percentages will be based on the number of subjects in each treatment group with responses. Shift tables for the slit-lamp biomicroscopy parameters will also be provided comparing post-treatment at Visit 1 and post-CAE® at Visit 2 to baseline. A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

### 15.4 Intranasal Examination

The intranasal examination will be performed as needed pre-treatment at Visit 1 and post-CAE® at Visit 2. The results in terms of Normal, Abnormal (NCS), and Abnormal (CS) will be summarized using counts and percentages for each treatment group for each nasal cavity (right and left). Percentages will be based on the number of subjects in each treatment group with responses. Shift tables will also be provided comparing results post-treatment at Visit 1 to pre-treatment at Visit 1. A subject listing will also be produced.

### 15.5 Pupil Diameter

Pupil diameter will be measured in mm pre- and post-treatment at Visit 1 and post-CAE® at Visit 2. The observed and change from baseline pupil diameter will be summarized for each eye (study eye and fellow eye) using continuous descriptive statistics by visit for each treatment group. A subject listing of pupil diameter will also be produced.

## 16. Other Analyses

### 16.1 Urine Pregnancy Test

The urine pregnancy test will be performed pre-treatment at Visit 1 and at Visit 2. A subject listing of urine pregnancy test results will be produced based on female subjects only.

## 17. Interim Analyses

There will be no interim analyses in this study.

## 18. Changes from Protocol-Stated Analyses

The [redacted] analysis of the EDS primary endpoint has been revised from a repeated measures [redacted] analysis to the analysis described herein. The [redacted] analyses of EDS and ocular discomfort during CAE® have been revised to include timepoint of qualification as a covariate. Analysis of pupil diameter as a safety endpoint has been added.

## 19. Revision History

Documentation of revision to the SAP will commence after approval of the Final version 1.0.

## 20. Tables

Tables that will be included in the topline delivery are shown in boldface font.

| Table Number | Title | Population |
|---|---|---|
| **TABLE 14.1.1** | **SUBJECT DISPOSITION** | **ALL RANDOMIZED SUBJECTS** |
| **TABLE 14.1.2.1** | **DEMOGRAPHICS** | **ITT** |
| TABLE 14.1.2.2 | DEMOGRAPHICS | SAFETY |
| **TABLE 14.1.3.1** | **BASELINE DISEASE CHARACTERISTICS (STUDY EYE)** | **ITT** |
| TABLE 14.1.3.2 | OCULAR MEDICAL HISTORY | ITT |
| TABLE 14.1.3.3 | NON-OCULAR MEDICAL HISTORY | ITT |

| Table Number | Title | Population |
|---|---|---|
| TABLE 14.1.4.1 | CONCOMITANT OCULAR MEDICATIONS BY TREATMENT GROUP, DRUG CLASS AND PREFERRED NAME | ITT |
| TABLE 14.1.4.2 | CONCOMITANT NON-OCULAR MEDICATIONS BY TREATMENT GROUP, DRUG CLASS AND PREFERRED NAME | ITT |
| **TABLE 14.2.1.1** | **SCHIRMER'S TEST IN STUDY EYE** | **ITT WITH ODO** |
| TABLE 14.2.1.2 | SCHIRMER'S TEST IN STUDY EYE | ITT WITH MCMC |
| TABLE 14.2.1.3 | SCHIRMER'S TEST IN STUDY EYE | PP WITH ODO |
| TABLE 14.2.1.4 | SCHIRMER'S TEST IN STUDY EYE BY SITE | ITT WITH ODO |
| TABLE 14.2.1.5 | SCHIRMER'S TEST IN STUDY EYE TIPPING POINT ANALYSIS | ITT WITH MCMC |
| TABLE 14.2.1.6 | SCHIRMER'S TEST IN STUDY EYE | ITT WITH PMM |
| TABLE 14.2.1.7 | SCHIRMER'S TEST IN STUDY EYE, INFERIOR CORNEAL STAINING SCORE < 1.5 | ITT WITH ODO |
| TABLE 14.2.1.8 | SCHIRMER'S TEST IN STUDY EYE, INFERIOR CORNEAL STAINING SCORE >= 1.5 | ITT WITH ODO |
| TABLE 14.2.1.9 | SCHIRMER'S TEST IN STUDY EYE, BASELINE EYE DRYNESS SCORE < 60 | ITT WITH ODO |
| TABLE 14.2.1.10 | SCHIRMER'S TEST IN STUDY EYE, BASELINE EYE DRYNESS SCORE >= 60 | ITT WITH ODO |
| **TABLE 14.2.1.11** | **SCHIRMER'S TEST IN FELLOW EYE** | **ITT WITH ODO** |
| TABLE 14.2.1.12 | SCHIRMER'S TEST IN FELLOW EYE | PP WITH ODO |
| TABLE 14.2.1.13 | SCHIRMER'S TEST IN FELLOW EYE, INFERIOR CORNEAL STAINING SCORE < 1.5 | ITT WITH ODO |
| TABLE 14.2.1.14 | SCHIRMER'S TEST IN FELLOW EYE, INFERIOR CORNEAL STAINING SCORE >= 1.5 | ITT WITH ODO |

