MA-RHO-18-002

A MULTICENTER, OPEN-LABEL STUDY OF RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% FOR THE REDUCTION OF ELEVATED INTRAOCULAR PRESSURE IN PATIENTS WITH GLAUCOMA OR OCULAR HYPERTENSION IN A REAL-WORLD SETTING

NCT03808688

15 August 2019

STATISTICAL ANALYSIS PLAN - MODULE I

STATISTICAL METHODOLOGY

PROTOCOL MA-RHO-18-002

A MULTICENTER, OPEN-LABEL STUDY OF RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% FOR THE REDUCTION OF ELEVATED INTRAOCULAR PRESSURE IN PATIENTS WITH GLAUCOMA OR OCULAR HYPERTENSION IN A REAL-WORLD SETTING

Protocol Number: MA-RHO-18-002
Protocol Version/Date: 18 Dec 2018

Trial Name: MOST: Multi-center, Open-label STudy

Prepared for: Aerie Pharmaceuticals, Inc.
2030 Main Street, Suite 1400
Irvine, CA 92614

Version and Author details:

Version Date:	15 Aug 2019
Version Number	Version 1.0
Author:	[redacted]

SIGNATURES

The undersigned have approved this Statistical Analysis Plan for use in this study.

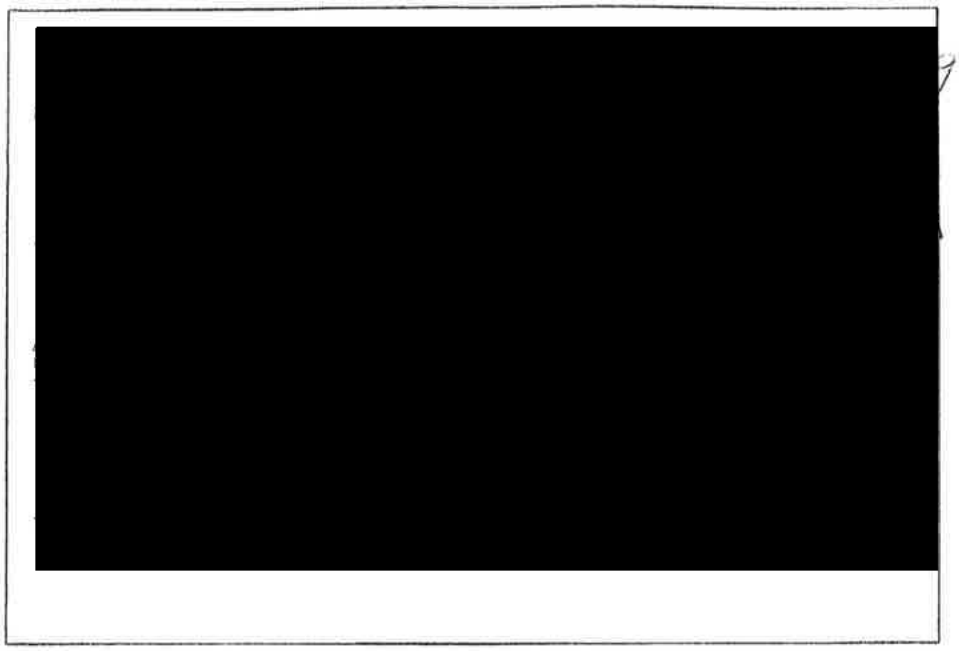

TABLE OF CONTENTS

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) – Module I is to describe the related procedures and statistical methodologies used to process the study data, analyze the study data, and report the results for Protocol MA-RHO-18-002 sponsored by Aerie Pharmaceuticals, Inc (Sponsor).

This SAP should be read in conjunction with the latest version of the designated study protocol, its case report forms (CRF), and the related SAP Module II – Tables, Graphs, Figures, and Listing.

1.1 Changes from Protocol

Not applicable.

2 STUDY OBJECTIVES

The study objective is to evaluate the intraocular pressure (IOP) lowering efficacy of netarsudil 0.02% when used as monotherapy or when used concomitantly with other IOP-lowering agents in subjects with elevated IOP due to open-angle glaucoma or ocular hypertension in a real-world setting.

