[redacted]

AD ST-07
Statistical Analysis Plan Approval Form

Sponsor: Ocuphire Pharma, Inc.
Protocol: OPI-NYRM-201
Protocol Title: Randomized, cross-over, double-masked, placebo-controlled study of the safety and efficacy of phentolamine mesylate ophthalmic solution to reverse pharmacologically induced mydriasis in normal healthy subjects
SAP Version: Final V1.0
SAP Date: 10OCT2019

The statistical analysis plan has been reviewed and approved.

Sponsor: *Ocuphire Pharma, Inc.*

[redacted]

Consultant: [redacted]

[redacted]

Author: [redacted]

[redacted]

[redacted] | CONFIDENTIAL

Ocuphire Pharma, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Title: Randomized, cross-over, double-masked, placebo-controlled study of the safety and efficacy of phentolamine mesylate ophthalmic solution to reverse pharmacologically induced mydriasis in normal healthy subjects

Study Number: OPI-NYXRM-201 (MIRA-1)

Phase: Phase 2b

Sponsor: [redacted]

Author: [redacted]

SAP Date: 2019-10-10

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
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
cm	centimeter
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DB	Database
DD	Drug Dictionary
DCNVA	Distance Corrected Near Visual Acuity
FAS	Full Analysis Set
FDA	Food and Drug Administration
HR	Heart Rate
IOP	Intra-Ocular Pressure
IRB	Institutional Review Board
ITT	Intent-To-Treat
LOCF	Last Observation Carried Forward
logMAR	logarithm of the Minimum Angle of Resolution
LSM	Least Squares Mean
MAR	Missing at Random
max	Maximum
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation/Term	Definition
Nyxol	Phentolamine Mesylate Ophthalmic Solution 1% (Nyxol®)
OD	Right Eye
OR	Odds Ratio
OS	Left Eye
OU	Oculus Uterque (both eyes or binocular)
PD	Pupil Diameter
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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
US	United States
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-NYXRM-201 (MIRA-1) (*Randomized, cross-over, double-masked, placebo-controlled study of the safety and efficacy of phentolamine mesylate ophthalmic solution to reverse pharmacologically induced mydriasis in normal healthy subjects*).

Reference materials for this statistical plan include the protocol OPI-NYXRM-201 Amendment 1 (24JUL2019) and Case Report Forms (CRFs; Final Version 18JUL2019).

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 purposes of the planned analyses described in this SAP are to evaluate the efficacy of Nyxol to expedite the reversal of pharmacologic mydriasis, to evaluate the safety of Nyxol, and to evaluate the effect of Lumify® to suppress conjunctival hyperemia (redness) potentially associated with administration of Nyxol. Results from the analyses completed will be included in the final clinical study report (CSR) for OPI-NYXRM-201, and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

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 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 efficacy of Nyxol to expedite the reversal of pharmacologic mydriasis.
- To evaluate the safety of Nyxol.
- To evaluate the effect of Lumify® to suppress conjunctival hyperemia (redness) potentially associated with administration of Nyxol

4.2. Study Endpoints

4.2.1. Primary Endpoints

The primary efficacy endpoint from the protocol is the change (in mm) in pharmacologically induced mydriatic (max) pupil diameter (0 minutes) at 2 hours post treatment in the study eye.

The primary safety measures are:

- [redacted]
- [redacted]
- Adverse events (AEs)

4.2.2. Secondary Endpoints

Secondary endpoints for efficacy and safety assessments include the following:

Efficacy:

Secondary efficacy endpoints will be analyzed by study eye, non-study eye and both eyes (the pooled data from the study eye and non-study eye) unless otherwise indicated, and will include:

- Change (in mm) from max pupil diameter (0 minutes) at each remaining time point (30 min, 1 hour, 4 hours, 6 hours).

- [redacted]
- Percentage of subjects achieving pupil diameter of no more than 0.5 mm above baseline (-1 hour) at each time point (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours).
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Change from baseline (-1 hour) in conjunctival hyperemia at each time point (0 min, 30 min, 1 hour, 2 hours, 4 hours, 6 hours), for study eye and non-study eye; in all subjects, in subjects taking Lumify®, and in subjects not taking Lumify. Please note that the variables related to subjects taking Lumify cannot be analyzed since no subjects took Lumify during the study.

