NCT04615403

PROSPECTIVE, NON-RANDOMIZED, OPEN-LABEL, MULTI-CENTER, SINGLE ARM STUDY OF EXCHANGE OF TRAVOPROST INTRAOCULAR IMPLANT

PROTOCOL # IDOS-106-EXCH

DATE: AUGUST 24, 2020

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]		14SEP2020
Name and Title (Print)	Signature of Sponsor	Date

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SYNOPSIS

This prospective, non-randomized, open-label, multi-center, single arm, clinical trial intends to exchange the implant in approximately [redacted] male and female subjects who were previously implanted with the Travoprost Intraocular Implant in the GC-009 study (1st Cycle). All subjects are required to meet eligibility criteria at Visit 1 (Screening). The purpose of this study is to evaluate the safety of the exchange of a Travoprost Intraocular Implant in subjects with a previously implanted Travoprost Intraocular Implant. Postoperatively, there are 6 follow-up visits over a 12 month period.

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

STUDY OBJECTIVE
The study objective is to evaluate the safety of the surgical exchange procedure of Travoprost Intraocular Implant in subjects with a previously implanted Travoprost Intraocular Implant.

STUDY TREATMENTS
Subjects will undergo an exchange of a Travoprost Intraocular Implant through a small temporal clear corneal incision.

Structure:	Single arm
Number of Centers:	Approximately 15 centers
Masking:	Open-label
Method of Subject Assignment: After Visit 1 (Screening), qualified subjects will be scheduled to undergo treatment with the G2TR-[redacted] implant.	
Randomization:	No
Total Sample Size:	Approximately [redacted] subjects
Statistical Rationale Provided:	Please refer to Statistical Section, Section 8

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 criteria at Visit 1 (Screening) may be scheduled for Visit 2 (Operative Exchange Day 0) (on a separate day).

Visit Schedule:
This study will consist of 8 visits over approximately a 12 month period: Visit 1 (Screening), Visit 2 (Operative Exchange Day 0), Visit 3 (Day 1 Post-Exchange), Visit 4 (Day 10 Post-Exchange), Visit 5 (Week 4 Post-Exchange), Visit 6 (Month 3 Post-Exchange), Visit 7 (Month 6 Post-Exchange), and Visit 8 (Month 12 Post-Exchange).

Study Measures will be collected for the study eye only:

Safety

- Intra-operative adverse events
- Post-operative adverse events
- Corrected visual acuity (logMAR score using ETDRS chart)
- Slit-lamp biomicroscopy findings
- Gonioscopy findings
- Specular microscopy findings
- Intraocular Pressure
- Ophthalmoscopy findings
- Visual field evaluation

Other

- Operative and surgical assessments

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

Power and Sample Size: The sample size of [redacted] who undergo an exchange of a Travoprost Intraocular Implant was determined empirically. This sample size is considered adequate to support the objective of this study.

STUDY VARIABLES AND STATISTICAL ANALYSIS

Efficacy Variable
There is no efficacy variable in this study. Intraocular pressure is assessed for safety.

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

Ocular safety variables, i.e., best spectacle corrected visual acuity, biomicroscopy findings, gonioscopy findings, specular microscopy findings, intraocular pressure, ophthalmoscopy findings (including cup-to-disc ratio), and visual field evaluation, will be summarized.

Analysis Populations
All subjects who undergo the exchange procedure will be included in the safety population. The safety population will be used for all 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
BAK	Benzalkonium chloride
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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IOP	Intraocular Pressure
IEC	Independent Ethics Committee
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
PAS	Peripheral Anterior Synechia
PE	Post-Exchange
PGA	Prostaglandin Analogue
PP	Per protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event
VA	Visual acuity

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 (PGAs). The PGAs 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 PGAs. 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 PGAs.

However, PGAs 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 will evaluate the second cycle of the Travoprost Intraocular Implant: Model G2TR-[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-[redacted] has been investigated in clinical trials conducted in [redacted] (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-[redacted] implant has long-term IOP-lowering effects and is also generally well-tolerated by study subjects. These results support the continued evaluation of the implant model in this clinical trial.

