CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218010Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	218010
Link to EDR	\\CDSESUB1\evsprod\NDA218010\0001
Submission Date	02/22/2023
PDUFA Goal Date	12/22/2023
Submission Type	505(b)(2)
Brand Name	iDose®TR
Generic Name	Travoprost intraocular implant
Dosage Form and Strength	An intraocular implant containing 75 mcg travoprost (b) (4) in a drug delivery system
Route of Administration	Ophthalmic intracameral administration
Proposed Indication	Reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
Proposed Dosage Regimen	• iDose®TR is administered intracamerally through a small and clear corneal incision and is anchored into the sclera at the iridocorneal angle of an eye. • (b) (4)
Applicant	Glaukos Corporation
Associated IND	120,995
OCP Review Team	Liping (Cindy), Pan, M.D., Ph.D., R.A.C.-Drugs Global Ping Ji, Ph.D.
OCP Division	Division of Inflammation and Immune Pharmacology

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1. EXECUTIVE SUMMARY

Travoprost intraocular implant (iDose® TR) is a drug-device combination product that is surgically delivered through a clear corneal incision and anchored in the anterior chamber angle of the eye. The implant is designed to release 75 mcg of travoprost (b) (4) in a controlled manner as a topical intraocular pressure (IOP)-lowering medication for patients with open-angle glaucoma (OGA) or ocular hypertension (OHT).

In support of the 505(b)(2) New Drug Application (NDA) for the proposed indication, the Applicant evaluated efficacy and safety of two versions of the implant comprising of 75 mcg of travoprost, Model G2-TR-063 and Model G2-TR-125, in one phase 2 trial (GC-009) and two phase 3 trials (GC-010 and GC-012) in adult subjects with OAG or OHT. Both models are identical, except for (b) (4) elution rate and duration. Under NDA218,010, the Applicant is seeking marketing authorization only for travoprost intraocular implant Model G2-TR-125 (iDose® TR) which has a lower elution rate when compared to Model G2-TR-063. Additionally, the safety of the surgical exchange procedure of travoprost intraocular implant Model G2-TR-125 was evaluated in an open-label 12-month trial (IDOS-106-EXCH) in subjects with OGA or OHT.

Clinical pharmacology of travoprost intraocular implant was characterized in the phase 2 trial of GC-009 in subjects with OGA and OHT following administration of travoprost intraocular implant Model G2-TR-125 or Model G2-TR-063.

1.1 Recommendations

The Office of Clinical Pharmacology Division of Inflammation and Immune Pharmacology has reviewed the clinical pharmacology data submitted under NDA 218,010. From a clinical pharmacology's perspective, the submission is recommended for approval for reduction of elevated IOP in subjects with OAG or OHT.

The key review findings with specific recommendations and comments are summarized in Table 1 .

Table 1 Key Review Issues and Recommendations

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Evidence of effectiveness was based on one phase 2 (GC-009) and two phase 3 trials (GC-010 and GC-012). Refer to the clinical and statistical reviews for details.

General dosing instructions	iDose®TR is administered intracamerally through a small and clear corneal incision and is anchored into the sclera at the iridocorneal angle. (b) (4)
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended as the eye is the route of drug administration and the targeted organ of drug action.
Bridge between the to-be-marketed product and the clinical trial product	Compared to the product used in the pivotal phase 3 trials, the proposed to-be-marketed (TBM) product will have a few minor process improvement (b) (4) (b) (4) (b) (4). Based on the Office of Pharmaceutical Quality's (OPQ's) recommendation, these minor changes are not likely to impact the drug delivery (for details, see the OPQ's reviews). Thus, there is no need to bridge the TBM product to the product used in the phase 3 trials.

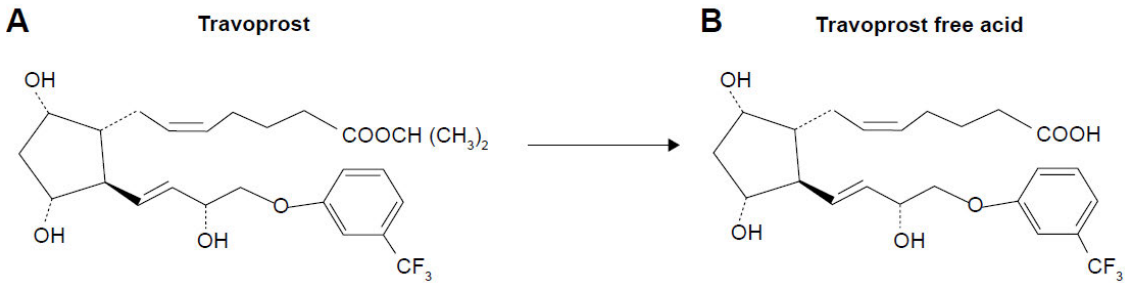
1.2 Post-Marketing Requirements/Commitments

None.