Each efficacy endpoint will be analyzed overall and by mydriatic agent (phenylephrine or tropicamide).

Safety and Tolerability:

- Vital signs (heart rate [HR] and blood pressure [BP])
- Intraocular pressure (IOP)
- Urine pregnancy tests for females of childbearing potential

5. STUDY METHODS

5.1. General Study Design and Plan

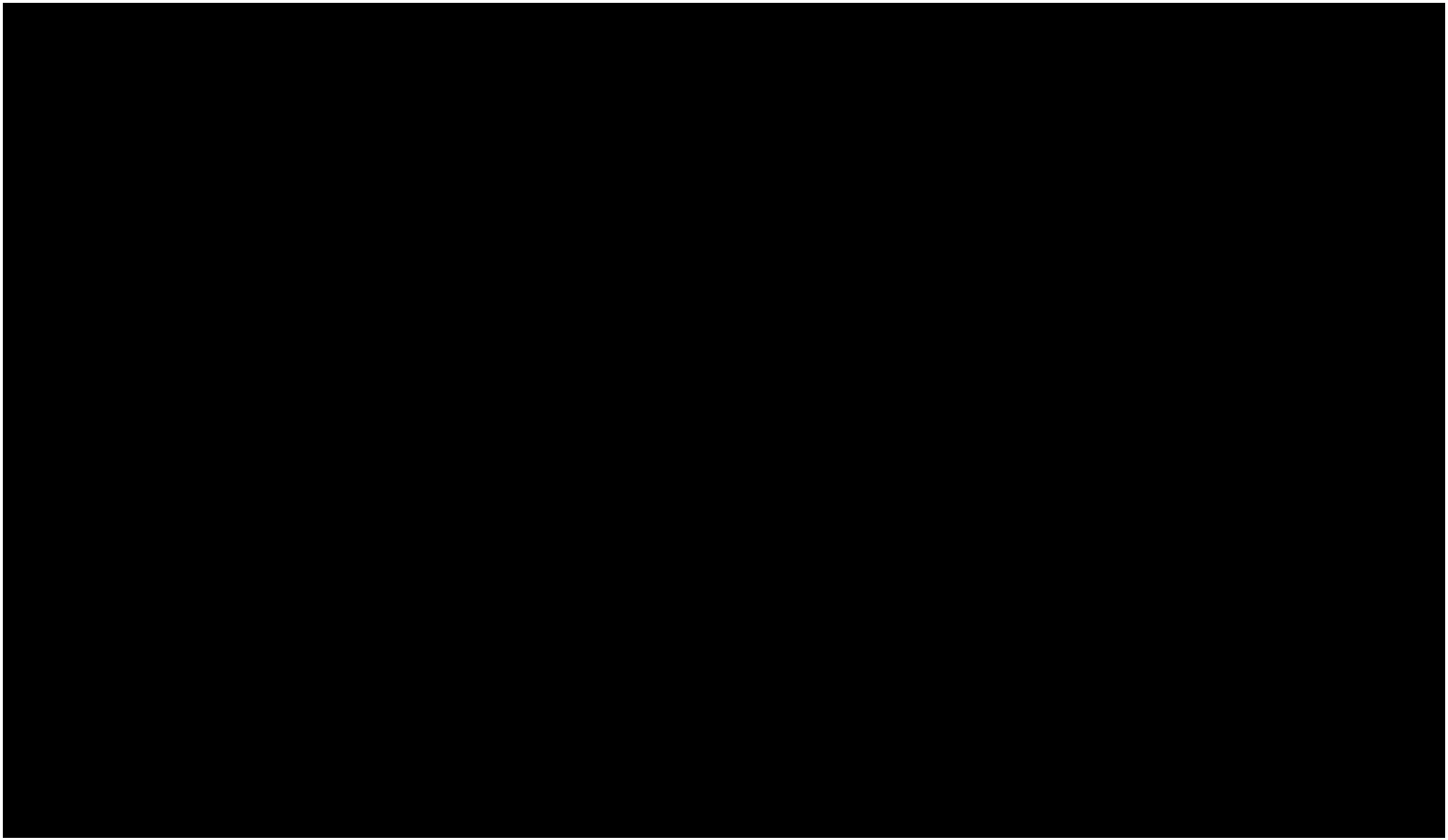
As background for the statistical methods presented below, this section provides an overview of the study design and plan of study execution. The protocol is the definitive reference for all matters discussed in what follows.

