SUMMITANALYTICAL	**CONFIDENTIAL**

Ocuphire Pharma, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Title:	Randomized, Parallel-Arm, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) to Reverse Pharmacologically Induced Mydriasis in Healthy Pediatric Subjects
Study Number:	OPI-NYXRMP-303 (MIRA-4)
Phase:	Phase 3
Sponsor:	Ocuphire Pharma, Inc. [redacted]
Author:	Summit Analytical, LLC [redacted]
SAP Date:	2022-04-13
Status:	FINAL V1.0

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation/Term	Definition
ADaM	Analysis Data Model
AE	adverse event
ANCOVA	analysis of covariance
ARP	All Randomized Population
ATC	Anatomical Therapeutic Chemical
BCDVA	best-corrected distance visual acuity
BP	blood pressure
CCLRU	Cornea and Contact Lens Research Unit
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CRF	case report form
CSR	clinical study report
DD	Drug Dictionary
HR	heart rate
ITT	Intention-to-treat
logMAR	logarithm of the minimum angle of resolution
LSM	least squares mean
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
Nyxol	Phentolamine Mesylate Ophthalmic Solution 1% (Nyxol®)
OD	right eye
OR	odds ratio
OS	left eye
PD	pupil diameter
PP	Per Protocol
PREA	Pediatric Research Equity Act
PT	preferred term
SAE	serious averse event
SAP	Statistical Analysis Plan

Abbreviation/Term	Definition
SDTM	Study Data Tabulation Model
SE	standard error
SOC	system organ class
SP	Safety Population
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
VA	visual acuity
WHO	World Health Organization

3. INTRODUCTION

3.1. Preface

This document presents a statistical analysis plan (SAP) for Ocuphire Pharma, Inc. Protocol OPI-NYXRMP-303 (MIRA-4) (*Randomized, Parallel-Arm, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Nyxol [0.75% Phentolamine Ophthalmic Solution] to Reverse Pharmacologically Induced Mydriasis in Healthy Pediatric Subjects*).

Reference materials for this statistical plan include the protocol OPI-NYXRMP-303 (26OCT2021) and Case Report Forms (CRFs; Version 03DEC2021).

The SAP described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to unmasking of any study data.

For the reasons stated here, the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan.

3.2. Purpose of Analyses

The MIRA-4 study is a randomized, parallel arm, double-masked, placebo-controlled study of the safety and efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) to reverse pharmacologically-induced mydriasis in healthy pediatric subjects.

The Sponsor intends to use this study to evaluate Nyxol in pediatric subjects aged 3 to 11 for the indication “the treatment of pharmacologically induced mydriasis produced by adrenergic (phenylephrine) or parasympatholytic (tropicamide) agents, or a combination thereof.”

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final CSR. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the CSR but will be fully detailed in the document containing the additional analyses.

3.3. Summary of Statistical Analysis Changes to the Protocol

The efficacy analyses described in the protocol included several factors in the modeling, including mydriatic agent and age group. These factors have been removed from the efficacy analysis due to small sample sizes. As a result, the sensitivity analysis, which is an analysis of the primary endpoint without mydriatic agent and age group in the model, is no longer required as a separate analysis. Also, a hierarchical analysis was added to formally test a family of efficacy endpoints. Otherwise, the analyses described in this analysis plan are consistent with the analyses described in the study protocol.

4. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints defined in the protocol include safety and efficacy endpoints. Objectives and pre-specified endpoints are as follows:

4.1. Study Objectives

The objectives of this study are as follows:

- To evaluate the safety of Nyxol in pediatric subjects
- To evaluate the efficacy of Nyxol to expedite the reversal of pharmacologically induced mydriasis in pediatric subjects

4.2. Study Endpoints

Efficacy endpoints will be analyzed by study eye and fellow eye and will include:

- Percentage of subjects returning to ≤ 0.2 mm from baseline (-1 hour) photopic **pupil diameter (PD)** at each remaining time point (
- Change (in mm) in photopic **PD** from max pupil dilation (0 minutes) at each time point
- Time (hours) to return to ≤ 0.2 mm from baseline (-1 hour) photopic PD (**time-savings analysis**)

Efficacy measurements:

- Pupil diameter will be measured with a pupillometer (mm) or other similar measurement

Safety endpoints will include:

- Change from baseline (-1 hour) in **conjunctival hyperemia** grading for the study eye and fellow eye
- Change from baseline (-1 hour) in **BCDVA** at 0 minutes, 90 minutes, 3 hours, and 24 hours for the study eye and fellow eye
- Change from baseline (-1 hour) in **vital signs (HR and BP)** at 3 hours and 24 hours