2. CLINICAL PHARMACOLOGY ASSESSMENT

Travoprost intraocular implant (iDose® TR) is a drug-device combination product containing approximately 75 mcg of travoprost (b) (4). Travoprost, an isopropyl ester prodrug (Figure 1), is absorbed through the cornea and is hydrolyzed by esterases to its biologically active free acid, travoprost free acid (Figure 1).

Figure 1 Travoprost Chemical Structure



Source: Quaranta L, Riva I, Katsanos A, Floriani I, Centofanti M, Konstas AG. Safety and efficacy of travoprost solution for the treatment of elevated intraocular pressure. Clin Ophthalmol. 2015 (9):633-643

2.1 Pharmacology and Clinical Pharmacokinetics of Travoprost Free Acid

Mechanism of Action

Travoprost free acid, a prostaglandin analog, is a selective FP prostanoid receptor agonist which is believed to reduce IOP by increasing uveoscleral outflow. The exact mechanism of action currently is currently unknown.

Pharmacokinetics

Systemic exposure to travoprost free acid was assessed at Week 1-2, Week 12, and Month 12 in subjects following administration of travoprost intraocular implant Model G2-TR-125 (n=54) or Model G2-TR-063 (n=51) in the phase 2 trial of GC-009. Plasma concentrations of travoprost free acid were analyzed via a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The study results indicated that systemic exposure to travoprost free acid in all samples was below the lower limit of quantification (BLLOQ) of 10 pg/mL.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

iDose® TR is administered intracamerally through a small clear corneal incision and is anchored into the sclera at the iridocorneal angle of the eye. (b) (4)

(b) (4)

2.2.2 Therapeutic individualization

Therapeutic individualization based on intrinsic or extrinsic factors is not necessary for iDose® TR as the eye is the route of drug administration and the targeted organ of drug action.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

None.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Travoprost intraocular implant (iDose® TR) is comprised of a titanium reservoir (also referred to as titanium container) with titanium anchor, containing approximately 75 mcg of travoprost

drug substance [redacted] (b) (4). The titanium reservoir is sealed with an EVA membrane held in place with a titanium crimp cap. The EVA membrane, which is in direct contact with the travoprost drug product formulation filled into the titanium reservoir, allows drug to elute through the membrane at a specific rate. The nominal dimensions of the assembled implant are 1.84 mm long by 0.494 mm in diameter.

The active ingredient in the iDose TR is travoporst which is also the active ingredient in FDA-approved Travatan and Travatan Z (0.004% travoprost ophthalmic solution, one drop in the affected eye once daily) with the same indication. Thus, the Applicant is seeking marketing authorization of the iDose TR through 505(b)(2) regulatory pathway.

The clinical development program for the iDose TR was designed to demonstrate the safety and efficacy of the implant for the reduction of elevated IOP in subjects with OAG or OHT following its initial administrations, as well as upon re-administration and removal of the prior implant.

At reviewing the Pre-IND meeting package (under IND 120,995) submitted on 2/26/2014, the clinical pharmacology review team recommended the Applicant evaluate the systemic pharmacokinetics (PK) of travoprost/travoprost free acid following the administration of the to-be-marketed travoprost implant in a subset of patients enrolled in the phase 2 or 3 trials. For details, see the clinical pharmacology review document authored by Dr. Zhang in DARRTS dated 3/14/2014 (Reference ID 3471613). In the current NDA submission, the PK data obtained from the phase 2 study of GC-009 was submitted as a part of the NDA submission.

3.2 General Pharmacology and Pharmacokinetic characteristics

The clinical pharmacology of travoprost is well characterized given its two decades of use as an IOP-lowering therapy in subjects with OAG or OHT. General clinical pharmacology and pharmacokinetics of travoprost free acid are summarized in Table 2.

