Statistical Analysis Plan

Prospective, Non-Randomized, Open-Label, Single Center Study to Evaluate [redacted] the Performance of the Travoprost Intraocular Implant

Protocol Number:	IDOS-402-IVIV
Product Name:	Travoprost Intraocular Implant, [redacted] (G2-TR-125)
Sponsor Name:	GLAUKOS CORPORATION 26600 Aliso Viejo Parkway Aliso Viejo, CA 92656
Version:	1.0
Date:	March 23th, 2022

ClinicalTrials.gov Identifier: NCT06582732

Statistical Analysis Plan Approval Signatures

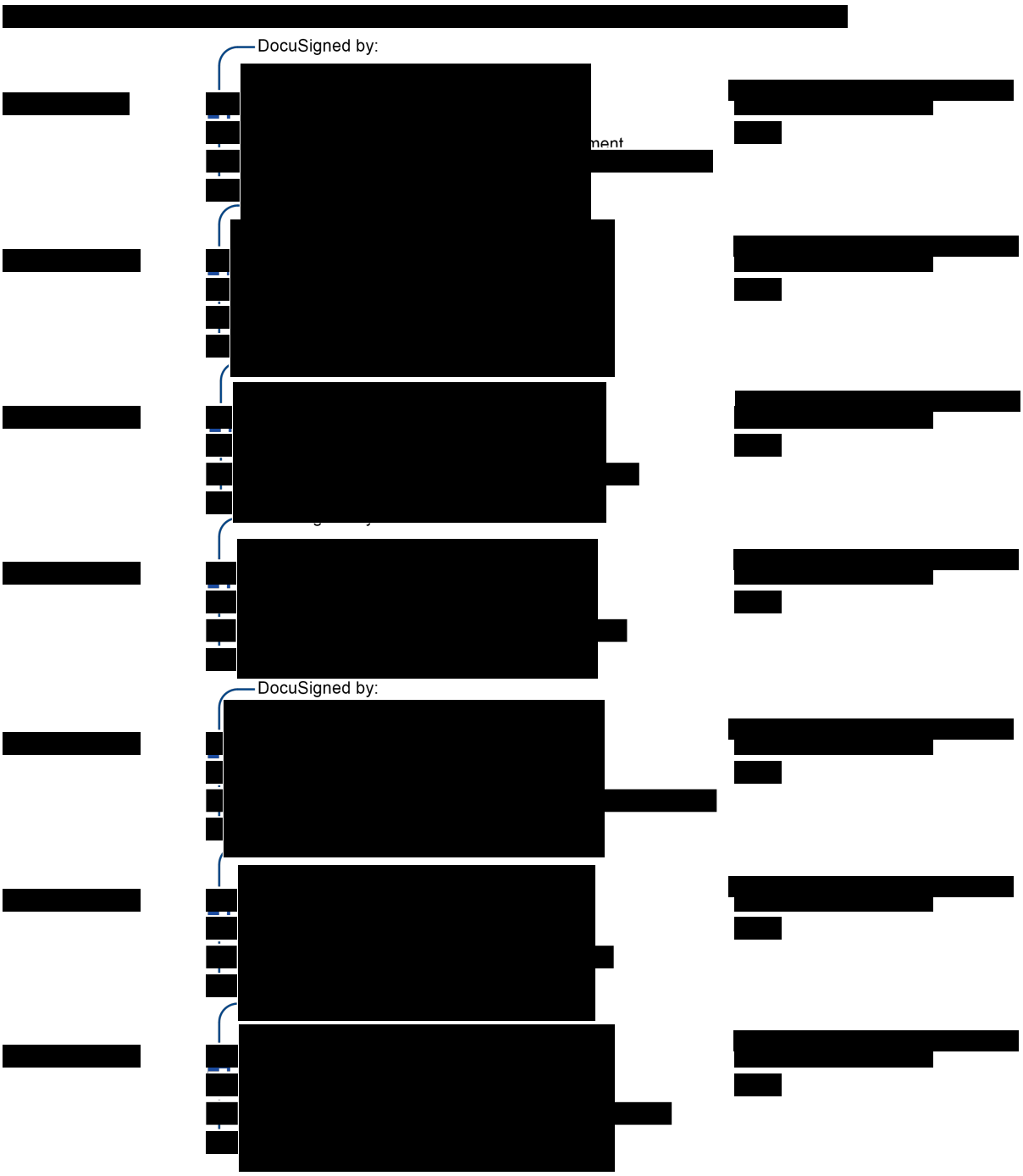


Table of Contents

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BSCVA	Best Spectacle Corrected Visual Acuity
CFB	Change from Baseline
CFPE	Change from Pre-Exchange
CRF	Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
IOP	Intraocular Pressure
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
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
WHO	World Health Organization

Version History

This Statistical Analysis Plan (SAP) for IDOS-402-IVIV is based on the protocol dated 18SEP2019.

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Original version

1. Introduction

This statistical analysis plan (SAP) describes the statistical methods to analyze all safety data from protocol IDOS-402-IVIV. Any changes to this plan will be reflected as amendments before the database lock and/or documented in the clinical study report. [redacted] One database lock will occur after all subjects have completed the Week 4 Post-Exchange (PE) visit or have exited the study prior to that time.