Safety measurements:

- Conjunctival hyperemia will be assessed visually with

- Best-corrected distance visual acuity will be measured in photopic conditions by a standard [redacted]. For subjects who are unable to read the letters on a standard ETDRS chart, the Patti Pics Series ETDRS chart will be used (Appendix 3 of the protocol)

5. STUDY METHODS

5.1. General Study Design and Plan

This is a randomized, parallel-arm, double-masked, placebo-controlled study in approximately 20 to 30 randomized pediatric subjects evaluating the safety and efficacy of Nyxol in pediatric subjects with pharmacologically induced mydriasis. Pediatric subjects will be recruited for the study into 2 age groups as follows:

- 3 to 5 years of age: 10 subjects
- 6 to 11 years of age: 10 subjects

In this young study population, it is anticipated that some randomized subjects may withdraw.

Following the successful completion of screening, each subject will be randomized to unmasked mydriatic agent and masked treatment. Treatment randomization will be 1:1 (Nyxol or placebo [vehicle]) and will be stratified 1:1 by subject age group (3–5 years of age: 6–11 years of age). Mydriatic agent randomization will be 3:1:1 (phenylephrine: tropicamide: Paremyd, respectively). Approximately 60% of the randomized subjects will receive 1 drop [redacted] (12 subjects), approximately 20% will receive 1 drop of 1% tropicamide OU [redacted] (4 subjects), and approximately 20% will receive [redacted] (4 subjects).

Subjects will have 1 drop of masked study treatment (Nyxol or placebo) administered in the study eye (right eye [OD]) and 1 drop administered in the fellow eye (left eye [OS]). The study eye and the fellow eye will both be evaluated at all assessments unless otherwise specified.

The study eye (OD) will always be treated and assessed first. If the subject is not amenable to receiving treatment in the fellow eye (OS), the subject can still participate in the study and only the study eye will undergo study assessments. The study eye and fellow eye will both be evaluated at all assessments unless otherwise specified.

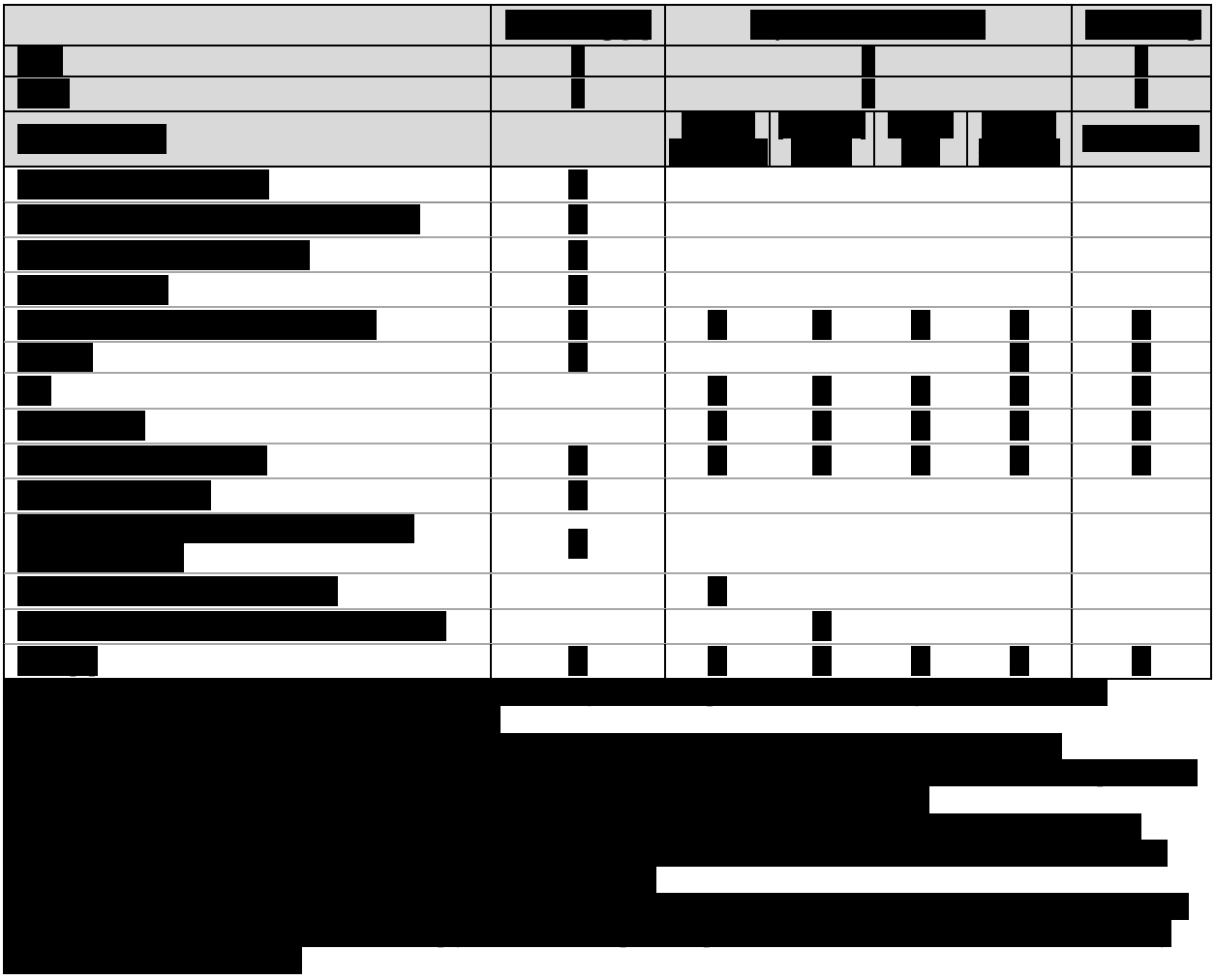
At Visit 1, measurements will be made before (-1 hour/baseline) and [redacted] after (max pupil dilation/0 minutes) the mydriatic agent instillation OU (i.e., right before the study treatment is administered). Additionally, measurements will be taken [redacted] hours after study treatment dosing.

