STATISTICAL ANALYSIS PLAN

A Multi-Center, Randomized, Double-Masked, Vehicle Controlled Phase 3 Study Evaluating the Efficacy and Safety of OTX-DP for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)

Sponsor: Ocular Therapeutix, Inc.

Protocol Number: CLN-Protocol-0052

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List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BOCF	Baseline Observation Carried Forward
CAC	Conjunctival Allergen Challenge
CI	Confidence Interval
CS	Clinically Significant
eCRF	Electronic Case Report Form
EDC	Electronic Data Transfer
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS Means	Least Squares Means
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
OD	*Oculus dexter* (Right Eye)
OS	*Oculus sinister* (Left Eye)
OTX-DP	Dexamethasone Ophthalmic Insert 0.4 mg
OU	*Oculus uterque* (Both Eyes)
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
PV	Placebo Vehicle
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WCO	Worst Case Observation
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol CLN-Protocol-0052, Revision 002 dated 29OCT2019.

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.

2. Study Objectives

The objective of this study is to evaluate the efficacy and safety of dexamethasone ophthalmic insert 0.4 mg (OTX-DP) when placed in the canaliculus of the eyelid for the treatment of the signs and symptoms of allergic conjunctivitis.

2.1 Study Variables

2.2 Primary Variables

The primary efficacy variable is:

- Ocular itching evaluated by the subject on Visit 6b (Day 8; 7 days post-insertion; 8 hours from Visit 6a) at 3(±1), 5(±1), and 7(±1) minutes post conjunctival allergen challenge (CAC) (0-4 scale, allowing half unit increments).

2.3 Secondary Variables

The key secondary efficacy variables include the following:

- Ocular itching at the following visits at 3(±1), 5(±1), and 7(±1) minutes post-CAC:
    - Visit 6a (Day 8; 7 days post-insertion)
    - Visit 5 (Day 7; 6 days post-insertion)
    - Visit 8b (Day 15; 14 days post-insertion; 8 hours from Visit 8a)
    - Visit 8a (Day 15; 14 days post-insertion)
    - Visit 7 (Day 14; 13 days post-insertion)

Other secondary efficacy measures are ocular itching at Visits 5, 6a, 6b, 7, 8a, and 8b at 10(±1) minutes post-CAC, and the following assessments made at Visits 5, 6a, 6b, 7, 8a, and 8b at 7(±1), 15(±1), and 20(±3) minutes post-CAC:

- Conjunctival redness evaluated by the Investigator (0-4 scale, allowing half unit increments)
- Ciliary and episcleral redness evaluated by the Investigator (0-4 scale, allowing half unit increments)
- Chemosis evaluated by the Investigator (0-4 scale, allowing half unit increments)
- Eyelid swelling evaluated by the subject (0-3 scale, NOT allowing half unit increments)
- Tearing/watery eyes evaluated by the subject (0-4 scale, NOT allowing half unit increments)
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject (0-4 scale, NOT allowing half-unit increments)
- Nasal symptom composite score based on the assessments of rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion (analyzed as a qualitative measure determined as the presence or absence of at least one nasal symptom [present/absent], and as a quantitative measure calculated as the sum of the four component symptom scores [ranging from 0 to 16])

2.4 Safety Variables

The safety variables include the following:

- Adverse Events (AEs) (reported, elicited, and observed)
- Best Corrected Visual Acuity (BCVA) using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart
- Slit-lamp biomicroscopy, including punctum exam
- Intraocular Pressure (IOP)
- Dilated Fundoscopy Examination

2.5 Statistical Hypotheses

The null and alternative hypotheses, based on the primary efficacy variable, are as follows:

H_{10}: There is no difference in mean ocular itching scores at Visit 6b (Day 8) between OTX-DP and placebo vehicle (PV) treated subjects for at least 1 of the 3 time points during Visit 6b.

H_{1a}: There is a difference in mean ocular itching scores at Visit 6b (Day 8) between OTX-DP and PV treated subjects for all 3 time points during Visit 6b.

Similar hypotheses will be tested for the key secondary efficacy endpoints of ocular itching at Visits 5, 6a, 7, 8a, 8b. Statistical significance will be determined using a two-sided significance level of 0.05.

3. Study Design and Procedures

3.1 General Study Design

This study will comprise of 13 office visits over a period of approximately 5 to 11 weeks. Visits 2, 3a, 3b, and 4a will be used to select a subject population that responds reproducibly to the CAC before being randomized at Visit 4b.

The series of CACs and re-challenge CACs during Visits 5, 6a, and 6b will be used for the primary efficacy measures at Visit 6b. Subjects will return to the office for Visits 7, 8a, and 8b for another series of CAC and re-challenge CACs and will return again for Visit 9 (Day 30+3) for the removal of OTX-DP or PV, if still present and the subject is experiencing any symptoms related to the inserts, and for final safety evaluations.

Study visits will be referred to in all tables and listings as the scheduled visit and the planned study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Table 1 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:

Table 1. Study Visit Windows

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day -45	+39 Days
Visit 2	Day -5	+ 1 Day
Visit 3a	Day -4	+ 1 Day
Visit 3b	Day -4 (8 hours post Visit 3a)	+1 Day
Visit 4a	Day -3 (24 +/- 6 hours post Visit 3a)	+1 Day
Visit 4b	Day 1	2-3 Days Post Visit 3a
Visit 5	Day 7 (6 days post-insertion)	N/A
Visit 6a	Day 8 (7 days post-insertion)	N/A
Visit 6b	Day 8 (7 days post-insertion; 8 hours post Visit 6a)	N/A
Visit 7	Day 14 (13 days post-insertion)	N/A
Visit 8a	Day 15 (14 days post-insertion)	N/A
Visit 8b	Day 15 (14 days post-insertion; 8 hours post Visit 8a)	N/A
Visit 9	Day 30	+3 Days

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided Table 2.