[redacted]

2. Objectives and Study Design

2.1. Objectives

The study objective 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]

2.2. Endpoints

Safety Endpoints:

- Intraoperative adverse events
- Postoperative 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

2.3. Study Design

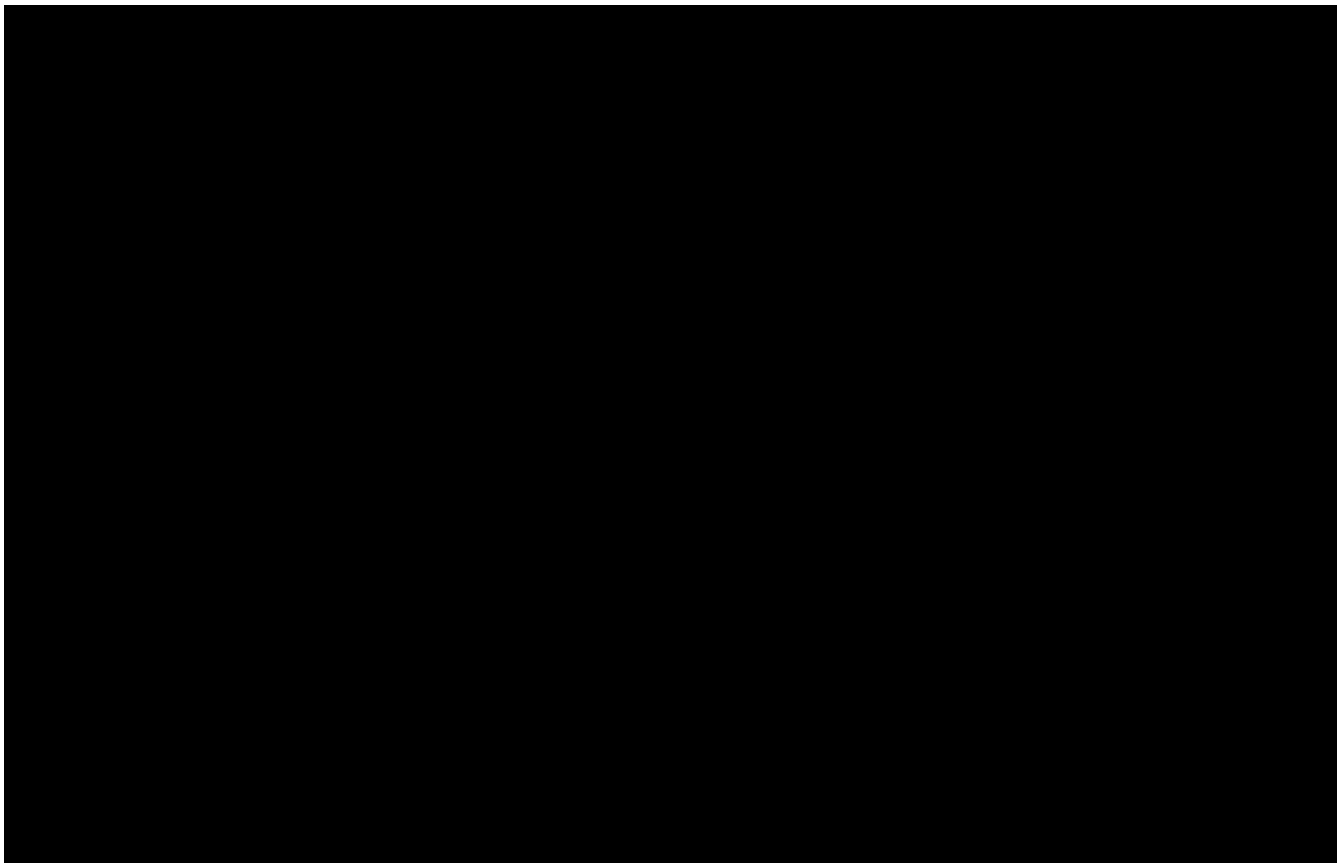
This is a prospective, non-randomized, open-label, single center trial evaluating [redacted] the performance of the Travoprost Intraocular Implant in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT). Approximately 210 total subjects [redacted] will be enrolled into the study. Subjects will be screened for qualification as per the inclusion/exclusion criteria (refer to Sections **6.2.1** and **6.2.2** of study protocol). Qualified subjects will be assigned to a cohort and will be implanted with the Travoprost Intraocular Implant (G2-TR-125 Implant) in one eye. [redacted] All enrolled subjects will undergo a second operative visit, the exchange of the Travoprost Intraocular Implant, at Visit 7. The duration of time for each cohort is the time between the implantation of the 1st implant at Visit 2 (Day 0) and the implantation of the 2nd implant at Visit 7 (Exchange procedure). Depending on the cohort assignment, subjects will be follow for 4 – 25 months postoperatively (3 – 24 months after 1st implantation and 4 weeks after the 2nd implantation). Study follow-up will continue until the Week 4 PE visit.

Depending on the cohort assignment, the study consists of 10 to 13 visits: 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 PE), Visit 9 (Day 10 PE), and Visit 10 (Week 4 PE). Subjects will exit the study at the conclusion of the Week 4 PE visit.

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 remaining 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 cohort sequentially as defined by the cohort order as they receive surgery. Each cohort must be filled prior to starting the next cohort.

