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®) Model (ARISE-3)

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Table of Contents

1. Introduction....7
2. Study Objectives....7
3. Study Variables....7
3.1 Primary Variables....7
3.2 Secondary Variables....7
3.3 Safety Variables....8
3.4 Statistical Hypotheses....8
4. Study Design and Procedures....9
4.1 General Study Design....9
4.2 Schedule of Visits and Assessments....10
5. Study Treatments....11
5.1 Method of Assigning Subjects to Treatment Groups....11
5.2 Masking and Unmasking....12
6. Sample Size and Power Considerations....12
7. Data Preparation....13
7.1 CDISC Compliance....13
8. Analysis Populations....14
8.1 Intent-to-Treat....14
8.2 Modified Intent-to-Treat....14
8.3 Per Protocol....14
8.4 Safety....14
9. General Statistical Considerations....14
9.1 Unit of Analysis....14
9.2 Missing or Inconclusive Data Handling....15
9.2.1 Missing Endpoint Data....15
9.2.2 Missing Start and/or End Dates for Concomitant Medications....16
9.3 Definition of Baseline....16
9.4 Data Analysis Conventions....17
9.5 Adjustments for Multiplicity....17
9.1 Early Termination Visits....18
10. Disposition of Subjects....18
11. Demographic and Baseline Disease Characteristic Variables....19
11.1 Demographic Variables....19
11.2 Pretreatment Variables and Baseline Disease Characteristics....19

12. Medical History, Prior and Concomitant Medications 20
12.1 Medical History 20
12.2 Prior and Concomitant Medications 20
13. Dosing Compliance and Treatment Exposure 21
13.1 Dosing Compliance 21
13.2 Treatment Exposure 21
14. Efficacy Analyses 22
14.1 Primary Analysis 22
14.1.1 Pre-CAE® to Post-CAE® Change in Inferior Fluorescein Staining 22
14.1.2 Pre-CAE® Ocular Discomfort from the Ocular Discomfort and 4-Symptom Questionnaire 25
14.2 Secondary Analyses 27
14.2.1 Fluorescein Staining 27
14.2.2 Lissamine Green Staining 27
14.2.3 Tear Film Break-Up Time (TFBUT) 28
14.2.4 Unanesthetized Schirmer's Test 28
14.2.5 Drop Comfort Assessment 29
14.2.6 Ocular Surface Disease Index© (OSDI) 29
14.2.7 Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire 30
14.2.8 Ocular Discomfort Using the Ora Calibra® Ocular Discomfort Scale 30
14.2.8.1 Ora Calibra® Ocular Discomfort Scale Outside the CAE® Pre- and Post-CAE® 30
14.2.8.2 Ora Calibra® Ocular Discomfort Scale During CAE® 31
14.2.9 Daily Diary 31
15. Safety Analyses 32
15.1 Adverse Events 32
15.2 Visual Acuity (ETDRS) 35
15.3 Slit-Lamp Biomicroscopy Examination 35
15.4 Undilated Fundoscopy Examination 35
15.5 Intraocular Pressure (IOP) 36
15.6 Corneal Sensitivity (Cochet–Bonnet) 36
16. Interim Analyses 36
17. Changes from Protocol-Stated Analyses 36
18. Revision History 36
19. Tables 36
20. Listings 40
21. Figures 42

List of Abbreviations

AE	Adverse Event
ADaM	Analysis Data Model
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BOCF	Baseline Carried Forward
CAE®	Controlled Adverse Environment®
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
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
ICFS	Inferior Corneal Fluorescein Staining
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeters
mmHG	Millimeters of Mercury
NCS	Not Clinically Significant
OD	*Oculus dexter* (Right Eye)
OS	*Oculus sinister* (Left Eye)
OSDI©	Ocular Surface Disease Index©
OU	*Oculus uterque* (Both Eyes)
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
QID	*Quatre in dis* (4 times a day)
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model

SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFBUT©	Tear Film Break-Up Time©
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 RGN-259/19-110-0002, amendment 2 dated 15Jul2020.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (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 (0.1% RGN-259) to the placebo ophthalmic solution (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 following:

- Change from baseline in inferior corneal fluorescein staining change from pre-controlled adverse environment (CAE®) to post-CAE® at Day 15 (Visit 4) using the Ora Calibra® Scale

The hierarchical primary efficacy variable is the following:

- Change from baseline in ocular discomfort at Day 15 (Visit 4) pre-CAE® using Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire

3.2 Secondary Variables

The secondary efficacy variables include the following:

- Fluorescein staining (Ora Calibra® Scale) at Visits 3 and 4 (change from pre-CAE® to post-CAE®, pre-CAE®, and post-CAE® in the following regions: [redacted], excluding the primary efficacy measure pre-CAE® to post-CAE® at Visit 4

- Lissamine green staining (Ora Calibra® Scale) at Visits 3 and 4 (change from pre-CAE® to post-CAE®, pre-CAE®, and post-CAE® in the following regions: [redacted]
- Tear Film Break-Up Time© (TFBUT©) at Visits 3 and 4 (change from pre-CAE® to post-CAE®, pre-CAE® and post-CAE®)
- Unanesthetized Schirmer's Test at Visits 3 and 4 (pre-CAE®)
- Drop comfort assessment (Ora Calibra®) after randomization at Visit 2
- Ocular Surface Disease Index© (OSDI©) at Visits 3 and 4 (pre-CAE®)
- Ocular Discomfort & 4-Symptom Questionnaire (Ora Calibra®) at Visits 3 and 4 (change from pre-CAE® to post-CAE®, pre-CAE®, and post-CAE®)
- Ocular discomfort outside CAE® at Visits 3 and 4 (Change from Pre-CAE® to Post-CAE®, Pre- and Post-CAE®)
- Ocular discomfort during CAE® at Visit 4
- Daily diary

Note that at Visit 3 the CAE® is not performed, therefore only 1 measure will be included which is equivalent to the pre-CAE® measures at other visits.

3.3 Safety Variables

The safety variables include the following:

- Visual acuity (Early Treatment of Diabetic Retinopathy Study [ETDRS]) at Visits 1, 2, 3, and 4
- Slit lamp biomicroscopy at Visits 1, 2, 3, and 4
- Corneal sensitivity (Cochet-Bonnet) at Visits 1 and 4 (pre-CAE®)
- Adverse event (AE) query at Visits 1, 2, 3, and 4
- Undilated fundoscopy at Visits 1 and 4
- Intraocular pressure (IOP) at Visits 1 and 4

3.4 Statistical Hypotheses

The null and alternative hypotheses are based on the primary variables and are stated in terms of one-sided hypotheses although statistical testing will be two-sided. The null and alternative hypotheses for the primary and hierarchical primary variables are as follows:

> H_{01}: There is no difference between 0.1% RGN-259 and placebo in the change from baseline in inferior corneal fluorescein staining change from pre-CAE® to post-CAE® at Day 15 (Visit 4) using the Ora Calibra® Scale.
>
> H_{11}: The change from baseline in inferior corneal fluorescein staining change from pre-CAE® to post-CAE® at Day 15 (Visit 4) using the Ora Calibra® Scale is less with 0.1% RGN-259 than with placebo.

If H_{01} is rejected, H_{02} will be tested.

> H_{02}: There is no difference between 0.1% RGN-259 and placebo in the change from baseline in ocular discomfort at Day 15 (Visit 4) pre-CAE® using the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire.
>
> H_{12}: The change from baseline in ocular discomfort at Day 15 (Visit 4) pre-CAE® using the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire is less with 0.1% RGN-259 than with placebo.

