STATISTICAL ANALYSIS PLAN

A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) Compared to Vehicle in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

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Protocol Number: ADX-102-AC-008

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Statistical Analysis Plan Approval

Prepared by:

Reviewed by:

Approved by:

Approved by:

Table of Contents

List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
AUC_{t1-t2}	Area Under the Curve [redacted]
CAC	Conjunctival Allergen Challenge
CI	Confidence Interval
CS	Clinically Significant (when used in the context of safety); Compound Symmetric (when used in the context of covariance structures)
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
GEE	Generalized Estimating Equation
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
LM	Linear Model
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NCS	Not Clinically Significant
OD	Right Eye
OS	Left Eye
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 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 ADX-102-AC-008, Version 1.0 dated 15FEB2018.

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

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

2. Study Objectives

The objective of this study is to evaluate the safety and efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) compared to Vehicle Ophthalmic Solution for the treatment of ocular itching associated with acute allergic conjunctivitis.

3. Study Design and Procedures

3.1 General Study Design

This is a multi-center, double-masked, randomized, parallel-group, vehicle-controlled Phase 3 clinical trial will enroll approximately [redacted] to evaluate the safety and efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) compared to Vehicle Ophthalmic Solution for the treatment of ocular itching associated with acute (seasonal) allergic conjunctivitis.

The trial will be comprised of [redacted] Subjects who meet the entry criteria for itching and redness response [redacted] to receive bilateral administration of either Reproxalap Ophthalmic Solution 0.25%, Reproxalap Ophthalmic Solution 0.5%, or Vehicle Ophthalmic Solution. [redacted]

Study visits will be referred to in all tables and listings as the visit and 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 (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
Screening	Day -22	- 39 Days
Visit 1	Day -21	± 3 Days
Visit 2	Day -14	± 3 Days
Visit 3	Day 1	NA

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.

[redacted]

4. Study Endpoints

4.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the following:

- Ocular itching score [redacted]

4.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the following:

- [redacted]

4.3 Additional Secondary Efficacy Variables

The additional secondary efficacy endpoints are the following:

- The time to response [redacted]
- Ocular itching score [redacted]
- [redacted]

4.4 Safety Variables

The safety variables include the following:

[redacted]

- Adverse Events (AE) (reported, elicited, and observed);
- Visual Acuity (VA) [redacted]
- Slit-lamp Biomicroscopy;
- Intraocular Pressure (IOP);
- Dilated Fundoscopy;
- Conjunctival Redness.

4.5 Statistical Hypotheses

The null and alternative hypotheses, based on the primary and key secondary efficacy endpoints, are as follows:

[redacted]

To control the overall Type I error rate, [redacted]

5. Study Treatments

The study consists of three treatment arms:

- Reproxalap Ophthalmic Solution 0.25%;
- Reproxalap Ophthalmic Solution 0.5%;

- Vehicle Ophthalmic Solution.

5.1 Method of Assigning Subjects to Treatment Groups

All subjects screened for the trial 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 a sequential order beginning with 001. Randomization will be used to avoid bias in the assignment of subjects to treatments, to increase the likelihood that known and unknown subject attributes [redacted]

Once a subject meets all qualification criteria [redacted] they will be enrolled and randomly assigned to masked treatment [redacted]. Subjects will be assigned the lowest 4-digit randomization number available at the investigative site within the appropriate stratum. [redacted]

5.2 Masking and Unmasking

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. The investigator should make every effort to contact Ora to discuss the subject's emergency situation and the need to unmask a trial subject prior to unmasking IP.

If the investigator determines that emergency unmasking is necessary, the investigator should identify the given subject's trial drug kit, which contains a scratch-off laminate under which the treatment is identified along with the associated lot number. In order to unmask, the investigator should scratch off the laminate, using a flat object and applying pressure, to reveal the treatment assigned for that subject. The emergency unmasking should be performed by the designated site personnel. The investigator must also indicate in source documents and in the electronic case report form (eCRF) that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or serious AE (SAE) associated with breaking the mask must be recorded and reported as specified in this protocol. The investigator has the responsibility to contact Ora within 24 hours of breaking the blind.