2 OBJECTIVE

The study objective is to evaluate the safety of the surgical exchange procedure of Travoprost Intraocular Implant in subjects with a previously implanted Travoprost Intraocular Implant.

3 STUDY DESIGN

This is a prospective, non-randomized, open-label, multi-center, single arm, clinical trial of the safety of the exchange of the Travoprost Intraocular Implant in subjects who were previously implanted with the Travoprost Intraocular Implant in the GC-009 study (1st Cycle). Approximately [redacted] will be enrolled into this study and will be followed through 12 months postoperative.

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

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

The eye previously implanted with a Travoprost Intraocular Implant in the GC-009 study (study eye) will be assessed at Visit 1 (Screening). The subject may then be scheduled for study treatment. Subjects will be treated unilaterally, only the implanted eye (study eye) will go through the study treatment. The fellow eye will be treated outside the parameters of the study per investigator discretion using their standard of care options.

Treatment Procedure:

The Operative and Postoperative scheduled visits are listed in the following table:

Visit Number	Visit Timepoint
2	Operative Exchange Day 0
3	Day 1 Post-Exchange
4	Day 10 Post-Exchange (10 days ± 3)
5	Week 4 Post-Exchange (28 days ± 3)
6	Month 3 Post-Exchange (91 days ± 14)
7	Month 6 Post-Exchange (182 days ± 30)
8	Month 12 Post-Exchange (365 days ± 30)

At Visit 2 (Operative Exchange Day 0), subjects will have the first implant which was inserted in Study GC-009 exchanged with a second G2TR- implant.

At Visit 1 (Screening), IOP can be measured at any time. At all other scheduled visits, Day 10 Post-Exchange, Week 4 Post-Exchange, Month 3 Post-Exchange, Month 6 Post-Exchange, and Month 12 Post-Exchange), IOP measurements will be taken once daily at the same time as screening ± 60 minutes. Study follow-up will continue until Visit 8 (Month 12 Post-Exchange), after which subjects will be exited from the study.

3.1 Discussion of Study Design

This prospective, non-randomized, open-label, multi-center, single arm, clinical trial intends to perform an exchange procedure on approximately male and female subjects who were previously implanted with the Travoprost Intraocular Implant in the GC-009 study (1st Cycle). All subjects are required to meet eligibility criteria at Visit 1 (Screening). The study objective is to evaluate the safety of the surgical exchange procedure of Travoprost Intraocular Implants in subjects with a previously implanted Travoprost Intraocular Implant. Postoperatively, there are 6 follow-up visits over a 12 month period.

4 STUDY MEASURES

4.1 Efficacy Measures

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

4.2 Safety Measures

Ocular safety measures include intra-operative adverse events, post-operative adverse events (TEAEs), IOP, corrected visual acuity, slit lamp biomicroscopy findings, gonioscopy findings, specular microscopy findings, intraocular pressure, ophthalmoscopy findings (including cup-to-disc ratio), and visual field evaluation.

4.3 Other

Operative and Surgical Assessments.