4. Study Design and Procedures

4.1 General Study Design

This is a Phase 3, multicenter, randomized, double-masked study designed to evaluate the efficacy and safety of 0.1% RGN-259 compared to placebo in subjects with dry eye. Approximately 700 male and female subjects at least 18 years of age with a subject-reported history of dry eye in both eyes and meeting all other study eligibility criteria will be randomized to receive treatment with 0.1% RGN-259 or placebo in a 1:1 ratio (expected approximately 350 subjects in each treatment group). This study will consist of 2 periods: a 14-day run-in period and a 2-week treatment period. During the run-in subjects will instill placebo four times a day (QID; morning, noon, afternoon and evening) in both eyes, and a 2-week 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®) 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® 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 2 weeks. At the conclusion of 2 weeks of treatment (Visit 4 [Day 15]), subjects will be challenged for [redacted] in the CAE® model.

Study visits will be referred to in all tables and listings as the scheduled visit and planned study day in the following format, Scheduled Visit (Planned Study Day) or Visit (Study Day), 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 is shown in Table 1.

Table 1. Study Visits

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	± 2 Days

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in Table 2.

Table 2. Schedule of Visits and Assessments

Procedure	Visit 1 Day -14 ± 1		Visit 2 Day 1		Visit 3 Day 8 ± 1	Visit 4 Day 15 ± 2	
	Pre-CAE®	Post-CAE®	Pre-CAE®	Post-CAE®		Pre-CAE®	Post-CAE®
Informed Consent/HIPAA	X						
Medical/Medication History and Demographic Data	X						
Run-in Placebo Collection			X				
Study Drug Collection					X	X	
Diary Collection			X		X	X	
Medical/Medication History Update			X		X	X	
Adverse Event Query		X	X	X	X	X	X
Pregnancy Test	X[1]					X[1]	
Ocular Discomfort & 4-Symptom Questionnaire - Ora Calibra® Scale	X	X	X	X	X	X	X
Discomfort outside CAE® - Ora Calibra® Ocular Discomfort Scale	X	X	X	X	X	X	X
OSDI© Questionnaire	X		X		X	X	
Visual Acuity (ETDRS)	X		X		X	X	
Review of Qualification Criteria	X	X	X	X			
Slit Lamp Biomicroscopy	X	X	X	X	X	X	X
TFBUT©	X	X	X	X	X	X	X
Fluorescein Staining - Ora Calibra® Scale	X	X	X	X	X	X	X
Lissamine Green Staining - Ora Calibra® Scale	X	X	X	X	X	X	X
Corneal Sensitivity (Cochet-Bonnet)	X					X	
Unanesthetized Schirmer's Test	X		X		X	X	
CAE® Exposure	X		X			X	
Discomfort During CAE® - Ora Calibra® Ocular Discomfort Scale	X[2]		X[2]			X[2]	
Intraocular Pressure (IOP)		X					X
Undilated Fundus Exam		X					X
Run-in Placebo Dispensation		X					
Randomization				X			
Subject Self-instillation of study drug				X	X		
Ora Calibra® Drop Comfort Assessment				X	X		
Study Drug Dispensation				X	X[3]		
Diary Dispensation		X		X	X		
Exit Subject from Study							X

X[1] = For females of childbearing potential, X[2] = Procedure started at time [redacted] CAE® exposure, X[3] = IP will be collected and re-dispensed at Visit 3.

5. Study Treatments

Run-In:

- Placebo Ophthalmic Solution (Vehicle)

Randomized Study Treatments:

- 0.1% RGN-259 Ophthalmic Solution
- Placebo Ophthalmic Solution (Vehicle)

5.1 Method of Assigning Subjects to Treatment Groups

On Day -14 (Visit 1), subjects who provide verbal and written informed consent will be assigned a unique 5-digit subject ID, which consists of the 2-digit site number (ranging from 70-94) plus a unique 3-digit screening number (beginning with 001 within each site). The 3-digit screening numbers must be assigned in ascending consecutive order at the site. The 5-digit subject ID will be used to identify subjects in all datasets and listings for this study.

Subjects who are enrolled in the study multiple times will be assigned a separate subject ID each time they are enrolled. Throughout the study, the subject will be identified by the subject ID that applies to each respective enrollment event. A unique subject identifier will be used in the SDTM and ADaM datasets to demark that the subject enrolled multiple times and to uniquely identify the subject.

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 using a 1:1 assignment ratio to receive either 0.1% RGN-259 or placebo. The Interactive Response Technology (IRT) within iMedNet will be used to account for the stratification factors.

Randomization will be stratified by the following factors:

1. Change from pre-CAE® to post-CAE® in inferior corneal fluorescein staining (Ora Calibra® Scale) at Visit 2 (≤1 and >1) in the worst eye (see Section 9.1 of this SAP for the worst eye definition).
2. Ocular discomfort (Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire) pre-CAE® at Visit 2 (<3 and ≥3).

The subjects will be assigned a randomization number and study drug kit number. Both the randomization number and the dispensed study drug kit number will be recorded on the patient's source document and electronic case report form (eCRF). The randomization number is a 4 digit number ranging from 3001 to 4408. The kit numbers consist of a 5-digit ID number ranging from 60001 to 61500. Subjects who meet all eligibility criteria will be randomly assigned a treatment group within their stratum. If a randomized subject is discontinued from the study for any reason, their randomized study drug kit number will not be reassigned.

A back-up block of study drug kits will be available at each site to be used for study treatment replacement through the IRT.

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. The randomization schedule and study drug kit was created by an unmasked independent 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 IRT.

Further functional specifics about unmasking or emergency unmasking are detailed in the IRT Plan and the Safety Management Plan.

6. Sample Size and Power Considerations

This study is expected to enroll approximately 350 subjects in each of the 2 treatment arms, for a total of 700 randomized subjects.

The primary endpoint is the change from baseline in inferior corneal fluorescein staining change from pre-CAE® to post-CAE® at Day 15 (Visit 4) using the Ora Calibra® Scale. The study will be considered successful if and only if this endpoint is met. Accounting for a 5% discontinuation or drop-out rate (related to the COVID-19 pandemic) and a sample size of 332 subjects per treatment arm, the study will have 91% power to detect a difference as low as -0.20 between 0.1% RGN-259 and placebo for the primary endpoint of change from baseline in inferior corneal fluorescein staining change from pre-CAE® to post-CAE® at Day 15 (Visit 4) using the Ora Calibra® Scale. This assumes a two-sided test at alpha = 0.05 and a common standard deviation (SD) of 0.774 in both treatment arms.

The hierarchical endpoint of the change from baseline in ocular discomfort at Day 15 (Visit 4) pre-CAE® using the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire is also considered in terms of statistical power. 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 332 subjects randomized per treatment arm, and a difference between 0.1% RGN-259 and placebo of -0.30, the study will have 95% power to detect a treatment difference. This assumes a two-sided test at alpha = 0.05 and a common SD of 1.07 in both treatment arms.

With this sample size, the study will have 86% power to show statistical significance for both the primary endpoint and the hierarchical endpoint.

The primary analysis will include all subjects by accounting for missing data at Day 15 (Visit 4). However, to maintain robust power, the sample size will be increased to 350 subjects per treatment arm, or a total of 700 subjects, to account for up to 5% missing data related to COVID-19. Estimates for sample size calculations are derived from prior RGN-259 studies.

7. Data Preparation

All reported study data will be recorded on the eCRFs supplied by Statistics & Data Corporation (SDC) using iMedNet which is an Electronic Data Capture (EDC) system. 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 Management Plan and Data Validation Manual as separate documents. 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, in consultation with SDC.

