STATISTICAL ANALYSIS PLAN

A Multi-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of 0.1% RGN-259 Ophthalmic Solution for the Treatment of Dry Eye Using the Controlled Adverse Environmental (CAE^{SM}) Model (ARISE-2)

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Protocol Number: RGN-259/16-110-0008 (NCT02974907)

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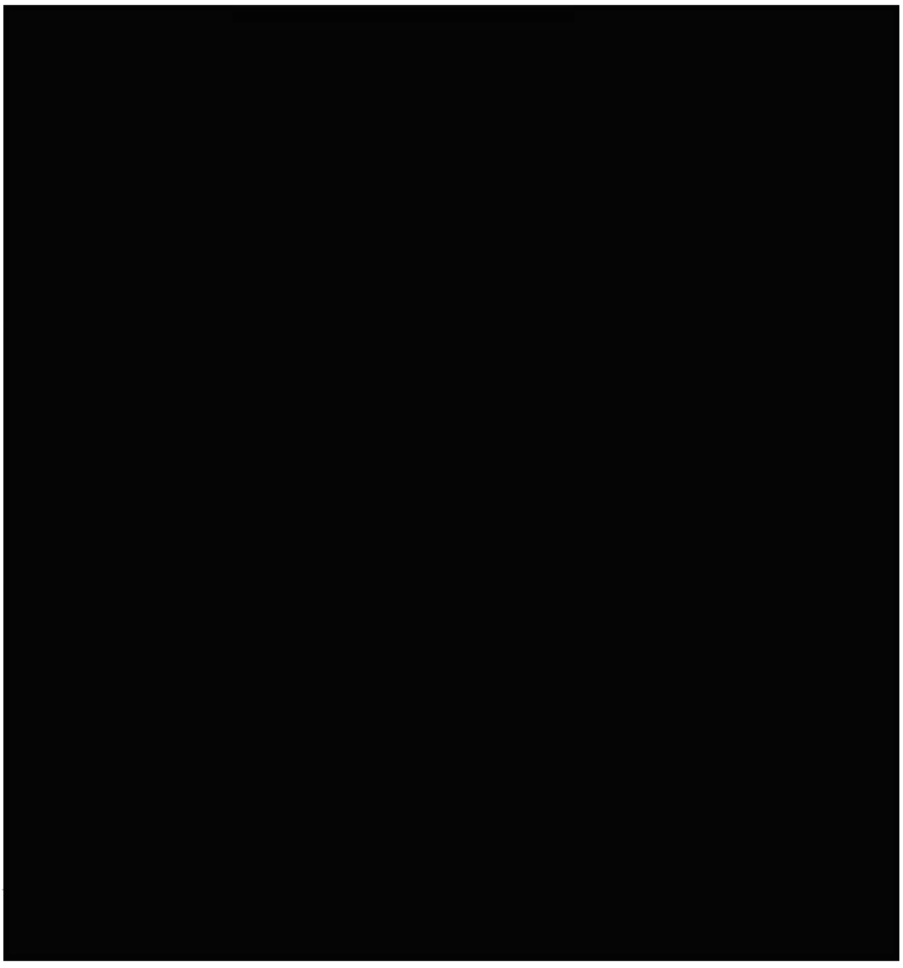
Statistical Analysis Plan Approval



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List of Abbreviations

Abbreviation	Definition
ADaM	Analysis Dataset Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CAE^{SM}	Controlled Adverse Environment
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
IBI	Inter-blink Interval
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
ITT	Intent-to-Treat
IVRS/IWRS	Interactive Voice/Web Response System
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
OPI	Ocular Protection Index
OSDI	Ocular Surface Disease Index©
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
QID	Four Times a Day
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TFBUT	Tear Film Break-up Time

Abbreviation	Definition
ADaM	Analysis Dataset Model
VA	Visual Acuity

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol RGN-259/16-110-0008, version 2.0 dated 21JUL2017.

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.

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 clinical study report (CSR).

2. Study Objectives

The objective of this study is to compare the safety and efficacy of 0.1% RGN-259 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye.

3. Study Variables

3.1 Primary Variables

The primary efficacy variable is the change from baseline in ocular discomfort change from pre-CAE[SM] [redacted] to post-CAE[SM] [redacted] at Day 29 (Visit 5) using the Ora Calibra [M] Ocular Discomfort Scale.

The primary hierarchical efficacy variable is the change from baseline in inferior corneal staining at Day 29 pre-CAE[SM] [redacted] using the Ora Calibra [M] Scale.

3.2 Secondary Variables

The secondary efficacy variables are listed below.

- Corneal fluorescein staining (Ora Calibra [M] Scale) at Visits 3, 4, and 5 (change from pre-CAE[SM] to post-CAE[SM], pre- and post-CAE[SM]; regions: [redacted]
- Corneal fluorescein staining (Ora Calibra [M] Scale) at Visits 3, 4, and 5 (change from pre-CAE[SM] to post-CAE[SM], pre- and post-CAE[SM]; regions: [redacted]

[redacted]

- Lissamine green staining (Ora Calibra ᴹ Scale) at Visits 3, 4, and 5 (change from pre-CAE^{SM} to post-CAE^{SM},pre- and post-CAE^{SM}; regions: [redacted])
- Tear film break-up time at Visits 3, 4, and 5 (pre- and post-CAE^{SM})
- Ocular Protection Index (OPI) 2.0 at Visit 5 (pre-CAE^{SM})
- Unanesthetized Schirmer's Test at Visit 5 (pre-CAE^{SM})
- Drop comfort assessment after randomization at Visit 2
- Ocular Surface Disease Index© (OSDI) at Visits 3, 4, and 5 (pre-CAE^{SM})
- Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire at Visits 3, 4, and 5 (change from pre-CAE^{SM} to post-CAE^{SM}, pre- and post-CAE^{SM})
- Ora Calibra™ Ocular Discomfort Scale at Visits 3, 4, and 5 (change from pre-CAE^{SM} to post-CAE^{SM}, pre- and post-CAE^{SM})
- Ocular discomfort during CAE^{SM} exposure at Visits 4 and 5
- Daily diary

3.3 Safety Variables

The safety variables include the following:

- Adverse event (AE) query at Visits 1, 2, 3, 4 and 5
- Visual acuity (ETDRS) at Visits 1, 2, 3, 4 and 5
- Slit-lamp biomicroscopy at Visits 1, 2, 3, 4 and 5
- Corneal sensitivity at Visits 1 and 5 (pre-CAE^{SM})
- Undilated fundoscopy at Visits 1 and 5
- Intraocular pressure (IOP) at Visits 1 and 5 (post-CAE^{SM})

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 RGN-259 Ophthalmic Solution (0.1%) and placebo in the change from baseline in ocular discomfort change from pre-CAE^{SM} [redacted] to post-CAE^{SM} [redacted] at Day 29 (Visit 5) using the Ora Calibra ᴹ Ocular Discomfort Scale.
>
> H_{11}: The change from baseline in ocular discomfort change from pre-CAE^{SM} [redacted] to post-CAE^{SM} [redacted] at Day 29 (Visit 5) using the Ora Calibra ᴹ Ocular Discomfort Scale is less with RGN-259 Ophthalmic Solution (0.1%) than with placebo.