At Visit 2 (Follow-Up Visit), which is 1 day after Visit 1, measurements will be taken 24 hours after study treatment dosing..

The schedule for assessments and timing of events is presented in

Table 1.

Table 1 Screening and Mydriatic/Treatment Schedule



5.2. Inclusion – Exclusion Criteria and General Study Population

The study population will be approximately 20 to 30 healthy pediatric subjects 3 to 11 years of age, inclusive. Written informed consent will be obtained from the legal guardian of each subject. A signed assent form will be obtained for all minors ages 7 to 11, as well as a separate parental/Legal Guardian consent.

The inclusion and exclusion criteria defined in the protocol apply to all subjects and are not repeated herein the SAP. Reference is made to the final protocol for the specific inclusion and exclusion criteria for study subjects.

5.3. Randomization and Blinding

A randomization code for allocating subjects to treatment will be prepared by a masked biostatistician not connected with the study. At the initiation of study related procedures, every potential subject is assigned a Screening number in numerical order per strata. Once a subject is qualified for the study, the subject is assigned a randomization number in the order provided by the biostatistician.

Treatment randomization will be 1:1 (Nyxol or placebo [vehicle]) and will be stratified 1:1 by subject age group (3–5 years of age: 6–11 years of age). Mydriatic agent randomization will be 3:1:1 (phenylephrine: tropicamide: Paremyd, respectively). Approximately 60% of the randomized subjects will receive 1 drop of 2.5% phenylephrine in both eyes (OU) 1 hour before treatment (12 subjects), approximately 20% will receive 1 drop of 1% tropicamide OU 1 hour before treatment (4 subjects), and approximately 20% will receive 1 drop of Paremyd OU 1 hour before treatment (4 subjects).

The study medications will be masked to both Investigator and study subjects, as well as Ocuphire. Only in case of medical emergency or occurrence of serious adverse events (SAEs) will the randomization code be unmasked by the study pharmacist and made available to the Investigator, Ocuphire, and/or other personnel involved in the monitoring or conduct of this study. Rules for unmasking a subject for safety reasons are fully described in the protocol and not repeated herein this SAP.

5.4. Analysis Variables

Variables to be summarized include demographics and baseline characteristics, medical (non-ocular) and ocular history, concomitant medications, and study drug accountability.

The only efficacy variable is Pupil diameter.

Safety variables include:

- Conjunctival hyperemia (eye redness) measured [redacted]

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

- BCDVA (i.e., Distance VA)
- AEs
- Vital signs (HR and BP)

6. SAMPLE SIZE

A sample size of approximately 20 subjects (approximately 10 treated with Nyxol) in this study will result in a total of > 300 subjects treated with Nyxol in the reversal of mydriasis program (including prior studies); this number of subjects is needed to meet the minimum number of subjects exposed to Nyxol to assess safety in this population as specified in the Pediatric Research Equity Act (PREA) plan. This safety study is not powered for efficacy. In accordance with the Sponsor Pediatric Safety Plan for the indication of reversal of pharmacologically induced mydriasis, the sample size of 20 subjects divided between 2 age groups is adequate to evaluate safety in the 3- to 11-year-old pediatric population.