Table 1. Cohorts in the Study[1]



2.3.1. Study Period

All data will be categorized into one of two study periods which are referred to as the initial and post-exchange (PE) study periods. The initial study period includes all data collected prior to the exchange of the intraocular implant at Visit 7 (Second Operative/ Exchange). The PE study period includes all data collected after the exchange of the intraocular implant at Visit 7 (Second Operative/ Exchange), including any data collected during the exchange procedure. Data may be summarized for the initial study period, PE study period, or across both periods (total study period) as indicated.

[1] Table 1 can be found in Section 3 of protocol.

2.4. Sample Size Determination

The sample size of 210 subjects who undergo implantation and exchange of a Travoprost Intraocular Implant was determined to support the study objectives and is not based on statistical power calculations. [redacted]

3. Analysis Sets

For the purposes of analysis, the following analysis set is defined:

Subject Analysis Set	Description
Safety analysis set	• All subjects who receive an implant.

The safety analysis set will be used for all data tabulations and listings.

4. General Statistical Considerations

Demographic and safety data collected on the case report forms (CRFs) will be displayed in tabulations and data listings. Only data from scheduled visits will be used in tabulations unless otherwise specified. In general, summary tables will be presented [redacted]. Data may also be summarized by study period if indicated. Data listings will present data either recorded on or derived using the CRF. [redacted]

No formal statistical testing will be performed. All data summaries [redacted] will be performed using SAS® software, Version 9.4 or higher.

Continuous data will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Continuous data may also be dichotomized, or otherwise split, into clinically meaningful categories and may be further analyzed as categorical data as specified in the individual endpoints.

Categorical data will be summarized using frequency counts and percentages. Unless otherwise stated, subjects with missing visit data will be omitted from both the numerator and denominator of such calculations.

4.1. Definition of Variables

4.1.1. Baseline Measure

The baseline measure is defined as the last non-missing measure prior to the implantation of the 1st Travoprost intraocular implant at Visit 2 (First Operative Day 0).

4.1.2. Pre-Exchange Measure

The pre-exchange measure is defined as the last non-missing measure prior to the implantation of the 2nd Travoprost intraocular implant at Visit 7 (Second Operative/Exchange).

4.1.3. Change from Baseline/Pre-Exchange

The change from baseline (CFB) and the change from pre-exchange (CFPE) values are calculated as

- CFB value = follow-up visit value – baseline value.
- CFPE value = follow-up visit value – pre-exchange value.

4.1.4. Study Days

Two sets of study days are defined and will be referred to as the initial and PE study days. The number of initial study days is defined relative to the First Operative visit (Visit 2), with the First Operative visit as study day 1. The number of PE study days is defined relative to the Second Operative visit (Visit 7), with the Second Operative visit as study day 1. For both sets of study days, the study day value increases by 1 for each date following the corresponding Operative visit. For each date prior to the corresponding Operative visit, the study day value decreases by 1, with the date preceding the Operative visits as study day -1.

5. Demographic and Baseline Characteristic Analyses

5.1. Subject Disposition

The number and percentage of subjects who were screened, screened but not enrolled (i.e., screen failures), and enrolled will be provided. A subject is considered enrolled at the time the subject undergoes surgery at the First Operative visit (Visit 2). Reason(s) for screen failure will also be presented in a table and subject listing.

Subject disposition will be summarized [redacted] for all enrolled subjects. The summary will include the number and percentage of subjects who completed the study and the number and percentage of subjects who exited early (with reasons for study exit) prior to the Week 4 PE examination. The reasons for early study exit include:

- Adverse Event
- Death
- Investigator Decision
- Lost to Follow-up
- Termination of Study by Sponsor or Regulatory Authority
- Withdrew Consent
- Other

Subject disposition will also be summarized [redacted] for the initial and PE study periods. The summary will include the number and percentage of subjects who completed the respective study period and the number and percentage of subjects who exited early (with reasons for study exit) during the respective study period.

Subject disposition and exit status will be listed by subject.

5.2. Protocol Deviations

Protocol deviations will be captured by the site and reviewed by a medical monitor during the study. Classification of major deviations will be decided by the study team prior to the database lock. For the safety analysis set, a summary of protocol deviations will be tabulated [redacted] for the initial, PE, and total study periods. A listing of all protocol deviations will be provided.

5.3. Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be tabulated [redacted] for the safety analysis set. Demographic variables include age, sex, race, ethnicity, and eye color. Age will be calculated for each subject by (Informed Consent Date – Date of Birth) ÷ 365.25 and rounded down to the nearest integer. In addition to being summarized continuously, age will be summarized categorically for the following age groups: < 65 and ≥ 65 years of age.

The following baseline characteristics will be summarized [redacted] for the study eye:

- Type of Disease (OAG or OHT)
- Number of Ocular Hypotensive Medication Classes
- Medication Class

- IOP (mmHg)
- Best Spectacle Corrected Visual Acuity (BSCVA) - LogMAR
- Vertical Cup-to-Disc Ratio
- Corneal Thickness (μm)
- Shaffer Angle Grade
- Study Eye (OD or OS)

Demographic and baseline characteristic data will be listed.

5.4. Medical and Surgical History

All medical and surgical history will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) nomenclature, Version 21.0. Medical and surgical history will be tabulated by System Organ Class (SOC) and preferred term (PT) [redacted]. Separate tabulations will be provided for study eye, non-study eye, and non-ocular histories. Subjects with more than one medical history within a given SOC or PT will only be counted once within that SOC or PT. Ocular and non-ocular medical and surgical history will be listed.

