PROSPECTIVE, NON-RANDOMIZED, OPEN-LABEL, SINGLE CENTER STUDY TO EVALUATE [redacted] THE PERFORMANCE OF THE TRAVOPROST INTRAOCULAR IMPLANT

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Sponsor:

GLAUKOS CORPORATION

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INVESTIGATOR SIGNATURE PAGE

I have read this study protocol and agree that it contains all the information required to implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices (GCP) and all applicable laws and regulations.

Maintain all information supplied by Glaukos in confidence, and when this information is submitted to an institutional review board (IRB), independent ethics committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

Name of Investigator (Print)	Signature	*Date

***Date of signature indicates date of approval**

Acknowledged By Sponsor:

[redacted]	[redacted]	12FEB2021
Name and Title (Print)	Signature of Sponsor	Date

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SYNOPSIS

This is a prospective, open-label, single center, clinical study of the Travoprost Intraocular Implant, [redacted] (G2TR-125) in subjects diagnosed with open-angle glaucoma (OAG) or ocular hypertension (OHT). The purpose of this study is to evaluate [redacted] the performance of the Travoprost Intraocular Implant and the *in vivo* drug elution rate to be used to establish a correlation model and analysis.

The study is designed to enroll and implant [redacted] (approximately 210 total subjects). Subjects who meet criteria at Visit 1 (Screening) may be scheduled for surgery at Visit 2 during which they will be implanted with the G2TR-125 implant. Depending on the cohort, each subject will be followed for 3 – 24 months at which time the subject will undergo the exchange procedure consisting of removal of the implant and implantation of a new implant. At this visit, aqueous humor samples and the extracted implant will be collected. Following the exchange procedure, all subjects will be followed for an additional 4 weeks.

Test Article(s): Travoprost Intraocular Implant, [redacted] (G2TR-125)

STUDY OBJECTIVE

The objective of this study is to evaluate [redacted] the performance of the Travoprost Intraocular Implant and to study the drug elution rate *in vivo,* as derived from the residual drug in the explant of the Travoprost Intraocular Implant, [redacted]

STUDY TREATMENT

Subjects will undergo implantation and exchange of a Travoprost Intraocular Implant (G2TR-125) through a small temporal clear corneal incision.

Structure:	Multiple cohort
Number of Centers:	Single center
	Open-label

Method of Subject Assignment:
After Visit 1 (Screening), qualified subjects will be scheduled to undergo treatment with the model G2TR-125 implant.

Total Sample Size:	Approximately 210 subjects

STUDY OVERVIEW

Subjects will be assessed for inclusion/exclusion criteria at Visit 1 (Screening). At this visit, all subjects must meet all entry criteria. Subjects who meet the eligibility criteria at Visit 1 (Screening) can be scheduled for Visit 2 (First Operative Day 0) on a separate day.

Visit Schedule:
Depending on the cohort assignment, this study will consist of 10 to 13 visits over approximately 4 to 25 months as follows: Visit 1 (Screening), Visit 2 (First Operative Day 0), Visit 3 (Day 1), Visit 4 (Day 10), Visit 5 (Week 4), Visit 5.1 (Month 6), Visit 5.2 (Month 12), Visit 5.3 (Month 18), Visit 6 Pre-exchange Exam (within 10 days prior to Visit 7), Visit 7 (Second Operative / Exchange), Visit 8 (Day 1 Post-Exchange), Visit 9 (Day 10 Post-Exchange), Visit 10 (Week 4 Post-Exchange).

Study Measures will be collected for the study eye only as shown below:

Safety

- Intra-operative adverse events
- Post-operative adverse events
- Intraocular pressure (IOP)
- Corrected visual acuity (logMAR score using ETDRS chart)
- Slit-lamp biomicroscopy findings
- Gonioscopy findings
- Ophthalmoscopy findings

Other

- Operative and surgical assessments
- Aqueous humor samples and exchanged implants will be collected for analysis of travoprost free acid concentration
- Exchanged implants will be analyzed for residual travoprost.

Specified Plan for Data Analysis: Yes (refer to Section 8)

Power and Sample Size: The sample size of 210 subjects who undergo implantation and exchange of a Travoprost Intraocular Implant was determined empirically. This sample size is considered adequate to provide information on the safety of the exchange procedure. [redacted]

STUDY VARIABLES AND STATISTICAL ANALYSIS

Efficacy Variable

There is no efficacy variable in this study. IOP is assessed for safety.

Safety Variables

Adverse events (intra-operative and post-operative adverse events [TEAEs]) in the study eye will be monitored.

IOP, best spectacle corrected visual acuity, slit lamp biomicroscopy findings, gonioscopy findings, and ophthalmoscopy findings (including cup-to-disc ratio) will be assessed.

Operative and Surgical Assessments will be collected.

Analysis Populations

All subjects contributing aqueous humor samples and/or exchanged implants will be included in the correlation model development and analysis population. All subjects who receive an implant will be included in the safety population. The safety population will be used for all safety data tabulations and listings.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
α-agonists	α-adrenergic receptor agonists
AC Tap	Anterior Chamber Aqueous Humor Sample
AE	Adverse Event
β-blockers	β-adrenergic receptor antagonists
BSCVA	Best Spectacle Corrected Visual Acuity
CAI	Carbonic Anhydrase Inhibitor
CRF	Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IOP	Intraocular Pressure
IRB	Institutional Review Board
IEC	Independent Ethics Committee
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
OAG	Open-angle Glaucoma
OHT	Ocular Hypertension
PE	Post Exchange
PG	Prostaglandin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
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 currently is the only proven treatment for glaucoma.

Treatment for open-angle glaucoma (OAG) traditionally has started with topical ocular hypotensive medical therapy. Development of more effective medications has increased the popularity of this approach 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. Other advantages of this class of medications 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 α-agonists (e.g., allergic reactions), and cholinergic agents (e.g., reduced vision), do not seem to manifest with the use of PGs.

However, 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, can sometimes hinder the proper use of topical medications.[6,7] Some patients may possess or develop an intolerance to topical medications or the preservatives in their formulations.

The Travoprost Intraocular Implant was developed to remove or minimize the issue of patient compliance with topical hypotensive medication. This clinical protocol [redacted]

[redacted]

One of the study objectives is to compare the [redacted] elution rates as derived from the residual drug in the explants [redacted]

This implant has the potential for providing important benefits to patients. The long duration of drug therapy provided by the implant 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.