All subjects will be randomized into the study in a 1:1 ratio to 1 of the 2 treatment arms (Nyxol or placebo), with a 1:1 stratification by subject age group (3–5 years of age: 6–11 years of age). Furthermore, subjects will be randomized into the study at a ratio of 3:1:1 to mydriatic agent (phenylephrine: tropicamide: Paremyd, respectively). Therefore, if 12 subjects are randomized to 2.5% phenylephrine, then 4 subjects will be assigned to 1% tropicamide, and 4 subjects will be assigned to Paremyd, resulting in 20 total subjects.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

The following analysis populations will be defined for this study.

7.1.1. Modified Intention-to-Treat (mITT)

The mITT Population will include all randomized subjects who received 1 drop of study treatment in the study eye and completed at least 1 scheduled post-treatment PD measurement during Visit 1 in the study eye. The mITT Population will be used to analyze selected efficacy endpoints, with subjects included in their randomized treatment regardless of the treatment they actually received.

7.1.2. Per Protocol Population (PP)

The PP Population includes all subjects in the mITT Population who had 1 drop of study treatment in the study eye, had all scheduled PD measurements during the Treatment Visit in the study eye, had an increase of > 0.2 mm in PD in the study eye at 0 minutes compared to baseline (-1 hour), and had no major protocol deviations considered to have significant impact on treatment outcome. The PP Population will be used to analyze selected efficacy endpoints, with subjects included in their randomized treatment regardless of the treatment they actually received.

7.1.3. All Randomized Population (ARP)

The ARP will include all randomized subjects. This population is also known as the Intent-to-Treat (ITT) Population. The ARP may be used in confirmatory efficacy analyses, with subjects included in their randomized treatment regardless of the treatment they actually received.

7.1.4. Safety Population (SP)

The SP will include all randomized subjects who received at least 1 drop of study treatment. The SP will be used to summarize safety variables, using the treatment they actually received.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

Planned covariates include baseline values for the given assessment.

7.2.2. Planned Subgroups

Subgroup analyses by age group (3-5 years and 6-11 years), and by mydriatic agent (phenylephrine, tropicamide, Paremyd) will be completed for efficacy endpoints. An additional mydriatic agent subgroup, combining 1% tropicamide and the Paremyd subjects into a "tropicamide" group, will be used for efficacy endpoints.

Other subgroups, such as light/dark irides, sex, and race, may be summarized as well.

7.3. Management of Analysis Data

7.3.1. Data Handling

Data from unscheduled visits will not be included in the analysis of efficacy or safety but will be listed.

7.3.2. Missing Data

There will be no substitutions made to accommodate missing data points for efficacy data. All data recorded on the CRF will be included in data listings that will accompany the CSR.

Safety data will be imputed in limited situations. If the severity of an AE is missing, then the severity will remain missing. If relationship of the AE to study drug is missing, the relationship will remain missing. Missing or partial dates for AEs or concomitant medications will be imputed as described in Section 7.3.2.1. Otherwise, all summaries of safety endpoints will be completed using observed cases in the SP; no imputation will be completed.

7.3.2.1. Handling of Missing Date Values

Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for AEs and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.

2) If the month is unknown, then:

i) If the year matches the first dose date year, then impute the month and day of the first dose date.

ii) Otherwise, assign 'January.'

3) If the day is unknown, then:

i) If the month and year match the first dose date month and year, then impute the day of the first dose date.

ii) Otherwise, assign the first day of the month.

B. Stop Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.

2) If the month is unknown, then assign 'December.'

3) If the day is unknown, then assign the last day of the month.

7.3.2.2. Missing Baseline Data

Every effort will be made to ensure that accurate baseline information on the subjects is collected. In the event that a subject is missing relevant baseline information, the subject will be included in the SP for assessment of safety but excluded from the efficacy analyses. Each case of missing baseline data will be evaluated for potential inclusion in the analysis. All baseline data will be observed cases, without imputation.

7.3.3. Handling of Early Termination Visit Information

In the event that a subject is terminated early from this study on Day 1, the early termination data for safety variables will be assigned to the closest scheduled time point on Day 1. If the closest time point has valid data, the early termination data will be assigned to the next available time point.

7.3.4. Pooling of Investigational Sites

The data from all study centers will be pooled together for all planned analyses.

7.3.5. Coding Conventions for Events and Medications

All AEs and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 25.0) system for reporting (preferred term and body system).

Prior and concomitant medications will be coded using WHO-DD (World Health Organization Drug Dictionary) (Global Version 2022-01).

7.3.6. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final CSR will detail what software was used and for what purposes.