5 MATERIALS

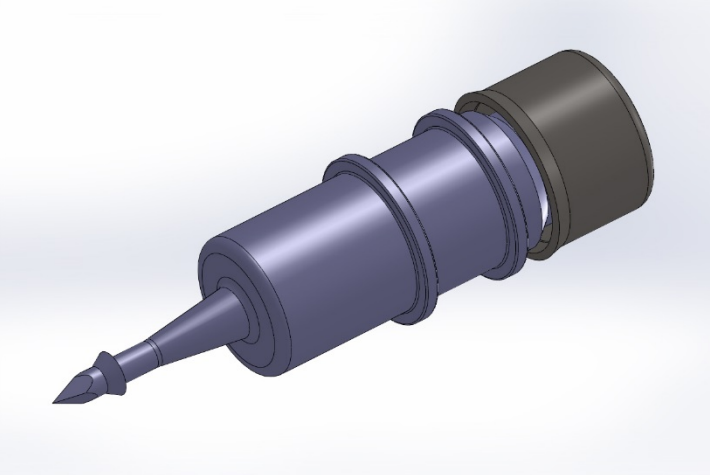
5.1 Study Medications

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

5.1.1 TEST ARTICLE: TRAVOPROST INTRAOCULAR IMPLANT MODEL G2TR-[redacted]

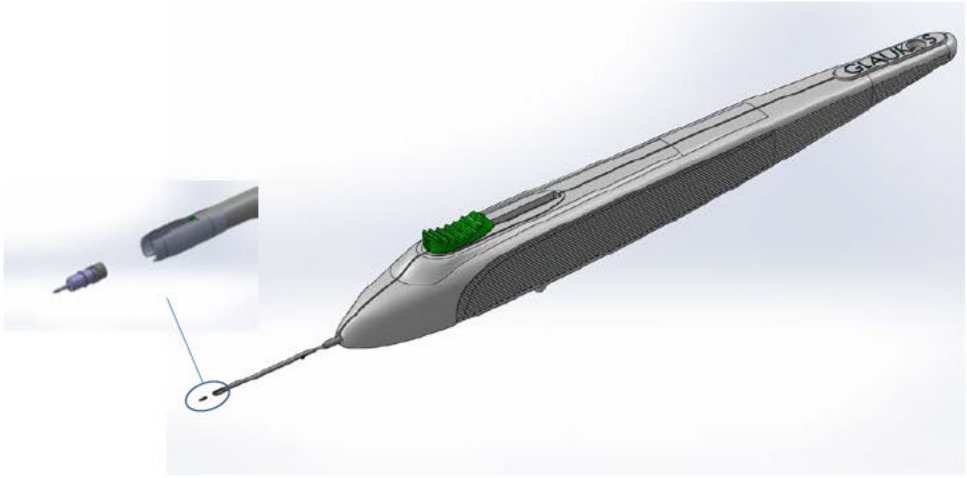
[redacted].

Figure 1. Glaukos Travoprost Intraocular Implant



[redacted]

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).

The implant study products will be shipped in a refrigerated container at 2-8°C (36-46°F). The implant study products will be stored at the study site in a refrigerated condition at 2-8°C (36-46°F).

6 METHODS

6.1 Subjects

Approximately 15 centers that enrolled subjects in the GC-009 clinical trial will participate in this study. Approximately 45 subjects who were previously implanted with the Travoprost Intraocular Implant in the GC-009 study (1st Cycle) will have their first implant exchanged with a second Travoprost Intraocular Implant (2nd Cycle). 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 the Visit 1 (Screening), all subjects must meet the following criteria:

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

2) Best spectacle corrected visual acuity of 20/80 or better in each eye.

3) Previously implanted with the Travoprost Intraocular Implant in the GC-009 study that is present in the study eye (1st Cycle). Only the eye with the Travoprost Intraocular Implant may be assessed for exchange at Visit 1 (Screening).

All subjects (OAG and OHT) must meet the rest of the following criteria:

4) Angle anatomy defined as follows:
   a. [redacted]

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. [redacted]

2) Corneal status as follows:
   a. any active inflammation or edema [redacted]
   b. clinically significant dystrophy [redacted]
   e. [redacted] 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 [redacted]

4) [redacted]

[redacted]

6) Other ocular status as follows:
   a. clinically significant sequelae from trauma [redacted]
   b. history or chronic ocular inflammatory disease or presence of active ocular inflammation [redacted]

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 their participation in the study
   c. current participation in any study, or participation within 30 calendar days of Visit 1 (Screening)
   d. immunodeficiency conditions
   e. [redacted]

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 2nd Cycle 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 timeframe 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 may 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 in APPENDIX A: SCHEDULE OF VISITS AND MEASUREMENTS

6.3.1 DURATION OF STUDY

Following the initial implantation, the treatment period will be 3 months in duration.

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.