Model G2TR-125 has been investigated in clinical trials conducted in Armenia (Phase 1/2) as well as the United States (Phase 2 and Phase 3). The results from the U.S. Phase 2 trial have demonstrated that the Model G2TR-125 implant has long-term IOP-lowering effects and is also generally well-tolerated by study subjects. These results support the evaluation of the implant model in this clinical trial.

2 OBJECTIVE

The objective of this study is to evaluate [redacted] the performance of the Travoprost Intraocular Implant and to study the drug elution rate *in vivo,* as derived from the residual drug in the explant of the Travoprost Intraocular Implant, [redacted]

3 STUDY DESIGN

This is a prospective, non-randomized, open-label, single center trial evaluating [redacted] the performance of the Travoprost Intraocular Implant in subjects with OAG or OHT. Approximately 210 subjects will be enrolled into this study and, depending on the cohort assignment, will be followed for 4 to 25 months postoperative.

Screening Procedure:
After providing informed consent, prospective subjects will be evaluated against the eligibility criteria. At Visit 1 (Screening), all subjects must meet all entry criteria to continue in the study.

Subjects who qualify at Visit 1 (Screening) may be scheduled for Visit 2 (First Operative Day 0) (on a separate day).

If both eyes are assessed at Visit 1 (Screening), the eye that qualifies will be the study eye. If both eyes qualify, the RIGHT eye will be selected as the study eye. The subject may then be scheduled for study treatment.

Treatment Procedure:

[redacted] Each cohort has a specified duration and implant membrane type. The duration is the time between the implantation at Visit 2 (Day 0) and Visit 7 (the exchange procedure and collection of the aqueous humor sample and explant). All subjects will have visits at post-operative Day 1, Day 10, Week 4, pre-exchange, and post-exchange Day 1, Day 10, and Week 4.

Table 1 summarizes the additional visits for each cohort along with other cohort information. Appendices A-G show the schedule of visits and measurements for each cohort.

Subjects will be assigned to their cohorts sequentially as defined by the cohort order as they receive surgery. Each cohort must be filled prior to starting the next cohort.

[redacted]

c. [redacted]

At all visits, (Screening, Day 1, Day 10, Week 4, Month 6, Month 12, Month 18, Pre-Exchange, Day 1 Post-Exchange, Day 10 Post-Exchange, and Week 4 Post-Exchange), IOP measurements will be taken once daily, unless surgery is performed.. Study follow-up will continue until Visit 10 (Week 4 Post-Exchange), after which subjects will be exited from the study.

3.1

All subjects are required to meet eligibility criteria at Visit 1 (Screening). The study objective is to evaluate [redacted] the performance of the Travoprost Intraocular Implant. In addition, the *in vivo* drug elution rates will be determined [redacted] Postoperatively, depending on which cohort the subject is assigned to, there are 8 to 13 follow-up visits over a 4- to 25-month period.

4 STUDY MEASURES

4.1 Efficacy

There are no efficacy measures in this study. IOP is assessed for safety.

4.2 Safety

- Adverse events (intra-operative and post-operative adverse events [TEAEs]) in the study eye will be monitored.
- IOP, best spectacle corrected visual acuity, slit lamp biomicroscopy findings, gonioscopy findings, and ophthalmoscopy findings (including cup-to-disc ratio) will be assessed.
- Operative and Surgical Assessments will be collected.

4.3 Other

Aqueous humor samples and exchanged implants will be collected for analysis of travoprost free acid concentration and residual travoprost, respectively, using validated analytical methods.

5 MATERIALS

5.1 Study Medications

Subjects will undergo surgery to receive the implants using the test articles described below in Section 5.1.1.

5.1.1 TEST ARTICLE: TRAVOPROST INTRAOCULAR IMPLANT MODEL G2TR-125

The Travoprost Intraocular Implant is a microscopic titanium container, 1.84 mm in length and 0.494 mm in outer diameter (see Figure 1). The implant is filled with Travoprost formulation, then [redacted] The [redacted] Each implant is designed to be surgically anchored into the anterior chamber angle and elute the drug component slowly.

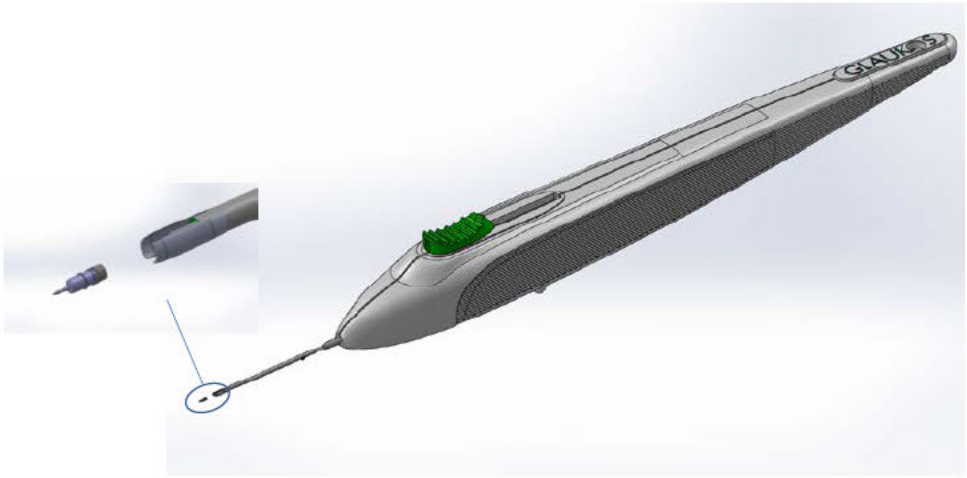
Figure 1. Glaukos Travoprost Intraocular Implant

The Travoprost Intraocular Implant is provided sterile and pre-loaded 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 implant, and designed to deliver the implant through the trabecular meshwork to the implant site.

Figure 2. Glaukos Travoprost Intraocular Implant and Inserter



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 METHODS

6.1 Subjects

Approximately 210 subjects diagnosed with OAG or OHT will be implanted at a single clinical site [redacted] After signing informed consent, prospective subjects will be evaluated to determine whether they meet all other eligibility requirements at Visit 1 (Screening).

