CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218010Orig1s000

SUMMARY REVIEW

Summary Review of NDA 218010

Cross Discipline Team Leader, Deputy Division Director, Division Director Review

Review Completion Date	See DARRTS Stamp Date
From	Rhea Lloyd, MD, William Boyd, MD, Wiley Chambers, MD
Subject	Summary Review
NDA #	218010
Applicant	Glaukos Corporation, Inc.
Received Date(s)	February 22, 2023
PDUFA Goal Date	December 22, 2023
Proprietary Name	iDose TR
Established Name	travoprost intraocular implant, 75 mcg
Dosage Form(s)	Intraocular implant, administered intracamerally
Applicant Proposed Indication(s)/Population(s)	Reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
Applicant Proposed Dosing Regimen	(travoprost intraocular implant), 75 µg, administered intracamerally, single use only
Regulatory Action	**APPROVAL**

NDA 218010 Review Team Role	**Reviewer**
OND RPM	Lois Almoza
CDTL	Rhea Lloyd
Clinical Reviewer	Martin Nevitt
Pharmacology/Toxicology Reviewer	Muriel Saulnier
Statistical Reviewer	Wonyul Lee
Clinical Pharmacology Reviewer	Cindy (Liping) Pan
OND Labeling Reviewer	Derek Alberding
Application Technical Lead	Chunchun Zhang
Drug Substance	Joseph Leginus
Drug Product	Milton Sloan
Manufacturing	Krishnakali Ghosh
Microbiology	David Bateman
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OPDP Reviewer	Carrie Newcomer
Deputy Division Director	William Boyd
Division Director	Wiley Chambers
Deputy Office Director/ Office Director	Alexander Gorovets/ Charles Ganley

1. Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IOP	intraocular pressure
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OAG	open angle glaucoma
OCS	Office of Computational Science
OHT	ocular hypertension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report

PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

2. Summary

iDose TR (travoprost intraocular implant) 75 µg is a sterile, sustained-release, implant preloaded in a single use inserter, administered intracamerally through a small, clear corneal incision anchored into the sclera at the iridocorneal angle. The implant is designed to provide a controlled and sustained release of travoprost for at least 3 months for the reduction of intraocular pressure (IOP). The proposed indication is for the reduction of IOP in patients 18 years or older with open-angle glaucoma or ocular hypertension.

iDose TR (travoprost intraocular implant) 75 µg demonstrated efficacy in two adequate and well controlled clinical trials (Studies GC-010 and GC-012) at Day 10, Week 6 and Month 3 for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. GC-010 and GC-012, were successful for the primary efficacy endpoint, change from baseline in IOP (8 am and 10 am) compared to timolol for both G2-TR implants (b) (4) at Day 10, Week 6, and Month 3 based on the primary efficacy endpoints. For the key secondary efficacy endpoints at Month 12, neither clinical trial GC-010, or GC-012 demonstrated non-inferiority to timolol.

The Safety Data demonstrated safety of the implant for single use only. There is insufficient safety data to support more than a single use of the iDose TR implant. The most common adverse events occurring in ≥ 3% of subjects in any treatment group were iritis (5%), intraocular pressure increased (4%), visual field defect (3%) and dry eye (3%).

Approval is recommended for iDose TR (G2-TR-125 (b) (4) implant) to lower IOP for 3 months. (b) (4)
(b) (4)

3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of iDose TR (travoprost intraocular implant) 75 µg, when given as an intracameral insertion. The implant for most patients provides a significant lowering of intraocular pressure through Month 3, single use only. Studies GC-010 and GC-012 demonstrated that the IOP lowering ability of iDose TR (travoprost intraocular implant) 75 µg was noninferior to the IOP lowering achieved by timolol maleate ophthalmic solution 0.5% dosed BID through 3 months.

The safety profile of Travoprost intraocular implant is similar to other marketed topical prostaglandin analogues with the exception of a 1.6% risk of corneal endothelial mean cell loss through Month 12 after one implant, and a 6.5% corneal endothelial mean cell loss after removal and a second implant insertion. Due to the increased loss of endothelial cells with removal and reinsertion of the implant, single use only is recommended, and removal of the implant is not recommended. Based on currently available information, the benefit/risk of Travoprost intraocular implant for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension is favorable for single use only, administered in each eye.

Travoprost intraocular implant (iDose TR) should not be used in patients with corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy) given its increased risk of corneal endothelial cell loss and should be used with caution in patients with limited corneal endothelial cell reserve. Further investigations will be needed to identify circumstances in which a two or more implants can be administered to per eye.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated intraocular pressure (IOP).	Lowering intraocular pressure is currently the only modifiable factor for preserving visual function in patients with glaucoma and ocular hypertension.
Current Treatment Options	There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues.	Compliance with topical ophthalmic drop administration is a significant problem leading to inadequate treatment. A product which could be administered for a three month period may provide a significant advantage in the treatment of elevated intraocular pressure.
Benefit	Clinically significant reductions in IOP measured at multiple time points was demonstrated in studies GC-010 and GC-012 through Month 3.	Studies GC-010 and GC-012 demonstrated Travoprost intraocular implant, 75 µg, (iDose TR) was non-inferior to the active-control, timolol maleate ophthalmic solution 0.5% and lowered intraocular pressure by a clinically significant amount through Month 3.
Risk and Risk Management	The risk for using this drug is consistent with currently U.S. marketed prostaglandin analogues with the exception of increased loss of corneal endothelial cells. There is an increased risk of corneal endothelial cell loss with explantation of the implant and insertion of an additional implant.	The safety database contained in this application established the safety of Travoprost intraocular implant,75 µg, intracameral insertion administered once through Month 3. Routine monitoring and reporting of all adverse events are adequate.

4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed
	☒	Clinical outcome assessment (COA) data, such as		Section 6
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Section 6.1 Clinical Primary Endpoints
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
☐	Patient experience data was not submitted as part of this application.			

5. Product Quality

iDose TR (travoprost intraocular implant) is a sterile intraocular implant containing 75 µg of travoprost, a prostaglandin analog. The intraocular implant consists of a titanium implant reservoir with a membrane controlling the sustained release of travoprost. The sterile implant is preloaded in a sterile single-use inserter to facilitate insertion directly through the trabecular meshwork of the anterior chamber angle of the eye and implantation into the sclera.

Travoprost is a prostaglandin analog. Its chemical name is 5-heptenoic acid, 7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-buten-1-yl]cyclopentyl]-, 1-methylethyl ester, (5Z)-. Travoprost has a molecular formula of $C_{26}H_{35}F_3O_6$ and a molecular weight of 500.55 g/mol.

Travoprost Drug Substance Specifications

Test	Method	Acceptance Criteria
Physical Appearance[1]	Visual	Colorless to yellow oil
Identification by RT of HPLC[1]	USP Monograph for Travoprost	The retention time of the major peak of the Sample solution corresponds to that of the Standard solution
Identification by thin layer chromatography[1]	USP Monograph for Travoprost	The RF value of the principal spot obtained from the test solution corresponds to that of the obtained from the Standard solution
Assay (HPLC, % w/w on anhydrous, solvent free basis)[1]	USP Monograph for Travoprost	96.0% - 102.0%
Impurities (HPLC, % w/w)[1] Related Cpd A (b) (4) Epoxide Derivative 15-*epi* Diastereomer 5,6-*trans*-Isomer 15-Keto-Derivative Any other individual impurity Total Impurities	USP Monograph for Travoprost	 NMT 0.2 NMT 0.4 NMT 0.1 NMT 3.5 MNT 0.3 NMT 0.1 NMT 4.0
Optical Rotation[1]	USP Monograph for Travoprost	$[\alpha]^{25}$ (c = 20 mg/mL in Ethanol): 365 +52.0° to +58.0° at 365 nm
Water Determination (KF. %w/w)[1]	USP Monograph for Travoprost	NMT 1.0%
Limit of Ethyl Acetate (GC, ppm)[1]	USP Monograph for Travoprost	(b) (4)
Residual Solvents	Refer to Vendor's CoA	(b) (4)
Microbial Testing (CFU/g) Total aerobic microbial count Total yeasts and molds count	Refer to Vendor's CoA	(b) (4)

NMT = Not More Than

[1] Test performed by (b) (4)

Drug Product Specification of Travoprost Intraocular Implant

Test	Test Method	Acceptance Criteria
Physical Appearance	M16818 (Microscope 30X Magnification)	All components are present. Cap is secured to container. Cap, membrane, and container do not appear damaged. Packaging components do not appear damaged.
Identity (HPLC UV Retention Time)[a]	M16727 (HPLC/UV)	Positive for travoprost
Identity (HPLC UV Spectrum)[a]	M16727 (HPLC/UV)	Positive for travoprost
Assay (% of Label Claim)	M16727 (HPLC/UV)	(b) (4)
Specified Impurities (%) (b) (4)	M16727 (HPLC/UV)	(b) (4)
Individual Unspecified Impurities (%)	M16727 (HPLC/UV)	(b) (4)
Total Impurities (%)	M16727 (HPLC/UV)	
Uniformity of Dosage Unit (Content Uniformity)[a]	M16727 (HPLC/UV)	Conforms to test requirements per USP <905>
Accelerated Elution (% of Label Claim)	M19382 (HPLC/UV)	(b) (4) Conforms to L1, L2, or L3 Criteria[b]
Subvisible Particulate Matter[a] (particles/implant)	M20814[c] (Light Obscuration Particle Count Test)	(b) (4)
Bacterial Endotoxins Test (EU)[a]	USP <85> (LAL)	(b) (4) (tip with implant)[d] (b) (4) (inserter hand piece)[e]
Sterility	USP <71>	Conforms to test requirements[f]

HPLC: high-performance liquid chromatography UV: ultraviolet
NMT: not more than ; NLT: not less than EU: endotoxin units
Note: For clarity the components expected to be present are: titanium reservoir with titanium cap and EVA membrane; the EVA membrane and titanium cap are secured to the container.

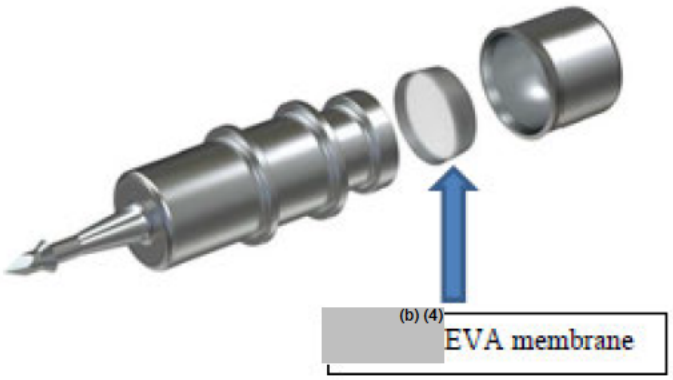
a: Test not performed on stability.
b: Criteria as shown in aligned with USP <724>
c: Test method based on modification of USP <788> Method 1 Light Obscuration Particle Count Test; interpretation of data per USP <789> with data reported as particles per implant.
d: Glaukos commits to perform this test for the implant with inserter tip using the sample preparations per both (b) (4) for the process validation batches; following the approval of the NDA, Glaukos commits to performing this test using the sample preparation per (b) (4) only for commercial batches.
e: Glaukos commits to perform this test for the inserter hand piece using the sample preparation per (b) (4) for the process validation batches and commercial batches.
f: Glaukos commits to perform this test for the implant with inserter tip using the sample preparation per (b) (4) and that for the inserter hand piece using the sample preparation per (b) (4) for the process validation batches and commercial batches.

