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RESEARCH**

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CLINICAL REVIEW(S)

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

CLINICAL REVIEW of NDA 218010

Application Type	NDA
Application Number	218010
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Reviewer Name(s)	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	October 11, 2023
Established/Proper Name	(travoprost intraocular implant), 75 µg
(Proposed) Trade Name	iDose TR
Applicant	Glaukos Corporation
Dosage Form(s)	Intraocular implant, administered intracamerally
Applicant Proposed Dosing Regimen(s)	(travoprost intraocular implant), 75 µg, administered intracamerally
Applicant Proposed Indication(s)/Population(s)	Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT)
Recommendation on Regulatory Action	Approval is recommended for (travoprost intraocular implant), 75 µg, G2-TR-125 implant, single use only
Recommended Indication(s)/Population(s)	In patients 18 years or older with open-angle glaucoma (OAG) or ocular hypertension (OHT)

Table of Contents

Glossary	4
1. Executive Summary	6
1.1. Product Introduction.....	6
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	6
1.3. Benefit-Risk Assessment	7
Benefit-Risk Integrated Assessment	7
1.4. Patient Experience Data.....	9
Patient Experience Data Relevant to this Application (check all that apply).....	9
2. Therapeutic Context.....	10
2.1. Analysis of Condition.....	10
2.2. Analysis of Current Treatment Options	10
3.1. U.S. Regulatory Actions and Marketing History.....	12
3.2. Summary of Presubmission/Submission Regulatory Activity	12
3.3. Foreign Regulatory Actions and Marketing History	13
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	14
4.1. Office of Scientific Investigations (OSI)	14
4.2. Product Quality	14
4.3. Clinical Microbiology.....	15
4.4. Nonclinical Pharmacology/Toxicology	16
4.5. Clinical Pharmacology	16
4.6. Devices and Companion Diagnostic Issues	17
5. Sources of Clinical Data and Review Strategy	18
5.1. Table of Clinical Studies	18
5.2. Review Strategy	26
6. Review of Relevant Individual Trials Used to Support Efficacy	26
6.1. Study GC-010 and Study GC-012: Prospective, Randomized Phase 3 Study Comparing Two Models of Travoprost Intraocular Implant to Timolol Maleate Ophthalmic Solution, USP, 0.5% 26	

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

6.1.1. Study Design	26
6.1.2. Study Results	32
7. Integrated Review of Effectiveness	47
7.1. Assessment of Efficacy Across Trials	47
7.1.1. Other Endpoints.....	47
8. Review of Safety	49
8.1. Safety Review Approach	49
8.2. Review of the Safety Database	49
8.2.1. Overall Exposure	49
8.2.2. Adequacy of the safety database:	50
8.3. Adequacy of Applicant’s Clinical Safety Assessments	50
8.3.1. Categorization of Adverse Events	50
8.3.2. Routine Clinical Tests	51
8.4. Safety Results	51
8.4.1. Deaths	51
8.4.2. Serious Adverse Events	52
8.4.3. Significant Adverse Events	53
8.4.4. Treatment Emergent Adverse Events and Adverse Reactions	53
8.4.6 Laboratory Findings.....	54
8.5. Analysis of Submission-Specific Safety Issues	54
8.5.1. Specific Potential Safety Issues	54
8.6. Safety Analyses by Demographic Subgroups	60
8.7. Specific Safety Studies/Clinical Trials.....	60
8.8. Additional Safety Explorations	60
8.8.1. Human Reproduction and Pregnancy	60
8.8.2. Pediatrics and Assessment of Effects on Growth	60
8.9. Safety in the Postmarket Setting	60
8.10. Integrated Assessment of Safety	60
9. Advisory Committee Meeting and Other External Consultations	61
10. Labeling Recommendations	61

11. Risk Evaluation and Mitigation Strategies (REMS).....	61
12. Postmarketing Requirements and Commitments.....	61
13. Appendices.....	62
120-Day Safety Update	62
13.1. Financial Disclosure.....	64

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

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

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

1. Executive Summary

1.1. Product Introduction

iDose TR (travoprost intraocular implant) 75 µg is a sterile, sustained-release, implant preloaded in a single use inserter, administered intracamerally through a 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.

1.2. Conclusions on the Substantial Evidence of Effectiveness

iDose TR (travoprost intraocular implant) 75 µg demonstrated efficacy in two adequate and well controlled clinical trials (Studies GC-010 and GC-012) at Month 3 for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension in patients 18 years or older. 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 Month 3 based on the primary efficacy endpoints.

For the key secondary efficacy endpoints at Month 12, clinical trial GC-010, did not demonstrate non-inferiority to timolol for the G2-TR-063, (b) (4), implant. For clinical trial GC-012, non-inferiority to timolol was not demonstrated for either G2-TR implant. At Month 12 based on the efficacy results, given the (b) (4) G2-TR-63 implant failed in both trials, and the (b) (4) G2-TR-125 was successful in only one trial (GC-010), approval at Month 3 is recommended only for the G2-TR-125, (b) (4) implant.

The Safety Data demonstrated safety of the implant for single use only with subsequent removal of the implant at Month 3 or more. 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 (5.1%), intraocular pressure increased (4.4%), visual field defect (3.0%) and dry eye (2.8%).

Approval is recommended for iDose TR (G2-TR-125 (b) (4) implant). (b) (4)

1.3. 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 diurnal 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.

The safety profile of Travoprost intraocular implant is similar to other marketed topical prostaglandin analogues with the exception of a 2% increased 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. After corneal endothelial cell loss, the most common ocular adverse events occurring in ≥ 3 % of subjects are intraocular pressure increase, iritis, dry eye and visual field defect. 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 every three months 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 one 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.

1.4. Patient Experience Data

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

X	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
X	Clinical outcome assessment (COA) data, such as	
	☐ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
X	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)	
☐	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	
	☐ Other: (Please specify)	
Patient experience data was not submitted as part of this application.		

2. Therapeutic Context

2.1. 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 for progression of glaucoma to blindness is elevated intraocular pressure (IOP). It affects one in 200 people over the age of 40. The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy. When maximal tolerated medical therapy does not adequately control IOP, surgical therapy is the next option.

2.2. Analysis of 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 analogs.

Current Pharmacologic Treatment Options for Lowering Intra-ocular Pressure

Pharmacologic Class	Trade Name	Established Name	Dosage Form
<i>Alpha-2 Agonists</i>			
	Alphagan P	Brimonidine Tartrate 0.1%	Solution
	Brimonidine Tartrate	Brimonidine Tartrate 0.2%	Solution
<i>Beta-Adrenergic Blockers</i>			
	Betoptic S	Betaxolol Hydrochloride 0.25%	Suspension
	Betaxolol	Betaxolol Hydrochloride 0.5%	Solution
	Betagan 0.5%	Levobunolol Hydrochloride	Solution
	Timoptic 0.25% and 0.5% In Ocusose	Timolol Maleate 0.25%	Solution
	Timoptic	Timolol Maleate	Solution
	Timoptic-XE	Timolol Maleate	Solution
	Istalol	Timolol Maleate	Solution
	Timoptic In Ocusose	Timolol Maleate	Solution
	Timolol GFS	Timolol Maleate Ophthalmic Gel Forming solution	Gel forming Solution
	Betimol	Timolol 0.25%, 0.5%	Solution
<i>Carbonic Anhydrase Inhibitors</i>			
	Trusopt	Dorzolamide Hydrochloride	Solution

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Pharmacologic Class	Trade Name	Established Name	Dosage Form
	Diamox	Acetazolamide	Oral/Tablet and extended-release capsule
	Azopt	Brinzolamide	Suspension
<i>Cholinergic Receptor Agonist</i>			
	Isopto Carpine	Pilocarpine Hydrochloride 2%, 4%	Solution
<i>Prostaglandin Analogues</i>			
	Zioptan	Tafluprost	Solution
	Lumigan 0.03%	Bimatoprost	Solution
	Lumigan 0.01%	Bimatoprost	Solution
	Durysta	Bimatoprost	Intracameral Implant
	Vyzulta	Latanoprostene Bunod	Solution
	Travatan Z	Travoprost	Solution
	Xalatan	Latanoprost	Solution
	Xelpros	Latanoprost	Solution
<i>Rho Kinase Inhibitor</i>			
	Rhopressa	Netarsudil	Solution
<i>Combination Products</i>			
	Rocklatan	Netarsudil and Latanoprost Ophthalmic Solution, 0.02%/0.005%	Solution
	Simbrinza	Brinzolamide/Brimonidine Tartrate	(b) (4)
	Simbrinza	Brinzolamide/Brimonidine Tartrate	Suspension
	Combigan	Brimonidine Tartrate/Timolol Maleate 0.2%/0.5%	Solution
	Cosopt	Dorzolamide Hydrochloride and Timolol Maleate	Solution
	Cosopt PF	Dorzolamide Hydrochloride and Timolol Maleate	Solution

3.1. U.S. Regulatory Actions and Marketing History

Glaukos Corporation (Glaukos) has submitted this original New Drug Application (NDA) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Travoprost Intraocular Implant, 75 µg for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT). The application relies on the Agency's previous finding of nonclinical safety for the reference listed drug (RLD) Travatan® (travoprost ophthalmic solution) 0.004%, approved under NDA 021257.