6.2 Eligibility Requirements

6.2.1 INCLUSION CRITERIA

6.2.1.1 Visit 1 (Screening) Inclusion Criteria

At Visit 1 (Screening), all subjects must meet the following criteria:

1) Subject status as follows:
   a. male or female, 18 years of age or older
   b. able and willing to attend scheduled follow-up exams for the duration of the study
   c. able and willing to provide written informed consent on the IRB/IEC-approved Informed Consent Form

   Both eyes may be assessed at Visit 1 (Screening).

2) Diagnosis of either OAG (i.e. primary, pseudoexfoliation, or pigmentary glaucoma) or OHT.

All subjects must meet the rest of the following criteria:

3) Zero to three topical IOP lowering medications at the time of Visit 1 (Screening) exam. Combination medications (e.g., Cosopt®, Combigan®) are to be counted as two medications.

4) Best spectacle corrected visual acuity of 16 letters or more correctly read at 4 meters or better in each eye.

5) Angle anatomy defined as follows:
   a. open angle as defined by Shaffer grade ≥ 3 at slit-lamp at the planned implantation site
   b. normal anatomy as determined by gonioscopy
   c. absence of peripheral anterior synechia (PAS), rubeosis or other angle abnormalities that could impair proper placement of the product at the planned implantation site.

6) Lens status as follows:
   a. Phakic, with crystalline lens that does not have visually significant cataract expected to require cataract surgery for the duration of the study, OR
   b. Pseudophakic, with uncomplicated cataract surgery performed > 90 days prior and with implanted posterior chamber IOL fixated in the capsular bag

7) Central corneal thickness ≥ 440 microns and ≤ 620 microns.

6.2.2 EXCLUSION CRITERIA

6.2.2.1 Visit 1 (Screening) Exclusion Criteria

Subjects who meet any of the following criteria in the study eye at Visit 1 (Screening) are not eligible to participate in the study:

1) Glaucoma status as follows:
   a. Traumatic, uveitic, neovascular, or angle-closure glaucoma; or glaucoma associated with vascular disorders
   b. Functionally significant visual field loss, including severe nerve fiber bundle defects
   c. Prior incisional glaucoma surgery

2) Corneal status as follows:
   a. any active inflammation or edema (e.g., keratitis, keratoconjunctivitis, kerato-uveitis)
   b. clinically significant dystrophy (e.g., bullous keratopathy, Fuch's dystrophy)
   c. clinically significant guttata
   d. significant scarring or irregularities (including scars from prior corneal surgery such as PKP, RK, etc.), during the course of the study, that may interfere with IOP measurement reliability
   e. anticipated surgery of any type (including LASIK, LASEK, PRK, etc.), during the course of the study, that may interfere with IOP measurement reliability
   f. opacities or disorders that would inhibit visualization of the nasal angle.

3) Congenital or traumatic cataract (except Mittendorf dots).

4) Choroidal detachment, effusion, choroiditis, neovascularization, or any active choroidopathy.

5) Retinal or optic nerve disorders, either degenerative or evolutive, that are not associated with the existing glaucoma condition, including proliferative diabetic retinopathy, central retinal artery occlusion, central retinal vein occlusion, wet age-related macular degeneration, advanced dry age-related macular degeneration, (e.g., presence of numerous large drusen associated with disturbance to or elevation of the retinal pigment epithelium), significant retinal pigment epithelial changes or optic atrophy.

6) Other ocular status as follows:
   a. clinically significant sequelae from trauma (e.g., chemical burns, blunt trauma, etc.)
   b. history or chronic ocular inflammatory disease or presence of active ocular inflammation (e.g., uveitis, iritis, iridocyclitis, retinitis, ocular herpes)
   c. any pathology for which, in the investigator's judgment, the following would be either at risk or contraindicated:
      i. implantation of Travoprost Intraocular Implant
      ii. compliance to elements of the study protocol (e.g., ophthalmic examinations, follow-up visits).

7) Fellow eye status as follows:
   a. fellow eye actively enrolled in this trial or any other clinical trial.

8) Subject status as follows:
   a. pregnant or planning to become pregnant during the course of the study
   b. uncontrolled systemic disease (e.g., diabetes, hypertension) that could compromise participation in the study
   c. current participation in any study, or participation within 30 calendar days of Visit 1 (Screening)
   d. immunodeficiency conditions
   e. change in an existing chronic systemic therapy that could substantially affect IOP or the study outcomes within 30 days prior to Visit 1 (Screening), or anticipated change in such therapy during the study duration
   f. anticipated to need a topical prostaglandin analogue medication for the duration of the study
   g. known allergy, hypersensitivity or contraindication to the study medications or their components, namely prostaglandin analogues
   h. any ocular disease or condition that in the opinion of the investigator or Medical Monitor may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study. In addition, the investigator or the Medical Monitor may declare any subject ineligible for any sound medical reason.

9) The inability to visualize the implantation site via surgical gonioscopy.

6.2.3 CRITERIA FOR EARLY STUDY EXIT

Subjects may voluntarily withdraw from the study at any time. The investigator may elect to discontinue any subject for reasons unrelated to the study product. Details of a subject's exit from the study should be recorded in the subject's clinical records. Subjects who prematurely discontinue the study may be replaced. Subjects exited after signing the informed consent form and prior to study completion will be handled as follows:

6.2.3.1 Prior to Implantation

Subjects will be ineligible for the study if they fail to meet eligibility criteria (Section 6.2), if they withdraw consent, or if study enrollment goals have been met.

6.2.3.2 After Implantation

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

6.2.3.3 Lost to Follow-up

Subjects who miss postoperative study visits and cannot be contacted within a reasonable time frame via letter or telephone, will be considered lost to follow-up. The site will make at least three attempts to contact the subject via telephone. If unsuccessful, the site will send a letter 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, and the site will send a second letter to notify the subject of study exit due to lack of response to the telephone calls and first registered letter. A Study Exit CRF should then be completed for the subject.

All attempts to contact the subject (including telephone call logs, copies of letters) must be documented and maintained with the subject's study source documentation.

6.2.4 STUDY TERMINATION

The study may be terminated by Glaukos at any time following appropriate notification to the study site and subjects.

