PROSPECTIVE, RANDOMIZED PHASE II STUDY COMPARING TWO ELUTION RATES OF GLAUKOS TRAVOPROST INTRAOCULAR IMPLANTS TO TIMOLOL MALEATE OPHTHALMIC SOLUTION, USP, 0.5%

PROTOCOL #GC-009

DOCUMENT CONTROL # AND REVISION #: CR-0412-2015 REV 2

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Sponsor:

GLAUKOS CORPORATION

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SUMMARY

IND Study Phase: II

TEST Article(s): Travoprost Intraocular Implant, high elution rate (Model G2TR-[redacted])
Travoprost Intraocular Implant, low elution rate (Model G2TR-[redacted])

Concurrent Control: Timolol Maleate Ophthalmic Solution, USP, 0.5% (timolol)

Study Dosage:

Subjects will be randomized to receive one of the following three treatments:

- G2TR-[redacted] implant and one drop of [redacted] instilled in the study eye only [redacted]
- G2TR-[redacted] implant and one drop of placebo eyedrops instilled in the study eye [redacted]
- Sham surgical procedure and one drop of [redacted]

After undergoing either implantation of G2TR-[redacted], G2TR-[redacted] or a sham surgical procedure, subjects will instill masked study medication twice a day in their study eye for 3 years. One drop of medication will be instilled at approximately 8:00 am, and one drop of medication will be instilled at approximately 8:00 pm. [redacted]

Active Ingredient(s):	Two Implant groups:	Travoprost
Active Ingredient(s):	Medication control group:	Timolol Maleate Ophthalmic Solution, USP, 0.5%
Route of Administration:	Two Implant groups:	Intraocular surgical procedure
	Medication control group:	Topical

Date:	Phase:	Protocol No.:
September 16, 2016	Phase II Study	GC-009

Objective:
To compare the safety and initial 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).

Clinical Hypotheses:
- Intraocular implants containing travoprost are at least as effective as timolol in achieving lowered intraocular pressure (IOP) in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT)
- Intraocular implants containing travoprost are well-tolerated

Study Population:
Approximately 150 subjects diagnosed with OAG or OHT will be randomized. Subjects must meet all entry criteria at the Screening Visit. Subjects on 0 medications at the Screening Visit must have an IOP of [redacted] in the study eye, and then complete a 3-day waiting period and return for a Baseline exam. Subjects on 1-3 medications must complete a required medication washout/waiting period. At the Baseline visit, all subjects must have mean diurnal IOP of [redacted] in the study eye, and meet all other entry criteria.

Structure:	parallel groups
Multicenter:	Yes
Masking:	- Observer-masked (IOP readings, assessments of symptomatology) - Subject-masked

Method of Subject Assignment:
After the 4:00 pm IOP measurement at Visit 2 (Baseline), qualified subjects will be scheduled to undergo treatment with the G2TR-[redacted] implant, the G2TR-[redacted] implant, or timolol in a ratio of 1:1:1.

Randomization:	Yes
Estimated Total Sample Size:	Approximately 150 subjects
Statistical Rationale Provided:	Not Applicable

Visit Schedule:
This study will consist of 19 visits over a 3-year period: Visit 1 (Screening), Visit 2 (Baseline), Visit 3 (Operative), Visit 4 (Day 1-2), Visit 5 (Week 1-2, Day 10), Visit 6 (Week 4), Visit 7 (Week 6), Visit 8 (Week 12), Visit 9 (Month 6), Visit 10 (Month 9), Visit 11 (Month 12), Visit 12 (Month 15), Visit 13 (Month 18), Visit 14 (Month 21), Visit 15 (Month 24), Visit 16 (Month 27), Visit 17 (Month 30), Visit 18 (Month 33) and Visit 19 (Month 36).

Study Measures:

Efficacy Measure

The efficacy measurement in this study is IOP. The primary evaluation will be IOP from 1 week through 12 weeks post-treatment.

Safety Measures

- Surgical complications
- Adverse events
- Best spectacle-corrected visual acuity (BCVA; measured as logMAR score using ETDRS chart)
- Slit-lamp biomicroscopy 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)

Specified Plan for Data Analysis: Yes (refer to Statistical Section, Section 9)

[redacted]

Study Variables and Statistical Analysis:

Efficacy Variable

The primary efficacy variable will be the IOP at 1 week through 12 weeks. Refer to the Statistical Analysis Section for the statistical analysis methodology.

Safety Variables

Surgical complications and adverse events will be summarized.

Ocular safety variables, i.e. best spectacle-corrected visual acuity, biomicroscopy findings, gonioscopy findings, ophthalmoscopy findings (including cup/disc ratio), pachymetry, visual field test evaluation and endothelial cell parameters, will be summarized. In addition, changes from baseline in conjunctival hyperemia, periorbital measurements, iris (color) and eyelashes (density and length) will be analyzed, if feasible.

Blood plasma testing will be performed to assess systemic exposure to the implant study medication (travoprost free acid).

Analysis Populations

Refer to Statistical Analysis Section (Section 9).

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
AA	Alpha agonist
AREDs	Alpha agonist
AE	Adverse event
BAK	Benzalkonium chloride
BB	Beta blocker
BSCVA	Best spectacle corrected visual acuity
CAI	Carbonic anhydrase inhibitor
CRF	Case report form
ECD	Endothelial cell density
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good clinical practice
ICH	International Conference on Harmonization
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
LogMAR	Logarithm of the minimum angle of resolution
MA	Medical Affairs
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of mercury
OAG	Open-angle glaucoma
OHT	Ocular hypertension
OTC	Over the counter
PG	Prostaglandin
PVG	Pharmacovigilance
SAE	Serious adverse event
SOC	System organ class
TEAC	Treatment Emergent Adverse Event
VF	Visual field

1. INTRODUCTION

Glaucoma is a group of eye diseases characterized by progressive, irreversible and largely asymptomatic vision loss caused by optic nerve damage, which is most commonly associated with elevated levels of intraocular pressure. Glaucoma is a chronic condition that progresses slowly over long periods of time and can have a devastating impact on a patient's vision and quality of life. Reducing intraocular pressure is the only proven treatment for glaucoma.

Treatment for open-angle glaucoma (OAG) has started traditionally with topical ocular hypotensive medical therapy. Development of more effective medications has increased the popularity of this approaches as initial treatment compared to more invasive incisional or drainage device surgery. Furthermore, the more benign medication treatments preserve the ocular tissues in the event that more invasive surgical approaches are eventually required.

The various topical ocular medications available to reduce IOP include miotics, β-adrenergic receptor antagonists (β-blockers), carbonic anhydrase inhibitors (CAIs), α-adrenergic receptor agonists (α-agonists), and prostaglandin analogues (PGs). The PGs are a class of ocular hypotensive agents that have been proven effective in lowering IOP in subjects with OAG or OHT. Advantages of this class of medications over other classes is that the systemic side effects associated with α-agonists (e.g., dry mouth, drowsiness) and β-blockers (e.g., depression, fatigue, bradycardia) do not appear to be associated with PGs. Furthermore, the ocular side effects typically associated with a-agonists (e.g., allergic reactions), and cholinergic agents (e.g., reduced vision), do not seem to manifest with the use of PGs.

In spite of these apparent advantages, PGs have been shown to be associated with side effects such as ocular hyperemia, iris hyperchromia, periorbital atrophy, increased eyelash growth, general ocular surface discomfort and headache.[1-5] These side effects and other factors including cost, compliance, and the difficulty of proper instillation, hinder the proper use of topical medications.[6,7] Some patients may possess or develop an intolerance to topical medications.

The Travoprost Intraocular Implant was developed to remove or minimize the problem of patient compliance with prescription medication. This clinical protocol will evaluate two versions of the Travoprost Intraocular Implant: Model G2TR-[redacted] and Model G2TR-[redacted]. The implants are identical except that they are designed to elute travoprost at two different elution rates. For the purposes of this protocol, Model G2TR-[redacted] is the high elution rate implant and Model G2TR-[redacted] is the low elution rate implant).

These implants have the potential for providing important benefits to patients. The long duration of drug therapy provided by the implants (up to 3 years) avoids the problem of compliance with topical ocular hypotensive medications. In addition, the small clear corneal incision required for implantation and the minimally invasive implant size avoids some of the complications of more invasive surgical procedures for treating glaucoma.

Earlier versions of both models of the implant have been investigated in a clinical trial conducted in Armenia. The results from this trial have demonstrated the Model G2TR[redacted] and G2TR-[redacted] implants to be potent IOP-lowering implants, with effectiveness being observed through up to 18 months. The implants were also generally well tolerated. Based on the overall efficacy and safety results from this initial international trial, the Model G2TR[redacted] and Model G2TR-[redacted] implants are proposed for further clinical investigation in a U.S. and Philippines Phase II trial.

2. OBJECTIVE

The objective of this study is to evaluate safety and efficacy of intraocular implants containing travoprost at two different elution rates, specifically, the Travoprost Intraocular Implant, high elution rate (Model G2TR[redacted]) and the Travoprost Intraocular Implant, low elution rate (Model G2TR[redacted]), 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).

3. CLINICAL HYPOTHESES

The following are the hypotheses for the study:

- Intraocular implants containing travoprost are at least as effective as timolol in achieving lowered intraocular pressure (IOP) in subjects with OAG or OHT.
- Intraocular implants containing travoprost are well-tolerated.

