16.1.9. DOCUMENTATION OF STATISTICAL METHODS (STATISTICAL ANALYSIS PLAN)

STATISTICAL ANALYSIS PLAN

A Single-Center, Double-Masked Evaluation of the Efficacy and Safety of PRX-100 in the Treatment of Early to Moderate Presbyopia

Sponsor: Presbyopia Therapies, LLC
915 Ocean Blvd.
Coronado, CA 92118

Protocol Number: PRX100.FDAIIb

Author: [redacted]
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Statistics & Data Corporation

Date: 3Jul2018
Version: Final v1.0

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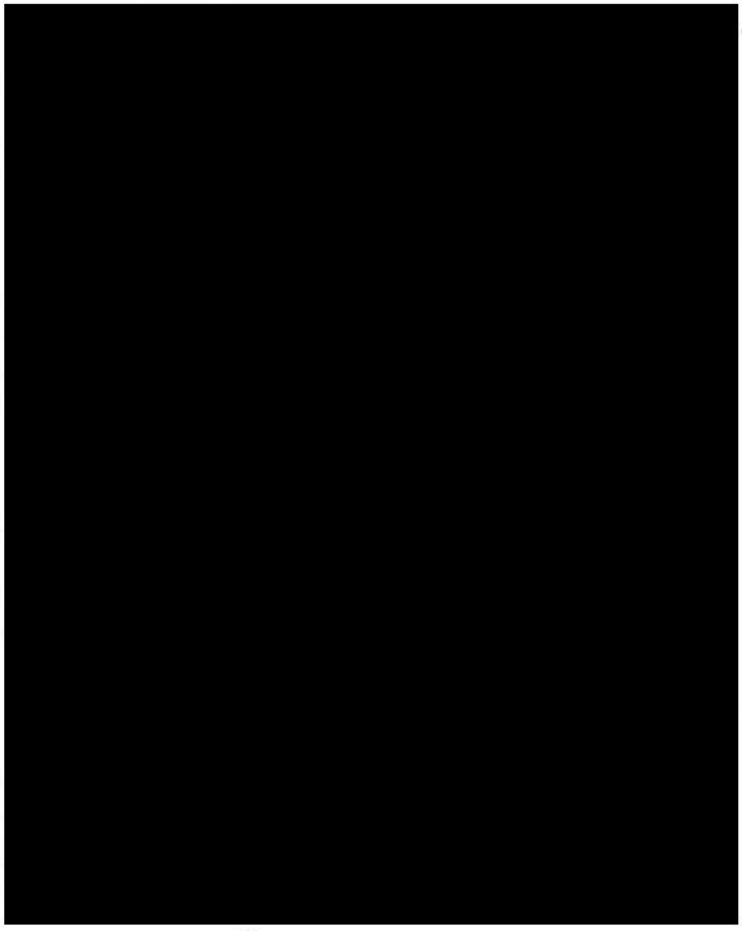
Statistical Analysis Plan Approval



Prepared by:

Reviewed by:

Approved by:

Approved by:

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Prepared by: [redacted]

Reviewed by:

Approved by:

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List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Distance Visual Acuity
CI	Confidence Interval
CRF	Case Report Form
CS	Clinically Significant
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
GEE	Generalized Estimating Equations
IB	Investigators' Brochure
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IP	Investigational product
ITT	Intent-to-Treat
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of observations
NCS	Not clinically significant
OD	Right eye
OS	Left eye
OU	Both eyes
p	*p*-value
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
ROPI	Report of Prior Investigations
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	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol PRX100.FDAIIb, amendment 5 dated 3Jul2018.

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.

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

2. Study Objectives

The objective of the study is to evaluate the safety and efficacy of PRX-100 compared with [redacted] Aceclidine and Vehicle in the treatment of early to moderate presbyopia.

3. Study Variables

All best-corrected distance visual acuity measures in the protocol utilize the subject's manifest refraction obtained within three months of Visit 1 and will hereby be referred to as best-corrected visual acuity (BCVA) at whichever distance is applicable. Efficacy variables include monocular BCVA at 45 cm and a [redacted] and binocular BCVA at 45 cm and [redacted] The 45 cm distances will be repeated for pre-treatment and at 0.5, 1, 3, 4, 5 and 7 hours post-treatment. The [redacted]. Primary analyses will use the number of subjects who meet or exceed 3-lines of improvement from pre- to post-treatment in the monocular 45 cm BCVA, Monocular BCVA at 45 cm also be analyzed by 1-letter increments in this phase 1 trial. LogMAR units will be used for all visual acuity safety and efficacy measures. Pupillometry will also be measured.

3.1 Primary Variables

Percentage of subjects who achieve a 3-line (15-letter) or greater improvement from pre-treatment (baseline) in the study eye measured with monocular best-corrected VA (BCVA) at 45 cm at 1 hour post-treatment.

3.2 Secondary Variables

The secondary variables are:

- Percentage of subjects who achieve a 1-line (5-letter) to 3-line (15-letter) or greater improvement from pre-treatment (baseline) by 1-letter increments measured with monocular BCVA at 45 cm at 0.5, 1, 3, 4, 5 and 7 hours post-treatment
- Percentage of subjects with at least a 3-line (15-letter) improvement from pre-treatment (baseline) in the study eye measured with monocular BCVA at [redacted]
- Mean change from pre-treatment monocular BCVA (logMAR) in the study eye at 0.5, 1, 3, 4, 5 and 7 hours post-treatment
    - Two near testing distances will be assessed: 45 cm (at 0.5, 1, 3, 4, 5 and 7 hours post-treatment) and [redacted]
- Percentage of subjects with at least a 3-line (15-letter) improvement from pre-treatment (baseline) measured with binocular BCVA at 45 cm at 0.5, 1, 3, 4, 5, and 7 hours post-treatment
- Percentage of subjects with at least a 3-line (15-letter) improvement from pre-treatment (baseline) measured with binocular BCVA at [redacted]
- Mean change from pre-treatment (baseline) binocular BCVA (logMAR) at 0.5, 1, 3, 4, 5, and 7 hours post-treatment
    - Two near testing distances will be assessed: 45 cm (at 0.5, 1, 3, 4, 5, and 7 hours post-treatment) and [redacted], [redacted]

