STATISTICAL ANALYSIS PLAN

A Single-Center, Randomized, Double-Masked, Vehicle and Active-Controlled, Dose-Ranging Phase 2 Study Evaluating the Efficacy and Safety of PRT-2761 for the Treatment of Acute and Chronic Allergic Conjunctivitis Using the Conjunctival Allergen Challenge Model (Ora-CAC®)

Sponsor: Ora, Inc.

Protocol Number: 17-100-0008

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Statistics & Data Corporation

Date: 27NOV2017

Version: 1.0

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Statistical Analysis Plan Approval

Prepared by: _____ 28-NOV-2017

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List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
BOCF	Baseline Observation Carried Forward
CAC	Conjunctival Allergen Challenge
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
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	Least Squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
NCS	Not clinically significant
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
WHO DD	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol 17-100-0008, version Amendment 2.0 dated 18OCT2017.

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

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

2. Study Objectives

The objective of this study is to evaluate the efficacy and safety of two concentrations of PRT-2761 (0.5% and 1%) as a topical ophthalmic solution for the treatment of the signs and symptoms of acute and chronic allergic conjunctivitis.

2.1 Primary Efficacy Measures

The primary efficacy measures are:

- Ocular itching evaluated by the subject at Visits 4b and 5a (for Duration and Onset of action, respectively) at 5(±1), 7(±1), and 10(±1) minutes post-Conjunctival Allergen Challenge (CAC, 0-4 scale, allowing half-unit increments)
- Conjunctival redness evaluated by the Investigator at Visits 4b and 5a (for Duration and Onset of action, respectively) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)

2.2 Secondary Efficacy Measures

The secondary efficacy measures are:

- Ocular itching evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 5(±1), 7(±1), and 10(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Conjunctival redness evaluated by the Investigator at Visits 5b, 6a, 6b, and 7 at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Episcleral and ciliary redness evaluated by the Investigator at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)

- Chemosis evaluated by the Investigator at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Tearing evaluated by the subject at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)
- Eyelid swelling evaluated by the subject at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-3 scale, NOT allowing half-unit increments)
- Rhinorrhea, nasal pruritis, ear or palate pruritis, and nasal congestion evaluated by the subject at all dosing Visits (4b, 5a, 5b, 6a, 6b, 7) at 7(±1), 15(±1), and 20(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)

2.3 Safety Measures

The safety measures include the following:

- Slit Lamp Biomicroscopy conducted at Visits 2, 3, 4a, 4b, 5a, 5b, 6a, 6b and 7
- Dilated Ophthalmoscopy conducted at Visits 2 and 7
- Distance Visual Acuity (VA) using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart conducted at Visits 2, 3, 4a, 4b, 5a, 5b, 6a, 6b and 7
- Intraocular Pressure (IOP) Visits 2 and 7
- Adverse Events (AE) (reported, elicited, and observed) assessed at Visits 1, 2, 3, 4a, 4b, 5a, 5b, 6a, 6b and 7

2.4 Tolerability Measures

The tolerability measures include the following:

- Drop comfort assessment (0-10 unit scale) assessed by subject immediately upon instillation, at 30 seconds, and 1 minute post-instillation at Visit 4a
- Drop comfort descriptor questionnaire at 3 minutes post-instillation at Visit 4a

2.5 Exploratory Measures

The exploratory measures include the following:

- Ocular itching evaluated by the subject at Visit 5b, 6a, 6b, and 7 at 15(±1), 20(±1), 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Tearing evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)
- Eyelid swelling evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-3 scale, NOT allowing half-unit increments)

- Rhinorrhea, nasal pruritis, ear or palate pruritis, and nasal congestion evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments).
- Conjunctival, episcleral, and ciliary redness evaluated by the investigator at Visit 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).
- Chemosis evaluated by the investigator at Visit 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).
- In a subset of approximately 36 subjects who agree to undergo confocal microscopy, conjunctival inflammation as measured by confocal microscopy (0-4 scale, NOT allowing half-unit increments) at Visits 3, 4b, and 7.
- In the same subset of subjects who undergo confocal microscopy, tears will be collected from both eyes (prior to confocal microscopy) at Visit 3, 4b, and 7. At Visit 3, tears will be collected at two separate time points post-CAC: prior to the confocal microscopy procedures and again at 2 (+1) hours after instillation of the anesthetic used for the confocal microscopy procedures. At Visit 4b tears will be collected prior to the confocal microsopy procedures post-CAC. At Visit 7 tears will be collected 2 (+1) hours after instillation of the anesthetic used for the confocal microscopy procedures post-CAC. Tears will be analyzed for cytokine levels.
- Diary assessments for the subset of subjects undergoing confocal microscopy at Visits 3 and 4b. Additionally, all subjects will be dispensed diaries at Visits 5b and 6b. Assessments of ocular itching, ocular redness, and eyelid swelling will occur prior to bedtime and upon awakening (all use a 0 to 4 scale, except eyelid swelling, 0 to 3).
- In the same subset of subjects who undergo confocal microscopy, digital photographs will be taken at-home of each eye prior to subjects completing diary assessments following Visits 5b and 6b.
- Digital photographs will be taken in-office of all subjects pre-CAC and within 30 minutes of the last post-CAC assessment at Visit 4b and Visit 5a.

2.6 Statistical Hypotheses

[redacted]

[redacted]

3. Study Design and Procedures

3.1 General Study Design

This is a prospective, single-center, randomized, double-masked, vehicle and active-controlled, dose-ranging study to evaluate the efficacy and safety of PRT-2761 in two concentrations compared to Vehicle, Patanol® and Patanol®/Pred forte® for the treatment of the signs and symptoms of chronic allergic conjunctivitis.

