Statistical Analysis Plan

Prospective, Randomized Phase 2 Study Comparing Two Elution Rates of Glaukos Travoprost Intraocular Implants to Timolol Maleate Ophthalmic Solution, USP, 0.5%

Protocol Number:	GC-009
Product Name:	Travoprost Intraocular Implant, [redacted] Travoprost Intraocular Implant,
Sponsor Name:	GLAUKOS CORPORATION 229 Avenida Fabricante San Clemente, CA 92672
Version:	1.0
Date:	06JAN2022

NCT02754596

Statistical Analysis Plan Approval Signatures

Prepared by: _____ Date

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Approved by: _____ Date

Approved by: _____ Date

Approved by: [redacted] Date

Approved by: [redacted] Date

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List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
BSCVA	Best Spectacle Corrected Visual Acuity
C/D	Cup-to-Disc
CI	Confidence Interval
COV	Coefficient of Variation
CRF	Case Report Form
CS	Compound Symmetry
dB	Decibels
ECD	Endothelial Cell Density
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICE	Intercurrent Events
IOP	Intraocular Pressure
ITT	Intent-To-Treat
LogMAR	Logarithm of the Minimum Angle of Resolution
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MCMC	Monte Carlo Markov Chain
MNAR	Missing Not At Random
mmHg	Millimeters of Mercury
MMRM	Mixed Model for Repeated Measures
NRI	Non-Responder Imputation
OAG	Open-Angle Glaucoma
OC	Observed Case

OHT	Ocular Hypertension
PP	Per-Protocol Analysis set
PT	Preferred Term
SAE	Serious Adverse Event
[redacted]	[redacted]
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TOEPH	Toeplitz
UN	Unstructured
VF	Visual Field

Version History

This Statistical Analysis Plan (SAP) for GC-009 is based on the protocol dated on 16SEP2016.

1. Introduction

This Phase 2 study evaluates the safety and efficacy of two intraocular implants that elute travoprost at different rates in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT). The study duration is 36 months postoperative. One database lock will occur after all subjects have either completed the Month 36 visit or discontinued prematurely.

An analysis will be conducted after all subjects either completed the Month 3 visit or have discontinued prematurely prior to Month 3. At that time, the randomization code will be unmasked to the project team after all the data queries related to the efficacy and safety outcomes are resolved and corresponding data revisions are completed in the database.

This statistical analysis plan provides details of the planned analyses to be performed at the time of the Month 36 database lock. Shells of tables, listings and figures are presented in a separate document.

This document is based on Protocol Amendment 2 (16 September 2016). The statistical definitions and analytical methods described in this SAP supersede that in the protocol. Any revisions to the primary endpoint analyses and significant revisions to the secondary endpoint analyses will be made prior to the database lock. Reasons for such revisions will be described in the final Clinical Study Report (CSR).

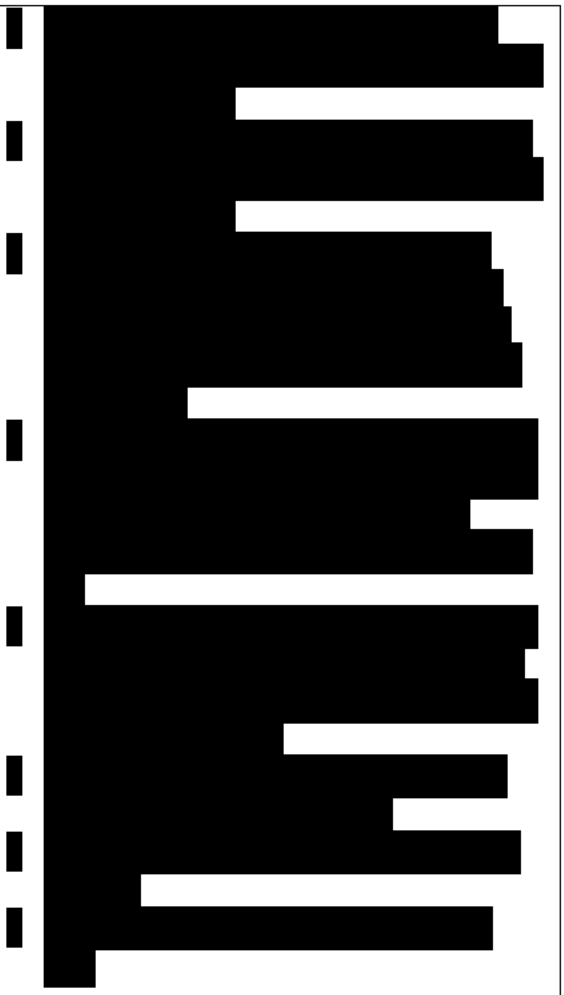
Protocol and Amendment History

Version	Approval Date
Original Protocol	14 November 2015
Amendment 1	08 July 2016
Amendment 2	16 September 2016

2. Objectives and Study Design

2.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Efficacy	
To compare the efficacy of intraocular implants containing travoprost at two different elution rates versus Timolol Maleate Ophthalmic Solution, USP, 0.5% (timolol) in reducing elevated intraocular pressure in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT)	Primary Efficacy Endpoint: • The primary efficacy endpoint is the diurnal IOP in the study eye at 8AM, 10AM, and 4PM at each of Day 10, Week 6, and Month 3 visits (9 timepoints). [redacted]

	
Safety	
To compare the safety of intraocular implants containing travoprost at two different elution rates versus Timolol Maleate Ophthalmic Solution, USP, 0.5% (timolol) in reducing elevated intraocular pressure in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT)	• Adverse events • Surgical complications • Best spectacle-corrected visual acuity • Slit-lamp examination findings • Gonioscopy findings • Ophthalmoscopy findings • Pachymetry • Visual field evaluation • Endothelial cell assessment • Conjunctival hyperemia • Periorbital assessment • Iris assessment (color) • Eyelash assessments (density, length) • Blood laboratory testing of human plasma (systemic exposure to travoprost free acid)

Estimand: the four attributes of the estimand are defined as the following:
1. Population: ITT population including all randomized subjects. Subjects with open-angle glaucoma or ocular hypertension defined through enrollment criteria. [redacted]
2. Variable (endpoint): Post-baseline IOP at 8AM, 10AM and 4PM at each of Day 10, Week 6, and Month 3 visits (9 timepoints).
3. [redacted]
4. Population-level summary parameter: difference in post-baseline IOP means between treatment groups for evaluating of non-inferiority.