3 STUDY DESIGN

This is a phase 4, prospective, multi-center, open-label, single arm study. Approximately **250** study subjects in about **32** study sites in the U.S. will be enrolled. **Both** eyes of each subject will be treated and evaluated, but only one eye will be included in the efficacy analysis (see study protocol Section 11.3.2.1).

Study subjects must be diagnosed with open-angle glaucoma or ocular hypertension and meet the study Inclusion/Exclusion Criteria (see study protocol Sections 4.3.1 and 4.3.2).

3.1 Study Measurements

3.1.1 Primary Efficacy Measure

The primary efficacy measurement is **IOP** (mmHg) measured using a Goldmann applanation tonometer affixed to a slit lamp.

3.1.2 Safety Assessments

1) Adverse Events

2) Best-corrected Visual Acuity (BCVA)

BCVA will be measured for both eyes by the investigator (or designee) at the Baseline Visit (Visit 1) and at both Visit 2 (Week 6) and Visit 3 (Week 12) using a Snellen Visual Acuity Chart (see protocol Appendix 5 for detailed information on this examination).

3) Biomicroscopy

Biomicroscopy will be performed by the investigator (or designee) for both eyes at all visits by slit lamp examination without pupil dilation for the following locations:

- **Lids/Lashes (upper and lower)** – erythema, edema
- **Conjunctiva (Palpebral and Bulbar)** – Hyperemia, Edema, Follicles
- **Cornea** – Edema, Staining/Erosion
- **Anterior Chamber** – Cells, Flare
- **Lens Status** - Aphakic, Phakic, Pseudophakic, Not done. And if phakic, **Lens Appearance**

Observations for the slit lamp Biomicroscopy examination (except lens status) will be graded on a 5-point scale as follows (see protocol appendix 5 - Examination Procedures for detailed grading definition for each assessment):

- 0 = None
- 0.5 = Trace
- 1 = Mild
- 2 = Moderate
- 3 = Severe

4) Pregnancy Testing

A urine human chorionic gonadotropin (hCG) pregnancy test (negative, positive). Only at Baseline Visit for females who are not diagnosed as postmenopausal or surgically sterile.

5) Blood Pressure (mmHg)

At all visits. Systolic and Diastolic

6) Central Corneal Thickness (µm)

Baseline only.

3.1.3 Exploratory/Other Assessments

1) Patient Questionnaire

At Week 12 (Visit 3) only. A [redacted]investigator-administrated patient questionnaire (see protocol Appendix 1) as the end-of-study assessment of treatment. [redacted]

2) Investigator Questionnaire

At Week 12 (Visit 3) only. A [redacted]investigator-administrated questionnaire (see protocol Appendix 2) as the end-of-study assessment of treatment. [redacted]

3.2 Study Visits and Schedule of Events

Subjects will participate in the study for approximately **12** weeks. There will be a total of 3 clinic visits: Screening/Baseline (Day 0), 2 in-treatment visits at Week 6 (±7 days) and Week 12 (±7 days). Activities and medical procedures to be performed at each study visit are summarized in the study protocol Appendix 4.

3.3 Sample Size Considerations

Approximately 250 subjects will be enrolled at about 32 sites. No sample size calculation was performed.

3.4 Randomization and Masking

Not applicable.

3.5 Study Drug Administration and Compliance

Subjects will receive [redacted]netarsudil 0.02% at the Baseline Visit (Visit 1) and at the Week 6 (Visit 2). They will self-administer the eye drop in **each** eye in the evening. (See protocol Section 5.1.4 and 5.1.5 for details).

No washout period required for subjects replacing prior IOP-lowering therapy.

3.6 Concomitant Therapy

If netarsudil 0.02% is to be used concomitantly with other topical ophthalmic drug products to lower IOP, each drug product should be administered at least 5 minutes apart to prevent washout.

Therapy considered necessary for a subject's welfare will be given at the discretion of the investigator and documented during the course of the study. The use of any concurrent medication (prescription or over-the-counter, including herbal medications) is to be recorded in a subject's source documentation (charts), as well as in the case report forms (CRFs), noting the date, dosage, frequency, start date, and reason for taking the medication(s).

