Oyster Point Pharma, Inc.

Clinical Protocol: OPP-003:

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

Statistical Analysis Plan

Version 1.0

October 4, 2018

CONFIDENTIAL

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Synopsis

Protocol title	A multicenter, randomized, controlled, double-masked clinical trial to evaluate the efficacy of OC-02 nasal spray on signs and symptoms of dry eye disease (the RAINIER study)
Protocol number	OPP-003
Investigational product	2.0% OC-02 nasal spray
Study objective	To evaluate the safety and effectiveness of OC-02 Nasal Spray as compared to placebo on signs and symptoms of dry eye disease (DED)
Treatment assignment	Approximately 45 subjects will be randomized in a 2:1 ratio to the two treatment groups: placebo, 2.0% OC-02 treatment
Analysis population	Efficacy: the Intent-To-Treat (ITT) population consists of all randomized subjects classified according to the treatment to which they were randomized. Safety: the safety population includes all randomized subjects who received at least one dose of the study drug. Analysis using the safety population will group subjects according to the treatment actually received.
Primary endpoint	Change in Schirmer's Test Score (STS) from baseline to Visit 5 (Day 28)
Statistical method for primary efficacy analysis	[redacted]
Sample size and power	[redacted]

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Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BCVA	best corrected visual acuity
BID	twice daily
CAE®	Controlled Adverse Environment®
CRF	Code of Federal Regulations
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
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
MMRM	mixed model for repeated measures
μL	microliter
mm	millimeter
nAChR	nicotinic acetylcholine receptor
OSDI©	Ocular Surface Disease Index©
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
STS	Schirmer's Test Score
TEAE	treatment-emergent adverse event
US	United States

1. Introduction

This statistical analysis plan (SAP), which is based on Amendment 1.0 of the study protocol dated 11 July 2018, defines the methods and analyses that Oyster Point Pharma, Inc, (henceforth, Oyster Point) plans to use to analyze the data from Protocol OPP-003. 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 is governing.

2. Investigational plan

2.1. Study design

Oyster Point's protocol OPP-003 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 dry eye disease (DED). Subjects with DED who provide signed informed consent and meet enrollment criteria (that is, all inclusion criteria and none of the exclusion criteria) will be randomized in a 2:1 ratio to be treated with OC-02 nasal solution delivered as a 50 microliter (μL) intranasal spray in each nostril BID for a total of 4 weeks:

- Placebo (vehicle) nasal spray[control]
- 2.0% OC-02 nasal spray[treatment]

All enrolled subjects will receive treatment according to the protocol's schedule of visits and procedures (see Appendix 1). [redacted]

2.2. Study objectives and outcome measures

The Protocol OPP-003 is designed to evaluate the safety and efficacy of 2.0% OC-02 nasal spray compared to placebo in subjects with DED. See Table 1 for the study objectives and outcome measures.

Table 1. Study objectives and outcome measures

Primary Objective: to determine if 2.0% OC-02 is superior to placebo with respect to change from baseline in Schirmer's Test Score (STS) at Visit 5 (Day 28) Outcome: change in STS from baseline to Visit 5
Exploratory & Safety Objective 1: to evaluate the difference in efficacy between 2.0% OC-02 and placebo with respect  Objective 2: to compare the safety and tolerability of 2.0% OC-02 nasal spray and placebo with respect to the following outcomes: • Change in best corrected visual acuity (BCVA) • Slit-lamp biomicroscopy • Intranasal examination • Adverse events

2.3. Randomization and masking

Randomization will occur at Visit 1 (Day 1). Each qualified subject will be assigned a subject number in strict numerical sequence at a clinical site; no number will be skipped or omitted. If all inclusion and exclusion criteria are met at Visit 1, each qualifying subject will be assigned a randomization number.

Randomization will be performed electronically once the subject has been deemed eligible for the study. The site staff will give the patient a study kit labeled with a kit number that will correspond to the system-assigned randomization number. The randomization number and kit 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.