5.5. Prior and Concomitant Medications

Prior medications are defined as those medications taken within 30 days prior to the start of Screening with a stop date prior to study drug administration. Concomitant medications are defined as those medications taken (1) prior to study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug.

Medications will be coded using the World Health Organization (WHO) Drug Dictionary (Version MAR2018) and will be summarized to the anatomical therapeutic chemical (ATC) class and preferred name. The number and percentage of subjects on medications will be tabulated by ATC, preferred name, [redacted]

- Prior medications in the study eye
- Prior medications in the non-study eye
- Non-ocular prior medications
- Concomitant medications in the study eye for the initial, PE, and totally study periods
- Concomitant medications in the non-study eye
- Non-ocular concomitant medications

Subjects will be counted only once under each ATC class or preferred name for which they have at least one medication. All prior and concomitant medications will be listed.

5.6. Concurrent Ocular Procedures

Concurrent ocular procedures are defined as any ocular procedures that occurred in the study eye on or after the date of the First Operative visit at Visit 2. Ocular procedures will be coded using the MedDRA nomenclature, Version 21.0. Ocular procedures will be tabulated by SOC, PT, [redacted] for each study period. Subjects with more than one ocular procedure within a given SOC or PT will only be counted once within that SOC or PT. All concurrent ocular procedures will be listed.

6. Efficacy Analyses

6.1. Primary Endpoint Efficacy Analysis

There are no primary efficacy endpoints in this study.

6.2. Secondary Endpoint Efficacy Analysis

There are no secondary efficacy endpoints in this study.

6.3. Exploratory Endpoint Efficacy Analysis

There are no exploratory efficacy endpoints in this study.

7. Safety Analyses

All safety analyses will be based on the safety analysis set and will be described in more detail in the following sections.

7.1.1. Extent of Exposure

Summaries of the extent of exposure to study treatment, which include the number of participants exposed and descriptive statistics of the duration of exposure in study days, will be provided [redacted] for each study period. Extent of exposure to study treatment in days will be calculated differently by study period. For the total study period, extent of exposure will be calculated as date of study exit – date of 1st Operative visit + 1. For the initial study period, extent of exposure will be calculated as date of 2nd Operative visit – date of 1st Operative visit + 1. For the PE study period, extent of exposure will be calculated as date of study exit – date of 2nd Operative visit + 1. If the date of study exit, or the date of 2nd Operative visit for the initial study period, is missing for a subject with early study exit, the date of the last recorded visit will be used for calculations. A listing of extent of exposure will be provided.

7.1.2. Adverse Events

Adverse events (AEs) will be coded to the MedDRA nomenclature, Version 21.0. Treatment Emergent Adverse Events (TEAEs) are defined as AEs that occur after the initiation of the first surgery at Visit 2 (First Operative Day 0).

AEs will be categorized into either the initial or PE study periods, as described in Section **2.3.1**. AEs that extend between study periods (i.e., beginning during the initial study period and extending into the PE study period), will be categorized into the initial study period. However, if an increase in severity or change in relationship to study treatment occurs during the PE study period, the AE will be categorized into both the initial and PE study periods.

A summary of the number and percentage of subjects with TEAEs [redacted] will be provided for each study period. The summary will include study eye TEAEs, non-ocular or non-study eye TEAEs, treatment-related TEAEs, TEAEs by maximum severity, TEAEs resulting in study discontinuation, serious TEAEs, and deaths.

The number and percentage of subjects with study eye TEAEs, non-study eye TEAEs, and non-ocular TEAEs will be provided by SOC, PT, [redacted] for:

- TEAEs
- TEAEs related to study treatment
- TEAEs by maximum severity
- Serious TEAEs

Tabulations of study eye TEAEs for each of the above categories will be provided for each study period.

All AEs will be presented in a listing by subject. Separate listings for intraoperative AEs, serious adverse events (SAEs), AEs leading to deaths, AEs leading to study discontinuation, and AEs leading to removal of implant will also be presented.

Relationship to study treatment is defined as the possibility that the study treatment caused the event and is described in the study protocol. The relationship to study treatment categories utilized on the CRF are definitely unrelated, unlikely related, possibly related, probably related, and definitely related. For all tabulations presenting relationship to study treatment, the categories of possibly related, probably related, and definitely related will be classified as related and only related AEs will be presented. AEs with missing relationships are counted as related. Subjects experiencing more than one treatment related AE within a given SOC or PT will be counted once within that SOC or PT.

Severity is a measure of intensity and is graded on a 3-point scale as outlined in the study protocol. AEs will be rated as either mild, moderate, or severe. AEs with missing severities are counted as severe. For all tabulations, subjects experiencing more than one AE within a given SOC or PT will be counted once within that SOC or PT at the maximum severity.

7.1.3. Additional Safety Assessments

Additional safety measures will be summarized for the Safety analysis set. Only data in the study eye will be presented in tabulations. Data may be tabulated by visit and/or for the overall study period (i.e. subjects with at least one finding during the study period) as indicated. Summaries for the overall study period will include data from unscheduled visits.

The change in safety data may be summarized by study period as indicated. In general, only the CFB will be presented for visits belonging to the initial study period and both the CFB and the CFPE will be presented for visits belonging to the PE study period.

