CLINICAL TRIAL PROTOCOL: ST266-AC-201/16-100-0005

A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)

NCT02978183

SAP Date: 05 January 2017

Noveome Biotherapeutics, Inc.
100 Technology Drive, Suite 200
Pittsburgh, PA 15219

STATISTICAL ANALYSIS PLAN

A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)

Sponsor: Noveome Biotherapeutics, Inc.

Protocol Number: ST266-AC-201

Author: [redacted]

Date: 05 January 2017

Version: Final 1.0

Protocol Title

A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)

Protocol Number: **ST266-AC-201**

Version: **Final 1.0**

Date: **05 January 2017**

Statistical Analysis Plan Approval

Prepared by: _____ _____

[redacted]

Reviewed by: _____ _____

[redacted]

Approved by: _____ _____

[redacted]

Approved by: _____ _____

[redacted]

Protocol Title

A Multi-Center, Double-Masked, Randomized, Phase 2 Evaluation of the Effectiveness of ST266 Ophthalmic Drops Compared to Placebo for the Treatment of Allergic Conjunctivitis Using a Modified Conjunctival Allergen Challenge Model (Ora-CAC®)

Protocol Number:	ST266-AC-201
Version:	Final 1.0
Date:	05 January 2017

Statistical Analysis Plan Approval

[redacted]

Table of Contents

List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
CAC	Conjunctival Allergen Challenge
CI	Confidence Interval
CS	Clinically Significant
CSR	Clinical Study Report
DVM	Data Validation Manual
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCP	Good Clinical Practice
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 Means	Least Squares Means
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
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
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol ST266-AC-201, version 2.0 dated 31OCT2016.

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 primary objective of this study is to evaluate the efficacy of ST266 ophthalmic drops compared to placebo for the treatment of the signs and symptoms of allergic conjunctivitis.

3. Study Variables

3.1 Primary Variables

The primary efficacy variables are the following:

- Ocular itching evaluated by the subject at all time points [redacted]) at Visits 5b and 6.
- Conjunctival redness evaluated by the investigator at all time points [redacted] at Visits 5b and 6.

3.2 Secondary Variables

The following secondary efficacy assessments will occur pre-CAC and at [redacted] post-CAC [redacted] at Visits 5b and 6:

- Ciliary redness evaluated by the investigator
- Episcleral redness evaluated by the investigator
- Chemosis evaluated by the investigator
- Eyelid swelling evaluated by the subject
- Tearing evaluated by the subject
- Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion evaluated by the subject
- A composite score of presence or absence of at least one nasal symptom evaluated by the subject

All assessments will be evaluated at pre-CAC and [redacted] minutes post-CAC at Visits 4a, 4b, and 5a.

3.3 Exploratory Variables

The exploratory efficacy variables include the following:

- Conjunctival Inflammation Score (CIS) evaluated by a masked clinician using confocal microscopy post-CAC [redacted] Visit 6 (subset of [redacted] subjects at one center).
- Diary assessments for all subjects. Assessments of ocular itching, ocular redness, and eyelid swelling will occur prior to bedtime and upon awakening from Visit 4b to Visit 6 ([redacted]

3.4 Safety Variables

The safety variables include the following:

- Adverse Events
- Visual Acuity at Distance Utilizing an ETDRS chart
- Slit-lamp Biomicroscopy
- Intraocular Pressure
- Dilated Fundoscopy

3.5 Statistical Hypotheses

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

[redacted]

All hypothesis testing will be two-sided with a type I error rate (α) of [redacted]. The above hypothesis tests will be applied to Visit 5b and Visit 6 separately. No multiplicity corrections will be employed in this Phase 2 exploratory efficacy study. Specifics of the statistical tests are provided in Section 14.