4. STUDY DESIGN

4.1. Description of Study Design

This is a prospective, randomized, double-masked, active-controlled, parallel-group, multicenter trial comparing the efficacy and safety of the Model G2TR-[redacted] Travoprost Intraocular Implant and the Model G2TR-[redacted] Travoprost Intraocular Implant to topical timolol in subjects with OAG or OHT. Approximately 150 subjects will be randomized in the study. Subjects will be followed through 3 years. Throughout the entire study, both the study staff performing certain measures (see Section 7.3) and the subject will remain masked as to the identity of the study medication. There are two phases to the study - a screening phase and a 3-year treatment/follow-up phase.

Screening Phase

The screening phase will consist of Visit 1 (Screening), a washout/waiting period, and Visit 2 (Baseline). At the Screening visit, prospective subjects will be evaluated to determine if they meet the screening criteria. Subjects who qualify for screening will undergo a washout of any current topical IOP-lowering medication in the designated study eye according to the following schedule:

[redacted]

Subjects who have not used topical ocular hypotensive medications within [redacted] weeks prior to the Screening visit must wait at least [redacted] days before being scheduled for the Baseline visit.

Following the required washout/waiting period, subjects will return for the Baseline visit, and IOP will be measured at 8:00 am, 10:00 am and 4:00 pm. To qualify for the study, subjects must have, at the Baseline exam, mean diurnal IOP between [redacted] and [redacted] in the study eye; and they must meet all other entry criteria. Qualified subjects will be scheduled for treatment.

Treatment Phase

Subjects will begin treatment following Visit 2. The visits scheduled during the treatment phase are: Visit 3 (Operative), Visit 4 (Day 1-2, 1-2 days), Visit 5 (Week 1-2, 10 days ± 3), Visit 6 (Week 4, 28 days ± 3), Visit 7 (Week 6, 42 days ± 3), Visit 8 (Week 12, 91 days ± 7), Visit 9 (Month 6, 182 days ± 14), Visit 10 (Month 9, 274 days ± 14), Visit 11 (Month 12, 365 days ± 14), Visit 12 (Month 15, 455 days ± 30), Visit 13 (Month 18, 547 days ± 30), Visit 14 (Month 21, 637 days ± 30), Visit 15 (Month 24, 730 days ± 60), Visit 16 (Month 27, 820 days ± 60), Visit 17 (Month 30, 910 days ± 60), Visit 18 (Month 33, 1000 days ± 60) and Visit 19 (Month 36, 1095 days ± 60).

There are three treatment groups in the study and 1:1:1 randomization. Subjects will be randomized at the operative exam to receive treatment with either a high elution rate implant with placebo eyedrops instilled twice daily, a low elution rate implant with placebo eyedrops instilled twice daily, or a sham surgical procedure and twice-daily timolol. The operative exam will consist of surgery to implant one of the two implant designs in subjects randomized to one of the travoprost-eluting implant groups, or a sham surgical procedure in subjects randomized to the timolol group.

Following the surgical visit, all subjects will be provided with masked study medication and instructed to instill their medication twice a day in the designated eye for 3 years. [redacted] Subjects will instill masked study medication twice a day in the designated eye(s) for 3 years, beginning on the evening of the operative exam and continuing until the evening before the Month 36 exam (Visit 19). One drop of medication will be instilled at approximately 8:00 am, and one drop of medication will be instilled at approximately 8:00 pm.

At Day 1, Week 4 and Months 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36, IOP will be measured at 8:00 am only. At Week 1-2 (10 days ± 3), Week 6 and At Week 12, IOP will be measured at 8:00 am, 10:00 am and again at 4:00pm. Subjects will exit the study at the conclusion of the Month 36 visit.

4.2. Discussion of Study Design

To qualify for the study, subjects currently using topical ocular hypotensive medication will be required to complete a washout of their medications according to the schedule described above in Section 4.1. These washout intervals were chosen to ensure that the diurnal IOP measurements obtained at the Baseline visit adequately represent the subjects' untreated IOP. They are also in accordance with the intervals included in the recent trials conducted for other anti-glaucoma agents. At selected study visits, IOP will be measured at three time points during the day (8:00, 10:00 am and 4:00 pm).

To provide a comparative evaluation of the efficacy and safety of the travoprost-eluting stents, a commercially available β-adrenergic blocking agent, timolol, was selected as an appropriate active control. Consistent with the current FDA-approved labeling, timolol will be instilled twice a day. In order to facilitate masking of the study medications, subjects assigned to the implant groups will be instructed to instill their study medication in the morning and in the evening.

5. STUDY MEASURES

5.1. Efficacy Measure

The efficacy measurement in this study is IOP. The primary evaluation will be at 1 week through 12 weeks post-treatment.

5.2. Safety Measures

Ocular safety variables include surgical complications, adverse events, BCVA, slit-lamp biomicroscopy findings, gonioscopy findings, ophthalmoscopy findings (including cup/disc ratio), pachymetry, visual field evaluation and endothelial cell parameters.

Changes from baseline in conjunctival hyperemia, periorbital measurements, iris color and eyelash density and length will be analyzed, if feasible.

Blood plasma testing will be performed to assess systemic exposure to the implant study medication (travoprost free acid).

Note: See Appendix A for a schedule of visits and assessments, and Appendix I for a detailed description of the study procedures.

6. MATERIALS

6.1. Study Medications

Subjects randomized to the implant groups in the study will undergo surgery to receive the implants using the test articles described below in Section 6.1.1, before receiving their placebo eyedrops. At the conclusion of the surgical implantation procedure, these subjects will then be dispensed bags with study bottles containing the placebo eyedrops (as described in Section 6.1.3, Other Articles), for use in the morning and in the evening.

Subjects randomized to the timolol topical medication group will first undergo a sham surgical procedure using a syringe (as described in Section 6.1.3, Other Articles) before receiving their timolol study medication. At the conclusion of the sham surgical procedure, these subjects will then be dispensed bags with study bottles containing the timolol medication (as described in Section 6.1.2, Control Article), for use in the morning and in the evening.

Regardless of randomization group, each bottle of study medication (placebo eyedrops or timolol) will be labeled with the study number, unique kit number, and instructions (including dosing time and storage conditions). Study medication bottles will be packaged into kits. Kits will be labeled with the study number, unique kit number, and instructions. The kit label will not denote the type of study medication (placebo eyedrops or timolol) inside.

During the study period, kits containing study medication will be dispensed to the subjects at Day 0, Week 12, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30 and Month 33.

6.1.1. Test Articles (for use in subjects randomized to the implant treatment groups)

Travoprost Intraocular Implants: G2TR-[redacted] Implant and G2TR-[redacted] Implant

[redacted]he implant is filled with

[redacted]

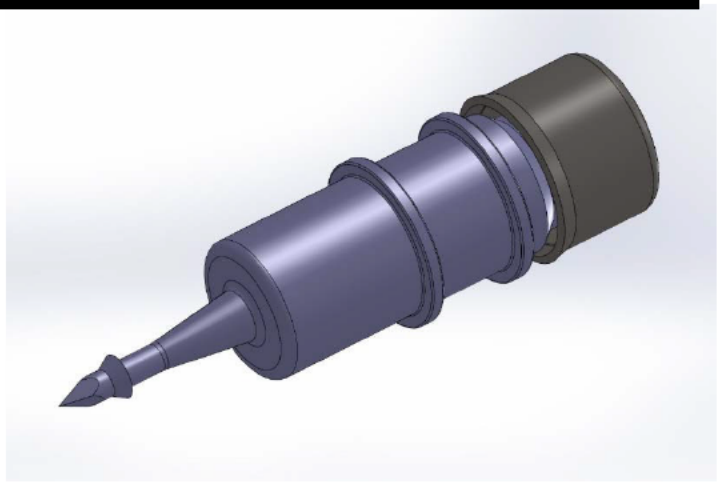


Figure 1. Glaukos Travoprost Eluting Intraocular Implant

The Travoprost Intraocular Implant is provided sterile preloaded onto an inserter in a blister tray, pouch and unit carton. Each tray lid is labeled with the required product identification information. The surgeon should use the provided pre–loaded inserter to implant the product.

The inserter (**Figure 2**) is a sterile, single-use insertion system, pre-loaded with one G2TR implant, and designed to deliver the implant through the trabecular meshwork to the implant site. Surgical instructions are provided in Appendix E.

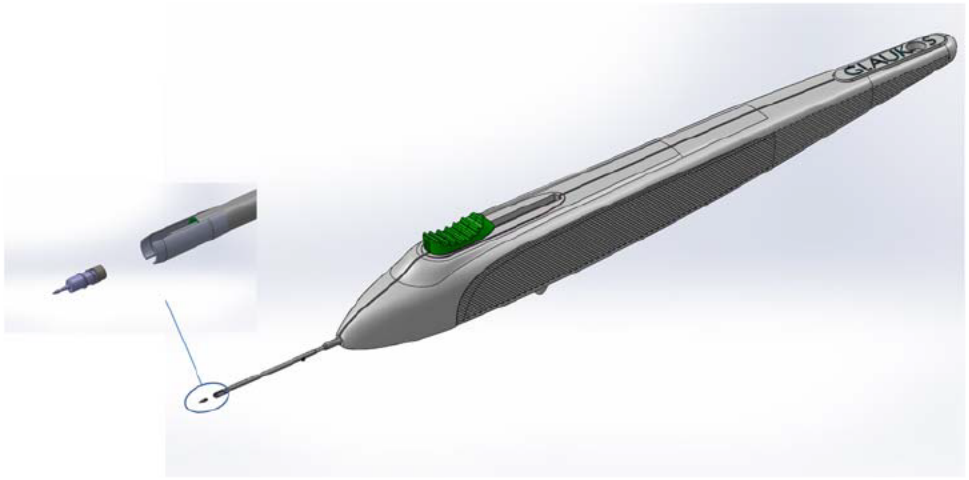


Figure 2. Glaukos Travoprost Eluting Intraocular Implant and Injector

Each unique product is packaged in a pouch and outer carton labeled with the study number, unique kit number, and instructions (including storage conditions).