2.2. Study Design

This is a prospective, randomized, double-masked (IOP observer and subject), active-controlled, parallel-group, multicenter trial. A total of approximately 150 males and females ≥18 years of age who were diagnosed with either Open-angle glaucoma (OAG) or Ocular hypertension (OHT) will be randomized to one of three treatment arms in a 1:1:1 allocation:

- [redacted]: Travoprost Intraocular Implant, model [redacted] (high elution rate) with masked postoperative one drop twice daily (BID) artificial tears in the study eye.
- [redacted] Travoprost Intraocular Implant, model [redacted] (low elution rate) with masked postoperative one drop BID artificial tears in the study eye.
- Control: Sham surgery with masked postoperative one drop BID topical timolol maleate, ophthalmic solution, 0.5% in the study eye.

Subjects are required to meet all eligibility criteria at the Screening visit. If the subject is using ocular hypotensive medications at this visit, she/he is required to complete the appropriate medication washout period before returning for the Baseline visit. [redacted]

Following completion of the baseline visit, eligible subjects are scheduled for the operative examination. At this visit, subjects will be randomized to treatment and per randomized assignment, either implanted with [redacted], or have the sham surgical procedure performed.

Follow-up visits are scheduled at postoperative Day 1-2, Day 10, Weeks 4, 6, Month 3 and every 3 months thereafter through Month 36. [redacted]

Postoperatively, for the duration of the study, subjects in the [redacted] arms are instructed to use topical eye drops (artificial tears) twice daily in the study eye, while subjects in the control arm, following sham surgery, are instructed to instill topical timolol 0.5% eye drops, solution twice daily in the study eye. The investigator could administer or prescribe ocular hypotensive medication [redacted] at [redacted] or later after the operative exam. [redacted]

The pre-specified primary efficacy endpoint is IOP at each of the nine time points through 3 months postoperative (8:00 am, 10:00 am, and 4:00 pm at Day 10, Week 6, and Month 3). No formal statistical hypotheses for the efficacy endpoint were specified.

Safety parameters included adverse events and complications, best spectacle-corrected visual acuity, visual field, specular microscopy, cup/disc ratio, slit-lamp examination, fundus examination, and gonioscopy.

2.3. Assessment Schedule

[redacted]

2.4. Sample Size Determination

[redacted]

[redacted]

3. Analysis Sets

Intent to Treat Analysis Set (ITT)

This analysis set includes all subjects who are randomized. [redacted]

Safety Analysis Set

The safety analysis set will contain all subjects who are randomized and receive at least one dose of study treatment. Subjects will be grouped according to their actual treatment received, [redacted]

Per-Protocol Analysis Set (PP)

The Per-Protocol analysis set is a subset of the ITT analysis set. It includes all the ITT subjects who received the study treatment based on the randomization schedule and do not have major protocol deviations likely to impact the primary efficacy endpoints. [redacted]

4. General Statistical Considerations

Continuous data will be summarized with the number of non-missing values, mean, standard deviation, minimum, median, and maximum. Other selected percentiles, such as the 25th percentile and 75th percentile may be presented for parameters that are not normally distributed or are suspected of exhibiting that tendency. Categorical data will be summarized with the number of non-missing values and the numbers of values equal to each of the possible values. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the relevant cohort of the corresponding analysis set, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

All inferential statistical analyses will be performed with a two-sided confidence level of 95% or a two-sided significance level of 0.05, except when stated otherwise using SAS® software, Version 9.4, or higher.

Data displays produced for this study will include three types: summary tables, data listings, and figures.

Data listings will simply list the data recorded on the case report form (CRF) or derived for each subject. They will be ordered by treatment, subject number, study eye, and time of assessment. Additional levels of ordering may be employed as appropriate. Data listings will not display subject initials.

In general, summary tables will be presented by treatment group:

- [redacted] Implant
- [redacted] Implant
- Sham/Timolol

4.1. Definition of Variables

4.1.1. Baseline

Baseline for analysis purposes is defined as the last assessment prior to treatment start date/time.

[redacted]

4.1.2. Change and Percent Change from Baseline

- Change from baseline is defined as the post baseline value minus the baseline value.
- Percent change from baseline is calculated as follows: Percent change = (Change from baseline / Baseline) * 100.

4.1.3. Study Days

Study day for analysis purposes is defined as (date of event – surgery date) (+1 if the event occurs on or after surgery start date).

Study Day 1 is the date of surgery. Study Day relative to date of surgery will appear in the listings where applicable.

4.2. Analysis Windows

Data at each scheduled follow up visit will be analyzed according to the nominal visit identified on the data record. The order of nominal visits will be consistent with chronological order of the study visit date. All assessments including scheduled and unscheduled will be presented in the data listings.

4.3. Adjustment for Covariates

[redacted]

4.4. Handling Missing Data

4.4.1. Handling of Missing Data/Intercurrent Events for Efficacy Variables

Please see section 6.1.3 for handling missing IOP data/intercurrent events for the primary analysis.

4.4.2. Imputation of Incomplete Medication/AE Dates

For analyses of adverse events (AEs) and concomitant medication usage, a complete date must be established in order to correctly identify the AE or medication as occurring during treatment or not. For purposes of imputing missing components of partially reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication will be displayed as reported in the subject data listings (i.e., no imputed values will be displayed in data listings).

[redacted]

[redacted]

4.5. Multiple Study Centers

[redacted]

5. Demographic and Baseline Characteristic Analyses

5.1. Subject Disposition

Reasons for screen-failure (including baseline-failure, i.e., subjects enrolled but not randomized) will be tabulated.

Exit status will be classified as completed or discontinued (including reason for discontinuation) for each randomized subject. The reasons for premature discontinuation are:

Exit status will be summarized as number and percent by treatment group and overall for the ITT analysis set.

The number of subjects who were randomized and the number of subjects within each analysis set (ITT, Safety, and PP) will be summarized by treatment group.

Subject disposition data will be provided in a listing. A separate listing describing each subject's inclusion or exclusion status for each of the analysis sets will also be provided.

5.2. Protocol Deviations

Protocol deviations will be captured in the eCRF and reviewed by medical monitor during the study. Classification between major or minor deviations will be decided by the study team prior to database lock. Subjects with major protocol deviations will be excluded from PP analysis set.

All protocol deviations will be listed and summarized by type and treatment group for the ITT analysis set.

5.3. Demographic and Baseline Characteristics

Demographic and baseline subject characteristics will be summarized for the ITT analysis set. Demographics will include age, sex with child-bearing potential for females, race, and ethnicity.