Travoprost Intraocular Implant Drug Product Formulation

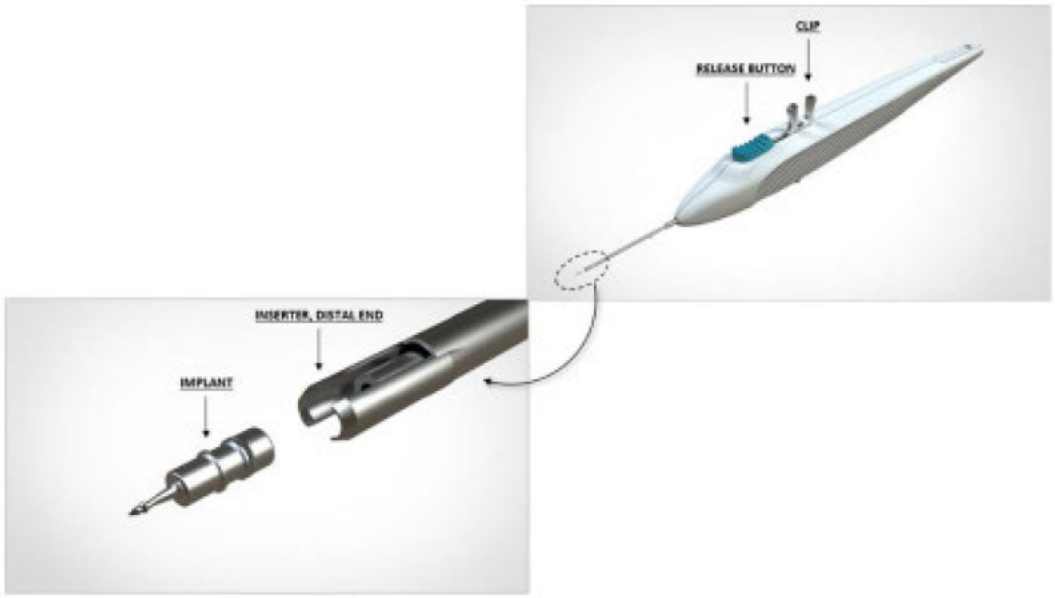
Component	Amount per Implant (µg)	Composition (%)	Function	Quality Standard
Travoprost	75	(b) (4)	Active Ingredient	USP
(b) (4)				USP/NF
Total	(b) (4)			

Assembled View of Travoprost Intraocular Implant

Exploded View of Travoprost Intraocular Implant



Travoprost Intraocular Implant Inserter



Facilities

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Glaukos Corporation 229 Avenida Fabricante, San Clemente, CA, 92672	3012341472	Drug substance release. Drug product manufacturing, packaging, labeling, and release. (b) (4)	Approve - Based on PAI
(b) (4)			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
			No evaluation Necessary
			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History

CMC Recommendations:
Satisfactory information and responses have been submitted to support the drug substance, drug product, manufacturing process, biopharmaceutics and quality microbiology aspects. The product is regulated as a drug and device combination product per the Genus decision. CDRH consults evaluated the device and found adequate on 10/3/2023.

The compliance status of the drug product manufacturing facility, Glaukos Corporation (FEI#3012341472) was determined acceptable based on the most recent pre-approval inspection. OPMA issued an overall recommendation of "approval" on Oct 5, 2023. Therefore, NDA 218010 is recommended Approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

6. Nonclinical Pharmacology/Toxicology

From the Nonclinical Pharmacology/ Toxicology review finalized on November 20, 2023:

The preclinical development of Travoprost Intraocular Implant included Sponsor's performed studies (i.e., a primary pharmacology and toxicity study in cynomolgus monkeys, and an ocular pharmacokinetics study in New Zealand White rabbits, and GLP studies (i.e., an ocular distribution and safety study in New Zealand White rabbits and a 6-month toxicity study in Yucatan Miniature Swine (minipigs))). All studies were performed with the implant administered by intracameral injection.

During development, the drug product label claim for the travoprost content of Travoprost Intraocular Implant Including Model G2-TR-125 was updated to 75 µg (from (b) (4)). A quality information amendment was submitted to the IND correcting the values (IND 120995, Sequence Number 0046). The original nonclinical reports reviewed by Dr. McDougal in DO, referred to Travoprost Intraocular Implant (b) (4), although the actual drug product value was about 75 µg.

[The nonclinical] reviewer's comment: For this NDA submission, the change in label claim from (b) (4) *to 75 µg content in the drug product in the device had no impact on the outcomes of the pharmacology and toxicology review.*

The application relies on the Agency's previous finding of nonclinical safety (genotoxicity, carcinogenicity and reproductive and developmental toxicity) from the reference listed drug (RLD) Travatan® (travoprost ophthalmic solution) 0.004%, approved under NDA 21-257.

PHARMACOLOGY
No new pharmacology studies were conducted by the Sponsor. Travoprost free acid, a prostaglandin analog, is a relatively selective false positive (FP) prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

PHARMACOKINETICS/TOXICOKINETICS

Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its 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-tetranor analogs, *via* oxidation of the 15-hydroxyl moiety, as well as *via* reduction of the 13,14 double bond. The elimination of travoprost free acid from the plasma is rapid and levels are generally below the limit of quantification within one hour after dosing. Less than 2% of the topical ocular dose of travoprost is excreted in the urine within 4 hours as the travoprost free acid.

CONCLUSION

Pharmacology/toxicology supports approval of iDose® TR (Travoprost Intraocular Implant, 75 µg) despite some limitations of the nonclinical program. Interpretation of the preclinical findings was limited by the suboptimal designs of the toxicity studies (i.e., not enough number of animals at each necropsy, lack of recovery periods in both studies, no tissues analyzed by histopathology for either ocular or systemic rabbit studies, lack of sensitivity of the method for measuring TFA levels in the animal studies). In addition, compared to the systemic NOAEL in the minipig, the clinical systemic safety margin was less than 10X. The safety margin could only be derived by dose comparison due to the lack of sensitivity of the analytical method used by the Sponsor in the pig study (Lower Level of Quantitation (LLOQ); 200 pg/mL nonclinical studies compared to 10 pg/mL clinical studies), which produced plasma levels below LLOQ and that could not be compared to clinical exposures. Safety margins based on dose were also low due to limitations of dose administration in the animal – more than 2 implants per eye in the minipig may have been infeasible in the study so only a maximal dose of 150 µg could be achieved. However, the ocular safety margins of 1X and 2X were found to be acceptable, since the ocular toxicity of travoprost is known from reference to Travatan, and the implants were left for 6 months without obvious toxicity findings.

To establish a systemic safety bridge with the LD, the Sponsor compared the clinical systemic exposure to TFA after the implant was placed in one eye of patients *vs* the LD applied to each eye and demonstrated that plasma exposure from the implant was lower than the LD. Also, the clinical pharmacology team determined by review that this scientific bridge to the LD Travatan was acceptable with 1 implant in one eye or, 1 implant in each eye (see Clinical Pharmacology review by Liping Pan).

Based on this clinical pharmacology bridge, the sponsor may rely on the LD Travatan and previous findings of nonclinical safety of the Travatan product as described in labeling.

7. Clinical Pharmacology

From the Clinical Pharmacology review finalized on October 19, 2023:

The Office of Clinical Pharmacology Division of Inflammation and Immune Pharmacology has
reviewed the clinical pharmacology data submitted under NDA 218010. 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 below.

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.
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.

8. Clinical Efficacy

Two trials (GC-010 and GC-012) were Phase 3 trials conducted in the U.S. and Philippines and in the U.S. and Armenia, respectively. These trials were multi-center, prospective, randomized, double-masked, parallel group, sham/timolol-controlled trials. Travoprost Intraocular Implant model G2-TR-063 was designed for (b) (4) elution and model G2-TR-125 was designed for a (b) (4) (b) (4) elution.

In addition, safety results are presented for the IDOS-106-EXCH trial, which was a prospective, multi-center, single arm 12-month trial designed to evaluate the safety of the surgical exchange procedure of Travoprost Intraocular Implant (model G2-TR-125) in subjects implanted previously with a Travoprost Intraocular Implant (either model G2-TR-063 or G2-TR-125) in the GC-009 trial.

Demographic Characteristics in Phase 3

Regarding GC-010: Baseline characteristics were well balanced among the treatment groups with regard to demographic data. All study eyes had either OAG (512 subjects, 86.8%) or OHT (78 subjects [13.2%]). Mean IOP was well balanced across the 3 treatment groups.

Regarding GC-012: Baseline characteristics were well balanced among the treatment groups with regard to demographic data. All study eyes had either OAG (443 subjects [79.1%]) or OHT (117 subjects [20.9%]. Mean IOP was well balanced across the 3 treatment groups in study eyes.

Demographics GC-010 (ITT Analysis Set) and Baseline Characteristics

	G2-TR-063 Implant (N=200)	**G2-TR-125 Implant (N=197)**	**Timolol (N=193)**
Age (years)			
Mean (SD)	63.8 (11.5)	63.2 (12.6)	63.8 (11.4)
Median	64.0	66.0	65.0
Min, Max	22, 86	24, 89	28, 94
Age Category, n (%)			
≥18 to < 65 years	102 (51.0)	91 (46.2)	93 (48.2)
≥ 65 years	98 (49.0)	106 (53.8)	100 (51.8)
Gender, n (%)			
Male	91 (45.5)	98 (49.7)	85 (44.0)
Female	109 (54.5)	99 (50.3)	108 (56.0)
Race, n (%)			
White	143 (71.5)	120 (60.9)	128 (66.3)
Black or African American	38 (19.0)	50 (25.4)	41 (21.2)
Asian	15 (7.5)	19 (9.6)	16 (8.3)
Native Hawaiian or Other Pacific Islander	1 (0.5)	0	0
American Indian or Alaska Native	0	0	2 (1.0)
Other	3 (1.5)	7 (3.6)	5 (2.6)
Unknown	0	1 (0.5)	1 (0.5)
Ethnicity, n (%)			
Hispanic or Latino	9 (4.5)	15 (7.6)	10 (5.2)
Not Hispanic or Latino	191 (95.5)	179 (90.9)	180 (93.3)
Unknown	0	3 (1.5)	3 (1.6)
Region, n (%)			
US	186 (93.0)	183 (92.9)	179 (92.7)
Philippines	14 (7.0)	14 (7.1)	14 (7.3)
Type of Disease, n (%)			
Open-Angle Glaucoma (OAG)	175 (87.5)	170 (86.3)	167 (86.5)
Ocular Hypertension (OHT)	25 (12.5)	27 (13.7)	26 (13.5)
Number of Ocular Hypotensive Medication Classes Used at Screening, n (%)			
0	43 (21.5)	54 (27.4)	46 (23.8)
1	116 (58.0)	99 (50.3)	100 (51.8)
2	37 (18.5)	38 (19.3)	41 (21.2)
3a	4 (2.0)	6 (3.0)	6 (3.1)
Screening IOP (mmHg)			
Mean (SD)	19.52 (4.50)	19.77 (4.46)	19.67 (4.35)
Min, Max	7.0, 32.0	8.0, 33.0	10.0, 34.0
Baseline IOP (mmHg) at 8AM			
Mean (SD)	24.72 (3.40)	24.37 (3.25)	24.72 (3.51)
Min, Max	17.0, 35.0	17.0, 36.0	17.0, 35.0
Baseline IOP (mmHg) at 10AM			
Mean (SD)	24.27 (3.27)	24.09 (3.32)	24.03 (3.10)
Min, Max	19.0, 34.0	19.0, 35.5	17.5, 34.0
Baseline IOP (mmHg) at 4PM			
Mean (SD)	23.57 (3.14)	23.59 (3.15)	23.61 (3.17)
Min, Max	15.0, 34.0	15.0, 35.0	17.0, 35.0
Baseline Mean Diurnal IOP			
Mean (SD)	24.18 (2.78)	24.02 (2.81)	24.12 (2.68)
Min, Max	21.0, 33.0	21.0, 33.7	21.0, 34.7
≤ 25 mmHg	141 (70.5)	141 (71.6)	138 (71.5)
> 25 mmHg	59 (29.5)	56 (28.4)	55 (28.5)
Best Spectacle Corrected Visual Acuity – log MAR			
Mean (SD)	0.036 (0.102)	0.027 (0.102)	0.052 (0.117)