The criteria for clinical significance varies by measure. Unless otherwise specified,

- [redacted]

7.1.3.1. Visual Acuity

Best spectacle corrected visual acuity (BSCVA) is measured at Screening using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart. Corrected VA (ETDRS) is collected at Week 4, Month 6, Month 12, Month 18, Pre-Exchange, and Week 4 PE unless a decrease of 2 or more lines (≥ 10 letters) from Screening occurs, at which time BSCVA is also measured. Pinhole VA (Snellen) is collected at the Day 1, Day 10, Day 1 PE and Day 10 PE visits.

Corrected VA and BSCVA will be presented in tabulations. If both corrected VA and BSCVA are collected, only BSCVA will be presented in the tabulations.

The worst change in VA will be summarized [redacted] for the total, initial, and PE study periods. The worst change in VA is defined as the largest decrease, or smallest increase if there is no decrease, in number of letters read correctly across all

postoperative visits (scheduled or unscheduled) in the study period. For the initial and total study periods, only the worst CFB will be presented. For the PE study period, the worst CFPE will also be presented. The number and percentage of subjects with a worst decrease of greater than or equal to 15 letter (3 lines) will also be summarized for each study period.

The actual and CFB in number of letters read correctly will be summarized by visit [redacted]. The number and percentage of subjects with a decrease of greater than or equal to 15 letters (3 lines) will also be summarized by visit [redacted]. For visits belonging to the PE study period, the CFPE will also be summarized both continuously and categorically as outlined.

A visual acuity subject listing will be provided for all visual acuity data including pinhole VA.

7.1.3.2. Slit Lamp Examinations

Slit lamp measures collected on the CRF include corneal edema, corneal opacity, epithelium, endothelium, guttata, anterior chamber depth, anterior chamber cells, anterior chamber flare, and pupil. All slit lamp measures are collected at Screening and each postoperative visit within both study periods (Day 1, Day 10, Week 4, Month 6, Month 12, Month 18, Pre-Exchange, Day 1 PE, Day 10 PE, and Week 4 PE).

For each measure, the number and percentage of subjects in each severity grade/category will be summarized by visit [redacted].

Slit lamp findings will also be summarized by time interval within each study period. For the initial study period, the time intervals will consist of after Baseline through Week 4, after Week 4 to Month 12, and after Month 12 to Month 24. For the PE study period, only the time interval of after pre-exchange to Week 4 PE will be summarized. The summaries will include the number and percentage of subjects with at least one clinically significant worsening during the specified time interval (including data from unscheduled visits)[redacted]. For the initial study period, only a clinically significant worsening from baseline will be presented. For the PE study period, both a clinically significant worsening from baseline and a clinically significant worsening from pre-exchange will be presented. [redacted] For findings not associated with a severity grade, a status change from normal/absent to abnormal/present at any postoperative visit during the time interval will be summarized.

All slit lamp data will be listed. Two additional slit lamp listings will be provided – one for subjects with a worsening from baseline and one for subjects with a worsening from pre-exchange. For each subject, the listings will present findings at each visit only for measures with either

(1) at least one clinically significant worsening at any follow-up visit during the study for findings associated with severity grade or
(2) a status change (i.e., a change from normal/absent to abnormal/present at a follow up visit) at any follow-up visit during the study for findings not associated with severity grade.

Other slit lamp findings will also be listed.

7.1.3.3. Lens Findings

Lens measures are collected at Screening and each postoperative visit within both study periods (Day 1, Day 10, Week 4, Month 6, Month 12, Month 18, Pre-Exchange, Day 1 PE, Day 10 PE, and Week 4 PE). Lens measures include lens status, posterior capsule opacification, nuclear lens opacity, cortical lens opacity, and posterior subcapsular lens opacity.

For each measure, the number and percentage of subjects in each severity grade/category will be summarized by visit [redacted]

Lens findings will also be summarized by time interval within each study period. For the initial study period, the time intervals will consist of after Baseline to Week 4, after Week 4 to Month 12, and after Month 12 to Month 24. For the PE study period, only the time interval of after pre-exchange to Week 4 PE will be summarized. The summaries will include the number and percentage of subjects with at least one clinically significant worsening for the specified time interval (including data from unscheduled visits) [redacted]. For the initial study period, only a clinically significant worsening from baseline will be presented. For the PE study period, both a clinically significant worsening from baseline and a clinically significant worsening from pre-exchange will be presented.

All lens data will be listed. Two additional listings of lens findings will be provided – one for subjects with a worsening from baseline and one for subjects with a worsening from pre-exchange. For each subject, the listings will present findings at each visit only for measures with at least one clinically significant worsening at any follow-up visit during the study. Other lens findings will also be listed. Lens status (phakic or pseudophakic) will be listed and not tabulated.

7.1.3.4. Ophthalmoscopy Examinations

Dilated fundus, nerve abnormality, and vertical cup-to-disc ratio assessments are evaluated at Screening. All ophthalmoscopy data will be presented in a listing.

7.1.3.5. Gonioscopy

Gonioscopy assessments are performed at Screening, Week 4, Month 6, Month 12, Month 18, Pre-Exchange, and Week 4 PE. Gonioscopy findings include goniosynechiae, angle rubeosis, and other angle abnormalities.

The number and percentage of subjects with gonioscopy findings will be provided by visit [redacted].

A summary of status change findings will be provided [redacted] for each study period. For the initial and total study periods, only the number and percentage of subjects with a status change from baseline will be provided by visit and for the overall study period. For the PE study period, the number and percentage of subjects with a status change from pre-exchange will also be provided by visit and for the overall study period.