3.3 Exploratory Efficacy Variables

- [redacted]

- [redacted]

3.4 Other Measures

- [redacted]

3.5 Safety Variables

The safety variables include the following:

- Adverse events (AE) (reported, elicited, and observed)
- Monocular and binocular BCVA (10 feet)
- Monocular and binocular low-luminance BCVA (10 feet)
- Slit lamp biomicroscopy
- Conjunctival redness
- Intraocular pressure (IOP)
- Urine pregnancy test

3.6 Statistical Hypotheses

The statistical hypotheses are as follows:

Null: There is no difference in the percentage of subjects with a 3-line (15-letter) or greater improvement from baseline in BCVA at 45 cm between PRX-100 versus Vehicle or [redacted] Aceclidine versus Vehicle at 1-hour post-treatment.

Alternative: The percentage of subjects with a 3-line (15-letter) or greater improvement from baseline in BCVA at 45 cm is different for the PRX-100 compared to Vehicle or for the [redacted] Aceclidine compared to Vehicle at 1 hour post-treatment.

4. Study Design and Procedures

4.1 General Study Design

This is a randomized, double-masked, cross-over design, single-center evaluation of the efficacy and safety of PRX-100 ophthalmic solution compared to [redacted] Aceclidine and Vehicle ophthalmic solution for PRX-100. Subjects will receive all 3 treatments over the course of 3 visits, noting a 2-week gap of no treatment in-between dosing. The study will screen approximately 60 subjects to complete 30 subjects per treatment arm to evaluate the safety of PRX-100 and the magnitude and duration of effects on improving near-vision acuity. Subjects will be randomly assigned to receive 1 of the following treatment sequences and will receive a different treatment at each visit taken bilaterally. The treatment sequences are shown in the table below.

	Visit 2	Visit 3	Visit 4
Sequence A	PRX-100	[redacted] Aceclidine	Vehicle
Sequence B	[redacted] Aceclidine	Vehicle	PRX-100

Sequence C	Vehicle	PRX-100	[redacted] Aceclidine

- Sequence A: PRX-100 (at Visit 2); [redacted] Aceclidine (at Visit 3); Vehicle (at Visit 4)
- Sequence B: [redacted] Aceclidine (at Visit 2); Vehicle (at Visit 3); PRX-100 (at Visit 4)
- Sequence C: Vehicle (at Visit 2); PRX-100 (at Visit 3); [redacted] Aceclidine (at Visit 4);

Randomization is at a ratio of 1:1:1 of the three different sequences. Screening procedures will be carried out during Visit 1. All efficacy and safety procedures will be carried out at each visit changing only the drug administered.

4.2 Study Eye Definition:

Dynamic Study Eye: One eye per subject will be designated as the study eye at each visit. The study eye will be the eye that meets all the inclusion criteria and none of the exclusion criteria. If both eyes qualify, the eye with the worse (i.e. highest logMAR score) baseline monocular best-corrected distance VA at 45 cm at each visit will be selected as the study eye for that visit. If both eyes have the same VA at 45cm, the study eye will be selected as the eye with [redacted] If both eyes have equal sphere, the right eye will be selected as the study eye.

Static Study Eye: A definition of the study eye based on the Visit 1 measures.

Dynamic study eye will be used with mITT population and the static study eye will used with other populations.

4.3 Study Visit Schedule

Study visits should be conducted in the following order:

Visit 1 (Day 1)

- Informed consent and HIPAA
- Demographics
- Medical/medication history
- Urine pregnancy test (for females of child-bearing potential)
- Inclusion/exclusion criteria review
- Screening assessments:
  - Screening monocular BCVA at 45 cm*
  - Screening monocular BCVA at three meters (10 feet)*
- Slit lamp biomicroscopy
- Fluorescein staining

Day 1: [redacted]

- [redacted]

Visits 2, 3, 4 (Days 15±7, 29±7, 43±7)

- Medical and medication history update
- Urine pregnancy test (for females of child-bearing potential)
- Pre-treatment baseline assessments:
  - Pupillometry [redacted]
  - Monocular BCVA at 45 cm*
  - Binocular BCVA at 45 cm*
  - Monocular BCVA at [redacted]
  - Binocular BCVA at [redacted]
  - Monocular BCVA*
  - Binocular BCVA*
  - Monocular low-luminance BCVA*
  - Binocular low-luminance BCVA*
  - [redacted]
  - Slit lamp biomicroscopy
  - Conjunctival redness assessment
- Randomization will occur at Visit 2 for all qualified subjects. All randomized subjects will receive each treatment once at each Visit 2, 3 and 4 (crossover study design). Subjects will be randomized by treatment sequence or for which treatment will be administered at each study visit.

Treatment Administration

- Instillation of PRX-100, [redacted] Aceclidine, or Vehicle OU

- [redacted]

Post-Treatment Assessments***

- AE query post-treatment and 1 hour post-treatment
- The following assessments will be made 0.5, 1, 3, 4, 5 and 7 hours post-installation of the test agent:
  - Conjunctival redness assessment
  - Pupillometry [redacted]
  - Monocular BCVA at 45 cm*
  - Binocular BCVA at 45 cm*
  - Monocular BCVA*
  - Binocular BCVA*
  - Monocular low-luminance BCVA*
  - Binocular low-luminance BCVA*
- [redacted]
  - [redacted]
  - [redacted]
- The following assessments will be made [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Following the 7 hour post-treatment assessments:
  - Slit lamp biomicroscopy
  - IOP
  - AE query

Assessment for Study Exit

- Subjects will be assessed for study exit. Study exit can occur at either Visit 1, 2, 3, or 4. If a subject completes the study, study exit will occur at Visit 4.

* VA to be assessed with best distance-correction [redacted]

4.4 Schedule of Assessments

The schedule of assessments is provided below.