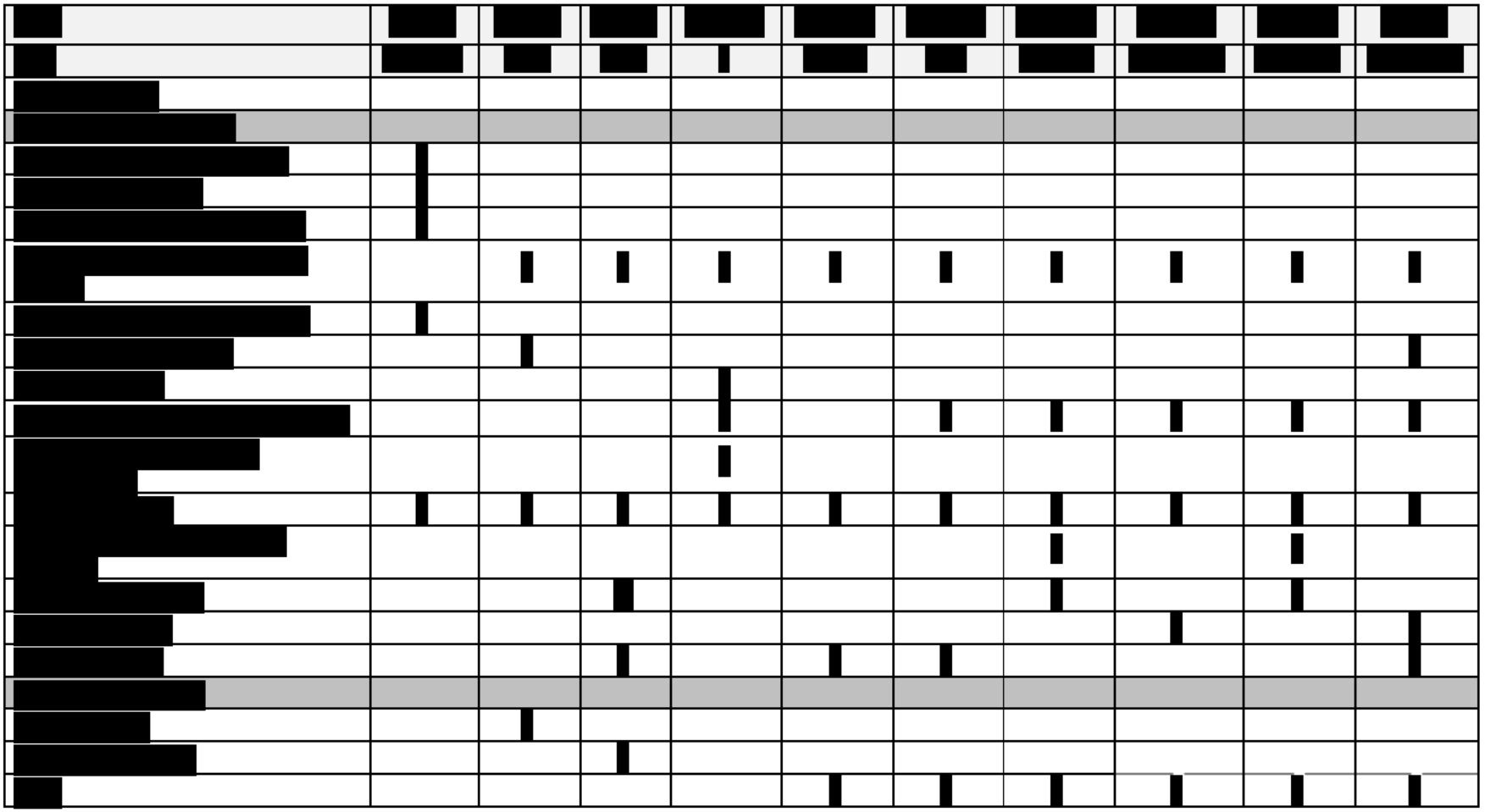
The trial will comprise of 10 office visits over a period of up to 9 weeks. Part 1 will be a conventional CAC protocol. Subjects who meet the entry criteria for itching and redness response to the CAC at Visits 2 and 3 will be randomized at Visit 4a (Day 1, Duration of Action Visit) in a 1:1:1:1 (PRT-2761 0.5%: PRT-2761 1%: Vehicle:Patanol®) assignment ratio in the acute phase. Subjects randomized to the Patanol® treatment for the acute phase will further be randomized using a 1:1 (Patanol®: Pred forte®) assignment ratio for the chronic phase. After 8 hours, subjects will return for Visit 4b to be challenged with signs and symptoms assessed post-CAC. Subjects will return 14 days later for Visit 5a (Day 15, Onset of Action Visit), at which time they will be challenged 15 minutes after dosing with the same concentration of PRT-2761, vehicle, or Patanol® as randomized at Visit 4a. This will conclude Part 1 of the study.

Part 2 will be the assessment of chronic allergy and subjects will be challenged 15 minutes after dosing. If subjects were randomized to receive PRT-2761 0.5%, PRT-2761 1%, or vehicle at Visit 4a, subjects will continue to receive the same treatment at (Visits 5b, 6a, 6b and 7 at 8, 24, 32 and 48 hours from Visit 5a, respectively). Subjects who were randomized to receive Patanol® at Visit 4a will be further randomized into 2 groups. One group will continue to receive Patanol® through Visit 7. The other group will be dosed with Pred forte® at Visits 5b through 7. At Visit 7, final exit procedures will also be conducted and subjects will exit the study.

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

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day -50 to -22	N/A
Visit 2	Day -21	+/- 3 Days
Visit 3	Day -14	+/- 3 Days
Visit 4a	Day 1	N/A
Visit 4b	Visit 4a + 8 hour	+1 Hour
Visit 5a	Day 15	+/- 3 Days
Visit 5b	Visit 5a + 8 hours	+1 Hour
Visit 6a	Visit 5a + 24 hours	+/- 6 Hours
Visit 6b	Visit 6a + 8 hours	+1 Hour
Visit 7	Visit 6a + 24 hours	+/- 6 Hours

[redacted]



4. Study Treatments

Subjects will be assigned to one of the following treatments:

- PRT-2761 0.5%
- PRT-2761 1%
- Vehicle
- Patonol® (active reference)
- Patanol® during the acute phase / Pred forte® during the chronic phase (active reference)

4.1 Method of Assigning Subjects to Treatment Groups

All subjects screened for the study who sign an informed consent form will be assigned a 3-digit screening number that will be entered in the Screening and Enrollment Log. Screening numbers will be assigned in sequential order beginning with 001. Randomization will be used to avoid bias in the assignment of subjects to treatment and time point, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups and across time points, and to enhance the validity of statistical comparisons.