If treatment assignment is unmasked, the IP will be discontinued immediately, and the subject will be discontinued from the trial.

6. Sample Size and Power Considerations

[redacted]

[redacted]

7. Data Preparation

All reported study data will be recorded on the eCRFs supplied by SDC [redacted]. Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

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

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

- [redacted]

8. Analysis Populations

8.1 Intent-to-Treat

The Intent-to-Treat (ITT) population consists of [redacted]

8.2 Per-Protocol

The Per-Protocol (PP) population is [redacted].

8.3 Safety

The Safety population includes [redacted]

9. General Statistical Considerations

9.1 Unit of Analysis

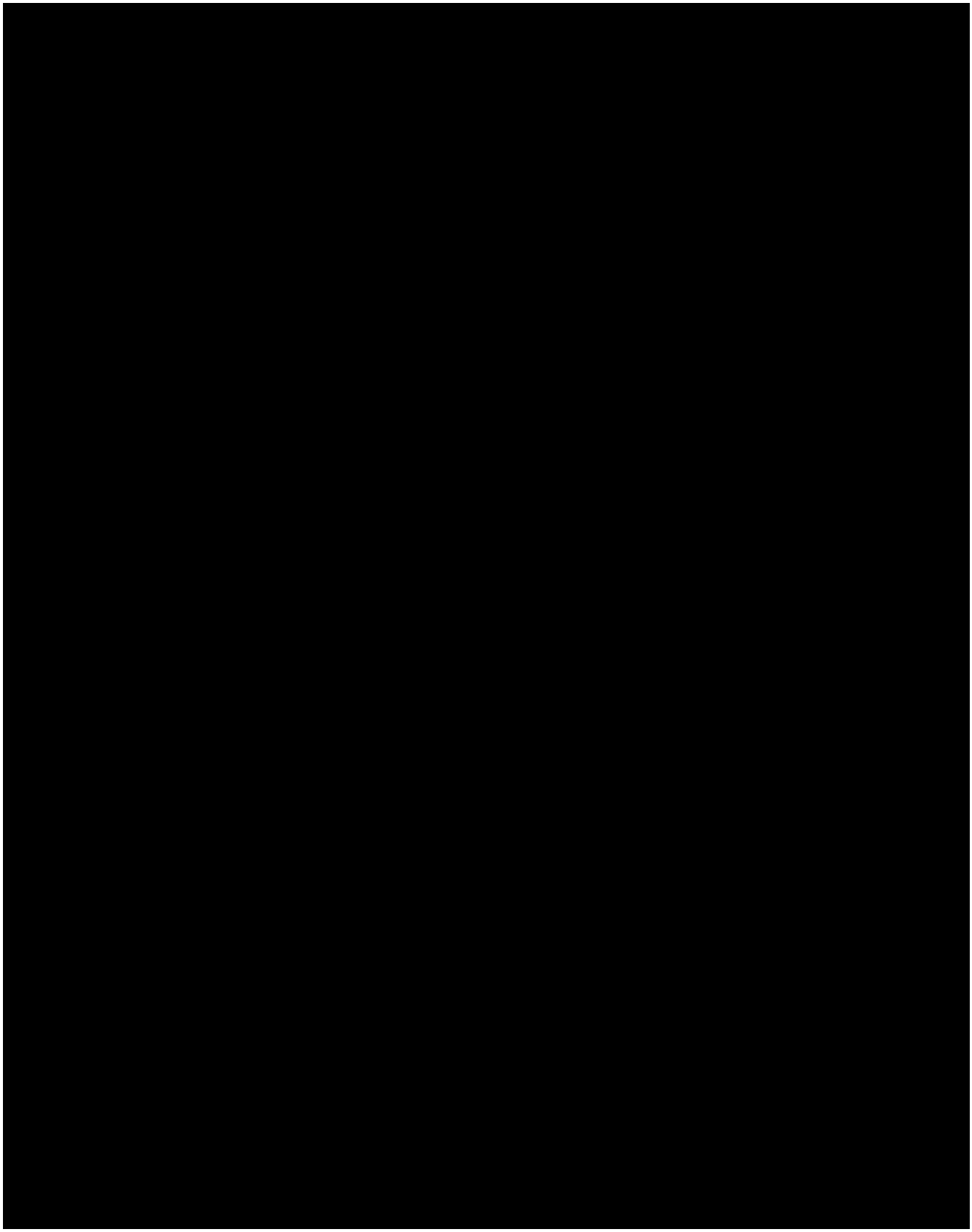
[redacted]