Study Parameter	Visit 1 (Day 1)	Visit 2 (Day 15 ± 7)	Visit 3 (Day 29 ± 7)	Visit 4 (Day 43 ± 7)
Informed consent / HIPAA	X			
Demographic data	X			
Medical and medication history	X			
Medical and medication history update		X	X	X
Urine pregnancy test (for females of child-bearing potential)	X	X	X	X
Inclusion/exclusion criteria review	X			
Baseline pupillometry [redacted]		X	X	X
Screening monocular BCVA at 45 cm[1]	X			
Baseline monocular BCVA at 45 cm[1]		X	X	X
Baseline binocular BCVA at 45 cm[1]		X	X	X
Baseline monocular BCVA at [redacted]		X	X	X
Baseline binocular BCVA at [redacted]		X	X	X
Screening monocular BCVA[1]	X			
Baseline monocular BCVA[1]		X	X	X
Baseline binocular BCVA[1]		X	X	X
Baseline monocular low-luminance BCVA[1]		X	X	X
Baseline binocular low-luminance BCVA[1]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
Slit lamp biomicroscopy	X	X	X	X
Baseline conjunctival redness assessment		X	X	X
Randomization		X		
Fluorescein staining[2]	X			
[redacted]	X			
[redacted]	X			
[redacted]	X			
Instillation of PRX-100, [redacted] Aceclidine or Vehicle treatment OU[4]		X	X	X
Adverse event query (post-treatment and 1 hour post-treatment)[3]		X	X	X
Post-treatment conjunctival redness assessment (0.5, 1, 4, 5, 6, 7 hours post-treatment)[3]		X	X	X
Post-treatment pupillometry under [redacted]		X	X	X
Post-treatment monocular BCVA at 45 cm (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X

Study Parameter	Visit 1 (Day 1)	Visit 2 (Day 15 ± 7)	Visit 3 (Day 29 ± 7)	Visit 4 (Day 43 ± 7)
Post-treatment binocular BCVA at 45 cm (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X
Post-treatment monocular BCVA at [redacted]		X	X	X
Post-treatment binocular BCVA at [redacted]		X	X	X
Post-treatment monocular BCVA (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X
Post-treatment binocular BCVA (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X
Post-treatment monocular low-luminance BCVA (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X
Post-treatment binocular low-luminance BCVA (0.5, 1, 3, 4, 5, 7 hours post-treatment) [1, 3]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
[redacted]		X	X	X
End of visit slit lamp biomicroscopy	X	X	X	X
IOP	X	X	X	X
Adverse event query	X	X	X	X
Selection of study eye	X			
Assessment for study exit	X	X	X	X
Study exit	X[5]	X[5]	X[5]	X[5]

1. Visual acuity to be assessed with best distance-correction [redacted]
2. Subject should wait thirty minutes with his/her eyes closed following fluorescein staining prior to instillation of placebo.
3. Best effort will be made to adhere to post-placebo/post-treatment assessment time points. No minimum/maximum windows are defined for any post-placebo/post-treatment assessment time point.
4. [redacted]
5. Study exit can occur at either Visit 1, 2, 3 or 4. If a subject completes the study, Study Exist will occur at Visit 4.

5. Study Treatments

The study treatments are PRX-100 (Aceclidine [redacted] and Tropicamide 0.01%) Ophthalmic Solution, [redacted] Aceclidine Ophthalmic Solution and Vehicle Ophthalmic Solution for PRX-100 (sterile saline solution). An unmasked trained study technician will prepare study drugs immediately prior to administration. [redacted]

5.1 Method of Assigning Subjects to Treatment

Each subject who signs an informed consent form will be assigned a screening number. Screening numbers will be assigned in sequential order beginning with 001 and proceed with the assessment schedule. At Visit 2, once a subject meets all qualification criteria, he/she will be randomized into one of three treatment sequences in a 1:1:1 ratio (Sequence A: Sequence B: Sequence C), and assigned a 4-digit subject number. Each sequence will follow a pre-defined schedule where subjects will receive one drug at each visit.

- Sequence A: PRX-100 (at Visit 2); [redacted] Aceclidine (at Visit 3); Vehicle (at Visit 4)
- Sequence B: [redacted] Aceclidine (at Visit 2); Vehicle (at Visit 3); PRX-100 (at Visit 4)
- Sequence C: Vehicle (at Visit 2); PRX-100 (at Visit 3); [redacted] Aceclidine (at Visit 4);

Subject numbers will be assigned in a sequential order starting at the lowest number available. No numbers will be skipped or omitted.

A trained technician will be instructed to dispense the appropriate bottle of investigational drug that corresponds to the assigned subject number according to the randomization list.

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

5.2 Masking and Unmasking

An independent unmasked designee who is not otherwise involved in the trial will generate the complete randomized study drug kit list. The subject, Sponsor, Investigators, and study staff will be masked during the randomization process and throughout the study.

When medically necessary, the Investigator may need to determine what treatment has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the Sponsor should be notified

before unmasking investigational product (IP). A two-panel clinical label with scratch offs will be used for unmasking.

In emergency situations, the investigator must notify the sponsor within 24 hours after determining that it is necessary to unmask the treatment assignment. If the investigator determines that emergency unmasking is necessary, the investigator should identify and scratch off the emergency unmasking drug label for the given subject. 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.

5.2.1 Unmasking to Monitor mITT Enrollment

To ensure there are 30 completed subjects per treatment arm in the mITT population, an unmasked statistician from SDC will monitor mITT qualification criteria and provide a recommendation regarding how many additional subjects to enroll into the study. The unmasked statistician will only evaluate pre-treatment monocular best-corrected distance VA at 45 cm at visits 2, 3 and 4 to make enrollment recommendations. No mention of which treatments, if any, have reached 30 subjects will be made. At most twice monthly enrollment projections will be made with [redacted] as requested by the Sponsor.