Two hours post treatment, subjects may request the administration of Lumify® (to be provided) in the non-study eye as needed (site shall record such usage).

The study eye is defined as the eye with the largest pupil diameter at maximum (1 hour after instillation of the mydriatic agent; 0 minutes) at Visit 1. If both eyes have the same pupil diameter at maximum, then the study eye will be the right eye. This is the study eye for both Visit 1 and Visit 2 assessments.

The schedule for assessments and timing of events is presented in Table 1.

Table 1 Screening and Mydriatic/Treatment Schedule



[redacted]

5.2. Inclusion – Exclusion Criteria and General Study Population

The study population will be approximately 32 normal healthy subjects between 18 years of age and 45 years of age inclusive, with approximately 28 completed subjects. 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

Subjects will be randomized in a 1:1 ratio to one of two treatment sequences (placebo at Visit 1, followed by Nyxol 1%/active treatment at Visit 2; Nyxol 1%/active treatment at Visit 1, followed by placebo at Visit 2).

A randomization code for allocating subjects to treatment sequence 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. Once a subject is qualified for the study, the subject is assigned a randomization number in the order provided by the biostatistician

The study medications will be masked to both Investigator and study subjects, as well as Ocuphire. Assignment to treatment sequence will be masked to the Investigator, Ocuphire, and the subjects. Only in case of medical emergency or occurrence of 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.

Efficacy variables include:

- Pupil diameter
- Accommodation

- [redacted]
- [redacted]

Safety variables include:

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- AEs
- Vital signs (HR and BP)
- IOP
- Urine pregnancy tests for females of childbearing potential

6. SAMPLE SIZE

A sample size of 28 completed subjects is needed for the study. [redacted] dditionally, it is assumed that there will be approximately 10% drop-out between Visit 1 and Visit 2. To account for this drop-out, a total of 32 subjects will be randomized into the study in a 1:1 ratio to one of two treatment sequences. Randomization for each mydriatic agent was capped at approximately 16

subjects; that is, one half of the randomized subjects received phenylephrine, one half received tropicamide.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

[redacted]

7.1.1. Full Analysis Set Population (FAS)

The Full Analysis Set (FAS) will include all randomized subjects who received both doses of study treatment and have both a Visit 1 and Visit 2 pupil diameter measurement. The FAS will be used to analyze efficacy endpoints. Subjects included in the FAS will be analyzed as randomized.

7.1.2. Per Protocol Population (PP)

[redacted]

7.1.3. All Randomized Population (ARP)

[redacted]

7.1.4. Safety Population (SP)

The Safety Population (SP) will include all randomized subjects who have received at least one dose of study medication. The SP will be used to summarize safety variables. Subjects who are members of the SP will be analyzed as treated.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

Planned covariates include baseline values for the given assessment.

7.2.2. Planned Subgroups

[redacted]

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

The primary efficacy endpoint is the change in pharmacologically induced mydriatic (max) pupil diameter (0 minutes) at 2 hours post treatment in the study eye. For the analysis of the primary efficacy endpoint, observed case data will be used (no imputation will be performed for missing efficacy data) for the analysis using the FAS. However, confirmatory analyses will be performed using the ARP, with imputation performed for missing data as specified in Section 7.3.2.3.

Otherwise 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 adverse events 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 baseline information, the subject will be included in the SP for assessment of safety, and excluded from the primary analyses. Each case of missing baseline data will be evaluated for potential inclusion in the exploratory endpoints. All baseline data will be observed cases, without imputation.

7.3.2.3. Imputation Methods

Imputation for efficacy data will only be performed for the confirmatory analysis of the primary efficacy endpoint, using the ARP. If 5% or fewer data are missing in all treatment groups, an analysis with last observation carried forward (LOCF) for missing data will be applied within a treatment group. If more than 5% of data in any treatment group are missing, multiple imputation will be employed to analyze incomplete data sets under the assumption that the mechanism responsible for the missing data is at worst characterized as missing at random (MAR).