H_{02}: There is no difference between RGN-259 Ophthalmic Solution (0.1%) and placebo in the change from baseline in inferior corneal staining at Day 29 (Visit 5) pre-CAE[SM] [redacted]

H_{12}: The change from baseline in inferior corneal staining at Day 29 (Visit 5) pre-CAE[SM] [redacted] with RGN-259 Ophthalmic Solution (0.1%) than with placebo.

To maintain a type I error rate of 5% over the comparison of the active treatment group to placebo, a hierarchical testing procedure will be used for the primary endpoints. First, change from baseline in ocular discomfort for 0.1% RGN-259 Ophthalmic Solution change from pre-CAE[SM] [redacted] to post-CAE[SM] [redacted] at Day 29 (Visit 5) will be tested versus placebo at $\alpha = 0.05$. If there is a significant difference in change from baseline in ocular discomfort between 0.1% RGN-259 Ophthalmic Solution and placebo, then the change from baseline in inferior corneal staining at Day 29 (Visit 5) pre-CAE[SM] for 0.1% RGN-259 Ophthalmic Solution will be tested versus placebo at $\alpha = 0.05$ [redacted]

4. Study Design and Procedures

4.1 General Study Design

This is a phase 3, multicenter, randomized, double-masked, placebo controlled safety and efficacy study. It consists of two treatment arms, 0.1% RGN-259 Ophthalmic Solution and placebo ophthalmic solution, randomized in a 1:1 ratio. There are five scheduled visits over approximately 6 weeks (43 days including screening), with approximately 800 subjects being screened in order to enroll 594 subjects (approximately 297 subjects per treatment arm). This study will consist of two periods: a 14-day run-in period, during which subjects will instill placebo four times a day (QID; morning, noon, afternoon and evening) in both eyes, and a 28-day treatment period, during which subjects will instill randomized study medication QID in both eyes. Visit 1 (Day -14) is the screening visit. Subjects will be challenged for [redacted] in the Controlled Adverse Environment (CAE[SM]) model and will be assessed for eligibility. At Visit 2 (Day 1), subjects will be reassessed for eligibility, re-challenged for [redacted] in the CAE[SM] model, and have baseline measures assessed. Eligible subjects will be randomized to receive one of the two study drugs. Randomized subjects will then begin using study drug bilaterally QID for approximately 4 weeks. At the conclusion of 2 and 4 weeks of treatment (Visit 4 [Day 15] and Visit 5 [Day 29, study exit]), subjects will be challenged for [redacted] in the CAE[SM] model.

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. Note that there is no Day 0; Day -1 is directly followed by Day 1. Also, note that Day 1 corresponds to the day of randomization and where most baseline measurements are taken. The

following table shows the scheduled study visits, their planned study day and the acceptable visit window for each study visit.

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day -14	± 1 Day
Visit 2	Day 1	N/A
Visit 3	Day 8	± 1 Day
Visit 4	Day 15	± 1 Day
Visit 5	Day 29	± 2 Days

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.

Procedure	Visit 1 Day -14 ± 1		Visit 2 Day 1		Visit 3 Day 8 ± 1	Visit 4 Day 15 ± 1		Visit 5 Day 29 ±2	
	Pre CAE℠	Post CAE℠	Pre CAE℠	Post CAE℠		Pre CAE℠	Post CAE℠	Pre CAE℠	Post CAE℠
Informed Consent / HIPAA	X								
Medical / Medication History and Demographic	X								
Run-in Placebo Collection			X						
Study Drug Collection					X	X		X	
Diary Collection			X		X	X		X	
Medical / Medication History Update			X		X	X		X	
Adverse Event Query		X	X	X	X	X	X	X	X
Pregnancy Test	X[1]							X[1]	
Ocular Discomfort and 4-Symptom Questionnaire – Ora Calibra™ Scale	X	X	X	X	X	X	X	X	X
Ocular Discomfort – Ora Calibra™ Scale	X	X	X	X	X	X	X	X	X
OSDI Questionnaire	X		X		X	X		X	
Visual Acuity (ETDRS)	X		X		X	X		X	
Review of Qualification Criteria	X	X	X	X					
Slit-lamp Biomicroscopy	X	X	X	X	X	X	X	X	X
Ocular Protection Index (OPI) 2.0 System – Ora Calibra™ Scale			X					X	
TFBUT	X	X	X	X	X	X	X	X	X
Fluorescein Staining – Ora Calibra™ Scale	X	X	X	X	X	X	X	X	X
Lissamine Green Staining – Ora Calibra™ Scale	X	X	X	X	X	X	X	X	X
Corneal Sensitivity (Cochet-Bonnet)	X							X	
Unanesthetized Schirmer's Test	X		X		X	X		X	
CAE℠ Exposure	X		X			X		X	

CAE[SM] D scomfort – Ora Ca bra™ Ocu ar D scomfort Sca e	X[2]		X[2]			X[2]		X[2]	
Tear Co ect on				X[3]			X[3]		X[3]
Intraocu ar Pressure		X							X
Und ated Fundus Exam		X							X
Run- n P acebo D spensat on		X							
Random zat on				X					
Subject Se f- nst at on of study drug				X	X		X		
Ora Ca bra™ Drop Comfort Assessment				X	X		X		
Study Drug D spensat on				X	X		X		
D ary D spensat on		X		X	X[4]		X		
Ex t Subject from Study									X

X[1] = For fema es of ch dbear ng potent a , X[2] = [redacted] X[3]= Tears may be co ected after a 30 m nute wa t per od from ssam ne nst at on, X[4] = Invest gat ona product w be co ected and re-d spensed at V s t 3.