All gonioscopy data will be listed by subject. Two additional listings will be provided – one for subjects with status change findings from baseline and one for subjects with status change findings from pre-exchange. For each subject, the listings will present findings at each visit only for measures with at least one status change at any follow-up visit during the study.

7.1.3.6. Implant Visibility

Implant visibility is collected at Week 4, Month 6, Month 12, Month 18, Pre-Exchange, and Week 4 PE. [redacted] implant visibility will be summarized discretely by visit for the following implant visibility categories:

- Original Target Position
- Anchored but Migrated
- Not Anchored (if implant visibility in original target position is reported as "No" and the implant is not "anchored but migrated")

A data listing will be provided for all implant visibility data.

7.1.3.7. Corneal Pachymetry

Corneal pachymetry assessments are performed at Screening. All pachymetry data, including central corneal thickness (μm), will be presented in a listing.

7.1.3.8. Intraocular Pressure

IOP is assessed for safety and is measured at Screening and all postoperative visits within each study period (Day 1, Day 10, Week 4, Month 6, Month 12, Month 18, Pre-Exchange, Day 1 PE, Day 10 PE, and Week 4 PE). IOP measurements will be taken once daily, unless surgery is performed. At each visit, IOP may be collected at any time of the day.

The actual and CFB in IOP (mmHg) will be summarized by visit [redacted]. The number and percentage of subjects will also be tabulated by visit [redacted] for the following categories:

- IOP ≥ 30 mmHg
- IOP Increase ≥ 10 mmHg

For visits belonging to the PE study period, the CFPE will also be summarized both continuously and categorically as outlined.

A subject listing presenting all IOP data will be provided.

8. Other Analyses

Other analyses will be summarized as outlined in the subsequent sections.

8.1.1. Operative and Surgical Analyses

[redacted]

8.1.2. Subgroup Analyses

No subgroup analyses are planned.

9. Interim Analysis

No interim analyses will be performed.

10. Changes to Protocol-planned Analyses

No changes to the protocol-planned analyses have occurred.

11. Supporting Documentation

11.1. 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

11.2. 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

11.3. 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

11.4. 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

11.5. 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

11.6. 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

11.7. 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

11.8. Appendix H: Data Derivation Rules

[redacted]

12. References

There are no references.

Pharmacokinetic Data Analysis Plan

Prospective, Non-Randomized, Open-Label, Single Center Study to Evaluate [redacted] the Performance of the Travoprost Intraocular Implant

Protocol Number:	IDOS-402-IVIV
Product Name:	Travoprost Intraocular Implant, [redacted] (G2-TR-125)
Sponsor Name:	GLAUKOS CORPORATION 26600 Aliso Viejo Parkway Aliso Viejo, CA 92656
Version:	1.0
Date:	January 10, 2024

Pharmacokinetic Data Analysis Plan Approval Signatures

The signatures below indicate approval of the Pharmacokinetic Data Analysis Plan for this study.

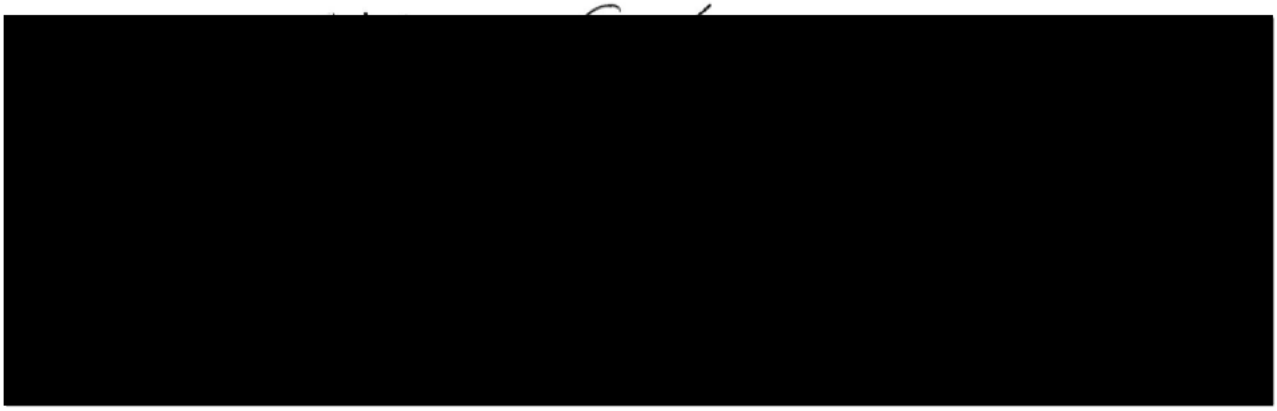


Table of Contents

List of Abbreviations

Abbreviation	Definition
AH	Aqueous Humor
CSR	Clinical Study Report
DAP	Data Analysis Plan
EDC	Electronic Data Capture
OAG	Open-Angle Glaucoma
OHT	Ocular Hypertension
PE	Post-Exchange
PK	Pharmacokinetics
SAP	Statistical Analysis Plan
TFA	Travoprost Free Acid

Version History

This Pharmacokinetic Data Analysis Plan (PK DAP) for IDOS-402-IVIV is based on the protocol dated 18SEP2019.