Multiple imputation is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed datasets can then be analyzed using standard analysis methods. Rubin (1987) presented rules for how to combine the multiple sets of estimates to produce overall estimates, confidence intervals, and tests that adequately incorporate missing data uncertainty.

Missing values for pupil diameter will be imputed simultaneously based on an underlying joint normal distribution using a Markov Chain Monte Carlo (MCMC) method.

The imputations will be done separately for each treatment group and will include the following variables in the imputation model: pupil diameter at Day 1 (30 min, 1 hour, 2 hours, 4 hours, 6 hours) and Day 8 (30 min, 1 hour, 2 hours, 4 hours, 6 hours). No imputation will be applied to the max pupil diameter (0 minutes) time points at Day 1 and Day 8.

The number of imputations will be set to 500. The outcomes of interest (change from baseline) will be calculated from these imputed datasets. The treatment difference for each imputed dataset will be evaluated using mixed models. See Section 11 for details on these models. The estimates and standard errors of the differences in LS means based on the 500

imputed datasets are then combined by applying Rubin's rules for multiple imputed datasets. T-tests are also provided. [redacted] The averaged difference in LS means with the corresponding 95% confidence interval will also be presented.

Example [redacted]

7.3.3. Handling of Early Termination Visit Information

In the event that a subject is terminated early from this study, the early termination visit data for safety variables will be assigned to the closest scheduled visit within the same treatment period. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

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 adverse events, and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 22.0) system for reporting (preferred term and body system).

Prior and Concomitant medications will be coded using WHO-DD (Drug Dictionary) (Version January 2019).

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; there is no electronic data capture tool.

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 [redacted]

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 sequence (Sequence 1: placebo to Nyxol or Sequence 2: Nyxol to placebo) or each treatment group (Nyxol or placebo) separately.

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 sequence or treatment group. For categorical variables, the counts and proportions of each value will be tabulated by treatment

sequence or 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

For all efficacy endpoints except pupil diameter, Baseline for a specific day (Visit 1 / Day 1, Visit 2 / Day 8) is defined as -1 hour prior to treatment. That is, change from baseline is based on -1 hour data. For pupil diameter, change analyses for each visit will be based on max time point (0 minutes), during which maximum pupil diameter is expected. That is, change from max is based on 0 minute data.

8. SUMMARY OF STUDY DATA

8.1. Subject Disposition

A summary of the analysis sets includes the number and percentage of subjects by treatment sequence and overall for the following categories: subjects in the ARP, subjects in the SP, and subjects in the FAS. 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 sequence and overall. The demographic data and baseline characteristics will be summarized for the SP and FAS.

The demographics and baseline characteristics consist of age (year), sex, race, ethnicity, and study eye (OD [right eye] or OS [left eye]), iris color (brown, non-brown), and mydriatic agent (phenylephrine or tropicamide). 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, 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 OD and OS, and for study eye, fellow eye, and all eyes, at Visit 1 / Day 1 and Visit 2 / Day 8 using descriptive statistics:

- Pupil diameter (-1 hour)
- Max Pupil diameter (0 minutes)
- [redacted]
- [redacted]
- [redacted]

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 sequence and overall. Non-ocular and ocular medical history will be summarized separately.

Medical history will be coded using the MedDRA Version 22.0. 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 sequence.

8.6. Treatment Administration

The number and percentages of subjects with assigned treatment administered will be presented by treatment group and visit. The number and percentages of subjects with Lumify® administered in the non-study eye will also be presented.

9. EFFICACY ANALYSES

Unless otherwise noted, all efficacy analyses will be completed using the FAS. Confirmatory analysis of the primary efficacy endpoint will be performed using the ARP and PP Population. The FAS will be the primary analysis population for efficacy. All efficacy analyses will be completed using the planned treatment.

9.1. Clinical Efficacy

The evaluations of clinical efficacy will be performed using the FAS (and ARP and PP Population, for primary efficacy), as specified below. Baseline values are generally taken at the -1 Hour time point at each visit (Visit 1 / Day 1 and Visit 2 / Day 8). For pupil diameter, change analyses will be based on max time point (0 minutes) at each visit, during which maximum pupil diameter is expected.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the change in pharmacologically induced mydriatic (max) pupil diameter (0 minutes) at 2 hours post-treatment in the study eye. The primary efficacy endpoint will be analyzed using a mixed model with change from max pupil diameter (0 minutes) to 2 hours in mean pupil diameter (mm) as the dependent variable, treatment sequence, period, treatment and mydriatic agent as fixed effects, subject within treatment sequence as a random effect, and max pupil diameter (0 minutes) as the covariate. Example SAS code is as follows:

The analysis will be performed using the FAS, with subjects included in their randomized treatment sequence regardless of the treatment they actually received. Observed case data only will be used; that is, missing values will not be imputed. The least-squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

In addition, the primary efficacy endpoint will be analyzed by mydriatic agent using the same model as above but without mydriatic agent as a factor.