Glaukos started development under the IND 120995 with two models of the Travoprost Intraocular Implant, Model G2-TR-063 and Model G2-TR-125. Both models have the same travoprost formulation and composition and are differentiated by the drug release rate from the titanium implant reservoir (b) (4)

Both models were investigated in one Phase 2 trial (GC-009) and two Phase 3 trials (GC-010 and GC-012). The clinical development program for the Travoprost Intraocular Implant was designed to demonstrate the safety and efficacy of the implant for the reduction of elevated IOP in patients with OAG or OHT following its initial administration, as well as upon re-administration and removal of the prior implant ("exchange"), as studied in the exchange trial (US IDOS-106- EXCH).

The Travoprost Intraocular Implant has not been marketed in any country.

3.2 Summary of Presubmission/Submission Regulatory Activity

Glaukos (or its predecessor Dose Medical) sought advice from the FDA on clinical and/or statistical issues on the following occasions:

- March 28, 2014 - Pre-IND meeting
- December 4, 2017 - EOP2 Meeting,
- December 2018 - Type C Clinical Guidance Meeting
- June 7, 2021 - Type C Multidisciplinary Guidance Meeting
- May 9, 2022 - Type B Pre-NDA Biostatistics meeting
- November 29, 2022 - Pre-NDA Clinical/Biostatistics meeting

At the Pre-IND meeting, the Agency advised Dose Medical that trials of 3-months duration were generally needed to be able to determine an efficacious dose, that the primary efficacy endpoint should be the treatment group difference in mean IOP rather than a change from baseline in IOP, and that one equivalence trial to travoprost ophthalmic solution or 2 noninferiority/superiority trials (to a prostaglandin analogue solution or timolol solution) were recommended to support the efficacy of the product. In addition, the Agency advised that

equivalence was defined as the 2-sided 95% confidence interval (CI) being < 1.5 mm Hg at each direct group comparison over multiple times over the 3-month period and < 1.0 mm Hg for the majority of direct group comparisons. The timepoints were to include both the peak and trough efficacy times (of both the test product and the control product).

In addition, it was recommended that the clinical program include enough patients to identify adverse events that occur at a rate of 1% or greater. Safety was to be demonstrated in at least 300 patients who have completed the expected duration that the implant will elute after implantation, and that at the time of NDA submission, safety data for at least 1 year in patients using the “to be marketed” Travoprost Intraocular Implant should be submitted.

Finally, the Agency indicated that studies should be masked to minimize potential bias, and that if a sham is included, at 2 active dose groups should be included in addition to the sham group. In accordance with this advice, the Phase 2 trial (GC-009) was designed as a 36-month trial with the primary efficacy endpoint based on the difference in mean IOP between treatment groups at the 8AM, 10AM, and 4PM timepoints at Day 10, Week 6, and Month 3. These timepoints took into account peak and trough efficacy times for the timolol comparator and the Travoprost Intraocular Implant. Per the Agency’s request to minimize potential bias, the Phase 2 trial was designed with 2 active dose groups (G2-TR-063 and G2-TR-125) in addition to the sham group.

At the EOP2 Meeting, the Agency indicated that mean IOP change from baseline at each timepoint for each post-baseline visit be analyzed using an analysis of covariance (ANCOVA) and that the minimum duration of effect needed to claim a reduction in IOP is 3 months.

At a Type C Clinical Guidance Meeting (Dec 2018), agreement was reached on the overall approach proposed by Glaukos to evaluate the safety of the exchange of Travoprost Intraocular Implants, including the sample size and duration of follow-up. In accordance with this agreement, the IDOS-106-EXCH protocol (where the implant would be explanted and a G2-TR 125 would be inserted) was finalized.

At the Type C Multidisciplinary Guidance Meeting (June 2021), the Agency agreed that since the product was an intraocular implant with continual elution of travoprost, it was acceptable for the trials to evaluate efficacy at the active comparator peak and trough, that for an endpoint based on 6 timepoint comparisons, non-inferiority would be established if the upper 2-sided 95% CI for the IOP mean differences (implant – control) was ≤ 1.5 mmHg at all of the 6 IOP timepoints and ≤ 1.0 mmHg at 3 or more of the 6 timepoints. In accordance with the Agency’s recommendation, Glaukos did not lock the databases and unmask and analyze the data until all subjects had reached Month 12 or discontinued prior to that visit.

3.3 Foreign Regulatory Actions and Marketing History

The Travoprost Intraocular Implant has not been marketed in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No issues were identified in the review of the clinical portion of the NDA to suggest a problem with data integrity. Routine clinical inspections were requested from OSI. From the Clinical Inspection Summary finalized on October 23, 2023: 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.

4.2. Product Quality

iDose TR (travoprost intraocular implant) is a sterile intraocular implant containing 75 µg of travoprost, a prostaglandin analog, with (b) (4). 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 C₂₆H₃₅F₃O₆ and a molecular weight of 500.55 g/mol.

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)

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Specified Impurities (%) (b) (4)	M16727 (HPLC/UV)	(b) (4)
Individual Unspecified Impurities (%)	M16727 (HPLC/UV)	(b) (4)
Total Impurities (%)	M16727 (HPLC/UV)	(b) (4)
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.

4.3. Clinical Microbiology

Not applicable. The drug product is not an antimicrobial.

4.4. Nonclinical Pharmacology/Toxicology

Carcinogenesis

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The highest dose of 100 µg/kg/day is 1,840-times the human systemic exposure (calculated based on estimated human plasma TFA concentration of 10 pg/mL from Travoprost Intraocular Implant [i.e., the LLOQ] and rat plasma C_{max} of 18.4 ng/mL at the 100 mcg/kg subcutaneous dose).

Mutagenesis

Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Fertility

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day which corresponds to 1,840-times the human systemic exposure (calculated based on an estimated human plasma TFA concentration of 10 pg/mL from Travoprost Intraocular Implant [i.e., the LLOQ] and a plasma C_{max} of 18.4 ng/mL in rat at a subcutaneous dose of 100 mcg/kg). At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day, 179-times the human systemic exposure (calculated based on estimated human plasma TFA concentration of 10 pg/mL from Travoprost Intraocular Implant [i.e., the LLOQ] and rat plasma C_{max} of 1.79 ng/mL at a subcutaneous dose of 10 mcg/kg).

4.5. Clinical 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 is unknown at this time. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics

Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea and other intraocular tissues 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.

Data from a pharmacokinetic study of 105 subjects evaluating two models of the travoprost intraocular implant with different elution rates have shown that the plasma concentrations of travoprost free acid are below 10 pg/mL (the quantitation limit of the assay, LLOQ) in all subjects at day 10, week 12 and month 12 following administration of iDose TR.

4.6. Devices and Companion Diagnostic Issues

The Travoprost Intraocular Implant has been developed as a pharmaceutical product over the last decade based on 21 CFR 200.50(c).

The changes in the regulatory landscape due to the Genus decision issued on April 16, 2021, by the U.S. Court of Appeals for the District of Columbia Circuit changed the regulation of this product to a drug-led, drug-device combination product. As the drug constituent travoprost provides the IOP lowering primary mode of action, the Center for Drug Evaluation and Research (CDER) is the lead Center, with a consultation from the Center for Devices and Radiological Health (CDRH).

Container Closure System

The Travoprost Intraocular Implant is comprised of an implant titanium reservoir (also referred to as titanium reservoir) with titanium anchor, containing 75 µg of travoprost drug substance formulated with (b) (4). The titanium reservoir is sealed with an ethylene vinyl acetate (EVA) membrane held in place with a titanium crimp cap. The implant filled with drug product is loaded onto an inserter. The pre-loaded inserter is packaged inside a sealed tray (primary packaging) enclosed by a sealed pouch with an oxygen absorber (secondary packaging). The sealed pouch is packaged into a carton for tertiary packaging.

Travoprost Intraocular Implant (Assembled View)



5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The clinical development program for the Travoprost Intraocular Implant was designed to demonstrate the safety and efficacy of the implant for the reduction of elevated IOP in patients with OAG or OHT following its initial administration, as well as upon re-administration and removal of the prior implant (“exchange”).

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) and model G2-TR-125 was designed for a (b) (4).

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.

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects ^a	Study Population	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

Reviewer's Comment:

Trials GC-010 and GC-012 form the basis of review for the IOP-lowering effect of the Travoprost Intraocular Implant based on non-inferiority margins compared to topical Timolol BID. The primary efficacy endpoint was at Month 3 and the secondary efficacy endpoint was at Month 12. Trials (GC-010 and GC-012) are 36-month trials. The data for these trials has been submitted after all subjects have reached their 12-month follow-up at which time the data set was "locked."