9.2 Missing or Inconclusive Data Handling

The primary analysis of ocular itching will be conducted [redacted]

- [redacted]
- [redacted]

[redacted]



The key secondary endpoint [redacted] will be analyzed [redacted]

9.3 Definition of Baseline

For the primary efficacy endpoin [redacted]

When analyzing ocular itching scores [redacted]

9.4 Data Analysis Conventions

Data analysis will be performed by SDC using [redacted] Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation. [redacted]

[redacted]

[redacted].

9.5 Adjustments for Multiplicity

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10. Disposition of Subjects

Subject disposition will be presented [redacted]

[redacted]

[redacted].

Subject listings will be provided [redacted].

Protocol violations will be summarized [redacted] A subject listing will be provided [redacted]

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

The demographic variables collected [redacted]

[redacted]

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

11.2 Pretreatment Variables

[redacted]

will be provided in a subject listing.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 21.0.

[redacted]

Listings of medical history will be generated [redacted]

12.2 Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary [redacted]

[redacted] Listings of concomitant medications will be generated separately for ocular and non-ocular data.

13. Exposure to Investigational Product

[redacted].

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

14. Efficacy Analyses

14.1 Primary Analysis

The primary efficacy variable is ocular itching score [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

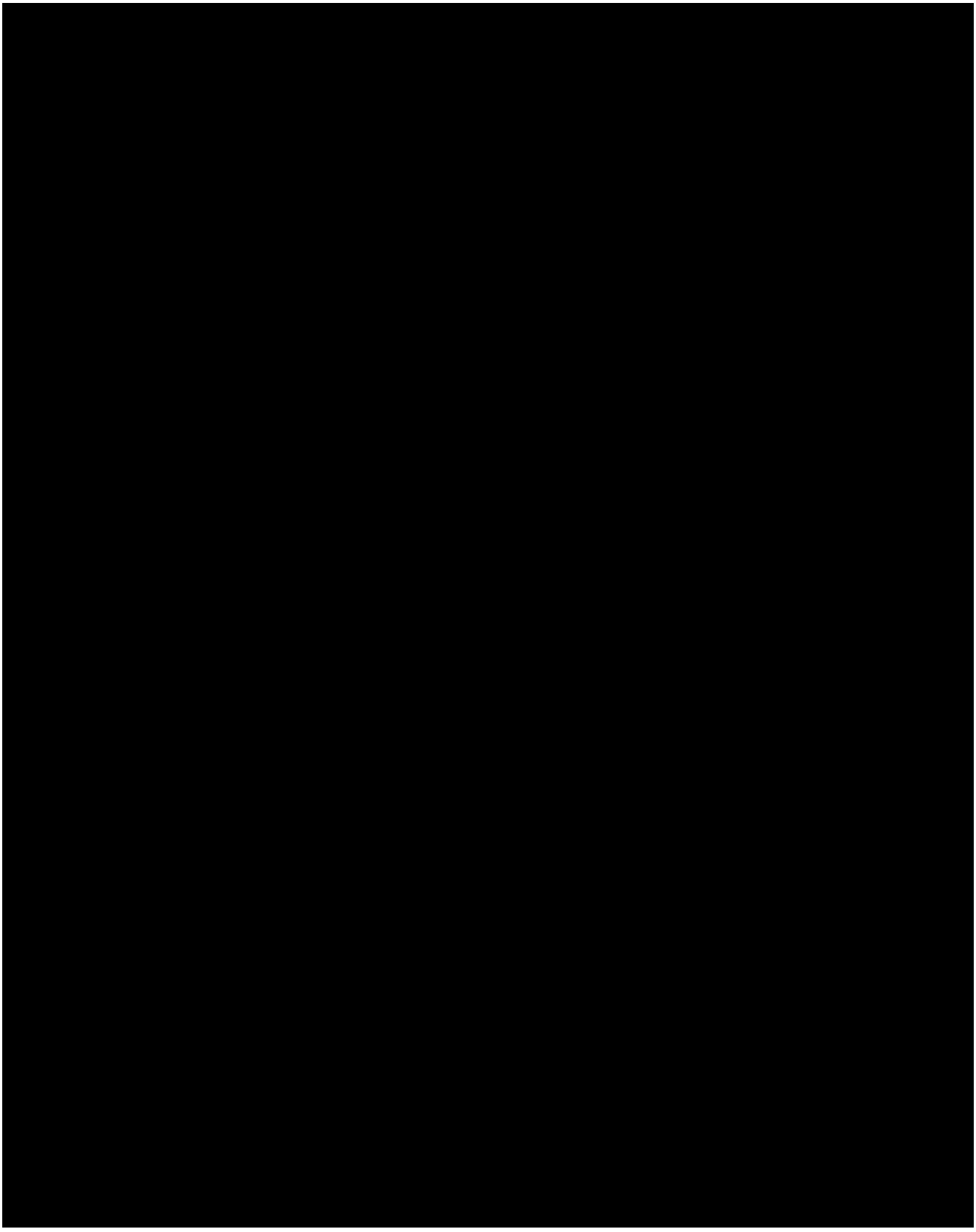
[redacted]

