STATISTICAL ANALYSIS PLAN

A MULTI-CENTER, DOUBLE-MASKED, PLACEBO-CONTROLLED, PHASE 3 STUDY OF THE SAFETY AND EFFICACY OF FIXED COMBINATION PHENYLEPHRINE 2.5% - TROPICAMIDE 1% OPHTHALMIC SOLUTION ADMINISTERED WITH A MICRODOSE DISPENSER FOR DILATION OF THE PUPIL (THE MIST-2 STUDY)

Sponsor: EYENOVIA, INC.
295 MADISON AVENUE, SUITE 2400
NEW YORK NY 10017
USA

Protocol Number: **EYN-MYD-TP-32 VERSION C**

Author: Brian Kilgallen, MS
Senior Principal Biostatistician
Statistics & Data Corporation

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A Multi-Center, Double-Masked, Placebo-Controlled, Phase 3 Study of the Safety and Efficacy of Fixed CombinationPhenylephrine 2.5% - Tropicamide 1% Ophthalmic Solution Administered with a Microdose Dispenser for Dilation of the Pupil (The MIST-2 Study)

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Statistical Analysis Plan Approval

Prepared by: _____ _____

Brian Kilgallen, MS — Date

Senior Principal Biostatistician

Statistics & Data Corporation

Reviewed by: _____ _____

Kirk Bateman, MS — Date

Senior Director, Biostatistics

Statistics & Data Corporation

Approved by: _____ _____

Ginger Clasby, MS — Date

Vice President, Clinical Operations

Eyenovia, Inc.

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List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
BCDVA	Best-Corrected Distance Visual Acuity
CF	Count Fingers
CI	Confidence Interval
CPRA	Cumulative Proportion of Responders Analysis
CRO	Contract Research Organization
eCRF	Eelectronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
GAT	Goldmann Applanation Tonometer
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOL	Intraocular Lens
IOP	Intraocular Pressure
ITT	Intent to Treat
logMAR	Logarithm of the Minimum Angle of Resolution
LP	Light Perception
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MiDD	Eyenovia MicroDose Dispenser
MNAR	Missing Not at Random
MPP	Modified Per Protocol
OD	Oculus Dexter (right eye)
OS	Oculus Sinister (left eye)
OU	Oculus Uterque (both eyes - in this protocol, OU does not connote simultaneous treatment/evaluation)
PDF	Portable Document Format
PLR	Pupillary Light Reflex
PP	Per Protocol
PT	Preferred Term
RDC	Remote Data Capture
RTF	Rich Text Format

SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SLE	Slit-Lamp Examination
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLR	Total Letters Read
UCDVA	Uncorrected Distance Visual Acuity
US	United States
VA	Visual Acuity
WHO DD	World Health Organization Drug Dictionary
µD	Microdose
µL	Microliter

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for Eyenovia protocol MYD-TP-32 version C, dated 20-November-2018.

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 and will be identified in the CSR.

2. Study Objectives

The primary objective of this study is to evaluate the safety and efficacy of Eyenovia's fixed combination of combination of phenylephrine 2.5 %-tropicamide 1% microdose ophthalmic solution administered with Eyenovia's microdose dispenser (MiDD) for dilation of the pupil as compared to placebo.

3. Study Variables

3.1 Primary Variable

The primary performance endpoint is mean change in pupil diameter at 35 minutes from the time of first treatment dose (T0) versus baseline, as measured by digital pupillometry in highly photopic conditions. The highly photopic condition will be established using a fully-charged transilluminator (muscle light) at the brightest setting. Baseline in the setting of the primary variable refers to the period-specific baseline on the day of treatment.

3.2 Exploratory Variables

Additional exploratory outcomes include:

- Proportion of eyes achieving pupil diameter of 6.0 mm or greater at 35 minutes
- Proportion of eyes achieving pupil diameter of 7.0 mm or greater at 35 minutes
- Mean change in pupil diameter at other timepoints (20, 50, 65, 80 120, and 180 minutes)
- Distribution of pupil diameters at 20, 35, 50, 65, 80, 120, and 180 minutes
- Time from baseline to maximal pupil dilation

These exploratory outcomes will also be measured using digital pupillometry in highly photopic conditions.

Although not explicitly listed as an efficacy variable within the protocol, pupillary light reflex (PLR) will be collected at each treatment visit and also summarized within the analysis.

3.3 Safety Variables

The safety variables include the following:

- Slit-lamp examination (SLE) findings
- Occurrence of adverse events (AE)
- Intraocular pressure (IOP) measured at 65 minutes post-administration
- Visual acuity (VA) changes

3.4 Statistical Hypotheses

The null and alternative hypotheses for comparison of Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution with placebo, are defined as follows:

H_0: The mean change per visit in pupil diameter at 35 minutes versus baseline, as measured by digital pupillometry in highly photopic conditions, is not different between Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution and placebo

H_A: The mean change per visit in pupil diameter at 35 minutes versus baseline, as measured by digital pupillometry in highly photopic conditions, is different between Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution and placebo

4. Study Design and Procedures

4.1 General Study Design

This trial is a double-masked, placebo-controlled, cross-over superiority study evaluating Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution versus placebo.