6. Sample Size and Power Considerations

Approximately 60 subjects will be screened to complete at least 30 evaluable subjects per treatment arm in the mITT population at a single site. As this is a phase 2 trial and [redacted] onservative power estimations were calculated assuming a non-cross over, 2 independent group, [redacted] Under these conservative assumptions the primary endpoint will have 84.7% power if [redacted] ([redacted] of the PRX-100 treated subjects have a 3-line (15-letter) or greater improvement from the pre-dose measurement of monocular BCVA while the Vehicle arm has [redacted] with a 3-line improvement. With these same assumptions, the study will have 90.1% power to show a difference between treatments if the PRX-100 arm has [redacted] of the subjects with a 3-line or greater improvement.

7. Data Preparation

All reported study data will be recorded on the electronic case report forms (eCRFs) supplied by Statistics & Data Corporation (SDC) using iMedNet™. 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.

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.

8. Analysis Populations

8.1 Modified Intent-to-Treat Populations

The modified Intent-to-Treat (mITT) population consists of the study eye with baseline/pre-treatment monocular best-corrected distance VA [redacted] for each visit of all subjects who are randomized. [redacted]. The mITT population will be analyzed as treated and will be the primary population used for the primary and monocular secondary efficacy analyses.

Pairwise comparisons between treatment groups and changes from pre-treatment will use the mITT population using only those study eyes which have baseline/pre-treatment monocular best-corrected distance VA at [redacted]. Because inclusion in the mITT is assessed at each treatment visit separately it is possible subjects are included at some visits/treatments but not at others.

All mITT populations will use the dynamic study definition for the study eye.

For exploratory purposes another analysis will use the monocular eye from mITT above for baseline (pre-treatment) and binocular post-treatment BCVA.

Other modified populations will be defined similarly to mITT but at other specified baseline (pre-treatment) cutoffs, per visit, below:

- [redacted]
- [redacted]

8.2 Intent-to-Treat Population

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

secondary monocular efficacy endpoints. The ITT population will be the primary population used to assess the secondary binocular efficacy endpoints.

8.3 Per Protocol Population

The Per Protocol (PP) population is a subset of the ITT population and includes the study eye of subjects with no major protocol violations/deviations likely to affect the primary efficacy endpoint. This population will be analyzed as treated using observed data only for confirmatory and sensitivity analyses.

8.4 Safety Population

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

8.5 Exploratory Population

Data analysis for some exploratory populations will be done at sponsor discretion. Known populations of interest include [redacted]

9. General Statistical Considerations

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 or higher. Outputs 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 (or treatment sequence where applicable), visit, and time point (where applicable) based on all randomized subjects. Screen failures will not be captured in the database.

All quantitative/continuous study assessments will be summarized by treatment (or treatment sequence) and time point (as applicable) using descriptive statistics (number of observations [n], 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. All qualitative/categorical study assessments will be summarized by treatment (or treatment sequence), and where applicable time point using frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%).

Statistical testing, unless otherwise indicated, will be performed at a two-sided alpha = 0.10 significance level. When applicable, two-sided 80% and 90% CIs will be reported. All *p*-values (*p*) will be displayed to four decimal places, with *p* less than 0.0001 presented as '< 0.0001' and *p* greater than 0.9999 presented as '> 0.9999'.

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

9.1 Unit of Analysis

For measurements taken at the subject level, the unit of analysis will be the individual subject and for measurements taken at the eye level, the unit of analysis will be the study eye defined in Section 4.1 and the exploratory study eyes defined in Section 8.5. The only exception is pupil diameter for which the unit of analysis is the average of three measurements in each of the subjects' eyes at each time point.

9.2 Definition of Baseline

For all variables, baseline is defined as the pre-treatment measurement taken prior to administration of study drug at each Visit. If the pre-treatment measurement is not available, then screening will be used as baseline for all treatments/visits. Change from baseline will be calculated as follow-up measure minus baseline/pre-treatment measure.

9.3 Adjustments for Multiplicity

There will be no adjustments for multiplicity in testing the primary efficacy endpoint in this proof of concept study. There will be no adjustments for multiplicity for multiple treatment arms and multiple comparisons to Vehicle either.

9.4 General Imputation Methods

As sensitivity analyses of the primary endpoint, missing data will be imputed once as failures in the study eye which do not meet the mITT criteria at either 1 or both treatments in the pairwise treatment comparisons. A similar imputation will be done imputing missing data (data not meeting the mITT criteria) as successes in the mITT GEE analysis. Additionally, analysis on the primary efficacy variable will be performed on the ITT and PP populations will be analyzed as treated using observed data only.

Secondary binocular efficacy analyses and pupillometry will not be imputed. Any analyses on the fellow eye will not be imputed.

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 sequence for all randomized subjects.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment sequence for all randomized subjects. The reasons for study discontinuation that will be summarized include: AE, protocol violation, administrative reasons, sponsor termination of study, withdrew consent, and Investigator's discretion, and other. A subject listing will be provided which includes the date and reason for premature study discontinuation.

The number of subjects in each of the analysis populations (ITT, PP and Safety) will be displayed by treatment and percentages of number of subjects will be calculated using randomized subjects as the denominator. Additionally, the number of subjects in each mITT will be listed by treatment and visit.

The number and percentage of subjects with major protocol deviations will be summarized by treatment sequence and overall for all randomized subjects. Protocol deviations will be classified as major or minor prior to the closure of the database during a masked review of each protocol deviation. Major deviations will be defined as those deviations that potentially impact the primary outcome of the study. The protocol deviations and their associated codes that will be summarized include:

Deviation Code = Deviation Category

1 = Informed Consent

2 = Inclusion/Exclusion and Randomization

3 = Test Article/Study Drug Instillation

4 = Improper Protocol Procedures at Site (missed, repeated, not per protocol)

5 = Site's Failure to Report SAE/AE

6 = Visit out of Window (missed, early, late)

7 = Subject Use of Prohibited Concomitant Medication(s)

8 = Subject's Failure to Follow Instructions

9 = Other

A subject listing will be provided which 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 include randomization/treatment sequence (actual vs assigned), informed consent date and exclusions from the PP population.