3. Study schedule

Subjects are expected to attend 5 visits over the study period of approximately 4 weeks (28 days) of participation in the study. They are examined at screening (Day 1, randomization), Visit 2 (Day 7), Visit 3 (Day 14), Visit 4 (Day 21), and Visit 5 (Day 28). See Appendix 1 for the schedule of visits.

3.1. **Study days**

Study days will be calculated from the date of randomization, which will be designated as Day 1 (Visit 1). Positive study days will be measured forward in time from randomization while negative study days will be measured backward from randomization (e.g., Day 2 will represent the day after randomization while Day -1 will represent the day before randomization).

3.2. **Unscheduled visits**

Unscheduled visits may be performed to ensure safety of the subject. The study investigator or designee should record all information gathered at unscheduled visits on the Unscheduled Visit/Early Exit Visit pages of the Source Document and corresponding electronic Case Report Form (eCRF). If a randomized subject does not attend a scheduled visit, the eCRF pages for the missed visit will be skipped. All reasonable efforts should be made to schedule subjects for an Exit Visit to complete Exit Procedures.

4. Analysis populations

4.1. **Intent-To-Treat population**

The Intent-To-Treat (ITT) population will include all randomized subjects. Analyses using the ITT population will group subjects according to the treatment to which they were randomized. The ITT analyses will be considered the primary analysis population for efficacy outcomes.

4.2. Safety population

The safety population will include all randomized subjects who received at least one dose of the study drug. Analysis using the safety population will group subjects according to the treatment actually received. The safety analysis will not exclude any data because of protocol violations.

5. Sample size determination and power calculation

The study will randomize approximately 45 subjects in a 2:1 ratio to the two treatment groups. Approximately 28 subjects of the 30 subjects in the 2.0% OC-02 treatment group and 13 of the 15 subjects in the placebo (OC-02 vehicle) nasal spray are expected to complete their assigned treatment and have endpoint assessments at Visit 5.

The primary hypothesis underlying the study is that 2.0% OC-02 nasal spray is superior to the placebo group with respect to mean change in STS from baseline to Visit [redacted]

[redacted]

[redacted]

6. Protocol deviations

[redacted]

Prior to database lock, masked members of study team will review the data for each subject to assess whether an important deviation has occurred. The data management plan will describe the process planned for those reviews.

7. Statistical analysis: general considerations and conventions

Descriptive and inferential statistics will be used to summarize results of Protocol OPP-003. Continuous variables will be summarized using the number of subjects (n), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Discrete variables will be summarized using 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 will be presented by treatment group. Summaries will be provided for demographics, medical history, concomitant medications, and subject disposition. For the summaries of medical history, concomitant medications, and AEs, Medical Dictionary for Regulatory Activities (MedDRA®) and World Health Organization Drug dictionaries, as appropriate, will be used.

All data listings, summaries, and statistical analyses will be generated using SAS® Version 9.4 or higher or other validated software.

The following sections describe the analyses to be used for the study.

7.1. **Unit of analysis**

For efficacy endpoints, the unit of analysis will be the study eye 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 eye with the lower basal Schirmer's score at screening will be the study eye. If there is no difference for either measure, the right eye will be used as the study eye.

Both eyes will be analyzed for safety variables.

7.2. Definition of time

For visits (or events) that occur on or after randomization, time is calculated in days as:

Time = Visit (or event) date – Date of randomization + 1

For visits (or events) that occur prior to randomization, time is calculated in days as:

Time = Visit (or event) date – Date of randomization

For listings (e.g., for adverse events), the number of days since first (or last) dose is defined as:

Days since first (or last) dose = Visit (or event) date – Date of randomization + 1

For summaries that present distribution of time expressed in weeks and months, weeks will be defined as days divided by 7 and months as days divided by 30.4375.

7.3. Missing and partial data

[redacted]

8. Subject characteristics, disposition, and exposure to study drug

8.1. Demographic and baseline characteristics

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.

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 randomization- Date of birth) + 1] / 365.25.

Unless otherwise stated, percentages will be calculated relative to the number of subjects randomized. All demographic data will be presented.

Summary tables will describe baseline ocular characteristics for each treatment group.