Once a subject meets all qualification criteria at Visit 4a, they will be enrolled and randomly assigned to masked treatment using a 1:1:1:1 (PRT-2761 0.5%: PRT-2761 1%:Vehicle:Patanol®) assignment ratio for the acute phase. Subjects randomized to the Patanol® treatment in the acute phase will further be randomized using a 1:1 (Patanol®:Pred forte®) assignment ratio for the chronic phase. Subjects will be randomized at Visit 4a (Day 1) by assignment of the lowest 4-digit randomization number available within the appropriate stratum. Randomization will be stratified by average post-CAC itching scores [redacted] at baseline (Visit 3), by qualifying allergen type [redacted] and by confocal participation (yes and no) to ensure balance for the primary endpoint of ocular itching. The randomization numbers will start from x001, where x refers to the subject's stratum as follows:

- x = 1 for subjects in the low baseline itching, seasonal allergy, no confocal participation stratum
- x = 2 for subjects in the low baseline itching, perennial allergy, no confocal participation stratum
- x = 3 for subjects in the high baseline itching, seasonal allergy, no confocal participation stratum
- x = 4 for subjects in the high baseline itching, perennial allergy, no confocal participation stratum
- x = 5 for subjects in the low baseline itching, seasonal allergy, confocal participation stratum
- x = 6 for subjects in the low baseline itching, perennial allergy, confocal participation stratum
- x = 7 for subjects in the high baseline itching, seasonal allergy, confocal participation stratum
- x = 8 for subjects in the high baseline itching, perennial allergy, confocal participation stratum

The first 36 subjects who qualify after post-CAC assessments at Visit 3 and had tear collection at Visit 2, will be in the confocal microscopy subset. This number is estimated to ensure approximately 30

subjects in the confocal microscopy subset complete the trial. At Visit 4, these individuals will be assigned to a kit number from Stratum 5, 6, 7, or 8.

Once 36 subjects have completed confocal microscopy at Visit 3, any subjects who had tear collection at Visit 2, will not have additional tear collections or confocal microscopy. At Visit 4, these individuals will be assigned to a kit number from Stratum 1, 2, 3, or 4.

No randomization numbers will be skipped or omitted.

At Visit 4a, if a subject requires a kit from their assigned stratum, based on the above criteria, and there are no longer any kits available for that stratum, the subject will not be randomized and will be deemed a screen failure. A five-digit subject ID (two-digit site number and the three-digit screening number separated by a hyphen [i.e., nn-nnn]) will be used to identify subjects in all datasets, listings, and tables for this study.

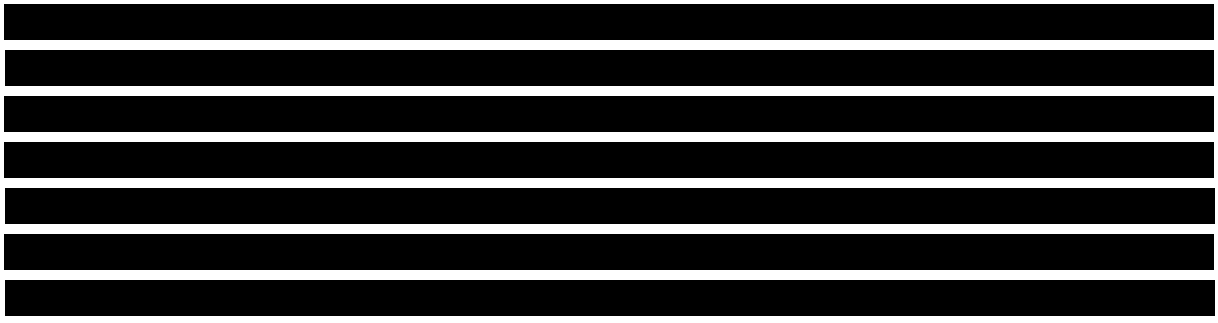
4.2 Masking and Unmasking

When medically necessary, the Investigator may need to determine what treatment has been assigned to a subject. The Investigator will contact Ora with the details of the emergency unmasking request. Ora will make the final determination if the unmasking request will be granted. If granted, the Investigator will be permitted to use the code-break instructions available on site.

Each kit will be labeled with a two panel scratch off label. The right panel of the label, containing the scratch off portion, should be placed in the corresponding subject binder. If the Investigator determines that emergency unmasking is necessary, the Investigator should locate the subject binder containing the label and scratch off the laminate section to reveal the assigned treatment. The Investigator must also indicate in source documents and in the CRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or serious AE (SAE) associated with breaking the mask must be recorded and reported as specified in this protocol.

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

5. Sample Size and Power Considerations



[redacted]

6. Data Preparation

All reported study data will be recorded on the electronic case report forms (eCRF) supplied by Statistics & Data Corporation (SDC) using iMedNet™. Data from source documents will be entered into the eCRF by site personnel.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor and Ora in consultation with SDC.

All 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 personnel;
- Protocol deviations have been identified and status defined (major/minor deviations);
- Analysis populations have been determined; and
- Randomized treatment codes have been unmasked.

7. 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 5a (Day 15) with no major protocol violations. This population will be analyzed as treated using observed data only for confirmatory analyses.

7.3 Safety

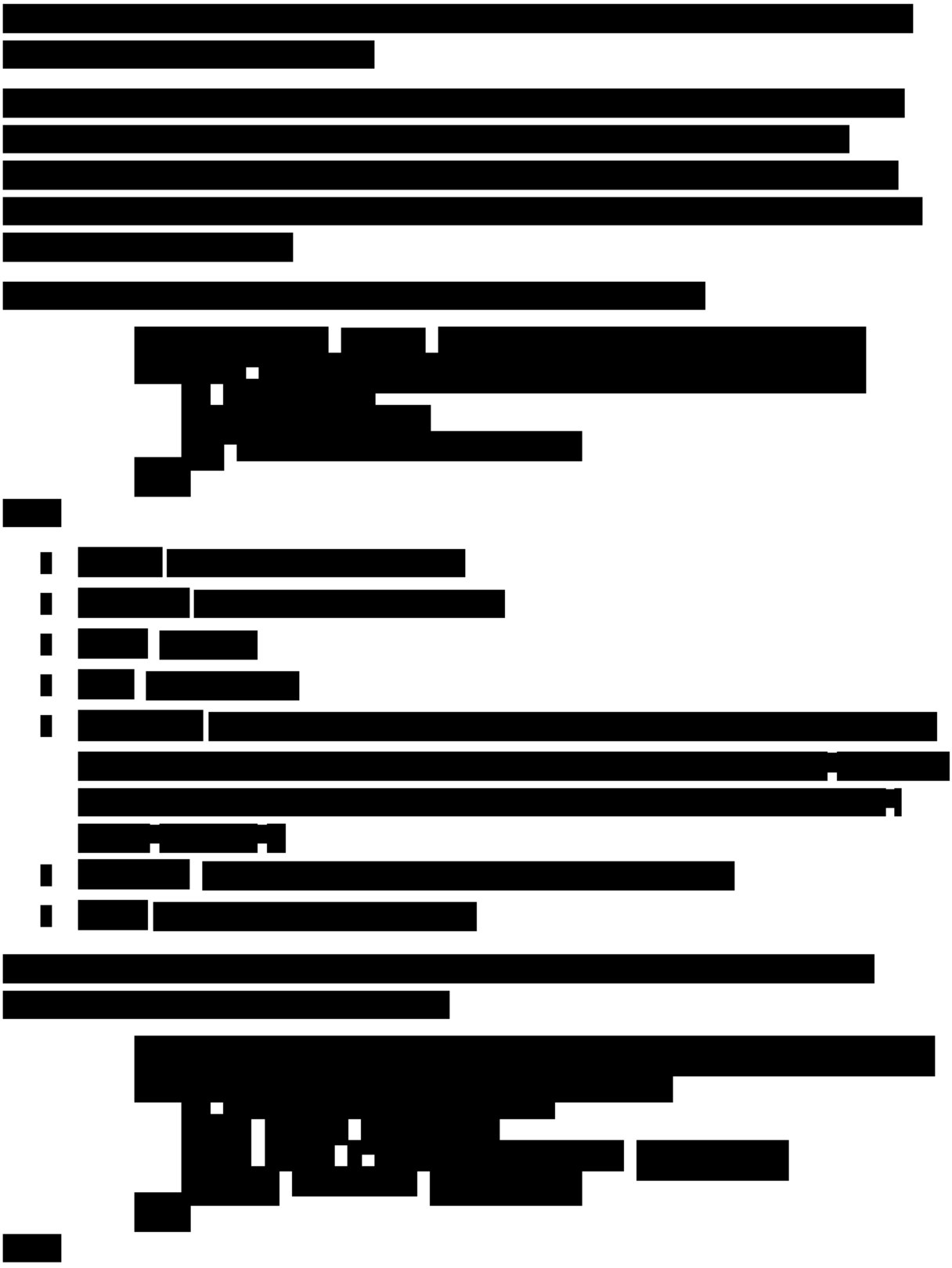
The safety population includes all randomized subjects who received at least one dose of investigational treatment. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