11. Demographic and Pretreatment Variables

11.1 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. Iris color will be presented at the subject level with a category for heterochromia. Sex, race, ethnicity, and iris color will be presented using descriptive summary statistics with counts and percentages. Age (years) will be summarized, overall and by treatment sequence, using continuous descriptive statistics. 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

Demographic variables will be summarized for the ITT by treatment sequence and overall in tables. A subject listing that includes all demographic variables will be provided.

11.2 Pretreatment Variables

Pretreatment variables are measured to ensure the safety and eligibility of subjects at Visit 1 and to confirm their previous results taken within 3 months of Visit 1 have not changed. Subject level listings will be used to present pretreatment information from the ITT population at the eye level when appropriate. The baseline pretreatment characteristic variables will be included on listings only and include the following variables:

- Fluorescein Staining (pre-placebo instillation)
- Manifest Refraction
- Dark Adaptive Pupillometry

Pre-treatment best-corrected distance visual acuity (BCVA) measured using an ETDRS chart in logMAR units will be assessed for screening and study eye selection at Visit 1 pre- and post-placebo instillation and will be presented with the Safety Population on the listings and tables of appropriate distances. A pre-placebo measurement of BCVA (at 10 feet) will confirm the BCVA assessed with [redacted] A pre- and 0.5 hours post-placebo measurement of BCVA at 45 cm is measured for screening purposes and selection of the study eye further explained in Section 4.1. The Investigator will indicate on the CRF whether VA was measured with or without correction, and if pin-hole was used.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment sequence 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.

12.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary, Version Enhanced B2, March 2017 and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name (generic drug name).

All medications taken 30 days prior to Visit 1 until the study end will be collected in the database. Prior medications are defined as those with an end date before the first treatment (Visit 2) in the sequence. Concomitant medications for each treatment are defined as those that are in use during dosing or started after dosing but ended before the next treatment in the sequence or study completion/discontinuation.

Both ocular and non-ocular concomitant medications will be summarized using the ITT population. Medications will be tabulated for each treatment 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 subjects in each treatment.

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

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

The study drug will be administered as a single dose by a trained study technician; therefore, dosing compliance and exposure cannot be calculated. Treatment administration will be listed by subject.

14. Efficacy Analyses

14.1 Primary Analysis

The primary efficacy variable in this study is the proportion of subjects with at least a 3-line (15-letter) improvement from the pre-treatment measurement of BCVA at 45 cm (monocular assessment) to 1 hour

post-treatment in the study eye. Early Treatment of Diabetic Retinopathy Study (ETDRS) format VA charts will be used for all distances of VA. All VA measurements will be assessed using best distance correction obtained by [redacted]

The primary analysis will compare the PRX-100 arm versus the Vehicle arm and the [redacted] Aceclidine arm versus the Vehicle arm separately. PRX-100 will also be compared against [redacted] Aceclidine as a secondary analysis, calculated as PRX-100 versus [redacted] Aceclidine. The primary time point is at 1 hour post-treatment only. Other time points, 0.5, 3, 4, 5 and 7 hours will be compared in secondary analyses. All time points are secondary when analyzing PRX-100 versus [redacted] Aceclidine.

Descriptive statistics for the fellow eye will be displayed on separate tables than the study eye and only in the ITT and PP populations with observed data. Descriptive statistics will be presented in tables for the study eye, time point, and distance by treatment in the mITT as primary and for sensitivity in the mITT with missing data imputed as success, mITT with missing data imputed as failure, ITT and PP populations with observed data. A subject listing of BCVA will also be produced. Testing of the proportion of subjects with at least a 3-line (15-letter) improvement from pre-treatment will be completed accounting for the correlations between treatments and periods within a subject using a logistic (binomial error and logit link) model estimated by GEE methods. Aspects of the model include:

- Response measure: indicator of whether the subject had at least a 3-line (15-letter) improvement from pre-treatment in the binocular assessment of BCVA at 45 cm.
- Fixed effect explanatory measures: sequence, period and treatment.
- Random effect measure: subject within sequence, to account for the correlation between treatments and periods within a subject.
- Repeated measures correlation will be estimated with an unstructured variance-covariance matrix in the GEE model.

Example SAS code is shown here:

[redacted]

[redacted]

odds, and standard errors, for each treatment and odds ratios, , CIs (80% and 90%), and *p*-values for the difference between treatments will be presented . Separate models will be built for each distance (with 45 cm being primary and 54 cm being secondary), time point (1 hour is primary time points, all other time points are secondary), and eye (study eye and fellow eye). Pairwise comparisons among treatments will also be made at each distance and time point using McNemar's tests. An example of McNemar's test in SAS is:

[redacted]

See Section 16.1 of the SAP to review changes to sensitivity analyses.

14.2 Secondary Efficacy Analyses

Secondary efficacy measures include the following:

1. Percentage of subjects who achieve a 1-line (5-letter) to 3-line (15-letter) or greater improvement from pre-treatment (baseline) by 1-letter increments measured with monocular BCVA at 45 cm at 0.5, 1, 3, 4, 5 and 7 hours post-treatment
2. Proportion of subjects with at least a 3-line (15-letter) improvement in the study eye in the measurement of BCVA at 45 cm comparing baseline to
    a. 0.5, 1, 3, 4, 5 and 7 hours post-treatment
3. Proportion of subjects with at least a 3-line (15-letter) improvement in the study eye in the measurement of post-treatment monocular BCVA at 54 cm compared to baseline monocular BCVA at [redacted]
4. Mean monocular BCVA in logMAR units in the study eye

   a. 0.5, 1, 3, 4, 5 and 7 hours post-treatment assessments compared to baseline assessment
   b. Two near testing distances will be assessed: 45 cm (all post-treatment time points) and [redacted]
5. Proportion of subjects with at least a 3-line (15-letter) improvement in the measurement of post-treatment binocular BCVA at 45 cm compared to baseline binocular BCVA at 45 cm
   a. 0.5, 1, 3, 4, 5, and 7 hours post-treatment
6. Proportion of subjects with at least a 3-line (15-letter) improvement in the measurement of post-treatment binocular BCVA at [redacted] compared to baseline binocular BCVA a [redacted]
7. Mean binocular BCVA
   a. 0.5, 1, 3, 4, 5, and 7 hours post-treatment assessments compared to baseline assessment
   b. Two near testing distances will be assessed: 45 cm (all post-treatment time points) and [redacted]
8. Measurement of pupil diameter via pupillometry under [redacted]

The categorical secondary efficacy measures (Bullet Points 1, 2, 3, 5, and 6) will be analyzed using the same model used for the primary analyses. Separate models will be built for each distance and time point. Pupil diameter (Bullet Point 8) will be analyzed using descriptive statistics only. The individual averages for both eyes will be averaged for the tables. Listings will also be created for all measures.