4. Study Design and Procedures

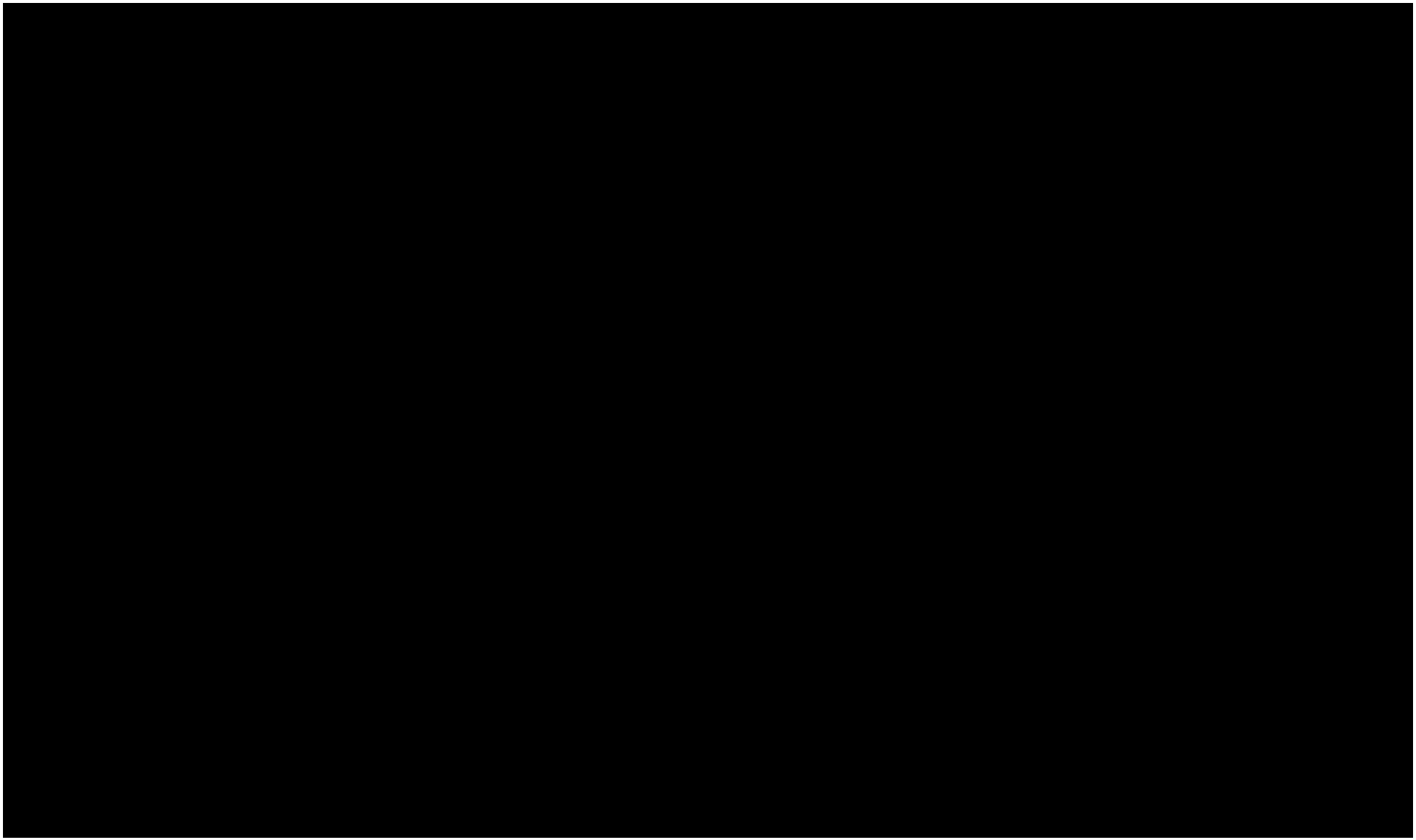
4.1 General Study Design

Study visits will be referred to in all tables and listings as the expected study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit

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

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.



5. Study Treatments

The investigational treatment for this study is ST266 ophthalmic drops. The control is placebo (0.9% Sodium Chloride) ophthalmic drops.