8. General Statistical Considerations

8.1 Unit of Analysis

The subject will be considered the unit of analysis for all variables with exceptions of slit-lamp biomicroscopy and dilated fundoscopy examination. For the variables using subject as the unit of the analysis, the average of both eyes of each subject will be used for statistical summaries and analyses in cases where data are collected for each eye. For slit-lamp biomicroscopy and dilated fundoscopy examination results, the eye will be the unit of analysis and summaries will be provided for all eyes combined.

8.2 Missing or Inconclusive Data Handling



[redacted]

[redacted]

8.3 Definition of Baseline

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

Baseline for all secondary efficacy variables is defined in a manner similar to the baseline for the primary efficacy variables. For all safety variables, baseline is defined as the last measurement prior to the first dose of study medication.

8.4 Data Analysis Conventions

All data analysis will be performed by SDC. 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/time point (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, SD, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than

reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between active treatment groups and vehicle or active control will be calculated as active minus vehicle or active control 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 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999".

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

8.5 Adjustments for Multiplicity

There will be no adjustment for multiplicity for having two endpoints as statistical significance is required for both ocular itching and conjunctival redness for treatment success. There will also be no adjustment necessary for testing multiple time points within a given visit, as significance at all post-CAC time points is required.

Since this is a proof of concept study, there will be no adjustment for multiplicity of testing two concentrations of PRT-2761 versus placebo.

9. Disposition of Subjects

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

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all randomized subjects. The reasons for study discontinuation that will be summarized include: AE, protocol deviation, administrative reasons, manifest signs of allergic conjunctivitis at Visit 5a , sponsor termination of study and other. A subject listing will be provided that includes the date of and reason for premature study discontinuation.

Subject listings will be provided that include informed consent date, inclusion and exclusion criteria, deviations, and exclusions from the PP population.

Protocol deviations will be summarized by treatment group for all randomized subjects for each deviation category (informed consent, inclusion/exclusion and randomization, test article/study drug instillation and assignment at site, improper protocol procedures at site, site failure to report SAE, visit out of

window [missed, early, late], subject's non-compliance with test article/study drug, subject use of prohibited concomitant medication, subject's failure to follow instructions, other) and severity (minor, major) using counts and percentages. Percentages will be based on the total number of subjects randomized in each treatment group. A subject listing will be provided that includes the date of the deviation, the deviation description, and the classification of whether the deviation was judged to be major or minor.

10. Demographic and Pretreatment Variables

10.1 Demographic Variables

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

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

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

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, ethnicity, iris color, average post-CAC itching scores at baseline [redacted] allergen type, and confocal participation.

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

10.2 Pretreatment Variables

At Visit 1 (Day -50 to -22), subjects signing the informed consent and Health Insurance Portability and Accountability Act (HIPAA) forms may be given a diagnostic test for allergic disease (skin test). Results from this test will be provided in a subject listing.

11. Medical History and Concomitant Medications

11.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.

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

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

11.2 Concomitant Medications

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD, Enhanced B2, September 2017) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins) then the drug name will be summarized as the preferred name.

Concomitant medications will be summarized using the ITT population. Medications will be tabulated for each treatment group using frequencies and percentages. 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. Percentages will be based on the number of randomized subjects in each treatment group. Listings of concomitant medications will be generated separately for ocular and non-ocular data.

12. Exposure to Investigational Product

The number and percentage of subjects instilled with IP will be summarized by visit and treatment group for the Safety population. Percentages will be calculated based on the total number of subjects in each treatment group with responses.

A listing of IP instillation for all subjects will also be provided.

13. Efficacy Analyses

13.1 Primary Analysis

The primary efficacy endpoints are ocular itching assessed by the subject at 5(±1), 7(±1), 10(±1) minutes post-CAC (0-4 scale, allowing half-unit increments) and conjunctival redness evaluated by the Investigator at 7(±1), 15(±1), 20(±1) minutes post-CAC (0-4 scale, allowing half-unit increments) at Visit 4b (duration of action visit) and 5a (onset of action visit).

Ocular itching will be evaluated by the subject using the following Ora Calibra® CAC Ocular Itching Scale:

[redacted]

[redacted]

Conjunctival redness will be evaluated by the investigator using the following Ora Calibra® Ocular Hyperemia Scale (half unit increments are allowed):

[redacted]

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

The primary efficacy analyses for ocular itching and conjunctival redness will be conducted on the ITT population with LOCF for missing data using analysis of covariance (ANCOVA) models. These statistical models will include treatment group (including all four treatments: PRT-2761 0.5%, PRT-2761 1%, Vehicle, Patanol®) and the time point specific post-CAC scores at Visit 3 as a measure of baseline. Least square (LS) means for each treatment, the estimated treatment differences and their corresponding 95% CI, and p-values will be calculated from these ANCOVA models and will be used to compare each concentration of PRT-2761 and Patanol® to Vehicle and each concentration of PRT-2761 to Patanol®.