Medical history will be coded using the MedDRA and summarized, for each treatment group, by system organ class (SOC) and preferred term (PT). Medical history may also be listed for all subjects in the ITT. Medical history may be sorted by treatment group and descending overall frequency, by SOC and PT, in the summary tables. Medical history will be presented separately for ocular and non-ocular events.

8.2. **Subject disposition**

The study has four times of evaluation after baseline: Visit 2 (Day 7), Visit 3 (Day 14), Visit 4 (Day 21), and Visit 5 (Day 28). At each of these times, the disposition of all subjects will be listed and summarized by treatment group. Tables will present the number and percentage of subjects who were screened, randomized, received treatment, or withdrew from the study early by treatment group and overall. For subjects who were randomized but withdrew from the study early, the number and percentage withdrawing by reason will be presented by treatment group and overall.

The Case Report Form (CRF) lists the following reasons why subjects may discontinue treatment before completing of the study:

- Adverse event (AE) or serious adverse event (SAE)
- Protocol deviation
- Administrative reason (e.g.: inability to continue, lost to follow-up)
- Sponsor termination of study
- Voluntary withdrawal or withdrawal of consent

In addition, a subject may be discontinued for any sound medical reason at the discretion of the Investigator.

8.3. **Treatment exposure**

Duration of exposure to study treatment, in weeks, will be summarized for all randomized subjects. Summary statistics for duration of exposure will be presented by visit and treatment group.

8.4. **Concomitant medications and therapies**

[redacted]

9. Baseline, post-baseline, and unscheduled measurements

Baseline is defined as the last non-missing measurement prior to randomization (Visit 1). Unless otherwise specified, if a subject has more than one baseline value, the value recorded closest to the date and time of randomization prior to the first dose of study treatment will be used as the baseline measurement.

The clinical study report (CSR) will include listings of all repeated measurements collected prior to first dose indicating whether they were included in the calculation of baseline.

If a laboratory result is retested and the laboratory subsequently considers the original result valid, the original result will be used and the second (i.e., 'retested') result will be ignored. Otherwise, if the laboratory detects an error through the retesting, the retested result will be used as the scheduled measurement and the original result will be ignored.

For post-baseline measures, specific time points will be calculated relative to randomization, rather than solely on the visit labels in the clinical database.

Results of unscheduled tests will be presented in data listings, but they will not be included in summaries of safety for the analysis of change in STS unless otherwise specified.

9.1. **Ocular assessments**

Ocular assessments, which will occur at baseline and each study visit, collect results in terms of grade, clinical significance, and relatedness to administration procedure and study drug. These results will be listed, summarized in tables, and presented in figures as appropriate.

9.1.1. Schirmer's Test

The Schirmer's Test with topical anesthetic will be used to assess tear production. At Visit 1, the first Schirmer's Test, which should be performed after corneal fluorescein staining, will be used as the baseline Schirmer's Test score. A second Schirmer's Test with nasal stimulation using cotton swab will occur 10 minutes after the first Schirmer's Test. An additional Schirmer's Test with topical anesthetic will be assessed after the first treatment at Visit 1. At Visits 2, 3, and 5, the Schirmer's Tests will be performed concurrent with treatment.

9.1.2. Eye Dryness Score

The Eye Dryness Score (EDS) will be assessed using a Visual Analog Scale (VAS). EDS scoring is performed by subjects at Visit 1 (baseline), Visit 4 (pre-CAE®), Visit 4 (pre-treatment CAE® exposure, post-treatment CAE® exposure every 5 minutes within the CAE® for a total of 120 minutes), and Visit 5. Participants will be asked to rate their ocular symptoms (both eyes simultaneously) due to eye dryness every 5 minutes during CAE® exposure. 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. [redacted]

9.1.3. BCVA

Visual function of the study and fellow eye will be assessed using the best corrected ETDRS protocol starting at 10 feet. 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.