3.7 Adverse Events (AE)

An AE is defined as any untoward medical occurrence in a subject during the course of a study. An AE can, therefore, be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational or marketed medicinal product, whether or not considered related to the investigational or marketed medicinal product. AEs include any illness, sign, symptom, or clinically significant laboratory test abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the study medication(s) under study.

AEs may be either spontaneously reported or elicited during questioning and examination of a subject.

The following information will be collected and tabulated for all AEs:

- AE description
- AE location (OD, OS, OU, Non-ocular)
- Start date
- Whether the AE is ongoing (Yes, No)
- End date
- Severity (Mild, Moderate, Severe. See protocol section 10.1.1 for severity definition)
- Whether the AE is serious (Yes, No)
- Whether the AE is congenital anomaly or birth defect (Yes, No)
- Whether the AE led to death (Yes, No)
- Whether the AE led to disability or permanent damage (Yes, No)
- Whether the AE led to hospitalization (Yes, No)
- Whether the AE is life threatening (Yes, No)
- Whether the AE led to other important medical event (Yes, No)
- Relationship to study treatment (Not related, Unlikely related, Possibly related, Related)
- Action taken with study treatment (Not changed, Drug interrupted, Drug withdrawn, N/A)
- Whether a concomitant or additional treatment given (Yes, No)

- Whether the AE led to study discontinuation (Yes, No)
- Whether any other action(s) taken (Yes, No. If yes, specification for other actions)
- Outcome (Fatal, Not Recovered/Not resolved, Recovered/Resolved, Recovered/Resolved with sequelae, Recovering/Resolving, Unknown)

The AEs and SAEs will be collected from visits 2 and 3 as well as upon subject report after visit 1 and will continue until the final protocol required visit and/or continue through resolution, or stabilization or the investigator assesses them as chronic or stable or the subject's participation in the trial ends, whichever occurs first.

4 STUDY PARAMETERS

4.1 Subject Disposition

Subjects who completed the Week 12 (Visit 3) visit will be considered as having reached Study Completion, otherwise, they will be classified in the Study Discontinuation group.

Reason(s) for study discontinuation will be recorded and could include the following:

- Adverse event
- Lost to follow-up
- Other

Time in the study will be computed as following:

Time in Study (Study Duration) = Last Date in study – Date of First Dose + 1

4.2 Study Treatment Group

All subjects will receive netarsudil 0.02% either as first-line monotherapy, as a replacement of prior IOP-lowering medication or used concomitantly with other IOP-lowering medications as determined by the treating physician.

4.3 Primary Efficacy Endpoints

The primary efficacy measure is the intraocular pressure (IOP, mmHg). The primary efficacy endpoint is the percent (%) IOP reduction from baseline.

The primary efficacy analysis will be performed for mITT and PP populations. There will be no imputation for missing Week 12 assessment.

4.4 Exploratory/Other Assessments

[redacted]

4.5 Safety Endpoints

The Medical Dictionary for Regulatory Activities nomenclature (MedDRA V22.0 at time of SAP publication, or the current version when superseded) will be used to code AEs.

Treatment-emergent AEs are any AEs with an onset date equal to or after the date of the first dose of the study eye drop. A pre-existing event that worsens after the first dose date is considered a treatment emergent event. Treatment-related AEs are any AEs with a relationship of unlikely related, possibly related or related to study treatment, or AEs with a missing relationship.

Safety endpoints include:

- Adverse events
- Best-corrected visual acuity
- Biomicroscopy
- Blood pressure

All treatment-emergent AEs/SAEs will be summarized with frequency distributions by treatment group, system organ class, and preferred term as well as by ocular versus non-ocular. Specific AEs/SAEs occurring with a frequency of 5% or more will be summarized in a separate listing.

5 ANALYSIS POPULATIONS

Four (4) analysis populations will be defined and used in the statistical analyses: (1) Intent-to-treat (ITT) population; (2) modified intent-to-treat (mITT) population; (3) per-protocol (PP) population; and (4) safety population.

5.1 Intent-to-treat Population

The intent-to-treat (ITT) population will include all subjects who were enrolled into the study.

5.2 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will include all subjects who received at least one dose of study medication and had at least one follow-up visit with a completed IOP measurement.