For continuous secondary endpoints (Bullet Points 4 and 7), a mixed effects linear model will be employed. The mixed effects linear model will include change from baseline as the response variable; sequence, period and treatment as fixed effects; and subject within sequence as a random effect with a variance component covariance matrix to account for the correlation among measures within a subject. Mean differences between treatments (PRX-100 vs Vehicle; [redacted] Aceclidine vs Vehicle, PRX-100 vs [redacted] Aceclidine), standard errors, *p*-values, and two-sided 80% and 90% CIs, will be provided. Separate models will be built for each distance and time point.

[redacted]

Pairwise comparisons among treatment will also be made at each distance and time point using two-sample t-tests. The ITT population with no imputation is used for all secondary efficacy variables. All monocular assessments will analyze the study eye and fellow eye separately. For all secondary efficacy variables, descriptive statistics will be presented for each time point and distance as well as for the change from pre- to each post-treatment time point and distance by treatment. All secondary efficacy endpoints will also be presented in listings. The 45 cm and [redacted] BCVA listings will include a variable that indicates if a subject had a 3-line (15-letter) improvement from baseline.

14.3 Exploratory Efficacy Analyses

Exploratory efficacy measures include the following:

1. Proportion of subjects with at least a 3-line (15-letter) improvement in the study eye in the measurement of BCVA at 45 cm comparing baseline to
    a. 0.5, 1, 3, 4, 5 and 7 hours post-treatment
2. [redacted]

Exploratory efficacy endpoints will be analyzed for all available data similarly to the primary and secondary endpoints in the mITT population and in the ITT population for sensitivity. All exploratory variables will include percentage based and mean based analyses, similar to the primary and secondary endpoints. Pairwise treatment comparisons will be calculated where possible, along with changes from pre-treatment; otherwise, analyses will be limited to within treatment statistics.

15. Safety Analyses

All safety analyses will be conducted using the Safety Population. The percentage of subjects with treatment-emergent adverse events (TEAEs) will be summarized for each treatment. Incidence will be tabulated by MedDRA SOC and PT within each SOC. Slit lamp biomicroscopy, IOP, conjunctival redness, BCVA, low-luminance BCVA will be summarized descriptively using quantitative and qualitative summary statistics by visit and time point, as appropriate.

15.1 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 investigational product, 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, patient characteristics that may impact medical device performance (e.g. anatomical limitations), and therapeutic parameters (e.g. energy applied, sizing, dose release) associated with a 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 in the eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and will be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to investigational product, expectedness, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

AEs will be collected from the time the informed consent is signed through study exit.

Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an adverse event as determined by the Investigator or reported to him/her by the patient/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 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.

Relationship to Investigational Product

The relationship of each AE to the IP should be determined by the Investigator using these explanations:

- Suspected: A reasonable possibility exists that the IP caused the AE.
- Not Suspected: A reasonable possibility does not exist that the IP caused the AE.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the IP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. Types of evidence that would suggest a causal relationship between the IP and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (e.g. tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the investigational product-treatment group than in a concurrent or historical control group.

Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- Unexpected: an AE that is not listed in the Investigator's Brochure (IB) or Report of Prior Investigations (ROPI) or is not listed at the specificity or severity that has been observed.
- Expected: an AE that is listed in the IB or ROPI at the specificity and severity that has been observed.
- Not applicable: an AE unrelated to the investigational product.

Adverse events that are mentioned in the IB or ROPI as occurring with a class of products or as anticipated from the pharmacological/ mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The Investigator will initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

Serious Adverse Events (SAE)

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

- Death;
- A life-threatening AE;
    - Note: An AE is considered “life-threatening” if, in the view of either the Investigator or sponsor, its occurrence places the patient or 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 any inpatient admission (even if less 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.
    - 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 patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

AE Summaries

All AEs will be coded using the MedDRA Version 20.0.

TEAEs are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated. All AEs collected in the eCRFs will be presented in data listings, but only TEAEs will be summarized.

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. This summary will also include breakdowns of TEAEs further categorized as ocular or non-ocular, expected or unexpected TEAEs, treatment-emergent SAEs, TEAEs by maximum severity, related TEAEs, TEAEs leading to study treatment withdrawal, and TEAEs leading to death.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by SOC and PT. Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment at the subject level by SOC and PT. Ocular TEAEs 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. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC. The occurrence of non-ocular and ocular TEAEs will also be tabulated by SOC and PT for the following: maximal severity and suspected relationship to study drug. Expected and unexpected TEAEs and treatment-emergent SAEs will also be summarized by SOC and PT.

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

- All AEs
- Ocular TEAEs
- Non-ocular TEAEs
- Expected TEAEs
- Unexpected TEAEs
- Treatment-related TEAEs
- Serious TEAEs
- TEAEs leading to study discontinuation
- TEAEs by Maximum Severity

All AEs will be presented in a subject listing, with ocular AEs listed separately from non-ocular AEs. TEAEs leading to study treatment discontinuation will be listed separately. In addition, all serious AEs will be presented in a separate listing.

15.2 Best-Corrected Distance Visual Acuity (BCVA)

Best-Corrected Distance Visual Acuity measured at the three meters or 10 feet distance is a safety variable. Measurements are done monocularly and binocularly pre-treatment and at 0.5, 1, 3, 4, 5, and 7 hours post treatment at each visit. The Investigator will indicate on the CRF whether VA was measured with or without correction, and if pin-hole was used. Monocular assessments will refer to a study eye and fellow eye.