The baseline clinical characteristics include the following variables:

- Type of disease (OAG or OHT)
- Disease Duration from Time of Diagnosis (years)
- [redacted]
- Baseline Study Eye IOP
- Baseline best spectacle corrected visual acuity in study eye - LogMAR
- Iris Color for study eye

- Visual Field Mean Deviation (dB) for study eye
- Visual Field Pattern Standard Deviation (dB) for study eye
- Vertical Cup-to-Disc Ratio for study eye
- Corneal Thickness (µm) for study eye

A listing of demographic and baseline information will be provided.

5.4. Medical and Surgical History

Medical and surgical history including ocular and non-ocular (systemic) medical/surgical history will be collected in the eCRF. Ocular and non-ocular medical/surgical history will be presented in listings.

5.5. Prior and Concomitant Medications/Procedures

Prior and Concomitant Medications

Prior medication is defined as any medication taken prior to the date of the surgery. Concomitant medication is defined as any medication taken on or after the surgery date. If any medication is taken before the surgery date and continues after the surgery date, it will be considered as both a prior and concomitant medication.

Prior/concomitant medications will be coded to therapeutic class and preferred term using the World Health Organization Drug Dictionary [redacted]

The number and percentage of subjects who had taken prior/concomitant medications will be summarized by therapeutic class and preferred term, and by treatment group. Subjects taking the same medication multiple times will only be counted once for that therapeutic class and preferred term. A subject level listing will also be presented.

Concurrent Ocular Procedures

Concurrent ocular procedure is defined as any ocular procedures performed for the study eye after the surgery date. Concurrent ocular procedures will be provided in a listing.

Non-study IOP Lowering Medications

A non-study IOP-lowering medication is defined as a non-study IOP-lowering medication taken for the study eye. [redacted]

The number and percentage of subjects [redacted] will be summarized by type of disease and treatment group.

A listing of the prior and concomitant non-study IOP-lowering medications for study eye will be provided.

6. Efficacy Analyses

6.1. Primary Efficacy Endpoints Analysis

6.1.1. Definition of Endpoints

The primary efficacy measure in this study is IOP. Diurnal IOP (measured at 8AM, 10AM, and 4PM) is evaluated at Baseline, Day 10, Week 6, and Month 3. Standard IOP (measured at 8AM) is evaluated at Week 4 and Months 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36. [redacted]

The primary efficacy endpoint is the diurnal IOP in the study eye at 8AM, 10AM, and 4PM at each of Day 10, Week 6, and Month 3 visits (9 timepoints).

6.1.2. Statistical Hypotheses

[redacted]

6.1.3. Handing of Missing Data/Intercurrent Events for Efficacy Variables

The approaches listed below will be used for handling missing data/intercurrent events:

- **Observed Case (OC):** Missing data are not imputed. Only subjects with available data at the given time point are considered. OC will be the primary approach in the analysis of continuous efficacy variables.
- **Last Observation Carried Forward (LOCF)**: The LOCF analyses will use the last observed non-missing, time consistent, evaluation for efficacy measures assessed to impute missing data at later visits. Baseline efficacy evaluations will not be carried forward. LOCF will be the secondary approach for sensitivity analysis of primary and secondary efficacy endpoints.

[redacted]

- **Non-Responder Imputation (NRI):** Subjects who have missing data or intercurrent events at the timepoint of interest are treated as though they did not respond to the treatment. NRI will be applied to the responder analyses.

6.1.4. Multiplicity Adjustment

[redacted]

6.1.5. Primary Analysis

The primary analysis will be performed for the ITT analysis set based on the observed case (OC), i.e., without missing data imputation.

[redacted]

6.1.6. Sensitivity Analyses

To evaluate the robustness of the primary analysis results, the following sensitivity analyses of the primary efficacy endpoints will be performed, including different imputation methods for missing data:

1. **Sensitivity Analysis 1**

   Same as the primary analysis, a t-test will be performed for the Per-Protocol analysis set on observed case (OC). [redacted]

2. **Sensitivity Analysis 2**

   [redacted]

3. **Sensitivity Analysis 3**

   A t-test using the last observation carried forward (LOCF) method described in Section 6.1.3 will be performed for the ITT analysis set.