6.3 Procedures

Study visits and assessments are listed below; a table overview of study procedures by visit is provided for each cohort in APPENDICES A-G: SCHEDULE OF VISITS & MEASUREMENTS

6.3.1 DURATION OF STUDY

Following the initial implantation, the treatment period will be 4 to 25 months in duration depending on their cohort assignment.

6.3.2 ENROLLMENT

All subjects must give written informed consent before undergoing any study-related change in their treatment or any study related procedures. A subject is considered enrolled at the time the subject undergoes surgery at the First Operative visit (Visit 2). At this visit the subject will be assigned to a cohort in sequential order of study entry. Each individual cohort must have the complete number of subjects (Table 1) enrolled before a subject can be assigned to the next cohort.

Each subject will be assigned a unique subject numbe [redacted] If a subject is discontinued from the study for any reason, the subject number will not be reused.

6.3.3 PREOPERATIVE PROCEDURES

6.3.3.1 Visit 1 (Screening)

1) Written informed consent.
2) Assign subject number.
3) Demographics, medical and surgical history, current ocular and systemic conditions, prescription medications, and medications known or suspected to lower IOP.
4) A pregnancy test (if applicable) may be administered at any time during this visit.

5) Measure best spectacle corrected visual acuity through manifest refraction (ETDRS) in each eye.
6) Perform slit-lamp biomicroscopy (including crystalline lens).
7) Measure IOP (can be measured at any time) and record the time.
8) Pachymetry.
9) Perform a gonioscopic examination.
10) Perform a dilated ophthalmoscopy/fundus examination.
11) Assess optic nerve abnormality (ophthalmoscopy).
12) Assess vertical C/D ratio.
13) Review screening inclusion and exclusion criteria. Do not continue screening any subject who does not meet the screening eligibility requirements.

<u>If the subject is qualified:</u>

1) Schedule the subject for Visit 2 (First Operative Day 0).
2) [redacted]
3) Advise the subject to discontinue taking their topical hypotensive medication beginning the morning of visit 2 (First Operative Day)

[redacted]

<u>If the subject is ineligible for the study, complete the appropriate CRF.</u>

6.3.4 TREATMENT PROCEDURES

6.3.4.1 Visit 2 (First Operative Day 0)

1) Assess demographics, medical and surgical history, current ocular and systemic conditions, prescription medications, and medications known or suspected to lower IOP.
2) Assess any adverse events.
3) Prepare subject for surgery.

4) Administer an additional drop of antibiotic 30 minutes preoperatively.
5) Visually confirm Shaffer grade angle and target implant location.
6) Obtain a treatment kit.
7) Administer anesthetic (topical, general, retrobulbar, peribulbar).
8) Perform surgery.
9) Record clinical data from the surgical procedure on the First Operative Day 0 CRF, noting study eye intra-operative AEs and post-operative AEs.

Postoperatively:

10) Schedule the subject to return for Visit 3 (Day 1).
11) Dispense other postoperative medications and instruct the subject as follows:

6.3.4.2 Visit 3 (Day 1 Exam, 1 days postoperative)

1) Update subject's medical status and concomitant medications.
2) Assess study eye adverse events.
3) Measure pinhole visual acuity (Snellen).
4) Perform slit-lamp biomicroscopy.
5) Measure IOP (can be measured at any time) and record the time (observer).
6) Schedule the subject to return for Visit 4 (Day 10).

6.3.4.3 Visit 4 (Day 10 Exam, 10 ± 3 days postoperative)

1) Update subject's medical status and concomitant medications.
2) Assess study eye adverse events.
3) Measure pinhole visual acuity (Snellen).
4) Perform slit-lamp biomicroscopy.
5) Measure IOP (can be measured at any time) and record the time (observer).

6) Schedule the subject to return for Visit 5 (Week 4).

6.3.4.4 Visit 5 (Week 4 Exam, 28 days ± 3 postoperative)

1) Update subject's medical status and concomitant medications.
2) Assess study eye adverse events.
3) Measure corrected visual acuity (ETDRS). A manifest refraction and best spectacle corrected visual acuity (ETDRS) should be performed if corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
4) Perform slit-lamp biomicroscopy.
5) Measure IOP (can be measured at any time) and record the time (observer).
6) Perform a gonioscopic examination.
7) Schedule the subject to return for the next visit(s) if applicable (see next section)

6.3.4.5 Depending on the cohort, the subject may have one or more of the following visits (please see APPENDIX A-G: SCHEDULE OF VISITS & MEASUREMENTS):

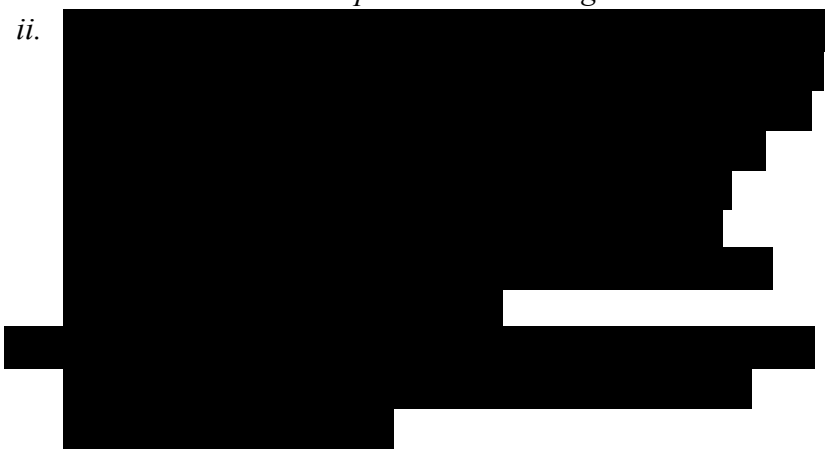
Visit 5.1, (Month 6, 182 days ± 14)

Visit 5.2, (Month 12, 365 days ± 14)

Visit 5.3, (Month 18, 547 days ± 14)

1) Update subject's medical status and concomitant medications.
2) Assess study eye adverse events.
3) Measure corrected visual acuity (ETDRS). A manifest refraction and best spectacle corrected visual acuity (ETDRS) should be performed if corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
4) Perform slit-lamp biomicroscopy.
5) Measure IOP (can be measured at any time) and record the time (observer).
6) Perform a gonioscopic examination.
7) Schedule the subject to return for Visit 6 (Pre-Exchange Exam). Remind the subject of the following:
   i. *Visit 6 (Pre-Exchange Exam) is the visit prior to the Second Operative Visit*
   ii. [redacted]

6.3.4.6 Visit 6 (Pre-exchange Exam), to occur within 10 days prior to Visit 7 (Second Operative / Exchange Exam)

1) Update subject's medical status and concomitant medications.
2) Assess study eye adverse events.
3) Measure corrected visual acuity (ETDRS). A manifest refraction and best spectacle corrected visual acuity (ETDRS) should be performed if corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
4) Perform slit-lamp biomicroscopy.
5) Measure IOP (can be measured at any time) and record the time (observer).
6) Perform a gonioscopic examination.
7) Schedule the subject to return for Visit 7. Remind the subject of the following:
    i. Visit 7 is the Second Operative / Exchange Visit
    ii. 