9.1.4. [redacted] Ocular Discomfort Scale

Participants will grade themselves on the [redacted] Ocular Discomfort Scale (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 4 will be used to determine treatment administration. Treatment of investigational drug or placebo will be administered upon a participant's reporting an ODS ≥ 3 at two or more consecutive time points in at least one eye during CAE® exposure (participants 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 [redacted] Scale. ODS will be summarized by visit, pre-CAE® and every 5 minutes in CAE® at Visit 4, and treatment group for both the study and fellow eye.

9.1.5. Ocular Surface Disease Index©

The Ocular Surface Disease Index© (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).

9.1.6. Corneal Fluorescein Staining

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.

9.1.7. Slit Lamp Biomicroscopy

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.

9.2. **Intranasal assessments**

Intranasal assessments collected at the screening visit, the post-treatment CAE® evaluation at Visit 4, and the early termination visit 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.

10. Efficacy analyses

[redacted]

10.1. **Primacy efficacy analysis**

[redacted]

[redacted]

Appendix 2 provides details of the planned methodology, including sample SAS code.

[redacted]

10.2. **Exploratory efficacy analyses**

10.2.1. Exploratory efficacy endpoints

[redacted]

[redacted]

10.2.2. Exploratory efficacy analysis methods

[redacted]

[redacted]

11. Safety analyses

The safety population will be used for all safety analyses. All recorded safety parameters will be listed.

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. AE will be coded using version 20.1 or later 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 as well as by system organ class (SOC) and preferred term (PT), seriousness, severity, and relation to study medications. AEs will be summarized by subject, not event.

All AE presentations will summarize treatment-emergent adverse events (TEAEs) defined as AEs with onset on or after first dose of investigational drug or placebo.

The following presentations of AEs will be generated:

- Overall adverse events summary (including any AEs, ocular AEs, resolved ocular AEs, non-ocular AEs, 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 AEs by SOC and PT;
- All non-ocular AEs by SOC and PT;
- AEs suspected to be related to the study medication;
- AEs leading to treatment discontinuation.
- AEs leading to study discontinuation.

All AE data will be presented in listings. Selected AEs will be listed for ocular TEAEs, AEs leading to treatment discontinuation, AEs leading to study discontinuation, and AEs related to the study medication. In addition, for the safety population "traffic light" plots will present reported AEs by severity over time by treatment group.

BCVA will be summarized by treatment group and study visit for both study and fellow eyes.