A confirmatory analysis of the primary efficacy endpoint will be performed, using the ARP with missing Visit 1 / Day 1, Hour 2 and Visit 2 / Day 8, Hour 2 values imputed. See Section 7.3.2 for imputation methods.

Another confirmatory analysis of the primary efficacy endpoint will be performed using the PP population. No imputation of missing values will be applied.

Finally, plots displaying the least squares mean ± standard error (SE) of pupil diameter will be presented by time point for the FAS. Similar plots will be generated for pupil diameter by mydriatic agent.

Secondary Efficacy Endpoints:

Secondary efficacy endpoints are indicated in Section 4.2.2. Secondary efficacy endpoints will be analyzed by study eye, non-study eye and both eyes (the pooled data from the study eye and non-study eye) unless otherwise indicated. [redacted] All secondary efficacy assessment data, regardless of whether they are included in the analysis, will be presented in by-subject listings.

For each of the continuous secondary efficacy endpoints, the same mixed model for the primary efficacy endpoint will be used, with the respective baseline (-1 hour) value included as the covariate (note that all of the secondary efficacy endpoints are in relation to baseline [-1 hour], whereas the primary efficacy endpoint is in relation to max [0 minute]). Each analysis will be performed using the FAS with subjects included in their randomized treatment sequence regardless of the treatment sequence they actually received. Only observed case data will be used; that is, missing values for post-randomization assessments will not be imputed. The output from each model will include the LSM and SE for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

For each of the secondary endpoints related to percent of subjects achieving certain criteria, [redacted]

For each analysis, the percentage of subjects in each treatment group meeting the criteria, the odds ratio (OR) with 95% CI and p-value will be provided. For these endpoints, the FAS will be used with subjects included in their randomized treatment sequence regardless of the treatment sequence they actually received.

In addition, each secondary efficacy endpoint will be analyzed by mydriatic agent using the same model indicated above but without mydriatic agent as a factor.

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.

For HR and BP, Baseline for a specific day (Visit 1 / Day 1, Visit 2 / Day 8) is defined as the -1 hour baseline value. HR and BP values will be summarized by treatment group and time point (-1 hour, 2 hours, 6 hours; at Visit 1 and at Visit 2). Change from Baseline in the values will be summarized at the same timepoints, except for -1 hour.

For IOP, the only pre-dose assessment is at the screening visit, so the screening IOP will be employed as the baseline value for all post-baseline change from baseline assessments.

10.1. Adverse Events

Adverse events will be coded using MedDRA, Version 22.0.

Treatment-emergent adverse events (TEAEs) are defined as any adverse event that begins or worsens after initiation of the investigational product and through the subject's last study visit (study completion or early termination) or follow-up telephone call. Serious adverse events will be recorded from the date of informed consent, throughout the clinical trial.

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

TEAEs will be assigned to the treatment group most recently administered to the subject as of the TEAE start date.

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 system organ class and preferred term by treatment group and overall. At each level of tabulation (e.g., at the preferred term level) subjects will be counted only once if they had more than one such event reported during the AE collection period.

Note that in MedDRA, ocular events are coded to the SOC of "special senses". 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 highest relationship level to study drug by SOC and PT (not related, possibly related, related)
- Summary table of TEAEs by maximum severity by SOC and PT (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

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 serious adverse events (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. [redacted]

[redacted]

[redacted]

10.4. [redacted]

[redacted]

10.5. Vital Signs

Descriptive statistics of observed values will be presented for vital sign data by time point, 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.

All vital sign data will be presented in a by-subject listing. Unscheduled visit or repeated results will not be summarized but will be included in the listings.