6.3.4.7 Visit 7 (Second Operative / Exchange Exam)

Depending on the cohort, the subject may have their Visit 7 (Second Operative / Exchange Exam) occur on one of the following visits (please see APPENDIX A-G: SCHEDULE OF VISITS & MEASUREMENTS):

(Month 12, 365 days ± 14)

(Month 3, 91 days ± 14)

(Month 6, 182 days ± 14)

(Month 24, 730 days ± 14)

(Month 21, 637 days ± 14)

(Month 18, 547 days ± 14)

(Month 15, 456 days ± 14)

1) Update subject's medical status and concomitant medications.
2) Assess study eye adverse events.
3) Prepare subject for surgery.
4) [redacted]

The following steps will be performed in the Operating Room:

5) Visually confirm Shaffer grade angle and target implant location.
6) Collect an anterior chamber aqueous humor sample (AC tap). Please follow instructions in the procedure manual.

After collecting the AC Tap and performing all assessments:

7) Obtain a treatment kit.
8) Administer anesthetic [redacted]
9) Perform second surgery (Exchange).
10) Collect the first implant for shipment back to sponsor.
11) Record clinical data from the surgical procedure on the Second Operative CRF, noting study eye intra-operative AEs and post-operative AEs.
12) Schedule the subject to return for Visit 8 (Day 1 Post Exchange).

6.3.4.8 Visit 8 (Day 1 Post-Exchange Exam)

1) Update subject's medical status and concomitant medications.
2) Assess study eye adverse events.
3) Measure pinhole visual acuity (Snellen).
4) Perform slit-lamp biomicroscopy
5) Measure IOP (can be measured at any time) and record the time (observer).
6) Schedule the subject to return for Visit 9 (Day 10 Post - Exchange).

6.3.4.9 Visit 9 (Day 10 Post -Exchange Exam, 10 days ± 3)

1) Update subject's medical status and concomitant medications.
2) Assess study eye adverse events.
3) Measure pinhole visual acuity (Snellen).
4) Perform slit-lamp biomicroscopy
5) Measure IOP (can be measured at any time) and record the time (observer).
6) Schedule the subject to return for Visit 10 (Week 4 Post-Exchange)

6.3.4.10 Visit 10 (Week 4 Post-Exchange Exam, 28 days ± 3)

1) Update subject's medical status and concomitant medications.
2) Assess study eye adverse events.
3) Measure corrected visual acuity (ETDRS). A manifest refraction and best spectacle corrected visual acuity (ETDRS) should be performed if corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
4) Perform slit-lamp biomicroscopy
5) Measure IOP (can be measured at any time) and record the time (observer).
6) Perform a gonioscopic examination.

6.4 Concomitant Therapies

6.4.1 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]

6.4.2 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 medication.

7 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

All subjects will be implanted with a Travoprost Intraocular Implant. All subjects will then be implanted with a second Travoprost Intraocular Implant (at either month 12, 3, 6, 24, 21, 18, or 15, depending on cohort assignment) to exchange with the first one that will be explanted. All subjects will be followed for 4 weeks following the exchange procedure for a total duration of 4 to 25 months.

8 STATISTICAL ANALYSES

One database lock is planned after all subjects have exited from the study. Prior to the database lock, a Statistical Analysis Plan (SAP) will be approved. [redacted]

8.1 Sample Size

The sample size of 210 subjects who undergo implantation and exchange of a Travoprost Intraocular Implant was determined empirically. This sample size is considered adequate to provide information on the safety of the exchange procedure. [redacted]

8.2 Analysis Populations

All subjects contributing aqueous humor samples and/or exchanged implants will be included in the correlation model development and analysis population. All subjects who receive an implant will be included in the safety population. The safety population will be used for all data tabulations and listings.

8.3 General Statistical Methods

All demographic and safety data collected will be displayed in data listings. No formal statistical testing will be performed.

Continuous measures will be summarized with descriptive statistics including the number of observations, mean, standard deviation, median, minimum, and maximum. Summary statistics for categorical measures include the percentage and number of cases. All data tabulations will be by cohort as well as overall.

8.4 Efficacy Analyses

There are no efficacy measures in this study. IOP is evaluated for safety.

8.5 Safety Analyses

8.5.1 ADVERSE EVENTS

Adverse events (AEs) in the study eye will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) nomenclature. Treatment Emergent Adverse Events (TEAE) are defined as those AEs that occur after the initial treatment at Visit 2 (Operative Day 0).

AEs that occur on the date of the procedure are classified as either intra-operative or post-operative. Post-operative AEs are considered to be TEAEs. Intra-operative AEs and TEAEs will be summarized separately.

A line listing of serious adverse events will be provided.

8.5.2 OTHER SAFETY MEASURES

Details of analyses for other safety measures (see Section 4.2) will be provided in the SAP.

8.6 Other

[redacted] derived from the explant analyses and aqueous humor drug concentration levels will be summarized.

8.7 Interim Analyses

No interim analyses are planned.

9 ADVERSE EVENTS

An Adverse Event (AE) is defined as any untoward and unintended medical occurrence (e.g., sign, symptom, disease, syndrome) that occurs in a study subject, regardless of the suspected cause during the study. Adverse events will be clearly documented on the study source document and monitored throughout the course of the study.

Events occurring after signing the informed consent but prior to the implant procedure should be documented in the medical history. Events observed during or after the initial implant or exchange procedure until the final study visit, are to be recorded as AEs if they are in the study eye and deemed related to the implant or procedure.