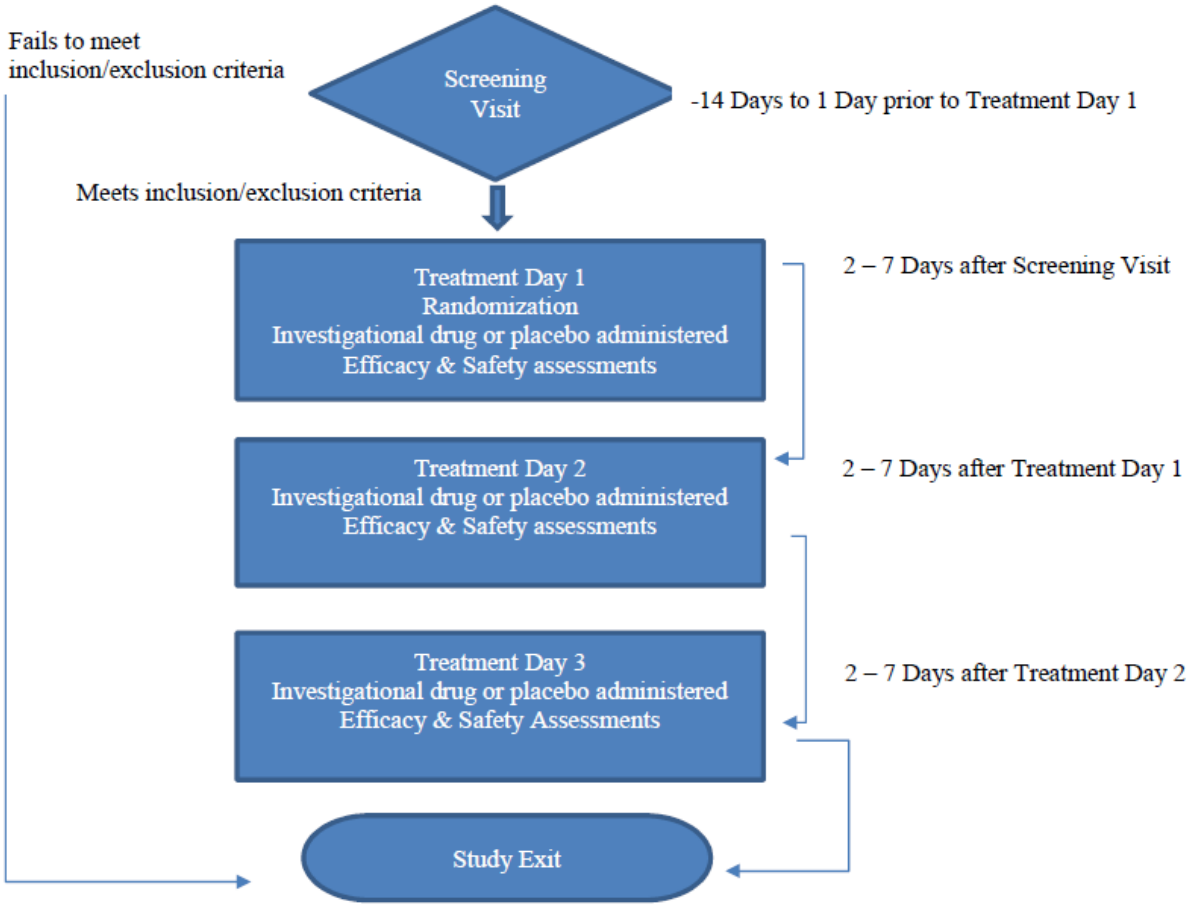
Volunteer participants from 2-3 United States (US)-based investigational sites will be screened for study eligibility during a Screening Visit and enrolled after signing the study-specific informed consent form (ICF). Subjects meeting all inclusion/exclusion criteria will be scheduled for 3 treatment visits, which must occur at least 2 days, but no more than 7 days apart. At each treatment visit, baseline measurements will be taken, then either study drug or placebo will be administered in both eyes in two instances approximately 5 minutes apart, after which efficacy and safety assessments will be performed at specific time intervals. The study drug administration schedule for subjects will be equally randomized across 2 sequences of 2 study treatments and 3 periods.

This study will be double-masked. There will be no differences in the presentation of study drug or placebo administered and all study personnel conducting ophthalmic assessments will be masked to treatment assignment. Study drug administration will be performed by at least 3 different trained personnel during the study.

4.2 Schedule of Visits and Assessments

Study visits include a Screening Visit, which must occur between 1 and 14 days prior to treatment; followed by Treatment Day 1, Treatment Day 2, and Treatment Day 3. Treatment visits must occur at least 2 days and not more than 7 days apart. The study visit schedule is presented in flow chart form in Figure 1.

Figure 1: Study Visit Flow Chart



The schedule of visits and assessments is provided below in Table 1.

Table 1: Schedule of Medication Administration and Examinations

Assessment/Procedure	Screening Visit (Day -14 to Day -1)	Treatment Visit 1 (Day 1)[1], Visit 2[1] and Visit 3[1]								
		Baseline[0]	Time 0[2]	Time 1 T0+20 min (± 2 min)	Time 2 T0+35 min (± 5 min)	Time 3 T0+50 min (± 5 min)	Time 4 T0+65 min (± 5 min)	Time 5 T0+80 min (± 10 min)	Time 6 T0+120 min (± 10 min)	Time 7 T0+180 min (± 10 min)
Informed consent	X									
Demographics	X									
Medical history	X									
Ocular history	X									
Prior/concomitant medication use	X									
Urine pregnancy test[3]	X	X[3]								
Manifest refraction (OU)	X									
BCDVA (OU)[4]	X	X								X
Study drug administration sequence determination (OU)		X								
Study drug administration (OU)			X							
Slit lamp biomicroscopy (OU)[5]	X	X								X
Van Herrick Angle Assessment (OU)[6]	X									
IOP (OU)[7]	X	X					X			
Pupil diameter assessment (OU)[8]	X	X		X	X	X	X	X	X	X
Pupillary light reflex (OU)		X			X		X			X
Study eligibility determination	X									
Dilated fundus exam (OU)	X									
AE assessment		X			X					X

[0] Baseline refers to evaluations made at each Treatment Day prior to study medication administration.
[1] Treatment Visit 1, 2 and 3 must be separated by at least 2 days; but may be up to 7 days apart to allow for scheduling flexibility.
[2] Time 0 starts at the point the first of two study medication doses is administered in second eye of the study subject
[3] A urine pregnancy test will be conducted in females of childbearing potential at the Screening Visit and at the last visit (Treatment Visit 3). The test may be administered at any time during the Screening and Treatment Day 3 Visits. If the subject terminates study participation prior to Treatment Visit 3, this test must be administered promptly at the time of termination.
[4] BCDVA to be measured using ETDRS methods. For younger pediatric subjects, UCDVA may be measured using age-appropriate methods per investigator's usual practice.
[5] For younger pediatric subjects who cannot cooperate with a traditional SLE, a portable slit lamp model may be used, if necessary.
[6] Performed as part of slit lamp examination.
[7] IOP to be measured using Goldmann Applanation tonometry. For younger pediatric subjects, IOP may be measured using age-appropriate methods per investigator's usual practice.
[8] Performed using Neuroptics pupillometer – VIP 300. For younger pediatric subjects for whom the pupillometer cannot be successfully used, a ruler or pupil gauge may be used. At Treatment Visit 3 - Time 7, subjects whose pupil diameter is larger than baseline may be followed at hourly intervals up to 6 hours after medication administration to gather additional data regarding the duration of study treatment effect.