The primary efficacy endpoint was the change from baseline in IOP in the study eye at 8 AM and 10 AM at Day 10, Week 6, and Month 3 visits (6 timepoints). Since the product was an intraocular implant with continual elution of travoprost, it was acceptable for the trials to evaluate efficacy at the active comparator peak and trough. For an endpoint based on 6 timepoint comparisons, non-inferiority would be established if the upper bound of the 2-sided 95% CI for the IOP mean differences (implant – control) was ≤ 1.5 mm Hg at all of the 6 IOP timepoints and ≤ 1.0 mm Hg at 3 or more of the 6 timepoints.

Additionally, after subjects had been treated with the implant for 36 months in Study GC-009, thirty-three subjects were enrolled in Study IDOS-106-EXCH, the "exchange" trial. This was a prospective, multi-center, non-randomized, open-label, single arm 12-month trial designed to evaluate the safety of the surgical exchange procedure (explantation and reinsertion) of the Travoprost Intraocular Implant. The non-randomized and open-label design of this trial may limit the interpretation of its results.

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

GC-10 List of Principal Investigators

Region/Principal Investigator	Investigator Number	Study Site Address	Number of Subjects Screened	No. of Subjects Randomized
North America/ United States:				
Atodaria, Neil, MD	202	Barnet Dulaney Perkins Eye Center 4800 N. 22nd Street Phoenix, AZ 85016	12	5
Baartman, Brandon, MD	244	Vance Thompson Vision (NE) 4909 S. 118th Street Omaha, NE 68137	5	2
Basha, Mahdi, MD	211	Fraser Eye Care Center 33080 Utica Road Fraser, MI 48026	18	13
Bashford, Kent, MD	203	Eye Center of Northern Colorado, PC 3151 Precision Drive Ft Collins, CO 80528	12	10
Berdahl, John, MD	204	Vance Thompson Vision (ND) 3101 West 57th Street Sioux Falls, SD 57108	58	34
Brubaker, Jacob, MD	246	Sacramento Eye Consultants 1515 Response Road, Sacramento, CA 95815	8	4
Burden, James, MD	205	Skyline Vision Clinic and Laser Center 3155 North Union Boulevard Colorado Springs, CO 80907	34	29
Chin, Patrick, MD	248	Westwood Ophthalmology Associates 300 Fairview Avenue, Westwood, NJ 07675	10	6
Chu, Ralph, MD	206	Chu Vision Institute 9117 Lyndale Ave. South Bloomington, MN 55420	10	5
Cotter, Frank, MD	207	Vistar Eye Center 707 South Jefferson Street, Roanoke, VA 24016	45	26
Crane, Charles, MD	209	Northern New Jersey Eye Institute, PA 71 Second Street, South Orange, NJ 07079	12	8
ElMallah, Mohammed, MD	212	Ocala Eye, PA 4414 SW College Road Ocala, FL 34474	20	10
Flynn, William, MD	213	R and R Eye Research, LLC 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	7	5
Gira, Joseph, MD	215	Ophthalmology Consultants, Ltd. 12990 Manchester Avenue, St. Louis, MO 63131	14	12
Goldberg, Damien, MD	216	Wolstan & Goldberg Eye Associates 23600 Telo Avenue, Suite 100 Torrance, CA 90505	10	4
Greenwood, Michael, MD	217	Vance Thompson Vision (ND) 505 32nd Avenue E Suite B, West Fargo, ND 57104	20	7
Heersink, Sebastian, MD	219	Eye Center South DBA Trinity Research Group, 2800 Ross Clark Circle Dothan, AL 36301	43	29
Jones, Jason, MD	220	Jones Eye Clinic & Surgery Center 4405 Hamilton Boulevard, Sioux City, IA 51104	10	9
Kim, Joshua, MD	222	Center For Sight 2601 S. Tamiami Trail Sarasota, FL 34239	23	16

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Lambright, Benjamin, MD	224	North Coast Clinical Research 6122 W Corporate Oaks Drive Crystal River, FL 34429	15	7
Lee, Andy, MD	223	Total Eye Care 388 E. Hwy 67 Duncanville, TX 75137	59	38
Lehmann, Robert, MD	225	Lehmann Eye Center 5300 North Street Nacogdoches, TX 75965	17	12
Marquis, Robert, MD	228	Keystone Research, Ltd. 5717 Balcones Drive Austin, TX 78731	11	10
Marsh, Barbara, MD	245	Eye Associates of New Mexico 5757 Harper Drove NE Albuquerque, NM 87109	8	3
McCabe, Cathleen, MD	229	The Eye Associates of Manatee, LLP 6002 Pointe West Blvd Bradenton, FL 34209	11	5
Myers, Jonathan, MD	230	Wills Eye Hospital 840 Walnut Street, Suite 1140 Philadelphia, PA 19107	13	6
Nguyen, Betsy, MD	231	Coastal Vision Medical Group 293 S. Main Street, Suite 100 Orange, CA 92868	16	7
Paauw, James, MD	227	Piedmont Eye Center 116 Nationwide Drive Lynchburg, VA 24502	24	12
Sarkisian, Steven, MD	232	MIGS Consulting, LLC DBA Oklahoma Eye Surgeon's, PLLC 5600 N Portland Avenue Oklahoma City, OK 73112	73	63
Shah, Pankajkumar, MD	233	DCT-Shah Research, LLC dba Discovery Clinical Trials 1506 E. Griffin Parkway Mission, TX 78572	1	1
Sharpe, Elizabeth, MD	234	Carolina Eyecare Physicians, LLC 242 Mathis Ferry Road Suite 100 Mt. Pleasant, SC 29464	33	18
Shetty, Rajesh, MD	235	Florida Eye Specialists 11512 Lake Mead Avenue, Suite 534 Jacksonville, FL 32256	16	7
Shultz, Mitchell, MD	236	Shultz Chang Vision 18350 Roscoe Blvd Suite 101 Northridge, CA 91325	17	6
Silverstein, Bruce, MD <i>Former PI:</i> Lin, Christopher, MD	226	Shasta Eye Medical Group, Inc. 900 Butte Street Redding, CA 96001	6	5
Smith, Stephen, MD	221	Eye Associates of Fort Myers 4225 Evans Avenue Ft. Myers, FL 33901	17	12
Sorenson, Robert, MD	238	Inland Eye Specialists 3953 W. Stetson Avenue Hemet, CA 92545	12	6
Swan, Russell, MD	218	Vance Thompson Vision (MT) 1925 N 22nd Ave Suite 201 Bozeman, MT 59718	15	4

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Swarup, Jitendra, MD	237	Albemarle Clinical Trials 1503 North Road Street Elizabeth City, NC 27909	24	16
Tyson, Farrell, MD	239	Argus Research at Cape Coral Eye Center 4120 Del Prado Blvd. South Cape Coral, FL 33904	3	0
Tyson, Sydney, MD	240	SurgiCenter of Vineland & Eye Associates 251 S. Lincoln Ave Vineland, NJ 08361	11	9
Vold, Steven, MD	241	Vold Vision, PLLC 2783 North Shiloh Drive Fayetteville, AR 72704	39	25
Wellish, Kent, MD	242	Wellish Vision Institute 2110 East Flamingo Road, Suite 210, Las Vegas, NV 89119	27	8
Wu, Bin, MD Former PI: D'Ambrosio, Francis, MD	210	D'Ambrosio Eye Care, Inc. 479 Old Union Turnpike Lancaster, MA 01523	21	7
Zaman, Fiaz, MD	243	Houston Eye Associates 2855 Gramercy Street Houston, TX 77025	35	27
Asia/Philippines:				
Ang, Robert, MD	201	Asian Eye Institute 8th to 10th Floor, Rockwell Center, PHINMA Plaza Building Makati City, 01200 PHL	59	42

GC-12 List of Principal Investigators

Geographic Region/Principal Investigator	Investigator Number	Study Site Address	Number of Subjects Screened	Number of Subjects Randomized
North America/ United States:				
Amir, Ahmad, MD	343	Pacific Eye Surgeons 3855 Broad Street, Suite B San Luis Obispo, CA 93401	5	1
Bacharach, Jason, MD	302	North Bay eye Associates, Inc. 104 Lynch Creek Way, Suite 15, Petaluma, CA 94954	9 ^a	5 ^a
Barber, Kevin, MD	311	Central Florida Eye Specialists 1592 South SR 15-A DeLand, FL 32720	36 ^b	21 ^b
Bettis, Daniel, MD	340	Moyes Eye Center 5151 NW 88th Street Kansas City, MO 64154	13 ^a	7 ^a
Borisuth, Navaneet, MD	304	Virdi Eye Clinic 4600 30th Street Rock Island, IL 61201	55	32
Bretz (Chapman), Kristin, MD	338	The Eye Institute of Utah 755 East 3900 South Salt Lake City, UT 84107	7 ^c	5 ^c
Cameron, Bruce, MD	357	NW Eye Surgeons 332 NE Northgate Way Seattle, WA 98125	3	3
Chaudhry, Iftikhar, MD	358	IC Laser Eye Care 3046 Knights Road Bensalem, PA 19020	5	3
Christie, William, MD	344	Scott & Christie and Associates, 105 Brandt Dr, Suite 201, Cranberry Township, PA 16066	15	9