[redacted]

6.1.2. Control Article (for subjects randomized to the topical medication control group)

Timolol Maleate Ophthalmic Solution, USP, 0.5%. Each mL contains: [redacted]. Each bottle is packaged in an outer carton labeled with the study number, unique kit number, and instructions (including dosing time and storage conditions).

6.1.3. Other Articles

For subjects randomized to the intraocular implant treatment group: [redacted] are to be used as placebo eyedrops.

This product contains:

Active ingredients: [redacted] Each bottle is packaged in an outer carton labeled with the study number, unique kit number, and instructions (including dosing time and storage conditions).

For subjects randomized to the topical medication control group: The syringe used for the sham surgical procedure syringe is a packaged [redacted] with a removable needle. Each syringe is packaged in a pouch and outer carton labeled with the study number, unique kit number, and instructions (including storage conditions).

Laboratory urine pregnancy test kits and kits for obtaining blood specimens will be provided by Glaukos.

7. METHODS

7.1. Subjects

Approximately 150 subjects diagnosed with OAG or OHT will be randomized at up to [redacted] in the United States and Philippines. If both eyes of a subject meet the IOP criteria at the Screening visit, then the right eye will be designated as the study eye. Qualified subjects must complete a required washout/waiting period and meet all other eligibility requirements at the Baseline exam.

7.2. Eligibility Requirements

7.2.1. Inclusion Criteria

7.2.1.1. Screening Inclusion Criteria

Subjects of any race must meet all of the following inclusion criteria:

1) Glaucoma criteria (only for subjects with OAG) as follows:

- [redacted]

2) [redacted]

[redacted]

4) [redacted]

[redacted]

-

tions at screening, mean diurnal IOP ≥ 21 mm Hg and ≤ 36 mm Hg

7.2.2. Exclusion Criteria

7.2.2.1. Screening Exclusion Criteria

Subjects with any of the following conditions (for ocular conditions, in the study eye) are not eligible to participate in the study:

1) Females who are pregnant, nursing or planning a pregnancy, females of childbearing potential who are not using a reliable method of contraception, or females who breast-feed or wish to breast-feed

2) Glaucoma criteria as follows:
   - Traumatic, uveitic, neovascular, or angle-closure glaucoma; or glaucoma associated with vascular disorders

[redacted]

7) [redacted]

[redacted]

8) Other ocular status as follows:

- [redacted]

[redacted]

10) Subject status as follows:

- uncontrolled systemic disease (e.g., diabetes, hypertension) that could compromise their participation in the study

[redacted]

- [redacted]

In addition, the investigator or the Glaukos Medical Monitor may declare any subject ineligible for any sound medical reason.

7.2.3. Criteria for Subject Exit Prior to Study Completion

Subjects exited after signing the informed consent form and prior to study completion will be handled according to the procedure stated in the protocol for enrolled, exited subjects as follows:

7.2.3.1. Prior to Randomization

Subjects may be exited from the investigation if they fail to meet screening criteria, baseline criteria or randomization criteria as outlined in Sections 4.1, 4.2 and 6.2, if they withdraw consent, or if study randomization goals have been met.

7.2.3.2. After Randomization

Subjects may be exited (discontinued) from the investigation in the event of a condition that may cause them harm if participation were to be continued. Subjects may also withdraw involuntarily.

[redacted]

7.2.3.2.1. Subjects Lost to Follow-up

Subjects who do not return for their postoperative study visits and cannot be contacted within a reasonable timeframe via letter or telephone, will be considered lost to follow-up. The site will make at least three (3) telephone calls to the subject. If the three telephone contacts are unsuccessful, the site will send a registered letter with return receipt to the subject. The letter will request the subject to contact and return to the study site. If the subject does not contact the site within a week after the letter was received, he/she will be considered lost to follow-up. If the subject cannot be located or reached, the site will send a second registered letter (with return receipt) to the subject notifying them that they have been exited from the study due to lack of response on the part of the subject to the telephone calls and first registered letter. The site will then exit the subject from the study using the Study Exit CRF.

All attempts at contacting the subject (including telephone call logs, copies of registered letters and registered letter receipts) must be documented and maintained with the subject's study source documentation and CRFs.

7.2.4. Study Termination

This study may be stopped by Glaukos at any time following appropriate notification.

7.3. Procedures

Study visits and assessments are listed below, are provided in a table in Appendix A, and are detailed in Appendix I.

7.3.1. Duration of Study

Following a required washout/waiting period, the treatment period will be 3 years in duration.

7.3.2. Methods to Monitor Subject Compliance

In order to obtain reliable efficacy and safety data, it is critical that each study subject complies with the dosing schedule specified in this protocol. The following precautions will be taken to assure subject compliance during the study:

- [redacted]

7.3.3. Enrollment

All subjects must give written informed consent before undergoing any study-related change in their treatment or any study related procedures. [redacted]

7.3.4. Screening Phase

7.3.4.1. Visit 1 (Screening)

[redacted]

[redacted]

7.3.4.2. Visit 2 (Baseline)

[redacted]

[redacted]

7.3.5. Treatment Phase

[redacted]

[redacted]

7.3.5.2. Visit 4 (Day 1-2 Exam, 1-2 days)

[redacted]

7.3.5.3. Visit 5 (Week 1-2 Exam, 10 days ± 3)

[redacted]

7.3.5.4. Visit 6 (Week 4 Exam, 28 days ± 3)

[redacted]

[redacted]

7.3.5.5. Visit 7 (Week 6 Exam, 42 days ± 3)

[redacted]

[redacted]

[redacted]

7.3.5.7. Visit 9 (Month 6 Exam, 182 days ± 14)

[redacted]

7.3.5.8. Visit 10 (Month 9 Exam, 274 days ± 14)

[redacted]

[redacted]

[redacted]

[redacted]

7.3.5.10. Visit 12 (Month 15 Exam, 455 days ± 30)

[redacted]

[redacted]

7.3.5.11. Visit 13 (Month 18 Exam, 547 days ± 30)

[redacted]

[redacted]

7.3.5.12 Visit 14 (Month 21 Exam, 637 days ± 30)

[redacted]

[redacted]

7.3.5.13. Visit 15 (Month 24 Exam, 730 days ± 60)

[redacted]

7.3.5.14. Visit 16 (Month 27 Exam, 820 days ± 60)

[redacted]

[redacted]

7.3.5.15. Visit 17 (Month 30 Exam, 910 days ± 60)

[redacted]

[redacted]

7.3.5.16. Visit 18 (Month 33 Exam, 1000 days ± 60)

[redacted]

7.3.5.17. Visit 19 (Month 36 Exam, 1095 days ± 60)

[redacted]

If a subject exits from the study before completing Visit 19, then to the extent possible, all follow-up safety assessments that are to be performed at Visit 19 should be performed on the day of exit.

7.4. Concomitant Therapies

7.4.1. Prohibited Medications or Treatments

[redacted]

7.4.2. Permitted Medications or Treatments

Therapy considered necessary for the subject's welfare that will not interfere with the evaluation of the study medication may be given at the discretion of the investigator.

[redacted]

7.4.3. Use of Contact Lenses

Contact lens wear is allowed in this study. Subjects are to be instructed to remove their contact lenses in the study eye prior to instillation of study medications, and to wait for 20 minutes before inserting their contact lenses after instillation of study medication.

7.5. Post-Treatment Management of IOP

7.5.1. Management of Postoperative Intraocular Pressure

[redacted]

[redacted]

7.5.2. IOP Increase to [redacted]

Subjects implanted with Travoprost Intraocular Implants

[redacted]

Subjects in the Topical Timolol Group

[redacted]

7.5.3. IOP Increase to ≥ [redacted]

[redacted]

7.5.4. IOP of [redacted] or Later

[redacted]

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

Following the surgical procedure, all subjects will instill study medication (eyedrops) twice a day for 3 years. For those subjects assigned to the implant and placebo medication groups, the study medication will be artificial tears. For those subjects assigned to the sham surgical procedure and timolol group, the study medication will be topical timolol.

To ensure compliance with the treatment regimen, [redacted]

9. STATISTICAL SECTION

Statistical Methodology

9.1. Power Calculation and Determination of Sample Size

[redacted]

9.2. Statistical Hypotheses and Level of Significance

[redacted]

9.3. Unmasking of Randomization

[redacted] For the final analyses, when all subjects have completed the 12-week Visit, the randomization code will be unmasked to the project team after all the data queries related to the efficacy and safety outcomes have been resolved and corresponding data revisions have been completed in the database.

9.4. General Principles of Data Handling

9.4.1. Data Quality Review

Data screening will be conducted in a masked fashion periodically during the conduct of the study. The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses. Any questionable values or situations will be reported to the Medical Monitor for review and confirmation.