Study visits will be referred to in all tables and listings. The following table shows the scheduled study visits and their planned timing for each study visit:

Scheduled Visit	Visit Timing
Screening	Day -14 to Day -1
Treatment Visit 1	Day 1
Treatment Visit 2	Day +3 to Day +8
Treatment Visit 3	Day +5 to Day +15

Subjects will receive Eyenovia fixed combination or placebo control at more than one treatment visit, and based on planned seqences of ABB/BAA, subjects will receive the same treatment at both Treatment Visits 2 and 3. For summaries by visit, a derived “all visits combined” will also be defined for analysis (as necessary) as follows:

- For continuous outcomes, the value for analysis will be defined as the single value if subjects have a given treatment once (eg, the value of treatment A at Visit 1 for subjects are randomized to sequence ABB), or based on the mean of the two values if the subject has received the treatment twice (eg the mean of values from Visits 2 and 3 for subjects are randomized to sequence BAA).
- For categorical and time to event outcomes, the value for analysis will be derived from the values at Visits 1 and 2, values form Visit 3 will not be considered.

In addition, time point number and planned study time will be included in tables and listings to enable reviewers to understand the assessment timing without referring to the protocol schedule for time points within a treatment visit. The following table shows the scheduled study time points, their planned study time, and the acceptable time window for each study visit:

Scheduled Time	Planned Study Time	Time Window
Time 0	Minute 0 (pre-treatment)	N/A
Time 1	20 Minutes Post-Dose	±2 minutes
Time 2	35 Minutes Post-Dose	±5 minutes
Time 3	50 Minutes Post-Dose	±5 minutes
Time 4	65 Minutes Post-Dose	±5 minutes
Time 5	80 Minutes Post-Dose	±10 minutes
Time 6	120 Minutes Post-Dose	±10minutes
Time 7	180 Minutes Post-Dose	±10 minutes

Data from unscheduled visits, unscheduled time points or unplanned repeat assessments will be included in the data listings. In general, these data will be excluded from the summary tables unless otherwise specified.

5. Study Treatments

Two study treatments administered by Eyenovia's MiDD will be evaluated in this study. The treatments evaluated are:

- Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution
- Placebo

5.1 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, subjects who provide verbal and written informed consent will be assigned a unique subject ID number. This subject ID will be used to identify subjects in all datasets and listings for the study.

Each eligible subject will be randomly assigned to receive one of 2 sequences of drug administration (ABB and BAA, where "A" is one of the two study treatments and "B" is the other) where 1 of the 2 study medications will be administered in both eyes at each of the 3 treatment visits. After Treatment Visit 3, each study subject will have been treated with both study medications, and one of the study treatments will have been received twice. The study drug administration schedule is equally distributed across 2 randomization sequences, balanced for carryover. This is the optimal three-period, two-group design (Jones and Kenward, 2015, section 3.5).

Subject treatment assignments will be prepared using a computer-generated randomization scheme by an independent statistician who is not involved in the day-to-day conduct of the study. Each individual subject's treatment assignment sequence will be provided in paper format contained in a sealed envelope. The study randomization scheme will be stratified by iris color. Note that if the study includes more than one site, the randomization will effectively be stratified by site in order to supply randomization envelopes to each site and maintain treatment sequence balance within each site.

5.2 Masking and Unmasking

The study drug administered will be masked to the study subject, the Investigator, and study staff administering the drug and/or performing clinical assessments. The Sponsor (or designee) involved in day-to-day study management will also be masked to treatment assignments.

This study will be double-masked so that there are no differences in presentation (Eyenovia's fixed combination mydriasis agent is formulated as a multi-dose microdroplet spray and placebo is also administrated as a microdroplet spray). To maintain masking of the study drug assignments for staff administering investigational product and/or performing clinical evaluations, study inventory storage and management will be performed by a pharmacy associated with the study site. The Sponsor, or designee, will ship study drug kits to each site pharmacy. Each kit will be labeled with the study protocol number, study drug code, product storage requirements, and the Caution – New Drug – Limited by Federal (US) Law to Investigational Use label.

For each treatment day, one or more new MiDD base units and cartridges containing the study drug(s) to be administered will be provided by the pharmacy for use. Each MiDD will appear the same except for a label indicating the study drug code. New MiDDs must be prepared by the pharmacy for use by site personnel on each treatment day. To maintain masking of site personnel, the MiDD containing each of the 3 study drugs will be labeled with the appropriate study randomization code, pharmacy preparation date and "use by" date, then forwarded to study drug administrator for use. The label containing the study drug code should not be revealed to individual subjects or otherwise disclosed in any way to personnel at the site who are performing post-drug administration ophthalmic assessments during the study.

Unmasking of treatment assignments can only occur in the event of a medical emergency or occurrence of an AE that, in the opinion of the Investigator, warrants such action. In the absence of medical need, the treatment assignment code will not be available to the Investigator, site staff, or Sponsor (or designee) representative involved in day-to-day study management until study completion and database lock.

In the event an Investigator considers unmasking of a subject's treatment assignment to be necessary, he/she must first contact the study Medical Monitor (or designee) to discuss the case. Only after consultation with the study Medical Monitor will the decision be made regarding unmasking. Treatment assignments will be revealed only for the subjects approved for unmasking, thus leaving masking on remaining subjects intact.

6. Sample Size and Power Considerations

Up to 90 subjects who have provided informed consent for study participation will be enrolled in the study. It is estimated that 65 subjects will be randomized in order to achieve the goal of having 54 subjects evaluable for the primary efficacy endpoint.

A sample size of 27 subjects per sequence, 54 total (the study has two sequences, ABB and BAA where A is the Eyenovia fixed combination, and B is the placebo control), will have 95% power to detect a difference in means of 0.5 mm, assuming a standard deviation of differences of 1.0 mm, using a paired t-test with a 0.05 two-sided significance level.

Power calculations are provided for additional exploratory outcomes below on an informational basis.

When the sample size is 54, a two-sided 95% exact confidence interval for a single proportion will have a half-width of 13.9% or less.

- For evaluation of the proportion of eyes achieving pupil diameter of 6.0 mm or greater at 35 minutes: if the observed proportion in the fixed combination treatment is 70.4% (38/54), then

the exact 95% confidence interval for the proportion will be [56.4%, 82.0%], with a half-width of 12.8%.

- For evaluation of the proportion of eyes achieving pupil diameter of 7.0 mm or greater at 35 minutes: if the observed proportion in the fixed combination treatment is 40.7% (22/54), then the exact 95% confidence interval for the proportion will be [27.6% 55.0%], with a half-width of 13.7%.

7. Data Preparation

All reported study data will be recorded on the electronic case report forms (eCRF) supplied by Statistics and Data Corporation, Incorporated (SDC). 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 the clinical contract research organization ([CRO], if applicable), in consultation with SDC.

All 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 All Enrolled Subjects

The all enrolled subjects population will include all subjects who have provided informed consent and entered the study, including screen failures.

8.2 Randomized Subjects

The randomized subjects population will include all subjects who were randomized to a treatment sequence.