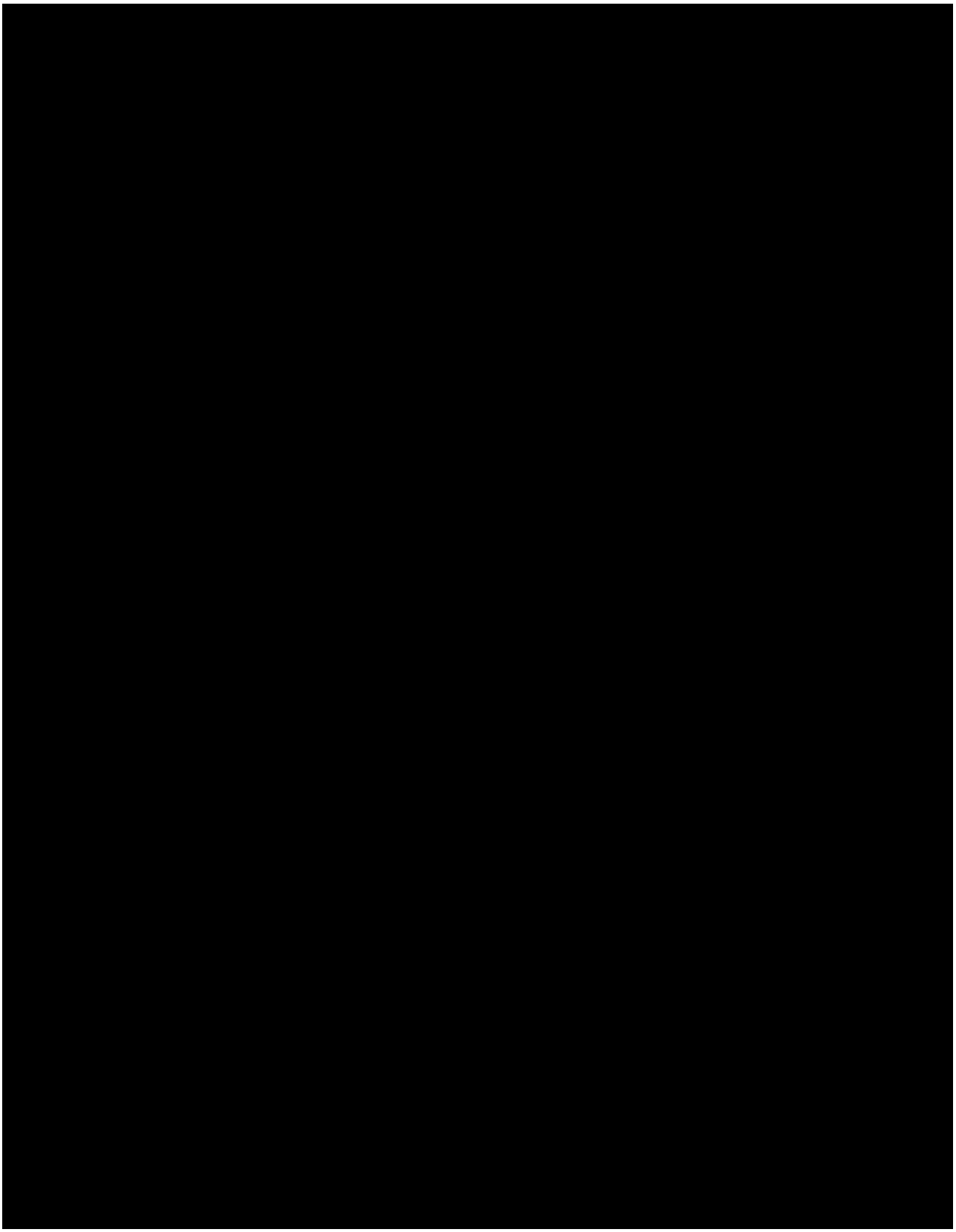
4. **Sensitivity Analysis 4**

   [redacted]

5. **Sensitivity Analysis 5**

   [redacted]

6.1.7. Summary of Planned Analyses



6.1.8. Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy endpoint in the ITT analysis set on observed case. The subgroups are defined as follows:

- Age (<65 vs. ≥ 65)
- Sex (Male vs. Female)
- Race (White vs. Non-White)
- Type of disease (OAG vs. OHT)
- Maximum IOP at Baseline

7. Safety Analyses

The safety analyses will be based on the safety analysis set.

7.1.1. Extent of Exposure

Duration of exposure to study treatment in days will be calculated using the study exit date – surgery date + 1. If the study exit date is missing for subjects with early termination, then the date of last visit will be used as the study exit date. Study duration will be summarized as continuous variable by treatment group for the Safety analysis set. A subject listing will be provided.

7.1.2. Adverse Events

All adverse event (AE) summaries will be restricted to Treatment Emergent Adverse Events (TEAE), which are defined as those AEs that occurred on/after the initial treatment at Visit 3. Verbatim terms reported by the study sites will be mapped to system organ classes (SOC) and preferred terms assigned using MedDRA (Medical Dictionary for Regulatory Activities) [redacted] for summary purposes. The adverse event listings will be displayed by treatment group. The number and of percentage subjects experiencing a particular event will be presented.

For a given AE and subject, if more than 1 severity grade is reported, the highest severity grade will be used for analysis.

If a subject experienced more than 1 relationship within an AE, the subject is counted once under maximum relationship. AEs with a missing relationship will be considered related for this summary; events classified as ‘possibly’, ‘probably’ or ‘definitely’ from eCRF will be considered ‘related’.

Adverse events will be classified into ocular AEs and non-ocular/non-study eye AEs. An ocular AE will be determined as indicated on the AE form of eCRF for the study eye only; a non-ocular/non-study eye AEs will include AEs with primary SOCs of eyes for non-study eye and AEs with primary SOCs not for eye.

All TEAEs, ocular TEAEs and non-ocular/non-study eye TEAEs will be summarized by treatment group separately in the following tables:

- Summary of adverse events
- TEAE by SOC and preferred term
- TEAE by SOC, preferred term and maximum severity.
- TEAE by SOC, preferred term and relationship (Related/Not Related) to study treatment.
- Serious TEAEs by SOC and preferred term.
- Ocular TEAEs by preferred term.

The TEAE listings will be prepared, sorted chronologically within subjects for the following types of AEs. Each listing will be displayed by treatment group.

- All AEs
- Serious AEs
- TEAEs leading to death
- TEAEs leading to withdrawal [redacted]

7.1.3. Best Spectacle Corrected Visual Acuity (BSCVA)

BSCVA will be measured for both eyes using the logMAR chart at all scheduled visits except on the surgery day, Day 1-2, and Day 10. Number of letters correct at 4 meters will be collected.

[redacted]

The number and percentage of subjects in each category will be presented. Similar analyses on change in number of letters correct from baseline will be conducted by visit.

In addition, the actual value and change from baseline in number of letters correct will be calculated for each post-baseline visit and summarized as continuous variable by treatment group.

7.1.4. Slit Lamp Examination and Implant Assessment

The slit lamp examination will include the measurement of aqueous cell and flare by a standard grading system and an evaluation for the presence of corneal abnormalities, pupillary irregularities, iris atrophy and pigment dispersion. Crystalline lens status (for phakic subjects) will also be assessed. Slit lamp examination will be performed for the study eye at each scheduled visit except the surgery day. Severity grades for the findings are:

[redacted]

[redacted]

For the evaluation of aqueous cells and flare, the following grading schemes are used:

[redacted]

[redacted]

The frequency distribution for the severity grade at each scheduled visit will be summarized by treatment group for the study eye.

[redacted]

[redacted]

Slit lamp examination and implant assessment will be presented in data listings.

7.1.5. Gonioscopy

Gonioscopy will be used to assess angle abnormalities including presence of goniosynechiae, angle anatomy and implant location (in subjects with implants). At the screening exam, t[redacted]

[redacted]

The number and percentage of subjects in each category will be summarized.

Gonioscopy findings include abnormal anatomy, goniosynechiae, rubeosis, and other angle abnormalities. The number and percentage of subjects with the gonioscopy findings at each scheduled visit will be summarized by treatment group for the study eye.

[redacted]

7.1.6. Ophthalmoscopy

Ophthalmoscopy will be performed with pupil dilation to examine the fundus and nerve abnormalities for the study eye at Screening, Weeks 4, 6, Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36. The dilated fundus exam will include evaluation of the macula and vessels as well as peripheral fundus examination.

[redacted]

In addition, the number and percentage of subjects with any clinically significant findings at any post-baseline visits, and at each scheduled post-baseline visit will be also presented by treatment group.

7.1.7. Visual Field

Visual fields will be obtained with standard, white-on-white, automated threshold perimetry using Humphrey 24-2, SITA Standard, or Octopus 24-2 Dynamic, or equivalent at Screening, Months 6, 12, 18, 24, 30, and 36.

The same test methodology must be used throughout the entire study for a given subject. Visual field mean deviation (MD) and pattern standard deviation (PSD) will be recorded in decibels (dB). The actual value and change from baseline in MD, and pattern standard deviation will be calculated for each post-baseline visit and summarized as continuous variable by treatment group.