Table 2. Schedule of Visits and Assessments

Visit **Visit Window**	V1 -45 to -6	V2 -5+1	V3a -4+1	V3b[1] (V3a+8hrs)	V4a[2] (V3a+24 ±6 hrs)	V4b (2-3 days post V3a)	V5 7	V6a 8	V6b[1] (V6a+8hrs)	V7 14	V8a 15	V8b[1] (V8a+8hrs)	V9 30+3
Visit Day *(Number of days post insertion)*							6	7	7	13	14	14	29-32
PROCEDURE													
General Assessments													
Informed Consent & HIPAA	X												
Demographic Data	X												
Medical & Medication History	X												
Update Medical & Medication History		X	X	X	X	X	X	X	X	X	X	X	X
Allergic Skin Test	X												
Urine Pregnancy Test[3]		X											X
Randomization						X							
AE Assessment						X	X	X	X	X	X	X	X
Allergen Challenge													
CAC		X[4]	X[5]	X[5]	X[5]		X	X[6]	X[6]	X[6]	X[6]	X[6]	
Signs and Symptoms Assessments[7]		X	X	X	X		X	X	X	X	X	X	
Visual/Systems Exams													
Best Corrected Visual Acuity	X	X	X	X	X		X	X	X	X	X	X	X
Slit Lamp Biomicroscopy including punctum exam		X	X	X	X		X	X	X	X	X	X	X
Intracanalicular Insert Visualization						X	X	X	X	X	X	X	X
IOP[8]		X							X			X	X
Dilated Fundoscopy Examination		X											X
Study Therapy													

Visit Visit Window	V1 -45 to -6	V2 -5+1	V3a -4+1	V3b[1] (V3a+8hrs)	V4a[2] (V3a+24 ±6 hrs)	V4b (2-3 days post V3a)	V5 7	V6a 8	V6b[1] (V6a+8hrs)	V7 14	V8a 15	V8b[1] (V8a+8hrs)	V9 30+3
Visit Day *(Number of days post insertion)*							6	7	7	13	14	14	29-32
PROCEDURE													
Digital Photographs/Videos[9]						X	X	X	X	X	X	X	X
IP Insertion						X							
Removal of Inserts													X[10]
Exit from Study													X

[1] Visits 3b, 6b, and 8b to occur 8 hours + 1 hour after Visits 3a, 6a, and 8a respectively.
[2] Visit 4a to occur 24±6 hours after Visit 3a.
[3] At Visits 2 and 9, for all women of childbearing potential.
[4] Titration CAC
[5] Confirmatory CAC
[6] Re-challenge CAC
[7] Ocular (itching; conjunctival, episcleral, and ciliary redness; chemosis; eyelid swelling; tearing/watery eyes) and Nasal (pruritis; rhinorrhea; ear or palate pruritis; congestion) pre- and post- CAC
[8] Measured following the last CAC assessments when all other evaluations are complete
[9] Digital photographs and/or videos may be taken of each subject's eyes before, during, and/or after IP insertion, visualization, and/or removal.
[10] If the inserts are still present, and the subject is experiencing symptoms related to the inserts, the Investigator will remove them according to the removal procedures. Inserts do not need to be removed for asymptomatic subjects.

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

Subjects who meet the entry criteria for itching and redness response to the CAC at Visits 2, 3a, 3b, and 4a will be randomized at a 1:1 ratio (active:vehicle) at Visit 4b (Day 1) to receive one of the following treatment arms bilaterally:

- OTX-DP (N=40 subjects) or
- PV (N=40 subjects)

4.2 Masking and Unmasking

In the case of a medical emergency or occurrence of a serious adverse event (SAE), the randomization code may be unmasked and made available to the Investigator, Sponsor, and/or other study personnel involved in the conduct of the study. In the absence of medical need, the randomization code will not be available to the above individuals until after the study is completed and the database is locked.

In the event of a medical need, the Investigator will treat each subject, as medically required. If the Investigator feels it is necessary to unmask a subject's treatment assignment after an emergency situation, the Investigator may call the Medical Monitor and notify the Sponsor. The treatment assignment will be revealed on a subject-by-subject basis with the approval of the Medical Monitor and Sponsor, leaving the masking of the remaining subjects intact.

The site will receive one emergency unmasking envelope for every product received and the envelopes should be stored in a secured location. The envelopes and product will both be labeled with the same randomization number. The envelopes are sealed and contain the unmasked treatment information for the corresponding study product.

Ocular Therapeutix will make the final determination if the unmasking request will be granted. Once the unmasking request is granted the Investigator or designee should identify and retrieve the emergency unmasking envelope for the given subject. The emergency unmasking envelope should be opened by the designated site personnel. The Investigator must also indicate in source documents and in the electronic case report form (eCRF) that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with breaking the mask must be recorded and reported as specified in this protocol.

Subjects will have the investigational product (IP) removed immediately if treatment assignment is unmasked.

5. Sample Size and Power Considerations

Approximately 80 subjects will be randomized at Visit 4b in a 1:1 ratio across the two treatment arms (40 OTX-DP; 40 PV). Up to approximately 10 additional subjects may be enrolled to make up for any subjects who did not complete Visit 6b CAC procedures.

A total of 40 subjects in each treatment arm will provide 97.0%, 99.8%, and 99.9% power to demonstrate a statistically significant difference in ocular itching between OTX-DP and PV treated subjects at each of the 3-, 5-, and 7-minute post-CAC time points of Visit 6b, respectively, assuming a treatment difference of 0.87 units at 3 minutes post-CAC, 1.08 units at 5 minutes post-CAC, and 1.13 units at 7 minutes post-CAC; a standard deviation of 1.0 unit at all time points; and a two-sided Type I error of 0.05.

Assuming independence between time points, 40 subjects per group will have at least 96.7% power to demonstrate a statistically significant difference over all three primary post-CAC time points at Visit 6b for ocular itching between OTX-DP and PV treated subjects.

6. Data Preparation

6.1 Input Data

Study data will be recorded on the eCRFs supplied by Statistics & Data Corporation (SDC) using IBM clinical, version 2019.4.0.1. When all prerequisites for database lock have been met, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask the study. 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 analysis will be carried out after the following have occurred:

- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Database lock has occurred.
- Randomized treatment codes have been unmasked.