8.3 Intent to Treat

The intent to treat (ITT) population will consist of all randomized subjects who received a dose of study medication. Subjects will be analyzed according to the planned sequence of treatments.

8.4 Per Protocol

The per protocol (PP) population will consist of all ITT subjects who completed all planned assessments (relevant to conducting the analysis of the primary performance endpoint) without major protocol violations. Subjects who have not received treatment at all three treatment visits will be excluded from the PP population.

Subjects to be excluded from the PP population will be selected prior to unmasking treatment assignment. Subjects will be analyzed according to the sequence of treatments received.

8.5 Modified Per Protocol

The modified per protocol (MPP) population is defined similarly to the PP population, except that classification will be made for each subject at the individual treatment visit level, rather than at the subject level. Unlike the PP population, subjects who only complete 1 or 2 of the 3 treatment visits may be included.

The MPP will consist of all ITT subjects who completed all planned assessments without major protocol violations for the given treatment visit. Subjects to be excluded from the MPP population will be selected prior to unmasking treatment assignment. Subjects will be analyzed according to the sequence of treatments received.

8.6 Safety

The safety population will consist of all ITT subjects. Subjects will be analyzed according to the sequence of treatments received.

9. General Statistical Considerations

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 individual eye unless otherwise indicated.

9.2 Missing or Inconclusive Data Handling

By definition, the PP population is limited to subjects who complete the study and completed all planned assessments, therefore there should not be missing data for the primary efficacy analysis as data from individual subjects are wholly included or excluded. In the event of missing data for sensitivity analyses of the primary efficacy variable, the SAS PROC MIXED procedure uses all available data to produce

maximum likelihood parameter estimates. In such a setting the missing observations are ignorable if data are missing at random (MAR).

Adverse events with unknown severity will be summarized as being severe, and adverse events with relationship to study drug not specified will be summarized as being related to study drug.

For all other variables, missing data will not be imputed, observed values will be presented.

9.3 Definition of Baseline

For all variables, the "pre-randomization" baseline value is defined as the last pre-treatment measurement taken prior to administration of study drug at Visit 1. Normally this will be the value obtained from the Visit 1 Baseline time point value, however for assessments collected at the Screening visit only (or if the value from Visit 1 Baseline is unavailable) the Screening visit value will be used.

For variables collected after dosing at each Treatment Visit (eg, pupil diameter assessment), a "period-dependent" baseline value is also defined as the last pre-treatment measurement taken prior to administration of study drug at that Visit (eg, Visit X Baseline time point, where X corresponds to Treatment Visit 1, 2, or 3). If Treatment Visits 2 or 3 are done but the baseline value is unavailable, the Baseline value will be imputed from previous treatment visit for analysis (eg, missing period-specific baseline value for Treatment Visit 2 would be imputed using the period-specific baseline value from Treatment Visit 1; missing period-specific baseline value for Treatment Visit 3 would be imputed using the period-specific baseline value from Treatment Visit 2).

Change from baseline will be calculated as follow-up measure minus pre-randomization baseline/period-dependent baseline value measure.

Analyses of changes from baseline will include the applicable baseline value (pre-randomziation or period-dependent) as a covariate in the statistical model, or will adjust for baseline in the case of categorical analyses, unless otherwise specified.

9.4 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum). Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional

decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Change from baseline will be calculated as follow-up visit (or follow-up time point) minus baseline.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999".

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

For analyses where a 'seed' is specified within SAS® in order to replicate results, the seed for final analysis will be based on the database lock date (eg, 20190101 if the study had locked on 01-JAN-2019).

9.5 Adjustments for Multiplicity

All time points for pupil diameter will be analyzed separately; however, only the 35-minute time point will support statistical inference.

As this study contains a single hypothesis being tested on a single endpoint with only two treatment groups, no adjustment for multiplicity is necessary.

10. Disposition of Subjects

Disposition of subjects will be summarized for all enrolled subjects. The total number of enrolled subjects with the number and percentage of not randomized subjects will be summarized. The reasons for screen failure will be displayed with the percentages calculated using total number of enrolled subjects as the denominator.

Disposition of subjects will also be summarized for all randomized subjects. The number of subjects in each of the analysis populations (ITT, PP, MPP, and Safety) will be displayed by treatment sequence. Study completion will be assessed in terms of completion of treatment visits and overall study completion. The number and percentage of subjects completing each treatment visit, completing the study, prematurely discontinuing from the study and the reasons for study discontinuation will be summarized by treatment sequence for all randomized subjects. A subject listing will be provided which includes the date and reason for premature study discontinuation.

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 and for all subjects.

The number and percentage of subjects with major protocol deviations will be summarized by category (eg, Informed Consent, Inclusion/Exclusion, etc.), treatment sequence and overall for all randomized subjects. The eCRF contains a pre-defined set of options for deviation category that is assigned by study site personnel, however, for consistency in reporting, sponsor-defined deviation categories will be determined by Eyenovia for use within the analysis during a review of all protocol deviations prior to database lock and unblinding. 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. A subject listing will be provided which includes the date of the deviation, the sponsor-defined deviation category, the deviation description and the classification of whether the deviation was judged to be major or minor.

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

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

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

Age (years) will be summarized, overall and by treatment sequence, using continuous descriptive statistics. Age will also be categorized using categories defined as < 17 years and ≥17 years, as well as based on observed quartiles in the actual data. 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

Iris color will be combined into categories defined as:

- Light: blue, green, hazel, gray
- Dark: brown, black

Any iris color values of “other” category will be allocated to the light or dark category in accordance with the stratum used for the study randomization.

The number and percentage of subjects will be presented, overall and by treatment sequence, for age category, sex, race, ethnicity,iris color, and dichotomoized iris color .

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

11.2 Pretreatment Variables

Pretreatment variables will be summarized for the ITT population.

Baseline best-corrected distance visual acuity (BCDVA) at the Screening visit, expressed in logarithm of the minimum angle of resolution (logMar) units, will be summarized for each eye, for all subjects (refer to Section 15.2 for details) and by treatment sequence using continuous descriptive statistics.

Manifest refraction is performed as a pre-BCDVA assessment at the Screening visit and will be summarized for each eye, for all subjects and by treatment sequence using continuous descriptive statistics. Manifest reaction results will be summarized within the baseline characteristics table and also listed.

Van Herrick angle assessment will be performed as part of slit lamp examination at the Screening Visit. The distribution of grades will be tabulated for each eye, for all subjects and by treatment sequence.

Using ophthalmoscopy, the fundus will be examined and evaluated by the Investigator to be either normal or abnormal at the Screening Visit. Results will be tabulated for each eye, for all subjects and by treatment sequence.