7.3.7. Study Data

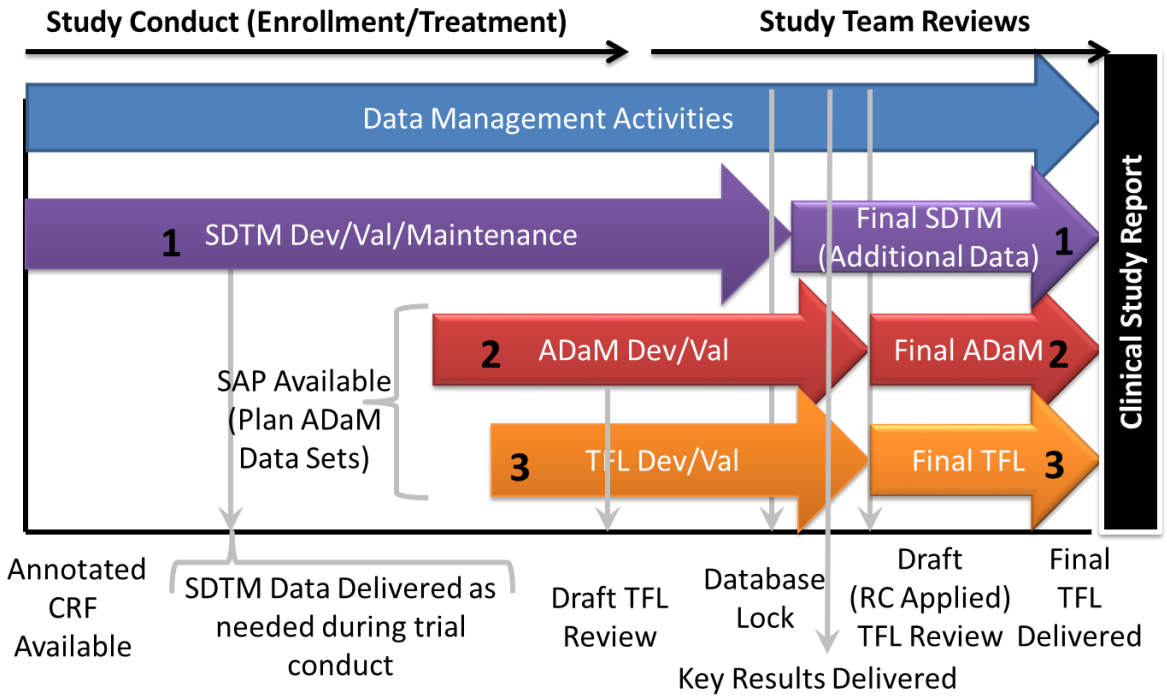
Study data identified in the schedule for time and events (

Table 1) are collected, and source verified, on paper CRFs.

All study data will be formulated into regulatory-compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture.

The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 1.

Figure 1 SDTM, ADaM, and TFL Development and Validation



Where:

1. Development, validation, and maintenance of SDTM domains
2. Development and validation of ADaM data sets, with input source the appropriate SDTM domains.
3. Development and validation of tables, figures, and listings (TFL), with input data source the SDTM domains and analysis specific ADaM data sets.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

Categories for data presentation and analysis will consist of each treatment group (Nyxol or Placebo).

All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n), mean, standard deviation, median, minimum, and maximum will be tabulated by treatment group. For categorical variables, the counts and proportions of each value will be tabulated by treatment group. Expansion of descriptive table categories within each treatment may occur if such elaborations are thought to be useful.

All study-related data collected will be presented in listings. Study-related data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

7.4.2. Interim Analyses and Data Monitoring

No formal interim analysis or safety monitoring committee is planned for this study.

7.4.3. Final Analysis and Publication of Study Results

The final analysis will be completed after all subjects have completed the study.

7.5. Multiple Testing Procedures

There will be no adjustments for multiplicity and no formal multiple testing procedures are to be implemented with this analysis plan.

7.6. Baseline Values

Baseline values are the values obtained prior to any drug administration on Day 1 (study drug or mydriatic agent), usually the -1 hour time point. If the Day 1 value is missing or the assessment is not completed at the -1 hour time point, the value at Screening will be treated as the baseline.

8. SUMMARY OF STUDY DATA

8.1. Subject Disposition

A summary of the analysis sets includes the number and percentage of subjects by treatment group and overall for the following categories: subjects in the ARP, subjects in the SP, subjects in the mITT Population, and subjects in the PP Population. All percentages will be based on the number of subjects in the ARP.