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Darlington, Jason, MD	306	The Eye Institute 1995 W. Nasa Blvd., Suite 200, Melbourne, FL 32904	38	25
Davidson, John, MD	307	Miramar Eye Specialists 3085 Loma Vista Road Ventura, CA 93003	15	7
Flowers, Brian	308	Ophthalmology Associates 1201 Summit Avenue Fort Worth, TX 76102	24	20
Fox, James, MD	309	Icon Eye Center 1000 Wellington Ave, Grand Junction, CO 81501	48	31
Gallardo, Mark, MD	310	El Paso Eye Surgeons 1201 N. Mesa, Suite G El Paso, TX 79902	49 ^b	41 ^b
Jiang, Shunai, MD	326	Marietta Eye Clinic 895 Canton Road, Building 200, Marietta, GA 30060	7	0
Johnson, Duncan, MD	312	Inland Eye Specialists 25395 Hancock Avenue Suite 100, Murrieta, CA 92562	2	1
Jorgensen, Adam, MD Former PI: Khachikian, Stephen, MD	327	Black Hills Regional Eye Institute 2800 Third Street, Rapid City, SD 57701	15	9
Kandavel, Ganesha, MD	351	Colvard-Kandavel Eye Center, 5363 Balboa Blvd., Suite 540, Encino, CA 91316	2	1
Kao, Andrew, MD	313	Empire Eye and Laser Center, 4105 Empire Drive, Bakersfield, CA 93309	31	10
Khatana, Anup, MD	314	Cincinnati Eye Institute 1945 CEI Drive Cincinnati, OH 45242	14	7
Krassin, Jabin, MD	347	South West Eye Care 1200 Chaka Creek Way Suite 110, Chaska, MN 55318	8	8
Kubal, Aarup, MD	315	Your Eye Specialists 2200 N. Commerce Parkway Suite 110, Weston, FL 33326	8	0
Kuzin, Aaron, MD	363	Northwest Eye Surgeons 1306 Roosevelt Ave Mount Vernon, WA 98273	3	3
Lehrer, Richard, MD	317	Ohio Eye Alliance Inc. 985 South Sawburg Avenue, Alliance, OH 44601	9	6
Levenson, Jeffrey, MD	336	Levenson Eye Associates 751 Oak Street, Suite 200, Jacksonville, FL 32204	20	11
Liang, Eva, MD	318	Center for Sight 330 S. Rampart Blvd., Suite 360, Las Vegas, NV 89145	50	27
Lutz, Daniel, MD	353	Eye Care Specialists 703 Rutter Avenue Kingston, PA 18704	7	2
Martinez, Carlos, MD	319	Eye Physicians of Long Beach 2925 Palo Verde Avenue Long Beach, CA 90815	12	6
Mayer, Hylton, MD	320	The Eye Doctors of Washington 2 Wisconsin Circle, Suite 230, Chevy Chase, MD 20815	13	6
Meier, Edward, MD	366	Apex Eye - Mason Location 6150 Radio Way, Mason, OH 45040	4	1

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Millender, Tarra, MD	328	Carolina Eye Associates 2170 Midland Road Southern Pines, NC 28387	2	0
Nattis, Alanna, DO	334	Lindenhurst Eye Physicians and Surgeons 500 W. Main Street, Suite 210, Babylon, NY 11702	18	6
Parkhurst, Gregory, MD	321	Parkhurst-NuVision 9725 Datapoint Dr., Suite 106, San Antonio, TX 78229	87	38
Poulsen, Eric, MD	348	Insight Vision Center 1360 E. Herndon Avenue, Suite 201, Fresno, CA 93720	9	3
Reck, Stephen, MD	322	Clarus Eye Center 345 College Street SE, Suite C, Lacey, WA 98503	4	2
Reish, Eric, MD	349	Louisiana Eye and Laser Center 231 Windermere Blvd., Alexandria, LA 71303	18	13
Reiss, George, MD	323	Eye Physicians and Surgeons of Arizona 6677 W. Thunderbird Road Suite F-101 Glendale, AZ 85306	45 ^c	34 ^c
Reznik, Alena, MD	350	Southern California Eye Institute 1300 North Vermont Avenue Suite 101 Los Angeles, CA 90027	0	0
Rhode, John, MD	324	Illinois Eye Center 8921 N. Wood Sage Road Peoria, IL 61615	19 ^b	12 ^b
Sadri, Ehsan, MD	325	Visionary Eye Institute 361 Hospital Road, Suite 324, Newport Beach, CA 92663	60	22
Sato, Michelle, MD	316	East West Eye Institute 420 E. 3rd Street, Suite 603, Los Angeles, CA 90013	9	5
Sawhney, Gagan, MD	352	GA Eye Partners 1100 Johnson Ferry Road, NE, Bldg 1, Suite 140, Atlanta, GA 30342	7	4
Singh, Inder Paul	329	Eye Center of Racine and Kenosha 3805B Spring Street, Suite 140, Racine, WI 53405	35	16
Stiles, Michael, MD	335	Stiles Eyecare Excellence & Glaucoma Institute 7200 W. 129th Street Overland Park, KS 66213	23	15
Summerfield, Michael, MD	361	Washington Eye Institute 7500 Greenway Drive, Suite 300, Greenbelt, MD 20770	5	1
Tate, Stephen, MD	341	New Vision Eye Center 1055 37th Place Vero Beach, FL 32960	10	7
Taylor, Jeffery, MD	354	The Ophthalmology Group, LLC 4630 Village Square Dr, Paducah, KY 42001	8	6
Tubbs, Carl, MD	331	Insight Vision Group 11960 Lioness Way, Suite 190, Parker, CO 80134	5	1
Whitman, Jeffrey, MD	332	Key-Whitman Eye Center 11442 N. Central Expressway Dallas, TX 75243	11	5
Wilcox, Michael, MD	333	Utah Eye Centers 4360 Washington Blvd., Ogden, UT 84403	20	12
Armenia:				

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Voskanyan, Lilit A, MD, PhD	359	Ophthalmological Center after Malayan CJSC 30 Fuchik St, Yerevan, Armenia 0048	97	50

a 1 subject from Bacharach 302 transferred to Bettis 340

b 1 subject from Gallardo 310 transferred to Barber 311 and 1 subject from Rhode 324 transferred to Barber 311

c 1 subject from Reiss 323 transferred to Bretz 338

Reviewer's Comment(s):

No individual site enrolled a disproportionate number of subjects in either clinical trial.

5.2. Review Strategy

Study GC-009 was a Phase 2 trial conducted in the U.S. and Philippines, and Studies GC-010 and GC-012 were Phase 3 trials conducted in the U.S. and Philippines and in the U.S. and Armenia, respectively.

Study IDOS-106-EXCH “exchange” trial was a prospective, multi-center, non-randomized, open-label, single arm 12-month trial designed to evaluate the safety of the surgical exchange procedure of Travoprost Intraocular Implant after subjects had completed the 36 month follow up in the GC-009 trial.

Studies GC-010 and GC-012 form the basis of review for the IOP-lowering effect of the Travoprost Intraocular Implant based on non-inferiority margins compared to topical Timolol BID. The primary efficacy endpoint was at Month 3 and the secondary efficacy endpoint was at Month 12. Both Phase 3 trials (GC-010 and GC-012) were performed under the same (identical) protocols.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study GC-010 and Study GC-012: Prospective, Randomized Phase 3 Study Comparing Two Models of Travoprost Intraocular Implant to Timolol Maleate Ophthalmic Solution, USP, 0.5%

6.1.1. Study Design

Overview and Objective

To compare the efficacy of intraocular implants containing travoprost at 2 different elution rates versus Timolol Maleate Ophthalmic Solution, USP, 0.5% (timolol) in reducing elevated intraocular pressure (IOP) in subjects with OAG or OHT.

Trial Design

These ongoing 3-year, prospective, randomized, double-masked (subject and observer), active-controlled, parallel-group, multicenter studies compare the efficacy and safety of the Travoprost Intraocular Implant (Models G2-TR-063 and G2-TR-125; referred to as G2TR-063 and G2TR-125 in the protocol) to topical Timolol Maleate Ophthalmic Solution, USP, 0.5% (hereafter referred to as timolol) in subjects with OAG or OHT.

For the Phase 3 trials (GC-010 and GC-012) the protocols were identical, and the primary database lock occurred after all subjects had completed the Month 12 visit or prematurely discontinued prior to that time. Efficacy and safety results are presented based on 12-month data for all 3 trials. The Phase 3 trials are ongoing with the last exam scheduled at Year 3.