Final 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.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Final locked data has been transferred from Data Management to Biostatistics.
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

7.1 CDISC Compliance

The final locked data collected in the iMedNet database will be transformed into submission-ready, study data tabulation model (SDTM) and analysis data model (ADaM) datasets. To comply with CDISC standards the below steps will be followed:

- Final locked data will be transformed using the SDTM Implementation Guide version 3.2 to conform to previous RGN-259 studies.
- SDTM will be transformed into analysis datasets via the 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 3.0.0 or later.

8. Analysis Populations

Subjects who are randomized in the study twice, with 2 subject IDs, will be analyzed once per the first occurrence of randomization for the ITT, mITT and PP populations. The first occurrence of randomization will be the subject ID with the earliest randomization date.

For the Safety Population subjects who are treated in the study twice will be analyzed twice as treated.

8.1 Intent-to-Treat

The intent-to-treat (ITT) population includes all randomized subjects. All efficacy analyses will be performed on the ITT population and subjects will be analyzed as randomized.

8.2 Modified Intent-to-Treat

The modified intent-to-treat (mITT) population includes all randomized subjects who did not discontinue or have missing primary efficacy data due to COVID-19 or any other pandemic reasons. Subjects discontinued due to other reasons but would have discontinued due to COVID-19 had they remained on study (e.g., from sites that discontinued subjects as of a certain date when the subject would have been on study) will also be excluded. Subjects in the mITT population will be analyzed as randomized.

8.3 Per Protocol

The per protocol (PP) population includes all subjects in the mITT population without significant protocol deviations that may have an impact on the primary efficacy outcome and who complete the study. Protocol deviations will be assessed and decisions regarding subject evaluability will be made prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.

8.4 Safety

The safety population includes all subjects who receive at least 1 dose of the investigational product. All safety assessments will be analyzed with the safety population. 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

The unit of analysis in this study will be the study eye for all efficacy and safety summaries where appropriate. Both eyes will be presented, study eye and fellow eye, for all appropriate safety summaries, while efficacy summaries and analyses will generally focus on the study eye only.

Study eye (worst eye) definition: Eyes are eligible for analysis if they meet 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 inferior

corneal fluorescein staining from pre-CAE® to post-CAE® at Visit 2. If the inferior corneal fluorescein staining increase is the same in both eyes, then the worst eye will be the eye with worse (higher) ocular discomfort outside CAE® according to the Ora Calibra® Ocular Discomfort Scale at Visit 2 pre-CAE®. If the ocular discomfort is the same in both eyes then the right eye (OD) will be selected as the worst eye.

Subject-level questionnaires (OSDI, Drop Comfort Questionnaire, and Ocular Discomfort and 4-Symptom Questionnaire), dosing exposure and compliance, non-ocular AEs and non-ocular medical history will be presented at the subject level.

9.2 Missing or Inconclusive Data Handling

9.2.1 Missing Endpoint Data

Primary efficacy data missing due to the COVID-19 pandemic will not be imputed in the mITT (primary) population or the sensitivity PP population. If the missing data is unrelated to the pandemic then missing data will be imputed in the mITT and PP populations. The ITT sensitivity analyses will impute any missing data regardless of the reason for missing data. Very little (approximately 5%) missing data is expected for the primary analysis at Day 15. However, the primary endpoints will be evaluated thoroughly to assess the impact of missing data on the study conclusions.

For the primary analysis of the change from baseline in the change from pre-CAE® to post-CAE® inferior corneal fluorescein staining at Day 15 (Visit 4), Markov Chain Monte Carlo (MCMC) multiple imputation methodology will be used to impute missing data in the mITT population and in the ITT population as a sensitivity analysis. Missing change from pre-CAE® to post-CAE® will be imputed based on MCMC methodology by imputing the missing change from pre-CAE® to post-CAE® values. If a subject has a pre-CAE® value but is missing a post-CAE® value, the change from pre-CAE® to post-CAE® will be imputed rather than just the post-CAE® value. For the sensitivity analysis of inferior staining at Day 15 (Visit 4), the last value from the previous CAE® exposure visit will be carried forward for change from pre-CAE® to post-CAE®, meaning the baseline assessment from Day 1 (Visit 2) will be carried forward if no other data is available in the mITT and ITT populations. No individual pre-CAE® or post- CAE® values will be imputed, only the change pre-CAE® to post-CAE® will be imputed.

The hierarchical efficacy analyses will also be performed using the MCMC multiple imputation method for missing values. For the sensitivity analysis of ocular discomfort scores pre-CAE® measured with the Ocular Discomfort & 4-Symptom Questionnaire at Day 15 (Visit 4) using LOCF, the last value matching the pre-CAE® assessments from the previous visits will be carried forward, meaning the sole assessment from Day 8 (Visit 3), or the pre-CAE® assessment at Day 1 (Visit 2). No post-CAE® values will be imputed for pre-CAE® time points and vice versa.

For both primary endpoints an analysis using observed data at Day 15 (Visit 4) only will also be performed in the mITT, ITT and PP populations. Additionally, control-based pattern mixture modeling will investigate the pattern of missingness not-at-random for sensitivity in the mITT and ITT populations.

No secondary efficacy endpoints or safety endpoints will be imputed.

9.2.2 Missing Start and/or End Dates for Concomitant Medications

In general there will be no imputation of missing datapoints other than for partial or missing dates of concomitant medications as stated below. Imputation of dates will only be used to determine if a medication is concomitant or not. Medical history and AE dates will not be imputed.

Partial/missing start dates for concomitant medications will be imputed as follows:

- Start dates missing only the day will be imputed as the 1st of the month unless month and year are same as month and year of first dose of study medication, in which case missing day will be imputed as the first dose day.
- Start dates with both day and month missing will be imputed as 1 Jan unless year is same as year of first dose of study medication in which case missing day and month will be imputed as the first dose day and month.
- Completely missing dates will not be imputed; medications with missing start dates will be considered concomitant if the medication end date is after the date of first dose of study medication or ongoing.

Partial/missing end dates for concomitant medications will be imputed as follows:

- If the ongoing flag is missing or “Yes,” then date will not be imputed. If ongoing is “No” and the date is completely missing, then the end date will be imputed as the last dose date.
- End dates with missing only the day will be imputed as the last day of the month unless month and year are same as month and year of the last dose, in which case missing day will be imputed as the last dose date.
- End dates with both day and month missing will be imputed as 31 Dec unless year is same as year of the last dose, in which case missing day and month will be imputed as the last dose day and month.

The original dates will be displayed in data listings and the imputed dates will be used to determine concomitant medication status only.

9.3 Definition of Baseline

Baseline for each measure is defined as the last measure prior to the initiation of study treatment at Day 1 (Visit 2) unless otherwise stated. Measurements taken at both pre-CAE® and post-CAE® will have baselines for change from pre-CAE® to post-CAE®, pre-CAE®, and post-CAE®.

For measures from daily symptom 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 for each symptom.

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) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, visit, time point, and eye, as applicable, based on all randomized subjects unless otherwise specified for all randomized subjects. Subjects who complete the study more than once will have all data listed on listings per the subject ID corresponding to each enrollment event with an * after each ID and the relationship between subjects stated in the footnote.