[redacted]

[redacted]

To demonstrate efficacy for ocular itching, PRT-2761 in any concentration needs to show clinical superiority over vehicle by [redacted] post-CAC time points, 5(±1), 7(±1), 10(±1) minutes post-CAC and at least 1 unit for the majority [redacted] of the post-CAC time points. The same criteria will be used to demonstrate efficacy for conjunctival redness.

If ocular itching meets the efficacy measures as defined above with statistical significance ([redacted] the study will be considered a success for ocular itching. Similarly, if conjunctival redness meets the efficacy measures as defined above with statistical significance, then the study will be considered a success for conjunctival redness.

If both ocular itching and conjunctival redness meet the efficacy measures as defined above with statistical significance, then the study will be considered a success for both ocular itching and conjunctival redness.

Two-sample t-tests and non-parametric Wilcoxon rank sum tests will be used as unadjusted sensitivity analyses at each post-CAC time point. At each post-CAC time point, treatment differences will be considered statistically significant for each primary endpoint if they are significant at a two-sided significance level of $\alpha = 0.05$.

Sensitivity or supportive analyses will be performed on the following:

- ITT population with multiple imputation using MCMC methods for missing data;
- ITT population with BOCF for missing data;
- ITT population with observed data only;
- PP population with observed data only.

The number of subjects with itching scores less than one and with itching scores equal to zero will be summarized with counts and percentages by treatment group for each post-CAC time point at Visits 4b, 5a, 5b, 6a, 6b, and 7. For Visits 4b and 5a (acute phase), the number of subjects in each concentration of PRT-2761 and Patanol® will be compared to Vehicle and the number of subjects in each concentration of PRT-2761 will be compared to Patanol®. For Visits 5b, 6a, 6b, and 7 (chronic phase), the number of

subjects in each concentration of PRT-2761 and Patanol® will be compared to Pred forte® in addition to the treatment comparisons being made for the acute phase. A Fisher's exact test will be used to compare treatments for the number of subjects in each category and the corresponding p-values will be reported. Conjunctival redness scores will be summarized in a similar manner using categories of scores less than or equal to one and scores equal to zero.

Figures will be produced to show mean ocular itching score for each treatment arm by time point and visit (Visits 4b and 5a) for the ITT and PP populations with observed data only. Mean change from baseline of ocular itching scores for each treatment arm will be presented in a similar figure for the ITT population with observed data only. Mean conjunctival redness scores and mean change from baseline of conjunctival redness scores will also be presented in similar figures.

Separate listings of ocular itching scores and conjunctival redness scores for all subjects will also be provided.

13.2 Secondary Analyses

Secondary endpoints include ocular itching; conjunctival, episcleral, and ciliary redness; chemosis; tearing/watery eyes; eyelid swelling; rhinorrhea; nasal pruritus; ear or palate pruritus; and nasal congestion. All secondary endpoints will be analyzed in a manner similar to the primary endpoints for the ITT population with observed data only and for the PP population with observed data only. The ANCOVA models used will include treatment group (including all five treatments: PRT-2761 0.5%, PRT-2761 1%, vehicle, Patanol®/Patanol®, Patanol®/Pred forte®) and the time point specific post-CAC scores at Visit 3 as a measure of baseline. For the acute phase (Part 1), LS means for each treatment, the estimated treatment differences and their corresponding 95% confidence intervals, and p-values will be used to compare each concentration of PRT-2761 and Patanol® to vehicle and each concentration of PRT-2761 to Patanol®. For the chronic phase (Part 2), LS means for each treatment, and the estimated treatment difference and their corresponding 95% confidence intervals, and p-values will be used to compare each concentration of PRT-2761, Patanol®/Patanol® and Patanol®/Pred forte® to vehicle. Each concentration of PRT-2761 will also be compared to Patanol®/Patanol® and Patanol®/Pred forte® separately.

In addition, repeated measures ANCOVA models will be run for each visit, with treatment, time point, and time appropriate baseline as covariates. These models account for correlations between time points within each subject. LS means for each treatment, the estimated treatment differences and their corresponding 95% confidence intervals (as described previously for each phase) will be calculated from these repeated measures ANCOVA models. SAS code to implement this repeated measures ANCOVA model for each visit is as follows:

The Kenward-Roger method will be used to determine denominator degrees of freedom. 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.

The secondary analysis variables will be presented in subject listings by visit and time point as appropriate.

13.2.1 Ocular Itching

Ocular itching will be evaluated by the subject at 5(±1), 7(±1), 10(±1) minutes post-CAC (0-4 scale, allowing half-unit increments) at Visits 5b, 6a, 6b and 7 using the Ora Calibra® CAC Ocular Itching Scale defined in Section 13.1 and will be analyzed as quantitative variables as described at the beginning of Section 13.2.

13.2.2 Conjunctival, Ciliary and Episcleral Redness

Conjunctival redness will be evaluated by the Investigator at 7(±1), 15(±1), 20(±1) minutes post-CAC at Visits 5b , 6a, 6b, and 7.

Episcleral and ciliary redness will be evaluated by the Investigator at 7(±1), 15(±1) and 20(±1) post-CAC at Visits 4b, 5a, 5b , 6a, 6b, and 7.

All three redness assessments will use the Ora Calibra® Ocular Hyperemia Scale defined in Section 13.1 and will be analyzed separately as quantitative variables as described at the beginning of Section 13.2.

13.2.3 Chemosis

Chemosis will be evaluated by the Investigator at 7(±1), 15(±1) and 20(±1) post-CAC at all dosing visits (Visits 4b, 5a, 5b, 6a, 6b and 7) using the following Ora Calibra® Chemosis Scale (half unit increments are allowed):

[redacted]

[redacted] described at the beginning of Section 13.2.

13.2.4 Tearing/Watery Eyes

Tearing/watery eyes will be evaluated by the subject at 7(±1), 15(±1) and 20(±1) post-CAC at all dosing visits (Visits 4b, 5a, 5b, 6a, 6b, and 7) using the following Ora Calibra CAC Tearing/Watery Eyes Scale (half unit increments are NOT allowed):

[redacted]

Tearing/watery eyes will be analyzed as a quantitative variable as described at the beginning of Section 13.2.