5.1 Method of Assigning Subjects to Treatment Groups

On Day -2 (Visit 1), subjects who provide verbal and written informed consent will be assigned a unique 4-digit subject ID, which consists of the 1-digit site number plus a unique 3-digit screening number (beginning with 001 within each site). The 3-digit screening numbers must be assigned in ascending consecutive order.

Once a subject meets all qualification criteria, they will be randomly assigned to masked treatment using a [redacted] assignment ratio. Subjects will be randomized on Visit 3 (Day 1) by assignment of the next 4-digit randomization number available at each investigative site. The randomization number will be stratified by the average post-CAC itching scores [redacted] at baseline [redacted] to ensure balance within treatment groups for the primary endpoint of ocular itching. No randomization numbers will be skipped or omitted.

A computer-generated randomization schedule will be produced prior to study enrollment by an unmasked statistician who is not otherwise involved in the study. Each randomization number will correspond to a treatment group assignment and subject supplies will be labeled according to the randomization list and dispensed at each site.

The 4-digit subject ID will be used to identify subjects in all datasets and listings for this study.

5.2 Masking and Unmasking

An independent biostatistician who is not otherwise involved in the trial will generate the complete randomized study drug kit list. Subjects, Investigators and Ora/SDC staff will be masked during the randomization process and throughout the study.

With each shipment of study drug, sites will receive one emergency unmasking envelope for every study drug kit received. The envelopes and kits will both be labeled with the same 4-digit study drug kit number. The envelopes are sealed and contain the unmasked treatment information for the corresponding study drug kit. Envelopes should be stored in a secured location.

Under normal circumstances, the mask should not be broken. When medically necessary, an investigator may need to determine what treatment has been assigned to a subject. The investigator will contact Noveome Biotherapeutics, Inc. with the details of the emergency unmasking request. Noveome Biotherapeutics, Inc. 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. If the investigator determines that emergency unmasking is necessary, the investigator 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 eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Subjects should have their study drug discontinued immediately if treatment assignment is unmasked.

The overall randomization code will be broken only for reporting purposes. This will occur once all final clinical data have been entered into the database, data queries have been resolved, and assignment of subjects to the analysis populations has been completed. The database will be kept masked until after the database lock has occurred.

6. Sample Size and Power Considerations

This Phase 2 study, designed to evaluate the safety and effectiveness of ST266 for the treatment of allergic conjunctivitis, is exploratory in nature. Given there are no data available on which to base a formal power calculation, a sample size of [redacted] subjects per group has been selected based on the Investigators' judgment and experience conducting similar Phase 2 studies of this nature in individuals diagnosed with allergic conjunctivitis.

7. Data Preparation

Data management procedures, including database design, selection of the data dictionary, and coding of all adverse events and medications, will be performed by Statistics & Data Corporation (SDC). All reported study data will be recorded on the electronic Case Report Forms (eCRFs) supplied by SDC using iMedNet™ v1.163.3 or higher. Clinical personnel at the study center and Ora, Inc. are responsible for ensuring that the protocol is followed and that the eCRFs are properly completed.

After data are entered into the clinical study database, electronic edit checks will be performed, including checks for missing data, out of range values, discrepancies within and across visits, and cross checks between different data tables. All data validation specifications and procedures are detailed in the Data Validation Manual (DVM). When the database has been declared to be complete and accurate, the database will be locked and treatment codes unmasked. Any changes to the database after that time can only be made with the approval of the Sponsor in consultation with Ora, Inc. and SDC.

All analyses outlined in this document will be performed after:

- All data management requirements are met according to SDC's Standard Operating Procedures (SOPs), including performance of edit and validation checks, documentation and resolution of

data queries, and database lock with written authorization provided by appropriate SDC and Ora/Sponsor personnel;

- All protocol deviations have been classified as major or minor and the Per Protocol population has been determined; and
- The treatment codes have been unmasked.

8. Analysis Populations

8.1 Intent-to-Treat

The Intent-to-Treat (ITT) population consists of [redacted] All data will be included and no subjects will be excluded because of protocol violations. The ITT population will be analyzed as [redacted]

8.2 Per Protocol

The Per Protocol (PP) population is a [redacted]. This population will be analyzed as [redacted].