5. Study Treatments

The study treatments are 0.1% RGN-259 Ophthalmic Solution and placebo ophthalmic solution (vehicle).

5.1 Method of Assigning Subjects to Treatment Groups

Prior to initiation of study run-in (at Visit 1), each subject who qualifies for entry 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 Visits 1 and 2, each qualifying subject will then be assigned a randomization number at the end of Visit 2. The Interactive Voice/Web Response System (IVRS/IWRS) will be used to account for the stratification factors.

Subjects will be stratified using the worst eye. The worst eye is the eye that meets all of the inclusion criteria. In the case that both eyes are eligible for analysis, the worst eye will be the eye with the largest increase in ocular discomfort from pre-CAE[SM] [redacted] to post-CAE[SM] [redacted] at Visit 2. If the ocular discomfort symptom increase is the same in both eyes then the worst eye will be the eye with worse (higher) inferior corneal staining pre-CAE[SM] at Visit 2. If the [redacted] is the same in both eyes then the right eye will be selected as the worst eye.

Subject's will be stratified by the following factors and cut-offs:

1. Change from pre-CAE[SM] [redacted] to post-CAE[SM] [redacted] in ocular discomfort (Ora Calibra Ocular™ Discomfort Scale) at Visit 2 (Day 1).

   [redacted]

   [redacted]

2. Pre-CAE[SM] inferior corneal fluorescein staining (Ora Calibra™ Scale) at Visit 2 (Day 1).

   [redacted]

   [redacted]

5.2 Masking and Unmasking

This is a double-masked study. All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments for the duration of the study. The randomization schedule was created by an unmasked statistician who is not otherwise involved in the conduct of the study.

Under normal circumstances, the mask should not be broken. 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), Ora and/or the study Sponsor should be notified before unmasking study drug. Any required unmasking should be performed through the process setup with the IWRS.

6. Sample Size and Power Considerations

The study is expected to enroll 297 subjects in each of the two treatment arms for a total of 594 randomized subjects. Assuming a 5% drop out rate, 282 subjects per group are expected to complete the study.

With 297 subjects randomized per treatment arm, and a difference between RGN-259 and placebo as low as [redacted] the study will have [redacted] power to detect a treatment difference. This assumes a two-sided test at $\alpha = 0.05$ and a common standard deviation (SD) of [redacted] in both treatment arms. Accounting for up to 5% dropouts in the study, 282 randomized subjects per treatment arm, or 564 total subjects are required to have [redacted] power to detect a difference for the primary endpoint. Difference and SD estimates are derived from the phase 2b/3 study.

The hierarchical endpoint of the change from baseline in inferior corneal staining at Day 29 (Visit 5) pre-CAE^{SM} is also considered in terms of statistical power. It is assumed that 50% ([redacted] of 282 completed subjects accounting for 5% dropouts) of the subjects will have a baseline tear [redacted]. This endpoint will be tested conditionally upon the primary endpoint being successful, thereby maintaining the study-wide type I error rate for both endpoints. With a sample size of 141 subjects per treatment arm with a [redacted] will yield [redacted] power to detect a difference as low as [redacted] between 0.1% RGN-259 Ophthalmic Solution and placebo. This assumes a two-sided test at $\alpha = 0.05$ and a common SD of [redacted] in both treatment arms. To show a range of power using the same assumptions and accounting for fewer subjects with a [redacted], if only [redacted] of subjects ([redacted] completed subjects per treatment arm) have a baseline [redacted] then the study will have [redacted] power to detect a treatment difference between RGN-259 and placebo. Difference and SD estimates are conservatively derived from the phase 2b/3 study, [redacted]

7. Data Preparation

All reported study data will be recorded on the electronic case report form (eCRF) supplied by Statistics and Data Corporation (SDC) using iMedNet™. Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

Diary data will be collected from subjects at the protocol specified visits and entered by the site staff.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the

database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor and Ora in consultation with SDC.

All analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to SDC standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC and Sponsor personnel;
- Protocol deviations have been identified and status defined (major/minor deviations);
- Analysis populations have been determined; and
- Randomized treatment codes have been unmasked.

7.1 CDISC Compliance

The raw data collected in the iMedNet database and it will be transformed into submission-ready, SDTM and analysis datasets (ADaM). To comply with CDISC Standards the below steps will be followed:

- Raw data will be transformed using the Study Data Tabulation Model (SDTM) Implementation Guide version 3.2.
- SDTM will be transformed into analysis datasets via the Analysis Dataset Model (ADaM) Implementation Guide version 1.1.
- For submission purposes, the SDTM and ADaM metadata will be described within define.xml following Define-XML 2.0 Specifications.
- SDTM and ADaM datasets and the define.xml documents will be validated with Pinnacle 21 version 2.2.0.

8. Analysis Populations

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 Intent-To-Treat (ITT) population. The primary efficacy analyses will also be performed on the Per Protocol (PP) population as sensitivity analyses

8.1 Intent-to-Treat

The ITT population includes all randomized subjects. The primary analysis will be performed on the ITT population with the Last Observation Carried Forward (LOCF) imputation method for missing values. The ITT population may also be analyzed with observed data only (i.e., without LOCF) and using multiple imputation methods to assess sensitivity. 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 complete the study. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as randomized.

8.3 Safety

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

9. General Statistical Considerations

All primary and secondary analyses will be 2-sided at a significance level of 0.05.

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, or "worst eye," as defined by the following:

Study eye (worst eye): Eyes are eligible for analysis if they meet all of the inclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with worst change in pre- to post-CAE^{SM} ocular discomfort at Visit 2. If the increase in ocular discomfort is the same in both eyes then the study eye will be the eye with the largest pre-CAE^{SM} [redacted] at Visit 2. If the change in ocular discomfort and the pre-CAE^{SM} [redacted] is the same in both eyes then the right eye will be selected as the study eye.

Additionally, non-ocular AEs and medical history will be presented at the subject level. Non-study eye safety summaries will also be presented as appropriate.