6.2 Output Data

Data from IBM clinical will be transferred to SDC Biostatistics and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM- and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

SDTM will follow the SDTM version 1.4 model and will be implemented using the SDTM Implementation Guide version 3.2 and the SDTM Controlled Terminology version 2016-06-24. ADaM data will follow the ADaM version 2.1 model and will be implemented using the ADaM Implementation Guide version 1.3. Both SDTM and ADaM will be validated using Pinnacle 21 version 2.2. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model.

7. Analysis Populations

7.1 Intent-to-Treat

The Intent-to-Treat (ITT) population consists of all subjects who are randomized. All data will be included and no subjects will be excluded because of protocol violations. The ITT population will be analyzed as randomized and will be used for the efficacy analyses.

7.2 Per Protocol

The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 6b (Day 8; 7 days post-insertion; 8 hours from Visit 6a) with no major protocol violations that would impact the efficacy of the drug. Protocol deviations will be assessed and decisions regarding subject evaluability will be made prior to database lock and unmasking. This population will be analyzed as treated using observed data only for confirmatory analyses.

7.3 Safety

The Safety population includes all randomized subjects who received the IP. The Safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

8. General Statistical Considerations

8.1 Unit of Analysis

The subject will be considered the unit of analysis for all efficacy variables (e.g., itching, redness). In cases where data are collected for each eye, the average of both eyes of each subject will be used for statistical summaries and analyses. Medical history, concomitant medications, and AEs will also be collected and presented at the subject level.

The eye will be considered the unit analysis for all safety variables (e.g., BCVA, IOP).

8.2 Missing or Inconclusive Data Handling

8.2.1 Imputation of Primary and Key Secondary Efficacy Variables

The impact of missing data on the primary and key secondary efficacy endpoints will be explored using the following variety of missing data handling techniques:

- Markov chain Monte Carlo (MCMC) multiple imputations
- Last observation carried forward (LOCF)
- Baseline observation carried forward (BOCF)
- Worst case observation (WCO)

Details related to the MCMC multiple imputation procedures are included in Section 12.1 as this imputation method will be used for the primary efficacy analysis. The screening visits (Visit 1, Visit 2, Visit 3a, Visit 3b and Visit 4a) will not be imputed nor summarized in the MCMC tables.

For the LOCF imputation, only post-challenge observations within the same visit will be carried forward. For example, there must be a 3-minute, post-CAC value at each visit available to implement LOCF at that visit. However, in the case that the 3-minute, post-CAC value is missing, only the subsequent non-missing assessments will be used in the analysis. The screening visits (Visit 1, Visit 2, Visit 3a, Visit 3b and Visit 4a) will not be imputed nor summarized in the LOCF table.

For the BOCF imputation, missing data post-baseline will be imputed with the time appropriate baseline data from Visit 4a. For example, if a subject's 3-minute, post-CAC value is missing at Visit 6b, then that subject's 3-minute, post-CAC value from Visit 4a will be used in its place. The screening visits (Visit 1, Visit 2, Visit 3a, Visit 3b and Visit 4a) will not be imputed nor summarized in the BOCF table.

For the WCO imputation, missing data due to a subject being prescribed anti-inflammatory or anti-allergy (rescue) medication will be imputed using the worst possible outcome (maximum observed value) from the subject's treatment group at the given visit and time point, starting at the first time point at which a subject takes an anti-inflammatory or anti-allergy medication. No other missing data will be imputed. Specific anti-inflammatory and anti-allergy medications triggering the WCO imputation will be identified prior to database lock by the study team. The screening visits (Visit 1, Visit 2, Visit 3a, Visit 3b and Visit 4a) will not be imputed nor summarized in the WCO table.

8.2.2 Imputation of Dates

Partial or missing dates will be imputed where complete dates are required to flag data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are the same as the month and year of the first dose of study medication, in which case the missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case the missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is the same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or “Yes” then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is “No” then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

8.3 Definition of Baseline

For all efficacy variables , baseline will refer to the time specific measure at Visit 4a (e.g., ocular itching at 3 minutes post-CAC at Visit 4a will be the baseline for ocular itching at 3 minutes post-CAC at Visits 6b, 6a, 5, 8b, 8a, and 7).

For all safety variables, baseline is defined as the last measurement prior to the first dose of study medication.

8.4 Data Analysis Conventions

Final 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, and visit (as applicable) based on all randomized subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include 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) unless otherwise specified. Confidence intervals (CIs) for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to 4 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. Listings will be sorted by treatment group, subject number, visit/time point, and parameter as applicable.

Unscheduled visits will not be included in summaries presented by visit (i.e. unscheduled visits will not be mapped to the nearest scheduled visit window and will not be included in the by-visit summaries). Early termination visits will be summarized together with Visit 9 (Day 30; Study Exit). Scheduled visits that are outside of the corresponding visit window will still be included in the applicable summary; however, such instances may be deemed to be a major protocol deviation resulting in an exclusion from the Per-Protocol population analyses. Listings will include data collected at all visits, including unscheduled visits.

8.5 Adjustments for Multiplicity

All six sets of hypotheses described in Section 2.5 will be tested in a hierarchical order, testing the primary hypotheses first (corresponding to Visit 6b), and then proceeding with the key secondary efficacy hypotheses in the order presented below.

1. Visit 6b
2. Visit 6a
3. Visit 5
4. Visit 8b
5. Visit 8a
6. Visit 7

If at any point in the hierarchical order, statistical significance is not demonstrated, testing will stop, and the remaining tests will be deemed not statistically significant.

There will be no adjustment necessary for testing multiple time points within a visit, as statistical significance at all three post-CAC time points is required for a visit to be deemed statistically significant.