14.2 Secondary Analyses

14.2.1 Ocular Itching Responders Analysis

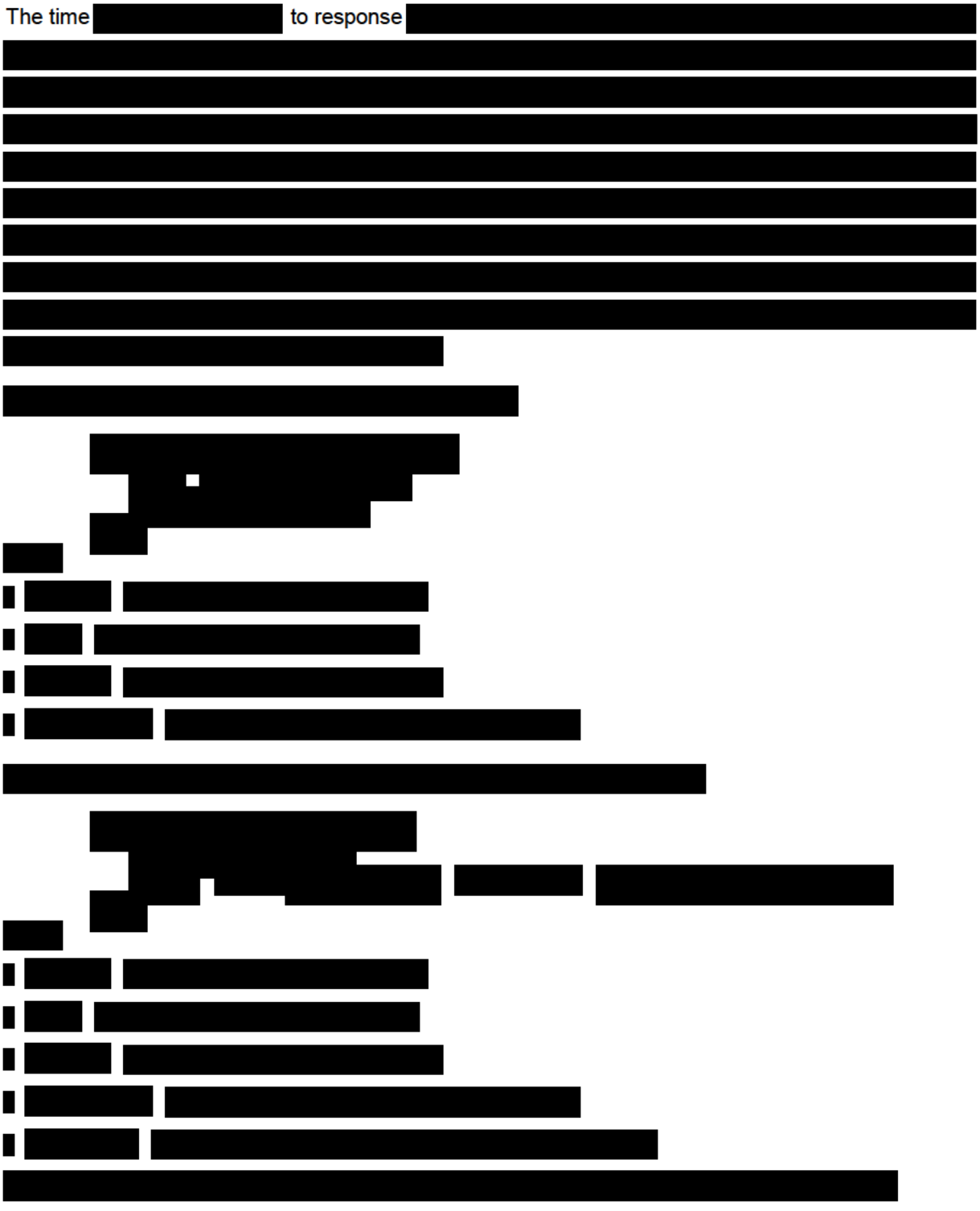
The key secondary efficacy endpoint [redacted]