8.3 Safety

The safety population includes [redacted]. The safety population will be analyzed as [redacted]. No data will be excluded for any reason.

9. General Statistical Considerations

9.1 Unit of Analysis

The subject will be considered the unit of analysis for all efficacy variables. [redacted]

9.2 Missing or Inconclusive Data Handling

Multiple imputation Markov Chain Monte Carlo (MCMC) methods will be employed to impute missing primary efficacy data. A separate model will be fit for each endpoint, visit and time point. The model will include variables for treatment, baseline measure and response measure.

Sensitivity analyses will be performed as described in the following text:

- ITT Population: [redacted]
- ITT population: [redacted].
- PP population: [redacted]

9.3 Definition of Baseline

For each parameter, the last valid assessment before randomization will be used as the baseline for all analyses of that parameter. For each efficacy variable, the last valid assessment before randomization will generally be at Visit 3.

9.4 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using SAS® Version 9.4.

Quantitative variables will be summarized using descriptive statistics including the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum values. For the ocular primary and secondary endpoints (itching, eyelid swelling, tearing, regional redness, and chemosis) the unit of analysis is the average of the subject's eyes. Therefore, for each of these variables, the minimum and maximum values will be reported to one decimal, irrespective of the number of decimals in the raw collected data. Similarly, means, medians, and confidence intervals will be reported to two decimal places and standard deviations to three. 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 the active treatment group and placebo will be calculated as Active minus Placebo and change from baseline will be calculated as follow-up visit - baseline.

All statistical tests will be two-sided with a significance level of [redacted] unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be [redacted]
All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999".

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

9.5 Adjustments for Multiplicity

Adjustments for multiplicity will not be employed in this exploratory Phase 2 study.

10. 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: adverse events, protocol violations, lost to follow up, consent withdrawn, sponsor termination of study, investigator decision, screen failure, and other. A subject listing will be provided that includes the date of and reason for premature study discontinuation.

The number and percentage of subjects with protocol deviations will be summarized by treatment group for all randomized subjects. 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.

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

11. Demographic and Baseline Variables

11.1 Demographic Variables

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

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

[redacted]

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, ethnicity and iris color. 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. A subject listing that includes all demographic variables will be provided.

11.2 Baseline Variables

The number and percentage of subjects with Visit 3 post-CAC® (baseline) itching scores [redacted] will be summarized. A subject listing that includes baseline itching will be provided.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by system organ class (SOC) and preferred term (PT). 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, then that SOC will only be reported once. Separate tables will be created for ocular and non-ocular medical history. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1. The summaries will be based on the ITT population.

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

12.2 Prior and Concomitant Medications

At the first screening visit, subjects will be asked what medications they are taking, as well as those the subject may have taken but discontinued within the 45 days prior to Visit 1. At each study visit, subjects will be asked what concomitant medications they are currently taking or if there have been any changes to their medication since their first visit.

All prior and concomitant ocular and non-ocular medications will be listed using the ITT population including generic name, route of administration, start date, stop date, dosage, and indication. Prior and concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHODD) enhanced version B2, September 2016, to the appropriate Anatomical Therapeutic Chemical (ATC) classification and WHO generic term.

Counts and percentages of ocular and non-ocular concomitant medications will be summarized separately using WHODrug ATC classification and preferred name. Summaries will be displayed by treatment group and for all subjects. Subjects with multiple medications in the same ATC class or preferred name will be counted only once for that respective ATC class or preferred name.

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

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

[redacted]

The number of actual doses received will be calculated and summarized using the number of dispensed versus returned, used study drug vials. The number of expected doses that will be used for calculating compliance will be calculated as [redacted] for all subjects, regardless of study completion status. A categorical compliance variable will also be derived as compliant [redacted] and non-compliant [redacted].

Treatment compliance (%) will be summarized for the Safety population using continuous descriptive statistics. The compliance categories defined above will be summarized with counts and percentages. A subject listing of compliance will also be produced.