	G2-TR-063 Implant (N=200)	G2-TR-125 Implant (N=197)	Timolol (N=193)
Min, Max	-0.18, 0.50	-0.30, 0.42	-0.20, 0.56
Iris Color, n (%)			
Blue	57 (28.5)	41 (20.8)	55 (28.5)
Brown	109 (54.5)	122 (61.9)	106 (54.9)
Green	7 (3.5)	7 (3.6)	7 (3.6)
Hazel	26 (13.0)	27 (13.7)	25 (13.0)
Other	1 (0.5)	0	0
Visual Field Mean Deviation (dB)			
Mean (SD)	-1.894 (2.919)	-1.732 (2.869)	-1.878 (3.034)
Min, Max	-11.84, 11.23	-11.48, 5.61	-11.50, 10.42
Vertical Cup-to-Disc Ratio			
Mean (SD)	0.54 (0.17)	0.56 (0.18)	0.57 (0.16)
Min, Max	0.1, 0.8	0.1, 0.8	0.2, 0.8
Corneal Thickness (µm)			
Mean (SD)	554.0 (36.3)	550.6 (35.6)	552.5 (36.5)
Min, Max	447, 620	440, 620	469, 620

Percentages were based on the number of subjects in each treatment group. Source: 14.1-3.2

Demographics GC-012 (ITT Analysis Set) and Baseline Characteristics

	G2-TR-063 Implant (N=185)	G2-TR-125 Implant (N=183)	Timolol (N=192)
Age (years)			
Mean (SD)	63.1 (11.8)	61.9 (12.8)	63.9 (12.1)
Median	65.0	63.0	65.0
Min, Max	29, 87	22, 88	21, 86
Age Category, n (%) ≥18 to < 65 years	92 (49.7)	100 (54.6)	93 (48.4)
≥ 65 years	93 (50.3)	83 (45.4)	99 (51.6)
Sex, n (%) Male	97 (52.4)	95 (51.9)	87 (45.3)
Female	88 (47.6)	88 (48.1)	105 (54.7)
Race, n (%) White	150 (81.1)	155 (84.7)	162 (84.4)
Black or African American	26 (14.1)	22 (12.0)	20 (10.4)
Asian	1 (0.5)	2 (1.1)	2 (1.0)
American Indian or Alaska Native	3 (1.6)	2 (1.1)	2 (1.0)
Multiple	1 (0.5)	0	1 (0.5)
Unknown	4 (2.2)	2 (1.1)	5 (2.6)
Ethnicity, n (%) Hispanic or Latino	30 (16.2)	25 (13.7)	39 (20.3)
Not Hispanic or Latino	153 (82.7)	157 (85.8)	153 (79.7)
Unknown	2 (1.1)	1 (0.5)	0
Region, n (%) US	168 (90.8)	167 (91.3)	175 (91.1)
Armenia	17 (9.2)	16 (8.7)	17 (8.9)
Type of Disease, n (%) Open-Angle Glaucoma (OAG)	149 (80.5)	139 (76.0)	155 (80.7)
Ocular Hypertension (OHT)	36 (19.5)	44 (24.0)	37 (19.3)
Number of Ocular Hypotensive Medication Classes Used at Screening, n (%)			
0	71 (38.4)	72 (39.3)	54 (28.1)
1	72 (38.9)	67 (36.6)	100 (52.1)
2	38 (20.5)	40 (21.9)	33 (17.2)
3a	4 (2.2)	4 (2.2)	5 (2.6)
Screening IOP (mmHg)			
Mean (SD)	21.01 (4.70)	20.93 (4.88)	20.45 (4.53)
Min, Max	8.0, 34.0	10.0, 35.5	10.5, 34.0

	G2-TR-063 Implant (N=185)	**G2-TR-125 Implant (N=183)**	**Timolol (N=192)**
Baseline IOP (mmHg) at 8AM			
Mean (SD)	24.73 (4.00)	24.57 (3.46)	24.75 (3.69)
Min, Max	17.5, 38.0	16.0, 36.0	16.5, 37.5
Baseline IOP (mmHg) at 10AM			
Mean (SD)	24.29 (3.61)	24.12 (3.16)	24.22 (3.29)
Min, Max	17.0, 38.5	18.5, 35.0	18.0, 35.5
Baseline IOP (mmHg) at 4PM			
Mean (SD)	24.10 (3.35)	23.60 (3.28)	24.00 (3.48)
Min, Max	18.0, 37.5	17.5, 36.0	15.0, 35.5
Baseline Mean Diurnal IOP			
Mean (SD)	24.38 (3.21)	24.09 (2.81)	24.32 (2.99)
Min, Max	21.0, 36.0	21.0, 34.7	21.0, 35.2
≤ 25 mmHg	129 (69.7)	135 (73.8)	133 (69.3)
> 25 mmHg	56 (30.3)	48 (26.2)	59 (30.7)
Best Spectacle Corrected Visual Acuity – log MAR			
Mean (SD)	0.046 (0.135)	0.037 (0.113)	0.052 (0.119)
Min, Max	-0.20, 0.60	-0.22, 0.60	-0.20, 0.44
Iris Color, n (%) Blue	40 (21.6)	48 (26.2)	51 (26.6)
Brown	102 (55.1)	100 (54.6)	110 (57.3)
Green	6 (3.2)	9 (4.9)	9 (4.7)
Hazel	35 (18.9)	25 (13.7)	21 (10.9)
Other	2 (1.1)	1 (0.5)	1 (0.5)
Visual Field Mean Deviation (dB)			
Mean (SD)	-2.397 (2.804)	-2.149 (2.853)	-2.665 (3.022)
Min, Max	-11.25, 5.78	-11.76, 2.17	-11.74, 2.83
Vertical Cup-to-Disc Ratio			
Mean (SD)	0.57 (0.17)	0.57 (0.17)	0.58 (0.17)
Min, Max	0.1, 0.8	0.1, 0.8	0.1, 0.8
Corneal Thickness (µm)			
Mean (SD)	556.0 (35.7)	559.0 (34.6)	556.5 (33.0)
Min, Max	443, 620	461, 618	445, 619

IOP = intraocular pressure, ITT = intent-to-treat, SD = standard deviation

[a] Subjects using 3 IOP-lowering medications at screening were consented prior to Protocol Revision 3, where subjects were allowed to use up to 3 IOP-lowering medications.

Percentages were based on the number of subjects in each treatment group. Source: 14.1-3.2

Proportion of Subjects Who Received Additional IOP-lowering Medications for the Study Eye by Visit Through Month 12 (Counting Subjects on Additional IOP-lowering Medication Separately at the Visit Level, ITT Analysis Set

	GC-010			GC-012		
	G2-TR-063	G2-TR-125	Sham/	G2-TR-063	G2-TR-125	Sham/
Visit,	Implant	Implant	Timolol	Implant	Implant	Timolol
n/N' (%)	(N=200)	(N=197)	(N=193)	(N=185)	(N=183)	(N=192)
Day 10	1/200 (0.5%)	1/197 (0.5%)	0	1/184 (0.5%)	2/182 (1%)	0
Week 4	4/197 (2%)	4/193 (2%)	4/190 (2%)	8/178 (4.5%)	1/180 (0.6%)	3/185 (2%)
Week 6	6/197 (3%)	3/192 (2%)	6/188 (3%)	9/180 (5%)	4/179 (2%)	7/188 (4%)
Month 3	10/197 (5%)	8/192 (4%)	13/187 (7%)	12/180 (7%)	8/180 (4%)	10/189 (5%)
Month 6	23/194 (12%)	12/192 (6%)	19/189 (10%)	18/180 (10%)	13/178 (7%)	12/182 (7%)
Month 9	37/193 (19%)	26/190 (14%)	25/186 (13%)	29/175 (17%)	21/179 (12%)	17/182 (9%)
Month 12	43/186 (23%)	36/190 (19%)	31/182 (17%)	38/175 (22%)	32/175 (18%)	23/177 (13%)

Source: Module 2.7.3 SCE Table 17; GC-009 Table 14.2-14.2; GC-010 Table 14.2-15.1; GC-012 Table 14.2-15.1
IOP = intraocular pressure; ITT = intent to treat
Note: Proportion (%) = 100 x n/N', where N' is the number of subjects at each visit.
If a subject is on additional IOP-lowering medication at a specific visit after Day 5 (or the washout window for the medication covers the day of the visit), then the subject is considered on additional IOP-lowering medication for that visit alone.

Study GC-010 Efficacy Results – Primary Endpoint

GC-010 Change from Baseline in IOP (mmHg) at 8AM and 10AM at Each Visit Through Month 3 (ANCOVA, Worse-Half Method for Multiple Imputation, Counting Subjects on Additional IOP-lowering Medication Separately at the Visit Level, ITT Analysis Set)

Visit	Hour	Statistic	G2-TR-063 Implant (N=200)	G2-TR-125 Implant (N=197)	Timolol (N=193)	G2-TR-063 vs. Timolol Difference (95% CI)[a]	G2-TR-125 vs. Timolol Difference (95% CI)[a]
Day 10	8AM	Mean (SD)	-8.47 (4.11)	-8.34 (3.90)	-7.76 (3.62)		
		LS Mean (SE)	-8.40 (0.24)	-8.48 (0.24)	-7.69 (0.24)	-0.72 (0.34)	-0.79 (0.34)
		95% CI	(-8.87, -7.94)	(-8.94, -8.01)	(-8.16, -7.21)	(-1.38, -0.06)	(-1.45, -0.13)
	10AM	Mean (SD)	-8.44 (4.02)	-8.42 (4.23)	-7.14 (3.55)		
		LS Mean (SE)	-8.35 (0.24)	-8.44 (0.24)	-7.20 (0.24)	-1.15 (0.34)	-1.24 (0.34)
		95% CI	(-8.83, -7.88)	(-8.92, -7.96)	(-7.68, -6.72)	(-1.83, -0.48)	(-1.92, -0.56)
Week 6	8AM	Mean (SD)	-7.41 (4.09)	-7.13 (3.90)	-7.16 (3.83)		
		LS Mean (SE)	-7.34 (0.24)	-7.26 (0.25)	-7.09 (0.25)	-0.25 (0.35)	-0.18 (0.35)
		95% CI	(-7.82, -6.86)	(-7.74, -6.78)	(-7.58, -6.60)	(-0.93, 0.43)	(-0.86, 0.51)
	10AM	Mean (SD)	-7.67 (4.03)	-7.60 (3.83)	-6.79 (3.65)		
		LS Mean (SE)	-7.59 (0.24)	-7.62 (0.24)	-6.85 (0.24)	-0.74 (0.34)	-0.77 (0.34)
		95% CI	(-8.06, -7.13)	(-8.09, -7.16)	(-7.32, -6.38)	(-1.40, -0.08)	(-1.43, -0.11)
Month 3	8AM	Mean (SD)	-6.64 (3.90)	-6.48 (4.12)	-6.75 (4.06)		
		LS Mean (SE)	-6.59 (0.26)	-6.59 (0.26)	-6.69 (0.27)	0.10 (0.37)	0.10 (0.37)
		95% CI	(-7.09, -6.08)	(-7.10, -6.09)	(-7.21, -6.17)	(-0.62, 0.83)	(-0.63, 0.82)
	10AM	Mean (SD)	-6.62 (3.95)	-6.66 (4.17)	-6.47 (3.93)		
		LS Mean (SE)	-6.56 (0.26)	-6.68 (0.26)	-6.52 (0.27)	-0.04 (0.37)	-0.16 (0.37)
		95% CI	(-7.07, -6.05)	(-7.19, -6.16)	(-7.04, -5.99)	(-0.77, 0.69)	(-0.89, 0.57)