Treatment groups:

- G2-TR-063 Implant Group: Travoprost Intraocular Implant, Model G2-TR-063 (b) (4) with 1 drop of masked post-operative placebo eyedrops (i.e., artificial tears) instilled twice daily (BID) in the study eye
- G2-TR-125 Implant Group: Travoprost Intraocular Implant, Model G2-TR-125 (b) (4) with 1 drop of masked post-operative placebo eyedrops instilled BID in the study eye
- Sham/Timolol Group (hereafter referred to as Timolol Group): Sham surgery with 1 drop of masked post-operative topical Timolol Maleate Ophthalmic Solution, USP, 0.5% (hereafter referred to as timolol) instilled BID in the study eye

After meeting eligibility requirements and appropriate washout from IOP-lowering therapy, eligible subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups: surgery to implant a (b) (4) implant followed by placebo eyedrops (G2-TR-063 implant group), surgery to implant a (b) (4) implant followed by placebo eyedrops (G2-TR-125 implant group), or a sham surgical procedure followed by timolol eyedrops (Sham/Timolol group; hereafter referred to as the Timolol group). Following the operative visit, all subjects were instructed to instill 1 drop of masked study medication twice daily (BID) at approximately 8AM and 8 PM in the study eye for 3 years (i.e., until Month 36 [Visit 19]).

Study Outline

		G2-TR-063 (b) (4)	-OR-	G2-TR-125 (b) (4)	Control Treatment Timolol
Study Eye	Surgical procedure	Travoprost Intraocular Implant Model G2-TR-063 (75 µg)		Travoprost Intraocular Implant Model G2-TR-125 (75 µg)	Sham Surgery (using a needle-less syringe)
	Post-operative drops	Masked Placebo (artificial tears ^a) (1 drop BID)		Masked Placebo (artificial tears) (1 drop BID)	Masked Timolol Maleate Ophthalmic Solution, USP, 0.5% (1 drop BID)
Non-study Eye	Standard of care				
• Advanced Eye Relief® Dry Eye Rejuvenation Lubricant Eyedrops (Bausch & Lomb)					

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

In addition, safety results are presented for the IDOS-106-EXCH trial.

Reviewer's comments: *The non-randomized and open-label design of IDOS-106-EXCH trial may limit the interpretation of its results.*

Study Endpoints

The primary endpoint was 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). Non-inferiority of the G2-TR implants to Timolol was established if the upper limit of the 2-sided 95% confidence interval for the difference in the mean of change from baseline in IOP was < 1.5 mmHg at each of the 6 post-baseline timepoints (8AM and 10AM at Day 10, Week 6, and Month 3 visits) and was < 1 mmHg at 3 or more of the 6 post-baseline timepoints.

The secondary efficacy endpoint was the change from baseline in IOP in the study eye at 8AM and 10AM at Month 12. The non-inferiority criteria for success were the same as for the primary endpoint.

Key Inclusion Criteria for GC-010 and GC-012:

Screening	Male or female, ≥ 18 years of age
Screening	Diagnosis of OAG (primary, pseudoexfoliative or pigmentary) or OHT
Screening	If diagnosed with OAG: • C/D ≤ 0.8 • Visual field defects (with MD not worse than -12 dB) or nerve abnormality characteristic of glaucoma (notching, disc hemorrhage, or nerve fiber layer loss)
Screening	On 0 to 2 IOP-lowering medications ^a
Screening	BSCVA of 20/80 or better in each eye
Screening	Open angle (Schaffer grade ≥ 3) with normal anatomy and absence of PAS, rubeosis, or other angle abnormalities
Screening	Pseudophakic with implanted PC IOL fixed in capsular bag or Phakic with no visually significant cataract
Screening	Corneal thickness ≥ 440 µm and ≤ 620 µm

- a Subjects were permitted initially to enter the Phase 3 trials on up to 3 classes of medications; this was revised with Rev 3 of Protocol GC-010 (dated 22-Jan-2019) and Rev 2 of Protocol GC-012 (dated 22 Jan-2019).

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

IOP Entry for Study Eye

Visit		GC-010 and GC-012
Screening	If on no IOP- lowering medication	IOP $\geq$ 21 mmHg and $\leq$ 36 mmHg
	If on IOP-lowering medication	No IOP criterion
Baseline	After medication washout (if on IOP-lowering medication at screening)	Mean diurnal IOP $\geq$ 21 mmHg and IOP at 8AM, 10AM, and 4PM $\leq$ 36 mmHg
	If on no IOP- lowering medication at screening	Mean diurnal IOP $\geq$ 21 mmHg and IOP at 8AM, 10AM, and 4PM $\leq$ 36 mmHg

IOP = intraocular pressure

Note: Mean diurnal IOP based on IOP measurements at 8AM, 10AM and 4PM

Statistical Analysis Plan

Efficacy:

To control the overall type I error at an alpha level of 0.05 for comparing the 2 test arms to timolol, a fixed sequence hierarchical testing procedure was used. The G2-TR-125 implant was first compared to timolol at a 2-sided alpha level of 0.05. The G2-TR-063 implant was then compared to timolol only if the non-inferiority criteria were met for the G2-TR-125 implant versus timolol comparison at a 2-sided alpha level of 0.05.

The primary analysis was performed on the ITT analysis set with the worse-half imputation method to handle missing ICEs at each visit and timepoint separately. In addition, additional IOP-lowering medication was accounted for at the visit level which was the default method. The analysis of covariance (ANCOVA) model with change from baseline in IOP at the given visit (Day 10, Week 6, and Month 3) and timepoint (8AM, 10AM) as the response, treatment as a main effect factor, and time-matched baseline IOP as a covariate was applied for each timepoint of each visit separately. Point estimates and corresponding 95% CI were provided for the difference between the G2-TR implant groups versus the Timolol group. To evaluate the robustness of the primary analysis results, sensitivity analyses of the primary efficacy endpoint were performed, including various imputation methods for missing data.

The key secondary efficacy endpoint (change from baseline in IOP in the study eye at 8AM and 10AM at Month 12), secondary efficacy endpoints, and other efficacy endpoints were evaluated for non-inferiority in the same manner as the primary efficacy endpoint using the ITT analysis set.

Subgroup analyses were performed for the primary efficacy endpoint in the ITT analysis set using the worse-half multiple imputation method. The subgroups were based on age (< 65 vs. $\geq$ 65 years); sex (male vs. female); race (white vs. non-white); type of disease (OAG vs. OHT); mean diurnal IOP at baseline ($\leq$ 25 vs. > 25 mmHg); number of IOP-lowering medication classes at screening (0 or 1 vs. 2 or 3); and pooled center based on geographic region (northeast US, southeast US, west US, midwest US, southwest US, and Philippines).

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Safety:

Safety analyses were based on the safety analysis set. No formal statistical testing was conducted for the safety analyses. Descriptive statistics were performed at each visit for the 3 treatment groups separately.

Protocol Amendments

A Protocol amendment to IND 120995 for the Study “Prospective Randomized Phase 3 Study Comparing Two Models of a Travoprost Intraocular Implant to Timolol Maleate Ophthalmic Solution, USP, 0.5%.” was submitted on May 19, 2022 (Sequence Number 00670).

The protocol was updated to align with the SAP and the primary endpoint that was changed from 3 time points (8 AM, 10 AM, and 4 PM) per visit to 2 time points (8 AM and 10 AM) per visit.

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Exam Schedule for GC-010 and GC-012

Parameter	Screening	Baseline	Operative Day 0	Day 1-2	Day 10, 10 days ± 3	Week 4, 28 days ± 3	Week 6, 42 days ± 5	Month 3, 91 days ± 14	Month 6, 182 days ± 30	Month 9, 274 days ± 30	Month 12, 365 days ± 30	Month 15, 455 days ± 30	Month 18, 547 days ± 30	Month 21, 637 days ± 30	Month 24, 730 days ± 60	Month 27, 820 days ± 60	Month 30, 910 days ± 60	Month 33, 1000 days ± 60	Month 36, 1095 days ± 60
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Informed Consent	x																		
Demographics, Medical/Ocular History	x	x																	
Pregnancy Test (Urine or Serum)		x																	
Concomitant Medication Assessment	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AE Assessment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization and surgical data			x																
Manifest Refraction and BSCVA (Snellen)	x																		
Pinhole VA (Snellen)				x	x														
Corrected VA (ETDRS)						x	x	x	x	x		x	x	x		x	x	x	
Manifest Refraction ^a and BSCVA (ETDRS)		x				x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visual Field ^b	x								x		x		x		x		x		x
Slit Lamp Exam	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Conjunctival Hyperemia		x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Iris Color		x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Specular Microscopy ^c		x						x			x				x				x
Standard IOP ^d	x			x		x			x	x		x	x	x		x	x	x	x
Diurnal IOP ^e		x			x		x				x				x				
Pachymetry (ultrasonic)	x										x				x				x
Gonioscopy	x				x	x	x	x	x		x		x		x		x		x
Dilated Fundus Exam	x										x				x				x
Nerve Abnormality Assessment (Ophthalmoscopy)	x								x	x	x	x	x	x	x	x	x	x	x
Vertical C/D Ratio	x								x		x		x		x		x		x
Dispense Masked Study Medication			x						x	x	x	x	x	x	x	x	x	x	

AE = adverse event, C/D = cup-to-disc, BSCVA = best spectacle corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, IOP = intraocular pressure, VA = visual acuity

a Required if corrected VA (ETDRS) decreased by 2 or more lines (≥ 10 letters) from Visit 2 (baseline) on Visits 6-10, 12-14, and 16-18.

b On diurnal days, visual field was assessed after the 10AM IOP measurement and prior to the 4PM IOP measurement on Visits 11 and 15.

c Specular microscopy was performed only at selected sites.

d Standard IOP was a single measurement taken at either 8AM, 10AM or 4PM (and at screening taken at any time).

e Diurnal IOPs were taken at 8AM, 10AM and 4PM.