The sites will convert number of letters read correctly to the logMAR scores, which will be used for all summaries. The observed and change from baseline in BCVA will be summarized by treatment using continuous descriptive summary statistics.

Best-Corrected Distance Visual Acuity data will be also presented in a listing. Listings for the 10 feet BCVA will be displayed separately from 45 cm and [redacted] BCVA.

15.3 Low-Luminance Best-Corrected Distance Visual Acuity

Binocular low-luminance BCVA and monocular low-luminance BCVA using an ETDRS chart calibrated for testing at three meters (10 feet) is conducted at baseline and at 0.5, 1, 3, 4, 5 and 7 hours post-treatment. Results will be recorded in logMAR units.

The observed and change from baseline low-luminance BCVA will be summarized for each eye (study eye and fellow eye for monocular low-luminance BCVA) and both eyes (for binocular low-luminance BCVA) using continuous descriptive statistics by time point for each treatment. A subject listing of low-luminance visual acuity will also be produced.

15.4 Slit Lamp Biomicroscopy Examination

A slit lamp biomicroscopy examination will be conducted on both eyes at all scheduled visits pre-treatment and at the last time point for each visit in the eyelid, conjunctiva, cornea, anterior chamber, iris, and lens. The results will be graded as normal, not clinically significant (NCS), or clinically significant (CS).

A table will summarize results using counts and percentages for each treatment at each time point and location for each eye. Percentages will be based on the number of subjects in each treatment with responses. Shift tables and subject level listings will also be provided.

15.5 Intraocular Pressure (IOP)

Intraocular pressure is measured at the end of every visit. IOP will be summarized by treatment for the study and fellow eye separately, using continuous descriptive summary statistics in a table. Change from baseline will also be calculated and summarized using descriptive summary statistics in a table. The data for IOP examinations will be presented in a listing.

15.6 Conjunctival Redness

Conjunctival redness is measured pre- and post-treatment at Visits 2, 3, and 4. Conjunctival redness will be summarized by treatment, for the right and left eye separately, using continuous descriptive summary statistics) in a table. Change from baseline will also be calculated and summarized using descriptive summary statistics in a table. The data for Conjunctival redness will be presented in a listing.

15.7 Urine Pregnancy Test

Female subjects of childbearing potential will have a urine pregnancy test at the site on the day of study visit 1, 2, 3, and 4. A subject level listing by visit will be produced.

16. Changes from Protocol-Stated Analyses

There are several changes from the protocol-stated analyses which include new populations, changes to the populations used for analyses and corresponding sensitivity analyses.

New analysis populations not mentioned in the protocol but specified in Section 8.1 of this SAP:

- monocular pre-treatment study eye compared to binocular post-treatment eyes
- [redacted]

The following endpoints are analyzed in the ITT population, with no sensitivity populations, per the Protocol but will now be analyzed in the mITT to keep consistent with the other primary and secondary endpoints. Additionally, the ITT is moved to sensitivity analysis for the variables below:

- Binocular BCVA 45
- Binocular BCVA [redacted]
- Pupillometry

Imputation sensitivity analysis methods specified in the protocol will no longer be used. The following endpoints will no longer be analyzed by imputing missing data once as a success and once as a failure:

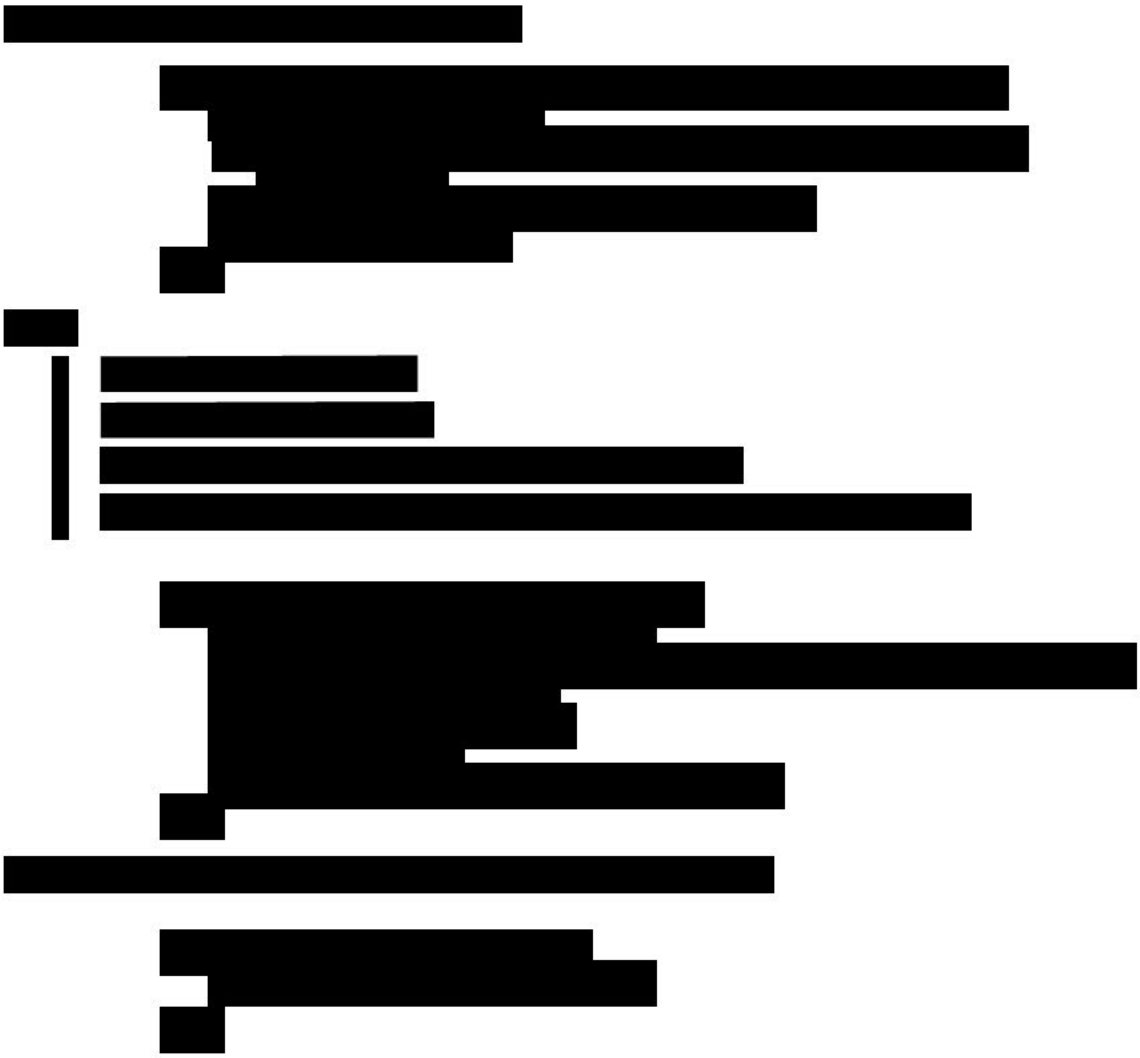
- Monocular BCVA 45 (includes primary endpoint)
- Monocular BCVA [redacted]