12. Subgroup analysis

13. Appendices

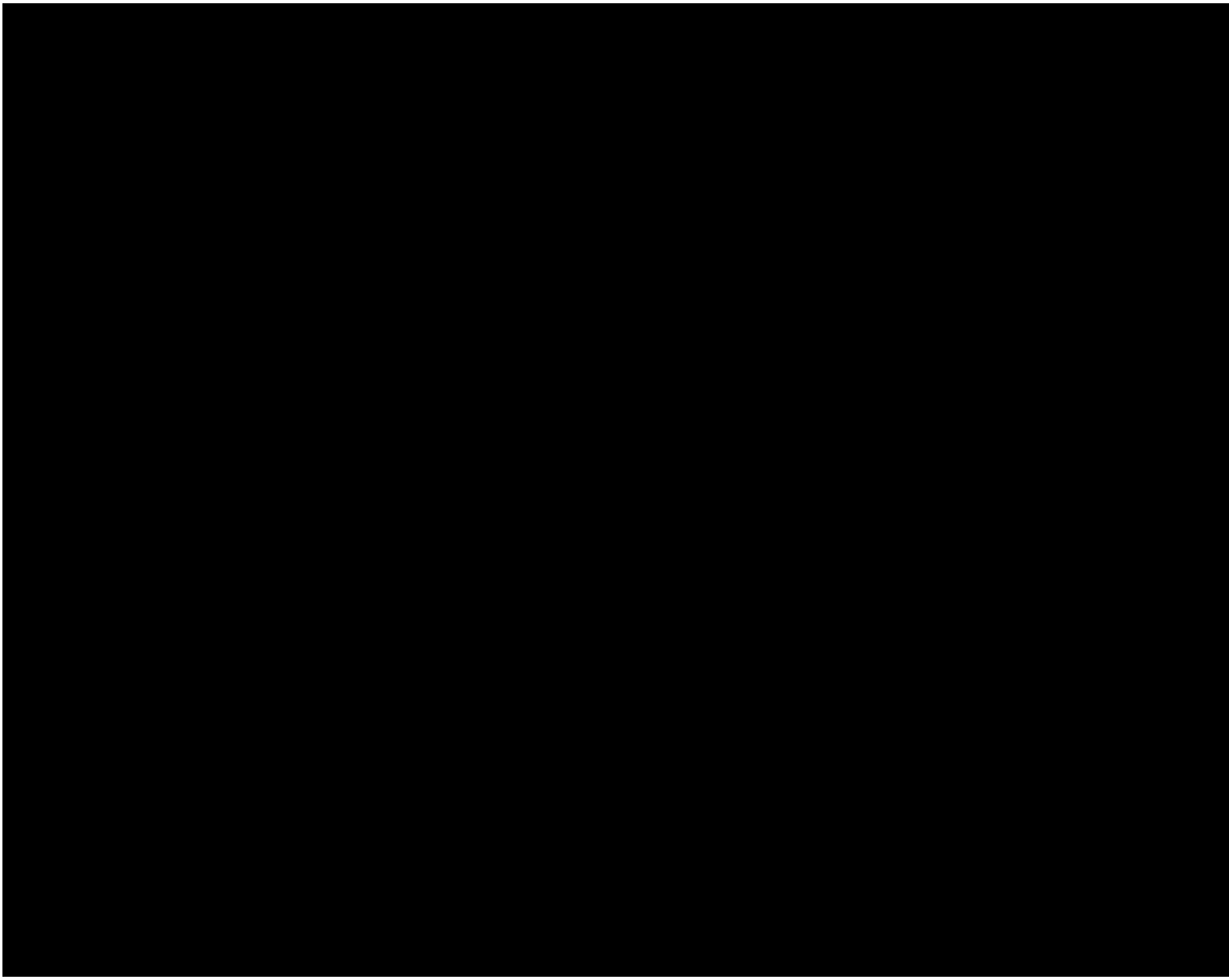
Appendix 1. Schedule of visits and measurements

Procedure	Screen/ Visit 1		Visit 2		Visit 3		Visit 4 (Day 21 ±2)			Visit 5	
	Day 1	Days 2-6	Day 7 ±2	Days 8-13	Day 14 ±2	Days 15-20	Pre-CAE®	Post-CAE®	Days 22-27	Day 28 ±2	ET
Informed consent/HIPAA	X										
Demographics	X										
Medical history, prior medication(s), ocular history and updates	X										
Eligibility criteria	X										
Urine pregnancy test	X_4						X_4				X_4
OSDI© questionnaire	X										
Eye Dryness Score (EDS)	X						X	X_5		X_2	
[redacted] Ocular Discomfort Scale	X						X	X_5			
BCVA	X_1		X_1		X_1			X_6		X_1	X
Slit lamp biomicroscopy	X_1		X_1		X_1			X_6		X_1	X
Corneal fluorescein staining	X									X_2	
Schirmer's test	X_1		X		X					X	
Schirmer's test with cotton swab stimulation	X										
Intranasal examination	X_1									X	X
Randomization	X										
Administer investigational drug / placebo	X_3	X	X_3	X	X_3	X	X		X	X_3	
Dispense investigational drug / placebo	X				X						
Concomitant medications	X		X		X		X			X	X
AE Query	X		X		X		X	X		X	X

X_1 = Pre- and Post-treatment procedures; X_2 = Post-treatment procedures X_3 = Concurrent with Schirmer's Test; X_4 = For females of childbearing potential; X_5 = Procedure started at time 0 and then conducted every 5 minutes thereafter during the 120 minute CAE® exposure; X_6 = Procedure may be performed after CAE® exit at the Investigator's discretion as needed

Appendix 2. Analysis for primary efficacy outcome with multiple imputation

Exhibit 1. Sample SAS code for assessing missing data patterns



[redacted]

Appendix 3. Sensitivity analysis using a mixed model for repeated measures

[redacted]

Appendix 4. Winsorized mean approach

[redacted]