7.1.8. Vertical Cup-to-Disc Ratio

The cup-to-disc (C/D) ratio is a numerical expression indicating the percentage of disc occupied by the optic cup. Vertical C/D ratio will be assessed, and a score from 0.1 to 0.9 (in 0.1 increments) will be recorded for the study eye at Screening, and Months 6, 12, 18, 24, 30, and 36. The change from baseline in C/D ratio at each follow-up visit will be categorized as:

[redacted]

The actual value and change from baseline in vertical C/D ratio for the study eye will be calculated for each post-baseline visit and summarized as continuous variable by treatment group.

The number and percentage of subjects in each category listed above will be provided by treatment group for the study eye as overall (i.e., based on the maximum change from baseline across any post-baseline visits), and by visit.

7.1.9. Pachymetry

Pachymetry is performed to determine corneal thickness for the study eye at Screening, and Months 12, 24, and 36. For each evaluation, three measurements are to be taken utilizing an ultrasonic pachymeter and the mean recorded for analysis. The actual value and change from baseline in corneal thickness will be calculated for each post-baseline visit and summarized by treatment group.

7.1.10. Specular Microscopy

Specular microscopy will be performed in all subjects. Specular microscopic images will be taken in three locations using the microscopes' internal fixation targets (temporal, central, and nasal) of study eyes at Screening, Month 3, Months 12, 24 and 36. Endothelial cell density, percent hexagonality, and the coefficient of variation (COV) will be assessed from calibrated specular microscope images. At each examination, average endothelial cell density for each eye will be reported by the reading center and used for analysis.

The actual, change from baseline, and percent change from baseline in central endothelial cell density will be calculated for each post-baseline visit and summarized by treatment group.

In addition, the number and percentage of subjects with the following categories of changes from baseline in central endothelial cell density will be summarized by treatment group for study eye as overall (i.e., based on the minimum change from baseline across any post-baseline visits), and by visit:

[redacted]

7.1.11. Conjunctival Hyperemia Assessment

Conjunctival hyperemia assessment will be performed at Baseline and all scheduled visits from Week 4. Conjunctival hyperemia will be scored [redacted]:

[redacted]

The number and percentage of subjects in each severity grade will be summarized by treatment group and visit for the study eye, using CRF data and Central Reading Center data separately.

[redacted]

A subject listing will be provided.

7.1.12. Iris Color, Eyelash and Periorbital Assessments

Iris color, eyelash and periorbital Assessments will be assessed at Baseline, Weeks 4, Months 3, 6, 12, 18, 24, 30, and 36. Iris color change and iris pigmentation change from baseline (No, Yes with generalized change or focal change) [redacted]