6.1.2. Study Results

Compliance with Good Clinical Practices

The clinical studies were conducted in accordance with current standard research approaches regarding the design, conduct, and analysis of the studies.

Subject Disposition

Subjects Withdrawn from Clinical Efficacy Trials GC-010 and GC-012 (All Randomized Subjects)

Number of Subjects, n (%)	Phase 3 GC-010				Phase 3 GC-012			
	G2-TR-063 Implant (N=200)	G2-TR-125 Implant (N=197)	Sham/Timolol (N=193)	Total (N=590)	G2-TR-063 Implant (N=185)	G2-TR-125 Implant (N=183)	Sham/Timolol (N=192)	Total (N=560)
Completed Month 3	196 (98.0)	195 (99.0)	189 (97.9)	580 (98.3)	182 (98.4)	182 (99.5)	190 (99.0)	554 (98.9)
Explanted Prior to Month 3 but Continued in Study	2 (1.0)	1 (0.5)	0	3 (0.5)	2 (1.1)	1 (0.5)	0	3 (0.5)
Discontinued Prior to or at Month 3	2 (1.0)	1 (0.5)	4 (2.1)	7 (1.2)	1 (0.5)	0	2 (1.0)	3 (0.5)
Withdraw Consent	1 (0.5)	0	0	1 (0.2)	1 (0.5)	0	1 (0.5)	2 (0.4)
Investigator Decision	1 (0.5)	0	0	1 (0.2)	0	0	0	0
Lost to follow-up	0	1 (0.5)	0	1 (0.2)	0	0	0	0
Death	0	0	2 (1.0)	2 (0.3)	0	0	0	0
Adverse Event	0	0	2 (1.0)	2 (0.3)	0	0	1 (0.5)	1 (0.2)
Completed Month 12	190 (95.0)	192 (97.5)	183 (94.8)	565 (95.8)	176 (95.1)	180 (98.4)	183 (95.3)	539 (96.3)
Explanted Prior to Month 12 but Continued in Study	2 (1.0)	1 (0.5)	0	3 (0.5)	2 (1.1)	1 (0.5)	0	3 (0.5)
Discontinued Prior to or at Month 12	8 (4.0)	4 (2.0)	10 (5.2)	22 (3.7)	7 (3.8)	2 (1.1)	9 (4.7)	18 (3.2)
Withdraw Consent	4 (2.0)	1 (0.5)	2 (1.0)	7 (1.2)	4 (2.2)	0	1 (0.5)	5 (0.9)
Investigator Decision	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)	1 (0.5)	0	1 (0.5)	2 (0.4)
Lost to follow-up	0	1 (0.5)	1 (0.5)	2 (0.3)	1 (0.5)	1 (0.5)	2 (1.0)	4 (0.7)
Death	1 (0.5)	0	4 (2.1)	5 (0.8)	1 (0.5)	1 (0.5)	2 (1.0)	4 (0.7)
Adverse Event	2 (1.0)	1 (0.5)	2 (1.0)	5 (0.8)	0	0	3 (1.6)	3 (0.5) ^a

Source: GC-009 Table 14.1-1.1; GC-010 Table 14.1-1.1; GC-012 Table 14.1-1.1

^aThe total number of subjects with discontinuations due to adverse events was 6; there were 3 additional subjects not captured due to lack of completed exit forms at the time of database lock: subjects (b) (6).

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Protocol Violations/Deviations

The proportion of subjects with major protocol deviations was 15.5% (87/560) in GC-012 and 17.8% (105/590) in GC-010.

Reviewer's comments: *In GC 010 and GC-012, the most common major protocol deviations were study procedures/assessments not conducted in accordance with the protocol (11.2% [66/590] in GC-010 and 7.9% [44/560] in GC-012) and out-of-window visits (5.4% [32/590] in GC-010 and 4.5% [25/560] in GC-012). No study had a disproportionate percentage of protocol deviations.*

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 (%)			

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

	G2-TR-063 Implant (N=200)	G2-TR-125 Implant (N=197)	Timolol (N=193)
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)
3 ^a	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)
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

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: [Table 14.1-3.2](#)

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

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 (%)	92 (49.7)	100 (54.6)	93 (48.4)
≥18 to < 65 years			
≥ 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 (%)	150 (81.1)	155 (84.7)	162 (84.4)
White			
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 (%)	149 (80.5)	139 (76.0)	155 (80.7)
Open-Angle Glaucoma (OAG)			
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)
3 ^a	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
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			

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

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: [Table 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 Implant (N=200)	G2-TR-125 Implant (N=197)	Sham/ Timolol (N=193)	G2-TR-063 Implant (N=185)	G2-TR-125 Implant (N=183)	Sham/ Timolol (N=192)
Visit, n/N' (%)						
Day 10	1/200 (0.5)	1/197 (0.5)	0	1/184 (0.5)	2/182 (1.1)	0
Week 4	4/197 (2.0)	4/193 (2.1)	4/190 (2.1)	8/178 (4.5)	1/180 (0.6)	3/185 (1.6)
Week 6	6/197 (3.0)	3/192 (1.6)	6/188 (3.2)	9/180 (5.0)	4/179 (2.2)	7/188 (3.7)
Month 3	10/197 (5.1)	8/192 (4.2)	13/187 (7.0)	12/180 (6.7)	8/180 (4.4)	10/189 (5.3)
Month 6	23/194 (11.9)	12/192 (6.3)	19/189 (10.1)	18/180 (10.0)	13/178 (7.3)	12/182 (6.6)
Month 9	37/193 (19.2)	26/190 (13.7)	25/186 (13.4)	29/175 (16.6)	21/179 (11.7)	17/182 (9.3)
Month 12	43/186 (23.1)	36/190 (18.9)	31/182 (17.0)	38/175 (21.7)	32/175 (18.3)	23/177 (13.0)

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.

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Reviewer's Comment:

In GC-010, at Month 12, 18.9% (36/190) of subjects in the G2-TR-125 implant group, 23.1% (43/186) of subjects in the G2-TR-063 implant group, and 17.0% (31/182) of subjects in the Timolol group received an additional IOP-lowering medication.

Similar results were observed in GC-012 in which 18.3% (32/175) of subjects in the G2-TR-125 implant group, 21.7% (38/175) subjects in the G2-TR-063 implant group, and 13.0% (23/177) subjects in the Timolol group received an additional IOP-lowering medication.

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)

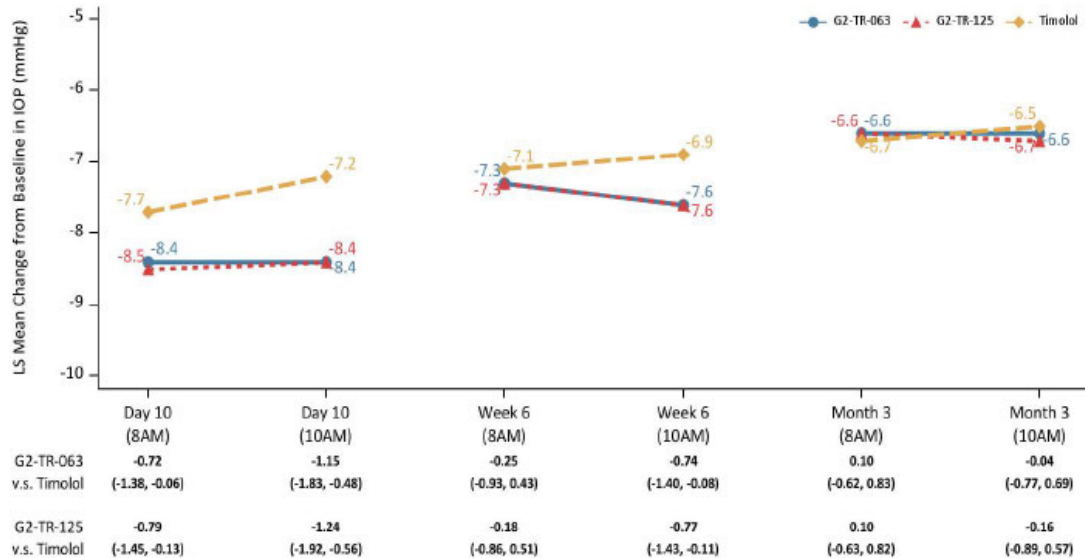
ANCOVA = analysis of covariance, CI = confidence interval, ICE = intercurrent event, IOP = intraocular pressure, ITT = intent-to-treat, LS = least squares, MCMC = Monte Carlo Markov Chain, SD = standard deviation, SE = standard error
^a 95% CI for treatment comparison was based on an ANCOVA model with 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)