5.3 Per Protocol Population

The per-protocol (PP) population will consist of all subjects in the mITT population who completed 12 weeks of study treatment without significant protocol violations.

The following subjects will be excluded from the per-protocol population:

- No efficacy evaluation at baseline, and/or have no follow-up visit
- Used any prohibited medications during the study period that would interfere with the study objectives
- Had any prohibited procedures during the study period that would interfere with the study objectives.

Sensitivity analyses of the primary efficacy analyses will be conducted using the PP population.

5.4 Safety Population

The safety population will include all subjects who received at least one (1) dose of study medication. All safety analyses will be conducted using the safety population.

6 STATISTICAL METHODS

All data processing, summarization, and analyses will be performed using SAS® Version 9.4 or higher.

Unless otherwise specified, for continuous variables, descriptive statistics will include the number of subjects/eyes (n), mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized using frequency and percentages.

Unless, otherwise stated, missing data will be handled as is, except when the aforementioned dates are required for calculations, the partial dates will have either '01' or 'Jan' imputed with an exception for dates related to AEs where the date closest to the last event (visit date, etc.) should be used rather than arbitrary '01' of that month.

All efficacy data will be summarized at each time point using appropriate descriptive statistics. Summaries will be presented for the ITT, mITT and PP populations. All summaries and analyses will be performed using data pooled across centers.

Baseline assessment will be those recorded prior to dosing. In cases where more than one pre-dose observation has been recorded, the **last recording** will be identified as the baseline assessment.

Study days will be numbered relative to the study stating date (Visit 1, presumably, the first dosing date).

Recorded data will be assigned to evaluation/assessment windows. If more than one clinical evaluation is made within a window for a particular visit, the record with the date closest to the targeted window will be used except for AEs where the **worst assessment** will be used.

Visit windows and analytical windows are defined as follow:

Visit	Targeted Window	Analytical Window
Visit 1 (Baseline, First dosing date)	Day 0	Day 0
Visit 2	Week 6 (± 7 day)	Day 2 to Day 63
Visit 3 (End of treatment visit)	Week 12 (± 7 days)	Day 64 to End of Study

6.1 Subject Disposition

The number and percentage of subjects will be summarized for the following:

- Subjects discontinued, completed treatment
- Subjects discontinued for each reason(s)
- Subjects in the mITT population

- Subjects in the PP population
- Subjects in the safety population
- Subjects at each investigational site

Screened failures, subjects discontinued, and subject excluded from efficacy analysis will be listed, respectively.

6.2 Treatments

6.2.1 Extent of Study Drug Exposure

Exposure (i.e., treatment time, days) will be determined as following:

Time in Study Treatment (Treatment duration) = Date of Last Dose – Date of First Dose + 1

Assumedly, the Date of Visit 1 (Baseline) is the First Dose Date, and the day before Date of Week 12 Visit (End of Study) is the Last Dose Date.

6.2.2 Concomitant Medications

Prior and concomitant medications will be presented for each subject coded per the World Health Organization (WHO) Drug dictionary (WHO Drug Sept 2018 version at the time of SAP publication, or the current version when superseded). When two medications are coded to the same preferred term, both will be counted.

The data will also be summarized by drug class and by preferred term, and by ocular-specific and non-ocular specific drugs. Medications will be ordered alphabetically by preferred term.

Medications with partial dates that do not allow determination of whether prior or concomitant will be considered concomitant.

Subject listing of prior and concomitant medication will be presented.

6.2.3 Treatment Discontinuation and Rescue Medications

No rescue medication is proposed in this study. The subject will be exited from the study after discontinuation from the study treatment.

Efficacy assessment collected from the treatment discontinuation exit will be mapped to the next scheduled visit and considered as observed data. (i.e., the mapping will be performed prior to any data imputation if any).

Safety assessment for the treatment discontinuation exit will not be mapped. Instead, it will be treated as the last assessment during treatment period.