Summaries for quantitative variables will include the number of observations (n), arithmetic mean, SD, median, minima, and maxima. For efficacy data analyzed by general linear models with covariates or repeated measures, least squares (LS) means, LS mean differences, and standard errors (SE) will also be presented. Minima and maxima will be reported with the same precision as the raw values; means, LS means, and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations and SEs will be presented to two additional decimal places than reported in the raw values. 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 ($\alpha = 0.05$). Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. 95% CIs will also be presented for each efficacy endpoint by treatment group. 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 2 comparisons of the active treatment group to placebo, a hierarchical testing procedure will be used for the primary endpoints. First, the change from baseline in inferior corneal fluorescein staining change from pre-CAE® to post-CAE® at Day 15 (Visit 4) for 0.1% RGN-259 will be tested versus placebo at $\alpha = 0.05$. If there is a significant difference in this inferior corneal

staining endpoint, then the hierarchical endpoint, the change from baseline in ocular discomfort at Day 15 (Visit 4) pre-CAE® for 0.1 % RGN-259 ophthalmic solution, will be tested versus placebo at α = 0.05.

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

9.1 Early Termination Visits

Early termination visits and data are captured in EDC as a separate visit 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. Any end of study disposition or screen failure reason related to COVID-19 will be listed and summarized. 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. The number of subjects who received randomized treatment or who were randomized and did not receive treatment will be displayed by treatment group and for all subjects. 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 (mITT, 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. COVID-19 related protocol deviations will be listed separately from other protocol deviations.

The number and percentage of subjects completed, prematurely discontinued from the study, and any 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 violation, administrative reasons, sponsor termination of study, withdrawal by subject, and other. A subject listing will be provided that includes the date of and reason for premature study discontinuation. Reasons for discontinuation will

use discontinued subjects in the denominator for percentage calculations, and the number of randomized subjects will be used for all other percentage calculations.

A second disposition table will be created to summarize dispositions in the mITT population. Summaries will include numbers and percentages of subjects who were randomized, completed the study, and discontinued from the study. The number of subjects who received randomized treatment or who were randomized and did not receive treatment will be displayed by treatment group and for all subjects. 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 and percentage of subjects with protocol deviations, including any deviation (major and minor) will be summarized by treatment group for all randomized subjects. COVID-19 related discontinuations and protocol deviations will be omitted from the table as they are no longer applicable in the mITT population.

The number of subjects in each of the analysis populations (mITT, PP, and Safety) will be displayed by treatment and percentages will be calculated using randomized subjects as the denominator.

In addition, subject listings will be provided that include informed consent date, randomization information, inclusion and exclusion criteria violations, and exclusions from any analysis populations.

11. Demographic and Baseline Disease Characteristic 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 Multiple Race. Demographic variables will be summarized for the mITT, 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 including All Subjects, for age category, sex, race, ethnicity, and iris color (for the 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 group for the mITT and ITT population. These will include baseline inferior corneal fluorescein staining and ocular discomfort from the Ocular Discomfort and 4-Symptom Questionnaire, with subgroups matching the

randomization strata; Ora Calibra® Ocular Discomfort Scale outside of CAE®; [redacted] TFBUT; unanesthetized Schirmer's test; and total OSDI. If signs or symptoms were performed both pre- and post-CAE® at Visit 2, then both time points will be presented.

The scales for each assessment are detailed in Section 14 of this SAP.

12. Medical History, Prior and Concomitant Medications

12.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0.

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. Tables will be sorted alphabetically by SOC and PT.

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

12.2 Prior and Concomitant Medications

For most prior and concomitant medications the documentation period starts 30 days prior to the initiation of study drug administration. For medications with longer washout periods and defined as exclusionary criteria in Protocol Section 5.4, those medications are documented only if taken within the specified washout periods of 45 days or 6 months, depending on the medication. Listings and Safety Population tables will only be produced for randomized subjects or for subjects who are treated with study drug; therefore, listings and tables are not expected to have instances of the exclusionary medications.

Prior and Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (WHODrug Global, B3, March 2019) 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 (e.g., 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 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 numbers and percentages. Subjects may have more than one medication per ATC class. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group. ATC class and preferred name within class will be sorted by descending frequency values based on subjects in the 0.1% RGN-259 group.

Listings of prior and 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 (Number of Attended Visits from Visit 2 to 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 Analysis

The primary and hierarchical primary analyses will be conducted in the mITT population. Sensitivity analyses will be conducted in the ITT and PP populations.

14.1.1 Pre-CAE® to Post-CAE® Change in Inferior Fluorescein Staining

Pre-CAE® and post-CAE® fluorescein staining in the inferior region of the cornea will be graded using the Ora Calibra® Corneal and Conjunctival Staining Scale. The Ora Calibra® Scale ranges from 0 to 4 [redacted]

Pre-CAE® to post-CAE® change in inferior corneal fluorescein staining scores will be summarized at Visit 4 (Day 15) by treatment group for the study eye using continuous summary statistics. Change from baseline in inferior corneal staining change from pre-CAE® to post-CAE® at Day 15 (Visit 4) using the Ora Calibra® Scale will be calculated as:

(Post-CAE® staining at Day 15 – Pre-CAE® staining at Day 15) – (Post-CAE® staining at Baseline – Pre-CAE® staining at Baseline)

With this calculation, a positive change indicates a worsening of dry eye signs compared to baseline. Changes from baseline in pre-CAE® to post-CAE® change in inferior corneal fluorescein staining will be compared between 0.1% RGN-259 and placebo using an analysis of covariance (ANCOVA) model that adjusts for baseline pre-CAE® to post-CAE® change 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 differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Two sample t-tests and Wilcoxon rank sum tests will also be conducted as sensitivity analyses to assess robustness of the results.

The primary analysis will use MCMC imputation to have a fuller accounting of the mITT population at Visit 4 (Day 15). The MCMC method will be performed using the SAS procedure PROC MI. The SAS code for obtaining multiple imputation data is:

```
PROC MI DATA = INDATA SEED = 2739451 OUT = OUTDATA NIMPUTE = 20
      MINIMUM = -4 MAXIMUM = 4 ROUND = 0.5;
```

```
    BY TREATMENT;
    MCMC INITIAL = EM;
    VAR BASE_PREPOST V4_PREPOST;
RUN;
```

where

- *INDATA* is the name of the input dataset
- *OUTDATA* is the name of the output dataset
- *TREATMENT* is the name of the treatment group variable
- *BASE_PREPOST* is the baseline change pre-CAE® to post-CAE® inferior corneal fluorescein staining score in the study eye
- *V4_PREPOST* is the change pre-CAE® to post-CAE® inferior corneal fluorescein staining score in the study eye at Visit 4 (Day 15)

If multiple imputation using MCMC fails to impute missing values using the above SAS code (i.e. if there is no missing data for 1 treatment), imputation will be reattempted by adding the baseline pre-CAE® and post-CAE® corneal [redacted] fluorescein staining score, and if imputing based on corneal [redacted] fails then the total [redacted] will be used. If MCMC imputation is still not successful at imputing missing values, then multiple imputation will be reattempted by removal of the `MINIMUM`, `MAXIMUM`, and `ROUND` options.