9.2 Missing or Inconclusive Data Handling

The primary efficacy analyses will be performed using the LOCF imputation method for missing values. For the analysis of ocular discomfort scores at Day 29 (Visit 5), the last value from the previous visits will be carried forward, matching pre-CAE^{SM} [redacted] or post-CAE^{SM} [redacted] time points. A pre-CAE^{SM} time point will never be imputed for a post-CAE^{SM} value, and vice versa. The change from pre- to post-CAE^{SM} ([redacted]) will be carried forward from the last visit with a calculable change from pre- to post-CAE^{SM}, rather than calculating the change from the carried forward pre- and/or post-CAE^{SM} values. For the analysis of inferior corneal fluorescein staining at Day 29 (Visit 5), the last pre-CAE^{SM} value from the previous visits will be carried forward.

An analysis using observed data at Day 29 (Visit 5) only will also be performed. Additionally, Markov Chain Monte Carlo (MCMC) multiple imputation methodology will be used to impute missing data for the analyses of the primary efficacy variables.

No secondary efficacy endpoints or safety endpoints will be imputed.

9.3 Definition of Baseline

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 2 (Day 1). If a measure is taken both pre-CAE^{SM} and post-CAE^{SM}, the baseline will be the time point matched value at Visit 2. For measures from daily subject diaries, baseline is defined as the average of all days during the run-in period, where daily scores are first obtained by averaging the morning and evening scores for that day, as applicable. The change from pre-CAE^{SM} to post-CAE^{SM} at Visit 2 will be considered the baseline value for visits 4 and 5 change from pre-CAE^{SM} to post-CAE^{SM}, unless any of the Visit 2 data is missing.

9.4 Data Analysis Conventions

All data analysis will be performed by 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 rich text format (RTF) format for tables and portable document format (PDF) format for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, visit (as applicable), and time point (as applicable) based on all randomized subjects unless otherwise specified.

Summaries for quantitative variables will include the number of observations (n), arithmetic mean, SD, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values. Means and medians will be rounded to one decimal more than the collected data; SDs will be rounded to two decimal places more than the collected data. Summaries for qualitative variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between active treatment groups and placebo will be calculated as active minus placebo and change from baseline will be calculated as follow-up visit minus baseline.

All statistical tests will be two-sided with a significance level of 0.05 (α = 0.05). Confidence intervals (CI) will be two-sided at 95% confidence. 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”.

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit and time point.

9.5 Adjustments for Multiplicity

To maintain a type I error rate of 5% over the two comparisons of each active treatment group to placebo, a hierarchical testing procedure will be used for the primary endpoints. First, the change from baseline in the change from pre- to post-CAE^{SM} ocular discomfort for 0.1% RGN-259 Ophthalmic Solution will be tested versus placebo at α = 0.05. If there is a significant difference in change from baseline ocular discomfort between 0.1% RGN-259 Ophthalmic Solution and placebo, then change from baseline in pre-CAE^{SM} inferior corneal fluorescein staining for 0.1% RGN-259 Ophthalmic Solution will be tested versus placebo at α = 0.05.

For the sign endpoint to be considered successful, significance is required for the primary symptom; therefore, the family-wise error rate is maintained at 0.05 through this fixed sequence testing.

9.6 Early Termination Visits

Early termination visits and data are captured in EDC as Visit 5 data regardless of when the visit occurred. Any early termination visit will be mapped to a scheduled visit if the visit date occurs within the scheduled visit window. If there are more than one visit in a visit window or the visit is outside the visit window, then the visit is mapped to an unscheduled visit. If an assessment is performed at an early termination visit but it was not part of the planned assessments for the scheduled visit, then the data for that early termination visit will be presented in the listings but will not be summarized in the tables.

10. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were screened failures, randomized, completed the study, and discontinued from the study. The total number of screened subjects will be displayed in a table with the reason for screen failure displayed in number and percentage of screen failure subjects. Percentages will be calculated using total number of screen failures as the denominator. 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 subjects in each of the analysis populations (ITT, PP, and Safety) will be displayed by treatment and percentages will be calculated using randomized subjects as the denominator.

The number and percentage of subjects with protocol deviations, including any deviation (major and minor) will be summarized by treatment group for all randomized subjects. A subject listing will be provided that includes the date of deviation, deviation description and classification of whether the deviation was judged to be major or minor.

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: adverse events (AE), protocol violation,

administrative reasons, Sponsor termination of study, subject choice and other. A subject listing will be provided that includes the date of and reason for premature study discontinuation.

In addition, subject listings will be provided that include informed consent date, protocol violations, and exclusions from the PP population.

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

The demographic variables collected in this study include age, sex, race, ethnicity, and iris color. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for the ITT and Safety populations, separately.

Age (years) will be summarized, overall and by treatment, 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, overall and by treatment, for age category, sex, race, ethnicity and iris color (by worst eye).

No statistical inference testing will be performed for the demographic variables. A subject listing that includes all demographic variables will be provided.

11.2 Pretreatment Variables and Baseline Disease Characteristics

Baseline dry eye signs and symptoms will be summarized for the worst eye by randomized treatment for the ITT population. These will include baseline inferior and total sum fluorescein staining and ocular discomfort (Ora Calibra ^{M} Ocular Discomfort Scale) with subgroups matching the randomization strata, lissamine green staining [redacted] TFBUT, unanesthetized Schirmer's test, and OSDI. If signs or symptoms were performed both pre- and post-CAE^{SM} at Visit 2, then both time points will be presented for the baseline summary.

A subject listing that includes all pretreatment variables will be provided.

12. Medical History, Prior and Concomitant Medications

12.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1.

Non-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 Safety population. Ocular medical history will be similarly summarized at the subject 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 Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (Enhanced B2, September 2016) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical (ATC) 4 classification) and preferred name (generic drug name).

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. Prior medications are defined as those medications listed as having been taken prior to initiation of study drug administration, but not taken after initiation of study drug administration.

Both ocular and non-ocular concomitant medications will be summarized using the Safety population. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than 1 medication per ATC 4 classification. 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.

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows:

$$\text{Compliance (\%)} = \frac{\text{Number of Actual Doses Received}}{\text{Number of Expected Doses}} \times 100\%$$

The number of actual doses received will be calculated based on the drug accountability case report form (CRF) pages, using the number of used vials/bottles as the number of doses received. The number of expected doses that will be used for calculating compliance will be calculated as: 4 x [(date of last dose – date of Visit 2 [Day 1]) +1] – 2 x [the number of attended visits from Visit 2 – Visit 4] for all subjects. Subtracting 2 times the number of attended visits will account for subjects not dosing on the day of a visit prior to the visit, on average.