End of trial information will also be summarized in this table, including the number of subjects completing the study, the number of subjects who prematurely discontinued the study with reasons for withdrawal, the number of subjects completing the study medication dosing, and the number of subjects who prematurely discontinued the study medication with reasons for study medication discontinuation.

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

8.2. Protocol Deviations

Major protocol deviations, as determined by a Sponsor blinded review of the data prior to database lock and unblinding of the study, may result in the removal of a subject's data from the PP Population. The Sponsor or designee will be responsible for producing the final deviation file; this file will include a description of the protocol deviation and clearly identify whether this violation warrants exclusion from the PP Population. This file will be finalized prior to database lock.

All protocol deviations will be presented in a by-subject data listing, with a flag to indicate if a deviation was considered major.

8.3. Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively by treatment group and overall. The demographic data and baseline characteristics will be summarized for the mITT Population, PP Population, SP, and ARP. If the mITT population is equivalent to any of the other populations, then only the mITT version will be generated rather than repeating equivalent summaries

The demographics consist of age (year), sex, race, ethnicity, and study eye (OD), iris color (light blue, dark blue, blue with peripupillary brown, uniform green, green with brown iris ring, central brown and peripheral green, brown with some peripheral green, or brown), irides type (light or dark), and mydriatic agent (phenylephrine, tropicamide, or Paremyd). A subject's age in years is calculated using the date of the informed consent and date of birth. Age will be summarized using descriptive statistics. The number and percentage of subjects by sex, race, ethnicity, study eye, iris color, irides type, and mydriatic agent will also be

reported. Percentages will be based on the total number of subjects in the study population presentation.

The following baseline characteristics will be summarized for study eye and fellow eye, using descriptive statistics:

- Pupil diameter (-1 Hour)
- Max pupil diameter (0 Minutes)
- BCDVA (-1 Hour)
- BCDVA (0 Minutes)

All demographic and baseline information will be presented in by-subject listings.

8.4. Medical History

The number and percent of subjects with individual medical histories will be summarized for all subjects by treatment group and overall. Non-ocular and ocular medical history will be summarized separately.

Medical history will be coded using the MedDRA Version 25.0 The number and percentage of subjects with any medical history will be summarized overall and for each system organ class (SOC) and preferred term (PT). Percentages will be calculated based on number of subjects in the SP.

Subject medical history data including specific details will be presented in by-subject listings.

8.5. Prior and Concurrent Medications

The number and percentages of all concomitant medications will be summarized by treatment group, Anatomical Therapeutic Chemical (ATC) level 4, and PT. The total number of concomitant medications and the number and percentages of subjects with at least 1 concomitant medication will be summarized by treatment group. All summaries will be performed using the SP.

A concomitant medication is defined as any medication taken on or after the day of first exposure to study drug.

Prior medications are defined as any medication that has a start and stop date prior to the day of first exposure to any study drug, collected from up to 30 days prior to Screening. The total number of prior medications and the number and percentages of subjects with at least 1 prior medication will be summarized by treatment group.

8.6. Treatment Administration

Treatment administration data for both the study drug and the mydriatic agent on Day 1 will be presented in by-subject listings.

9. EFFICACY ANALYSES

Unless otherwise noted, efficacy will be assessed using the mITT and PP populations, with subjects included in their randomized treatment regardless of the treatment they actually received. Observed data will be used for efficacy summaries; imputation will not be performed.

To formally test the significance of efficacy endpoints of interest, endpoints will be tested in a predefined sequence, each at the significance level 0.05, until the first nonsignificant test. The endpoints in the sequence are for the study eye only, but the analysis populations and time points will vary. The sequence is specified in Section 12.3.

All efficacy assessment data, regardless of whether they are included in the analysis, will be presented in by-subject listings.

9.1. Clinical Efficacy

For all efficacy endpoints, Baseline is defined as -1 hour prior to treatment on Day 1. This is the time when the mydriatic agent is administered, and the pupil diameter measurement is considered normal. Max timepoint is defined as time 0 minutes, during which maximum pupil diameter is expected; this is also the timepoint at which the treatment is administered (Nyxol or Placebo).

All efficacy data will be summarized by treatment group, study day, and time point (-1 hour [baseline], 0 minutes, 90 minutes, 3 hours, and 24 hours), as appropriate.

[redacted]

Example SAS code is as follows:

[redacted]

[redacted]

The analysis of the time (hours) to return to ≤ 0.2 mm from baseline pupil diameter (time savings analysis) endpoint will be performed using a Cox proportional hazards regression model with treatment as a factor and the baseline pupil diameter as a covariate. Subjects who do not return to ≤ 0.2 mm from baseline pupil diameter by the 6 hour time point will have their time to return censored at 8 hours. Example SAS code is as follows:

[redacted]
1
[redacted]

The output from the model will include the hazard ratio comparing treatment groups, its 95% CI and associated p-value. Time to return to baseline (-1 hour) pupil diameter will be measured beginning at the Max (0 hour) time point.