Urine pregnancy test results from the Screening Visit will be listed only.

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

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 (or higher). Medical History will be summarized for the ITT Population.

Ocular medical history is a subset of the overall medical history. Ocular medical history consists of those medical history records where the location field on the medical history eCRF is marked as location being oculus dexter (OD – right eye), oculus sinister (OS – left eye) or oculus uterque (OU – both eyes).

Non-ocular medical history will be summarized using discrete summary statistics and presented across all subjects at the subject and event 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 Drug Dictionary (WHO DD), Enhanced B3, September 2018 (or higher), and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] Level 4 classification) and preferred name. If the ATC Level 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (eg, multivitamins) then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of "Uncoded."

Prior medications are defined as those medications those with an end date before the first treatment (Visit 1) in the sequence. Concomitant medications for each treatment are defined as those that are in use at the start of study medication administration or started after dosing but initiation was prior to the next treatment in the sequence or study completion/discontinuation. With this definition, it should be noted it is possible for a medication to be concomitant for more than one treatment group.

Concomitant medications will be summarized for the Safety Population, and will be summarized separately for ocular and non-ocular medications. Ocular medications are a subset of the overall medications, and consist of those medication records where the location field on the eCRF is marked as location being OD, OS, or OU.

Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than 1 medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group.

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

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

As this study involves in-office administrations of each study drug, administered to both eyes (OU) across two separate instances approximately 5 minutes apart, dosing compliance will not be summarized. A subject listing of exposure will contain dosing times for each eye.

13.2 Treatment Exposure

Treatment exposure will be summarized using the Safety Population.

The number and percent of subjects receiving their administration at each of the 3 treatment visits in this study will be tabulated along with the number of individual doses received per treatment visit. The

number and percent of subjects receiving at least one individual dose at all 3 treatment visits, and the number and percent of subjects receiving both individual doses of all 3 treatment visits will also be summarized.

A subject listing of treatment exposure will also be produced.

14. Efficacy Analyses

14.1 Primary Analysis

The primary performance endpoint is mean change per visit in pupil diameter at 35 minutes versus period-dependent baseline, as measured by digital pupillometry in highly photopic conditions. The highly photopic condition will be established using a fully-charged transilluminator (muscle light) at the brightest setting.

Pupil diameter in adults will be measured using Neuroptic pupillometer – VIP 300. For younger subjects for whom the pupillometer cannot be successfully used, a ruler or pupil gauge may be used, with each measurement repeated 2-3 times for optimal accuracy. The pupil diameter value used for analysis will be either the mean (if 2 measurements are taken) or the median (if 3 measurements are taken) of the repeated measurements in each eye.

Primary efficacy analysis will be conducted on the PP population.

The ABB/BAA crossover design used in this study allows for within-subject (i.e. within-eye) estimates of both treatment effects (A and B) and carryover effects (AA, AB, BA, BB). Thus, there is no need to include random effects for subject or eye in the analysis model, we will use fixed effects ANOVA to analyze these data (Jones and Kenward, 2015, section 5.2) and tests will be based on within-eye variances. A SAS REPEATED statement will be used to adjust for correlation between fellow eyes. Hypothesis tests will be based on confidence intervals produced by the SAS LSMEANS option for the pairwise differences between treatment.

This study has both a “pre-randomization” covariate (iris color) and a “period-dependent” covariate (baseline pupil measurement) as discussed in Jones and Kenward (2015, section 5.4.4). We are assuming that the time between visits is sufficiently long that the baseline pupil measurement at each visit is unaffected by carryover.

Comparisons among treatments on mean pupil diameter will be by a fixed-effects analysis of variance model. The model will contain an effect due to subject, eye, period (1, 2, or 3), direct effect of treatment, first order carryover, period-dependent baseline pupil diameter, and iris color (dark vs light). Proc MIXED coding in SAS would be:

```
proc mixed;
        class subject eye period treatment carry iris;
```

```
      model deltaPD = subject*eye period treatment carry baselinePD iris / s;
      repeated eye / subject = subject type=cs;
      lsmeans treatment carry/pdiff cl;
run;
```

where

- deltaPD=change from period-dependent baseline in pupil diameter at Time 2 (T0 + 35 minutes)
- eye=OD, OS
- period=1, 2, or 3
- treatment:
  - Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution
  - Placebo
- carry=first order carryover. An indicator variable will be constructed containing the treatment the subject received in the previous period (set to A or B for Periods 2 and 3, and arbitrary value for Period 1, three levels total).
- baselinePD=period-dependent baseline pupil diameter
- iris=iris color (dark, light)

A compound symmetry covariance structure will be used for the model. If the model fails to converge, covariates will be removed one by one until the model converges. Iris color, carryover effect and period-dependent baseline pupil diameter are the candidate variables to be removed, in that order.

Carryover effect included within the model will be tested to assess the carryover assumption.

All time points for pupil diameter will be analyzed separately; however, only the 35-minute time point will support statistical inference. Success is defined as the fixed combination (provided by the LSMEANS statement) being statistically significantly better than placebo.

The SAS® PROC MIXED procedure uses all available data to produce maximum likelihood parameter estimates, in such a setting the missing observations are ignorable if data are MAR.

The primary analysis described above will be rerun on the MPP population as a sensitivity analysis.

As a further sensitivity analysis, multiple imputation based on reference-based multiple imputation will be used to impute missing data at the 35-minute time point based on a missing not at random (MNAR) assumption. Since the PP population contains only subjects with non-missing values, this analysis will be conducted using the ITT population, which may contain subjects who have only partially available information. Placebo treatment will serve as reference group for this approach. Each subject will be included for all three treatment visits for this approach, regardless of how many treatment visits were actually completed.

SAS code for the multiple imputation is as follows:

```
proc mi out=outmi nimpute=20;
  class trt period eye iris;
  monotone Reg(PD_35 = period eye iris baselinePD);
  mnar model(PD_35/ modelobs=(trt='Placebo'));
```

```
 var period eye iris baselinePD PD_35;
run;
```

The resulting dataset, OUTMI, will then rerun using the model previously described for primary analysis, with an additional 'by _imputation' statement included, and the least squares means differences from this will be combined using Proc MIANALYZE.

14.2 Secondary Analyses

The PP population will be used for the secondary analyses. Missing data will not be imputed. The secondary analysis variables will be presented in subject listings by visit.

14.2.1 Pupil Diameter at 35 Minutes Responder Analysis

The proportion of eyes achieving pupil diameter of 6.0 mm or greater at 35 minutes post-dose will be summarized by eye, by treatment group and visit (including across all visits) with descriptive statistics.