The change from pre- to post-CAE® and its change from baseline will be calculated for each imputed record. After obtaining twenty complete data sets calculating pre-CAE® to post-CAE® changes and calculating changes from baseline, the following SAS code will be used to run the ANCOVA model on each data set and combine the results from the twenty analyses:

```
PROC MIXED DATA = OUTDATA2;
    BY _IMPUTATION_;
    CLASS TREATMENT SITE;
    MODEL CFB = SITE BASELINE TREATMENT / SOLUTION COVB;
    LSMEANS TREATMENT / CL PDIFF;
    ODS OUTPUT LSMEANS = OUTLS DIFFS = OUTDIFFS;
RUN;
PROC SORT DATA = OUTLS; BY TREATMENT _IMPUTATION_; RUN;

/*Combine Results*/
PROC MIANALYZE DATA=OUTLS;
    BY TREATMENT;
    MODELEFFECTS ESTIMATE;
    STDERR STDERR;
RUN;

PROC SORT DATA=OUTDIFFS; BY TREATMENT _IMPUTATION_; RUN;
PROC MIANALYZE DATA=OUTDIFFS;
    BY TREATMENT;
    MODELEFFECTS ESTIMATE;
    STDERR STDERR;
RUN;
```

where

- OUTDATA2 is the OUTDATA dataset with the derived CFB calculated.
- *TREATMENT* is the name of the treatment group variable
- *SITE* is the site id
- *BASELINE* is the baseline pre-CAE® to post-CAE® change in inferior corneal fluorescein staining score in the study eye
- *CFB* is the change from baseline in pre-CAE® to post-CAE® change in inferior corneal fluorescein staining score in the study eye at Visit 4 (Day 15)
- *OUTLS* is the name of the output dataset that contains the statistical results for the treatment mean from the ANCOVA model that is run on each of the twenty imputation datasets
- *OUTDIFFS* is the name of the output dataset that contains the statistical results for the difference in treatment mean from the ANCOVA model that is run on each of the twenty imputation datasets

Similar SAS code will be used to conduct MCMC multiple imputation analysis for the t-test. Additionally for the interaction model, similar SAS code will be used with the following 2 changes to the model and least squares (LS) means statements shown here:

```
MODEL CFB = SITE BASELINE TREATMENT SITE*TREATMENT / SOLUTION COVB;

LSMEANS TREATMENT SITE*TREATMENT / CL PDIFF;
```

A sensitivity analysis will be performed on the mITT and ITT populations using control-based pattern mixture model imputation. First, non-monotone missing data will be imputed using MCMC multiple imputation to obtain a monotone missing pattern. Second, the monotone missing data will be imputed using a pattern mixture model based on the placebo arm data. The SAS code for obtaining pattern mixture model multiple imputation data is as follows:

```
PROC MI DATA = INDATA SEED = 3392765 OUT = MDATA NIMPUTE = 1
      MINIMUM = -4 MAXIMUM = 4 ROUND = 0.5;
    MCMC IMPUTE=MONOTONE;
    VAR BASE_PREPOST V4_PREPOST;
RUN;

PROC MI DATA = MDATA SEED = 8741542 OUT = OUTDATA NIMPUTE = 20
      MINIMUM = . -4 -4 -4 -4 MAXIMUM = . 4 4 4 4 ROUND = . 0.5 0.5 0.5
0.5;
    CLASS TREATMENT;
    MONOTONE REG(V4_PREPOST = BASE_PREPOST / DETAILS);
    MNAR MODEL(V4_PREPOST / MODELOBS=(TREATMENT='Placebo'));
    VAR TREATMENT BASE_PREPOST V4_PREPOST;
RUN;
```

where

- *INDATA* is the name of the input dataset
- *MDATA* is the name an intermediary dataset with a monotone missing pattern

- *OUTDATA* is the name of the output dataset
- *TREATMENT* is the name of the treatment group variable
- *BASE_PREPOST* is the baseline pre-CAE® to post-CAE® inferior corneal fluorescein staining score in the study eye
- *V4_PREPOST* is the pre-CAE® to post-CAE® inferior corneal fluorescein staining score in the study eye at Visit 4 (Day 15)

Analysis of the resulting data will be as described for MCMC multiple imputation.

If multiple imputation using pattern mixture models fails to impute missing values using the above code, imputation will be reattempted utilizing baseline pre-CAE® and post-CAE® corneal sum (sum of the central, superior, and inferior regions) fluorescein staining score, and if imputing based on corneal sum fails then the total sum (sum of all 5 regions) will be used. In addition, imputation will be attempted by removing the `MINIMUM`, `MAXIMUM`, and `ROUND` options as described for MCMC multiple imputation.

Sensitivity analyses will also be performed on the mITT, ITT and PP populations using observed data only, and on the mITT and ITT populations using last observation carried forward (LOCF) methodology. An example of the SAS code implementation of the ANCOVA model for the observed data only and LOCF analyses is as follows:

```
PROC MIXED;
       CLASS SITE TREATMENT;
       MODEL CFB = SITE BASE_PREPOST TREATMENT / SOLUTION COVB;
       LSMEANS TREATMENT / CL PDIFF;
RUN;
```

Because the pre-CAE® to post-CAE® change only occurs at Visit 1, 2 and 4 the LOCF imputation will effectively be a more conservative baseline observation carried forward (BOCF) analysis where `CFB` and `BASELINE` in the SAS code above are equal for subjects missing their Visit 4 (Day 15) values.

Two sample t-tests and Wilcoxon rank sum tests will also be conducted for the observed data only (mITT, ITT and PP) and LOCF analyses.

Pre-CAE® to post-CAE® change in inferior corneal fluorescein staining score change from baseline in the study eye at Visit 4 (Day 15) will be displayed graphically in a line graph with LS means and standard error bars by treatment group. Pre-CAE®, post-CAE® and the change from pre-CAE® to post-CAE® will be displayed by visit, and additionally by time point.

14.1.2 Pre-CAE® Ocular Discomfort from the Ocular Discomfort and 4-Symptom Questionnaire

Ocular discomfort scores will be subjectively graded by the subjects using the Ora Calibra® Ocular Discomfort and 4-Symptom Questionnaire at all scheduled visits. The ocular discomfort scale ranges from 0 to 5 [redacted]

Changes from baseline in the pre-CAE® ocular discomfort will be summarized at Visit 4 (Day 15) by treatment group using continuous summary statistics. Changes from baseline will be compared between 0.1% RGN-259 and placebo using an ANCOVA model that adjusts for baseline and 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 differences in means, two-sided 95% CIs for the difference in means, and p-values will be reported. Two sample t-tests and Wilcoxon rank sum test will also be conducted as sensitivity analyses to assess robustness of the results.

The primary analysis will use MCMC imputation on the mITT population at Visit 4 (Day 15). SAS code for the multiple imputation analysis will resemble the code in Section 14.1.1, except with the following changes to *SEED*, *ROUND* and *VAR:*

```
PROC MI DATA = INDATA SEED = 7823468 OUT = OUTDATA NIMPUTE = 20
      MINIMUM = 0 MAXIMUM = 5 ROUND = 1;
   BY TREATMENT
   MCMC INITIAL = EM;
   VAR BASE_PRE V3_PRE V4_PRE;
RUN;
```

where

- *INDATA* is the name of the input dataset
- *OUTDATA* is the name of the output dataset
- *TREATMENT* is the name of the treatment group variable
- *BASE_PRE* is the baseline pre-CAE® Ocular Discomfort from the Ocular Discomfort and 4-Symptom Questionnaire score in the study eye
- *V3_PRE* is the pre-CAE® Ocular Discomfort from the Ocular Discomfort and 4-Symptom Questionnaire score in the study eye at Visit 3 (Day 8)
- *V4_PRE* is the pre-CAE® Ocular Discomfort from the Ocular Discomfort and 4-Symptom Questionnaire score in the study eye at Visit 4 (Day 15)

Sensitivity analyses will be performed on the mITT, ITT and PP populations using observed data only, and on the mITT and ITT populations using LOCF methodology and pattern mixture model imputation. The random number seeds for pattern mixture model imputation described in Section 14.1.1 will be `SEED = 5797521` and `SEED = 1054603` for the non-monotone MCMC imputation and the pattern mixture modelling imputation, respectively, and only the pre-CAE® values will be imputed.