9.4.2. Visit Windows

[redacted]

9.4.3. Handling of Missing and Incomplete Data

[redacted]

9.5. General Statistical Considerations

9.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the IOP at 1 week through 12 weeks post-treatment. The difference in the mean IOP between the control group and each of the two [redacted]

9.5.2. Safety Outcomes

The safety outcomes include surgical complications, adverse events, BCVA, slit-lamp biomicroscopy findings, change in gonioscopy findings, ophthalmoscopy findings (including cup/disc ratio), pachymetry, visual field evaluation, endothelial cell parameters, change from baseline in conjunctival hyperemia, periorbital measurements, iris color and eyelash density and length, and blood plasma testing to assess systemic exposure to the implant study medication (travoprost free acid).

9.5.3. Planned Covariates

The mean IOP comparison will be analyzed adjusting for each of the following covariates separately and all covariates simultaneously.

- [redacted]

9.5.4. Analysis Populations

9.5.4.1. Intent to Treat Population (ITT)

This subset includes all subjects who are randomized. All baseline characteristics will be summarized based on ITT. Subjects in the ITT will be analyzed according to original treatment assignment, regardless of actual treatment received. The primary analyses of the mean IOP comparisons will be based on this ITT population.

9.5.4.2. Safety Population

The safety analysis population will contain all subjects who are randomized, receive treatment, and at least one study medication drop. Subjects will be grouped according to their actual treatment received, not according to their randomization assignment (as randomized). If subjects receive the incorrect medication eyedrops, they will be grouped according to the actual treatment they received, not the medication eyedrops they had been assigned.

9.5.4.3. Per Protocol Population (PP)

The Per Protocol Population is a subset of ITT. It includes all the ITT subjects who received the treatment and medication drops based on the randomization schedule and do not have the major protocol deviations. The major protocol deviations will be determined with the study Medical Monitor in a mask fashion prior to the database lock for the final analyses for the 12-week data. The PP population will be used in the sensitivity analysis for the mean IOP comparisons.

9.5.4.4. Subgroup Analysis Subsets

The mean IOP comparison between the control and each of the two implant groups will be evaluated for the subsets based on the categories of each covariate described in Section 9.5.3). These subgroups will be re-examined and may be re-categorized or eliminated due to small sample size [redacted]

9.5.5. Baseline Definition

Unless specified otherwise, the baseline value for each variable is the value recorded at the last visit on or before treatment. For IOP measurement, the baseline is the measurement taken at Visit 2.

9.6. Data Analyses

9.6.1. General Principles of Data Analyses

The primary analysis for this Phase II study will be performed and summarized after all randomized subjects have had an opportunity to complete their 12-week visit.

The analyses of the safety outcomes will be based on the safety population defined in Section 9.5.4.2. The primary analyses of the efficacy endpoint (IOP) will be based on the ITT population defined in Section 9.5.4.1. The PP population (Section 9.5.4.3) will be used for the sensitivity analyses for the IOP.

Continuous variables will be summarized with means, standard deviations, medians, minimums, maximums, and number of non-missing observations for each treatment group. 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 variables will be summarized by counts and by percentage of subjects in corresponding categories.

[redacted]

9.6.2. Subject Enrollment and Disposition

The reasons for subject enrolled but not randomized (including screen failures) will be provided. Subject disposition will be summarized for all the randomized subjects. The summary including the number and percentage (based on total number of subjects randomized) of subjects in each of the following categories will be prepared for each of the three treatment groups.

- [redacted]

Protocol deviations will also be summarized by the type of deviations and treatment groups.

9.6.3. Subject Demographic and Baseline Characteristics

The following parameters will be summarized by the standard methods for continuous and categorical variables described in Section 9.6.1.
The demographics include the following parameters:

- Age at informed consent
- Sex
- Race/Ethnicity
- Study eye

The baseline characteristics include the following:

- Type of disease (OAG or OHT)
- [redacted]
- Screening IOP
- Baseline IOP
- Baseline best spectacle corrected visual acuity (ETDRS)
- Baseline specular microscopy

- Gonioscopy at screening
- Dilated fundus finding at screening
- Nerve abnormality at screening
- Vertical cup-to-disc ratio at screening
- Visual field at screening
- Pachymetry at screening
- Conjunctival hyperemia assessment at baseline
- Periorbital assessment at baseline
- Iris assessment at baseline
- Eyelash assessment (density, length) at baseline
- [redacted]

[redacted]

9.6.4. Efficacy Analyses

9.6.4.1. Primary Efficacy Analysis

The primary analyses of the mean IOP comparison between the control group and each of the two implanted groups at each time point from 1 week to 12 weeks will be based on [redacted] For each of the two implant groups, the least-squares mean of the treatment difference (Implant - Control) at each time point and the corresponding 95% confidence interval will be derived.

9.6.4.2. Sensitivity Analysis

[redacted].

[redacted]

9.6.4.3. Analysis of Covariates

[redacted]

9.6.4.4. Subgroup Analysis

For each sub-group described in Section 9.5.4.4, the repeated measurement model will be performed within each sub-group [redacted]

[redacted]

9.6.4.5. Exploratory Analyses

[redacted]

[redacted]

9.6.5. Safety Analyses

No formal statistical testing will be conducted for the safety analyses. No imputation will be performed for the missing values. All summaries will be based on the available data of the safety population. The descriptive statistics described in Section 9.6.1 will be performed at each visit for the 3 treatment groups separately. Sections below described specific data handling for study drug exposure, surgical complications, adverse events, and best spectacle corrected visual acuity (BCVA).

9.6.5.1. Study Drug Exposure

Post-treatment systemic exposure to travoprost free acid will be evaluated by analyzing data from systemic drug concentrations in human plasma at Week 1-2, Week 12 and Month 12. The descriptive statistics for continuous variables will be

used to summarize the concentration levels and the change from the pre-dose levels at each visit.

9.6.5.2. Surgical Complications

It is expected that more surgical complications will be reported for the implant groups than the control group. [redacted]

9.6.5.3. Adverse Events

All adverse event (AE) summaries will be restricted to Treatment Emergent Adverse Events (TEAE), which are defined as those AEs that occurred after the initial treatment at Visit 3. [redacted]. It should be noted that AEs that occurred after during the baseline washout will be summarized separated. The adverse event listings will be displayed by treatment group. The number of subjects experiencing a particular event, the percentage of subjects experiencing the event, and the total number of events will be presented. The following summaries will be created:

- TEAE by SOC and preferred term
- TEAE by SOC, preferred term and maximum severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. AEs with missing severity will be considered severe for this summary.
- TEAE by SOC, preferred term and closest relationship to study treatment (Related/Not Related). [redacted]
- Serious TEAEs by SOC and preferred term.

9.6.5.4. Best Spectacle Visual Acuity (BSCVA)

The number of ETDRS letter reads correctly will be summarized descriptively at each visit using the statistics for the continuous variables described in Section 9.6.1 for each of the three treatment group. The change in the number of ETDRS letters from baseline to the follow-up visits will be calculated for each subject. The change in the

number of ETDRS will be summarized using the statistics for the continuous variables.

Additionally, the number and percentage of subjects will be summarized for each of the three treatment groups based on the following VA categories:

10. ADVERSE EVENTS

Adverse events will be monitored throughout the course of the study, and reported on an adverse event (AE) form. Any significant change in a subject's condition from baseline, regardless of causality, is to be considered an adverse event, unless the change is determined to be a continuation of a pre-existing condition that is documented in the subject's medical history. However, a clinically significant increase in frequency or worsening in severity of a pre-existing condition may indicate an adverse event. In addition, a clinically significant laboratory finding may also indicate an adverse event. Lack of efficacy of the study treatment for the condition being investigated is not an adverse event. Subjects should be asked using a general, non-direct question if there has been any change in how they feel from the previous visit (e.g., "How have you felt since the last visit?"). Direct questioning and examination should then be performed as appropriate. If an adverse event occurs, then an AE form must be completed including a description of the event, seriousness, severity, onset and duration, action taken, outcome, and relationship to study medication. A separate AE Form must be completed for each adverse event. All items on the AE form must be completed.

If an adverse event is ongoing at the time of study exit, then the investigator should perform reasonable follow-up efforts as necessary (e.g., telephone contact, post-study office visit) to determine the outcome of the event.

10.1. [redacted]

[redacted]

10.3. Serious Adverse Event

Serious adverse events are defined as any findings that suggest a significant hazard, contraindication, side effect, or precaution. Any adverse event is considered a serious adverse event if it results in any of the following outcomes:

- Death

- Life or sight threatening
- In-subject hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. A life-threatening event is any event that places the subject at immediate risk of death from the event as it occurred; it does not refer to an event that hypothetically might have caused death if it were more severe. A sight-threatening event is any event that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event.

Serious, alarming, and/or unusual adverse events must be reported to Glaukos within 24 hours of the investigator's knowledge of the event:

[redacted]

An AE Form and supplemental SAE Report Forms must be completed as much as possible for all serious adverse events and faxed to Glaukos within 24 hours of knowledge of the event. When new significant information (including the outcome of the event) is obtained, the investigator should inform Glaukos by telephone or facsimile as soon as possible. Depending on the nature and seriousness of the AE, Glaukos may request copies of the ophthalmic and medical record of the subject as well as results of laboratory tests. If the subject was hospitalized, a copy of the discharge summary must be forwarded to Glaukos as soon as possible.

10.4. Unexpected Adverse Event

An adverse event is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed, or is not consistent with the risk information described in the general investigational plan or protocol. For example, under this definition, hepatic necrosis would be unexpected.