13.2.5 Eyelid Swelling

Eyelid swelling will be evaluated by the subject at 7(±1), 15(±1) and 20(±1) post-CAC at all dosing visits (Visits 4b, 5a, 5b, 6a, 6b, and 7) using the following Ora Calibra® CAC Eyelid Swelling Scale (half unit increments are NOT allowed):

[redacted]

Eyelid swelling will be analyzed as a quantitative variable as described at the beginning of Section 13.2.

13.2.6 Rhinorrhea

Rhinorrhea (runny nose) will be evaluated by the subject at 7(±1), 15(±1) and 20(±1) post-CAC at all dosing visits (Visits 4b, 5a, 5b, 6a, 6b, and 7) using the following Ora Calibra® Rhinorrhea Scale (half unit increments are NOT allowed):

[redacted]

[redacted]

Rhinorrhea will be analyzed as a quantitative variable as described at the beginning of Section 13.2.

13.2.7 Nasal Pruritus and Ear or Palate Pruritus

Nasal pruritus (itchy nose) and ear or palate pruritus (itch ear or palate) will be evaluated by the subject at 7(±1), 15(±1) and 20(±1) post-CAC at all dosing visits (Visits 4b, 5a, 5b, 6a, 6b, and 7) using the following Ora Calibra® Nasal Pruritus / Ear or Palate Pruritus Scales (half unit increments are NOT allowed):

[redacted]

Nasal pruritus and ear or palate pruritus will be analyzed as quantitative variables as described at the beginning of Section 13.2.

13.2.8 Nasal Congestion

Nasal congestion will be evaluated by the subject at 7(±1), 15(±1) and 20(±1) post-CAC at all dosing visits (Visits 4b, 5a, 5b, 6a, 6b, and 7) using the following Ora Calibra® Nasal Congestion Scale (half unit increments are NOT allowed):

[redacted]

Nasal congestion will be analyzed as a quantitative variable as described at the beginning of Section 13.2.

14. Safety Analyses

All safety analyses will be conducted using the Safety population.

14.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without

any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release) associated with medical device.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the CRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Collection of AEs/SAEs will begin at the time of informed consent. Any AE that occurs or worsens after the first instillation of the IP will be classified as a treatment-emergent AE (TEAE). All AEs will be coded using the MedDRA Version 20.1.

An AE is considered serious if, in the view of either the investigator or sponsor/designee, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term “inpatient hospitalization” refers to an inpatient admission for more than 24 hours. For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

  An overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background does not need to be handled/documented as an SAE. Hospitalizations due to surgical procedures for pre-existing conditions that have been planned before enrolment of the subject are not considered SAEs.

Note: The term “prolongation of existing hospitalization” refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

  Note: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject’s eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.
- Important medical events that may not result in death, are 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 in this definition.

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 IP 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, requires no special treatment 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 IP should be determined by the investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the study drug caused the AE. A suspected AE can be further defined as:
  - *Definite:* Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
  - *Probable:* Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.

  - *Possible:* Relationship exists when the AE follows a reasonable sequence from the time of administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.

- *Not Suspected*: A reasonable possibility does not exist that the study drug caused the AE. A not suspected AE can further be defined as:
  - *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

An overall summary will be presented that includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE, by treatment group. This summary will also include breakdowns of TEAEs further categorized as ocular or non-ocular, serious TEAEs, TEAEs by maximum severity, TEAEs by maximum relationship to IP, TEAEs leading to IP withdrawal, and number of subjects with TEAEs resulting in death.

Additional summaries of AEs will be provided showing the number and percentage of subjects who experienced at least one AE. These summaries will be presented by SOC and PT. AEs will be summarized using counts and percentages and presented by treatment group at the subject level by SOC and PT. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in order of decreasing frequency for all subjects; PTs will be listed in order of descending frequency for all subjects within each SOC. The occurrence of non-ocular and ocular AEs will also be tabulated by SOC, PT and maximal severity. If a subject has multiple AEs coded to the same PT within the same SOC, the subject will be counted once under the maximal severity.

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

- All Ocular AEs
- All Ocular AEs by Study Phase
- All Non-Ocular AEs
- All Ocular TEAEs
- All Non-Ocular TEAEs
- All Ocular SAEs
- All Non-Ocular SAEs
- All Ocular TEAEs by Maximal Severity
- All Non-Ocular TEAEs by Maximal Severity

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

14.2 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination will be performed at Visits 2, 3, 4a, 4b, 5a, 5b, 6a, 6b, and 7 prior to the CAC and again post-CAC at Visit 7, and will consist of the examination of the following items:

- Anterior Chamber
- Conjunctiva
- Cornea
- Eyelid
- Lens

The results will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). The results will be summarized using counts and percentages for each treatment group for all eyes combined. Percentages will be based on the number of subject eyes in each treatment group with responses. A shift table will also be produced showing changes from baseline in slit-lamp examination results for each treatment and post-baseline assessment.

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

14.3 Dilated Ophthalmoscopy

Dilated fundoscopy examinations will be performed post-CAC at Visits 2 and 7. Counts and percentages of normal and abnormal results will be presented for all eyes combined by visit and treatment group for the following regions:

- Choroid
- Macula
- Optic Nerve
- Retina
- Vitreous

Percentages will be based on the number of subject eyes in each treatment group with responses. A shift table will also be produced showing changes from baseline in dilated fundoscopy examination results for each treatment and post-baseline assessment. Results will be listed for both eyes at each visit.

14.4 Visual Acuity

Visual acuity will be assessed using an ETDRS at Visits 2, 3, 4a, 4b, 5a, 5b, 6a, 6b, and 7 prior to the CAC. For Visit 7, it will be measured again post-CAC.

VA for each eye will be calculated as the last line in which a letter is read correctly. To this value will be added the number "N x 0.02" where "N" represents the total number of letters missed up to and included in the last line read. This total sum represents the logarithm of the minimum angle of resolution (logMAR) VA for that eye.

For Example: Subject correctly reads four (4) of five (5) letters on the 0.2 line, and two (2) of five (5) letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N x T (T=0.2)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR VA	= 0.18

VA in logMAR unit will be summarized by treatment using the average of both eyes for each subject with quantitative summary statistics. The number of subjects with worsening of acuity of 10 letters (0.2 logMAR) or more from Visit 2 will also be summarized with counts and percentages based on the total number of subjects in each treatment group with responses. Results for VA will be presented in a data listing.