Table 2 Summary of Clinical Pharmacology of Travoprost Free Acid

Pharmacology	
Mechanism of Action	Travoprost free acid, a prostaglandin analog is a selective FP prostanoid receptor agonist which is believed to reduce IOP by increasing uveoscleral outflow. The exact mechanism of action currently is unknown at this time.
Pharmacodynamics	The pharmacodynamic effect of travoprost free acid in reducing elevated IOP in subjects with OAG or OHT has not been characterized.
General Information	

Bioanalysis	Plasma concentrations of travoprost free acid were quantified using the validated LC-MS/MS bioanalytical method with the lower limit of quantitation of 10 pg/mL and the upper limit of quantitation of 5,000 pg/mL of travoprost free acid.
PK model	Not appliable.
Healthy vs. Patients	Systemic PK of travoprost free acid following administration of iDose® TR was characterized only in subjects with OAG or OHT.
Drug Exposure	Following administration of iDose® TR, systemic exposure to travoprost free acid at Week 1-2, Week 12, and Month 12 in subjects with OAG or OHT (n=54) was BLLOQ of 10 pg/mL in the phase 2 trial of GC-009[1)].
Dose Proportionality	Not applicable. Only 75 mcg of travoprost was studied in the clinical development program.
ADME	
Absorption	Following administration of iDose® TR, systemic exposure to travoprost free acid at Week 1-2, Week 12, and Moth 12 in subjects with OAG or OHT was BLLOQ of 10 pg/mL[1)]. TRAVTAN® (NDA021,257) and TRAVTAN Z® (NDA021,994) "Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Data from 4 multiple dose pharmacokinetic studies (totaling 107 subjects) have shown that plasma concentrations of the free acid are below 0.01 ng/mL (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N = 38), the mean plasma C_{max} was 0.018 ± 0.007 ng/mL (ranged 0.01 to 0.052 ng/mL) and was reached within 30 minutes. From these studies, travoprost is estimated to have a plasma half-life of 45 minutes. There was no difference in plasma concentrations between Days 1 and 7, indicating steady-state was reached early and that there was no significant accumulation."
Distribution	Not available.
Elimination	TRAVTAN® (NDA021,257) and TRAVTAN Z® (NDA021,994) "The terminal elimination half-life of travoprost free acid was estimated from fourteen subjects and ranged from 17 minutes and 86 minutes with the mean half-life of 45 minutes."
Metabolism	TRAVTAN® (NDA021,257) and TRAVTAN Z® (NDA021,994) "Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to it biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α (carboxylic acid) chain to give the 1,2-dinor and

	1,2,3,4-tertranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond."
Excretion	TRAVTAN® (NDA021,257) and TRAVTAN Z® (NDA021,994) "Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost free acid."

ADME=Absorption, Distribution, Metabolism, and Excretion.

[1)] The product used in the phase 2 trial of GC-009 was neither identical to the phase 3 product nor to the proposed TBM product. Based on the OPQ's recommendation, the proposed minor process changes in the TBM product are not likely to impact the drug delivery when compared to the products used in phase 2 and 3 trials. Refer to the OPQ's reviews for details.

3.3 Clinical Pharmacology Review Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

No. The clinical pharmacology information in this NDA does not provide supportive evidence of effectiveness. As the affected eye is the route of drug administration and the targeted organ of drug action, the systemic exposure to travoprost free acid is not expected to be predictive to the effectiveness.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The safety and efficacy of iDose® TR was assessed in subjects with OAG or OHT following the initial administration of iDose® TR in two phase 3 trials (GC-010 and Gc-012). We defer to the clinical and statistical review teams to address this question.

The plasma concentrations of traveoprost free acid were BLLOQ of 10 pg/mL in all samples analyzed from the subjects in the phase 2 study GC-009, supporting the systemic safety for the proposed regimen in the general patient population.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. An alternate dosing regimen or management strategy is not necessary for subpopulation based on intrinsic factors. As the affected eye is the route of drug administration and the targeted organ of drug action, the systemic exposure is not likely to influence the proposed drug product's efficacy and safety.

3.3.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

No clinical drug-drug interaction (DDI) studies were conducted, as the ADME properties of travoprost free acid indicate that travoprost free acid has a low potential for mediating a DDI with co-administered agents via CYP or drug transporter pathways.

4. Clinical Pharmacology Appendix

The clinical development program of the iDose TR included 4 clinical trials (Table 3) which were designed to demonstrate the safety and efficacy of the implant for the reduction of elevated IOP in subjects with OAG or OHT following its initial administration, as well as upon re-administration and removal of the prior implant ("exchange").