Unexpected adverse events must be reported to Glaukos within 24 hours of the investigator's knowledge of the event:

[redacted]

An AE Form and supplemental SAE Report Forms must be completed as much as possible for all unexpected adverse events and faxed to Glaukos within 24 hours of knowledge of the event. When new significant information (including the outcome of the event) is obtained, the investigator should inform Glaukos by telephone or facsimile as

soon as possible. Depending on the nature and seriousness of the AE, Glaukos may request copies of the ophthalmic and medical record of the subject as well as results of laboratory tests. If the subject was hospitalized, a copy of the discharge summary must be forwarded to Glaukos as soon as possible.

10.5. Non-Serious Adverse Event

A non-serious adverse event is any event that does not meet the criteria of a serious adverse event as described in Section 10.7 above

10.6. Intercurrent Events Prior to Randomization

Untoward events that occur during the screening or baseline phase (prior to randomization) will be considered intercurrent events. If an intercurrent event occurs during the screening phase of the study, it should be recorded in the subject's source document. For subjects enrolled in the study, the intercurrent event will also be recorded on the appropriate Visit 2 CRF. An AE form will not be completed for an intercurrent event.

10.7. Follow-up After Adverse Events

Adverse events must be followed and documented until complete resolution, resolution with sequelae, or until the subject exits from the study for conditions with no possibility of resolution (e.g., iris atrophy, macular degeneration).

Subjects with AEs will continue to be followed according to the protocol, unless continuing to do so would place the subject at undue risk (e.g., if they are hospitalized).

If a subject in either study group requires additional glaucoma surgery, the subject will continue to be seen for the duration of the study at required follow-up visits so that safety and efficacy can continue to be monitored.

11. MAINTAINING THE MASK

This will be a masked study, in which the treatments will be unknown to the subject and the site staff performing certain measurements. [redacted]

Glaukos must be informed of all instances where a subject's treatment was unmasked and the reasons for unmasking. In case of a medical emergency where it is necessary to know which study medication a subject received, the investigator may obtain the subject's treatment assignment by [redacted] The following

[redacted]

12. INFORMED CONSENT

The investigator or his/her designee will discuss the purpose and pertinent details of the study with each subject. The Informed Consent Form must be approved by the governing Institutional Review Board (IRB). Prior to undergoing any study related change in their treatment or any study related procedures, a subject must understand, sign, and date the appropriate IRB-approved Informed Consent Form. The subject's signature will be witnessed by the individual administering informed consent if other than the investigator. If the investigator administers informed consent, then the subject's signature should be witnessed by another individual (e.g., member of the site staff). The investigator will sign and date the Informed Consent Form where designated. The signed and dated Informed Consent Form will be retained with the study records, and a copy of the signed Informed Consent will be given to the subject.

13. INSTITUTIONAL REVIEW

This study must be reviewed and approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). A copy of the letter indicating IRB approval must be provided to Glaukos (or designee) prior to study initiation. Updates must be provided to the IRB by the investigator at least annually or as required by the IRB.

14. CONFIDENTIALITY/PUBLICATION OF THE STUDY

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information supplied to you that is indicated as confidential.

The data generated by this clinical study are the property of Glaukos (the Sponsor) and should not be disclosed without the prior written permission of Glaukos. These data may be used by Glaukos now and in the future for presentation or publication at Glaukos' discretion or for submission to governmental regulatory agencies. Glaukos reserves the right of prior review of any publication or presentation of data from this study.

In signing this protocol, the investigator agrees to the release of the data from this study, and acknowledges the above publication policy.

15. STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, good clinical practices (GCP), International Conference on Harmonization (ICH) guidelines, the Declaration of Helsinki, and applicable regulatory requirements.

16. RECORD KEEPING

16.1. Source Documents

The clinical investigator must maintain detailed source documents on all study subjects. Source documents include subject medical records, hospital charts, clinic charts, investigator subject study files, as well as the results of diagnostic tests (e.g., laboratory tests, visual field test printouts).

The following minimum information should be entered into the subject's medical record:

- The date the subject entered the study and the subject number
- The study protocol number and the name of Glaukos
- The date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all study related subject visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of study medication accountability, including a copy of study medication labels
- Occurrence and status of any adverse events
- The date the subject exited the study, and a notation as to whether the subject completed the study or was discontinued, including the reason for discontinuation

16.2. Data Collection

The clinical investigator must maintain detailed records on all enrolled subjects. Data for enrolled subjects will be collected with an electronic data capture system. The electronic database, which is Title 21 CFR Part 11 compliant, will be managed by a data management vendor. Access to the database will be granted to authorize study personnel based on their role after training; and the access will be password-protected. The data clarification process will be managed within the electronic data capture system by either system-generated or manually generated electronic queries. Accuracy of data will be verified by 100% source data verification at regular intervals, and all corrections to data will be made in the database.

Exit forms are completed for all enrolled subjects, regardless of their final study status (e.g., subject discontinuation, study termination).

16.3. Study Supply Accountability

The principal investigator is responsible for ensuring that an inventory is conducted upon receipt of the clinical supplies and that the clinical study supplies are received and stored as instructed. The receipt of clinical supplies should be completed, signed, and returned as directed by Glaukos (or designee). A copy must be maintained at the site for the investigator's records. The principal investigator will keep a current record of the inventory and dispensing of all study medications. This record will be made available to the Glaukos monitor (or designee) for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation. All supplies sent to the investigator must be accounted for and in no case will study medications be used in any unauthorized situation.

It is the responsibility of the principal investigator to return any used and unused supplies to the Glaukos monitor (or designee) at the conclusion of the study.

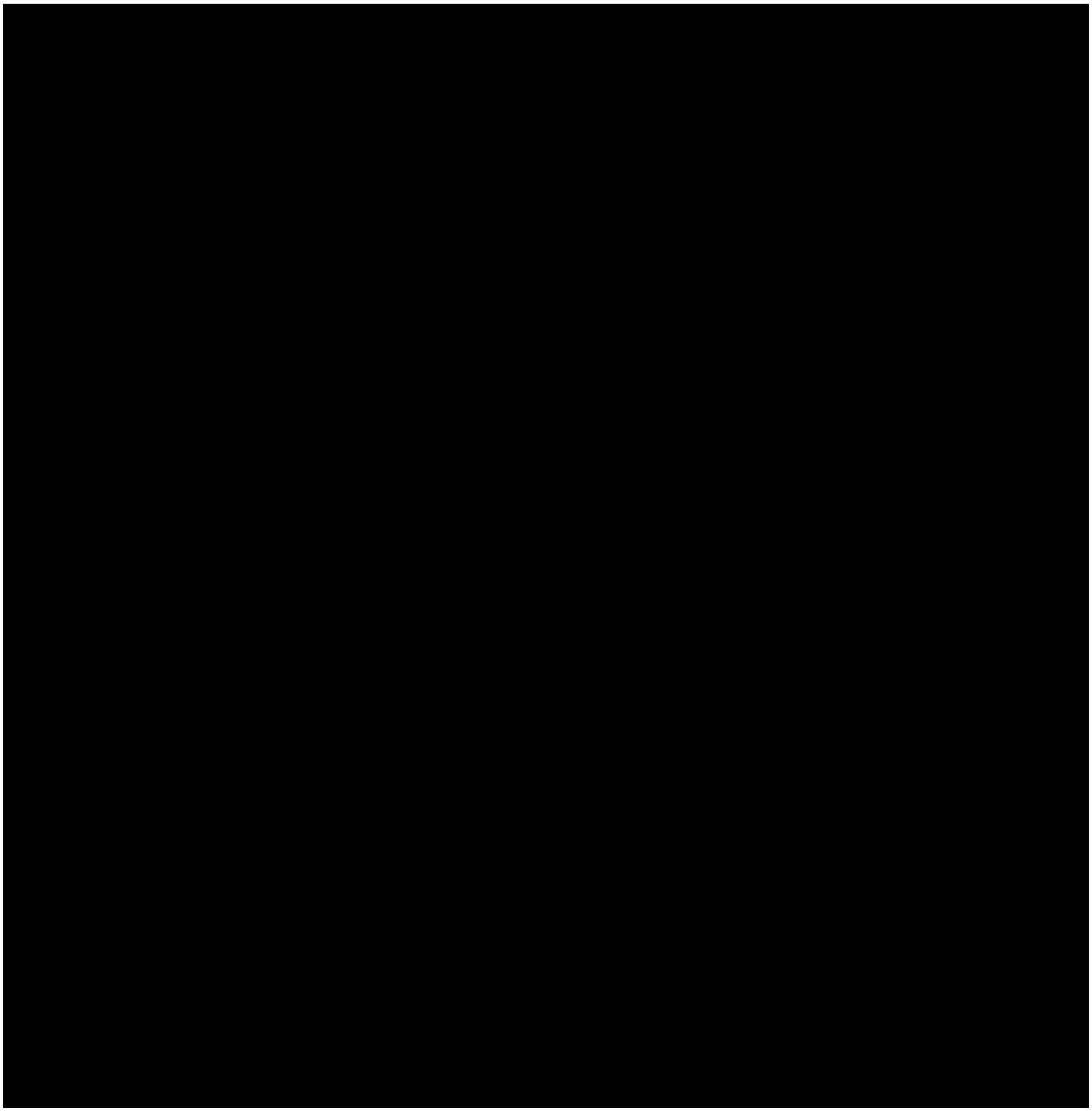
16.4. Record Retention

All records relating to the conduct of this study are to be retained by the investigator until notified by Glaukos that the records may be destroyed.

The investigator will allow representatives of Glaukos' monitoring team (or designee), the governing institutional review board, the Food and Drug Administration (FDA), and other applicable regulatory agencies to inspect all study records, CRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness, and exactness of the data being entered onto the CRF, and compliance with FDA or other regulatory agency regulations.