13.2 Treatment Exposure

Extent of exposure will be calculated in days using the following:

[redacted]

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

14. Efficacy Analyses

14.1 Primary Analysis

The primary efficacy endpoints are ocular itching assessed at all time points [redacted] and conjunctival redness assessed at all time points [redacted] at Visit 5b and Visit 6. [redacted]. Ocular itching and conjunctival redness will each be analyzed using an [redacted] Least squares means (LS Means) for each treatment, LS Means treatment differences, and 95% confidence intervals (CIs) for the LS Means treatment differences will be provided.

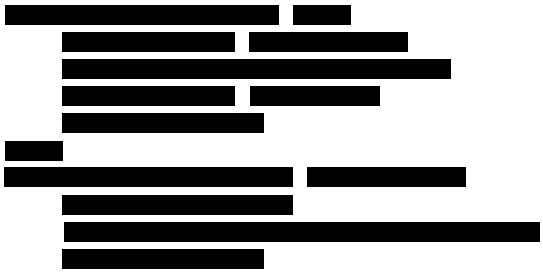
Multiple imputation employing the MCMC method will be performed for the primary analysis of the primary endpoints using the SAS procedure PROC MI by applying the following SAS code:

where

After obtaining twenty complete data sets, the following SAS code will be employed to run the model on each data set:

where

Then, the following SAS code will be used to analyze the combined data:



[redacted]

The primary efficacy analyses will be conducted on the ITT population using MCMC multiple imputation methodology for missing data, as described in Section 9.2 and above. Adjustments for multiplicity will not be employed in this exploratory Phase 2 study.

Sensitivity or supportive analyses will be performed on the ITT population, using LOCF and observed data only, as well as on the PP population with observed data only.

Two-sample *t*-tests will be used as additional sensitivity analyses at each post-CAC® time point, as well as non-parametric Wilcoxon rank sum tests for comparing ST266 ophthalmic drops and placebo. Mean treatment differences, 95% CIs for each of the means, and 95% CIs for the mean differences will be presented.

In addition, ANCOVA models will be run separately at Visit 5b and Visit 6 as secondary analyses, with treatment, time point, and time appropriate baseline as covariates for adjustment (accounting for repeated measurements). LS Means for each treatment, the LS Means treatment difference between ST266 ophthalmic drops and placebo, and the corresponding 95% CIs will be calculated from these ANCOVA models. SAS pseudo-code for the ANCOVA model accounting for repeated measures at each Visit follows:

[redacted]

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.

14.2 Secondary Analyses

The secondary endpoints will be measured at Visits 5b and 6. All secondary endpoints will be assessed pre-CAC and at [redacted] post-CAC® [redacted] at Visits 5b and 6.

Ocular allergic symptoms will be evaluated by the subject and include eyelid swelling [redacted] and tearing/watery eyes [redacted] Nasal allergic symptoms are also evaluated by the subject and include rhinorrhea, nasal pruritis, ear or palate pruritis, and nasal congestion. Nasal allergic symptoms are collected on a [redacted], NOT allowing half unit increments.

A binary nasal composite score of nasal allergic symptoms will be derived for each visit and time point at which nasal allergic symptoms are collected. The nasal composite score will be "Present" if [redacted], and "Absent" if [redacted] It will be considered missing if [redacted]

Ocular allergic signs will be evaluated by the Investigator and include ciliary redness, episcleral redness, and chemosis. Ocular allergic signs are collected on a [redacted] scale, [redacted]

Analyses will be performed on quantitative secondary endpoints in a manner similar to the primary endpoints for each visit. [redacted] The ST266 ophthalmic drops will be compared to placebo at each time point within each visit. The secondary endpoints will be analyzed for the ITT population with observed data only and for the PP population with observed data only.

14.3 Exploratory Analyses

Conjunctival inflammation scores, evaluated by a masked clinician using confocal microscopy post-CAC® [redacted] will be measured at Visit 6 in a subset of [redacted] subjects at one site. Descriptive statistics will be produced for this exploratory endpoint.