A categorical dosing compliance variable will also be derived as non-compliant (<80%), compliant (≥80% and ≤125%) and over compliant (>125%).

Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group, using the ITT population. The compliance category defined above will be summarized with discrete summary statistics.

A subject listing of dosing compliance will also be produced.

13.2 Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

Extent of Exposure (days) = (Date of last dose – date of Visit 2 [Day 1]) + 1

Extent of treatment exposure for subjects who were lost to follow-up will be calculated in days using the following:

Extent of Exposure (days) = (Date of last recorded visit – date of Visit 2 [Day 1]) + 1

Extent of treatment exposure (days) for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group, using the Safety population. A subject listing of treatment exposure will also be produced.

14. Efficacy Analyses

14.1 Primary Analyses

Ocular discomfort will be assessed pre-CAE[SM] and post-CAE[SM] for both eyes at Visit 1 (Day -14), Visit 2 (Day 1, prior to treatment), Visit 4 (Day 15) and Visit 5 (Day 29). The 5-unit scale for subject evaluation of ocular discomfort is given by the following: 0 as measured on the Ora Calibra™ Ocular Discomfort Scale. The worst eye (defined in Section 9.1) from each subject will be used for this analysis.

The primary analysis, change from baseline in ocular discomfort change from pre-CAE[SM] to post-CAE[SM] at Day 29 (Visit 5) using the Ora Calibra™ Ocular Discomfort Scale, will be calculated as:

(OD at Day 29 – OD at Day 29) – (OD at Baseline – OD at Baseline)

where OD0 = Ocular discomfort at in CAE[SM] (pre-CAE[SM]) and OD = Ocular discomfort at post-CAE[SM].

With this calculation, a positive change indicates a worsening of dry eye symptoms compared to baseline. In addition, treatment comparisons between active and placebo will be calculated as active minus placebo, such that a negative result indicates a better score for the active treatment (i.e., the active treatment had a smaller increase in dry eye symptoms during the CAE^{SM} compared to baseline than the placebo group).

Analysis of Covariance (ANCOVA) models will be used to compare the change from baseline to Day 29 (Visit 5) in the change from pre- to post-CAE^{SM} in ocular discomfort, as measured on the Ora Calibra™ Ocular Discomfort Scale, between 0.1% RGN-259 Ophthalmic Solution and placebo. The ANCOVA models will include terms for baseline change from pre- to post-CAE^{SM} ocular discomfort and study site. 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 primary analysis will use LOCF imputation to have a full accounting of the ITT population at Day 29 (Visit 5). Pairwise *t*-tests from the ANCOVA model will be used to compare treatment groups. An example of SAS code implementation of the ANCOVA model is as follows:

```
PROC M XED;
    C ASS TREATMENT S TE;
    MODE  Δ D SCOMFORT   S TE BASE  NE TREATMENT;
     SMEANS TREATMENT / C  PD FF;
RUN;
```

Sensitivity analyses will be performed on the ITT and PP populations using observed data only, and on the ITT population imputing missing data using multiple imputation methods.

The MCMC method will be performed using the SAS procedure PROC MI. The SAS code for obtaining multiple imputation data is:

```
PROC M  DATA    NDATA SEED   425754 OUT   OUTDATA1 NIMPUTE = 20;
    MCMC  N T A    EM;
    VAR BASE  NE TREATMENT Δ D SCOMFORT;
RUN;
```

where

- *INDATA* is the name of the input dataset
- *OUTDATA1* is the name of the output dataset
- *TREATMENT* is the name of the treatment group variable in numeric format
- *BASELINE* is the change from pre-CAE^{SM} [redacted] to post-CAE^{SM} [redacted] in ocular discomfort of the study eye at Visit 2 (Day 1)
- Δ_*DISCOMFORT* is the change from pre-CAE^{SM} [redacted] to post-CAE^{SM} [redacted] in ocular discomfort of the study eye at Visit 5 (Day 29) – *BASELINE*.

After obtaining twenty complete data sets, the following SAS code will be used to run the ANCOVA model on each data set: Then, the SAS procedure MIANALYZE will be used to analyze the results from the twenty complete data sets to generate a combined inference. The following SAS code will be used:

```
ODS OUTPUT STAT ST CS   OUTDATA2;
PROC M XED DATA   OUTDATA1;
    C ASS TREATMENT;
    MODE  Δ D SCOMFORT   BASE  NE TREATMENT;
     SMEANS TREATMENT / C  PD FF;
    BY   MPUTAT ON ;
RUN;

ODS OUTPUT PARAMETEREST MATES   OUTDATA3;
PROC M ANA YZE DATA OUTDATA2;
    C ASS TREATMENT;
    MODE EFFECTS  NTERCEPT BASE  NE TREATMENT;
RUN;
```

where

- *TREATMENT* is the name of the treatment group variable in numeric format
- *BASELINE* is the change from pre-CAE[SM] [redacted] to post-CAE[SM] [redacted] in ocular discomfort of the study eye at Visit 2 (Day 1)
- Δ_*DISCOMFORT* is the change from pre-CAE[SM] ([redacted] to post-CAE[SM] [redacted] in ocular discomfort of the study eye at Visit 5 (Day 29) – *BASELINE*
- *OUTDATA2* is the name of the output dataset that contains the statistical results from the ANCOVA model that is run on each of the twenty imputation datasets
- *OUTDATA3* is the name of the output dataset that contains all the information needed for the table.

As sensitivity analyses, two-sample *t*-tests and Wilcoxon rank sum tests will also be used to complete comparisons between the treatment groups. Change from pre- to post-CAE[SM] at each visit and time point will also be displayed in line plots.

The primary analysis variable will be presented in subject listings by visit and time point where relevant.

14.1.1 Primary Hierarchical Efficacy Analysis

Corneal fluorescein staining (Ora Calibra [M] Scale) will be performed pre-CAE[SM] and post-CAE[SM] for both eyes at Visit 1 (Day -14), Visit 2 (Day 1, prior to treatment), Visit 4 (Day 15) and Visit 5 (Day 29). The 5-unit scale for evaluation of staining in each of the regions [redacted], as measured on the Ora Calibra™ Scale. Only the change from baseline to Visit 5 (Day 29) in pre-CAE[SM] inferior corneal staining, in the worst eye (defined in Section 9.1), is a primary hierarchical efficacy variable. 0.1% RGN-259 Ophthalmic Solution will be compared to

placebo [redacted]. The change from baseline in pre-CAE[SM] [redacted] staining at Visit 5 (Day 29) will be summarized as a continuous variable for the [redacted] for the ITT and PP population.