In addition, efficacy endpoints will be summarized by age group, by mydriatic agent, and by irides type, but will not be analyzed due to the small sample size for each subgroup. The time savings analysis will not be summarized by age group. Each mydriatic agent will be summarized individually, and an additional summary combining 1% tropicamide and Paremyd subjects into a “tropicamide or Paremyd” group will be presented.

10. SAFETY ANALYSES

All safety analyses will be conducted using the SP. All safety analyses will be completed using the actual treatment a subject received. Observed case data will be used; no imputation will be performed for missing safety data except for the limited situations described in Section 7.3.2.

All safety data will be presented in by-subject listings. Unscheduled assessments will not be summarized but will be included in the listings.

10.1. Adverse Events

AEs will be coded using MedDRA, Version 25.0.

Treatment-emergent adverse events (TEAEs) are defined as any AE that begins or worsens after initiation of the investigational product and through the subject's last study visit (study completion or early termination).

If the onset of an AE is on or after the date of first dose of study medication or is increasing in severity after first dose of study medication, then the AE will be considered treatment emergent.

Only TEAEs will be summarized; all AEs (TEAE, non-TEAE) will be included in a by-subject listing.

The number and percent of subjects with any TEAEs will be summarized by SOC and PT by treatment group and overall. At each level of tabulation (e.g., at the PT level), subjects will be counted only once if they had more than one such event reported during the AE collection period. A separate summary by SOC, PT, and treatment group will be completed by mydriatic agent.

Note that in MedDRA, ocular events are coded to the SOC of "Eye Disorders". Thus, using SOC in the summaries will provide a separation of ocular and non-ocular adverse events.

The following summary tables will be presented for TEAE data:

- Overall summary of TEAEs
- Summary table of TEAEs by SOC and PT
- Summary table of TEAEs by SOC, PT, and by greatest relationship level to study drug (not related, unlikely related, possibly related, probably related, definitely related, or unknown)
- Summary table of TEAEs by SOC, PT, and maximum severity (mild, moderate, severe)
- Summary table of serious TEAEs by SOC and PT
- Summary table of TEAEs leading to withdrawal from the study by SOC and PT

- Summary table of TEAEs leading to study medication discontinuation by SOC and PT

If no TEAEs are observed during the study, only the overall summary of TEAEs will be generated.

10.2. Deaths, Serious Adverse Events and Other Significant Adverse Events

10.2.1. Deaths

The AE listing will include all AEs, including deaths, regardless of causality; one of the columns in the listing will specify whether the AE was fatal.

10.2.2. Serious Adverse Events

The AE listing will include all AEs, including SAEs; one of the columns in the listing will specify whether the AE was an SAE.

10.2.3. Adverse Events Leading to Withdrawal from the Study

The AE listing will include all AEs, including AEs leading to withdrawal from the study; one of the columns in the listing will specify whether the AE led to withdrawal from the study.

10.2.4. Adverse Events Leading to Discontinuation of Study Medication

The AE listing will include all AEs, including AEs leading to discontinuation of study medication; one of the columns in the listing will specify whether the AE led to discontinuation of study medication.

10.3. Conjunctival Hyperemia

Results from the conjunctival hyperemia assessment, measured with [redacted]

Additionally, conjunctival hyperemia will be summarized as a continuous variable. Treatments will be compared using the same ANCOVA model proposed for the change in photopic pupil diameter from max pupil dilation efficacy endpoint. A descriptive summary of conjunctival hyperemia will be presented by treatment and age group.

10.4. Visual Acuity

Assessments will be summarized at the timepoints - [redacted]

Treatments will be compared using the same ANCOVA model proposed for the change in photopic pupil diameter from max pupil dilation efficacy endpoint. A descriptive summary of BCDVA will be presented by treatment and age group.

Additionally, a categorical summary of BCDVA will be presented, with counts and percentages of subjects with Improvement or loss from baseline by treatment and time point.

10.5. Vital Signs

Descriptive statistics of observed values will be presented for vital sign data at each time point (Screening, 3 hours, and 24 hours), including systolic BP (mmHg), diastolic BP (mmHg), and HR (bpm) by treatment group and overall. Changes from baseline to each scheduled post-baseline time point will be presented.

10.6. Other Safety Measures

Results from the biomicroscopic examination, which is completed only at Screening, will also be presented in by-subject listings.