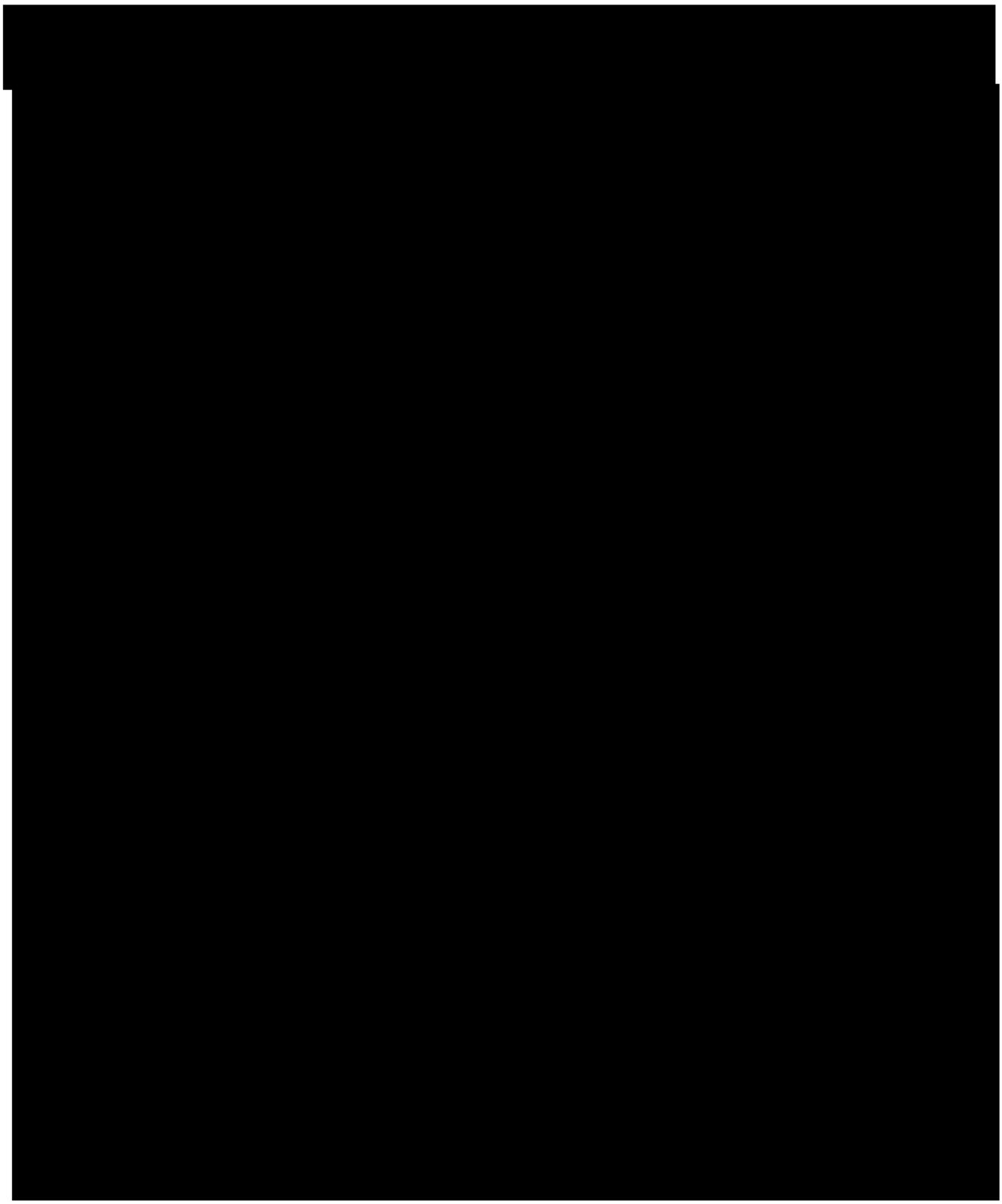
8. Other Analyses

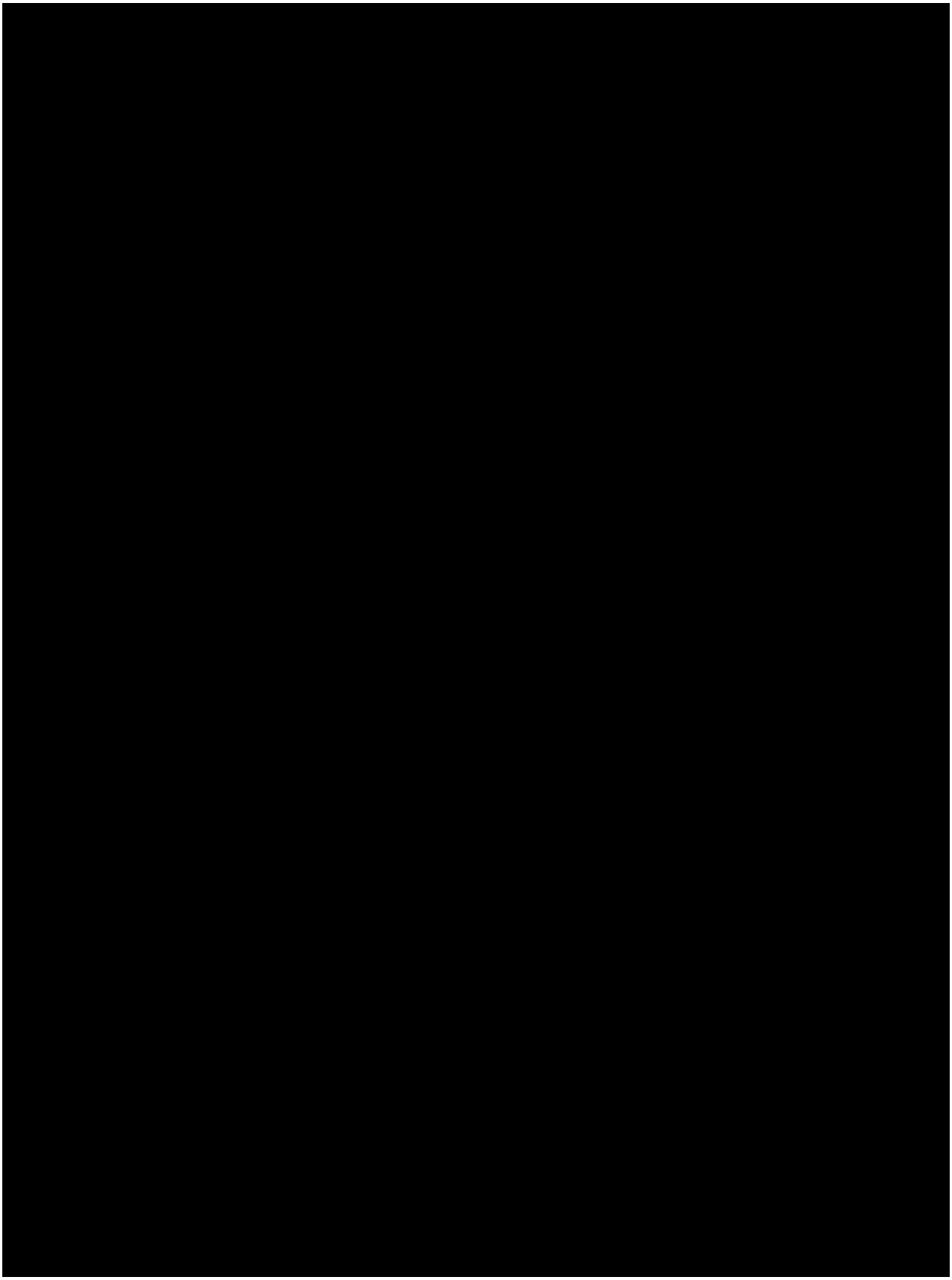
8.1.1. Plasma Sample

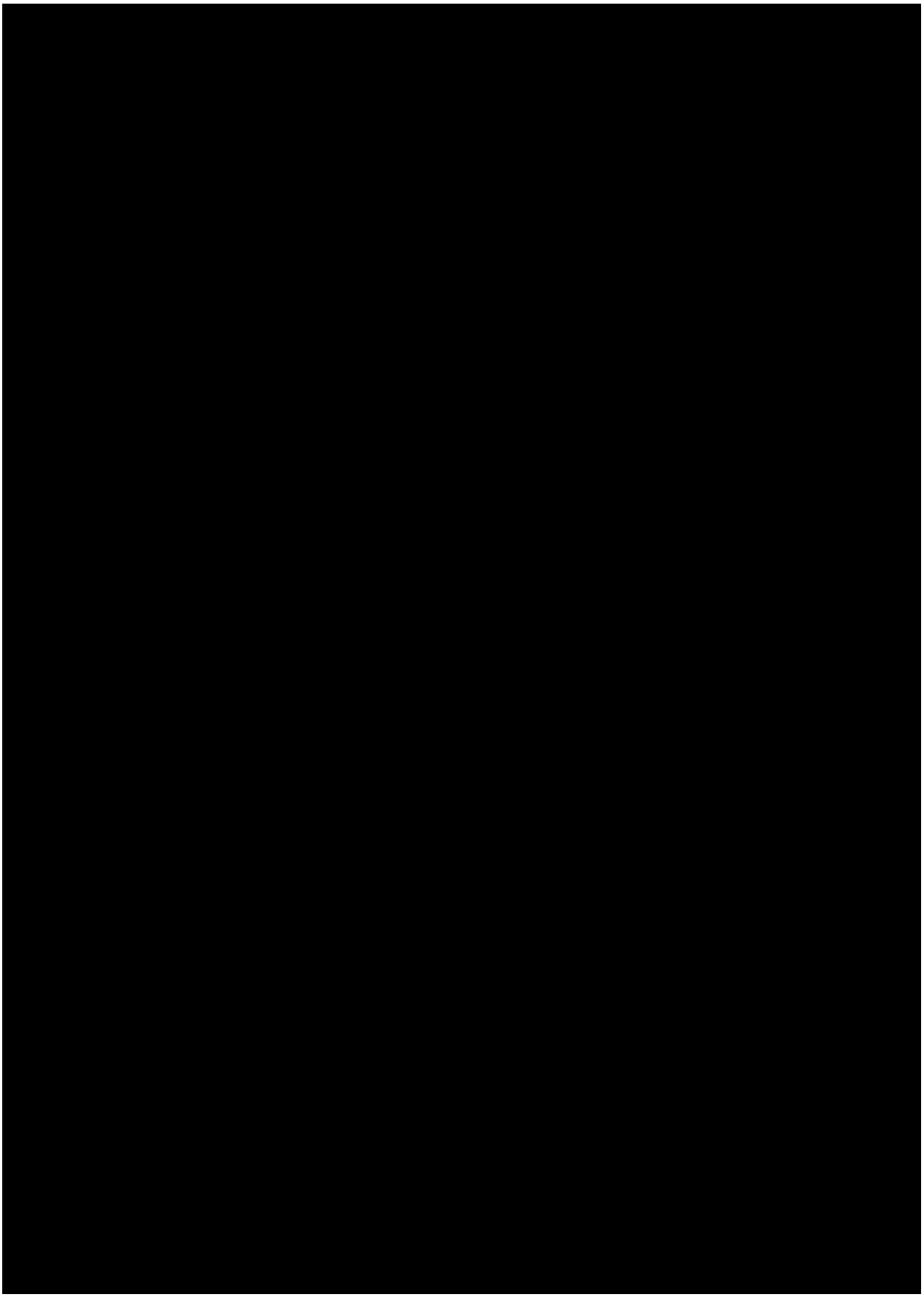
Blood sampling will be performed to evaluate systemic drug concentrations of the travoprost acid in subjects' plasma at the baseline, Day 10, Month 3, and Month 12 examinations. The drug concentration levels will be presented in a listing.