Any clinically significant change in a subject's condition after receiving the study treatments, 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. If an adverse event occurs, an AE form must be completed.

An AE includes any of the following:

- An exacerbation or an unexpected increase in frequency or intensity of a pre-existing condition, including intermittent or episodic conditions
- New conditions or illnesses detected or diagnosed after the implant procedure
- A suspected interaction with any of the study treatments
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either any of the study treatments or a concomitant medication
- Any clinically significant laboratory finding that was not present prior to receiving any of the study treatments

An AE does NOT include any of the following:

- Anticipated day-to-day fluctuations of any pre-existing conditions, including the disease under study (OAG and OHT).
- Medical or surgical procedure, (e.g., colonoscopy or hernia repair). The condition that led to the procedure may be an AE, if not present in medical history.
- Hospitalizations where an untoward medical occurrence did not occur (social or convenience admission to the hospital).
- Pre-existing conditions or diseases that were present before receiving any of the study treatments that do not worsen or that are chronic but stable
- Changes in a chronic condition or disease that are consistent with natural disease progression. (These medical conditions should be adequately documented).
- Lack of efficacy of the study treatment for the condition being investigated.

AEs will be graded on a 3-point scale and reported in detail as indicated on the CRF:

Mild:	easily tolerated, causing minimal discomfort and not interfering with normal everyday activities
Moderate:	sufficiently discomforting to interfere with normal everyday activities
Severe:	incapacitating and/or preventing normal everyday activities

The relationship of each AE to study treatment should be determined by the investigator using the following explanations:

Definitely Unrelated: the event is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject

Unlikely Related: the event is most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject; and does not follow a known response pattern to the study medication

Possibly Related: the event follows a reasonable temporal sequence from the time of drug administration; and/or follows a known response pattern to the study medication; but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject

Probably Related: the event follows a reasonable temporal sequence from the time of drug administration; and/or follows a known response pattern to the study medication; and is not likely to have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject

Definitely Related: the event follows a reasonable temporal sequence from the time of drug administration; and follows a known response pattern to the study medication; and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject

9.1 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
- Overnight hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

The terms “mild,” “moderate,” and “severe” are measures of intensity; thus a severe AE is not necessarily serious. For example, nausea of several hours duration may be rated as severe but may not be clinically serious.

Important medical events that may not result in death, be life-threatening, or require overnight 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 substantial 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 risk of permanently losing vision in either eye as a direct result of the event.

Serious adverse events must be reported to Glaukos immediately (preferably within 24 hours of knowledge of the event).

[redacted]

When new significant information (including the outcome of the event) is obtained, the investigator should inform Glaukos as soon as possible. Depending on the nature of the AE, Glaukos may request copies of the ophthalmic and medical records of the subject. If the subject was hospitalized for a study-treatment related serious adverse event, a copy of the discharge summary must be forwarded to Glaukos as soon as possible.

9.2 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.

Unexpected adverse events must be reported to Glaukos immediately (preferably within 24 hours of knowledge of the event).

[redacted]

When new significant information (including the outcome of the event) is obtained, the investigator should inform Glaukos as soon as possible. Depending on the nature of the AE, Glaukos may request copies of the ophthalmic and medical records of the subject. If the subject was hospitalized for a study-treatment related unexpected adverse event, a copy of the discharge summary must be forwarded to Glaukos as soon as possible.

9.3 Suspected, Unexpected, Serious, Adverse Reaction (SUSAR)

A Suspected, Unexpected, Serious, Adverse Reaction (SUSAR) is any AE for which there is evidence to suggest a causal relationship between the Travoprost Intraocular Implant and the AE, and which is assessed as both unexpected and serious. An unexpected adverse reaction, i.e. any untoward and unintended response to any of the study treatments, is one for which the nature and severity is inconsistent with the applicable reference safety information (e.g., Investigator's Brochure).

9.4 Adverse Events Follow-up

Adverse events will be followed and documented until the time of complete resolution, or resolution with sequelae, or exit from the study with an assessment of the outcome.

10 MAINTAINING THE MASK

Not applicable.

11 INFORMED CONSENT

The investigator or 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) or Independent Ethics Committee (IEC). 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.

12 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/IEC approval must be provided to Glaukos (or designee) prior to study initiation. Updates must be provided to the IRB/IEC by the investigator at least annually or as required by the IRB/IEC.

13 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.

14 STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, good clinical practices (GCP), and all applicable laws and regulations.

The clinical investigator must maintain all information supplied by Glaukos in confidence, and when this information is submitted to an institutional review board (IRB), independent ethics committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

The clinical investigator must ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

15 RECORD KEEPING

15.1 Source Documents

The clinical investigator must maintain detailed source documents on all study subjects. Source documents include investigator subject study files, subject medical records, hospital charts, clinic charts, 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 completed the screening visit and the subject number assigned
- The study protocol number and the name of Glaukos
- The date that informed consent was obtained including the version number and date of the consent form used
- 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

15.2 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 source data verification at regular intervals, and all corrections to data will be made in the database. CRF forms are completed for all enrolled subjects, regardless of their final study status (e.g., subject discontinuation, study termination).

15.3 Study Supply Accountability

The principal investigator is responsible for ensuring that study material, including investigational product, is logged and placed in inventory upon receipt of the clinical supplies and that the clinical study supplies are 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 or destroy any used and unused supplies to the Glaukos monitor (or designee) at the conclusion of the study.

15.4 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.