Table 3 Overview of Clinical Trials

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects [a]	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
GC-009	Phase 2 safety and efficacy	Prospective, randomized, double-masked, active-controlled, parallel-group, multicenter trial	G2-TR-063 intraocular implant + placebo eyedrops BID in the study eye G2-TR-125 intraocular implant + placebo eyedrops BID in the study eye Sham surgery + Timolol 0.5% eye drops BID in the study eye	270	Males or females ≥ 18 years of age with OAG or OHT	36 months
US IDOS-106-EXCH	Phase 2 safety of the exchange of a Travoprost Implant	Prospective, open-label, multi-center, single arm study	G2-TR-125 intraocular implant in the study eye	33	Males or females ≥ 18 years of age with OAG or OHT	12 months
GC-010	Phase 3 safety and efficacy	Prospective, randomized, double-masked, active-controlled, parallel-group, multicenter trial	G2-TR-063 intraocular implant + placebo eyedrops BID in the study eye G2-TR-125 intraocular implant + placebo eyedrops BID in the study eye Sham surgery + Timolol 0.5% eye drops BID in the study eye	590	Males or females ≥ 18 years of age with OAG or OHT	36 months (12-Month analysis included in NDA)
GC-012	Phase 3 safety and efficacy	Prospective, randomized, double-masked, active-controlled, parallel-group, multicenter trial	G2-TR-063 intraocular implant + placebo eyedrops BID in the study eye G2-TR-125 intraocular implant + placebo eyedrops BID in the study eye Sham surgery + Timolol 0.5% eye drops BID in the study eye	560	Males or females ≥ 18 years of age with OAG or OHT	36 months (12-Month analysis included in NDA)

a Intent-to-Treat Population
Timolol 0.5% = Timolol maleate ophthalmic solution USP, 0.5%
BID = twice daily; CSR = Clinical Study Report; N/A = not applicable; OAG = open-angle glaucoma; OHT = ocular hypertension

Source: 2.5 Clinical overview, Table 1

4.1 Summary of Biopharmaceutics Program

Two versions of the implant (Model G2-TR-063 and Model G2-TR-125), differentiated by the [redacted] (b) (4) elution rate and duration, have been evaluated in the clinic, although the Applicant is seeking approval for only the travoprost intraocular implant Model G2-TR-125. Both models have the same formulation comprising of 75 mcg of travoprost drug substance [redacted] (b) (4) .

The to-be-marketed product proposed for registration in this NDA will be identical to the drug product (Model G2-TR-125) used in the phase 3 trials, except for a few minor modifications [redacted] (b) (4) (b) (4) . The Clinical

Pharmacology's recommendations are summarized in Section 1 of the review. Refer to the OPQ's review for details.

4.2 Summary of Bioanalytical Method Validation and Performance

The Applicant developed and validated a LC-MS/MS analytical method for measurement of travoprost free acid concentrations in human plasma samples in the phase 2 trial (GC-009). The method is applicable for the quantitation of travoprost free acid within a nominal range of 10 to 5,000 pg/mL, with the lower limit of quantitation of 10 pg/mL. The validation parameters and performance of bioanalytical method for analysis of travoprost free acid in human plasma are summarized in Table 4.

Table 4 Summary of Validation Parameters of Bioanalytical Method for Analysis of Travoprost Free Acid in Human Plasma

Analyte	Travoprost free acid
Matrix	Human plasma
Anticoagulant	Dipotassium EDTA
Extraction Procedure	Anion exchange solid phase extraction
Instrument Platform	API 4000
Ionization	ESI (-)
Sample Volume (µL)	200 µL
Range	10-5000 pg/mL
Injection Volume	10 µL
Curve Fit	Quadratic regression with $1/x^2$ weighting
Internal Standard (IS)	Travoprost acid-d_4
Average Recovery of Travoprost Free Acid (%)	46.9 to 54.3%
Average Recovery of IS, travoprost acid-d_4 (%)	45.5 to 55.9%
Standard Curve Concentrations	10 pg/mL to 5000 pg/mL
QC Concentrations	LLOQ (10 pg/mL), Low QC (30 pg/mL), Mid QC (500 pg/mL), High QC (4000 pg/mL)
QC Intra-assay Statistics (%)	Accuracy ranged from 83.6-107%; precision ranged from 2.10-17.3%