These changes from protocol-stated analyses are Sponsor driven for this exploratory phase 2b study and based on the interest of other subgroup and population analyses.

16.1 Sensitivity Analyses

Protocol specified sensitivity analyses may be performed as specified below on rare occasions if sensitivity analysis is needed.

Sensitivity analysis on the primary efficacy variable will be performed on the ITT population imputing missing data as failures. Additional sensitivity analyses such as control-based pattern mixture model multiple imputation or tipping point analysis may be performed. Control-based pattern mixture model and tipping point analyses both examine the assumption that missing data is missing at random. Example SAS code for the control-based pattern mixture model imputation method is shown here:



17. References

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583. (E9)

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320. (E3)

18. Revision History

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

19. Tables

Topline tables are bolded and italicized. Exploratory population tables from Section 8.4 are not included in this list.

Table Number	Title	Population
14.1.1.1	***Subject Dispositions I***	***All Randomized Subjects***
14.1.1.2	***Subject Dispositions II***	***All Randomized Subjects***
14.1.2	Major Protocol Deviations	All Randomized Subjects
14.1.3	***Demographics***	***ITT Population***
14.1.4.1	Ocular Medical History	ITT Population
14.1.4.2	Non-Ocular Medical History	ITT Population
14.1.5.1	Ocular Concomitant Medications	Safety Population
14.1.5.2	Non-Ocular Concomitant Medications	Safety Population
[redacted]		

14.3.1.1	***Overall Summary of Treatment-Emergent Adverse Events***	***Safety Population***
14.3.1.2	Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.3	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.4	Treatment-Related Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.5	Treatment-Related Non-Ocular Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.6	Expected Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.7	Unexpected Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.8	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
14.3.1.9	Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximal Severity	Safety Population

14.3.1.10	Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximal Severity	Safety Population
14.3.2.1	Monocular Best-Corrected Visual Acuity (logMAR) at 10 feet	Safety Population
14.3.2.3	Monocular Low-Luminance Best-Corrected Visual Acuity (logMAR)	Safety Population
14.3.2.2	Binocular Best-Corrected Visual Acuity (logMAR) at 10 feet	Safety Population
14.3.2.4	Binocular Low-Luminance Best-Corrected Visual Acuity (logMAR)	Safety Population
14.3.3.1	Slit Lamp Biomicroscopy	Safety Population
14.3.3.2	Slit Lamp Biomicroscopy – Shifts from Pre- to Post-Dose	Safety Population
14.3.4	Conjunctival Redness	Safety Population
14.3.5	Intraocular Pressure (mmHg)	Safety Population

20. Listings

Listing Number	Title	Population
16.1.7	Randomization Schedule	ITT Population
16.2.1	Subject Disposition	ITT Population
16.2.2	Protocol Deviations	ITT Population
16.2.3.1	Subjects Excluded from Analysis Populations	ITT Population
16.2.3.2	Subjects Included in Exploratory Populations	ITT Population
16.2.4.1	Demographics	ITT Population
16.2.4.2	Ocular Medical History	ITT Population
16.2.4.3	Non-Ocular Medical History	ITT Population
16.2.4.4	Prior and Concomitant Ocular Medications	ITT Population
16.2.4.5	Prior and Concomitant Non-Ocular Medications	ITT Population
16.2.4.6	Baseline Characteristics: Manifest Refraction, BCVA +1.50	ITT Population
16.2.4.7	Baseline Characteristics: Fluorescein Staining	ITT Population
16.2.4.8	Baseline Characteristics: Placebo Administration	ITT Population
16.2.5	Study Drug Administration	ITT Population
[redacted]		

16.2.7.1	All Adverse Events	Safety Population
16.2.7.2	Ocular Treatment-Emergent Adverse Events	Safety Population
16.2.7.3	Non-Ocular Treatment-Emergent Adverse Events	Safety Population
16.2.7.4	Expected Treatment-Emergent Adverse Events	Safety Population
16.2.7.5	Unexpected Treatment-Emergent Adverse Events	Safety Population
16.2.7.6	Treatment-Related Treatment-Emergent Adverse Events	Safety Population
16.2.7.7	Serious Treatment-Emergent Adverse Events	Safety Population
16.2.7.8	Treatment-Emergent Adverse Events Leading to Study Discontinuation	Safety Population
16.2.8.1	Best-Corrected Visual Acuity (logMAR) at 3 meters (10 feet)	Safety Population
16.2.8.2	Low-luminance Best-Corrected Distance Visual Acuity (logMAR)	Safety Population
16.2.8.3	Slit Lamp Biomicroscopy	Safety Population
16.2.8.4	Conjunctival Redness	Safety Population
16.2.8.5	Intraocular Pressure (mmHg)	Safety Population
16.2.8.6	Urine Pregnancy Test Results	All Female Subjects

21. Figures

Figures will be produced for BCVA (logMAR) and pupillometry at 45 cm for different study eye definitions and different subgroups in the mITT population. Other figures will be produced at Sponsor discretion.