6.3 Demographic and Baseline/Screening Characteristics and Evaluations

All demographic and baseline data will be summarized by descriptive statistics using the mITT population. The following variables will be presented:

6.3.1 Demographics

- Age (years)
- Sex (Female, Male)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Child Bearing Potentials (for females with childbearing potential only – Yes, No)
- Pregnancy Test Results (for females with childbearing potential only – Negative, Positive)
- Race (check all that apply: American Indian or Alaska Native; Asian; Black or Africa American; Native Hawaiian or Other Pacific Islander; White, Other. If Other, list of specified.)
- Blood Pressure – Systolic, Diastolic (mmHg)
- Iris Color (Black, Blue, Brown, Green, Grey, Hazel, Other. If Other, list of specified.)
- Central Corneal Thickness (µm)

6.3.2 Medical History and Prior Ocular Procedures

- Medical history by system organ class and preferred term
- Prior ocular procedures

6.3.3 Ocular Hypertension and Glaucoma History

- Type of glaucoma
- Glaucoma History

6.3.4 Current IOP Lowering Medications

- [redacted]

6.4 Protocol Deviations

Number and percentage of protocol deviations will be summarized by the reason(s) for deviations.

Individuals subject listing of protocol deviation and reason(s) will be provided.

6.5 Efficacy Evaluation

Only **one** eye per subject will be included in the efficacy analysis.

If both eyes qualify for study inclusion, analyses will be provided for the worse eye at baseline. If both study eyes are the same at baseline, then data for only the right eye will be analyzed.

Efficacy analyses will be performed for the ITT, mITT and PP populations. Descriptive results will be presented for the overall group as well as for the Monotherapy and Concomitant Therapy groups.

There will be no statistical comparison between the Monotherapy and the Concomitant Therapy groups.

6.5.1 Primary Efficacy Variables

The primary efficacy variable is percent (%) reduction from baseline IOP.

6.5.2 Exploratory/Other Assessments

6.5.3 Sensitivity Analysis

Analyses on the primary efficacy outcome will be performed using the PP population.

6.6 Safety Analyses

The safety and tolerability of the study treatment will be determined by incidence and severity of treatment emergent AEs, clinical assessment of BCVA, IOP, eye examinations and biomicroscopy examinations.

All safety analysis will be based on the Safety population.

6.6.1 Adverse Events

All AEs reported during the study period reported for **both** eyes will be recorded and coded using MedDRA terminology and analyzed. An AE will be considered as treatment-emergent adverse event (TEAE) if it has an onset during the treatment period. A pre-existing event that worsens after the first dose date is considered a treatment emergent event.

The incidence of all TEAEs will be summarized using system organ class and preferred term. Adverse events will also be presented by relationship and severity. Further, serious adverse events and those events leading to discontinuation will also be presented.

Separate analyses will be performed for ocular and non-ocular TEAEs. For ocular TEAEs, the analytical unit will be eyes, and the total number of eyes in the safety population will be the denominator for incident rate of a specific ocular TEAE. For non-ocular TEAEs, subject will be the analytical unit and the number of subjects in the safety population will be the denominator for a specific non-ocular TEAE.

A subject/eye may have more than one AE per system organ class and preferred term. At each level of subject/eye summarization, a subject/eye will be counted once if 1 or more events were recorded and the highest severity will be reported. In cases where severity or relationship is missing, the most conservative approach will be taken (i.e. highest severity and assumed to be related).

The following summary tables of AEs will be presented:

- Adverse Events
    - Overall summary

- Ocular AEs
- By preferred term
- By preferred term and severity
- By frequency for SAEs
- By frequency for most common non-serious AEs

Most common non-serious AEs are any preferred term AE that at least 5% of the subjects report at least once.

- Treatment-Related AEs
  - Overall summary
  - By preferred term
  - By preferred term and severity
  - By preferred term and treatment session
  - Duration of AEs

The following overall summary will be presented:

- Total number and percentage of AEs
  - All AEs
  - Mild AEs
  - Moderate AEs
  - Severe AEs

  Percentages for the total number of mild, moderate, and severe AEs will be based on the total number of all AEs.

- Total number and percent of subjects with
  - At least one AE
  - At least one SAE
  - No severe AEs but at least one moderate AE
  - No severe/moderate AEs but at least one mild AE
  - At least one AE leading to discontinuation

- Total number and percent of subjects with
    - All ocular-related AE
    - Mild ocular-related AE
    - Moderate ocular-related AE
    - Severe ocular-related AE
    - At least one ocular-related AE leading to discontinuation

- Total number of subjects who died (Treatment-emergent only)

Subject level listing will be provided with related information that include AE onset/resolution date, study days, duration, preferred terms, relationship to study treatment, action taken, outcome, and sorted by subject ID and onset date.