17. BIBLIOGRAPHY

1. [redacted]



19. APPENDIX B - OBLIGATIONS OF INVESTIGATORS

In summary, the clinical investigator has agreed to the following obligations:

- Obtaining informed consent from every subject prior to enrollment in the study and maintaining records of consent as part of the study records.
- Obtaining approval from the Institutional Review Board (IRB) before enrolling any subject; submitting verification of the approval to the Sponsor; submitting periodic progress reports (at least annually) and final report to IRB.
- Approving the protocol and conducting the study according to the protocol and applicable regulations; informing the Sponsor of all deviations from the protocol.
- Informing the IRB of all protocol amendments/modifications; sending the Sponsor a copy of the letter from the IRB approving the amendment/modification.
- Reporting to the Sponsor and the IRB any adverse experiences that occur in the course of the investigation.
- Keeping careful and accurate records of all clinical study data (study records must be considerably more exact and complete than those kept in ordinary medical practice); maintaining records of all materials submitted to the IRB and of all action by the IRB regarding the study.
- Making study records available for inspection by the sponsor (Glaukos) and representatives of the Food and Drug Administration; keeping records until notified by the Sponsor that they may be destroyed.
- Maintaining proper control and documentation of all test and control articles.
- Submitting the following records and reporting to the Sponsor (See I, II, and III).

I. Prior to the Beginning of the Study
   - A signed Form FDA-1572 or Statement of Investigator.
   - A current curriculum vitae (CV) if not submitted to Glaukos previously or if updated.
   - CVs for all sub-investigators listed on the 1572.
   - A letter from the Institutional Review Board (IRB) indicating that the protocol was approved, including the name and address of the IRB.
   - A copy of the consent form approved by IRB.
   - A list of current members of the IRB.

II. While the Study is in Progress
   - Acknowledgment of receipt of the test and control articles; documentation of disposition of all test and control articles.
   - Original Case Report Forms for each subject enrolled in the study.

- Information regarding all deviations from the protocol.
- Information regarding all adverse medical events occurring to a subject while enrolled in the study.
- Annual progress report (if study is ongoing for more than one year). Letter from the IRB indicating approval of the annual progress report.

III. Once the Study is Completed
- Disposition of all used and/or unused test and control articles, as well as documentation of all drug accountability.
- A final study report (if requested).

20. APPENDIX C - ELEMENTS OF INFORMED CONSENT

I. Elements of Informed Consent

The following information must be provided to each subject in obtaining informed consent. If written consent is being obtained, the subject (or subject's legal representative) should be provided with a copy of the signed written informed consent.

1. State that the study involves RESEARCH.

   A. Explain the PURPOSE of the research.
   B. State the expected DURATION of the subject's participation.
   C. Describe the PROCEDURES to be followed.
   D. Identify any EXPERIMENTAL procedures.

2. Describe any reasonably foreseeable RISKS OR DISCOMFORTS to the subject.

3. Describe any BENEFITS to the subject or to others that may reasonably be expected from the research.

4. Note appropriate ALTERNATIVE procedures or courses of treatment, if any that might be advantageous to the subject.

5. a. Describe the extent, if any, to which CONFIDENTIALITY of records identifying the subject will be maintained.
   b. Note that the Food and Drug Administration MAY INSPECT the records.

6. For research involving more than minimal risk, explain if any COMPENSATION or medical treatments are available should injury occur. If so, explain (a) what they consist of, OR (b) where further information may be obtained.

7. a. Tell whom to contact for ANSWERS to pertinent questions about (a) the research, and (b) research subjects' rights.
   b. Tell whom to contact in the event of a research-related INJURY to the subject.

8. State that:
   a. Participation is VOLUNTARY,
   b. Refusal to participate will involve NO PENALTY or loss of benefits to which the subject is otherwise entitled, and
   c. The subject MAY DISCONTINUE participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

II. Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject.
6. The approximate number of subjects involved in the study.

The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

REFERENCE: 21 CFR Part 50.25 - PROTECTION OF HUMAN SUBJECTS, Elements of informed consent.

21. APPENDIX D - DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical principles for medical research involving human subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA

General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the

consent cannot be obtained in writing, the non-written consent must be formally cumented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

22. APPENDIX E – GLAUKOS TRAVOPROST INTRAOCULAR IMPLANT SURGICAL INSTRUCTIONS

Do not use the implant if the Tyvek lid on the blister tray has been opened or the packaging appears damaged. In such cases, the sterility of the implants may be compromised.

Surgical Instructions

1. The eye should be anesthetized using general, retrobulbar, peribulbar, or topical anesthesia per standard hospital or ambulatory surgery center procedures.
2. It is recommended that the implant surgery be performed from the temporal side, using a temporal clear corneal incision, to provide clear access for the surgical instruments. The implant will be implanted through the trabecular meshwork on the nasal side.
3. Create a clear corneal incision at the temporal limbus location using an instrument of the surgeon's choice.
4. A cohesive viscoelastic is added to the anterior chamber as needed to improve visualization of the angle, and to maintain IOP for use of the gonioscope.
5. A gonioscope is placed on the cornea and the surgical microscope and the patient are positioned as needed to visualize the angle, through the gonioprism, on the nasal side of the eye. Tilting the patient's head as far as practical away from the surgeon, and also tilting the microscope toward the surgeon will help viewing of the angle.
6. The angle is inspected using a gonioprism to ensure good visualization at the nasal implant location.
7. Remove the G2TR[redacted] or G2TR-[redacted] on its inserter from the blister tray. Inspect the implant on the tip of the inserter.
8. When ready for implantation, remove safety clip which holds trigger in place. Keep finger on trigger button to ensure it remains in the forward position and doesn't prematurely release implant.
9. Insertion of Model G2TR-[redacted] or G2TR-[redacted]
    a. Deepen the anterior chamber with additional viscoelastic to aid in chamber maintenance as needed.
    b. Enter the anterior chamber with the implant using supplied inserter.
    c. Advance to the pupillary margin before replacing the goniolens onto the eye.
    d. Care must be taken to avoid contact with the lens or cornea.
    e. Advance to the anterior chamber angle and approach the trabecular meshwork.
    f. Press the distal end of the implant directly into and through trabecular meshwork until the barb at the tip securely penetrates the sclera at the outer wall of Schlemm's canal, and the base of the cylindrical

reservoir is firmly in contact with and compressing the trabecular meshwork.

g. During scleral penetration, it may be necessary to apply firm and focused responsive pressure against the sclera on the outside of the eye to react against the penetration and keep the tissue from collapsing around the sharp tip of the implant thereby preventing penetration.
h. Once the tip barb of the implant is securely embedded in sclera, carefully slide the trigger button rearward to open the jaws of the gripper and thus release the implant from the inserter. Back the inserter away from the implant without allowing it to pull the implant of position.
i. Withdraw the insertion instrument from the eye.

10. High-magnification examination is performed to confirm that the implant is in proper position (i.e., the proximal end rests in the anterior chamber with an unobstructed membrane) and securely attached with the tip barb thoroughly embedded in sclera.
11. It is normal for an edge of the implant to make contact with iris, but most of the membrane should be unobstructed by iris.
12. The anterior chamber is irrigated and aspirated with balanced salt solution (BSS) through the corneal wound to remove all viscoelastic. The surgeon may press down on the posterior edge of the incision as needed to facilitate complete removal of viscoelastic.
13. The anterior chamber is inflated with saline solution as needed to achieve physiologic pressure.

Do not use the implant if the Tyvek lid on the blister tray has been opened or the packaging appears damaged. In such cases, the sterility of the implants may be compromised.

[redacted]