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Original version

1. Introduction

The data analyses outlined in this document are to support clinical study IDOS-402-IVIV. In this study, measurements will be made for travoprost (prodrug) in exchanged Travoprost Intraocular Implants and travoprost free acid (TFA, active moiety) in aqueous humor (AH). This data analysis plan (DAP) outlines how data analyses of these measurements will be conducted. Additional analyses not specified in the protocol include measurements for fluprostenol (also known as TFA) and other travoprost related substances in exchanged Travoprost Intraocular Implants, as defined in the analytical test method. Safety analyses are described separately in the Statistical Analysis Plan (SAP). Any changes to this plan will be reflected as amendments before the database lock and/or documented in the pharmacokinetic contributing report to the clinical study report.

2. Objectives and Study Design

2.1. Objectives

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

2.2. Endpoints

This data analysis plan describes analyses for the following study endpoints:

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

2.3. Study Design

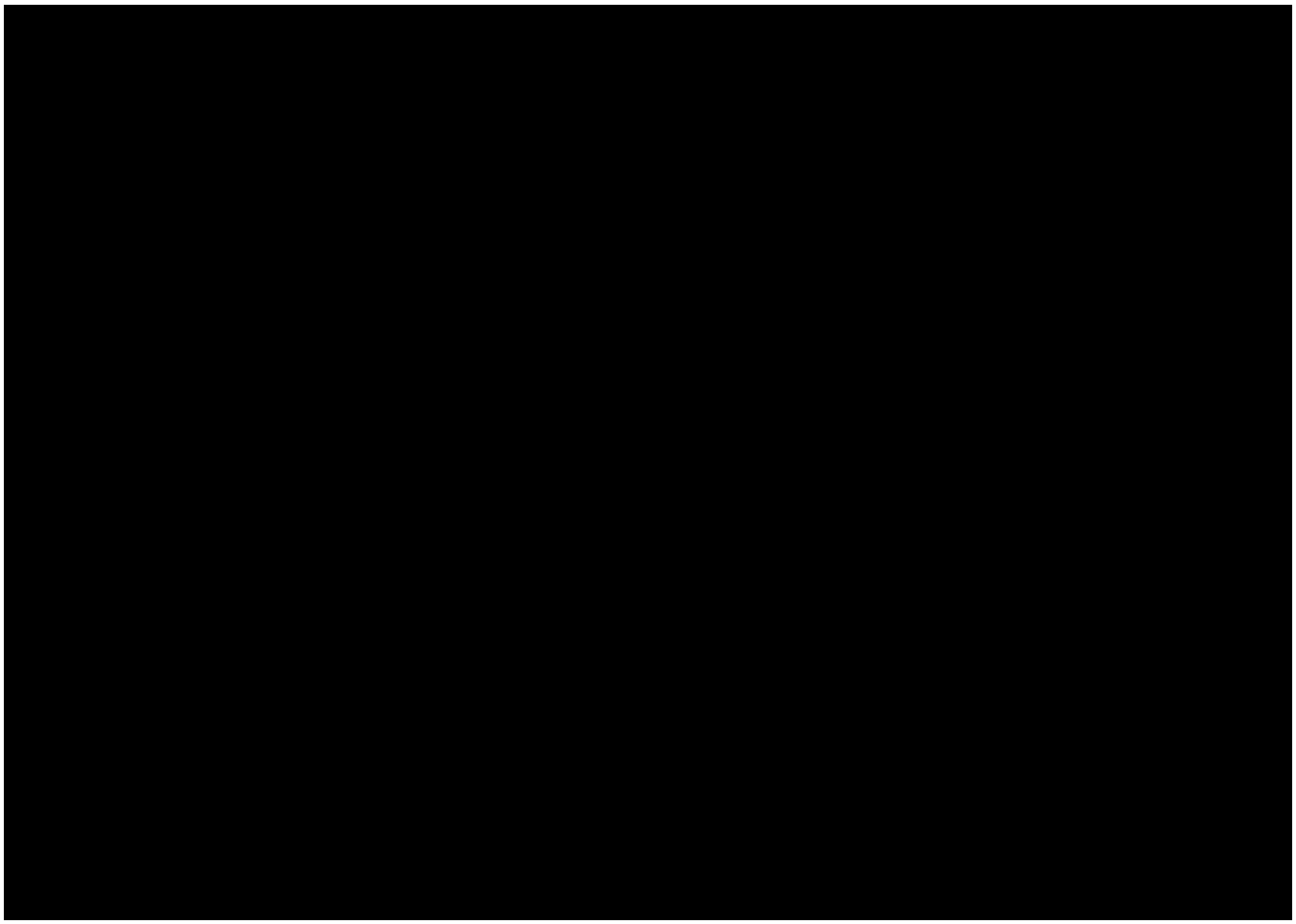
This is a prospective, non-randomized, open-label, single center trial evaluating [redacted] the performance of the Travoprost Intraocular Implant in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT). Approximately 210 total subjects (14 cohorts of 15 subjects) will be enrolled into the study. Subjects will be screened for qualification as per the inclusion/exclusion criteria (refer to Sections **6.2.1** and **6.2.2** of study protocol). Qualified subjects will be assigned to a cohort and will be implanted with the Travoprost Intraocular Implant (G2-TR-125 Implant) in one eye. Each cohort will consist of a specified duration [redacted] All enrolled subjects will undergo a second operative visit, the exchange of the Travoprost Intraocular Implant, at Visit 7. The duration of time for each cohort is the time between the implantation of the 1st implant at Visit 2 (Day 0) and the implantation of the 2nd implant at Visit 7 (Exchange procedure and collection of the aqueous humor and explant).