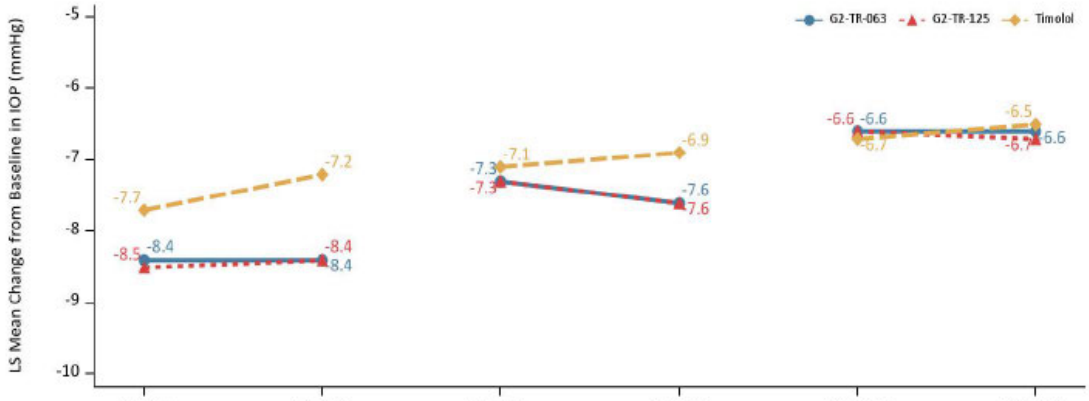
ANCOVA = analysis of covariance, CI = confidence interval, ICE = intercurrent event, IOP = intraocular pressure, ITT = intent-to-treat, LS = least squares, MCMC = Monte Carlo Markov Chain, SD = standard deviation, SE = standard error

a 95% CI for treatment comparison was based on an ANCOVA model with treatment group as factor and time-matched baseline IOP as covariate at each timepoint.

Note: If a subject was on additional IOP-lowering medication at a specific visit after Day 5 (or the washout window for the medication covered the day of the visit), then the subject was considered on additional IOP-lowering medication for that visit alone. For subjects without ICEs, multiple imputation technique (MCMC) was used to impute the missing data; for subjects with ICEs, worse-half MCMC was used for imputation.

Source: Module 5.3.5.1 Study GC-010 CSR Table 13 (Table 14.2-1.1.1)

GC-010 LS Mean Change from Baseline in IOP at 8AM and 10AM at Each Visit Through Month 3 (ANCOVA, Worse-Half Method for Multiple Imputation, Counting Subjects on Additional IOP-lowering Medication Separately at the Visit Level, (ITT Analysis Set)



ANCOVA = analysis of covariance, CI = confidence interval, ICE = intercurrent event, IOP = intraocular pressure, ITT = intent-to-treat, LS = least squares, Monte Carlo Markov Chain = MCMC
Note: 95% CI for treatment comparison was based on an ANCOVA model with treatment group as factor and time-matched baseline IOP as covariate at each timepoint. If a subject was on additional IOP-lowering medication at a specific visit after Day 5 (or the washout window for the medication covered the day of the visit), then the subject was considered on additional IOP-lowering medication for that visit alone. For subjects without ICEs, multiple imputation technique (MCMC) was used to impute the missing data; for subjects with ICEs, worse-half MCMC was used for imputation.
Source: Figure 1.1.1

Reviewer's Comments: *Across the 6 timepoints, the LS mean IOP changes from baseline ranged from −6.6 to −8.5 mmHg in the G2-TR-125 implant group, −6.6 to −8.4 mmHg in the G2-TR-063 implant group, and −6.5 to −7.7 mmHg in the Timolol group.*

The criteria for statistical and clinical non-inferiority to timolol was met for both G2-TR implant groups as the upper limit of the 95% CI of the difference between the G2-TR implant groups and the Timolol group was < 1 mmHg for all 6 timepoints.

GC-010 Key Secondary Efficacy Endpoint

Change from Baseline in IOP (mmHg) at 8AM and 10AM at Month 12 (ANCOVA, Worse-Half Method for Multiple Imputation, Counting Subjects on Additional IOP-lowering Medication Separately at the Visit Level, ITT Analysis Set)

Visit	Hour	Statistic	G2-TR-063 Implant (N=200)	G2-TR-125 Implant (N=197)	Timolol (N=193)	G2-TR-063 vs. Timolol Difference (95% CI)[a]	G2-TR-125 vs. Timolol Difference (95% CI)[a]
Month 6		Mean (SD)	-5.5 (4.4)	-5.7 (4.2)	-6.1 (4.1)		
		LS Mean (SE)	-5.4 (0.3)	-5.7 (0.3)	-6.1 (0.3)	0.7 (0.4)	0.4 (0.4)
		95% CI	(-6.0, 4.9)	(-6.3, 5.2)	(-6.7, -5.5)	(-0.1, 1.4)	(-0.4, 1.1)
Month 9		Mean (SD)	-5.5 (4.1)	-5.7 (4.5)	-5.9 (4.3)		
		LS Mean (SE)	-5.6 (0.3)	-5.7 (0.3)	(-5.9 (0.3)	0.4 (0.4)	0.3 (0.4)
		95% CI	(-6.1, -5.0)	(-6.2, -5.1)	-6.5, -5.3)	(-0.4, 1.1)	(-0.5, 1.0)
Month 12	8AM	Mean (SD)	-5.40 (4.39)	-5.42 (4.06)	-6.19 (3.93)		
		LS Mean (SE)	-5.36 (0.29)	-5.50 (0.28)	-6.15 (0.28)	0.8 (0.4)	0.6 (0.4)
		95% CI	(-5.93, -4.80)	(-6.05, -4.96)	(-6.69, -5.60)	(0.0, 1.6)	(-0.1, 1.4)
	10AM	Mean (SD)	-5.86 (3.93)	-5.50 (4.12)	-5.95 (3.58)		
		LS Mean (SE)	-5.81 (0.27)	-5.52 (0.26)	-5.99 (0.26)	0.2 (0.4)	0.5 (0.4)
		95% CI	(-6.33, -5.28)	(-6.02, -5.01)	(-6.50, -5.49)	(-0.5, 0.9)	(-0.2, 1.2)

ANCOVA = analysis of covariance, CI = confidence interval, ICE = intercurrent event, IOP = intraocular pressure, ITT = intent-to-treat, LS = least squares, MCMC = Monte Carlo Markov Chain, SD = standard deviation, SE = standard error
a 95% CI for treatment comparison was based on an ANCOVA model with treatment group as factor and time-matched baseline IOP as covariate at each timepoint.
Note: If a subject was on additional IOP-lowering medication at a specific visit after Day 5 (or the washout window for the medication covered the day of the visit), then the subject was considered on additional IOP-lowering medication for that visit alone. For subjects without ICEs, multiple imputation technique (MCMC) was used to impute the missing data; for subjects with ICEs, worse-half MCMC was used for imputation.
Source: Table 14.2-2.1.1

Reviewer's Comments:

In clinical trial GC-010 the non-inferiority to timolol was not met at Month 6, 9 or 12 for the G2-TR-063, or G2-TR-125 implants.

Study GC-012 Efficacy Results – Primary Endpoint

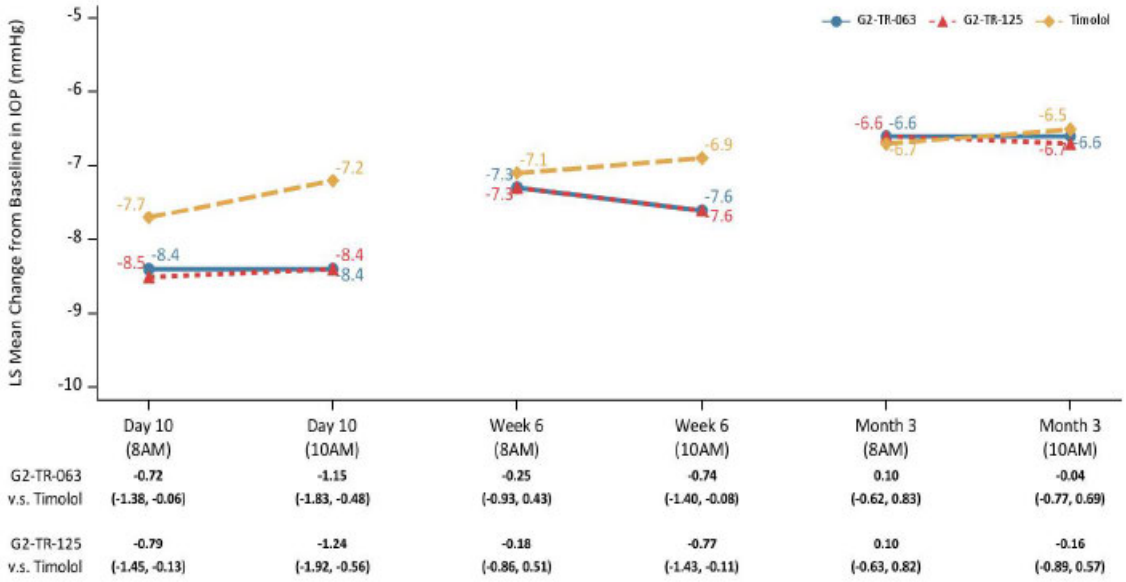
Change from Baseline in IOP (mmHg) at 8AM and 10AM at Each Visit Through Month 3 (ANCOVA, Worse-Half Method for Multiple Imputation, Counting Subjects on Additional IOP-lowering Medication Separately at the Visit Level, ITT Analysis Set)

			G2-TR-063 Implant	G2-TR-125 Implant	Timolol	G2-TR-063 vs. Timolol	G2-TR-125 vs. Timolol
Visit	**Hour**	**Statistic**	**(N=185)**	**(N=183)**	**(N=192)**	**Difference (95% CI)[a]**	**Difference (95% CI)[a]**
Day 10	8AM	Mean (SD)	-8.29 (4.69)	-8.33 (4.23)	-7.19 (3.97)		
		LS Mean (SE)	-8.26 (0.27)	-8.40 (0.27)	-7.16 (0.26)	-1.10 (0.38)	-1.25 (0.38)
		95% CI	(-8.79, -7.72)	(-8.94, -7.87)	(-7.68, -6.64)	(-1.84, -0.36)	(-1.99, -0.50)
	10AM	Mean (SD)	-8.25 (3.89)	-8.23 (4.00)	-7.08 (3.80)		
		LS Mean (SE)	-8.20 (0.25)	-8.28 (0.25)	-7.08 (0.24)	-1.13 (0.35)	-1.20 (0.35)
		95% CI	(-8.69, -7.72)	(-8.77, -7.79)	(-7.55, -6.60)	(-1.81, -0.45)	(-1.88, -0.52)
Week 6	8AM	Mean (SD)	-6.86 (4.58)	-7.12 (4.35)	-7.21 (4.05)		
		LS Mean (SE)	-6.83 (0.26)	-7.20 (0.26)	-7.17 (0.26)	0.33 (0.37)	-0.03 (0.37)
		95% CI	(-7.35, -6.31)	(-7.72, -6.68)	(-7.67, -6.66)	(-0.39, 1.06)	(-0.76, 0.69)
	10AM	Mean (SD)	-6.97 (4.04)	-6.78 (4.23)	-7.16 (3.71)		
		LS Mean (SE)	-6.92 (0.25)	-6.83 (0.25)	-7.15 (0.25)	0.23 (0.35)	0.32 (0.35)
		95% CI	(-7.42, -6.43)	(-7.33, -6.34)	(-7.64, -6.67)	(-0.46, 0.93)	(-0.37, 1.01)
Month 3	8AM	Mean (SD)	-6.32 (4.44)	-6.59 (4.33)	-6.86 (4.16)		
		LS Mean (SE)	-6.29 (0.28)	-6.66 (0.27)	-6.82 (0.27)	0.53 (0.38)	0.16 (0.38)
		95% CI	(-6.83, -5.75)	(-7.20, -6.12)	(-7.35, -6.29)	(-0.23, 1.28)	(-0.59, 0.91)
	10AM	Mean (SD)	-6.26 (4.16)	-6.74 (4.13)	-6.77 (4.12)		
		LS Mean (SE)	-6.21 (0.27)	-6.79 (0.27)	-6.76 (0.26)	0.55 (0.38)	-0.03 (0.38)
		95% CI	(-6.74, -5.68)	(-7.32, -6.26)	(-7.28, -6.24)	(-0.19, 1.29)	(-0.77, 0.71)