All sensitivity analysis and data displays provided for the primary endpoint of inferior corneal staining will also be performed and provided for the hierarchical primary endpoint of ocular discomfort.

Changes from baseline in the pre-CAE® Ocular Discomfort Scale in the study eye at Visit 4 (Day 15) will be displayed graphically in a line chart with LS means and standard error bars by treatment group. Pre-CAE®,

post-CAE® and the change from pre-CAE® to post-CAE® will be displayed by visit, and additionally by time point.

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, minima and maxima), 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 analysis variables will be presented in subject listings by eye, visit, and time point where applicable. The ITT population or all randomized subjects will be used for secondary summaries and listings.

14.2.1 Fluorescein Staining

Corneal and conjunctival fluorescein staining will be performed at all scheduled visits, on both eyes and graded using the Ora Calibra® Corneal and Conjunctival Staining Scale. Both pre-CAE® and post-CAE® assessments will be made at Visits 1 (Day -14), 2 (Day 1), and 4 (Day 15), while Visit 3 (Day 8) will be assessed at pre-CAE® only. The scale will grade the [redacted] The Ora Calibra® Corneal and Conjunctival Staining Scale ranges from 0 to 4 [redacted]

Fluorescein staining scores will be summarized for the study eye by visit, time point (pre-CAE®, post-CAE® and pre-CAE® to post-CAE®), and region [redacted] for the study eye using continuous summary statistics. [redacted]

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

Pre-CAE®, post-CAE®, and pre-CAE® to post-CAE® change in inferior corneal fluorescein staining score in the study eye will be displayed graphically in a line chart with means and standard error bars by visit and treatment group. Figures will include observed data only and will not include imputed data points for missing data.

14.2.2 Lissamine Green Staining

Corneal and conjunctival lissamine green staining will be performed at all visits, on both eyes and graded using the Ora Calibra® Corneal and Conjunctival Staining Scale. Both pre-CAE® and post-CAE®

assessments will be made at Visits 1 (Day -14), 2 (Day 1), and 4 (Day 15), while Visit 3 (Day 8) will be assessed at pre-CAE® only.

The Ora Calibra® Scale will grade the cornea and conjunctiva by [redacted] ranges from 0 to 4 ([redacted]

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

Statistical comparisons will employ pairwise two-sample t-tests as the primary method of analysis for 0.1% RGN-259 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)

Tear film break-up time will be measured at all scheduled visits on both eyes separately. Both pre-CAE® and post-CAE® assessments will be made at Visits 1 (Day -14), 2 (Day 1), and 4 (Day 15), while Visit 3 (Day 8) will be assessed at pre-CAE® only.

TFBUT will be measured in seconds at all scheduled visits, pre- and post-CAE®, 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., 3, 6, 9 seconds, 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®) using quantitative summary statistics. Change from pre- to post-CAE® within each visit as well as change from baseline will also be summarized for 0.1% RGN-259 and placebo.

Statistical comparisons will employ pairwise two-sample t-tests as the primary method of analysis for 0.1% RGN-259 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 Unanesthetized Schirmer's Test

Unanesthetized Schirmer's Test will be assessed on both eyes at all scheduled visits only at pre-CAE®. 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 compared to placebo. An ANCOVA model adjusting for baseline and site will also be assessed as a sensitivity analysis.

14.2.5 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, and at Visit 3 (Day 8).

- Ora Calibra® Drop Comfort Scale will be used to assess drop comfort for each eye separately [redacted] The scale ranges from 0 to 10, [redacted] The worst eye from each subject will be used for this analysis. Drop comfort will be summarized by visit using quantitative summary statistics. Statistical comparisons will employ pairwise two-sample t-tests as the primary method of analysis for 0.1% RGN-259 compared to placebo. A Wilcoxon rank sum test will also be assessed as a sensitivity analysis.
- Ora Calibra® Drop Comfort Questionnaire will be used to assess drop comfort [redacted] This analysis will be at the subject level. Drop Comfort Questionnaire responses will be summarized by visit using qualitative summary statistics. Subjects with at least one negative response will also be summarized by visit.

14.2.6 Ocular Surface Disease Index© (OSDI)

The Ocular Surface Disease Index© (OSDI) will be assessed at the subject level at all scheduled visits only at pre-CAE®. 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 compared to placebo. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed as sensitivity analysis.

14.2.7 Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire

Ocular discomfort and dry eye symptoms will be assessed at all scheduled visits at the subject level in regard to how both eyes feel. Both pre-CAE® and post-CAE® assessments will be made at Visits 1 (Day -14), 2 (Day 1), and 4 (Day 15), while Visit 3 (Day 8) will be assessed at pre-CAE® only. The Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire will be used, which includes rating of the severity of 5 symptoms: [redacted] Each symptom rating ranges from 0 to 5, [redacted]

Ocular discomfort and dry eye symptoms will be summarized by visit and time point (pre- and post- CAE®) using quantitative summary statistics. Change from pre- to post-CAE® 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 compared to placebo. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed as sensitivity analyses.

Pre-CAE®, post-CAE® and pre-CAE® to post-CAE® change in the study eye for all five dry eye symptoms will be displayed graphically in a line chart with standard error bars by visit and treatment group.

14.2.8 Ocular Discomfort Using the Ora Calibra® Ocular Discomfort Scale

Ocular discomfort scores will be subjectively graded by the subjects for both eyes using the Ora Calibra® Ocular Discomfort Scale at all scheduled visits. Both pre-CAE® and post-CAE® assessments will be made at Visits 1 (Day -14), 2 (Day 1), and 4 (Day 15), while Visit 3 (Day 8) will be assessed at pre-CAE® only. Ocular discomfort scores will also be assessed during the CAE® exposure, [redacted] The ocular discomfort scale ranges from 0 to 4 [redacted]

14.2.8.1 Ora Calibra® Ocular Discomfort Scale Outside the CAE® Pre- and Post-CAE®

Ocular discomfort scores measured pre- and post-CAE® will be summarized for the study eye by visit and time point using quantitative summary statistics. Change from pre- to post-CAE® 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 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®

Ocular discomfort scores will be summarized by visit and time point using quantitative summary statistics. The change from pre-CAE® [redacted] within the same visit and will also be summarized.