[redacted]

6.3.3 PREOPERATIVE PROCEDURES

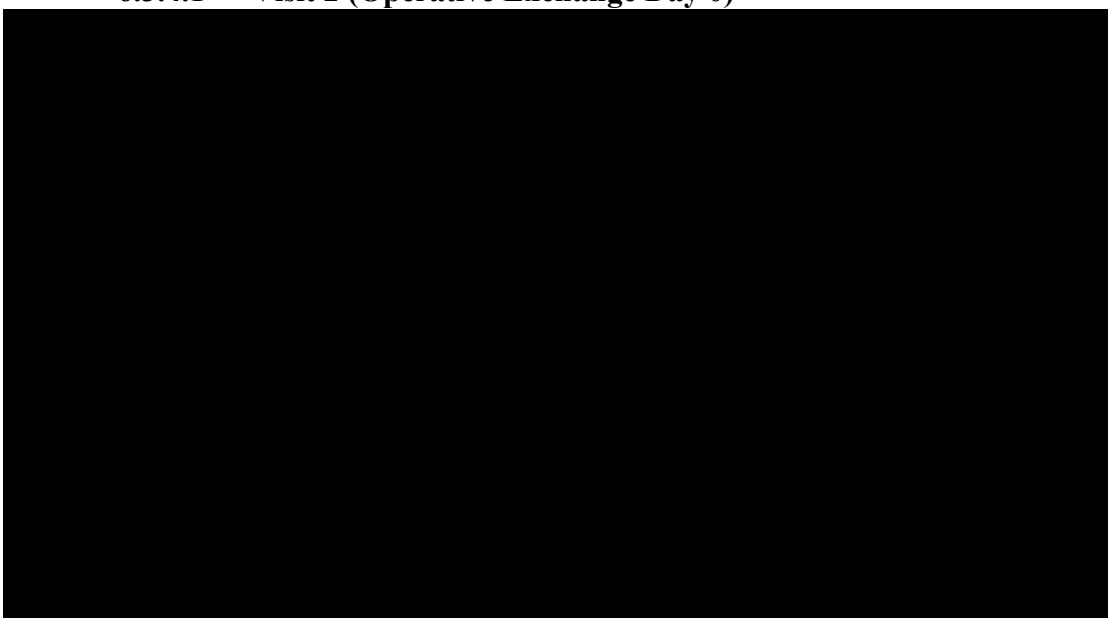
6.3.3.1 Visit 1 (Screening)

[redacted]

If the subject is ineligible for the study, complete the appropriate CRF.

6.3.4 TREATMENT PROCEDURES

6.3.4.1 Visit 2 (Operative Exchange Day 0)



[redacted]

6.3.4.2 Visit 3 (Day 1 Post-Exchange, 1 days)

[redacted]

6.3.4.3 Visit 4 (Day 10 Post-Exchange, 10 ± 3 days)

[redacted]

6.3.4.4 Visit 5 (Week 4 Post-Exchange, 28 days ± 3)

1) [redacted]

[redacted]

6.3.4.5 Visit 6 (Month 3 Post-Exchange, 91 days ± 14)

[redacted]

6.3.4.6 Visit 7 (Month 6 Post-Exchange, 182 days ± 30)

[redacted]

6.3.4.7 Visit 8 (Month 12 Post-Exchange, 365 days ± 30)

[redacted]

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.

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.

6.5 Post-Treatment Management of IOP and Rescue Medications

[redacted]

[redacted]

7 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

All subjects will be implanted with a second Travoprost Intraocular Implant to exchange with the previously implanted first one that will be explanted. All subjects will be followed for the duration of the study.

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.

8.1 Sample Size

[redacted]

8.2 Analysis Populations

All subjects who undergo the exchange procedure 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.

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 Exchange 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 and presented in separate listings.

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 5.2) will be provided in the SAP.

8.6 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, intercurrent illness) 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 o 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
- Required admission to the hospital or prolongation of an existing hospitalization (emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes)
- 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 admission to the hospital 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).

Email: [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).

Email: [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 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 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.