Diary assessments of ocular itching, ocular redness and eyelid swelling will occur for all subjects prior to bedtime and upon awakening from Visit 4b to Visit 6 [redacted] for all subjects. Two-sample *t*-tests will be used at each diary time point, as well as non-parametric Wilcoxon rank sum tests, for comparing ST266 ophthalmic drops and placebo. In addition to descriptive summary statistics, mean treatment differences, 95% CIs for each of the means, and 95% CIs for the mean differences will be presented.

15. Safety Analyses

The primary safety variable is the incidence of subjects with any adverse event (AE) during the entire study. The secondary safety variables are slit lamp biomicroscopy, dilated fundus examination, VA, and IOP. Safety variables will be summarized as appropriate. All safety analyses will be performed on the Safety population. No statistical inferential testing will be performed for safety variables.

15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an investigational product (IP) in humans, whether or not considered IP-related. Treatment-emergent AEs are defined as AEs that occur after the first use of IP. Per the protocol, only AEs that begin or worsen after receipt of the first dose of IP will be captured in the database for this study; therefore, treatment-emergent AEs 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. Their relationship to IP will be classified as suspected (definite, probable or possible) or not suspected (not related). The expectedness of an AE will be classified as unexpected, expected or not applicable. Documentation of AEs will include onset date, severity, action(s) taken, IP relationship, expectedness, outcome, resolution date, and seriousness. All AEs will be coded using MedDRA classifications with reference to SOCs and PTs (MedDRA version 19.1).

An adverse event 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 adverse event;
- 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.

An overall tabular summary of AEs will be presented that includes the number of events and the number and percentage of subjects who experienced at least one event, by treatment group and overall. This summary will also include breakdowns of AEs further categorized as ocular or non-ocular, SAEs, AEs by maximal severity, AEs leading to subject withdrawal and AEs resulting in death. Additional summaries of AEs will be provided showing the number and percentage of subjects who experienced at least one AE, separately for ocular and non-ocular AEs. Ocular and non-ocular AEs will be summarized separately using discrete summary statistics and presented by treatment group at the subject and event level by SOC and PT using the Safety population. 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. The occurrence of AEs suspected to be related to IP will also be tabulated by SOC and PT, separately for ocular and non-ocular events. SAEs will also be summarized separately for ocular and non-ocular events. All AEs will be presented in a listing.

15.2 Visual Acuity (ETDRS)

Visual acuity (VA) will be measured at every study visit prior to the CAC®. For Visit 6, it will be measured again post-CAC®. VA (logMAR) will be summarized at each visit using quantitative summary statistics for both eyes combined by treatment. [redacted] VA results will be presented in a data listing.

15.3 Slit-Lamp Biomicroscopy Examination

Slit lamp biomicroscopy examinations will be performed at every study visit prior to the CAC. For Visit 6, slit lamp biomicroscopy will be repeated post-CAC®. Qualitative summaries of biomicroscopy results will also be presented for both eyes combined by region (eyelid, conjunctiva, cornea, lens, and anterior chamber), treatment group and study visit in tabular form. Slit lamp biomicroscopy examination results will also be listed for both eyes at each visit.

15.4 Dilated Fundus Examination

Dilated fundus examinations will be performed at Visits 1 (post-CAC®) and 6 (post-CAC®). Counts and percentages of normal and abnormal results will be presented for both eyes combined by visit and treatment group for the following regions: vitreous, retina, macula, choroid, and optic nerve. A change from baseline will also be summarized as follows: [redacted] Results will be listed for both eyes at each visit.

15.5 Intraocular Pressure (IOP)

IOP will be measured at Visits 1 (post-CAC®) and 6 (post-CAC®). IOP will be summarized for both eyes combined by visit and treatment group using quantitative summary statistics. At Visit 6, an IOP of [redacted] AND [redacted] will be considered an Adverse Event, and presented in the tabular summary. IOP will be listed for both eyes at each visit.

16. Interim Analyses

No interim analyses are planned for this study.

17. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

18. References

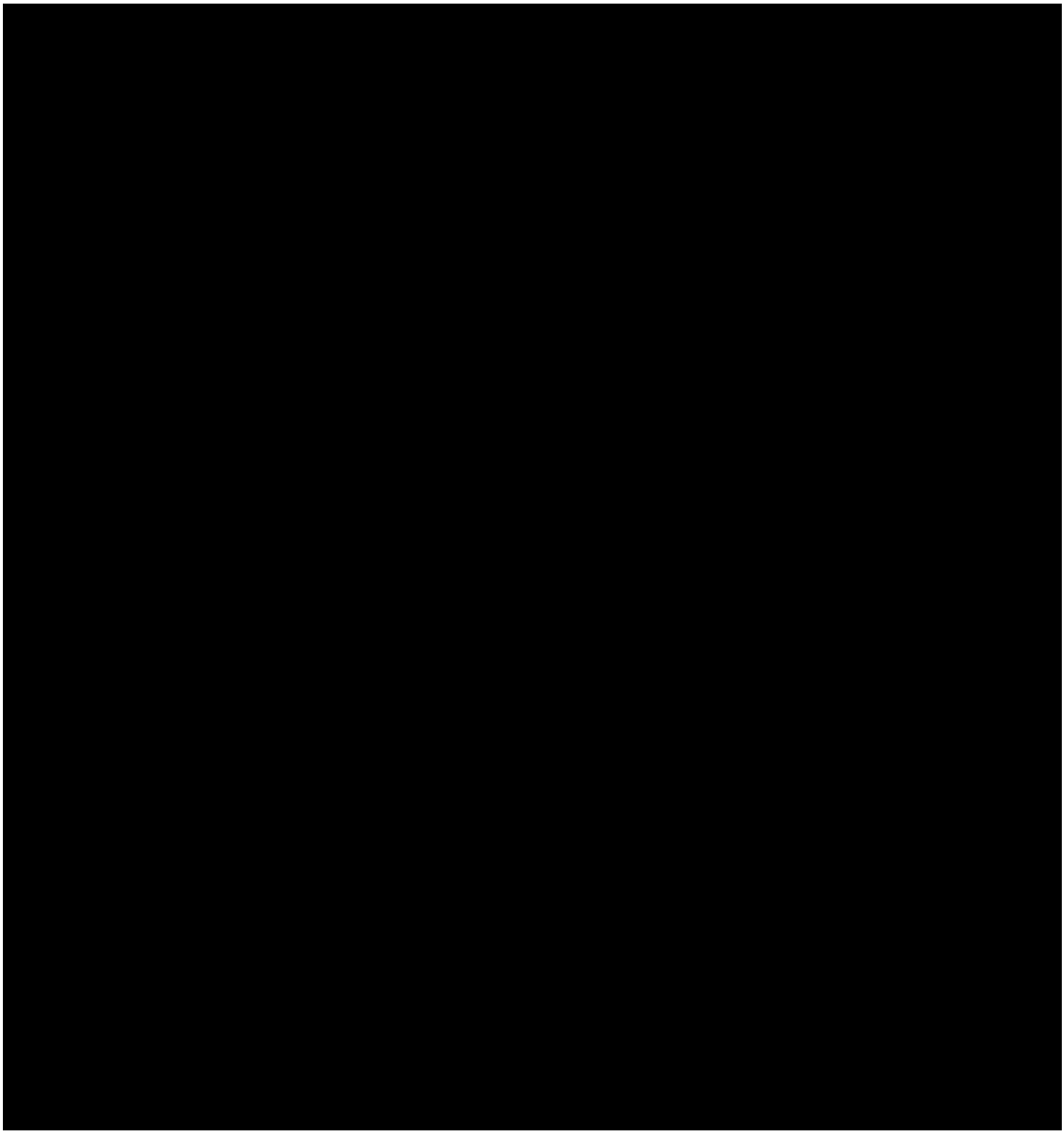
Not applicable

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.



[redacted]

21. Listings

[redacted]