14.5 Intraocular Pressure

Intraocular pressure will be measured and recorded in mmHg post-CAC at Visits 2 and 7 and will be summarized with quantitative summary statistics by treatment using the average of both eyes for each subject. The number of subjects at Visit 7 with an IOP greater than or equal to 30 mmHg and with an increase of at least 10 mmHg in IOP from baseline will be summarized separately with counts and percentages. IOP will be listed for each eye at each visit.

15. Tolerability Analysis

All tolerability analyses will be conducted using the Safety population.

15.1 Drop Comfort Scale

Drop comfort will be assessed for each eye immediately upon instillation, at 30 seconds, and one minute post-instillation of the IP following initial dosing at Visit 4a using the Ora Calibra® Drop Comfort Scale which ranges from 0 (very comfortable) to 10 (very uncomfortable) in one unit increments.

Subject response will be summarized with quantitative summary statistics by treatment using the average of both eyes for each subject in the Safety population. Two-sample t-tests will be used to

compare each active treatment to vehicle and each dose of PRT-2761 to Patanol® and the resulting p-values will be reported. Drop comfort scale responses will be listed for each eye at each time point.

15.2 Drop Comfort Questionnaire

Description of drop comfort will be assessed at three minutes following initial dosing at Visit 4a using the Ora Calibra™ Drop Comfort Questionnaire. The subjects will be asked to choose three words that best describe how each eye drop feels in both of his/her eyes. The following list will be provided to each subject as possible descriptor words:

- Burning
- Comfortable
- Cool
- Filmy
- Gentle
- Gritty
- Irritating
- Refreshing
- Smooth
- Soothing
- Sticky
- Stinging

The number and percentage of subjects in the Safety population selecting each of the descriptor words above (along with responses of "Other") will be presented by treatment group. A listing of the drop comfort questionnaire responses will also be provided.

16. Exploratory Analysis

The following exploratory measures will be collected using the respective scales as previously defined; select measures will be listed and summarized by treatment group, visit and time point as applicable:

- Ocular itching evaluated by the subject at Visit 5b, 6a, 6b, and 7 at 15(±1), 20(±1), 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments)
- Tearing evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments)
- Eyelid swelling evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-3 scale, NOT allowing half-unit increments)
- Rhinorrhea, nasal pruritis, ear or palate pruritis, and nasal congestion evaluated by the subject at Visits 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, NOT allowing half-unit increments).
- Conjunctival, episcleral, and ciliary redness evaluated by the investigator at Visit 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).
- Chemosis evaluated by the investigator at Visit 5b, 6a, 6b, and 7 at 25(±1) and 30(±1) minutes post-CAC (0-4 scale, allowing half-unit increments).

Ocular itching and conjunctival redness will each be summarized by allergen type (seasonal and perennial) in a manner similar to that described in Section 13.1 for the ITT population using observed data only.

16.1 Conjunctival Inflammation

Conjunctival inflammation in the left eye will be measured by confocal microscopy after all CAC assessments at Visits 3, 4b, and 7 in a subset of approximately 36 subjects who agree to undergo confocal microscopy using the following scale (0-4 scale, NOT allowing half-unit increments):

Conjunctival inflammation will be summarized with quantitative descriptive statistics using the ITT population with observed data only. A subject listing of conjunctival inflammation will also be provided.

16.2 Tear Collection, Diary Assessments, Digital Photographs

Collected data pertaining to diary assessments (ocular itching, ocular redness, and eyelid swelling prior to bedtime and upon awakening [all using a 0 to 4 scale, except eyelid swelling which uses a 0 to 3 scale]) will be presented in subject listings. Data pertaining to tear collection and digital photographs will not be analyzed or listed.

17. Interim Analyses

There are no planned interim analyses for this study.

18. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

19. Revision History

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

20. Tables

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

Table Number	Title	Population
Table 14.1.1.1	**Subject Disposition**	**All Enrolled Subjects**
Table 14.1.1.2	Protocol Deviations	All Randomized Subjects
Table 14.1.2.1	**Demographics**	**ITT Population**

Table Number	Title	Population
Table 14.1.2.2	Demographics	Safety Population
Table 14.1.3.1	Ocular Medical History	ITT Population
Table 14.1.3.2	Non-Ocular Medical History	ITT Population
Table 14.1.4.1	Prior and Concomitant Ocular Medications by Treatment Group, Drug Class and Preferred Name	ITT Population
Table 14.1.4.2	Prior and Concomitant Non-Ocular Medications by Treatment Group, Drug Class and Preferred Name	ITT Population
Table 14.1.5	Investigational Product Instillation	Safety Population
Table 14.2.1.1.1	**Ocular Itching for Primary Time Points**	**ITT Population with LOCF**
Table 14.2.1.1.2	Ocular Itching for Primary Time Points	ITT Population with Multiple Imputations (MCMC)
Table 14.2.1.1.3	Ocular Itching for Primary Time Points	ITT Population with BOCF
Table 14.2.1.1.4	Ocular Itching for Primary Time Points	ITT Population with Observed Data Only
Table 14.2.1.1.5	Ocular Itching for Primary Time Points	PP Population with Observed Data Only
Table 14.2.1.1.6	Ocular Itching for Primary Time Points by Qualifying Allergen Type	ITT Population with Observed Data Only
Table 14.2.1.1.7	Ocular Itching Post-CAC Responders	ITT Population with Observed Data Only
Table 14.2.1.2.1	**Conjunctival Redness for Primary Time Points**	**ITT Population with LOCF**
Table 14.2.1.2.2	Conjunctival Redness for Primary Time Points	ITT Population with Multiple Imputations (MCMC)
Table 14.2.1.2.3	Conjunctival Redness for Primary Time Points	ITT Population with BOCF
Table 14.2.1.2.4	Conjunctival Redness for Primary Time Points	ITT Population with Observed Data Only
Table 14.2.1.2.5	Conjunctival Redness for Primary Time Points	PP Population with Observed Data Only
Table 14.2.1.2.6	Conjunctival Redness for Primary Time Points by Qualifying Allergen Type	ITT Population with Observed Data Only
Table 14.2.1.2.7	Conjunctival Redness Post-CAC Responders	ITT Population with Observed Data Only
Table 14.2.2.1.1	Ocular Itching	ITT Population with Observed Data Only
Table 14.2.2.1.2	Ocular Itching	PP Population with Observed Data Only
Table 14.2.2.2.1	Conjunctival Redness	ITT Population with Observed Data Only
Table 14.2.2.2.2	Conjunctival Redness	PP Population with Observed Data Only
Table 14.2.2.3.1	Ciliary Redness	ITT Population with Observed Data Only
Table 14.2.2.3.2	Ciliary Redness	PP Population with Observed Data Only