9. Disposition of Subjects

Analysis populations, study completion, and withdrawal from the study will be summarized for the ITT population. The summary table will include the numbers of subjects randomized and included in the analysis populations by randomized treatment group for the ITT population and by actual treatment group for the PP and Safety populations. The summary table will also include the numbers of subjects who completed the study. The reasons for withdrawal will be summarized for the applicable subjects. Reasons for withdrawal will include AE, protocol deviation, lost to follow-up, consent withdrawn, Sponsor termination of study, Investigator decision, unsuccessful insertion, other.

Disposition data for all subjects in the ITT population will be presented in a listing. Protocol deviations for the ITT population will also be presented in a listing.

9.1 Demographic Variables

Subject demographic characteristics (age, sex, ethnicity, race, and iris color) will be summarized and presented by treatment group. These summaries will be based on the ITT population. Percentages will be based on the total number of subjects in each treatment group except for iris color, which will be based on the total number of eyes in each treatment group.

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

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

9.2 Pretreatment Variables

At Visit 1 (Day -45) a diagnostic test for allergic disease (skin test) will be performed on subjects without a documented skin test within the past 24 months and the pre- and post-dilation punctum size of each eye will also be assessed. Results from both assessments will be presented in subject listings.

10. Medical History and Concomitant Medications

10.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 20.0.

Non-ocular medical history will be summarized for the ITT population using discrete summary statistics and presented by treatment group at the subject level by System Organ Class (SOC) and Preferred Term (PT). 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. Percentages will be based on the number of subjects in each treatment group. In the summary, SOC will be listed in order of descending frequency for all subjects; PTs will be listed in order of descending frequency for all subjects within each SOC.

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

10.2 Prior and Concomitant Medications

A concomitant medication is any drug or substance administered from Visit 1 (Day -45) through the last study visit, Visit 9 (Day 30). A prior medication is any drug or substance administered prior to Visit 1 (Day -45). The generic name of the drug or substance, the dose, the route of administration, the duration of treatment (including the start and stop dates), the frequency, the indication, and whether or not the medication was taken due to an AE will be recorded for each drug or substance.

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (Enhanced B2, March 2017) and summarized to the therapeutic drug class (ATC 4 classification) and preferred name. If the ATC 4 classification is not provided, then 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.

Prior and concomitant medications will be summarized for the ITT population using discrete summary statistics and presented by treatment group, separated out by ocular and non-ocular medications. Percentages will be based on the number of subjects in each treatment group. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. In the summary, ATC classification will be listed in order of descending frequency for all subjects; preferred name will be listed in order of descending frequency for all subjects within each ATC.

Listings of prior and concomitant medications will be generated separately for ocular and non-ocular data.

11. Study Therapy Variables

Punctum size (pre- and post-dilation) and exposure to IP will be summarized using quantitative descriptive statistics. A subject will be considered exposed to study drug as long as at least one eye has a successful insertion. Exposure to IP will be calculated as: End Date – Date of Insertion + 1, where the end date is defined as the earliest date at which the insert is not visible in both eyes, the insert is removed from both eyes, or study exit date.

Ease of punctum insertion (easy/moderate/difficult), visualization (easy/moderate/difficult), and removal (minimal, moderate, extensive manipulation) will be presented in subject listings and summarized using counts and percentages. Percentages will be based on the total number of subjects in treatment group for the Safety population.

Punctum size, punctum insertion, visualization, and removal will all be presented in separate listings using the ITT population. Procedural exclusion criteria related to the punctum assessments will be presented in the same listing as study inclusion and exclusion criteria.

Data related to the CAC procedure (CAC time, qualifying allergen and dose) will be presented in a listing.

12. Efficacy Analyses

12.1 Primary Analysis

The primary efficacy variable is ocular itching evaluated by the subject at 3(±1), 5(±1), and 7(±1) minutes post-CAC at Visit 6b (Day 8; 8 hours from Visit 6a). Ocular itching will be evaluated using the following Ora Calibra™ CAC Ocular Itching Scale as defined in Appendix A.

The average of each subject's eyes' itching score at each post-CAC time point will be used as the unit of analysis for ocular itching.

The primary analysis of ocular itching will be performed on the ITT population with MCMC multiple imputation methodology for missing data using an ANCOVA model for each post-CAC time point at Visit 6b, with the time appropriate post-CAC itching scores at Visit 4a as a covariate and treatment group as the sole factor.

For multiple imputations using MCMC, twenty "complete" (imputed) datasets will be produced and analyzed. Results from the analyses on the twenty "complete" datasets will be combined for presentation using SAS PROC MIANALYZE.

A separate imputation model will be fit for each visit and time point. The imputation model will include variables for treatment, baseline measure (the time appropriate post-CAC scores at Visit 4a), and response measure.

The following SAS code will be used to produce twenty "complete" datasets:

```
PROC MI DATA = INDATA SEED = 59411 NIMPUTE = 20 OUT =
OUTDATA1 MINIMUM=. 0 0 MAXIMUM=. 4 4 ROUND =. 0.25 0.25;
   BY VISIT TIME;
   MCMC INITIAL = EM;
   VAR TREATMENT BASELINE SCORE;
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 time appropriate post-CAC scores at Visit 4a; and
- *SCORE* is the average (of right eye [OD] and left eye [OS] for each subject) ocular itching score.

After obtaining twenty "complete" datasets, the following SAS code will be employed to run the analysis of covariance (ANCOVA) models by time point on each dataset:

```
ODS OUTPUT SOLUTIONF = MIXPARMS LSMEANS = LS DIFFS = DIFF;
PROC MIXED DATA = OUTDATA1;
   BY VISIT TIME _IMPUTATION_;
   CLASS TREATMENT;
   MODEL SCORE = BASELINE TREATMENT / SOLUTION;
   LSMEANS TREATMENT / PDIFF CL;
RUN;
```

where

- *SUBJID* is the subject ID number;

- *BASELINE* is the time appropriate post-CAC scores at Visit 4a;
- *VISIT* is the visit; and
- *TIME* is the time point.

The following SAS code will then be used to combine results across imputations for the treatment means and differences respectively:

```
ODS OUTPUT PARAMETERESTIMATES = PE1;
PROC MIANALYZE DATA = LS;
    BY VISIT TIME TREATMENT;
    MODELEFFECTS ESTIMATE;
    STDERR STDERR;
RUN;

ODS OUTPUT PARAMETERESTIMATES = PE2;
PROC MIANALYZE DATA = DIFF;
   BY VISIT TIME TREATMENT;
   MODELEFFECTS ESTIMATE;
   STDERR STDERR;
RUN;
```

where the statement `WHERE _TREATMENT=2` identifies the differences for active minus vehicle. The detailed code will be determined based on the final data.

Least squares means (LS Means) for each treatment, LS Means treatment differences and corresponding 95% CIs as estimated by the ANCOVA model will be provided.

In addition, ANCOVA models accounting for repeated measures will be run at Visit 6b as another supportive analysis. This ANCOVA model will include the time appropriate post-CAC itching scores at Visit 4a as a covariate and treatment group and time point as factors. The LS Means for each treatment, the LS Means treatment difference between OTX-DP and PV, and the corresponding 95% CIs will be calculated from these ANCOVA models. SAS pseudo-code for the ANCOVA model accounting for repeated measures at Visit 6 for multiply imputed data follows (Note: the same imputation routine described above [PROC MI → PROC MIXED → PROC MIANALYZE] will be employed using the below PROC MIXED pseudo-code):

```
PROC MIXED DATA=INDATA;
    BY VISIT _IMPUTATION_;
    CLASS SUBJID TREATMENT TIME;
    MODEL SCORE = TREATMENT TIME BASELINE;
    REPEATED TIME / SUBJECT=SUBJID TYPE=UN;
    LSMEANS TREATMENT / PDIFF CL;
RUN;
```

where *INDATA* is the name of the input dataset sorted by *VISIT, _IMPUTATION_, SUBJID* and *TIME*.

An unstructured variance-covariance matrix will be used for the above repeated measures model. If the model does not converge using the unstructured matrix, the first order autoregressive structure and the compound symmetry structure will be employed, in that order.

Two-sample *t*-tests will also be used as unadjusted sensitivity analyses at each post-CAC time point, as well as non-parametric Wilcoxon rank sum tests for comparing OTX-DP and PV. Mean treatment differences, 95% CIs for each of the means, and 95% CIs for the mean differences will be presented for each post-CAC time point.

The following SAS code will be used for the t-test:

```
PROC TTEST DATA=INDATA;
BY VISIT TIME _IMPUTATION_;
CLASS TREATMENT;
VAR SCORE;
ODS OUTPUT STATISTICS = OUTPUTDF;
RUN;

PROC MIANALYZE DATA = OUTPUTDF;
BY VISIT TIME CLASS;
MODELEFFECTS MEAN;
STDERR STDERR;
RUN;
```

The following SAS code will be used for the Wilcoxon rank sum test:

```
ODS OUTPUT WILCOXONSCORES = WILCOXON (WHERE=(CLASS=:"1"));
PROC NPAR1WAY DATA = INDATA WILCOXON;
    BY VISIT TIME _IMPUTATION_;
    CLASS TREATMENT;
    VAR SCORE;
RUN;

DATA WILCOXON;
  SET WILCOXON;
  BY VISIT TIME;
  MEAN = (SUMOFSCORES - EXPECTEDSUM)/N;
  STDERR = STDDEVOFSUM/N;
RUN;