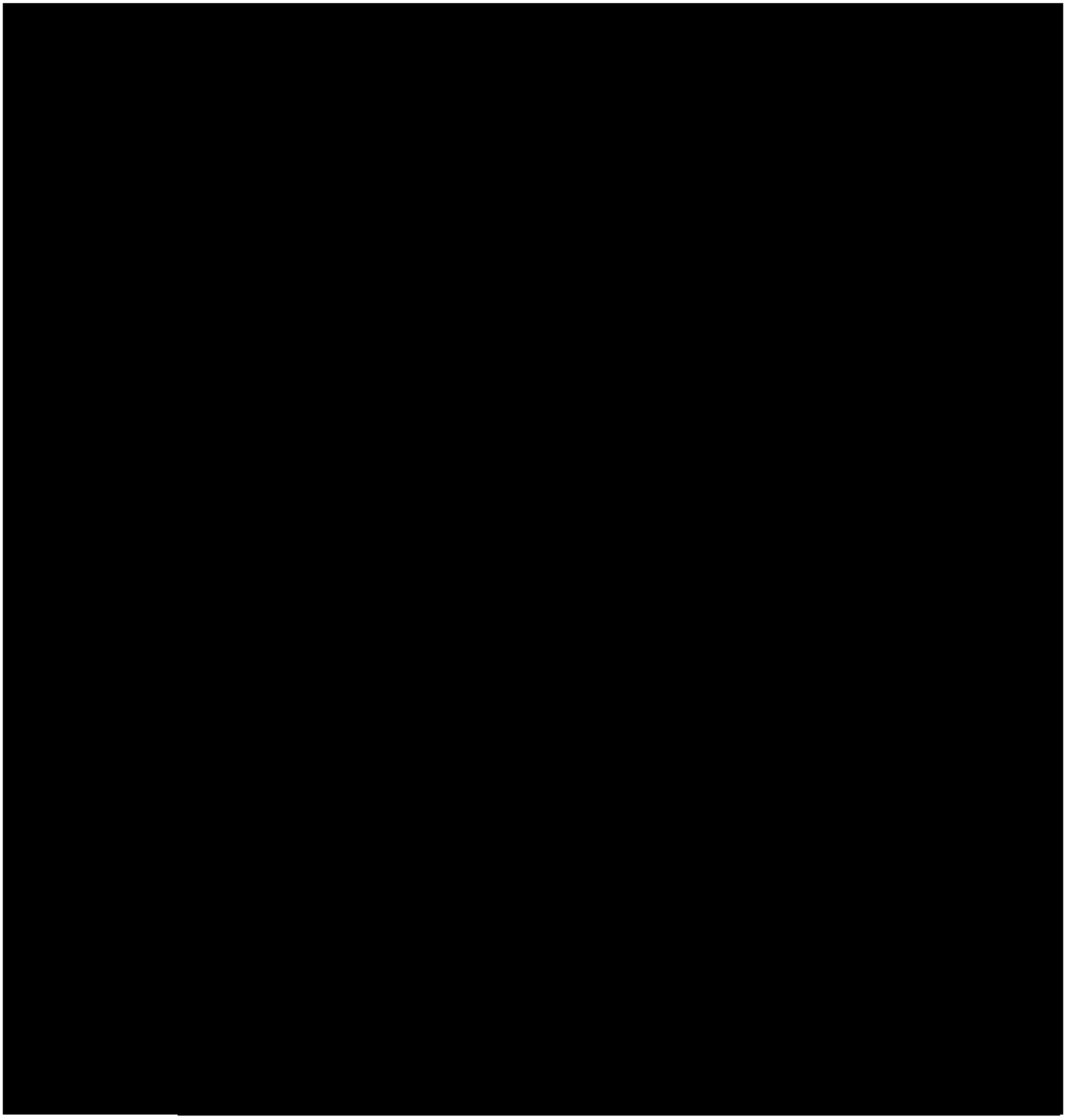
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

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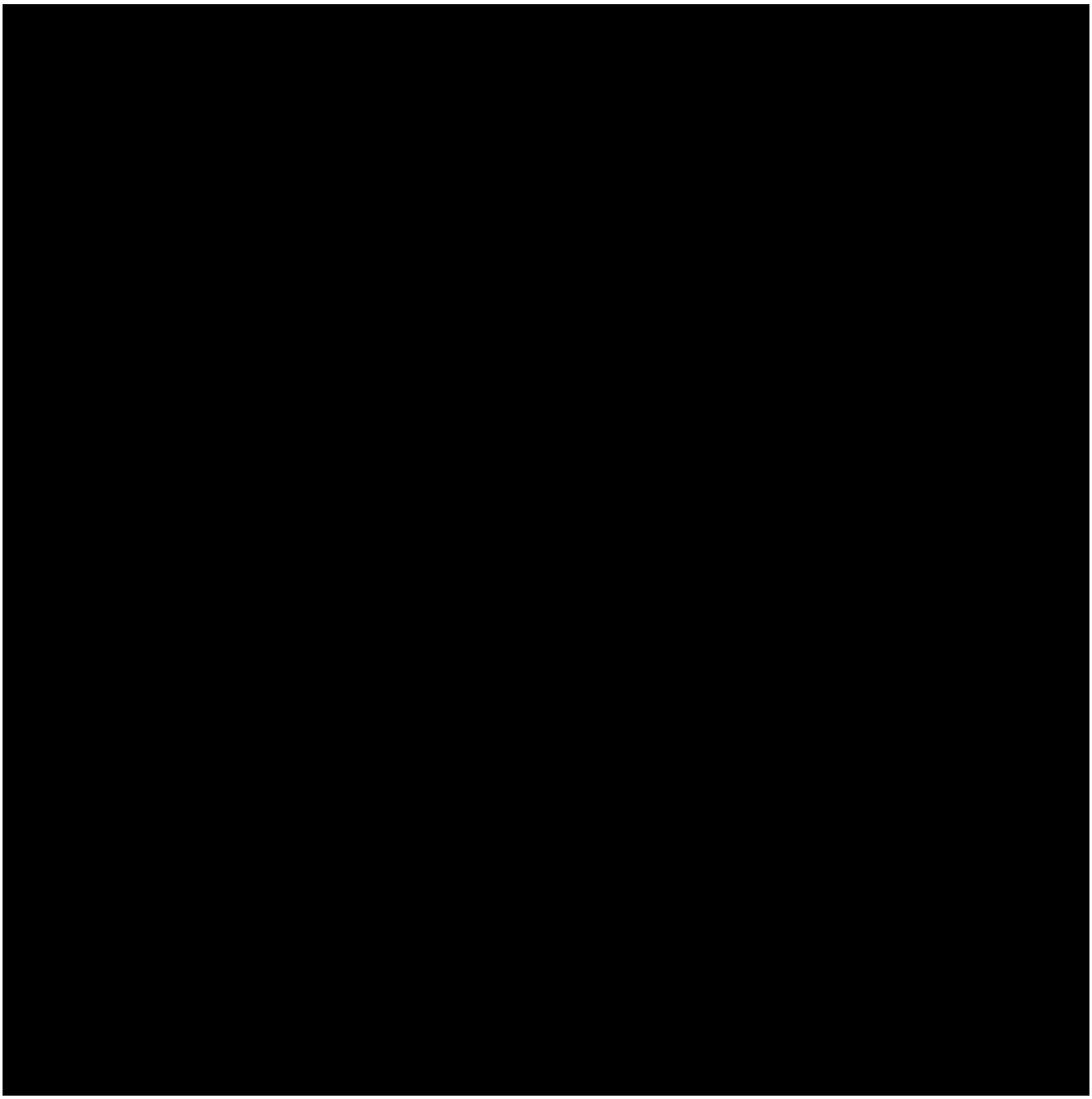
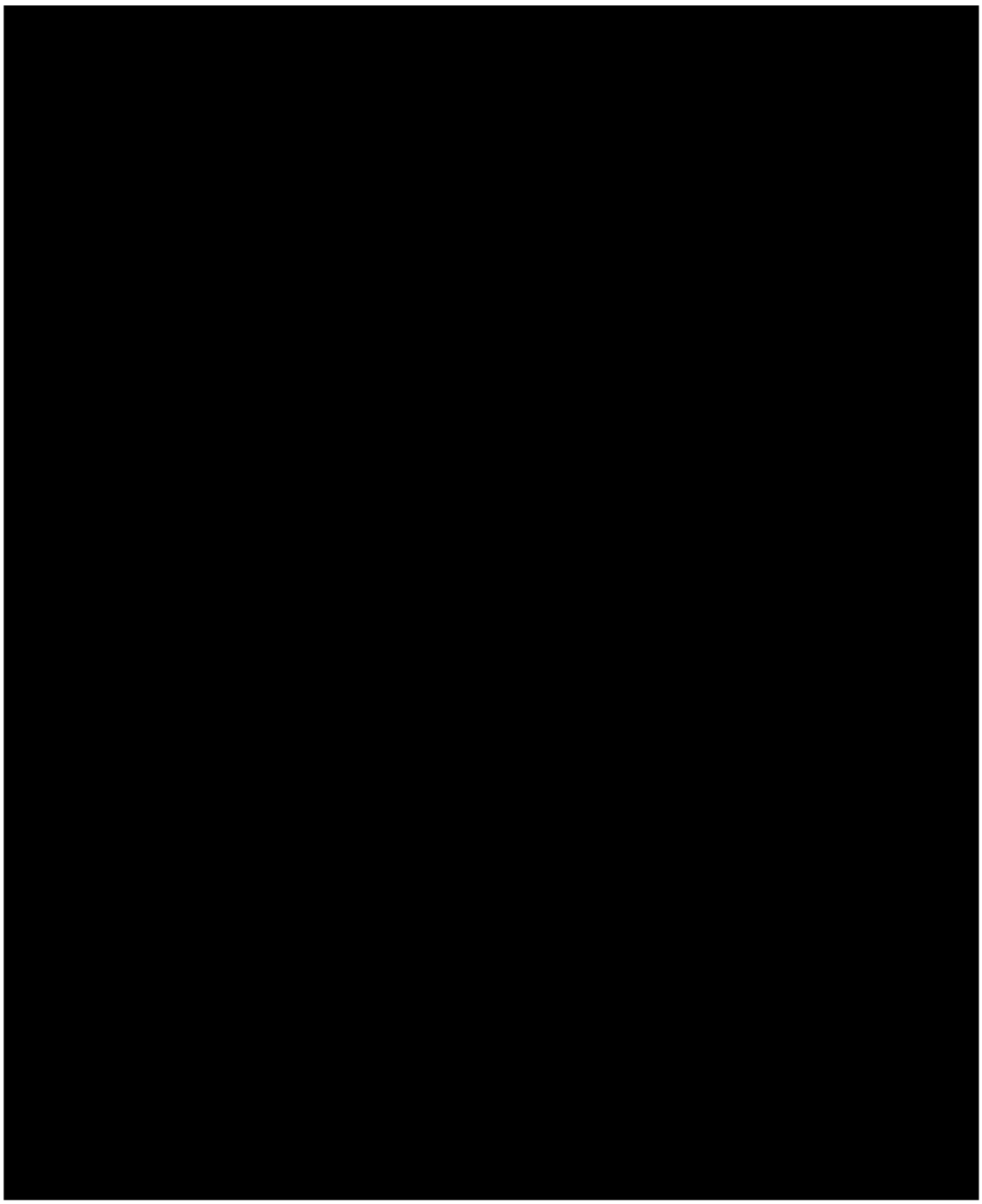
[redacted]