ANCOVA = analysis of covariance, CI = confidence interval, ICE = intercurrent event, IOP = intraocular pressure, ITT = intent-to-treat, LS = least squares, MCMC = Monte Carlo Markov Chain, SD = standard deviation, SE = standard error

a 95% CI for treatment comparison was based on an ANCOVA model with treatment group as factor and time-matched baseline IOP as covariate at each time point. Note: If a subject was on additional IOP-lowering medication at a specific visit after Day 5 (or the washout window for the medication covered the day of the visit), then the subject was considered on additional IOP-lowering medication for that visit alone. For subjects without ICEs, multiple imputation technique (MCMC) was used to impute the missing data; for subjects with ICEs, worse-half MCMC was used for imputation. Source: Table 14.2-1.1.1

GC-012 LS Mean Change from Baseline in IOP at 8AM and 10AM at Each Visit Through Month 3 (ANCOVA, Worse-Half Method for Multiple Imputation, Counting Subjects on Additional IOP-lowering Medication Separately at the Visit Level, ITT Analysis Set)



ANCOVA = analysis of covariance, CI = confidence interval, ICE = intercurrent event, IOP = intraocular pressure, ITT = intent-to-treat, LS = least squares, Monte Carlo Markov Chain = MCMC
Note: 95% CI for treatment comparison was based on an ANCOVA model with treatment group as factor and time-matched baseline IOP as covariate at each timepoint. If a subject was on additional IOP-lowering medication at a specific visit after Day 5 (or the washout window for the medication covered the day of the visit), then the subject was considered on additional IOP-lowering medication for that visit alone. For subjects without ICEs, multiple imputation technique (MCMC) was used to impute the missing data; for subjects with ICEs, worse-half MCMC was used for imputation.
Source: Figure 1.1.1

Reviewer's Comments:

Across the 6 timepoints, the LS mean IOP changes from baseline ranged from −6.6 to −8.5 mmHg in the G2-TR-125 implant group, −6.6 to −8.4 mmHg in the G2-TR-063 implant group, and −6.5 to −7.7 mmHg in the Timolol group.

The criteria for statistical and clinical non-inferiority to timolol was met for both G2-TR implant groups as the upper limit of the 95% CI of the difference between the G2-TR implant groups and the Timolol group was < 1 mmHg for all 6 timepoints .

GC-012 Key Secondary Efficacy Endpoint:

GC-012 Change from Baseline in IOP (mmHg) at 8AM and 10AM at Month 12 (ANCOVA, Worse-Half Method for Multiple Imputation, Counting Subjects on Additional IOP-lowering Medication Separately at the Visit Level, ITT Analysis Set)

			G2-TR-063 Implant	G2-TR-125 Implant	Timolol	G2-TR-063 vs. Timolol	G2-TR-125 vs. Timolol
Visit	**Hour**	**Statistic**	**(N=185)**	**(N=183)**	**(N=192)**	**Difference (95% CI)[a]**	**Difference (95% CI)[a]**
Month 6		Mean (SD)	-5.2 (4.7)	-5.4 (4.3)	-6.4 (4.1)		
		LS Mean (SE)	-5.1 (0.3)	-5.5 (0.3)	-6.4 (0.3)	1.2 (0.4)	0.9 (0.4)
		95% CI	(-5.7, 4.6)	(-6.0, -4.9)	(-6.9, -5.8)	(0.4, 2.0)	(0.1, 1.7)
Month 9		Mean (SD)	-5.0 (4.4)	-5.2 (4.1)	-6.3 (4.4)		
		LS Mean (SE)	-5.0 (0.3)	-5.2 (0.3)	-6.3 (0.3)	1.3 (0.4)	1.1 (0.4)
		95% CI	(-5.6, -4.4)	(-5.8, -4.6)	(-6.8, -5.7)	(0.5, 2.1)	(0.3, 1.9)
Month 12	8AM	Mean (SD)	-5.0 (4.3)	-4.9 (4.2)	-6.3 (4.0)	1.3 (0.4)	1.4 (0.4)
		LS Mean (SE)	-5.0 (0.3)	-4.9 (0.3)	-6.3 (0.3)	(0.5, 2.1)	(0.6, 2.1)
		95% CI	(-5.5, -4.4)	(-5.5, -4.3)	(-6.8, -5.7)		
	10AM	Mean (SD)	-5.2 (4.3)	-5.4 (4.3)	-6.5 (4.2)	1.3 (0.4)	1.0 (0.4)
		LS Mean (SE)	-5.1 (0.3)	-5.4 (0.3)	-6.5 (0.3)	(0.5, 2.1)	(0.3, 1.8)
		95% CI	(-5.7, -4.6)	(-6.0, -4.9)	(-7.0, -5.9)		

ANCOVA = analysis of covariance, CI = confidence interval, ICE = intercurrent event, IOP = intraocular pressure, ITT = intent-to-treat, LS = least squares, MCMC = Monte Carlo Markov Chain, SD = standard deviation, SE = standard error

a 95% CI for treatment comparison was based on an ANCOVA model with treatment group as factor and time-matched baseline IOP as covariate at each timepoint.

Note: If a subject was on additional IOP-lowering medication at a specific visit after Day 5 (or the washout window for the medication covered the day of the visit), then the subject was considered on additional IOP-lowering medication for that visit alone. For subjects without ICEs, multiple imputation technique (MCMC) was used to impute the missing data; for subjects with ICEs, worse-half MCMC was used for imputation.

Source: Table 14.2-2.1.1

Reviewer's comments:

In clinical trial GC-012, non-inferiority to timolol was not met at Month 6, 9, or 12 for either G2-TR implant.

Dose/Dose Response, Durability of Response, Persistence of Effect

Phase 3 Trials, GC-010 and GC-012, were successful for both G2-TR implants (b) (4) at Month 3 based on the primary efficacy endpoint. After Month 3, they were not equivalent to topical timolol.

Assessment of Efficacy Across Trials

Endpoint	Phase 3 Trials				Phase 2 Trial	
	GC-010		GC-012		GC-009*	
	G2-TR-63	G2-TR-125	G2-TR-63	G2-TR-125	G2-TR-63	G2-TR-125
	(b) (4)					
Primary Month 3	Successful	Successful	Successful	Successful	**Fail**	**Fail**
Secondary Month 12	**Fail**	**Fail**	**Fail**	**Fail**	N/A	N/A

Success / Fail based on non-inferiority
* Study not powered to detect non-inferiority, had three year follow up with 33 subjects subsequently enrolled in "exchange" trial and followed an additional 12 Months for safety data

9. Safety

Across studies GC-009, GC-010, and GC-012, a total of 868 subjects were exposed to the Travoprost Intraocular Implant of which 432 were exposed to the Model G2-TR-125, and 436 to the Model G2-TR-063. A total of 435 subjects were exposed to the comparator, sham surgery and timolol maleate ophthalmic solution, 0.5%. The mean (SD) duration of exposure was 359.8 (33.2), 354.2 (43.4), and 355.0 (44.4) days for the G2-TR-125 implant group, G2-TR-063 implant group, and Sham/Timolol group, respectively.

Extent of Exposure to Study Treatment (Safety Analysis Set GC-009, GC-010, and GC-012)

Extent of Exposure to Study Treatment (day)	G2-TR-063 Implant (N=436)	G2-TR-125 Implant (N=432)	Sham/ Timolol (N=435)
Mean (SD)	354.2 (43.4)	359.8 (33.2)	355.0 (44.4)
Min, Max	17, 441	43, 448	9, 429

Source: ISS Table 14.3-1
Note: Extent of Exposure to Study Treatment (day) = subject cut-off date – surgery date + 1; for subjects with explant of investigational product, Extent of Exposure to Study Treatment (day) = Date of explant – surgery date +1.

Reviewer's Comments:

Because the Travoprost Intraocular Implant is surgically anchored in the anterior chamber angle of the eye and releases travoprost slowly as a treatment for elevated IOP in patients with OAG or OHT, the duration of exposure to the implant was continuous throughout the trials, unless the implant was explanted.

Extent of Exposure for Study IDOS-106-EXCH

A total of 33 subjects were exposed to the Travoprost Intraocular Implant model G2-TR-125 in the IDOS-106-EXCH trial for a mean (SD) duration of 349 days. These subjects had previously received a Travoprost Intraocular Implant model G2-TR-063 or G2-TR-125 during their 3-year participation in the Phase 2 trial GC-009 (first implantation cycle). The exchange procedure was performed 3.8 to 4.9 years after the subject had received their initial implant, resulting in a total duration of exposure ranging from 4.5 to 5.8 years. A total of 32 of the 33 subjects (97.0%) completed Month 12.

Overall Extent of Exposure to Treatment for Subjects Who Underwent an Exchange Procedure (Safety Analysis Set)

	Ist Implant	2nd Implant	Overall
Extent of Exposure to Study Treatment (days)	**(N=33)**	**(N=33)**	**(N=33)**
Mean (SD)	1540.8 (123.7)	349.0 (21.1)	1888.8 (123.8)
Min, Max	1373, 1792	265, 390	1651, 2128

Source: IDOS-106-EXCH Ad hoc Table 14.3-1.2

Deaths

Of the 33 subjects who subsequently entered the IDOS-106-EXCH trial, mean (SD) age was 65.2 (11.3) years, with 45.5% (15/33) subjects < 65 years and 54.5% (18/33) ≥ 65 years. Female subjects comprised 51.5% (17/33) of the population. The IDOS-106-EXCH trial subject population was predominately White (84.8%, 28/33), and not of Hispanic or Latino ethnicity (93.9%, 31/33).

Across GC-009, GC-010, and GC-012, there were a total of 10 deaths, the most common cause of death was corona virus infection, reported in 3 of the 10 subjects with fatal serious adverse events.

Subject Listing for Deaths in Controlled Clinical Trials GC-009, GC-010, and GC-012

Study No.	Subject ID	Time to Death (study day)	Cause of Death (System Organ Class/Preferred Term)[1]	Treatment
GC-010	(b) (6)	325	Vascular disorders/Aortic aneurysm	G2-TR-063
GC-010		892	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Metastatic lung cancer	G2-TR-063
GC-010		316	Infections and infestations/ Corona virus infection	Timolol
GC-010		10	Cardiac disorders/Cardio-respiratory arrest	Timolol
GC-010		22	Infections and infestations/ Corona virus infection	Timolol
GC-010		303	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Breast cancer	Timolol
GC-012		166	Cardiac disorders/ Cardiac disorder	G2-TR-063
GC-012		277	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Hepatic cancer	G2-TR-125
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)/Oesophageal cancer	
GC-012		278	Injury, poisoning and procedural complications/ Road traffic accident	Timolol
GC-012		210	Infections and infestations/ Corona virus infection	Timolol

Source: ISS Listing 2

AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. Note: Hyperlinks are provided to Section 11.3 of the CSRs for brief narratives of the deaths

Reviewer's comments:

The reported deaths are unlikely to be related to the treatment and more likely related to the treated older patient population.

Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set GC-009, GC-010, and GC-012)

System Organ Class Preferred Term	G2-TR-063 Implant(N=436)	G2-TR-125 Implant (N=432)	Sham/ Timolol (N=435)
Subjects with Any Serious Adverse Event	23 (5.3)	26 (6.0)	21 (0.8)
Cardiac disorders	6 (1.4)	4 (0.9)	3 (0.7)
Myocardial infarction	1 (0.2)	2 (0.5)	0
Infections and infestations	2 (0.5)	3 (0.7)	6 (1.4)
Corona virus infection	0	0	3 (0.7)
Endophthalmitis	0	1 (0.2)	0
Musculoskeletal and connective tissue disorders	5 (1.1)	4 (0.9)	2 (0.5)
Arthritis	2 (0.5)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.5)	3 (0.7)	4 (0.9)
Colon cancer	0	0	2 (0.5)
Metabolism and nutrition disorders	0	4 (0.9)	1 (0.2)
Diabetes mellitus	0	2 (0.5)	0
Investigations	1 (0.2)	1 (0.2)	0
Intraocular pressure increased	1 (0.2)	1 (0.2)	0
Eye disorders	0	1 (0.2)	0
Retinal detachment	0	1 (0.2)	0

Source: ISS Table 14.3-2.5.1
AE = adverse event; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event
Note: If a subject experienced more than 1 adverse events within a SOC (or PT), the subject is counted once under that SOC (or PT). MedDRA dictionary Version 21.0 English is used for coding.
Percentages are based on the number of subjects in each treatment group.

Reviewer's Comments:

Systemic serious adverse events were reported in arthritis, colon cancer, coronavirus infection, diabetes mellitus and myocardial infection were each reported more than one subject (each less than 1%). Ocular serious adverse events included endophthalmitis (1 case in the G2-TR-125 implant group), intraocular pressure increased (1 in each of the G2-TR-063 and G2-TR-125 implant groups), and retinal detachment (1 case in the G2-TR-125 implant group).

In all 3 trials, the vast majority of subjects (ranging from 98.3% [580/590] in GC-010 to 100% [154/154] in GC-009) completed Month 3. Moreover, most subjects (ranging from 95.8% [565/590] to 97.4% [150/154]) completed Month 12. Of subjects who received an implant, 3 in each of the GC-010 (3/397 [0.8%]) and GC-012 (3/368 [0.8%]) trials were explanted prior to Month 3 but continued participation in the trials. No subjects in GC-009 were explanted.

Most Common Study Eye Adverse Events (Occurring in ≥ 1.0% of Subjects in Any Treatment Group) in the Pooled Population (Safety Analysis Set GC-009, GC-010, and GC-012)

System Organ Class Preferred Term	G2-TR-063 Implant (N=436)	G2-TR-125 Implant (N=432)	Sham/ Timolol (N=435)
Subjects with Any TEAEs	158 (36.2)	148 (34.3)	80 (18.4)
Eye disorders	127 (29.1)	124 (28.7)	56 (12.9)
Dry eye	15 (3.4)	12 (2.8)	10 (2.3)
Iritis	11 (2.5)	22 (5.1)	0
Conjunctival hyperaemia	11 (2.5)	8 (1.9)	2 (0.5)
Eye pain	9 (2.1)	11 (2.5)	1 (0.2)
Punctate keratitis	9 (2.1)	4 (0.9)	8 (1.8)
Ocular hyperaemia	12 (2.8)	7 (1.6)	1 (0.2)
Visual acuity reduced	5 (1.1)	12 (2.8)	3 (0.7)
Cataract	6 (1.4)	8 (1.9)	3 (0.7)
Conjunctival haemorrhage	6 (1.4)	10 (2.3)	0
Blepharitis	6 (1.4)	5 (1.2)	3 (0.7)
Photophobia	7 (1.6)	6 (1.4)	0
Eye irritation	7 (1.6)	3 (0.7)	2 (0.5)
Vitreous detachment	4 (0.9)	5 (1.2)	2 (0.5)
Conjunctivitis allergic	3 (0.7)	4 (0.9)	3 (0.7)
Eye inflammation	6 (1.4)	3 (0.7)	0
Foreign body sensation in eyes	3 (0.7)	6 (1.4)	0
Anterior chamber cell	2 (0.5)	6 (1.4)	0
Meibomian gland dysfunction	5 (1.1)	3 (0.7)	0
Vision blurred	6 (1.4)	1 (0.2)	0
Investigations	30 (6.9)	19 (4.4)	11 (2.5)
Intraocular pressure increased	29 (6.7)	19 (4.4)	10 (2.3)
Nervous system disorders	10 (2.3)	13 (3.0)	6 (1.4)
Visual field defect	10 (2.3)	13 (3.0)	5 (1.1)
Injury, poisoning and procedural complications	11 (2.5)	9 (2.1)	4 (0.9)
Corneal abrasion	7 (1.6)	3 (0.7)	1 (0.2)
Product issues	6 (1.4)	4 (0.9)	0
Device dislocation	6 (1.4)	4 (0.9)	0

Source: ISS Table 14.3-2.2.2
PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event
Note: If a subject experienced more than 1 TEAE within a SOC (or PT), the subject is counted once under that SOC (or PT). MedDRA dictionary Version 21.0 English is used for coding.

Reviewer's comments:

The most common adverse events occurring in ≥ 3% of subjects in any treatment group were increased intraocular pressure, iritis, dry eye, and visual field defect.

Central Corneal Endothelial Cell Density (cells/mm^2) -- Actual and Change from Baseline by Visit for Study Eye in the Pooled Population (Endothelial Cell Subset of the Safety Analysis Set (GC-009, GC-010, GC–012)

Visit		G2-TR-063 Implant (N=106)	G2-TR-125 Implant (N=99)	Sham/ Timolol (N=102)
Baseline (Actual)	n	106	99	102
	Mean (SD)	2360.63 (406.79)	2441.85 (408.73)	2432.79 (412.96)
	Min, Max	1207.3, 3199.5	1277.7, 3201.0	1199.3, 3536.8
Month 3	n	102	95	98
Change from Baseline	Mean (SD)	-25.04 (92.36)	-30.72 (81.57)	-4.16 (81.25)
	Min, Max	-531.5, 188.3	-339.6, 126.0	-428.5, 172.8
Percent Change from Baseline	Mean (SD)	-1.20 (4.45)	-1.20 (3.49)	-0.15 (3.36)
	Min, Max	-22.4, 7.8	-17.0, 7.7	-16.5, 7.9
Month 12	n	97	93	93
Change from Baseline	Mean (SD)	-37.16 (116.88)	-40.20 (103.05)	1.46 (90.68)
	Min, Max	-564.4, 260.8	-358.9, 253.5	-216.5, 517.2
Percent Change from Baseline	Mean (SD)	-1.92 (5.89)	-1.60 (4.80)	-0.05 (4.18)
	Min, Max	-34.5, 11.4	-18.8, 19.8	-11.4, 22.0

Source: ISS Table 75; Table 14.3-10.1, Table 14.3-10.2, SD = standard deviation
Note: For GC-010 and GC-012, specular microscopy is only captured at selected sites.

At baseline, mean (SD) central endothelial cell density was well balanced across the treatment groups. At Month 12, the mean (SD) percentage change from Baseline was similar in the G2-TR treatment groups (-1.60 [4.8] cells/mm^2 and -1.92 [5.9] cells/mm^2 in the G2-TR-125 and G2-TR-063 implant groups, respectively). These changes from baseline were negligible for both implant groups, as well as for the Sham/Timolol group (-0.05 [4.18] cells/mm2), and considered clinically not meaningful or significant.

Categorical Changes from Baseline in Central Endothelial Cell Density by Visit in the Pooled Population (Endothelial Cell Subset of the Safety Analysis Set GC-009, GC-010, GC–012)

Visit/ Change Categories, n (%)	G2-TR-063 Implant (N=106) n (%)	G2-TR-125 Implant (N=99) n (%)	Sham/ Timolol (N=102) n (%)
Month 3			
N	102	95	98
≥ 30% Loss	0	0	0
Month 12			
n	97	93	93
≥ 30% Loss	1 (1.0)	0	0

Source: ISS Table 14.3-10.3 Note: For GC-010 and GC-012, specular microscopy is only captured at selected sites. Percentage is based on the number of available subjects at each visit.

A single G2-TR implant subject (in the G2-TR-063 implant group) had a ≥ 30% loss in central endothelial cell density during the 12-month analysis period, representing 0.5% (1/205) of subjects with a G2-TR implant in whom endothelial cell density was evaluated prospectively in the Phase 2 and 3 trials. An adverse event of endothelial cell loss was reported for this G2-TR-063 implant subject after confirmation of sustained endothelial cell loss at Month 15. The subject had a number of confounding factors included advanced age, low baseline endothelial cell count, pre-existing compromised cornea,

endothelial damage from multiple past SLT procedures, early Fuch's dystrophy, polymegathism, and concurrent use of carbonic anhydrase inhibitors in the study eye.

Reviewer's Comment:

Over the 12 Month period, central corneal endothelial cell density decreased by a greater percentage in the Travoprost Intraocular Implant group compared with the Sham/Timolol group. Although this < 2% mean change in the Travoprost Intraocular Implant percentage is small, it was much greater than the 0.05% or less observed in the Sham/Timolol group.

Over the 12-month analysis period one subject (0.5%) had a ≥ 30% reduction in endothelial cell density Travoprost Intraocular Implant groups. At a Type C Pre-NDA meeting (November 2022), the Agency indicated a corneal endothelial cell loss of ≥ 30% from baseline would be considered a significant loss.

Corneal Endothelial Cell Loss Data for Study IDOS-106-EXCH

Eligible subjects were required to have been implanted previously in the 36-month Study GC-009 with either the G2-TR-063 or G2-TR-125 model of the Travoprost Intraocular Implant (first cycle). The subject's study eye underwent surgical exchange of the Travoprost Intraocular Implant which consisted of implantation of a Model G2-TR-125 (second cycle) and removal of the prior implant and followed for an additional 12 months.

Of the 33 enrolled subjects who underwent the exchange procedure and received the G2-TR-125 implant, 32 subjects (97.0%) completed the 12-month study. One subject discontinued the study due to death (from an unknown cause deemed not related to the study).

Central Endothelial Cell Density (cells/mm2) – Actual and Change from GC-009 Baseline Value by Visit (Safety Analysis Set GC-009, GC-010, GC–012)

Visit		G2-TR-125 Implant (N=33)
GC-009 Baseline (Actual)	n	33
	Mean (SD)	2333 (348)
	Min, Max	1278, 2906
Month 36 (Change from GC-009 Baseline)	n	30
	Mean (SD)	-70 (103)
	Min, Max	-342, 151
Baseline Pre-Exchange (Change from GC-009 Baseline)	n	33
	Mean (SD)	-105 (120)
	Min, Max	-350, 287
Month 3 Post-Exchange (Change from GC-009 Baseline)	n	33
	Mean (SD)	-146 (101)
	Min, Max	-406, 46
Month 12 Post-Exchange (Change from GC-009 Baseline)	n	32
	Mean (SD)	-154 (136)
	Min, Max	-549, 185

Source: ISS Table 80. IDOS-106-EXCH Ad hoc Table 14.3-11.6, SD = standard deviation

Note: Baseline is defined as the last non-missing measure prior to the initiation of the investigational product within Study GC-009. For the Baseline and Month 36 Visits which were in Study GC-009, subjects were implanted with either the G2-TR-063 or G2-TR-125 Implant. For the remaining Visits which were in Study IDOS-106-EXCH, subjects were implanted with the G2-TR-125 Implant.

Reviewer's comment:
No subject who participated in the IDOS-106-EXCH trial exhibited a ≥ 30% loss in endothelial cell density from their pre-GC-009 baseline, over a total implant duration ranging from 4.5 to 5.8 years.