The overall ocular discomfort during CAE® will be compared between 0.1% RGN-259 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, and the baseline ocular discomfort score as fixed effects, and subject as a random effect. The following SAS code will be used:

```
ODS OUTPUT LSMEANS = 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 Daily Diary

Each day during the at-home dosing period (including the run-in period), subjects will grade the severity of their dry eye symptoms in their diary [redacted] Subjects will rate the severity of each of the following symptoms, with regard to how both their eyes feel: [redacted] Each symptom rating ranges from 0 to 5, [redacted]

The worst symptom for each subject will be identified as the symptom with the highest daily average score during the run-in period (Days -14 to -1) as recorded in the subject diary. First daily averages, per symptom, from [redacted] entries will be calculated. Then the daily averages will be averaged for each symptom. The highest average symptom is called the worst symptom for each subject. In the case of

ties, the worst symptom will be selected in the order of [redacted] from among those with the highest average.

The worst symptom and each individual symptom will be analyzed for each period between visits (run-in period [from Visit 1 to Visit 2, or Day -14 to Day -1], Week 1 [from Visit 2 to Visit 3], and Week 2 [from Visit 3 to Visit 4]) using a two-sample t-test to compare 0.1% RGN-259 to placebo. This analysis will be completed separately for the [redacted] scores as well as the daily average score. Additionally, the average score for each period and time point ([redacted]) will also be analyzed separately using a Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site.

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 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 first dose of study drug, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of the study drug will also be considered a new AE and reported. The AE reporting period ends upon study exit. 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 22.0.

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. Adverse events recorded in the eCRF which began prior to randomized 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.

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 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.

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

Definite, probably, and possible categorizations of AEs are further grouped into 'Suspected' related AEs. Only suspected TEAEs are considered as treatment-related TEAEs. For TEAEs prior to rescue medication use, only those TEAEs with an onset date prior to the date that rescue medications were first used will be included.

Only TEAEs with a relationship of definite, probable, or possible, or with a missing relationship, will be considered as treatment-related TEAEs. An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one AE and TEAE, by treatment group. This summary will also include breakdowns of TEAEs further categorized as ocular (study eye and fellow eye) or non-ocular, TEAEs, serious adverse events (SAE), treatment-emergent SAEs (TE-SAEs), TEAEs by maximum severity, TEAEs by relatedness, subject withdrawals due to an AE and subject deaths due AEs.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. Non-ocular TEAEs 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). 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 descending order by the AE percentages of SOC for all subjects; PTs will be listed in order of descending frequency for all subjects within each SOC.

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 the maximum severity.

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

- Overall summary of AEs
- Ocular TEAEs by System Organ Class and Preferred Term (presented separately for all eyes, worst eyes, and fellow eyes)
- Non-Ocular TEAEs by System Organ Class and Preferred Term
- Ocular TEAEs by System Organ Class, Preferred Term and maximal severity
- Non-Ocular TEAEs by System Organ Class, Preferred Term and maximal severity
- Ocular TEAEs by System Organ Class, Preferred Term, maximal severity, and strongest relationship
- Non-Ocular TEAEs by System Organ Class, Preferred Term, maximal severity, and strongest relationship
- Treatment-related ocular TEAEs
- Treatment-related non-ocular TEAEs
- SAEs

Separate listings for the following will be produced:

- All AEs
- SAEs
- AEs leading to treatment discontinuation
- AEs leading to death

All subject listings will include the affected eye(s) for ocular AEs.

15.2 Visual Acuity (ETDRS)

Visual acuity (VA) will be assessed on both eyes at all scheduled visits pre-CAE® using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. The Investigator will indicate on the CRF whether VA was measured with or without correction, and if pin-hole was used. For each subject, the sites should obtain consistent VA measurements under the same lighting conditions and same correction if possible during the entire study.

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. VA 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). Counts and percentages will summarize any subject with an increase of >0.2 in their logMAR score. A subject listing of VA will also be produced. This listing will include a column that indicates if a subject had a VA change from baseline of increase >0.2 on the logMAR scale.

15.3 Slit-Lamp Biomicroscopy Examination

Slit-lamp biomicroscopy examinations will be conducted on both eyes at all scheduled visits, pre- and post-CAE®. 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®) to all observations at later study visits and time points. The data for slit-lamp biomicroscopy will be presented in a listing.

15.4 Undilated Fundoscopy Examination

Undilated fundoscopy examinations will be conducted on both eyes at Visit 1 (Day -14) and Visit 4 (Day 15) post-CAE®. 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 4 (Day 15) on the above variables. The data for undilated fundoscopy will be presented in a listing.

15.5 Intraocular Pressure (IOP)

IOP will be measured for both eyes at Visit 1 (Day -14) and Visit 4 (Day 15) post-CAE®. 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.

15.6 Corneal Sensitivity (Cochet–Bonnet)

Corneal sensitivity will be assessed at Visit 1 (Day -14) and Visit 4 (Day 15), pre-CAE® 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, for the study eye and fellow eye separately, using descriptive statistics.

A change from baseline will be calculated as the Visit 4 (Day 15) value minus the Visit 1 value and reported with the observed values using continuous summary statistics.

16. Interim Analyses

No interim analyses are planned for this phase 3 study.

17. Changes from Protocol-Stated Analyses

The summaries of TEAEs by strongest relationship were removed from the SAP. Summaries of both treatment-related TEAEs and TEAEs by both strongest relationship and maximal severity are included, which should provide a detailed summary of TEAEs by relationship.

18. Revision History

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

19. Tables

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

Table Number	Title	Population
Study Population Data		
Table 14.1.1	**Subject Disposition**	**ITT Population**
Table 14.1.2	**Subject Disposition**	**mITT Population**
Table 14.1.2.1	**Demographic Characteristics**	**mITT Population**
Table 14.1.2.2	Demographic Characteristics	ITT Population
Table 14.1.2.3	Demographic Characteristics	Safety Population
Table 14.1.2.4	Baseline Disease Characteristics (Worst Eye)	mITT Population
Table 14.1.2.5	Baseline Disease Characteristics (Worst Eye)	ITT Population
Table 14.1.3.1	Ocular Medical History	Safety Population
Table 14.1.3.2	Non-Ocular Medical History	Safety Population
Table 14.1.4.1	Ocular Concomitant Medications by Treatment Group, Drug Class, and Preferred Name	Safety Population
Table 14.1.4.2	Non-Ocular Concomitant Medications by Treatment Group, Drug Class, and Preferred Name	Safety Population
Table 14.1.5	Screen Failures and Reasons for Screen Failure	All Screen Failure Subjects
Primary Efficacy Analyses		
Table 14.2.1.1.1	**Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15)**	**mITT Population with MCMC**
Table 14.2.1.1.2	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15)	mITT Population with Observed Data Only
Table 14.2.1.1.3	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15)	ITT Population with MCMC
Table 14.2.1.1.4	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15)	ITT Population with Observed Data Only
Table 14.2.1.1.5	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15)	PP Population with Observed Data Only
Table 14.2.1.1.6	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15)	mITT Population with LOCF