Comparison of the fixed combination of phenylephrine 2.5%-tropicamide 1% microdose ophthalmic solution administered against placebo will be conducted with a generalized estimating equation (GEE) model for binomial outcome, implemented in SAS as follows:

```
proc genmod descending;
  class subject eye period treatment carry iris;
  model resp = period treatment carry baselinePD iris / link=logit dist=binomial;
  repeated subject = subject(eye)/ type=cs;
  lsmeans treatment / oddsratio diff cl;
run;
```

where

- resp=response; pupil diameter 6.0mm or greater at 35 minutes post-dose
- eye=OD, OS
- period=1, 2, or 3
- treatment:
  - Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution
  - Placebo
- carry=first order carryover. An indicator variable will be constructed containing the treatment the subject received in the previous period (set to A or B for Periods 2 and 3, and arbitrary value for Period 1, three levels total).
- baselinePD=baseline pupil diameter
- iris=iris color (dark, light)

The previously described analysis will be repeated using an alternate cutoff of 7.0mm.

In addition, a cumulative proportion of responders analysis (CPRA) will be created to graphically display the proportions of subjects with a pupil diameter at 35 minutes post-dose over the entire range of possible pupil diameter cut-offs (Farrar 2006), with separate lines for each treatment, combined visit,eye combination.

14.2.2 Pupil Diameter at All Time points

Pupil diameter, including actual value as well as change from period-dependent Baseline, will be summarized for each time point of treatment visits (20, 35, 50, 65, 80, 120, and 180 minutes) with descriptive statistics for continuous endpoint by treatment, by visit (including across all visits), and eye, and displayed graphically using mean and standard error. Missing values will not be imputed for these summaries. As pupil diameter at 35 minutes post-dose is the primary endpoint in the study, additional analyses of that time point are described in Section 14.1.

The distribution of pupil diameters at each time point of treatment visits will be summarized by treatment group in a summary table, as well as graphically.

14.2.3 Maximal Pupil Dilation

Maximal pupil dilation is defined as the maximum pupil value after study drug is administered to both eyes, and time to maximal pupil dilation is the time point corresponding to first occurrence of this maximal value. For this analysis, the actual clock time will be used to determine number of minutes from study drug administration rather than the nominal time point value. In order to exclude increases in pupil diameter which might reasonably be attributed to measurement variability, increases less than 1.0mm will be excluded for consideration. In other words, maximal pupil dilation will be based on the subset of measurements which are 1.0mm or greater.

Time to maximal pupil dilation will be analyzed based on Kaplan-Meier approach by treatment, and visit (including across all visits). Each subject will be considered to have an event at the time where maximal (period-dependent) post-Baseline pupil dilation with 1.0mm or greater increase from BL was first observed. Subjects who do not have any (period-dependent) post-Baseline increases in pupil diameter in either eye will be censored at the time of the last non-missing pupil measurement. Subjects who discontinue prior to completing all post-dose assessments will be evaluated based on the assessments which are available.

If all subjects experience an increase from period-dependent Baseline (ie, there are no censored observations), this analysis may be replaced by a summary of descriptive statistics for categorical outcome.

14.2.4 Pupillary Light Reflex

Pupillary light reflex (PLR) will be evaluated using a fully-charged transillumator, or muscle light. The response will be recorded on a scale ranging from 0 (non-responsive) to 3 (brisk).

The responses at each time point will be summarized by eye using counts and percentages in each response category for each treatment group at each visit (including across all visits) and time point.

Shifts from period-dependent baseline value to worst (period-dependent) post-Baseline response will also be tabulated by treatment group.

Pairwise comparisons of the responses at the 35 minute post-dose time point for the fixed combination of phenylephrine 2.5%-tropicamide 1% microdose ophthalmic solution administered against its individual components will be conducted with a generalized estimating equation (GEE) model for ordinal multinomial outcome, implemented in SAS as follows:

```
proc genmod descending;
  class subject eye period treatment carry iris;
  model resp = period treatment carry baselinePLR iris / dist=multinomial aggregate=treatment;
  repeated subject = subject(eye);
  lsmeans treatment / oddsratio diff cl;
run;
```

where

- resp=pupillary light response category (ordered categories as: non-responsive; minimally responsive; moderately responsive; and brisk) at 35 minutes post-dose
- eye=OD, OS
- period=1, 2, or 3
- treatment:
  - Eyenovia's fixed combination phenylephrine 2.5%-tropicamide 1% ophthalmic solution
  - Placebo
- carry=first order carryover. An indicator variable will be constructed containing the treatment the subject received in the previous period (set to A or B for Periods 2 and 3, and arbitrary value for Period 1, three levels total).
- baselinePLR=baseline pupillary light response category
- iris=iris color (dark, light)

A subject listing of PLR will also be produced.

15. Safety Analyses

All safety analyses will be conducted using the Safety Population.

15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the first dose of study drug, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of study drug will also be considered a new AE. The AE reporting period ends upon study exit. Study drug includes refers to Eyenovia's fixed combination or placebo which are administered by Eyenovia's MiDD (refer to Section 4.1) given during any stage of the study. All AEs will be coded using MedDRA, version 21.0 (or higher) Treatment group for the AE will be determined as the most recent treatment received by the subject. For example, an AE reported after dosing at Treatment

Visit 1 but prior to first dose at Treatment Visit 2 would be allocated to the treatment group given at Treatment Visit 1.

Summaries of AEs will be generally presented by treatment, where AE data from periods 2 and 3 of this crossover design will be combined since they will correspond to the same treatment (due to planned sequences of ABB and BAA).

Treatment-emergent adverse events (TEAE) are defined as any event that occurs or worsens on or after the day and time of first treatment is initiated. Only TEAEs are captured as AEs in this study, AEs with onset prior to first administration of study medication are recorded as Medical History for the subject. In the unexpected case that there are a dverse events recorded in the eCRF which began prior to treatment, these events will not be included in the summary tables but will be included in the AE data listings.

Ocular AEs are a subset of AEs, and are identified as those AEs where the location field on the AE eCRF is marked as OD, OS, or OU. Since both eyes are treated in this study with study drug, summaries of ocular events will include AEs with onset in either eye.

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

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 group at the subject and event level by SOC and PT. Due to the fact that both eyes are treated with study drug, ocular TEAEs will be summarized in a similar manner (eg, separate summaries per eye are not planned). 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.

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

- Ocular TEAEs
- Non-ocular TEAEs
- Treatment-related ocular TEAEs

- Treatment-related non-ocular TEAEs
- Expected TEAEs
- Unexpected TEAEs
- Serious TEAEs
- Serious ocular TEAEs

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Subject is aware of sign or symptom, but it is easily tolerated
- *Moderate:* Subject experiences discomfort enough to cause interference with usual activity.
- *Severe*: AE is incapacitating to subject, causing inability to work or do usual activity.