Analysis of the inferior corneal staining endpoint will be similar to that of the ocular discomfort scale described in Section 14.1, with change from baseline in inferior corneal staining replacing the change from baseline in the change from pre- to post-CAE[SM] ocular discomfort scores.

Sensitivity analyses will be performed following the same strategy as the primary endpoint using a different randomization seed from the primary analysis multiple imputation method. Observed values at each visit and time point, as well as changes from baseline, will also be analyzed to support the primary results.

14.2 Secondary Analyses

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (number of subjects (n), mean, SD, median, minimum and maximum), and analyzed with two-sample *t*-tests comparing the active treatment group to placebo. All visit-based data will be analyzed at each visit and change from baseline. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will be assessed where appropriate. The ITT population with no imputation is used for all secondary efficacy variables.

All secondary efficacy endpoints will also be presented in listings.

14.2.1 Fluorescein Staining

Corneal and conjunctival fluorescein staining will be performed at all scheduled visits, pre- and post-CAE[SM], on both eyes and graded using both the Ora Calibra™ Scale. The scale will grade the cornea and conjunctiva by five regions: [redacted]

Fluorescein staining scores will be summarized by scale, visit, time point (pre- and post-CAE[SM]), and region [redacted]) using quantitative summary statistics. The corneal sum score will be the sum of scores from the [redacted] The conjunctival sum score will be the sum of scores from the [redacted]. Change from pre- to post-CAE[SM] within each visit as well as change from baseline will also be summarized for 0.1% RGN-259 Ophthalmic Solution and placebo.

Statistical comparisons will employ pairwise two-sample *t*-tests as the primary method of analysis for 0.1% RGN-259 Ophthalmic Solution compared to placebo. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed as sensitivity analyses.

All statistical comparisons will be repeated for the [redacted]

Note: The change from pre- to post-CAE[SM] in [redacted] staining scores at Visit 5 (Day 29) in the [redacted] the primary hierarchical efficacy variable and will not be included in these summaries/analyses.

14.2.2 Lissamine Green Staining

The Ora Calibra™ Scale will grade the cornea and conjunctiva by five regions: [redacted]

The Ora Calibra™ Scale lissamine green staining scores will be summarized by visit, time point (pre- and post-CAE[SM]), and region [redacted] using quantitative summary statistics. The corneal sum score will be the [redacted] The conjunctival sum score will be the sum [redacted] The total score will be the [redacted]. Change from pre- to post-CAE[SM] within each visit as well as change from baseline will also be summarized for 0.1% RGN-259 Ophthalmic Solution and placebo.

Statistical comparisons will employ pairwise two-sample *t*-tests as the primary method of analysis for 0.1% RGN-259 Ophthalmic Solution compared to placebo. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed as sensitivity analyses.

14.2.3 Tear Film Break-Up Time

TFBUT will be measured in seconds at all scheduled visits, pre- and post-CAE[SM], on both eyes. For each eye, two measurements will be taken and averaged unless the two measurements are >2 seconds apart and are each <10 seconds, in which case, a third measurement would be taken and the two closest of the three will be averaged and used for analyses. If the differences between two sequential pairs of measurements are the same, e.g., [redacted], then the median of the three readings will be used for analysis.

TFBUT will be summarized by visit and time point (pre- and post-CAE[SM]) using quantitative summary statistics. Change from pre- to post-CAE[SM] within each visit as well as change from baseline will also be summarized for 0.1% RGN-259 Ophthalmic Solution and placebo.

Statistical comparisons will employ pairwise two-sample *t*-tests as the primary method of analysis for 0.1% RGN-259 Ophthalmic Solution compared to placebo. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed as a sensitivity analysis.

14.2.4 Ocular Protection Index

Ocular Protection Index (OPI) will be assessed at visits 2 and 5, pre-CAE^{SM}, on both eyes using the Ora Calibra™ OPI 2.0 System. OPI will be expressed as a percentage of the area of tear film break up in the eye and ranges from 0 to 100%. Interblink interval (IBI) will also be measured by the Ora Calibra™ 2.0 System, as a measure of the average time between blinks, in seconds. The Ora Calibra™ OPI System will monitor each subject over a one-minute time frame.

The OPI and IBI will be summarized by visit (pre-CAE^{SM}) using quantitative summary statistics. Statistical comparisons will employ pairwise two-sample *t*-tests as the primary method of analysis for 0.1% RGN-259 Ophthalmic Solution compared to placebo. An ANCOVA model adjusting for baseline and site will also be assessed as a sensitivity analysis.

14.2.5 Unanesthetized Schirmer's Test

Unanesthetized Schirmer's Test will be assessed on both eyes at all scheduled visits only at pre-CAE^{SM}. The Schirmer's test strip will be placed in the lower temporal lid margin of each eye. After 5 minutes, the test strip will be removed and the length of the moistened area will be recorded in millimeters (mm) for each eye. Lower values indicate less tears produced in the eye.

Unanesthetized Schirmer's Test will be summarized by visit using quantitative summary statistics. Change from baseline will be also summarized. Statistical comparisons will employ pairwise two-sample *t*-tests as the primary method of analysis for 0.1% RGN-259 Ophthalmic Solution compared to placebo. An ANCOVA model adjusting for baseline and site will also be assessed as a sensitivity analysis.

14.2.6 Drop Comfort Assessment

Two tools will be used to assess drop comfort, each of which will be assessed at Visit 2 (Day 1), following the first dose of study drug, Visit 3 (Day 8), and at Visit 4 (Day 15) post-CAE^{SM}.

- [redacted]

- [redacted]

14.2.7 Ocular Surface Disease Index®

The Ocular Surface Disease Index© (OSDI) will be assessed at the subject level at all scheduled visits only at pre-CAE^{SM}. Subjects will be asked 12 questions at each visit. Each question will be graded on a 0 to 4 scale, where 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 sum of the scores from all questions answered will be calculated. The total OSDI score will be calculated using the formula: OSDI = (Sum of scores) x 25 / (# of questions answered). The OSDI is on a scale of 0 to 100, with higher scores representing greater disability.