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

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: *At Month 3 the magnitude of the change from baseline in IOP (measured at the 8 AM and 10 AM timepoints) in study eyes was consistently greater in the G2-TR implant groups compared with the Timolol group for both timepoints at Day 10 and Week 6, and half of the timepoints at Month 3. 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 LS mean differences in IOP change from baseline at 8AM and 10AM for the G2-TR-125 implant group vs. the Timolol group were -0.79 mmHg and -1.24 mmHg, respectively, at Day 10, -0.18 mmHg and -0.77 mmHg at Week 6, and 0.10 mmHg and -0.16 mmHg at Month 3. For the G2-TR-063 implant group vs. the Timolol group, LS mean differences were -0.72 mmHg and -1.15 mmHg, respectively, at Day 10, -0.25 mmHg and -0.74 mmHg at Week 6, and 0.10 mmHg and -0.04 mmHg at Month 3. 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 < 1.5 mmHg and also < 1 mmHg for all 6 timepoints. Trial GC-010 was successful for both G2-TR implants at Month 3 based on the primary efficacy endpoint.*

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

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 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)	0.78 (0.39)	0.64 (0.39)
		95% CI	(-5.93, -4.80)	(-6.05, -4.96)	(-6.69, -5.60)	(0.01, 1.56)	(-0.12, 1.41)
	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)	0.19 (0.37)	0.48 (0.36)
		95% CI	(-6.33, -5.28)	(-6.02, -5.01)	(-6.50, -5.49)	(-0.54, 0.91)	(-0.23, 1.18)

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

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Reviewer's Comments:

The magnitude of the change from baseline in IOP in study eyes was the same or greater in the Timolol group compared with the G2-TR implant groups at Month 12. At the 8 AM and 10 AM timepoints, respectively, the LS mean IOP changes from baseline were -5.5 and -5.5 mmHg in the G2-TR-125 implant group, -5.4 and -5.8 mmHg in the G2-TR-063 implant group, and -6.2 and -6.0 mmHg in the Timolol group.

The LS mean differences in IOP change from baseline at 8 AM and 10 AM, respectively, were 0.64 mmHg and 0.48 mmHg for the G2-TR-125 implant group vs. the Timolol group, and 0.78 mmHg and 0.19 mmHg for the G2-TR-063 implant group vs. the Timolol group.

The criteria for statistical and clinical non-inferiority to timolol was met for the G2-TR-125, (b) (4) implant as the upper limit of the 95% CI of the difference between the G2-TR-125 implant group and the Timolol group was < 1.5 mmHg at both the 8AM and 10AM timepoints.

In clinical trial GC-010 the non-inferiority to timolol was not met at Month 12 (the secondary efficacy endpoint) for the G2-TR-063, (b) (4), implant, but was met for the G2-TR-125, (b) (4) implant.

Trial GC-010, at Month 12, was successful for only the G2-TR-125, (b) (4), implant.

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)

Visit	Hour	Statistic	G2-TR-063 Implant (N=185)	G2-TR-125 Implant (N=183)	Timolol (N=192)	G2-TR-063 vs. Timolol Difference (95% CI) ^a	G2-TR-125 vs. Timolol 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

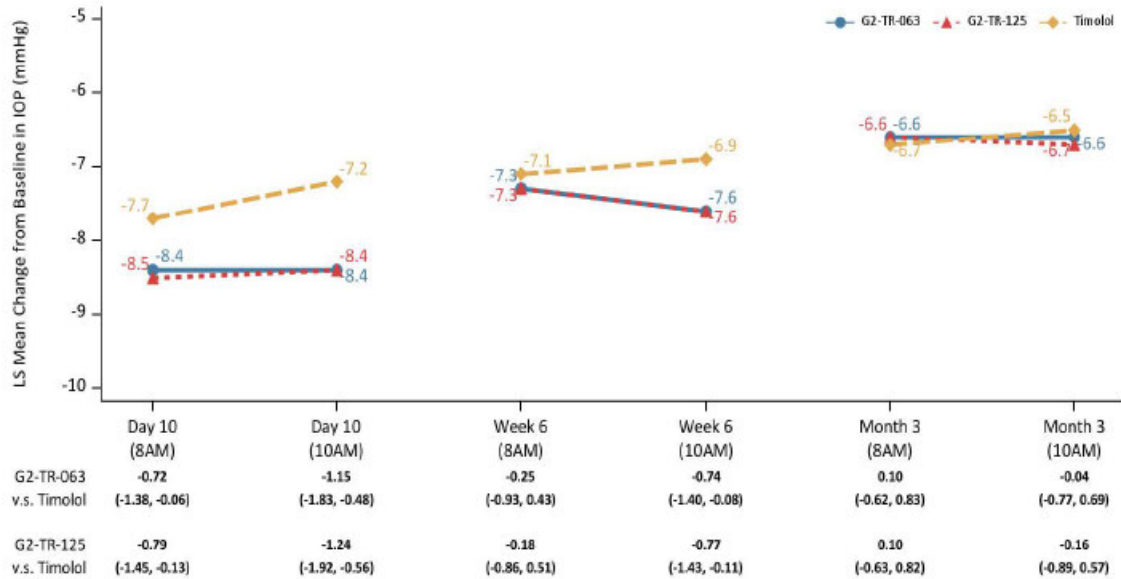
a 95% CI for treatment comparison was based on an ANCOVA model with treatment group as factor and time-matched baseline IOP as covariate at each time point. Note: If a subject was on additional IOP-lowering medication at a specific visit after Day 5 (or the washout window for the medication covered the 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

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

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:

The magnitude of the change from baseline in diurnal IOP (measured at the 8AM and 10AM timepoints) in study eyes was consistently greater in the G2-TR implant groups compared with the Timolol group for both timepoints at Day 10 and Week 6, and half of the timepoints at Month 3 (Table 8; Figure 4). 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 LS mean differences in IOP change from baseline at 8AM and 10AM for the G2-TR-125 implant group vs. the Timolol group were -1.25 mmHg and -1.20 mmHg, respectively, at Day 10, -0.03 mmHg and 0.32 mmHg at Week 6, and 0.16 mmHg and -0.03 mmHg at Month 3. For the G2-TR-063 implant group vs. the Timolol group, LS mean differences were -1.10 mmHg and -1.13 mmHg, respectively, at Day 10, 0.33 mmHg and 0.23 mmHg at Week 6, and 0.53 mmHg and 0.55 mmHg at Month 3.

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 < 1.5 mmHg and also < 1 mmHg for all 6 timepoints. Trial GC-012 was successful for both G2-TR implants at Month 3 based on the primary efficacy endpoint. Trials GC-010 and GC-012 were successful for both G2-TR implants at Month 3 based on the primary efficacy endpoint.

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

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)

Visit	Hour	Statistic	G2-TR-063	G2-TR-125	Timolol	G2-TR-063 vs.	G2-TR-125 vs.
			Implant	Implant		Timolol	Timolol
			(N=185)	(N=183)	(N=192)	Difference (95% CI) ^a	Difference (95% CI) ^a
Month 12	8AM	Mean (SD)	-4.98 (4.34)	-4.86 (4.22)	-6.30 (4.01)	1.31 (0.40)	1.37 (0.39)
		LS Mean (SE)	-4.96 (0.29)	-4.91 (0.29)	-6.28 (0.28)	(0.52, 2.11)	(0.60, 2.13)
		95% CI	(-5.53, -4.39)	(-5.47, -4.35)	(-6.82, -5.73)		
	10AM	Mean (SD)	-5.17 (4.34)	-5.39 (4.29)	-6.47 (4.17)	1.33 (0.40)	1.03 (0.40)
		LS Mean (SE)	-5.13 (0.30)	-5.43 (0.29)	-6.46 (0.28)	(0.54, 2.12)	(0.26, 1.81)
		95% CI	(-5.72, -4.55)	(-5.99, -4.87)	(-7.02, -5.90)		

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

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Reviewer's comments:

The magnitude of the change from baseline in IOP in study eyes was greater in the Timolol group compared with the G2-TR implant groups at Month 12. At the 8AM and 10AM timepoints, respectively, the LS mean IOP changes from baseline were -4.9 and -5.4 mmHg in the G2-TR-125 implant group, -5.0 and -5.1 mmHg in the G2-TR-063 implant group, and -6.3 and -6.5 mmHg in the Timolol group.