Summaries of TEAEs by maximal severity will be presented for ocular AEs and non-ocular AEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximal severity.

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

- *Not Related*: Evidence exists that the AE has a cause other than the study drug (e.g. pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.
- *Possibly Related*: A temporal relationship exists between event onset and administration of study drug. Although the AE may appear unlikely to be related to the study drug, it cannot be ruled out with certainty; and/or the event cannot be readily explained by the subject's clinical state or concomitant therapies.
- *Probably Related*: A temporal relationship exists between the event onset and administration of study drug; it appears with some degree of certainty to be related based on known therapeutic and pharmacologic actions of the study drug. It cannot be readily explained by the subject's clinical state or concomitant therapies.
- *Definitely Related*: Strong evidence exists that the study drug caused the AE. There is a temporal relationship between the event onset and administration of the study drug. There is strong therapeutic and pharmacologic evidence that the event was caused by the study drug. The subject's clinical state and concomitant therapies have been ruled out as a cause

For analysis purposes, AEs considered related to study drug (per Investigator) will include AEs with relationship equal to possibly related, probably related, or definitely related. Not related AEs will include AEs with relationship equal to "not related". In the event relationship is not specified, the event will be

assumed to be related. Summaries of related TEAEs will be presented for ocular AEs and non-ocular AEs separately.

Serious ocular AEs include, but are not limited to:

- A decrease in BCDVA of ≥ 30 total letters read (TLR) or ≥ 0.6 logMAR from the most recent previous measurement of BCDVA
- A decrease in BCDVA to light perception (LP) or worse that lasts > 1 hour
- An ocular event that, in the opinion of the investigator, requires medical or surgical intervention to prevent permanent loss of sight
- Severe intraocular inflammation; e.g., 4+ anterior chamber cell/flare or 4+ vitritis
- Corneal decompensation
- Retinal tear or detachment
- Central or branch retinal vein occlusion

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation. The Investigator will initially classify the expectedness of the AE on the eCRF, but the final classification is subject to the Medical Monitor's determination.

Separate listings of AEs will be produced to list all AEs, AEs leading to study discontinuation, and serious AEs.

15.2 Visual Acuity

Visual acuity measurements are done per eye, and assessed at Screening and at treatment visits at period-dependent Baseline and Time 7 (T0 + 180 minutes) time points. The pre-treatment evaluation of VA should be performed before the subject's pupils have been dilated. Distance VA measurements should be obtained at a testing distance of 4 meters by a physician or trained technician using Early Treatment of Diabetic Retinopathy Study (ETDRS) lighted charts.

Adult subjects' BCDVA will be determined using subjective manifest refraction. The subject should be seated so that the distance from the subject's eyes to the ETDRS chart (Chart 1 for right eye and Chart 2 for left eye) is 4 meters (157.5 inches) at a distance of 4 meters. Visual acuity in adults will be expressed in logMAR units, however, logMAR units may not be available for all pediatric methods. For

younger pediatric subjects who are unable to complete ETDRS testing, however, uncorrected distance visual acuity (UCDVA) should be measured using age-appropriate methods per the Investigator's usual practice.

The observed and change from period-dependent baseline in BCDVA will be summarized for adults by eye and by treatment and visit (including across all visits) using continuous descriptive summary statistics.

The number and proportion of subjects who are able to perform ETDRS testing with a decrease from period-dependent baseline value in BCDVA of ≥ 30 total letters read (TLR) or ≥ 0.6 logMAR, and decreases in BCDVA to light perception (LP) will be summarized by treatment, visit and time point.

Subject listings of visual acuity will also be produced, separately for adults and pediatric subjects who are unable to perform ETDRS testing. The listing for adults will include a variable that indicates if a subject had a visual acuity change from baseline of ≥0.6 on the logMAR scale.

For younger pediatric subjects who are unable to complete ETDRS testing, visual acuity will only be listed because of the variable testing methods appropriate for this subgroup.

15.3 Slit Lamp Biomicroscopy Examination

A slit lamp biomicroscopy examination of the anterior vitreous, cornea, conjunctiva, anterior chamber, iris, lens, lid, and sclera will be conducted on both eyes at the Screening Visit, and during treatment visits at the period-dependent Baseline and Time 7 (T0+180 minutes) time points. For pediatric subjects who cannot cooperate with a traditional SLE, a portable slit lamp model may be used according to the Investigator's usual practice. The individual assessments will be graded as either normal/abnormal, or as none/mild/moderate/severe. Grading of each assessment is described in Section 10 of the protocol.

The results (grade, or normal/abnormal classification, as applicable) of the assessment of each structure will be summarized using counts and percentages for each treatment group at each visit (including across all visits) and time point for each eye. Shift tables for the slit lamp biomicroscopy parameters will also be provided comparing the Time 7 (T0+180 minutes) result (grade, or normal/abnormal classification, as applicable) to baseline.

A subject listing of the slit lamp biomicroscopy parameters will also be produced, results obtained from portable slit lamp model will be listed separately.

15.4 Intraocular Pressure

After completion of slit lamp biomicroscopy, local anesthetic will be applied to facilitate intraocular pressure (IOP) measurements with the Goldmann Applanation Tonometer (GAT).

For adults who are able to undergo GAT, two consecutive IOP measurements of each eye must be obtained. If the 2 measurements differ by more than 2 mmHg, a third measurement must be obtained. IOP will be analyzed as the mean of these 2 measurements, or as the median of the 3 measurements. For pediatric subjects, IOP should be measured using age-appropriate methods per the Investigator's usual practice.

IOP will be collected at the Screening Visit, and during treatment visits at the period-dependent Baseline and Time 4 (T0+65 minutes) time points.

The IOP values and changes from period-dependent baseline for each eye will be summarized for adults using continuous descriptive statistics for each eye by visit (including across all visits))and time point, for each treatment group. A subject listing of IOP in adults will also be produced. This listing will include a variable that indicates if a subject had an IOP increase from period-dependent baseline of ≥6 or ≥10 mmHg.

For younger pediatric subjects who are unable to undergo GAT, intraocular pressure will only be listed because of the variable testing methods appropriate for this subgroup.

16. Pharmacokinetic Analyses

Not applicable.

17. Pharmacodynamic Analyses

Not applicable.

18. Quality of Life Analyses

Not applicable.

19. Interim Analyses

No interim analyses are planned for this study.

20. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

21. References

Farrar J.T., Dworkin R.H., Max M.B. Use of the Cumulative Proportion of Responders Analysis Graph to Present Pain Data Over a Range of Cut-Off Points: Making Clinical Trial Data More Understandable. Journal of Pain and Symptom Management. 2006; 31(4): 369-377.

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)

22. Revision History

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

23. Tables

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

Table Number	Title	Population
14.1.1.1	**Subject Disposition**	**Enrolled Subjects**
14.1.1.2	Subject DispositionReason for Screen Failure	Enrolled Randomized Subjects
14.1.2	Major Protocol Deviations	Randomized Subjects
14.1.3.1	**Demographics**	**ITT**
14.1.3.2	Demographics	Per Protocol
14.1.4	Baseline Characteristics	ITT
14.1.5.1	Ocular Medical History	ITT
14.1.5.2	Non-Ocular Medical History	ITT
14.1.6.1	Ocular Concomitant Medications	ITT
14.1.6.2	Non-Ocular Concomitant Medications	ITT
14.2.1.1	**Change from Baseline in Pupil Diameter at 35 Minutes – Fixed Effects ANOVA**	**Per Protocol**
14.2.1.2	**Change from Baseline in Pupil Diameter at 35 Minutes – Fixed Effects ANOVA**	**Modified Per Protocol**
14.2.1.3	**Change from Baseline in Pupil Diameter at 35 Minutes – Reference-Based Multiple Imputation**	**ITT**
14.2.2.1	**Proportion of Eyes Achieving Pupil Diameter of 6.0mm or Greater at 35 minutes Post-Dose**	**Per Protocol**
14.2.2.2	**Proportion of Eyes Achieving Pupil Diameter of 7.0mm or Greater at 35 minutes Post-Dose**	**Per Protocol**
14.2.3	**Change from Baseline in Pupil Diameter by Time Point – Fixed Effects ANOVA**	**Per Protocol**
14.2.4	**Distribution of Pupil Diameters by Time Point**	**Per Protocol**
14.2.5	**Time to Maximal Pupil Dilation with ≥1.0mm Increase from Baseline**	**Per Protocol**
14.2.6.1	Pupillary Light Reflex Responses by Time Point	Per Protocol
14.2.6.2	Pupillary Light Reflex Shift from Pre-Dose to Post-Dose	Per Protocol
14.3.1	**Overall Summary of TEAEs**	**Safety Population**
14.3.2.1	Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
14.3.2.2	Non-Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
14.3.3.1	Treatment Related Ocular TEAEs by System Organ Class and Preferred Term	Safety Population

Table Number	Title	Population
14.3.3.2	Treatment Related Non-Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
14.3.4.1	Expected TEAEs by System Organ Class and Preferred Term	Safety Population
14.3.4.2	Unexpected TEAEs by System Organ Class and Preferred Term	Safety Population
14.3.5.1	Serious Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
14.3.5.2	Serious Non-Ocular TEAEs by System Organ Class and Preferred Term	Safety Population
14.3.6.1	Ocular TEAEs by System Organ Class and Preferred Term and Maximum Severity	Safety Population
14.3.6.2	Non-Ocular TEAEs by System Organ Class and Preferred Term and Maximum Severity	Safety Population
14.3.7	Best-Corrected Distance Visual Acuity (logMAR) at 4 Meters	Safety Population –Subjects Able to Undergo ETDRS Evaluation
14.3.8.1	Slit Lamp Biomicroscopy	Safety Population
14.3.8.2	Slit Lamp Biomicroscopy Shifts from Pre- to Post-Dose	Safety Population
14.3.9	Intraocular Pressure	Safety Population –Subjects Who Are Able to Complete GAT
14.3.10	Treatment Exposure Across All Visits	Safety Population

24. Listings

Listing Number	Title	Population
16.1.7	Randomization Schedule	Randomized Subjects
16.2.1	Subject Disposition	Enrolled Subjects
16.2.2	Protocol Deviations	Randomized Subjects
16.2.3.1	Inclusion/Exclusion Criteria Subjects Excluded from Analysis Populations	Enrolled Subjects Randomized Subjects
16.2.3.2	Subjects Excluded from Analysis Populations	Enrolled Subjects
16.2.4.1	Demographics	Randomized Subjects
16.2.4.2	Baseline Characteristics	Randomized Subjects
16.2.4.3	Ocular Medical History	Randomized Subjects
16.2.4.4	Non-Ocular Medical History	Randomized Subjects
16.2.4.5	Prior and Concomitant Ocular Medications	Randomized Subjects
16.2.4.6	Prior and Concomitant Non-Ocular Medications	Randomized Subjects
16.2.5	Study Drug Administration	Safety

Listing Number	Title	Population
16.2.6.1	Pupillometry (mm)	Randomized Subjects
16.2.7.1	All Adverse Events	Randomized Subjects
16.2.7.2	Ocular Adverse Events	Randomized Subjects
16.2.7.3	Non-Ocular Adverse Events	Randomized Subjects
16.2.7.4	Adverse Events Leading to Study Discontinuation	Randomized Subjects
16.2.7.5	Serious Adverse Events	Randomized Subjects
16.2.8.1	Best-Corrected-Distance Visual Acuity (BCDVA) at 4 Meters using ETDRS Chart (logMAR)	Randomized Subjects Able to Undergo ETDRS Evaluation
16.2.8.2	Uncorrected Distance Visual Acuity	Randomized Subjects Unable to Perform ETDRS Evaluation
16.2.8.3	Slit Lamp Biomicroscopy – Traditional SLE	Randomized Subjects
16.2.8.4	Slit Lamp Biomicroscopy – Portable Model	Randomized Subjects
16.2.8.5	Intraocular Pressure (IOP) Using Goldmann Applanation Tonometer (GAT)	Randomized Subjects Able to Complete GAT
16.2.8.6	Intraocular Pressure (IOP)	Randomized Subjects Unable to Complete GAT
16.2.8.7	Pupillary Light Reflex (PLR)	Randomized Subjects

25. Figures

Figure Number	Title	Population
14.2.1.1	Change from Baseline in Pupil Diameter by Eye, Treatment and Time Point	Per Protocol
14.2.1.2	Change from Baseline in Pupil Diameter by Eye, Treatment and Time Point	Modified Per Protocol
14.2.1.1	Pupil Diameter by Eye, Treatment and Time Point	Per Protocol
14.2.1.3	Distribution of Pupil Diameters by Eye, Treatment and Time Points	Per Protocol
14.2.2	Cumulative Proportion of Responders Analysis of Pupil Diameter at 35 Minutes Post-Dose	Per Protocol
14.2.3	Time to Maximal Pupil Dilation with ≥1.0mm Increase from Baseline	Per Protocol