PROC MIANALYZE DATA = WILCOXON ALPHA = 0.05;
BY VISIT TIME;
MODELEFFECTS MEAN;
STDERR STDERR;
RUN;
```

The ordering of the above code should be adjusted accordingly for the real data, to make sure the tests are performed to compare the treatment group vs. the placebo group.

Sensitivity or supportive analyses will be performed on the ITT population using LOCF, BOCF, and WCO imputations as well as observed data only (see Section 8.2.1 for additional data imputation details). The primary analysis will also be repeated on the PP population with observed data only.

A line graph will be produced to show mean (+/- standard error [SE]) ocular itching score by treatment group (OTX-DP, PV), visit (Visit 6b, Visit 8b), and time point (3, 5, and 7 minutes post-CAC). Mean change from baseline (+/- SE) for each treatment arm will be presented in a similar figure. Both figures will be presented separately for the ITT population using observed data only.

A listing of ocular itching scores for all subjects will also be provided.

12.2 Secondary Analyses

12.2.1 Key Secondary Analyses

The key secondary efficacy variables include ocular itching at 3(±1), 5(±1), and 7(±1) minutes post-CAC at visits 5 (Day 7), 6a (Day 8), 7 (Day 14), 8a (Day 15), and 8b (Day 15; 8 hours from Visit 8a).

Ocular itching scores for these time points and visits will be analyzed in a manner similar to the primary analyses using the same analysis populations and imputation methodologies for missing data. All ocular itching scores (including both key secondary and other secondary timepoints) will be included in the listing for primary efficacy ocular itching scores.

12.2.2 Other Secondary Analyses

Other secondary efficacy variables include ocular itching at 10(±1) minutes post-CAC at visits 5 (Day 7), 6a (Day 8), 7 (Day 14), 8a (Day 15), and 8b (Day 15; 8 hours from Visit 8a), and conjunctival redness, episcleral and ciliary redness, chemosis, eyelid swelling, tearing/watery eyes, rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion assessed at Visits 5 (Day 7), 6a (Day 8), 6b (Day 8; 8 hours from Visit 6a), 7 (Day 14), 8a (Day 15), and 8b (Day 15; 8 hours from Visit 8a) at 7(±1), 15(±1), and 20(±3) minutes post-CAC. Scoring scales for each assessment are presented in Appendix A.

These secondary quantitative endpoints will be analyzed in a manner similar to the primary endpoint using the ITT and PP populations with observed data only. Note that ocular itching at 10(±1) minutes post-CAC will be analyzed together with the primary efficacy ocular itching scores (including imputing missing values) even though it is considered a secondary variable.

Additionally, a composite score of the presence or absence of at least one nasal symptom will be derived for each subject based on rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion scores. The composite score is “Present” if at least one nasal symptom is > 0, “Absent” if all symptoms are equal to zero, and missing if any symptoms are missing and the recorded symptoms are all equal to zero.

The nasal composite scores will be summarized using counts and percentages for each response category (present, absent, missing). Nasal composite scores will be analyzed using Fisher’s exact tests and Cochran-Mantel-Haenszel tests (controlling for time-appropriate Visit 4a post-CAC nasal composite scores

and including just the “Present” and “Absent” categories) at each time point for each of Visits 5 (Day 7) through 8b (Day 15).

Nasal composite scores will also be summarized as a quantitative measure calculated as the sum of the four component symptom scores (ranging from 0 to 16). If any of the four component symptom scores is missing, then the quantitative composite score will be missing. Quantitative nasal composite scores will be summarized using quantitative descriptive statistics. A two-sample test will be used to compare treatment groups at each timepoint for each of Visits 5 (Day 7) through 8b (Day 15).

All secondary efficacy endpoints will be presented in separate listings.

13. Safety Analyses

All safety analyses will be conducted using the Safety population. No inferential testing will be done for safety variables.

13.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP. Treatment-emergent adverse events (TEAE) are defined as AEs that occur after the first use of IP. Per the protocol, only AEs that begin or worsen after insertion of the IP will be captured in the database for this study; therefore, TEAEs and AEs are equivalent in this study and will be denoted as AEs.

All AEs will be assigned a severity grade of mild, moderate, or severe based on the following definitions:

- *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.

An AE is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Documentation of AEs will include onset date, resolution date, location (OD, OS, both eyes [OU], non-ocular), severity, action(s) taken, IP relationship, outcome, seriousness, reason for seriousness, expectedness, action taken with IP, and a description/narrative of the AE. All AEs will be coded using MedDRA classifications with reference to SOCs and PTs (MedDRA, version 20.0).

An overall summary table of AEs will be presented to report the number of AEs and the numbers and percentage of subjects who experienced at least one AE in the following categories:

- AEs
- Ocular AEs
- Non-Ocular AEs
- SAEs
- AEs by Severity
- AEs Leading to Subject Withdrawal
- AEs Resulting in Death

Additional AE summary tables will be presented by treatment and for all subjects showing the number of AEs and the number and percentage of subjects who experienced at least one AE. These summaries will be presented at the subject level by SOC and PT. If a subject reports mutliple AEs coded the same SOC and/or PT , that SOC and/or PT will only be reported once. For AE summaries by severity or relationship to IP, if a subject reports multiple AEs coded to the same PT within a given SOC, the subject will be counted once under the maximum (worst) severity or relationship to IP as applicable. In the summaries, SOC will be listed in order of descending frequency for all subjects; PTs will be listed in order of descending frequency for all subjects within each SOC. These summary tables will be presented for ocular and non-ocular AEs separately and include the following:

- All AEs
- All AEs suspected to be related to the IP
- All SAEs suspected to be related to the IP
- All AEs by Relationship to IP
- All AEs by Severity

Subject listings will be provided for all AEs, SAEs, AEs leading to death, and AEs leading to study treatment discontinuation.

13.2 Best Corrected Visual Acuity