11. REFERENCES

[1] ICH E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonized Tripartite Guideline, September 1998

[2] Hauck WM, Anderson S, and Marcus SM, Should We Adjust for Covariates in Nonlinear Regression Analyses of Randomized Trials? *Controlled Clin Trials* 1998;19:249–256

12. APPENDICES

12.1. List of Planned Tables

The list of planned tables includes all of the *main* tables to be presented for the study.

Table	Description of Table	ARP	Safety	mITT	PP
14.1.1	Subject Disposition	X			
14.1.2.1/2/3/4	Demographics and Baseline Characteristics	X	X	X	X
14.1.3.1	Non-ocular Medical History		X		
14.1.3.2	Ocular Medical History		X		
14.1.4.1	Prior Medications		X		
14.1.4.2	Concomitant Medications		X		
14.2.1.1/2	Percent of Subjects Returning to ≤ 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point			X	X
14.2.1.3/4	Percent of Subjects Returning to ≤ 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point and Mydriatic Agent			X	X
14.2.1.5/6	Percent of Subjects Returning to ≤ 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point and Age Group			X	X
14.2.1.7/8	Percent of Subjects Returning to ≤ 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point, Mydriatic Agent, and Age Group			X	X
14.2.1.9/10	Percent of Subjects Returning to ≤ 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Time Point and Irides Type			X	X
14.2.2.1/2	Change From Max (0 Minute) Pupil Diameter by Time Point			X	X
14.2.2.3/4	Change From Max (0 Minute) Pupil Diameter by Time Point and Mydriatic Agent			X	X

Table	Description of Table	ARP	Safety	mITT	PP
14.2.2.5/6	Change From Max (0 Minute) Pupil Diameter by Time Point and Age Group			X	X
14.2.2.7/8	Change From Max (0 Minute) Pupil Diameter by Time Point, Mydriatic Agent, and Age Group			X	X
14.2.2.9/10	Change From Max (0 Minute) Pupil Diameter by Time Point and Irides Type			X	X
14.2.3.1/2	Time (Hours) to Return to ≤ 0.2 mm of Baseline (-1 Hour) Pupil Diameter			X	X
14.2.3.3	Time (Hours) to Return to ≤ 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Mydriatic Agent				X
14.2.3.4	Time (Hours) to Return to ≤ 0.2 mm of Baseline (-1 Hour) Pupil Diameter by Irides Type				X
14.3.1.1	Overall Summary of Treatment Emergent Adverse Events (TEAE)		X		
14.3.1.2.1	Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term		X		
14.3.1.2.2	Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Mydriatic Agent		X		
14.3.1.3	Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Severity		X		
14.3.1.4	Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Relationship to Study Treatment		X		
14.3.1.5	Serious Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term		X		
14.3.1.6	Treatment-Emergent Adverse Events (TEAE) Leading to Withdrawal From the Study by System Organ Class and Preferred Term		X		

Table	Description of Table	ARP	Safety	mITT	PP
14.3.1.7	Treatment-Emergent Adverse Events (TEAE) Leading to Study Medication Discontinuation by System Organ Class and Preferred Term		X		
14.3.3.1	Categorical Summary of Conjunctival Hyperemia		X		
14.3.3.2	Summary of Mean Conjunctival Hyperemia Score by Time Point		X		
14.3.3.3	Summary of Mean Conjunctival Hyperemia Score by Time Point and Age Group		X		
14.3.4.1	Best Corrected Distance Visual Acuity (BCDVA) by Time Point (Letters Read)		X		
14.3.4.2	Best Corrected Distance Visual Acuity (BCDVA) by Time Point and Age Group (Letters Read)		X		
14.3.4.3	Percent of Subjects With Improvement or Loss From Baseline in BCDVA by Time Point		X		
14.3.5	Vital Signs by Time Point		X		

12.2. List of Planned Listings

Listing	Description of Listing
16.2.1.1	Subject Disposition
16.2.1.2	Eligibility and Randomization
16.2.2	Protocol Deviations
16.2.3	Treatment Assignment and Analysis Populations
16.2.4.1	Demographics
16.2.4.2	General Medical History (Non-ocular)
16.2.4.3	Ocular Medical History
16.2.4.4	Biomicroscopy Examination
16.2.4.5	Prior and Concomitant Medications
16.2.5	Mydriatic Agent and Study Drug Administration
16.2.6	Photopic Pupil Diameter
16.2.7	Adverse Events

Listing	Description of Listing
16.2.8	Conjunctival Hyperemia
16.2.9	Best-Corrected Distance Visual Acuity (BCDVA)
16.2.10	Vital Signs

12.3. Hierarchy of Sequential Testing