16 REFERENCES

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2. Ziai N, Dolan J, Kacere R, Brubaker R. The effects on aqueous dynamics of phXA41, a new prostaglandin f2 alpha Analogue, after topical application in normal and ocular hypertensive human eyes. *Arch Ophthalmol*. 1993; 111: 1351-1358.
3. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. *Ophthalmology*. 1995; 102: 1743-1752.
4. Mishima H, Masuda K, Kitazawa Y, Azuma I, Araie M. A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. *Arch Ophthalmol*. 1996; 114: 929-932.
5. Eisenberg D, Camras C. A preliminary risk-benefit assessment of latanoprost and unoprostone in open-angle glaucoma and ocular hypertension. *Drug Safety*. 1999; 20: 505-514.
6. Tsai JC, McClure CA, Ramos SE, et al. Compliance Barriers in Glaucoma: A Systematic Classification. *Journal of Glaucoma* 2003; 12:393-398.
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APPENDIX A: SCHEDULE OF VISITS & MEASUREMENTS: Group 12

(12 months from 1st Implant Insertion to 2nd Implant Insertion, [redacted])

Parameter	Screening	Operative Day 0	Day 1	Day 10, 10 days ± 3	Week 4, 28 days ± 3	Month 6, 182 days ± 14	Pre-exchange[3]	Month 12, 365 days ± 14	Day 1 Post Exchange (PE)	Day 10 PE, 10 days ± 3	Week 4 PE, 28 days ± 3
Visit Number	1	2	3	4	5	5.1	6	7	8	9	10
Informed Consent	x										
Pregnancy Test	x										
Demographics, Medical/Ocular History	x	x									
Concomitant Medication Assessment	x	x	x	x	x	x	x	x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x	x	x	x	x
Corrected VA (ETDRS)					x	x	x				x
Manifest Refraction & BSCVA (ETDRS)	x				x[1]	x[1]	x[1]				x[1]
Pinhole VA (Snellen)			x	x					x	x	
Slit Lamp Exam	x		x	x	x	x	x		x	x	x
IOP	x		x	x	x	x	x		x	x	x
Gonioscopy	x				x	x	x				x
Pachymetry	x										
Dilated Fundus Exam and Nerve Assessment, Vertical C/D ratio	x										
Aqueous Humor Sample (AC Tap)								x			
Operative Procedure and Surgical Assessments		x						x[2]			

1 Only required if Corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
2 Second Operative / Exchange is done AFTER collecting the anterior chamber aqueous humor sample and all assessments
3 Pre-exchange exam to occur within 10 days prior to Visit 7 (Second Operative / Exchange Exam)

Operative Visits are in Red

APPENDIX B: SCHEDULE OF VISITS & MEASUREMENTS: Group 3

(3 months from 1st Implant Insertion to 2nd Implant Insertion, [redacted])

Parameter	**Screening**	**Operative Day 0**	**Day 1**	**Day 10, 10 days ± 3**	**Week 4, 28 days ± 3**	**Pre-Exchange[3]**	**Month 3, 91 days ± 14**	**Day 1 Post Exchange (PE)**	**Day 10 PE, 10 days ± 3**	**Week 4 PE, 28 days ± 3**
Visit Number	1	2	3	4	5	6	7	8	9	10
Informed Consent	x									
Pregnancy Test	x									
Demographics, Medical/Ocular History	x	x								
Concomitant Medication Assessment	x	x	x	x	x	x	x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x	x	x	x
Corrected VA (ETDRS)					x	x				x
Manifest Refraction & BSCVA (ETDRS)	x				x[1]	x[1]				x[1]
Pinhole VA (Snellen)			x	x				x	x	
Slit Lamp Exam	x		x	x	x	x		x	x	x
IOP	x		x	x	x	x		x	x	x
Gonioscopy	x				x	x				x
Pachymetry	x									
Dilated Fundus Exam and Nerve Assessment, Vertical C/D ratio	x									
Aqueous Humor Sample (AC Tap)							x			
Operative Procedure and Surgical Assessments		x					x[2]			

1 Only required if Corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
2 Second Operative / Exchange is done AFTER collecting the anterior chamber aqueous humor sample and all assessments
3 Pre-exchange exam to occur within 10 days prior to Visit 7 (Second Operative / Exchange Exam)

Operative Visits are in Red

APPENDIX C: SCHEDULE OF VISITS & MEASUREMENTS: Group 6

(6 months from 1st Implant Insertion to 2nd Implant Insertion, [redacted])

Parameter	**Screening**	**Operative Day 0**	**Day 1**	**Day 10, 10 days ± 3**	**Week 4, 28 days ± 3**	**Pre-Exchange[3]**	**Month 6, 182 days ± 14**	**Day 1 Post Exchange (PE)**	**Day 10 PE, 10 days ± 3**	**Week 4 PE, 28 days ± 3**
Visit Number	1	2	3	4	5	6	7	8	9	10
Informed Consent	x									
Pregnancy Test	x									
Demographics, Medical/Ocular History	x	x								
Concomitant Medication Assessment	x	x	x	x	x	x	x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x	x	x	x
Corrected VA (ETDRS)					x	x				x
Manifest Refraction & BSCVA (ETDRS)	x				x[1]	x[1]				x[1]
Pinhole VA (Snellen)			x	x				x	x	
Slit Lamp Exam	x		x	x	x	x		x	x	x
IOP	x		x	x	x	x		x	x	x
Gonioscopy	x				x	x				x
Pachymetry	x									
Dilated Fundus Exam and Nerve Assessment, Vertical C/D ratio	x									
Aqueous Humor Sample (AC Tap)							x			
Operative Procedure and Surgical Assessments		x					x[2]			

1 Only required if Corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
2 Second Operative / Exchange is done AFTER collecting the anterior chamber aqueous humor sample and all assessments
3 Pre-exchange exam to occur within 10 days prior to Visit 7 (Second Operative / Exchange Exam)

Operative Visits are in Red

APPENDIX D: SCHEDULE OF VISITS & MEASUREMENTS: Group 24

(24 months from 1st Implant Insertion to 2nd Implant Insertion, [redacted])

Parameter	Screening	Operative Day 0	Day 1	Day 10, 10 days ± 3	Week 4, 28 days ± 3	Month 6, 182 days ± 14	Month 12, 365 days ± 14	Month 18, 547 days ± 14	Pre-Exchange[3]	Month 24, 730 days ± 14	Day 1 Post Exchange (PE)	Day 10 PE, 10 days ± 3	Week 4 PE, 28 days ± 3
Visit Number	1	2	3	4	5	5.1	5.2	5.3	6	7	8	9	10
Informed Consent	x												
Pregnancy Test	x												
Demographics, Medical/Ocular History	x	x											
Concomitant Medication Assessment	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x	x	x	x	x	x	x
Corrected VA (ETDRS)					x	x	x	x	x				x
Manifest Refraction & BSCVA (ETDRS)	x				x[1]	x[1]	x[1]	x[1]	x[1]				x[1]
Pinhole VA (Snellen)			x	x							x	x	
Slit Lamp Exam	x		x	x	x	x	x	x	x		x	x	x
IOP	x		x	x	x	x	x	x	x		x	x	x
Gonioscopy	x				x	x	x	x	x				x
Pachymetry	x												
Dilated Fundus Exam and Nerve Assessment, Vertical C/D ratio	x												
Aqueous Humor Sample (AC Tap)										x			
Operative Procedure and Surgical Assessments		x								x[2]			