Depending on the cohort assignment, subjects will be followed for 4 – 25 months postoperatively (3 – 24 months after 1st implantation and 4 weeks after the 2nd implantation). Study follow-up will continue until the Week 4 post-exchange (PE) visit.

Depending on the cohort assignment, the study consists of 10 to 13 visits: 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 [PE]), Visit 9 (Day 10 PE), and Visit 10 (Week 4 PE). Subjects will exit the study at the conclusion of the Week 4 PE visit.

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 remaining 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 cohort sequentially as defined by the cohort order as they receive surgery. Each cohort must be filled prior to starting the next cohort.



2.4. Sample Size Determination

The sample size of 210 subjects who undergo implantation and exchange of a Travoprost Intraocular Implant was determined to support the study objectives and is not based on statistical power calculations. [redacted]

3. Analysis Sets

For the purposes of analysis, the following analysis set is defined:

Subject Analysis Set	Description
Pharmacokinetic analysis set	• All subjects contributing aqueous humor and/or exchanged implants.

The safety analysis set will be used for all data tabulations and listings.

4. Methods

4.1. Software

Pharmacokinetic analysis, summarization of concentration-time data, statistical analysis, and graphical visualization of aqueous humor or implant exchange data will be performed using [redacted]

4.2. Methodology of Measurements

4.2.1. Aqueous Humor Collection and Analysis Methodology

A single aqueous humor sample will be collected from each subject at Visit 7 (Exchange visit). The timing of Visit 7 will be dependent on the cohort to which each subject is assigned and will occur at Month 3, Month 6, Month 12, Month 15, Month 18, Month 21, or Month 24 post-implantation. A total of 150 µL of aqueous humor will be collected through an anterior chamber tap. The aqueous humor sample will be separated into two 75 µL aliquots (a primary and backup) and stored at [redacted]

Aqueous humor concentrations of TFA will be determined using a validated liquid chromatography-tandem mass spectrometry method [redacted]

4.2.2. Implant Exchange and Travoprost Analysis Methodology

Travoprost Intraocular Implants will be exchanged at the timepoints noted in Section 4.2.1. Upon insertion of the second implant, the first implant will be explanted and collected for measurement

of remaining travoprost drug [redacted] Explants will be stored [redacted]

Residual travoprost [redacted] concentrations in explants will be determined using a validated high performance liquid chromatography method [redacted]

4.3. Data Handling and Storage

A source data file from [redacted] will be transferred to Applied Research Translational Sciences via a secure file transfer portal [redacted]. The data file will be manually reconciled and QC'd against the Electronic Data Capture (EDC) system.

Unless otherwise specified in subsequent sections, these general data handling instructions will be followed:

- All measured data will be used in analysis initially unless it may be excluded in accordance to regulatory guidances. Measured data not used and the reasons for its exclusion from the final analysis will be documented in the clinical study report (CSR).
- Nominal sample times will be used in the calculation of descriptive statistics.
- Concentration data below the quantitation limit (BQL) [redacted]

[redacted]

5. Data Analysis

5.1. Pharmacokinetics

No formal pharmacokinetic analyses are planned for this study.

In vitro-in vivo correlation will be assessed by visual comparison of in vitro vs. in vivo mean cumulative release and/or mean drug elution rate.

In vitro release testing of Travoprost Intraocular Implants is described in Technical Report RN-0709.

5.2. In Vivo Drug Elution Rate Calculations

In vivo cumulative percent (%) drug release from Travoprost Intraocular Implant will be calculated as follows:

Equation 1: [redacted] - Travoprost remaining (µg) at "timepoint") / [redacted] * 100 = cumulative percent (%) drug release

In vivo implant release rate will be calculated as follows:

Equation 2: (Travoprost remaining (µg) at T_1 – Travoprost remaining (µg) at T_2) / (T_2 – T_1) * 1000 = in vivo implant release rate (ng/day)

[redacted]

5.3. Data Summarization

Descriptive statistics (arithmetic mean, standard deviation, median, maximum, minimum) will be reported for the aqueous humor TFA and explant travoprost [redacted] at each nominal time point.

5.4. Statistical Analysis

Statistical differences in TFA AH concentrations and/or remaining explant travoprost [redacted] concentrations will be assessed [redacted]

5.5. Presentation of Final Results

Presentation of the data will be performed using the software described in Section 4.1. Analyses will include, but not be limited to, the following:

Tables:

- TFA aqueous humor concentrations (mean, standard deviation, median, min, max) by timepoint [redacted]
- Explant travoprost concentrations (mean, standard deviation, median, min, max) by timepoint [redacted]
- Explant TFA concentrations (mean, standard deviation, median, min, max) by timepoint [redacted]
- Explant travoprost + TFA (Total) concentrations (mean, standard deviation, median, min, max) by timepoint [redacted]
- Cumulative percent (%) release from explants (mean, standard deviation, median, min, max) by timepoint [redacted]
- Travoprost amount (µg) remaining in explants (mean, standard deviation, median, min, max) by timepoint [redacted]
- In vivo Travoprost Intraocular Implant release rate (ng/day) (mean, standard deviation, median, min, max) by timepoint [redacted]

[redacted]

6. References

[redacted]

7. Supporting Documentation

7.1. 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

7.2. 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

7.3. 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

7.4. 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

7.5. 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

7.6. 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

7.7. 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