The logarithm of the minimum angle of resolution (logMAR) visual acuity will be assessed at each visit except for Visit 4b (Day 1) using an ETDRS chart set at 4 meters from the subject. Any subject unable to read at least 20 or more letters on the ETDRS chart at 4 meters will be tested at 1 meter. The assessment is performed pre-CAC for visits when the CAC is administered.

The observed visual acuity (at 4 meters) and change from baseline will be summarized for each eye using continuous descriptive statistics by visit and treatment group for the Safety population. The number and percentage of subjects in each treatment group with a decrease of 10 or more letters (0.2 logMAR) from baseline will also be summarized.

A subject listing of visual acuity (including any 1-meter assessments) will also be produced.

13.3 Slit-Lamp Biomicroscopy and Punctum Examination

A slit-lamp biomicroscopy and punctum examination of the eyelid, punctal appearance, lid apposition, conjunctiva, sclera, anterior chamber, cornea, iris/pupil, and lens will be performed on each eye at each visit except for Visit 1 (Day -45) and Visit 4b (Day 1). The assessment is performed pre-CAC for visits when the CAC is administered. The results will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). The results will be summarized for the Safety population using counts and percentages for each treatment group at each visit for each eye. Percentages will be based on the number of subjects in each treatment group with responses.

A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

13.4 Intraocular Pressure (IOP)

Intraocular pressure will be assessed post-CAC by contact tonometry in each eye at Visits 2 (Day -5), 6b (Day 8), 8b (Day 15; 8 hours post Visit 8a), 9 (Day 30). The assessment is performed post-CAC for visits when the CAC is administered. Results will be taken from a single measurement and will be recorded in mmHg.

The observed IOP and change from baseline will be summarized using continuous descriptive statistics by visit, treatment group, and eye for the Safety population. The number of instances where IOP ≥ 30 mmHg and increases 10 mmHg over baseline will also be summarized using counts and percentages.

A subject listing of IOP will also be produced.

13.5 Dilated Fundoscopy Examination

A dilated fundoscopy examination of the vitreous, optic nerve, macula, retina, and choroid will be performed at Visit 2 (Day -5) post-CAC and Visit 9 (Day 30). The assessment is performed post-CAC for visits when the CAC is administered. The results will be graded as normal, abnormal NCS, or abnormal CS.

The results will be summarized using counts and percentages for each treatment group and for the Safety population at each visit for each eye. The number and percentage of subjects showing a worsening from baseline will be presented for the following categories:

- Normal to Abnormal (NCS)
- Normal to Abnormal (CS)
- Abnormal (NCS) to Abnormal (CS)

Percentages will be based on the number of subjects in each treatment group with responses.

A subject listing of the dilated fundoscopy parameters will also be produced.

14. Interim Analyses

No interim analysis is planned.

15. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

16. Revision History

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

17. Tables

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

Table Number	Title	Population
14.1.1	**Subject Disposition**	**ITT Population**
14.1.2	**Demographics**	**ITT Population**
14.1.3.1	Ocular Medical History	ITT Population
14.1.3.2	Non-Ocular Medical History	ITT Population
14.1.4.1	Ocular Prior and Concomitant Medications	ITT Population
14.1.4.2	Non-Ocular Prior and Concomitant Medications	ITT Population
14.1.5.1	Test Article Insertion and Removal	Safety Population
14.1.5.2	Test Article Visualization	Safety Population
14.1.5.3	Punctum Size Assessment	Safety Population
14.1.5.4	Exposure to Test Article	Safety Population
14.2.1.1	**Ocular Itching – Primary Timepoints**	**ITT Population with Multiple Imputation (MCMC)**
14.2.1.2	**Ocular Itching**	**ITT Population with Multiple Imputation (MCMC)**
14.2.1.3	Ocular Itching	ITT Population with LOCF
14.2.1.4	Ocular Itching	ITT Population with BOCF
14.2.1.5	Ocular Itching	ITT Population with WCO
14.2.1.6	**Ocular Itching**	**ITT Population with Observed Data Only**

14.2.1.7	**Ocular Itching**	**PP Population with Observed Data Only**
14.2.2.1	Conjunctival Redness	ITT Population with Observed Data Only
14.2.2.2	Conjunctival Redness	PP Population with Observed Data Only
14.2.3.1	Ciliary Redness	ITT Population with Observed Data Only
14.2.3.2	Ciliary Redness	PP Population with Observed Data Only
14.2.4.1	Episcleral Redness	ITT Population with Observed Data Only
14.2.4.2	Episcleral Redness	PP Population with Observed Data Only
14.2.5.1	Chemosis	ITT Population with Observed Data Only
14.2.5.2	Chemosis	PP Population with Observed Data Only
14.2.6.1	Eyelid Swelling	ITT Population with Observed Data Only
14.2.6.2	Eyelid Swelling	PP Population with Observed Data Only
14.2.7.1	Tearing/Watery Eyes	ITT Population with Observed Data Only
14.2.7.2	Tearing/Watery Eyes	PP Population with Observed Data Only
14.2.8.1	Rhinorrhea	ITT Population with Observed Data Only
14.2.8.2	Rhinorrhea	PP Population with Observed Data Only
14.2.9.1	Nasal Pruritus	ITT Population with Observed Data Only
14.2.9.2	Nasal Pruritus	PP Population with Observed Data Only
14.2.10.1	Ear or Palate Pruritus	ITT Population with Observed Data Only
14.2.10.2	Ear or Palate Pruritus	PP Population with Observed Data Only
14.2.11.1	Nasal Congestion	ITT Population with Observed Data Only
14.2.11.2	Nasal Congestion	PP Population with Observed Data Only
14.2.12.1	Nasal Composite Score – Qualitative	ITT Population with Observed Data Only
14.2.12.2	Nasal Composite Score – Qualitative	PP Population with Observed Data Only
14.2.12.3	Nasal Composite Score – Quantitative	ITT Population with Observed Data Only
14.2.12.4	Nasal Composite Score – Quantitative	PP Population with Observed Data Only
14.3.1.1	**Overall Adverse Event Summary**	**Safety Population**
14.3.1.2	**All Ocular Adverse Events**	**Safety Population**
14.3.1.3	All Non-Ocular Adverse Events	Safety Population
14.3.1.4	All Ocular Adverse Events Suspected to be Related to Investigational Product	Safety Population
14.3.1.5	All Non-Ocular Adverse Events Suspected to be Related to Investigational Product	Safety Population
14.3.1.6	All Ocular Serious Adverse Events Suspected to be Related to Investigational Product	Safety Population
14.3.1.7	All Non-Ocular Serious Adverse Events Suspected to be Related to Investigational Product	Safety Population
14.3.1.8	All Ocular Adverse Events by Severity	Safety Population
14.3.1.9	All Non-Ocular Adverse Events by Severity	Safety Population

14.3.1.10	All Ocular Adverse Events by Relationship to IP	Safety Population