9. Interim Analysis

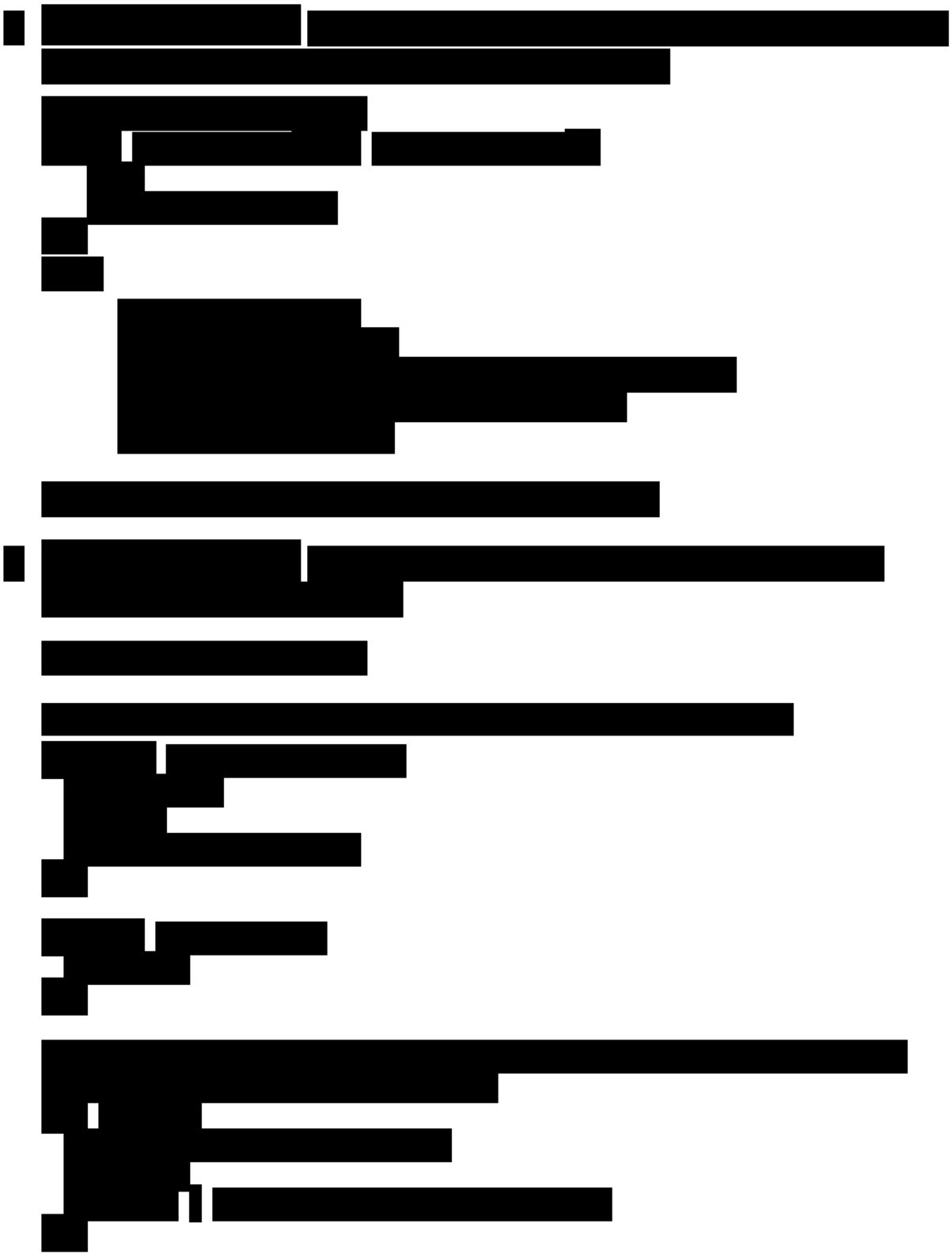
No interim analysis is planned for this study.