Run ID: 20160412_val_a

Conc. (pg/mL)	Intra-assay Mean	Accuracy	Precision (CV)
10 pg/mL	8.36	83.6	16.3
30 pg/mL	26.7	88.9	10.2
500 pg/mL	478	95.7	5.72
4000 pg/mL	3708	92.7	5.02

Run ID: 20160424_val_a

Conc. (pg/mL)	Intra-assay Mean	Accuracy	Precision (CV)
10 pg/mL	9.41	94.1	11.1
30 pg/mL	30.9	103	9.59
500 pg/mL	505	101	2.31
4000 pg/mL	4135	103	2.10

Run ID: 20160424_val_b

Conc. (pg/mL)	Intra-assay Mean	Accuracy	Precision (CV)
10 pg/mL	8.55	85.5	17.3
30 pg/mL	29.6	98.6	8.34
500 pg/mL	534	107	4.87
4000 pg/mL	4138	103	2.28

<table>
<tr><td>QC Inter-assay Statistics for Travoprost Free Acid (%)</td><td>Accuracy ranged from 87.7-101%; precision ranged from 6.04-15.0%
<table><tr><th>Conc. (ng/mL)</th><th>Inter-assay Mean</th><th>Accuracy</th><th>Precision (CV)</th></tr><tr><td>10 pg/mL</td><td>8.77</td><td>87.7</td><td>15.0</td></tr><tr><td>30 pg/mL</td><td>29.1</td><td>96.9</td><td>10.8</td></tr><tr><td>500 pg/mL</td><td>506</td><td>101</td><td>6.27</td></tr><tr><td>4000 pg/mL</td><td>3994</td><td>99.8</td><td>6.04</td></tr></table></td></tr>
<tr><td>QC Inter-assay Statistics for All QC Samples (%)</td><td><table><tr><th>Conc. (ng/mL)</th><th>Inter-assay Mean</th><th>Accuracy</th><th>Precision (CV)</th></tr><tr><td>10 pg/mL</td><td>9.30</td><td>93.0</td><td>18.0</td></tr><tr><td>30 pg/mL</td><td>29.5</td><td>98.4</td><td>16.0</td></tr><tr><td>500 pg/mL</td><td>494</td><td>98.8</td><td>8.46</td></tr><tr><td>4000 pg/mL</td><td>3927</td><td>98.2</td><td>10.0</td></tr></table></td></tr>
<tr><td>Room Temperature Stability</td><td>4 hours</td></tr>
<tr><td>Long-term Stability</td><td>112 days at -80°C</td></tr>
<tr><td>Post-preparative Stability</td><td>72 hours at 4°C</td></tr>
<tr><td>Freeze-thaw Stability (cycles)</td><td>Three cycles at -80°C</td></tr>
<tr><td>Stock Solution Stability (in 50% acetonitrile/water)
Travoprost acid, 31 ug/mL, -20°C</td><td>289 days</td></tr>
<tr><td>Working Solution Stability at LLOQ (in MeCN:H_20 (1:1))
Travoprost acid, 1 ng/mL, 2-8°C</td><td>225 days</td></tr>
<tr><td>Dilutional Integrity</td><td>20000 pg/mL diluted 20-fold</td></tr>
<tr><td>Selectivity</td><td>No plasma lots contained a chromatographic peak at the retention time of travoprost acid with area counts >20% of the LLOQ</td></tr>
</table>

Source: Summary of biopharmaceutic studies and associated analytical methods, Table 1.

4.3 Clinical Pharmacology Study GC-009

Study GC-009 was a prospective, randomized phase 2 study comparing two elution rates of Glaukos travoprost intraocular implants to timolol maleate ophthalmic solution, USP (timolol), 0.5%.

Study design

Eligible males and females aged ≥18 years with either OAG or OHT were to be randomized to 1 of 3 treatment arms in a 1:1:1 allocation (see below). The study duration was up to 3 years.

- G2-TR-063 implant group: Model G2-TR-063 + 1 drop of placebo eyedrops BID
- G2-TR-125 implant group: Model G2-TR-125 + 1 drop of placebo eyedrops BID
- Sham/timolol group (timolol group): Sham surgery + 1 drop of timolol 0.5% BID

Study population:

A total of 154 adult subjects with either OAG or OHT were enrolled in the study. Demographic information is summarized in Table 5.