Each individual response and the total OSDI score will be presented separately by visit using quantitative summary statistics. Change from baseline will also be summarized.

Statistical comparisons will employ pairwise two-sample *t*-tests as the primary method of analysis for 0.1% RGN-259 Ophthalmic Solution compared to placebo. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed as sensitivity analysis.

14.2.8 Ocular Discomfort Using the Ora Calibra™ Scale

Ocular discomfort scores will be subjectively graded by the subjects using the Ora Calibra™ Ocular Discomfort Scale at all scheduled visits, pre- and post-CAE^{SM}, and during CAE^{SM} exposure [redacted]

14.2.8.1 Ora Calibra™ Ocular Discomfort Scale Pre- and Post-CAE^{SM}

This secondary ocular discomfort score will be measured outside of the CAE^{SM} exposure but still measured pre- and post-CAE^{SM}. Ocular discomfort scores will be summarized by visit and time point using quantitative summary statistics. Change from pre- to post-CAE^{SM} within each visit as well as change from baseline will also be summarized.

Statistical comparisons will employ pairwise two-sample *t*-tests as the primary method of analysis for 0.1% RGN-259 Ophthalmic Solution compared to placebo. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed as sensitivity analyses.

14.2.8.2 Ora Calibra™ Ocular Discomfort Scale During CAE[SM] Exposure

Ocular discomfort scores during CAE[SM] at 0 [redacted] the primary endpoints. The Primary endpoints along with the other time points during CAE[SM] exposure will be summarized by visit and time point using quantitative summary statistics. The change from pre-CAE[SM] [redacted] will be the change from [redacted] within the same visit and will also be summarized.

The overall ocular discomfort during CAE[SM] will be compared between 0.1% RGN-259 Ophthalmic Solution and placebo using a mixed-effect model to account for the correlations among the repeated measurements for the same eye. This analysis will be performed for each visit separately, and include treatment, time (nominal time will be used), treatment by time interaction, any significant site interaction, and the baseline ocular discomfort score as fixed effects, and subject as a random effect. The following SAS code will be used:

```
ods output  SMeans   outdata1 Diffs   outdata2;
proc mixed data   indata method   ml;
   class subjid treatment time;
   model score   base treatment   time;
   repeated subject   subjid / type   COV;
   lsmeans treatment / pdiff cl;
run;
```

where

- *subjid* is the unique subject ID;
- *treatment* is the name of the treatment group;
- *time* is the nominal time of the measurement;
- *score* is the ocular discomfort score;
- *base* is the baseline ocular discomfort score; and
- *COV* is the appropriate variance-covariance structure.

The appropriate variance-covariance structure will be tested in the following order and only move to the next if convergence does not occur: *type* = *UN* (unstructured), then *EXCH* (exchangeable), then *AR(1)* (auto-regressive 1).

14.2.9 Ora Calibra™ Ocular Discomfort and 4-Symptom Questionnaire

Ocular discomfort and dry eye symptoms will be assessed at all scheduled visits, pre- and post-CAE[SM] at the subject level in regard to how both eyes feel. The Ora Calibra™ Ocular Discomfort & 4-Symptom Questionnaire will be used, which includes rating of the severity of [redacted]

[redacted].

Ocular discomfort and dry eye symptoms will be summarized by visit and time point (pre- and post-CAE[SM]) using quantitative summary statistics. Change from pre- to post-CAE[SM] within each visit as well as change from baseline will be also summarized.

Statistical comparisons will employ pairwise two-sample *t*-tests as the primary method of analysis for 0.1% RGN-259 Ophthalmic Solution compared to placebo. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed as sensitivity analyses.

14.2.10 Daily Diary

[redacted]

15. Exploratory Analyses

There are no exploratory analyses in this study.

16. Safety Analyses

All safety analyses will be conducted using the Safety Population.

16.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and

unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the study drug, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the study drug will also be considered a new AE and reported. Any medical condition present prior to the administration of the study drug that remains unchanged or improved should not be recorded as an AE at subsequent visits. All AEs will be coded using the MedDRA Version 19.1.

Study drug includes the investigational drug under evaluation and any comparator drug, placebo, or any other medications required by the protocol given during any stage of the study.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning.

Treatment-emergent adverse events (TEAE) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated. 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.

Serious adverse events (SAE) are defined as any event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapability, is a congenital anomaly/birth defect, or is medically significant.

An overall summary will be presented that includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE, by treatment group. This summary will also include breakdowns of TEAEs further categorized as ocular (worst eye and fellow eye separately) or non-ocular, treatment-emergent serious AEs (TESAE), TEAEs by maximum severity, TEAEs by maximum relationship, and TEAEs leading to subject withdrawal.

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 level 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 ascending alphabetical order; 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 and PT for the following: maximal severity and suspected relationship to study drug.

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

- Ocular TEAEs in the worst eye
- Ocular TEAEs in the fellow eye
- Non-ocular TEAEs
- Treatment-related ocular TEAEs
- Treatment-related non-ocular TEAEs
- SAEs

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to investigational product 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.

The relationship of each AE to the study drug should be determined by the investigator 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.

Only TEAEs with a relationship of definite, probable, or possible, or with a missing relationship, will be considered as treatment-related TEAEs.

Summaries of TEAEs by strongest relationship and 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 each of the strongest relationship and the maximal severity.

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- *Unexpected*: An AE that is not listed in the Investigator's brochure or is not listed at the specificity or severity that has been observed.
- *Expected*: An AE that is listed in the Investigator's brochure at the specificity and severity that has been observed.
- *Not Applicable*: Any AE that is unrelated to the study drug.

AEs that are mentioned in the Investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected. AEs that are reported as suspected with respect to relationship to study drug, and are also categorized as unexpected are to be reported directly to Ora, the sponsor, and other authorities as appropriate. Expectedness of the AE will be included in the subject level listings.

All AEs will be presented in a subject listing. The AEs leading to study treatment discontinuation will be listed separately. In addition, all serious AEs will be presented in a separate listing.

16.2 Visual Acuity (ETDRS)

Best corrected visual acuity (BCVA) will be assessed on both eyes at all scheduled visits pre-CAE^{SM} using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. The Investigator will indicate on the CRF whether visual acuity (VA) was measured with or without correction, and if pin-hole was used.