| Table Number | Title | Population |
|---|---|---|
| TABLE 14.2.1.15 | SCHIRMER'S TEST IN FELLOW EYE, BASELINE EYE DRYNESS SCORE < 60 | ITT WITH ODO |
| TABLE 14.2.1.16 | SCHIRMER'S TEST IN FELLOW EYE, BASELINE EYE DRYNESS SCORE >= 60 | ITT WITH ODO |
| **TABLE 14.2.2.1** | **EYE DRYNESS SCORE ONE-TIMEPOINT ANALYSIS** | **ITT WITH ODO** |
| TABLE 14.2.2.2 | EYE DRYNESS SCORE ONE-TIMEPOINT ANALYSIS | ITT WITH MCMC |
| TABLE 14.2.2.3 | EYE DRYNESS SCORE ONE-TIMEPOINT ANALYSIS | PP WITH ODO |
| TABLE 14.2.2.4 | EYE DRYNESS SCORE ONE-TIMEPOINT ANALYSIS BY SITE | ITT WITH ODO |
| TABLE 14.2.2.5 | EYE DRYNESS SCORE ONE-TIMEPOINT ANALYSIS TIPPING POINT ANALYSIS | ITT WITH MCMC |
| TABLE 14.2.2.6 | EYE DRYNESS SCORE ONE-TIMEPOINT ANALYSIS | ITT WITH PMM |
| TABLE 14.2.3.1 | EYE DRYNESS SCORE DURING CAE BY TIMEPOINT | ITT WITH ODO |
| TABLE 14.2.3.2 | EYE DRYNESS SCORE DURING CAE BY TIMEPOINT | PP WITH ODO |
| TABLE 14.2.3.3 | EYE DRYNESS SCORE POST-TREATMENT THREE-TIMEPOINT ANALYSIS | ITT WITH ODO |
| TABLE 14.2.3.4 | EYE DRYNESS SCORE POST-TREATMENT THREE-TIMEPOINT ANALYSIS | PP WITH ODO |
| TABLE 14.2.3.5 | EYE DRYNESS SCORE DURING CAE MMRM ANALYSIS | ITT WITH ODO |
| TABLE 14.2.3.6 | EYE DRYNESS SCORE DURING CAE MMRM ANALYSIS | PP WITH ODO |
| TABLE 14.2.3.7 | OCULAR DISCOMFORT [redacted] SCALE) DURING CAE BY TIMEPOINT | ITT WITH ODO |
| TABLE 14.2.3.8 | OCULAR DISCOMFORT [redacted] SCALE) DURING CAE BY TIMEPOINT | PP WITH ODO |
| **TABLE 14.3.1.1** | **ADVERSE EVENT SUMMARY** | **SAFETY** |
| TABLE 14.3.1.2 | ALL OCULAR ADVERSE EVENTS | SAFETY |
| TABLE 14.3.1.3 | ALL NON-OCULAR ADVERSE EVENTS | SAFETY |

| Table Number | Title | Population |
|---|---|---|
| **TABLE 14.3.1.4** | **ALL OCULAR TREATMENT-EMERGENT ADVERSE EVENTS** | **SAFETY** |
| **TABLE 14.3.1.5** | **ALL NON-OCULAR TREATMENT-EMERGENT ADVERSE EVENTS** | **SAFETY** |
| TABLE 14.3.1.6 | ALL OCULAR TREATMENT-RELATED TREATMENT-EMERGENT ADVERSE EVENTS | SAFETY |
| TABLE 14.3.1.7 | ALL NON-OCULAR TREATMENT-RELATED TREATMENT-EMERGENT ADVERSE EVENTS | SAFETY |
| **TABLE 14.3.1.8** | **ALL SERIOUS ADVERSE EVENTS** | **SAFETY** |
| TABLE 14.3.1.9 | ALL SERIOUS TREATMENT-RELATED TREATMENT-EMERGENT ADVERSE EVENTS | SAFETY |
| TABLE 14.3.1.10 | ALL OCULAR TREATMENT-EMERGENT ADVERSE EVENTS BY MAXIMAL SEVERITY | SAFETY |
| TABLE 14.3.1.11 | ALL NON-OCULAR TREATMENT-EMERGENT ADVERSE EVENTS BY MAXIMAL SEVERITY | SAFETY |
| TABLE 14.3.2 | BEST-CORRECTED VISUAL ACUITY - LOGMAR | SAFETY |
| TABLE 14.3.3.1 | SLIT LAMP BIOMICROSCOPY | SAFETY |
| TABLE 14.3.3.2 | SHIFT IN SLIT LAMP BIOMICROSCOPY | SAFETY |
| TABLE 14.3.4.1 | INTRANASAL EXAMINATION | SAFETY |
| TABLE 14.3.4.2 | SHIFT IN INTRANASAL EXAMINATION | SAFETY |
| TABLE 14.3.5 | PUPIL DIAMETER (MM) | SAFETY |
| TABLE 14.3.6 | EXPOSURE TO STUDY DRUG | SAFETY |