10.6. IOP

Descriptive statistics of observed values will be presented for IOP data by visit (6 hour time point only) and by treatment group and overall. Changes from screening to each scheduled post-baseline time point will be presented. Separate summaries will be created for the study eye and the non-study eye.

All IOP data will be presented in a by-subject listing. Unscheduled visit results will not be summarized but will be included in the listings.

10.7. Other Safety Measures

Urine pregnancy tests for females of childbearing potential but will be presented in by-subject listings. Results from biomicroscopic and ophthalmoscopic examinations (which are completed only at the Screening visit) will also be presented in by-subject listings.

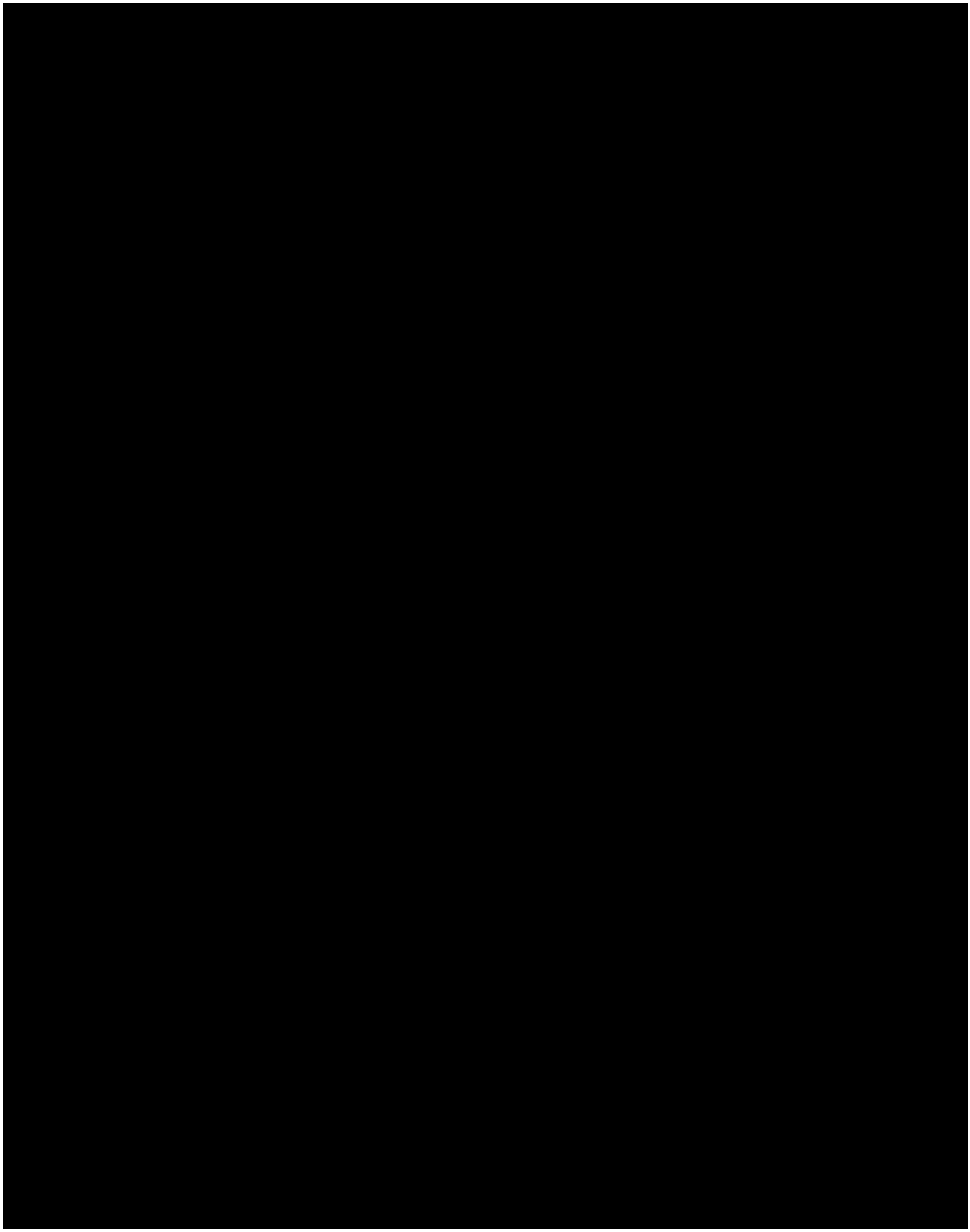
11. REFERENCES

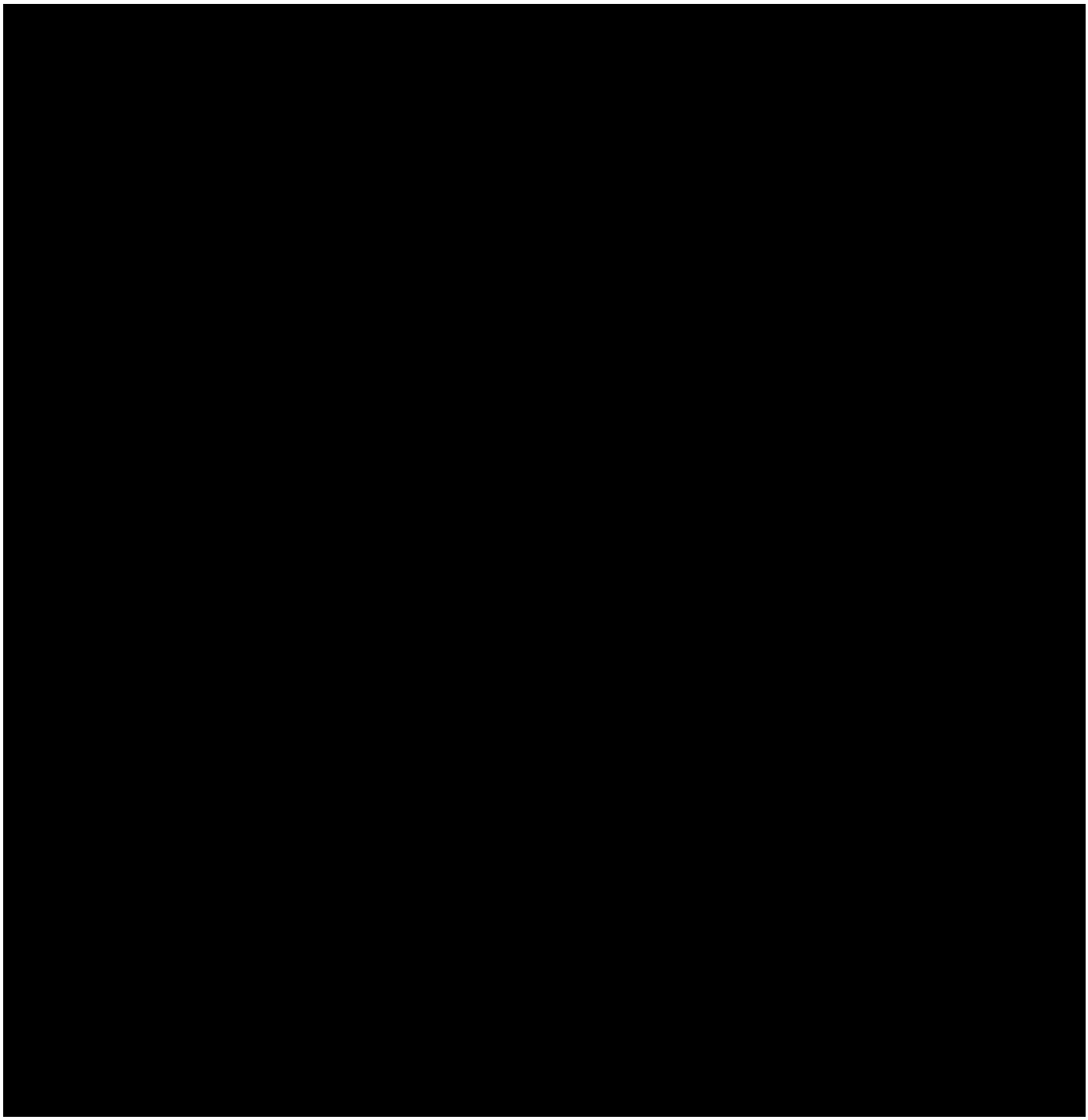
[redacted]

12. APPENDICES

12.1. List of Planned Tables

[redacted]





12.2. List of Planned Listings

[redacted]

12.3. List of Planned Figures

[redacted]