The sites will convert number of letters read correctly to the logarithm of the minimum angle of resolution (logMAR) scores and logMAR VA scores will be collected and used for all summaries. BCVA and change from baseline will be summarized by treatment group and visit, for the worst eye and fellow eye separately, using continuous summary statistics (mean, SD, median, minimum, and maximum). BCVA data will be also presented in a listing.

16.3 Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy examinations will be conducted on both eyes at all scheduled visits, pre- and post-CAE[SM]. The slit-lamp findings will include examinations of the cornea, conjunctiva, anterior chamber, iris, lens, and lid. Each parameter will be graded as normal or abnormal. Abnormal findings will be further classified as not clinically significant (NCS) or clinically significant (CS).

Slit lamp findings will be summarized by treatment group and visit, for the worst eye and fellow eye separately, using qualitative summary statistics (frequency counts and percentages). Percentages will be based on the number of subjects with non-missing values for the treatment group at a given visit.

A shift table will show changes from baseline (Visit 2 (Day 1), pre-CAE[SM]) to all observations at later study visits and time points. The data for slit-lamp biomicroscopy will be presented in a listing.

16.4 Undilated Fundoscopy

Undilated fundoscopy examinations will be conducted on both eyes at Visit 1 (Day -14) and Visit 5 (Day 29) post-CAE[SM]. The fundus pathology findings will include examinations of the vitreous, retina, macula, choroid, and optic nerve, and be recorded as normal, abnormal (NCS), or abnormal (CS). Summaries of undilated fundoscopy findings will be presented by treatment and visit, for the worst eye and fellow eye separately, using frequency counts and percentages. Percentages will be based on the number of subjects with non-missing values for the treatment group at a given visit.

A shift table will show changes from baseline (Visit 1 (Day -14)) to Visit 5 (Day 29) on the above variables. The data for undilated fundoscopy will be presented in a listing.

16.5 Intraocular Pressure (IOP)

IOP will be measured for both eyes at Visit 1 (Day -14) and Visit 5 (Day 29) post-CAE[SM]. IOP will be summarized by treatment group and visit, for the worst eye and fellow eye separately, using continuous summary statistics (mean, SD, median, minimum, and maximum).

Change from baseline will also be calculated and summarized using continuous summary statistics in a table. The data for IOP examinations will be presented in a listing.

16.6 Corneal Sensitivity (Cochet-Bonnet)

Corneal sensitivity will be assessed at Visit 1 (Day -14) and Visit 5 (Day 29), pre-CAE[SM] for each eye separately. Corneal sensitivity is measured in millimeters (mm) three times, and the average of the three measurements will be summarized by treatment group and visit using descriptive statistics.

A change from baseline will be calculated as the Visit 5 value minus the Visit 1 value and reported with the observed values using continuous summary statistics.

17. Interim Analyses

No interim analyses are planned for this study.

18. Changes from Protocol-Stated Analyses

There are no changes from protocol-stated analyses.

19. References

None

20. Tables

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

Tab e Number	Descr pt on	Popu at on
Study Population Data		
Table 14.1.1	**Subject Disposition**	**All Randomized Subjects**
Table 14.1.2.1	**Demographics**	**ITT Population**
Tab e 14.1.2.2	Demograph cs	Safety Popu at on
Tab e 14.1.3	Base ne D sease Character st cs (Worst Eye)	ITT Popu at on
Tab e 14.1.3.1	Ocu ar Med ca H story	Safety Popu at on
Tab e 14.1.3.2	Non-Ocu ar Med ca H story	Safety Popu at on
Tab e 14.1.4.1	Ocu ar Concom tant Med cat ons by Treatment Group, Drug C ass and Preferred Name	Safety Popu at on
Tab e 14.1.4.2	Non-Ocu ar Concom tant Med cat ons by Treatment Group, Drug C ass and Preferred Name	Safety Popu at on
Tab e 14.1.5	Screen Fa ures and Reasons for Screen Fa ure	A Screen Fa ed Sub ects
Primary Efficacy Analyses		
Table 14.2.1.1	**Ocular Discomfort Score Change from Pre-CAE [redacted] to Post-CAE ([redacted] at Visit 5 (Day 29)**	**ITT Population with LOCF**
Tab e 14.2.1.2	Ocu ar D scomfort Score Change from Pre-CAE [redacted] to Post-CAE [redacted] at V s t 5 (Day 29)	ITT Popu at on w th MCMC
Tab e 14.2.1.3	Ocu ar D scomfort Score Change from Pre-CAE [redacted] to Post-CAE [redacted] at V s t 5 (Day 29)	ITT Popu at on w th Observed Data On y
Tab e 14.2.1.4	Ocu ar D scomfort Score Change from Pre-CAE [redacted] to Post-CAE [redacted] at V s t 5 (Day 29)	PP Popu at on w th Observed Data On y
Table 14.2.2.1	**Inferior Corneal Fluorescein Staining Change from Pre-CAE at Visit 5 (Day 29) in the [redacted]**	**ITT Population with LOCF [redacted]**
Tab e 14.2.2.2	Infer or Cornea F uoresce n Sta n ng Change from Pre-CAE at V s t 5 (Day 29) n the [redacted]	ITT Popu at on w th MCMC [redacted]
Tab e 14.2.2.3	Infer or Cornea F uoresce n Sta n ng Change from Pre-CAE at V s t 5 (Day 29) n the [redacted]	ITT Popu at on w th Observed Data On [redacted]
Tab e 14.2.2.4	Infer or Cornea F uoresce n Sta n ng Change from Pre-CAE at V s t 5 (Day 29) n the [redacted]	PP Popu at on w th Observed Data On y [redacted]
Secondary Efficacy Analyses		
Table 14.2.3.1	**Corneal and Conjunctival Fluorescein Staining (Ora Calibra Scale)**	**ITT Population**
Table 14.2.3.2	**Corneal and Conjunctival Fluorescein Staining (Ora Calibra Scale) in the [redacted]**	**ITT Population [redacted]**
Tab e 14.2.3.3	L ssam ne Green Sta n ng (Ora Ca bra Sca e)	ITT Popu at on
Tab e 14.2.3.4	Tear F m Break-Up T me (TFBUT)	ITT Popu at on
Tab e 14.2.3.5	Ocu ar Protect on Index (OPI, Pre-CAE)	ITT Popu at on
Tab e 14.2.3.6	Unanesthet zed Sch rmer's Test (Pre-CAE)	ITT Popu at on
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