1 Only required if Corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
2 Second Operative / Exchange is done AFTER collecting the anterior chamber aqueous humor sample and all assessments
3 Pre-exchange exam to occur within 10 days prior to Visit 7 (Second Operative / Exchange Exam)

Operative Visits are in Red

APPENDIX E: SCHEDULE OF VISITS & MEASUREMENTS: Group 21

(21 months from 1st Implant Insertion to 2nd Implant Insertion, [redacted])

Parameter	**Screening**	**Operative Day 0**	**Day 1**	**Day 10, 10 days ± 3**	**Week 4, 28 days ± 3**	**Month 6, 182 days ± 14**	**Month 12, 365 days ± 14**	**Month 18, 547 days ± 14**	**Pre-Exchange[3]**	**Month 21, 637 days ± 14**	**Day 1 Post Exchange (PE)**	**Day 10 PE, 10 days ± 3**	**Week 4 PE, 28 days ± 3**
Visit Number	1	2	3	4	5	5.1	5.2	5.3	6	7	8	9	10
Informed Consent	x												
Pregnancy Test	x												
Demographics, Medical/Ocular History	x	x											
Concomitant Medication Assessment	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x	x	x	x	x	x	x
Corrected VA (ETDRS)					x	x	x	x	x				x
Manifest Refraction & BSCVA (ETDRS)	x				x[1]	x[1]	x[1]	x[1]	x[1]				x[1]
Pinhole VA (Snellen)			x	x							x	x	
Slit Lamp Exam	x		x	x	x	x	x	x	x		x	x	x
IOP	x		x	x	x	x	x	x	x		x	x	x
Gonioscopy	x				x	x	x	x	x				x
Pachymetry	x												
Dilated Fundus Exam and Nerve Assessment, Vertical C/D ratio	x												
Aqueous Humor Sample (AC Tap)										x			
Operative Procedure and Surgical Assessments		x								x[2]			

1 Only required if Corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
2 Second Operative / Exchange is done AFTER collecting the anterior chamber aqueous humor sample and all assessments
3 Pre-exchange exam to occur within 10 days prior to Visit 7 (Second Operative / Exchange Exam)

Operative Visits are in Red

APPENDIX F: SCHEDULE OF VISITS & MEASUREMENTS: Group 18

(18 months from 1st Implant Insertion to 2nd Implant Insertion, [redacted])

Parameter	Screening	Operative Day 0	Day 1	Day 10, 10 days ± 3	Week 4, 28 days ± 3	Month 6, 182 days ± 14	Month 12, 365 days ± 14	Pre-Exchange[3]	Month 18, 547 days ± 14	Day 1 Post Exchange (PE)	Day 10 PE, 10 days ± 3	Week 4 PE, 28 days ± 3
Visit Number	1	2	3	4	5	5.1	5.2	6	7	8	9	10
Informed Consent	x											
Pregnancy Test	x											
Demographics, Medical/Ocular History	x	x										
Concomitant Medication Assessment	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x	x	x	x	x	x
Corrected VA (ETDRS)					x	x	x	x				x
Manifest Refraction & BSCVA (ETDRS)	x				x[1]	x[1]	x[1]	x[1]				x[1]
Pinhole VA (Snellen)			x	x						x	x	
Slit Lamp Exam	x		x	x	x	x	x	x		x	x	x
IOP	x		x	x	x	x	x	x		x	x	x
Gonioscopy	x				x	x	x	x				x
Pachymetry	x											
Dilated Fundus Exam and Nerve Assessment, Vertical C/D ratio	x											
Aqueous Humor Sample (AC Tap)									x			
Operative Procedure and Surgical Assessments		x							x[2]			

1 Only required if Corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
2 Second Operative / Exchange is done AFTER collecting the anterior chamber aqueous humor sample and all assessments
3 Pre-exchange exam to occur within 10 days prior to Visit 7 (Second Operative / Exchange Exam)

Operative Visits are in Red

APPENDIX G: SCHEDULE OF VISITS & MEASUREMENTS: Group 15

(15 months from 1st Implant Insertion to 2nd Implant Insertion, [redacted])

Parameter	Screening	Operative Day 0	Day 1	Day 10, 10 days ± 3	Week 4, 28 days ± 3	Month 6, 182 days ± 14	Month 12, 365 days ± 14	Pre-Exchange[3]	Month 15, 456 days ± 14	Day 1 Post Exchange (PE)	Day 10 PE, 10 days ± 3	Week 4 PE, 28 days ± 3
Visit Number	1	2	3	4	5	5.1	5.2	6	7	8	9	10
Informed Consent	x											
Pregnancy Test	x											
Demographics, Medical/Ocular History	x	x										
Concomitant Medication Assessment	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x	x	x	x	x	x
Corrected VA (ETDRS)					x	x	x	x				x
Manifest Refraction & BSCVA (ETDRS)	x				x[1]	x[1]	x[1]	x[1]				x[1]
Pinhole VA (Snellen)			x	x						x	x	
Slit Lamp Exam	x		x	x	x	x	x	x		x	x	x
IOP	x		x	x	x	x	x	x		x	x	x
Gonioscopy	x				x	x	x	x				x
Pachymetry	x											
Dilated Fundus Exam and Nerve Assessment, Vertical C/D ratio	x											
Aqueous Humor Sample (AC Tap)									x			
Operative Procedure and Surgical Assessments		x							x[2]			

1 Only required if Corrected VA (ETDRS) has decreased by 2 or more lines (≥10 letters) from Visit 1 (Screening).
2 Second Operative / Exchange is done AFTER collecting the anterior chamber aqueous humor sample and all assessments
3 Pre-exchange exam to occur within 10 days prior to Visit 7 (Second Operative / Exchange Exam)

Operative Visits are in Red

APPENDIX H: OBLIGATIONS OF THE INVESTIGATOR

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 and representatives of the Food and Drug Administration and other applicable regulatory agencies; 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 Beginning 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).

APPENDIX I: 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
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA 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 in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical

research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. 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 adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, 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, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    - Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    - Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
    - and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.