14.3.1.11	All Non-Ocular Adverse Events by Relationship to IP	Safety Population
14.3.2	Visual Acuity (logMAR)	Safety Population
14.3.3	Slit-Lamp Biomicroscopy and Punctum Examination	Safety Population
14.3.4	Intraocular Pressure (mmHg)	Safety Population
14.3.5	Dilated Fundus Examination	Safety Population

18. Listings

Listing Number	Title	Population
16.1.7	Randomization Schedule	ITT Population
16.2.1	Subject Disposition	ITT Population
16.2.2.1	Protocol Deviations	ITT Population
16.2.2.2	Inclusion, Exclusion, and Procedural Exclusion Criteria	All Subjects
16.2.3	Subjects Excluded from the Per Protocol Population	ITT Population
16.2.4.1	Demographics	ITT Population
16.2.4.2	Ocular Medical History	ITT Population
16.2.4.3	Non-Ocular Medical History	ITT Population
16.2.4.4	Prior and Concomitant Ocular Medications	ITT Population
16.2.4.5	Prior and Concomitant Non-Ocular Medications	ITT Population
16.2.4.6	Allergic Skin Test	ITT Population
16.2.4.7	Punctum Size Assessment	ITT Population
16.2.5.1	Test Article Insertion	ITT Population
16.2.5.2	Test Article Visualization	ITT Population
16.2.5.3	Test Article Removal	ITT Population
16.2.5.4	Relief Medication Instillation	ITT Population
16.2.5.6	Conjunctival Allergen Challenge	ITT Population
16.2.6.1	Ocular Itching	ITT Population
16.2.6.2	Conjunctival Redness	ITT Population
16.2.6.3	Ciliary Redness	ITT Population
16.2.6.4	Episcleral Redness	ITT Population
16.2.6.5	Chemosis	ITT Population
16.2.6.6	Eyelid Swelling	ITT Population
16.2.6.7	Tearing	ITT Population
16.2.6.8	Nasal Symptoms	ITT Population
16.2.7.1	Adverse Events	ITT Population
16.2.7.2	Serious Adverse Events – Part 1	ITT Population
16.2.7.2	Serious Adverse Events – Part 2	ITT Population

16.2.7.3	Adverse Events Leading to Death	ITT Population
16.2.7.4	Adverse Events Leading to Study Treatment Discontinuation	ITT Population
16.2.8.1	Pregnancy Test Results for Female Subjects of Childbearing Potential	ITT Population
16.2.8.2	Visual Acuity (logMAR)	ITT Population
16.2.8.3	Slit-Lamp Biomicroscopy and Punctum Examination	ITT Population
16.2.8.4	Intraocular Pressure (mmHg)	ITT Population
16.2.8.5	Dilated Fundus Examination	ITT Population
16.2.8.7	Comments	ITT Population
16.2.8.8	Digital Photographs/Videos	ITT Population

19. Figures

Figure Number	Title	Population
14.2.1.1	Mean +/- SE Ocular Itching	ITT Population with Multiple Imputation (MCMC)
14.2.1.2	Change from Baseline in Ocular Itching (Mean +/- SE)	ITT Population with Multiple Imputation (MCMC)
14.2.1.3	Mean +/- SE Ocular Itching	ITT Population with Observed Data Only
14.2.1.4	Change from Baseline in Ocular Itching (Mean +/- SE)	ITT Population with Observed Data Only

20. Appendix A

Ora Calibra™ Conjunctival Allergen Challenge Ocular Itching Scale

Itching:

0 = None
0.5 = An intermittent tickle sensation possibly localized in the corner of the eye
1.0 = An intermittent tickle sensation involving more than just the corner of the eye
1.5 = An intermittent all-over tickling sensation
2.0 = A mild continuous itch (can be localized) without desire to rub
2.5 = A moderate, diffuse continuous itch with desire to rub
3.0 = A severe itch with desire to rub
3.5 = A severe itch improved with minimal rubbing
4.0 = An incapacitating itch with an irresistible urge to rub

0.5 unit increments ARE allowed

Ora Calibra™ Conjunctival Allergen Challenge Eyelid Swelling Scale

Eyelid Swelling:

0 = **None**
1.0 = **Mild** – Detectable swelling of lower and/or upper lid
2.0 = **Moderate** – Definite swelling of lower and/or upper lid
3.0 = **Severe** – Swelling of lower and/or upper lid to the point that there is a decrease in the space between your upper and lower lids

0.5 unit increments are NOT allowed

Ora Calibra™ Conjunctival Allergen Challenge Tearing/Watery Eyes Scale

Tearing/Watery Eyes:

0 = **None/Normal**
1 = **Mild** – A noticeably increased moistening of your eye
2 = Moderate – Your eye feels "full" of water; your lashes feel a little wet
3 = Severe – Feels like tears might drip down your face; very wet lashes
4 = Very Severe – Tears are dripping down your face

0.5 increments are NOT allowed

Ora proprietary scales – Not for distribution without permission

Subject-Evaluated Nasal Symptoms

Ora Calibra™ Rhinorrhea Scale

Rhinorrhea (Runny Nose):

0= None
1= Mild (sensation of nasal mucus flowing down nasal passage; no discharge present)
2= Moderate (may be associated with post nasal drip; nasal mucus flow more pronounced; will need to blow nose soon)
3= Moderate/Severe (nasal mucus discharge requiring occasional wiping with Kleenex)
4= Severe (uncontrolled nasal discharge; requiring frequent wiping and blowing nose)

0.5 unit increments ARE NOT allowed.

Ora Calibra™ Nasal Pruritus Scale

Nasal Pruritus (Itchy Nose):

0= None
1= Mild (An intermittent tickle sensation)
2= Moderate (A mild continuous itch)
3= Moderate/Severe (A severe itch with desire to rub)
4= Severe (Incapacitating itch with an irresistible urge to rub)

0.5 unit increments ARE NOT allowed.

Ora Calibra™ Ear or Palate Pruritus Scale

Ear or Palate Pruritus (Itchy Ear or Palate):

0= None
1= Mild (An intermittent tickle sensation)
2= Moderate (A mild continuous itch)
3= Moderate/Severe (A severe itch with desire to rub)
4= Severe (Incapacitating itch with an irresistible urge to rub)

0.5 unit increments ARE NOT allowed.

Ora Calibra™ Nasal Congestion Scale

Nasal Congestion:

0= None (No breathing difficulty)
1= Mild (Some sensation of blockage)
2= Moderate (Partial Blockage)
3= Moderate/Severe (Significant blockage but can still breathe through nose)
4= Severe (Cannot breathe through nose at all)

0.5 unit increments ARE NOT allowed.

Investigator-Evaluated Signs (Ocular)

Ora Calibra™ Ocular Hyperemia Scale

Regional Redness: **Hyperemia (ciliary, conjunctival, and episcleral). All evaluated separately by an Investigator with the slit lamp**

0 = None
1 = Mild – Slightly dilated blood vessels; color of vessels is typically pink; can be quadrantal
2 = Moderate – More apparent dilation of blood vessels; vessel color is more intense (redder); involves the majority of the vessel bed
3 = Severe – Numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red, may be less red or pink in presence of chemosis, is not quadrantic
4 = Extremely Severe – Large, numerous, dilated blood vessels characterized by unusually severe deep red color, regardless of grade of chemosis, which involves the entire vessel bed

0.5 unit increments ARE allowed

Ora Calibra™ Chemosis Scale

Chemosis:

0 = None
1.0 = Detectable only by slit lamp beam; definite separation of conjunctiva from sclera
2.0 = Visible in normal room light; more diffuse edema
3.0 = Conjunctival billowing at the limbus; very diffuse and noticeable
4.0 = Severe overall billowing of conjunctiva

0.5 unit increments ARE allowed