[redacted]



14.2.2 Time to Response

The time [redacted] to response [redacted]



14.2.3 Ocular Itching

Ocular itching scores [redacted]

[redacted]

[redacted]

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

15. Safety Analyses

The safety outcomes [redacted]

All safety analyses will be conducted using the Safety Population. [redacted]

15.1 Adverse Events/Adverse Drug Reactions

AEs, SAEs and adverse drug reactions are defined in the study protocol. All AEs will be coded using MedDRA 21.0. Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated.

Relationship to IP

The relationship of each AE to the IP should be determined by the investigator using the following categories:

- Not related;
- Unlikely to be related;
- Possibly related;
- Probably related;
- Definitely related.

[redacted]

Severity

Severity will be classified as mild, moderate or severe. Missing severity for AEs and TEAEs will be counted as 'Severe'.

- [redacted]

[redacted]

[redacted]

- [redacted]

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

15.2 Visual Acuity

VA will be measured [redacted]

Results for VA will be presented in a data listing.

15.3 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination will be performed [redacted]

[redacted]

[redacted]

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

15.4 Intraocular Pressure

IOP will be measured [redacted] IOP will be listed for each eye at each visit.

15.5 Dilated Fundoscopy Examination

Dilated fundus examinations will be performed [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted] Results will be listed for both eyes at each visit.

15.6 Conjunctival Redness

Conjunctival redness will be assessed [redacted]

[redacted]

[redacted]. Results will be listed [redacted].

16. Interim Analyses

No interim analysis is planned for this study.

17. Changes from Protocol-Stated Analyses

[redacted]

18. Revision History

[redacted]

19. Tables

Tables in italicized font will be produced contingent upon the amount of missing data as defined previously.

Table Number	Title	Population
14.1.1.1	Subject Disposition	ITT Population
14.1.1.2	Protocol Violations	ITT Population
14.1.2.1	Demographics and Baseline Characteristics	ITT Population
14.1.2.2	Demographics and Baseline Characteristics	Safety Population
14.1.3.1	Ocular Medical History	ITT Population
14.1.3.2	Non-Ocular Medical History	ITT Population
14.1.4.1	Prior and Concomitant Ocular Medications by Treatment Group, Drug Class and Preferred Name	ITT Population
14.1.4.2	Prior and Concomitant Non-Ocular Medications by Treatment Group, Drug Class and Preferred Name	ITT Population
14.1.5	Investigational Product Instillation	Safety Population
14.2.1.1	Summary of Ocular Itching [redacted]	ITT Population with Observed Data Only
14.2.1.2	*Summary of Ocular Itching* [redacted]	*ITT Population with Multiple Imputations (MCMC)*
14.2.1.3	*Summary of Ocular Itching* [redacted]	*ITT Population with Multiple Imputations (Control-Based Pattern Mixture Model)*
14.2.1.4	Summary of Ocular Itching [redacted]	PP Population with Observed Data Only
14.2.2.1.1	Ocular Itching [redacted]	ITT Population with Observed Data Only
14.2.2.1.2	*Ocular Itching* [redacted]	*ITT Population with Multiple Imputations (MCMC)*