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 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

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

15.4 Record Retention

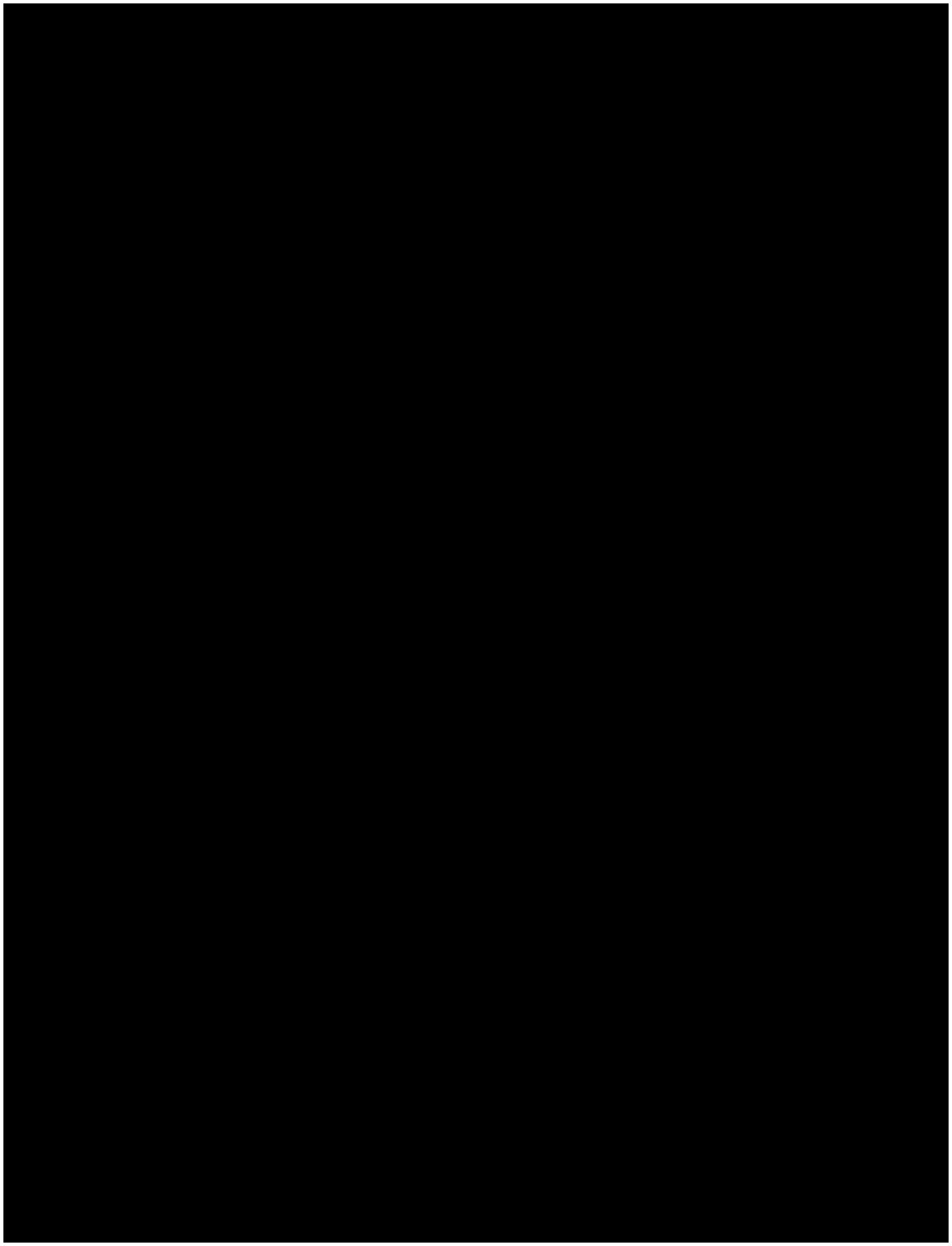
All records relating to the conduct of this study are to be retained by the investigator until notified by Glaukos that the records may be destroyed.

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

1. [redacted]

APPENDIX A: SCHEDULE OF VISITS AND MEASUREMENTS



APPENDIX B: 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).