## 21. Listings

| Listing Number | Title |
|---|---|
| LISTING 16.1.7 | RANDOMIZATION SCHEDULE |

| Listing Number | Title |
|---|---|
| LISTING 16.2.1 | SUBJECT DISPOSITION |
| LISTING 16.2.2 | PROTOCOL DEVIATIONS |
| LISTING 16.2.3 | STUDY POPULATION INCLUSION |
| LISTING 16.2.4.1 | DEMOGRAPHICS |
| LISTING 16.2.4.2 | OCULAR MEDICAL HISTORY |
| LISTING 16.2.4.3 | NON-OCULAR MEDICAL HISTORY |
| LISTING 16.2.4.4 | PRIOR AND CONCOMITANT OCULAR MEDICATIONS |
| LISTING 16.2.4.5 | PRIOR AND CONCOMITANT NON-OCULAR MEDICATIONS |
| LISTING 16.2.5.1 | IN-OFFICE STUDY MEDICATION INSTILLATION |
| LISTING 16.2.5.2 | STUDY DRUG EXPOSURE |
| LISTING 16.2.5.3 | URINE PREGNANCY TEST |
| LISTING 16.2.6.1 | SCHIRMER'S TEST |
| LISTING 16.2.6.2 | EYE DRYNESS SCORE |
| LISTING 16.2.6.3 | EYE DRYNESS SCORE (DURING CAE) |
| LISTING 16.2.6.4 | [redacted] OCULAR DISCOMFORT SCALE |
| LISTING 16.2.6.5 | [redacted] OCULAR DISCOMFORT SCALE (DURING CAE) |
| LISTING 16.2.6.6 | OCULAR SURFACE DISEASE INDEX (OSDI) |
| LISTING 16.2.6.7 | CORNEAL FLUORESCEIN STAINING (NEI SCALE) |
| LISTING 16.2.7.1 | ALL ADVERSE EVENTS |
| LISTING 16.2.7.2 | SERIOUS ADVERSE EVENTS |
| LISTING 16.2.7.3 | ADVERSE EVENTS LEADING TO TREATMENT DISCONTINUATION |
| LISTING 16.2.7.4 | ADVERSE EVENTS LEADING TO DEATH |
| LISTING 16.2.8.1 | VISUAL ACUITY |
| LISTING 16.2.8.2 | SLIT LAMP BIOMICROSCOPY |

| Listing Number | Title |
|---|---|
| LISTING 16.2.8.3 | INTRANASAL EXAMINATION |
| LISTING 16.2.8.4 | PUPIL DIAMETER |

## 22. Figures

| Figure Number | Title | Population |
|---|---|---|
| **FIGURE 14.2.1.1** | **PRE- TO POST-TREATMENT CHANGE IN SCHIRMER'S TEST BY TREATMENT GROUP** | **ITT WITH ODO** |
| **FIGURE 14.2.1.2** | **PRE- TO 1 MINUTE POST-TREATMENT CHANGE IN EDS BY TREATMENT GROUP** | **ITT WITH ODO** |
| FIGURE 14.2.2.1 | PRE- TO POST-TREATMENT CHANGE IN EDS DURING CAE BY TIMEPOINT AND TREATMENT GROUP | ITT WITH ODO |
| FIGURE 14.2.2.2 | PRE- TO POST-TREATMENT THREE TIMEPOINT AVERAGE CHANGE IN EDS BY TREATMENT GROUP | ITT WITH ODO |
| FIGURE 14.2.2.3 | PRE- TO POST-TREATMENT CHANGE IN EDS DURING CAE BY DURATION AND TREATMENT GROUP, MMRM ANALYSIS | ITT WITH ODO |
| FIGURE 14.2.2.4 | PRE- TO POST-TREATMENT CHANGE IN OCULAR DISCOMFORT [redacted] SCALE) DURING CAE BY TIMEPOINT AND TREATMENT GROUP | ITT WITH ODO |