Table Number	Title	Population
14.2.2.1.3	*Ocular Itching* [redacted]	*ITT Population with Multiple Imputations (Control-Based Pattern Mixture Model)*
14.2.2.2.1	Ocular Itching [redacted]	ITT Population with Observed Data Only
14.2.2.2.2	Ocular Itching [redacted]	PP Population with Observed Data Only
14.2.3.1	Ocular Itching [redacted]	ITT Population with Observed Data Only
14.2.3.2	Ocular Itching [redacted]	PP Population with Observed Data Only
14.2.4.1	Ocular Itching [redacted]	ITT Population with Observed Data Only
14.2.4.2	Ocular Itching [redacted]	PP Population with Observed Data Only
14.3.1.1	Adverse Event Summary	Safety Population
14.3.1.2	Summary of All Ocular Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.3	Summary of All Non-Ocular Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.4	Summary of All Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.5	Summary of All Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.6	Summary of All Ocular Treatment-Emergent Adverse Events Suspected to be Related to Investigational Product by System Organ Class and Preferred Term	Safety Population
14.3.1.7	Summary of All Non-Ocular Treatment-Emergent Adverse Events Suspected to be Related to Investigational Product by System Organ Class and Preferred Term	Safety Population
14.3.1.8	Summary of All Ocular Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.9	Summary of All Non-Ocular Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.10	Summary of All Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximal Severity	Safety Population
14.3.1.11	Summary of All Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximal Severity	Safety Population
14.3.2	Visual Acuity [redacted]	Safety Population
14.3.3.1	Slit-Lamp Biomicroscopy	Safety Population
14.3.3.2	Shift in Slit-Lamp Biomicroscopy	Safety Population
14.3.4	Intraocular Pressure [redacted]	Safety Population

Table Number	Title	Population
14.3.5.1	Dilated Fundus Examination	Safety Population
14.3.5.2	Shift in Dilated Fundus Examination	Safety Population
14.3.6	Conjunctival Redness	Safety Population

20. Listings

Listing Number	Title
16.1.7	Randomization Schedule
16.2.1	Subject Disposition
16.2.2	Protocol Violations
16.2.3.1	Study Population Inclusion
16.2.3.2	Inclusion and Exclusion Criteria
16.2.4.1	Demographics
16.2.4.2	Ocular Medical History
16.2.4.3	Non-Ocular Medical History
16.2.4.4	Prior and Concomitant Ocular Medications
16.2.4.5	Prior and Concomitant Non-Ocular Medications
16.2.4.6	Skin Test
16.2.5.1	Instillation of Investigational Product
16.2.5.2	Conjunctival Allergen Challenge
16.2.5.3	Relief Drop Instillation
16.2.6	Ocular Itching
16.2.7.1	All Adverse Events
16.2.7.2	All Serious Adverse Events
16.2.7.3	Adverse Events Leading to Death
16.2.7.4	Adverse Events Leading to Study Treatment Withdrawal
16.2.8.1	Visual Acuity [redacted]
16.2.8.2	Slit-Lamp Biomicroscopy
16.2.8.3	Intraocular Pressure [redacted]
16.2.8.4	Dilated Fundus Examination
16.2.8.5	Urine Pregnancy Test for Female Subjects
16.2.8.6	Conjunctival Redness

21. Figures

Figure Number	Title	Population
14.2.1.1	[redacted] Ocular Itching Score [redacted]	ITT Population with Observed Data Only
14.2.1.2	[redacted] Ocular Itching Score [redacted]	PP Population with Observed Data Only
14.2.1.3	[redacted] Ocular Itching Score [redacted]	ITT Population with Observed Data Only
14.2.1.4	[redacted] Ocular Itching Score [redacted]	PP Population with Observed Data Only