Central ECD in the study eye demonstrated a 6.5% mean decrease in cell density over the total duration of exposure to the G2-TR implant (which ranged from 4.5 to 5.8 years) across the GC-009 and IDOS-106-EXCH studies). This was an uncontrolled study, but at month 36 prior to the exchange procedure, this group had a 2.7 % mean decrease in endothelial cell density, a much lower incidence of endothelial cell loss prior to the exchange procedure.

Based on the potential increased risk of endothelial cell loss after one exchange, and not having results of the risk of endothelia cell loss after more than one exchange (explant implant with reinsertion of a new implant), it is recommended that the implant for be single use only.

Device Dislocation and Explantation

Of the 13 subjects with a device dislocation, none was part of the cohort in which endothelial cell density data were collected prospectively. Therefore, endothelial cell density (ECD) data in the study and non-study eye were not collected at baseline. Rather, upon identification of a device dislocation, endothelial cell data were collected on the study eye and non-study eye prior to explantation and for up to 1-year post-explantation (7 subjects) or following explantation and for 1-year post-explantation (6 subjects).

Subject Listing for Device Dislocation Resulting in Explantation

Study No.	Subject ID	Dislocation Observed (Study Day)	Explanted (Study Day)	Treatment	Severity
GC-010	(b) (6)	16	(b) (6)	G2-TR-063	Severe
GC-010		394		G2-TR-063	Mild
GC-010		356		G2-TR-063	Mild
GC-010		380		G2-TR-063	Mild
GC-010		364		G2-TR-063	Moderate
GC-010		473		G2-TR-063	Severe
GC-010		360		G2-TR-125	Severe
GC-010		10		G2-TR-125	Mild
GC-010		950		G2-TR-125	Mild
GC-012		39		G2-TR-063	Moderate
GC-012		549		G2-TR-063	Moderate
GC-012		366		G2-TR-125	Moderate
GC-012		55		G2-TR-125	Moderate

Source: ISS Table 39. GC-010 CSR section 14.4; GC-012 CSR section 14.4.

Explantations Due to an Adverse Event Other Than Device Dislocation

Four subjects underwent explantation of the G2-TR implant for reasons other than device dislocation. Adverse events leading to explantation of the G2-TR implant included dry eye, uveitis (2 subjects) and iritis.

Subject Listing for Explantations for Reason Other than Device Dislocation

Study No.	Subject ID	AE Start (Study Day)	Explanted (Study Day)	AE Stop (Study Day)	Adverse Event (SOC/PT)	Treatment	Severity
GC-010	(b) (6)	29	(b) (6)	299	Eye disorders/ Uveitis	G2-TR- 125	Severe
GC-010		44		245	Eye disorders/ Iritis	G2-TR- 125	Mild
GC-010		8		405	Eye disorders/ Uveitis	G2-TR- 063	Mild
GC-012		24		Ongoing	Eye disorders/ Dry eye	G2-TR- 063	Moderate

Source: ISS Table 40. GC-010 CSR section 11.2.4.4; GC-012 CSR section 11.2.4.2.
Hyperlinks are provided to short narratives found within the individual CSRs for subjects who had an explantation of the G2-TR implant during the 12-month analysis period.
Adverse events were coded using MedDRA version 21.0.

Reviewer's Comment:

Of the 13 subjects with a device dislocation, none was part of the cohort in which endothelial cell density data were collected prospectively. Only 1 (subject (b) (6)), had an endothelial cell density of <1,000 cells/mm2 post-explantation. Pre-explantation specular microscopy images for that eye were not gradable. Subject (b) (6) ECD has varied from 895 cells/mm^2 at Week 4, to 1404 cells/mm^2 at Month 6 to 1095 cells/mm^2 at Month 12. All other study eyes ECD post-explantation remained relatively stable.

Best Spectacle Corrected Visual Acuity (BSCVA)/Corrected Visual Acuity – Percentage with ≥ 15 Letter Decrease from Baseline for Study Eye by Visit and Overall in the Pooled Population (Safety Analysis Set GC-009, GC-010 and GC-010)

Visit		G2-TR-063 Implant (N=436) n (%)	G2-TR-125 Implant (N=432) n (%)	Sham/ Timolol (N=435) n (%)
Week 4	N	406	400	406
	Decrease of ≥ 15 letters	4 (1%)	4 (1%)	1 (0.2)
Week 6	N	428	423	426
	Decrease of ≥ 15 letters	2 (0.5%)	2 (0.5%)	0
Month 3	N	429	424	426
	Decrease of ≥ 15 letters	1 (0.2%)	2 (0.5%)	1 (0.2%)
Month 6	N	426	421	421
	Decrease of ≥ 15 letters	3 (0.7%)	5 (1%)	2 (0.5%)
Month 9	N	418	421	417
	Decrease of ≥ 15 letters	5 (1%)	4 (1%)	1 (0.2%)
Month 12	N	411	415	408
	Decrease of ≥ 15 letters	3 (0.7%)	6 (1%)	1 (0.2%)
Overall	N	435	431	432
(Worst Change)[1]	Decrease of ≥ 15 letters	14 (3%)	13 (3%%)	2 (0.5%)

Source: ISS Table 43. Table 14.3-3.2, ISS Table 14.3-3.1
Note: n is the number of subjects with BSCVA/Corrected VA assessment at post-baseline which is used as the denominator for percentage calculation. BSCVA is collected at Baseline, Months 12, 24, 36, and other scheduled visits if Corrected VA has decreased by 2 or more lines (≥10 letters) from baseline. If a subject has both BSCVA and Corrected VA data at a specific visit, BSCVA data is used in calculation of the change from baseline value. 1 The worst change for a given subject is the greatest decrease in number of letters correct from baseline across all scheduled post-baseline visits.

Reviewer's Comment:

Less than 1.5% of subjects in each G2-TR implant groups had a ≥ 15 letter reduction from baseline in visual acuity at any visit. Although this percentage is small, it was greater than the 0.5% in the Sham/Timolol group at each visit.

Integrated Assessment of Safety

1) Endothelial Cell Loss

A. Over the 12 Month period, central corneal endothelial cell density decreased by a greater percentage in the Travoprost Intraocular Implant group compared with the Sham/Timolol group, where endothelial cell density decreased by < 2% mean change in the Travoprost Intraocular Implant groups versus 0.05% in the Sham/Timolol group. (Additionally, one subject (0.5%) had a ≥ 30% reduction in endothelial cell density in the Travoprost Intraocular Implant groups; the Agency considers a corneal endothelial cell loss of ≥ 30% from baseline a significant loss.)

B. Central corneal endothelial cell density in the study eye demonstrated a 6.5% mean decrease in cell density over the total duration of exposure to the G2-TR implant (which ranged from 4.5 to 5.8 years) across the GC-009 and IDOS-106-EXCH studies. No subject who participated in the IDOS-106-EXCH trial exhibited a ≥ 30% loss in endothelial cell density from their pre-GC-009 baseline.

2) Device Dislocations and Corneal Endothelial Cell Loss

None of these subjects was part of cohort in which endothelial cell density were collected prospectively making it difficult to interpret this risk. One of the 13 study eyes (subject (b) (6)), that had a device dislocation and underwent explantation, had an endothelial cell density of <1,000 cells/mm^2 post-explantation increasing the risk for other corneal complications such as corneal edema, bullous keratopathy, etc.

3) Other Explantations for Reasons other than for Device Dislocations

Four subjects had explantations for Eye Disorders (two for Uveitis, one for Iritis and one for Dry Eye). All these explantations should be considered a complication related to treatment.

4) Best Spectacle Visual Acuity (BSCVA) Data For Studies GC-009, GC-010 and GC-012 Through Month 12

Less than 1.5% of subjects in each G2-TR implant group had a ≥ 15 letter reduction from baseline in visual acuity at any visit. Although this percentage is small, it was much greater than the 0.5% or less observed in the Sham/Timolol group at each visit.

5) Serious Adverse Events

Ocular serious adverse events included endophthalmitis (1 case in the G2-TR-125 implant group), intraocular pressure increased (1 in each of the G2-TR-063 and G2-TR-125 implant groups), and retinal detachment (1 case in the G2-TR-125 implant group).

6) Most Common Adverse Events Occurring in ≥ 3% of Subjects

The most common adverse events occurring in ≥ 3% of subjects in any treatment group were intraocular pressure increased, iritis, dry eye, and visual field defect:

10. Advisory Committee Meeting

There were no issues that were thought to benefit from a discussion at an Advisory Committee Meeting. No Advisory Committee Meeting was held for this supplemental application.

11. Pediatrics

This application triggers PREA as a new dosage form and has a PDUFA goal date of December 22, 2023. The Applicant requested a full waiver for the entire pediatric population as studies would be impossible or highly impracticable because patients are geographically dispersed. The Division agreed. In the October 24, 2023, meeting, the PeRC agreed with granting the full waiver as requested.

12. Biostatistics

From the Statistical Review finalized on 11/7/2023:

The primary efficacy endpoint of the two studies is the change from baseline in IOP in the study eye at 8AM and 10AM at each of Day 10, Week 6, and Month 3 visits (6 timepoints). The key secondary endpoint is the change from baseline in IOP in the study eye at 8AM and 10AM at Month 12. The prespecified NI criteria for the primary and key secondary endpoints are as follows:

- The primary efficacy endpoint: the upper limit of the 2-sided 95% confidence interval (CI) for the difference in the mean change from baseline in IOP is <1.5 mmHg at each of the 6 post-baseline timepoints and is < 1 mmHg at half or more of the 6 post-baseline timepoints.
- The key secondary efficacy endpoint: the upper limits of the 2-sided 95% CI for the difference in mean change from baseline in IOP is < 1.5 mmHg at each of the 2 post-baseline timepoints.

The table below summarizes the primary analysis results of the primary and key secondary efficacy endpoints. In each study, both G2-TR-063 and G2-TR-125 implant models met the prespecified NI criterion for the primary efficacy endpoint. However, the NI criterion for the key secondary endpoint was met only for the G2-TR-125 group in Study GC-012 and the upper limit was higher than the acceptable limit of 1.0 mmHg. The treatment differences (GR-TR implant minus Timolol) in the estimated mean IOP change from baseline ranged from -1.2 to -0.7 mmHg at Day 10, -0.8 to 0.3 mmHg at Week 6, -0.2 to 0.6 mmHg at Month 3, and 0.2 to 1.4 mmHg at Month 12.

In terms of comparison between the G2-TR-125 (the model which the Applicant seeks approval of) and Timolol groups, the results at Day 10 favor the G2-TR-125 group. The results at Month 3 are comparable between the two groups. The results at Month 12 favor the Timolol group.

Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, Month 3, and Month 12 (All Randomized Subjects)

	GC-010				GC-012	
	G2-TR-063 N = 200	**G2-TR-125 N = 197**	**Timolol N = 193**	**G2-TR-063 N = 185**	**G2-TR-125 N = 183**	**Timolol N = 192**
Baseline IOP						
8AM Mean (SD)	24.7 (3.4)	24.4 (3.2)	24.7 (3.5)	24.7 (4.0)	24.6 (3.5)	24.7 (3.7)
10AM Mean (SD)	24.3 (3.3)	24.1 (3.3)	24.0 (3.1)	24.3 (3.6)	24.1 (3.2)	24.2 (3.3)
Change from Baseline						
Day 10 8AM						
LS mean (SE)	-8.4 (0.2)	-8.5 (0.2)	-7.7 (0.2)	-8.3 (0.3)	-8.4 (0.3)	-7.2 (0.3)
Difference (CI)	**-0.7 (-1.4, -0.1)**	**-0.8 (-1.5, -0.1)**		**-1.1 (-1.8, -0.4)**	**-1.2 (-2.0, -0.5)**	
Day 10 10AM						
LS mean (SE)	-8.4 (0.2)	-8.4 (0.2)	-7.2 (0.2)	-8.2 (0.2)	-8.3 (0.2)	-7.1 (0.2)
Difference (CI)	**-1.2 (-1.8, -0.5)**	**-1.2 (-1.9, -0.6)**		**-1.1 (-1.8, -0.4)**	**-1.2 (-1.9, -0.5)**	
Week 6 8AM						
LS mean (SE)	-7.3 (0.2)	-7.3 (0.2)	-7.1 (0.2)	-6.8 (0.3)	-7.2 (0.3)	-7.2 (0.3)
Difference (CI)	**-0.3 (-0.9, 0.4)**	**-0.2 (-0.9, 0.5)**		**0.3 (-0.4, 1.1)**	**-0.0 (-0.8, 0.7)**	
Week 6 10AM						
LS mean (SE)	-7.6 (0.2)	-7.6 (0.2)	-6.9 (0.2)	-6.9 (0.3)	-6.8 (0.3)	-7.2 (0.2)
Difference (CI)	**-0.7 (-1.4, -0.1)**	**-0.8 (-1.4, -0.1)**		**0.2 (-0.5, 0.9)**	**0.3 (-0.4, 1.0)**	
Month 3 8AM						
LS mean (SE)	-6.6 (0.3)	-6.6 (0.3)	-6.7 (0.3)	-6.3 (0.3)	-6.7 (0.3)	-6.8 (0.3)
Difference (CI)	**0.1 (-0.6, 0.8)**	**0.1 (-0.6, 0.8)**		**0.5 (-0.2, 1.3)**	**0.2 (-0.6, 0.9)**	
Month 3 10AM						
LS mean (SE)	-6.6 (0.3)	-6.7 (0.3)	-6.5 (0.3)	-6.2 (0.3)	-6.8 (0.3)	-6.8 (0.3)
Difference (CI)	**-0.0 (-0.8, 0.7)**	**-0.2 (-0.9, 0.6)**		**0.6 (-0.2, 1.3)**	**-0.0 (-0.8, 0.7)**	
Month 12 8AM						
LS mean (SE)	-5.4 (0.3)	-5.5 (0.3)	-6.1 (0.3)	-5.0 (0.3)	-4.9 (0.3)	-6.3 (0.3)
Difference (CI)	**0.8 (0.0, 1.6)**	**0.6 (-0.1, 1.4)**		**1.3 (0.5, 2.1)**	**1.4 (0.6, 2.1)**	
Month 12 10AM						
LS mean (SE)	-5.8 (0.3)	-5.5 (0.3)	-6.0 (0.3)	-5.1 (0.3)	-5.4 (0.3)	-6.5 (0.3)
Difference (CI)	**0.2 (-0.5, 0.9)**	**0.5 (-0.2, 1.2)**		**1.3 (0.5, 2.1)**	**1.0 (0.3, 1.8)**	

Abbreviations: ITT = SD = standard deviation, SE = standard error, CI = confidence interval
Source: Table 11 of the SCE. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.
Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

Multiple supportive analyses of the primary efficacy endpoint provided consistent results. In the supportive analyses, the G2-TR-125 group met the NI criterion for the primary efficacy endpoint. See Section 3.2.4.1 of this review for details of supportive analyses.

While the Application includes adequate data to support NI of G2-TR implants over Timolol up to three months, the submitted data from the phase 3 studies do not provide sufficient evidence for NI of the G2-TR implant models beyond three months. The estimated mean IOP reductions from baseline at Months 6 and 9 were greater in the Timolol group compared with those in the G2-TR implant groups: -5.9 to -5.3 mmHg in the G2-TR implant groups vs. -6.7 to -6.4 mmHg in the Timolol group. As presented in Table 1, the estimated mean IOP reductions from baseline at Month 12 were also greater in the Timolol group compared with those in the G2-TR implant groups.

Regarding safety, the proportion of subjects with adverse events (AEs) was higher in the G2-TR implant groups compared with that in the Timolol group: 49.0% (G2-TR-063), 54.4% (G2-TR- 125), and 38.7% (Timolol) in Study GC-010 and 49.2% (G2-TR-063), 44.3% (G2-TR-125), and 38.0% (Timolol) in Study GC-012. The majority of the AEs were mild or moderate. The most commonly reported ocular AE in the study eye in the G2-TR-125 group was iritis. The proportion of subjects with iritis in the G2-TR-125 group was higher than that in the Timolol group: 6.2% vs. 0% in

Study GC-010 and 5.1% vs. 0% in Study GC-012. The reviewer defers to the medical reviewer for a comprehensive safety evaluation and for acceptability of the safety profile of G2-TR-125.

In summary, the reviewer concludes that this application provided substantial evidence of effectiveness up to three months to support an approval of iDose® TR (G2-TR-125) for reduction of elevated IOP in subjects with OAG or OHT. However, the application did not provide adequate sustained evidence to support NI of iDose® TR over Timolol beyond three months.

13. Financial Disclosure

Covered Clinical Study: GC-010 and GC-012

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 96		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 15		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 (Stock options 50K) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Disclosable Financial Arrangements

Investigator Name	Arrangement
(b) (6)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000.
(b) (6)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000. Glaukos Corporation granted stock options to (b) (6). The value of the options granted to (b) (6) exceeds $50,000 in value.
(b) (6)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000. Glaukos Corporation granted stock options to (b) (6). The value of the options granted to (b) (6) exceeds $50,000 in value.

(b) (6)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000.
(b) (6)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000.
(b) (6) (Sub-Investigator)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000.
(b) (6) (Sub-Investigator)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000.
(b) (6)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000.
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(b) (6) (Sub-Investigator)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000.
(b) (6)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022, exceeded $25,000.
(b) (6)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022, exceeded $25,000.
(b) (6)	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022, exceeded $25,000.
(b) (6) MD, PhD	(b) (6) received consulting fees for clinical and commercial advice to Glaukos. The total paid to (b) (6) between January, 2016 and December, 2022 exceeded $25,000.

The following steps were taken to minimize the potential bias of the results from the clinical studies.

- The study was a randomized multicenter trial with a large number of investigators (45 study centers).
- The study endpoints were pre-specified and objective, consisting of multiple masked measurements of intraocular pressure (IOP) following washout of ocular hypotensive medication.
- Multiple objective inclusion criteria were used for determination of patient eligibility and enrollment of study subjects.
- Numerous pre- and postoperative examinations were performed by designated clinical site personnel, not by the study investigators. It should be noted that it is standard practice in

ophthalmology practices for optometrists or technicians to perform visual acuity measurements and other elements of patient care other than in cases requiring medical review or intervention by the study investigators.
- No site was permitted to contribute more than 15% of the total number of randomized subjects in the trial.

14. Study Integrity

From the OSI Clinical Investigation Summary finalized October 23, 2023: Clinical data from Protocols GC-010 and GC-012 were submitted to the Agency in support of NDA 218010 for the use of iDose TR for the reduction of intraocular pressure (IOP). Two clinical investigators, Drs. Sarkisian and Parkhurst, were inspected in support of this NDA. Based on the results of these inspections, Protocols GC-010 and GC-012 appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the proposed indication.

15. DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized their review on 11/6/2023. DMEPA described their medication error issue concerns, described below. The clinical staff agreed with some of the recommendations and disagreed with others.

"Our review of the HF study identified that the removal and re-administration of the implant after implantation was not evaluated. We note that this limits our ability to interpret the study data and (b) (4) (b) (4); the development of fibrotic tissue around the implant was not evaluated in the HF validation study. Therefore, our ability to assess the (b) (4) (b) (4) effects of fibrotic tissue development around the implant are limited. We are concerned that simulated use human factors would not adequately assess (b) (4) (b) (4) this product given that this product is implanted into human tissue. As such, we defer to the Division of Ophthalmology (DO) to determine the additional information or data needed (b) (4)

Additionally, our review of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations in Table 4 for DO and Table 5 for Glaukos. We ask that DO convey the table below in its entirety to Glaukos. We advise these recommendations are implemented during this review cycle of NDA 218010.

These labeling changes can be implemented without submitting additional HF validation testing data for Agency review.

Identified Issues and Recommendations for Glaukos Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Tyvek lid Label and Carton Labeling			
1.	The route of administration is not present on the principal display panel.	Failure to include the route of administration on the principal display panel may lead to wrong route errors.	Add the route of administration "For intracameral administration" in accordance with 21 CFR 201.100(b)(3).
2.	As currently presented, the format for expiration date is not defined.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY- MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to separate the portions of the expiration date.
3.	The intended location of the linear barcode is not specified.	Required by 21 CFR 201.25(c)(2). The drug barcode is often used as an additional verification before drug administration in the hospital setting therefore it is an important safety	Include the product's linear barcode as required by 21 CFR 201.25(c)(2).

		feature that should be part of the label.	

Identified Issues and Recommendations for Glaukos Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
4.	The root name 'TR' appears in a smaller font compared to the device name 'iDose'. (b) (4) Additionally, the graphic above the root name distracts from the proprietary name. Furthermore, the (b) (4) (b) (4) font color against the white background decreases readability.	Required label statements must be displayed in a manner consistent with FDA regulations 21 CFR 201.15(a)(6), taking into account all pertinent factors, including typography, layout, contrast, and other printing features.	Revise the root name "TR' to appear in the same font size as the commensurate with the remainder of the proprietary name. Additionally, we recommend relocating the graphic to appear away from the proprietary name. Lastly, we recommend revising the (b) (4) (b) (4) font color within the proprietary name to a color (b) (4) (b) (4) that provides more contrast against the white background.
5.	As currently presented, the dosage statement reads (b) (4)	The terminology (b) (4) is not consistent with the terminology used to describe current labeling (i.e., Prescribing Information).	For clarity and consistency revise the dosage statement to *"Dosage: See Full Prescribing Information."*
Tyvek lid label			
1.	As currently presented, the manufacturer's name graphic 'GLAUKOS®' competes in prominence with the proprietary name, established name and strength statements. (b) (4)	The proprietary name, established name and strength statements, along with other critical product information should be presented as the most prominent information on the container label.	We recommend decreasing the prominence of the manufacturer name (e.g., decreasing the font size) and relocating away from the product name.

16. Post-marking Risk Management

There are no recommended post marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

17. Labeling

On December 7, 2023, a teleconference was held between the Agency and Glaukos regarding the draft labeling for iDose TR (travoprost intracameral implant). At that meeting, it was agreed that Glaukos would submit the following:

- Proposed labeling to be utilized in a limited commercial launch of iDose TR (travoprost intracameral implant) to include the Tyvek lid label, carton, and Tyvek/carton/patient stickers as presented in NDA amendment, Sequence Number 0013. For the limited commercial launch, a sticker printed with the linear barcode for the NDC number will be affixed to the outside of the unit carton, and the final approved prescribing information and patient ID/implant card with the revised established name, travoprost intracameral implant, will be placed inside the unit carton.
- Revised labeling components (i.e., Tyvek lid label, carton, patient ID/implant card, Tyvek/carton/patient stickers, and prescribing information) to be used for the full commercial launch. For the full commercial launch, Glaukos will utilize only product labeled with the final labeling approved by the Agency.
- Revised package insert incorporating the Agency's recommendations. Specifically, the removal of (b) (4), and revisions in Section 2.1 General Dosing Information, revised text in Section 14 Clinical Studies regarding the iDose TR clinical trials not meeting non-inferiority over the next 9 months.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

18. Regulatory Action

Reviewers from CMC, Pharmacology/Toxicology, Statistical, and Clinical Pharmacology have not identified any deficiencies. Manufacturing facility inspections verified that the proposed manufacturing facilities are in compliance with current Good Manufacturing Practices (cGMP).

NDA 218010 for iDose TR (travoprost intraocular implant) 75 µg will be approved for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension in patients 18 years or older (b) (4) . The Safety Data demonstrated safety of the implant for single use only. (b) (4) (b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RHEA A LLOYD
12/13/2023 08:24:04 AM

WILLIAM M BOYD
12/13/2023 08:36:27 AM

WILEY A CHAMBERS
12/13/2023 11:24:15 AM