24. APPENDIX G – ARTIFICIAL TEARS PACKAGE INSERT



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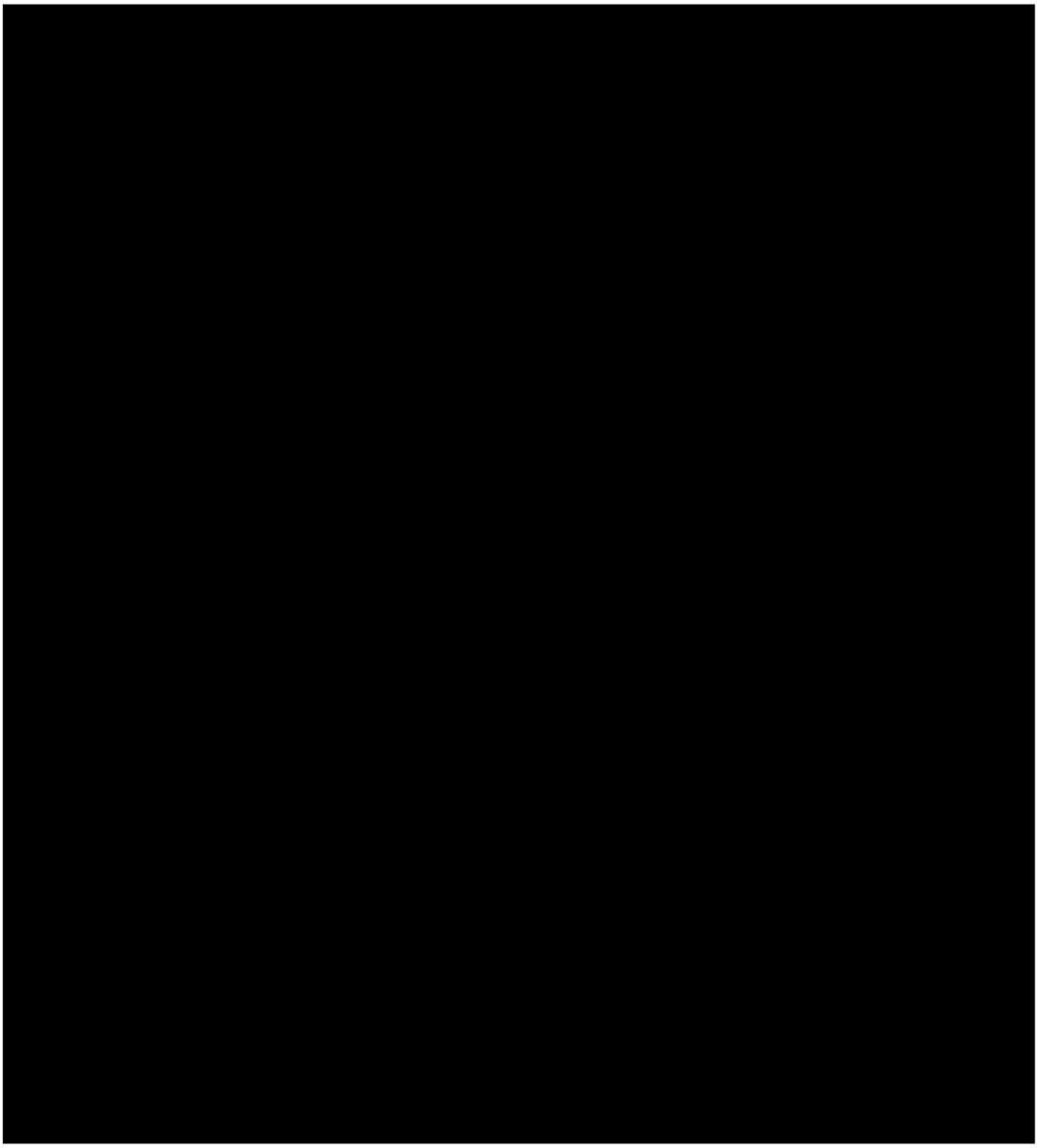
09



25. APPENDIX H – ASSIGNING SUBJECT NUMBERS AND KITS

Subject and kit numbers will be dispensed using in accordance with detailed instructions provided separately. The investigator or his/her designee must access the electronic data base to obtain details of subject randomization and kit use.

26. APPENDIX I - PROCEDURES FOR EXAMINATIONS

[redacted]

[redacted]

26.4. Gonioscopy

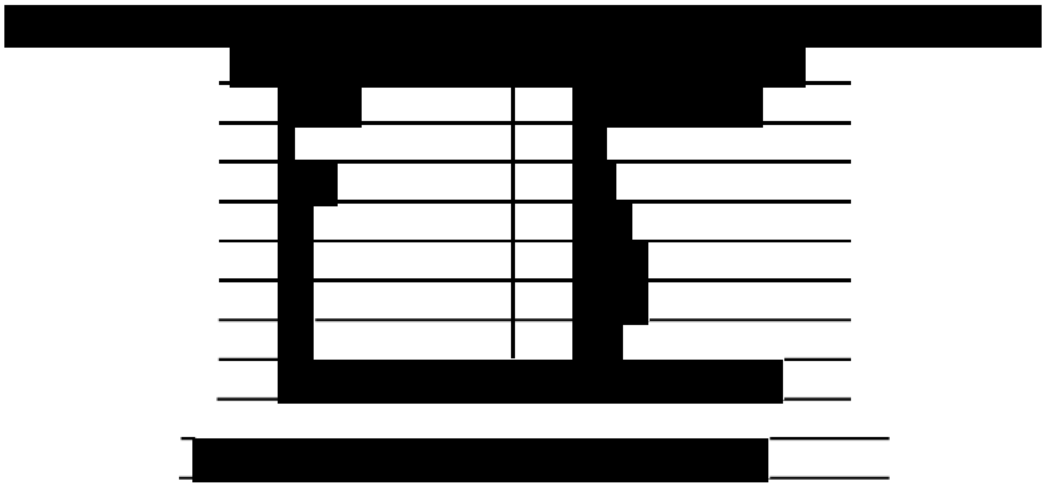
Gonioscopy will be used to assess angle abnormalities including presence of goniosynechiae, angle anatomy and implant location (in subjects with implants). At the screening exam, the Shaffer system for grading the angle anatomy will be used as follows:

NOTE: Gonioscopy is to be performed at all exams starting at Day 1 postoperative

[redacted]

26.5. Slit-lamp Biomicroscopy

The slit lamp exam 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.



[redacted]

[redacted]

General Instructions

[redacted]

[redacted]

[redacted]

26.6. Intraocular Pressure (IOP)

Applanation Tonometry using a Goldmann tonometer will be used to measure intraocular pressure at all visits except for the operative visit. At each visit, IOP will be measured prior to gonioscopy or dilation of the pupil.

[redacted]

[redacted]

[redacted]

26.6.1. Standard IOP Measurement

Standard postoperative IOP measurements will be taken at 8:00 am (± 30 minutes).

26.6.2. Diurnal IOP Measurement

Diurnal IOP measurements will be taken at 8:00 am ±30 minutes, 10:00 am ±30 minutes, and 4:00 pm ±30 minutes).

[redacted]

26.7. Ophthalmoscopy

Ophthalmoscopy will be performed with pupil dilation to examine the fundus and nerve abnormality(ies). The dilated fundus exam will include evaluation of the macula and vessels as well as peripheral fundus examination.

[redacted]

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 [redacted] will be recorded.

[redacted]

26.8. Visual Field

Visual fields must be automated threshold visual fields using [redacted] This program will be used for the duration of the study when required. Visual field testing can be performed dilated or undilated as long as the method is

consistent for each subject at each visit. There are no restrictions on how to prepare subject's eyes for the visual field exam. NOTE: Visual field exams conducted ≤ 6 months of the screening visit can be used as part of the subject's evaluation for inclusion in (or exclusion from) the study as long as the test is performed with [redacted] Values for mean deviation and pattern standard deviation will be recorded.

26.9. Specular Microscopy

Specular microscopy will be performed in all subjects in both groups. [redacted] Endothelial cell density, percent hexagonality and the coefficient of variation will be assessed from calibrated specular microscope images.

[redacted]

[redacted]

26.10. Conjunctival Hyperemia, Iris, Eyelash and Periorbital Assessments and Photographs and Blood Sampling

At the examinations specified in Section 7.3 and Appendix A, the site staff will perform conjunctival hyperemia, periorbital, iris and eyelash assessments at any time during the visit. [redacted]

[redacted]

[redacted]

26.10.1. Conjunctival Hyperemia

Conjunctival hyperemia will be scored [redacted]

26.10.2. Iris (Color) Assessment

Iris pigmentation will be evaluated by [redacted]

26.10.3. Eyelash (length and Density) Assessment

Eyelash length will be measured with the eyelid closed and the subject's head positioned to show the full length of the lashes. [redacted]

Eyelash density will be evaluated [redacted]

26.10.4. Periorbital Assessment

The distance from [redacted]

26.10.5. Blood Sampling

Blood sampling will be performed to evaluate systemic drug concentrations of the travoprost acid in subjects' plasma. As noted in Section 7.3 and Appendix A, at the

baseline, Week 1-2 (10 day ± 3), Week 12 and Month 12 examinations, blood samples will be obtained from each study subject at a lab in close proximity to the investigational site.