Table Number	Title	Population
Table 14.2.2.4.1	Episcleral Redness	ITT Population with Observed Data Only
Table 14.2.2.4.2	Episcleral Redness	PP Population with Observed Data Only
Table 14.2.2.5.1	Chemosis	ITT Population with Observed Data Only
Table 14.2.2.5.2	Chemosis	PP Population with Observed Data Only
Table 14.2.2.6.1	Eyelid Swelling	ITT Population with Observed Data Only
Table 14.2.2.6.2	Eyelid Swelling	PP Population with Observed Data Only
Table 14.2.2.7.1	Tearing	ITT Population with Observed Data Only
Table 14.2.2.7.2	Tearing	PP Population with Observed Data Only
Table 14.2.2.8.1	Rhinorrhea	ITT Population with Observed Data Only
Table 14.2.2.8.2	Rhinorrhea	PP Population with Observed Data Only
Table 14.2.2.9.1	Nasal Pruritus	ITT Population with Observed Data Only
Table 14.2.2.9.2	Nasal Pruritus	PP Population with Observed Data Only
Table 14.2.2.10.1	Ear or Palate Pruritus	ITT Population with Observed Data Only
Table 14.2.2.10.2	Ear or Palate Pruritus	PP Population with Observed Data Only
Table 14.2.2.11.1	Nasal Congestion	ITT Population with Observed Data Only
Table 14.2.2.11.2	Nasal Congestion	PP Population with Observed Data Only
Table 14.2.2.12	Conjunctival Inflammation	ITT Population with Observed Data Only
Table 14.3.1.1	**Adverse Event Summary**	**Safety Population**
Table 14.3.1.2.1	All Ocular Adverse Events	Safety Population
Table 14.3.1.2.2	All Ocular Adverse Events by Study Phase	Safety Population
Table 14.3.1.3	All Non-Ocular Adverse Events	Safety Population
Table 14.3.1.4	**All Ocular Treatment Emergent Adverse Events**	**Safety Population**
Table 14.3.1.5	**All Non-Ocular Treatment Emergent Adverse Events**	**Safety Population**
Table 14.3.1.6	All Ocular Serious Adverse Events	Safety Population
Table 14.3.1.7	All Non-Ocular Serious Adverse Events	Safety Population
Table 14.3.1.8	All Ocular Treatment Emergent Adverse Events by Maximal Severity	Safety Population
Table 14.3.1.9	All Non-Ocular Treatment Emergent Adverse Events by Maximal Severity	Safety Population
Table 14.3.2	Visual Acuity (logMAR)	Safety Population
Table 14.3.3.1	Slit-Lamp Biomicroscopy	Safety Population
Table 14.3.3.2	Shift in Slit-Lamp Biomicroscopy	Safety Population

Table Number	Title	Population
Table 14.3.4	Intraocular Pressure (mmHg)	Safety Population
Table 14.3.5.1	Dilated Ophthalmoscopy	Safety Population
Table 14.3.5.2	Shift in Dilated Ophthalmoscopy	Safety Population
Table 14.3.6	Drop Comfort Scale	Safety Population
Table 14.3.7	Drop Comfort Questionnaire	Safety Population

21. Listings

Listing Number	Title
Listing 16.1.7	Randomization Schedule
Listing 16.2.1	Subject Disposition
Listing 16.2.2.1	Protocol Deviations
Listing 16.2.2.2	Inclusion/Exclusion Criteria
Listing 16.2.3	Study Populations and Exclusion Reasons
Listing 16.2.4.1	Demographics
Listing 16.2.4.2	Ocular Medical History
Listing 16.2.4.3	Non-Ocular Medical History
Listing 16.2.4.4	Prior and Concomitant Ocular Medications
Listing 16.2.4.5	Prior and Concomitant Non-Ocular Medications
Listing 16.2.4.6	Skin Test
Listing 16.2.5.1	Investigational Product and Relief Drop Instillation
Listing 16.2.5.2	Conjunctival Allergen Challenge
Listing 16.2.6.1	Ocular Itching
Listing 16.2.6.2	Conjunctival Redness
Listing 16.2.6.3	Ciliary Redness
Listing 16.2.6.4	Episcleral Redness
Listing 16.2.6.5	Chemosis
Listing 16.2.6.6	Eyelid Swelling
Listing 16.2.6.7	Tearing
Listing 16.2.6.8	Rhinorrhea, Nasal Pruritus, Ear or Palate Pruritus, Nasal Congestion
Listing 16.2.6.9	Conjunctival Inflammation Score
Listing 16.2.6.10	Diary Assessments
Listing 16.2.7.1	All Adverse Events
Listing 16.2.7.2	All Treatment-Emergent Adverse Events (TEAE)
Listing 16.2.7.3	Serious Adverse Events
Listing 16.2.7.4	Adverse Events Leading to Death
Listing 16.2.7.5	Adverse Events Leading to Study Treatment Withdrawal
Listing 16.2.8.1	Visual Acuity (logMAR)
Listing 16.2.8.2	Slit-Lamp Biomicroscopy
Listing 16.2.8.3	Intraocular Pressure (mmHg)
Listing 16.2.8.4	Dilated Ophthalmoscopy
Listing 16.2.8.5	Drop Comfort Scale
Listing 16.2.8.6	Drop Comfort Questionnaire
Listing 16.2.8.7	Urine Pregnancy Test for Female Subjects
Listing 16.2.8.8	Follow-Up Phone Call

22. Figures

Figure Number	Title	Population
Figure 14.2.1.1	Mean +/- 1 SE Ocular Itching Score by Time Point, Treatment Group, and Visit	ITT Population with Observed Data Only
Figure 14.2.1.2	Mean +/- 1 SE Ocular Itching Score by Time Point, Treatment Group, and Visit	PP Population with Observed Data Only
Figure 14.2.1.3	Mean +/- 1 SE Change From Baseline in Ocular Itching Score by Time Point, Treatment Group and Visit	ITT Population with Observed Data Only
Figure 14.2.2.1	Mean +/- 1 SE Conjunctival Redness Score by Time Point, Treatment Group, and Visit	ITT Population with Observed Data Only
Figure 14.2.2.2	Mean +/- 1 SE Conjunctival Redness Score by Time Point, Treatment Group, and Visit	PP Population with Observed Data Only
Figure 14.2.2.3	Mean +/- 1 SE Change From Baseline in Conjunctival Redness Score by Time Point, Treatment Group, and Visit	ITT Population with Observed Data Only