Table 14.2.1.1.7	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15)	ITT Population with LOCF
Table 14.2.1.1.8	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15) by Site	mITT Population with MCMC
Table 14.2.1.1.9	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15) by Site	ITT Population with MCMC

Table 14.2.1.1.10	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15)	mITT Population with Control-Based Pattern Mixture Modeling
Table 14.2.1.1.11	Inferior Corneal Fluorescein Staining Change from Pre-CAE to Post-CAE at Visit 4 (Day 15)	ITT Population with Control-Based Pattern Mixture Modeling
Table 14.2.1.2.1	**Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15)**	**mITT Population with MCMC**
Table 14.2.1.2.2	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15)	mITT Population with Observed Data Only
Table 14.2.1.2.3	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15)	ITT Population with MCMC
Table 14.2.1.2.4	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15)	ITT Population with Observed Data Only
Table 14.2.1.2.5	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15)	PP Population with Observed Data Only
Table 14.2.1.2.6	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15)	mITT Population with LOCF
Table 14.2.1.2.7	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15)	ITT Population with LOCF
Table 14.2.1.2.8	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15) by Site	mITT Population with MCMC
Table 14.2.1.2.9	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15) by Site	ITT Population with MCMC
Table 14.2.1.2.10	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15)	mITT Population with Control-Based Pattern Mixture Modeling
Table 14.2.1.2.11	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) Change from Baseline Pre-CAE at Visit 4 (Day 15)	ITT Population with Control-Based Pattern Mixture Modeling
Secondary Efficacy Analyses		

Table 14.2.2.1	**Fluorescein Staining (Ora Calibra Corneal and Conjunctival Staining Scale)**	**ITT Population**
Table 14.2.2.2	Lissamine Green Staining (Ora Calibra Corneal and Conjunctival Staining Scale)	ITT Population
Table 14.2.2.3	Tear Film Break-Up Time (TFBUT)	ITT Population
Table 14.2.2.4	Unanesthetized Schirmer's Test (Pre-CAE)	ITT Population
Table 14.2.2.5	Ora Calibra Drop Comfort Scale	ITT Population
Table 14.2.2.6	Ora Calibra Drop Comfort Questionnaire	ITT Population
Table 14.2.2.7	Ocular Surface Disease Index (OSDI; Pre-CAE)	ITT Population
Table 14.2.2.8	**Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire**	**ITT Population**
Table 14.2.2.9	Ora Calibra Ocular Discomfort Scale outside the CAE	ITT Population
Table 14.2.2.10	Ora Calibra Ocular Discomfort Scale during the CAE	ITT Population
Table 14.2.2.11	Ocular Discomfort and Dry Eye Symptoms Reported on Subject Daily Diary	ITT Population
Safety Analyses		
Table 14.3.1.1	**Adverse Event Summary**	**Safety Population**
Table 14.3.1.2	**All Ocular Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term**	**Safety Population**
Table 14.3.1.3	**All Non-Ocular Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term**	**Safety Population**
Table 14.3.1.4	All Ocular Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Maximal Severity	Safety Population
Table 14.3.1.5	All Non-Ocular Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Maximal Severity	Safety Population
Table 14.3.1.6	All Ocular Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, Maximal Severity, and Strongest Relationship	Safety Population
Table 14.3.1.7	All Non-Ocular Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, Strongest Relationship, and Maximal Severity	Safety Population
Table 14.3.1.8	All Ocular Treatment-Related Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.9	All Non-Ocular Treatment-Related Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.10	**All Serious Adverse Events (SAE)**	**Safety Population**

Table 14.3.2	Best-Corrected Visual Acuity (logMAR; Pre-CAE)	Safety Population
Table 14.3.3.1	Slit Lamp Biomicroscopy	Safety Population
Table 14.3.3.2	Slit Lamp Biomicroscopy - Shift Table	Safety Population
Table 14.3.4.1	Undilated Fundoscopy (Post-CAE)	Safety Population
Table 14.3.4.2	Undilated Fundoscopy (Post-CAE) - Shift Table	Safety Population
Table 14.3.5	Intraocular Pressure (IOP; Post-CAE)	Safety Population
Table 14.3.6	Corneal Sensitivity (Cochet-Bonnet; Pre-CAE)	Safety Population
Table 14.3.7	Compliance with Study Drug	Safety Population
Table 14.3.8	Exposure to Study Drug	Safety Population

20. Listings

Listing Number	Title	
Listing 16.1.7	Randomization Schedule	All Randomized Subjects
Listing 16.2.1.1	Subject Disposition	All Randomized Subjects
Listing 16.2.1.2	Subject Dispositions Impacted by COVID-19	All Subjects Impacted by COVID-19
Listing 16.2.2.1	Protocol Deviations	All Randomized Subjects
Listing 16.2.2.2	Protocol Deviations Related to COVID-19	All Randomized Subjects
Listing 16.2.2.3	Inclusion/Exclusion Criteria	All Randomized Subjects
Listing 16.2.2.4	Screen Failures and Reasons for Screen Failure	All Screen Failure Subjects
Listing 16.2.3	Study Population Inclusion	All Randomized Subjects
Listing 16.2.4.1	Demographics	All Randomized Subjects
Listing 16.2.4.2	Ocular Medical History	All Randomized Subjects
Listing 16.2.4.3	Non-Ocular Medical History	All Randomized Subjects
Listing 16.2.4.4	Prior and Concomitant Ocular Medications	All Randomized Subjects
Listing 16.2.4.5	Prior and Concomitant Non-Ocular Medications	All Randomized Subjects
Listing 16.2.5.1	In-Office Study Medication Instillation	All Randomized Subjects
Listing 16.2.5.2	At-Home Study Medication Instillation (Diary)	All Randomized Subjects
Listing 16.2.5.3	Study Drug Exposure and Dosing Compliance	All Randomized Subjects
Listing 16.2.5.4	Study Drug Accountability	All Randomized Subjects
Listing 16.2.5.5	Childbearing Potential and Urine Pregnancy Test Results	All Randomized Female Subjects
Listing 16.2.6.1	Fluorescein Staining (Ora Calibra Corneal and Conjunctival Staining Scale)	All Randomized Subjects
Listing 16.2.6.2	Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire	All Randomized Subjects
Listing 16.2.6.3	Lissamine Green Staining (Ora Calibra Corneal and Conjunctival Staining Scale)	All Randomized Subjects
Listing 16.2.6.4	Tear Film Break-Up Time (TFBUT)	All Randomized Subjects
Listing 16.2.6.5	Unanesthetized Schirmer's Test (Pre-CAE)	All Randomized Subjects
Listing 16.2.6.6	Ora Calibra Drop Comfort Scale	All Randomized Subjects
Listing 16.2.6.7	Ora Calibra Drop Comfort Questionnaire	All Randomized Subjects
Listing 16.2.6.8	Ocular Surface Disease Index (OSDI; Pre-CAE)	All Randomized Subjects
Listing 16.2.6.9	Ora Calibra Ocular Discomfort Scale outside the CAE	All Randomized Subjects
Listing 16.2.6.10	Ora Calibra Ocular Discomfort Scale during the CAE	All Randomized Subjects
Listing 16.2.6.11	Ocular Discomfort and Dry Eye Symptoms Reported on Subject Daily Diary	All Randomized Subjects
Listing 16.2.7.1	All Adverse Events	All Randomized Subjects
Listing 16.2.7.2	Serious Adverse Events (SAE)	All Randomized Subjects
Listing 16.2.7.3	Adverse Events Leading to Treatment Discontinuation	All Randomized Subjects
Listing 16.2.7.4	Adverse Events Leading to Death	All Randomized Subjects
Listing 16.2.8.1	Visual Acuity by ETDRS Chart (Pre-CAE)	All Randomized Subjects
Listing 16.2.8.2	Slit-Lamp Biomicroscopy	All Randomized Subjects
Listing 16.2.8.3	Undilated Fundoscopy (Post-CAE)	All Randomized Subjects

Listing 16.2.8.4	Intraocular Pressure (IOP; Post-CAE)	All Randomized Subjects
Listing 16.2.8.5	Corneal Sensitivity (Cochet-Bonnet; Pre-CAE)	All Randomized Subjects

21. Figures

Figure Number	Title	Population
Figure 14.2.3.1	Inferior Corneal Fluorescein Staining by Visit – Worst Eye (Change from Pre-CAE to Post-CAE)	mITT Population with Observed Data Only
Figure 14.2.3.2	Inferior Corneal Fluorescein Staining by Visit – Worst Eye (Pre-CAE)	mITT Population with Observed Data Only
Figure 14.2.3.3	Inferior Corneal Fluorescein Staining by Visit – Worst Eye (Post-CAE)	mITT Population with Observed Data Only
Figure 14.2.3.4	Inferior Corneal Fluorescein Staining by Visit – Worst Eye (Change from Baseline by Time Point)	mITT Population with Observed Data Only
Figure 14.2.3.5	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) by Visit (Pre-CAE)	mITT Population with Observed Data Only
Figure 14.2.3.6	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) by Visit (Post-CAE)	mITT Population with Observed Data Only
Figure 14.2.3.7	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) by Visit (Change from Pre-CAE to Post-CAE)	mITT Population with Observed Data Only
Figure 14.2.3.8	Ocular Discomfort Score (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire) by Visit (Change from Baseline by Time Point)	mITT Population with Observed Data Only