6.6.2 Other Safety Assessments

Frequency and percent of subjects/eyes with findings on visual acuity, blood pressure and biomicroscopy will be summarized for each visit.

7 CONVENTIONS AND ALGORITHMS

7.1 Decimal Points

All summary tables involving percentages will round the percentages off to 1 decimal place.

All summary tables involving descriptive statistics of continuous variables will round the mean and median to 1 decimal place more than the variable's standard form and round the standard deviation to 2 decimal places more than the variable's standard form. The standard form of a percent change variable is 0 decimal places.

7.2 Study Days

Study days will be computed for each visit and AE event.

Study Days = Date of Visit/Event - Date of First Dose + 1

Or, if the visit/event occurs prior to the Day 1

Study Days = Date of Visit/Event - Date of First Dose

Date of First Dose is the Day 1 Visit date.

Last Date in study is the Day 84 Visit or the last visit where the subject was seen by the investigator. If lost-to-follow-up, the last date of contact is the Last Date in study.

If a subject had contact with the site after the final visit (e.g. for AE follow up), the last visit date will be the Last Date in study, not the contact date.

Time in Study (Study duration) = Last Date in study – Date of First Dose + 1

Time in Study Treatment (Treatment duration) = Date of Last Dose – Date of First Dose + 1

7.3 Multiple Occurrence of Events

When summarizing AEs, potentially clinically important laboratory findings, potentially clinically important vital signs, and subjects with multiple occurrences of an event will be counted only once in the summary. When AEs are summarized by severity, if the subject has multiple occurrences of the same AE, the most severe will be used for the summary.

When summarizing concomitant medications by drug class and by preferred term, if two medications are coded to the same preferred term, both will be counted for a subject.

7.4 Summary Tables/Listings

Summary tables, subject listings, graphs and any supportive SAS output will include a "footer" of explanatory notes that will indicate, when applicable:

- date of data extraction
- date and time of output generation
- SAS program name that generates the output

Null summary tables will be presented with a note stating that "No Subjects Met Criteria."

Individual subject listings will be provided as support for summary tables and serve as a data source substitute when a summary table is deemed either inappropriate or unnecessary. All subject listings will be sorted by subject number. When applicable, the subject listings will include the visit date, and days relative to the start of first treatment.

8 INTERIM ANALYSES

No interim analysis for efficacy is planned for this study.

9 QUALITY CONTROL AND VALIDATION

Derived datasets will be independently reprogrammed by a second programmer. The separate datasets produced by the two programmers must match 100%.

Tables will be independently reprogrammed by a second programmer for numeric results. Statisticians will be involved in the process of programming and validating tables that include inferential statistical results.

Figures will be checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

Please refer to the following [redacted] Standard Operating Procedures for details on related activities/procedures.

CN-SOP-6001 Preparation & Communications of Key Results
CN-SOP-6002 SAP Development and Maintenance
CN-SOP-6003 Analysis Datasets Development
CN-SOP-6301 Running of Statistical Programs
CN-SOP-8001 SAS Programming Standards
CN-SOP-8002 SAS Requirements Specifications
CN-SOP-8003 Program Design-Implementation
CN-SOP-8004 Program Verification and Validation
CN-SOP-8005 Running of SAS Programs

10 REFERENCES

1. Stein, C., Offen, W. (2005). Analysis of Clinical Trials Using SAS: A Practical Guide. SAS Press: Cary, NC.

(more in study protocol Section 13)

APPENDIX 1 GLOSSARY OF ABBREVIATIONS

AE	adverse event
AS-OCT	anterior-segment optical coherence tomography
BCVA	best-corrected visual acuity
CFR	Code of Federal Regulations
CI	confidence interval
CONSORT	consolidated Standards of Reporting Trials
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information
HREC	Human Research Ethics Committee
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	International Ethics Committee
IOP	intraocular pressure
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MOP	Manual of Procedures
PP	per-protocol
RLD	reference listed drug
QC	quality control
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States