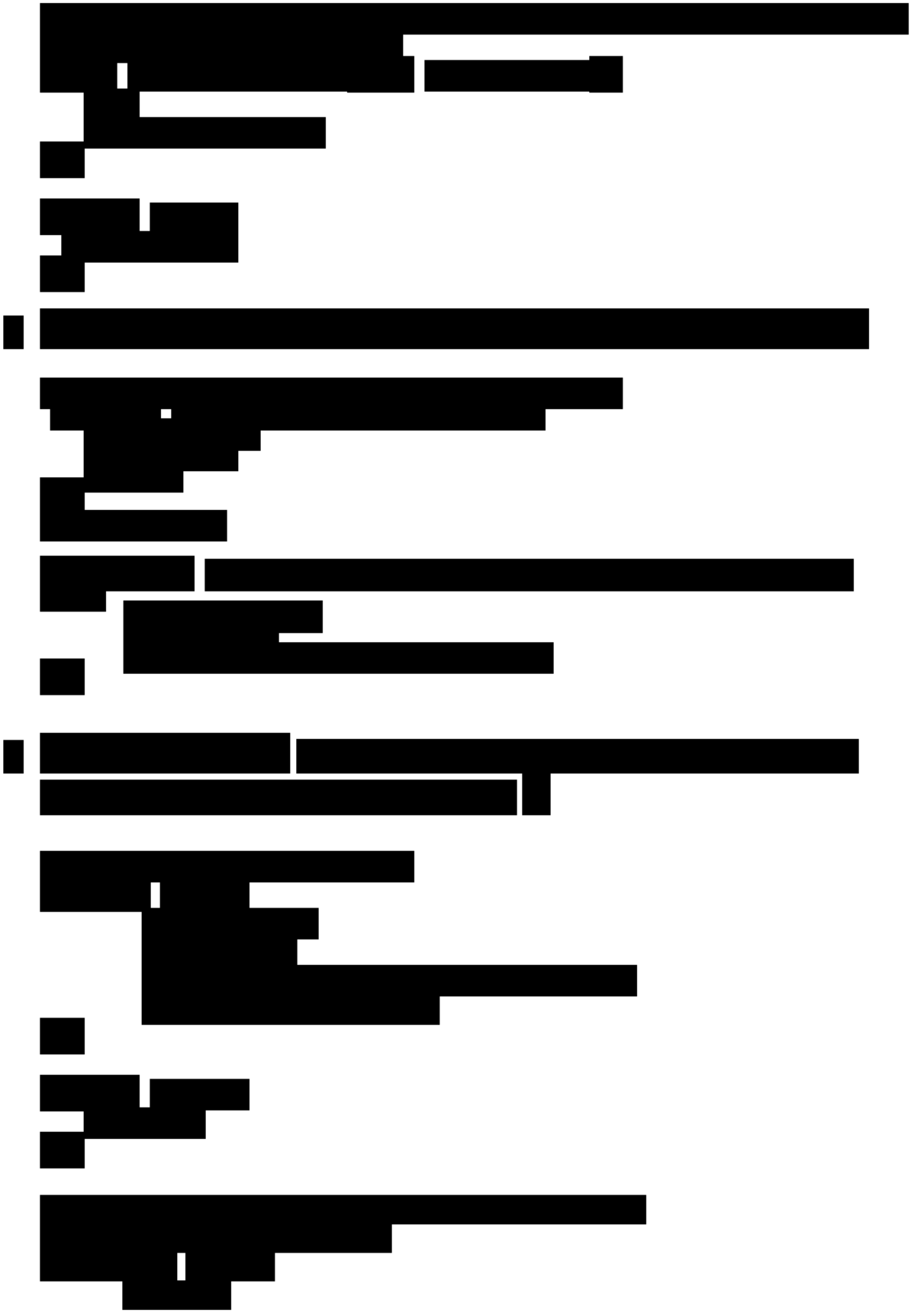


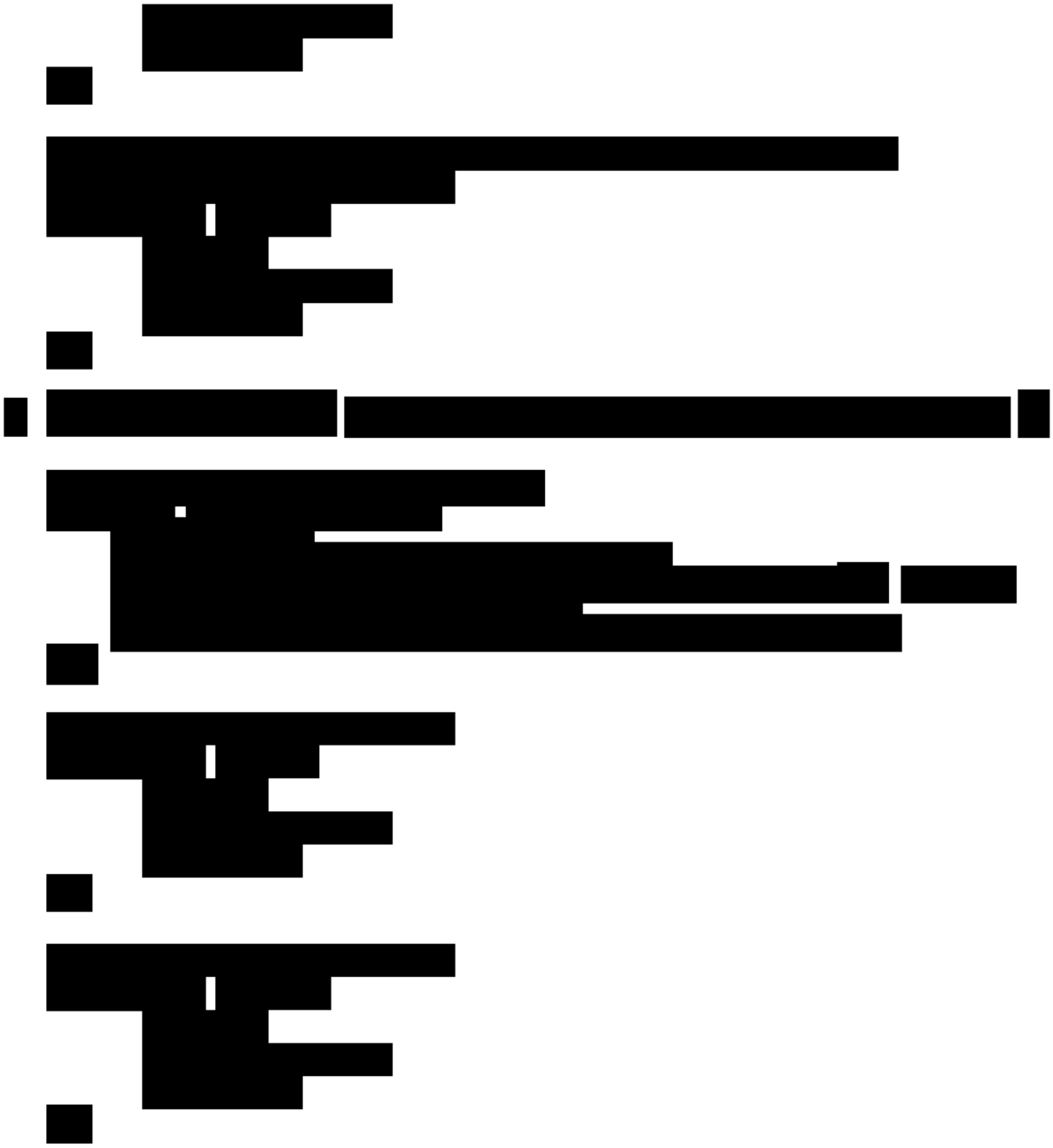




11. Supporting Documentation







12. References