Table 5 Demographic Information for Study GC-009 (ITT Analysis Set)

	G2-TR-063 Implant (N=51)	G2-TR-125 Implant (N=54)	Timolol (N=49)	Total (N=154)
Age (years)				
n	51	54	49	154
Mean (SD)	63.9 (9.8)	61.4 (13.9)	63.0 (12.6)	62.7 (12.2)
Median	63.0	64.0	65.0	64.0
Min, Max	40, 86	18, 86	23, 86	18, 86
Age Category, n (%)				
≥ 18 to < 65 years	28 (54.9)	30 (55.6)	24 (49.0)	82 (53.2)
≥ 65 years	23 (45.1)	24 (44.4)	25 (51.0)	72 (46.8)
Sex, n (%)				
Male	24 (47.1)	29 (53.7)	20 (40.8)	73 (47.4)
Female	27 (52.9)	25 (46.3)	29 (59.2)	81 (52.6)
Race, n (%)				
White	41 (80.4)	41 (75.9)	37 (75.5)	119 (77.3)
Black or African American	6 (11.8)	8 (14.8)	5 (10.2)	19 (12.3)
Asian	4 (7.8)	5 (9.3)	6 (12.2)	15 (9.7)
Native Hawaiian or Other Pacific Islander	0	0	0	0
American Indian or Alaska Native	0	0	0	0
Unknown	0	0	1 (2.0)	1 (0.6)
Ethnicity, n (%)				
Hispanic or Latino	4 (7.8)	1 (1.9)	3 (6.1)	8 (5.2)
Not Hispanic or Latino	47 (92.2)	53 (98.1)	46 (93.9)	146 (94.8)
Region, n (%)				
US	47 (92.2)	49 (90.7)	44 (89.8)	140 (90.9)
Philippines	4 (7.8)	5 (9.3)	5 (10.2)	14 (9.1)

SD = standard deviation
Percentages were based on the number of subjects in each treatment group.

Source: Clinical Study Report GC-009, Table 9.

Pharmacokinetics of travoprost free acid

The PK results (Table 6) indicated that plasma exposure to travoprost free acid in all samples analyzed from subjects in Study GC-009 was below the lower limit of quantification of 10 pg/mL.

Table 6 Summary of Systemic Plasma Exposure to Travoprost Free Acid in Study GC-009

Treatment Group	Subjects Type	Number of Subjects and Results at Each Timepoint			
		Baseline (prior to treatment)	Week 1-2	Week 12	Month 12
G2-TR-063 (Lot 92631K0) + placebo BID (8AM & 8PM) study eye	51 subjects with OAG or OHT	51 subjects 51 BLQ	51 subjects 51 BLQ	51 subjects 51 BLQ	46 subjects [b] 46 BLQ
G2-TR-125 (Lot 92631L0) + placebo BID (8AM & 8PM) study eye	54 subjects with OAG or OHT	53 subjects [a] 53 BLQ	54 subjects 53 BLQ + 1 IS	54 subjects 54 BLQ	52 subjects [c] 52 BLQ
Sham + Timolol 0.5% BID (8AM & 8PM) study eye	49 subjects with OAG or OHT	49 subjects 49 BLQ	49 subjects 49 BLQ	49 subjects 49 BLQ	46 subjects [d] 46 BLQ

Source: Bioanalytical Report 16GLAUP2GLPS318, Table 1,
BID: twice a day; BLQ: Below lower limit of quantitation (<10 pg/mL of travoprost acid); F: female; IS: Insufficient sample; M: male; NS: No sample collected (subject discontinued participation in study); OAG: open-angle glaucoma; OHT: ocular hypertension; TFA: travoprost free acid

a A sample was not collected from one G2-TR-125 subject at Baseline.

b Samples were not collected from 5 G2-TR-063 subjects at Month 12 (subjects had discontinued from study)

c Samples were not collected from 2 G2-TR-125 subjects at Month 12 (subjects had discontinued from study)

d Samples were not collected from 3 Sham/Timolol subjects at Month 12 (subjects had discontinued from study)

Source: Summary of Clinical Pharmacology Studies, Table 2.

<u>Reviewer's comment:</u> The observed plasma concentrations of travoprost free acid in subjects with OAG or OHT following administration of travoprost intraocular implants (either G2-TR-125 or G2-TR-063) were lower the mean plasma travoprost free acid C_{max} of 18±7 pg/mL (ranged 10 to 52 pg/mL) in subjects who received one drop of Travatan® or Travatan Z® (travoprost ophthalmic solution 0.004%) in the affected eye once daily. See labeling of Travatan® or Travatan Z®.

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