The LS mean differences in IOP change from baseline at 8AM and 10AM, respectively, were and 1.37 mmHg and 1.03 mmHg for the G2-TR-125 implant group vs. the Timolol group, and 1.31 mmHg and 1.33 mmHg for the G2-TR-063 implant group vs. the Timolol group.

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

The key secondary efficacy endpoint in Trial GC-012, non-inferiority to timolol at Month 12, failed for both G2-TR implants.

Two adequate and well controlled trials are recommended to support a drug approval to support treatment through Month 12.

Efficacy for the G2-TR implant was demonstrated only through Month 3.

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) (b) (4) at Month 3 based on the primary efficacy endpoint. At Month 12, the secondary efficacy endpoint: clinical trial GC-010, non-inferiority to timolol was not met for the G2-TR-063, (b) (4), implant, for clinical trial GC-012 non-inferiority was not met for either G2-TR implant. (Additionally, refer to the Secondary Efficacy Results in Section 6.1.2)

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

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

7.1.1. Other Endpoints

Change from Baseline in IOP at Months 6 and 9

NOTE: For all analyses of IOP measured at a single timepoint at Months 6 and 9 at 8AM or 10AM or 4PM, the IOP value was time-matched to the corresponding 8AM or 10AM or 4PM IOP value taken at baseline (Day 1).

Trial GC-010 at Months 6 and 9

GC-010 Change from Baseline in IOP (mmHg) at Months 6 and 9 (ANCOVA, Worse-Half Method for Multiple Imputation, Counting Subjects on Additional IOP-lowering Medication Separately at the Visit Level, ITT Analysis Set)

Visit	Statistic	G2-TR-063	G2-TR-125	Timolol	G2-TR-063 vs. Timolol	G2-TR-125 vs. Timolol
		Implant (N=200)	Implant (N=197)	(N=193)	Difference (95% CI) ^a	Difference (95% CI) ^a
Month 6	n	200	197	193		
	Mean (SD)	-5.48 (4.43)	-5.70 (4.16)	-6.07 (4.11)		
	LS Mean (SE)	-5.44 (0.28)	-5.72 (0.27)	-6.09 (0.28)	0.66 (0.39)	0.37 (0.39)
	95% CI	(-5.98, -4.89)	(-6.26, -5.19)	(-6.65, -5.54)	(-0.11, 1.43)	(-0.39, 1.14)
Month 9	n	200	197	193		
	Mean (SD)	-5.54 (4.12)	-5.67 (4.48)	-5.93 (4.30)		
	LS Mean (SE)	-5.56 (0.28)	-5.67 (0.28)	-5.92 (0.30)	0.36 (0.40)	0.25 (0.40)
	95% CI	(-6.12, -5.00)	(-6.21, -5.12)	(-6.50, -5.34)	(-0.43, 1.15)	(-0.53, 1.03)

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

Trial GC-012 at Months 6 and 9

GC-012 Change from Baseline in IOP (mmHg) at Months 6 and 9 (ANCOVA, Worse-Half Method for Multiple Imputation, Counting Subjects on Additional IOP-lowering Medication Separately at the Visit Level, ITT Analysis Set)

Visit	Statistic	G2-TR-063 Implant (N=185)	G2-TR-125 Implant (N=183)	Timolol (N=192)	G2-TR-063 vs. Timolol Difference (95% CI) ^a	G2-TR-125 vs. Timolol Difference (95% CI) ^a
Month 6	n	185	183	192		
	Mean (SD)	-5.21 (4.66)	-5.36 (4.27)	-6.38 (4.10)	1.22 (0.40)	0.90 (0.40)
	LS Mean (SE)	-5.14 (0.29)	-5.46 (0.29)	-6.36 (0.29)	(0.43, 2.01)	(0.11, 1.69)
	95% CI	(-5.71, -4.57)	(-6.02, -4.89)	(-6.92, -5.80)		
Month 9	n	185	183	192		
	Mean (SD)	-4.95 (4.37)	-5.19 (4.09)	-6.32 (4.36)	1.30 (0.41)	1.10 (0.40)
	LS Mean (SE)	-4.98 (0.30)	-5.19 (0.29)	-6.29 (0.28)	(0.50, 2.10)	(0.31, 1.88)
	95% CI	(-5.56, -4.41)	(-5.76, -4.63)	(-6.84, -5.73)		

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 14.2-3.1](#)

Reviewer's Comment(s):

Efficacy was not demonstrated at Months 6 and 9 for either G2-TR implant group.

8. Review of Safety

8.1. Safety Review Approach

The Summary of Clinical Safety provides evidence of the safety of Travoprost Intraocular Implant Model in subjects with OAG or OHT from 3 safety and efficacy trials (GC-009, GC-010, and GC-012). This Summary of Clinical Safety is based on 12-month data for the 3 trials which evaluated 2 models of the Travoprost Intraocular Implant, model G2-TR-063 ((b) (4) implant) and model G2-TR-125 ((b) (4) implant).

For the Phase 2 trial (GC-009), an analysis was performed after all subjects either completed the Month 3 visit or had discontinued prematurely prior to Month 3. In addition, a database lock occurred after all subjects had completed the Month 36 visit or discontinued prematurely prior to that time; for the Phase 3 trials (GC-010 and GC-012), the primary database lock occurred after all subjects had completed the Month 12 visit or prematurely discontinued prior to that time. Safety results also are presented separately for IDOS-106-EXCH.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

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 (21.1) 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)

Extent of Exposure to Study Treatment (days)	1st Implant (N=33)	2nd Implant (N=33)	Overall (N=33)
n			
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

SD = standard deviation

Note: Extent of Exposure to 1st Implant (days) = Date of Exchange Surgery -Date of 1st Operative Surgery + 1.

Extent of Exposure to 2nd Implant (days) = Date of Study Exit -Date of Exchange Surgery + 1.

Overall Extent of Exposure = Date of Study Exit -Date of 1st Operative Surgery + 1.

The date of the 1st Operative Surgery is the surgery date of the 1st implant (G2-TR-063/G2-TR-125) which was inserted in Study GC-009. The date of the Exchange Surgery is the surgery date of the 2nd implant (G2-TR-125) which was inserted in Study IDOS-106-EXCH. The date of study exit is from Study IDOS-106-EXCH.

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).

8.2.2. Adequacy of the safety database:

The safety database is adequate with respect to number of subjects enrolled, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Categorization of Adverse Events

All treatment-emergent adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 English.

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

8.3.2. Routine Clinical Tests

No clinical laboratory evaluations were performed in the Phase 2 or Phase 3 trials. This is justified because the active ingredient, travoprost, has been marketed as an ophthalmic solution that is administered topical ocularly, both as a monotherapy (in the US and ex-US) for greater than 20 years and in fixed combination with timolol (ex-US) for approximately 15 years, and its systemic risks are well established. In addition, plasma exposure to travoprost free acid from the Travoprost Intraocular Implant is below the lower limit of quantitation (10 pg/mL).

8.4. Safety Results

8.4.1. Deaths

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 older, treated patient population.

8.4.2. Serious Adverse Events

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.

8.4.3. Significant Adverse Events

Refer to Section 8.5.1 and Device Dislocations and Corneal Endothelial Cell Loss.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Most Common Study Eye Adverse Events (Occurring in $\geq 1.0\%$ 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 intraocular pressure increased, iritis, dry eye, and visual field defect reported in the following percentage of subjects in the G2-TR-125 implant group, G2-TR-063 implant group, and Timolol group, respectively:

- *Intraocular pressure increased: 4.4% (19/432); 6.7% (29/436); 2.3% (10/435)*
- *Iritis: 5.1% (22/432); 2.5% (11/436); 0% (0/435)*
- *Dry eye: 2.8% (12/432); 3.4% (15/436); 2.3% (10/435)*
- *Visual field defect: 3.0% (13/432); 2.3% (10/436); 1.1% (5/435)*

8.4.6 Laboratory Findings

No clinical laboratory evaluations were performed in the Phase 2 or Phase 3 trials. This is justified because the active ingredient, travoprost, has been marketed as an ophthalmic solution that is administered topically, both as a monotherapy (in the US and ex-US) for greater than 20 years and in fixed combination with timolol (ex-US) for approximately 15 years, and its systemic risks are well established. In addition, plasma exposure to travoprost free acid from the Travoprost Intraocular Implant is below the lower limit of quantitation (10 pg/mL).

8.5. Analysis of Submission-Specific Safety Issues

Specific potential safety issues identified include 1) Corneal Endothelial Cell Loss, 2) Loss of Three lines of Best Spectacle Visual Acuity (BSCVA), 3) Device Dislocations and Corneal Endothelial Cell Loss and 4) Explantations Other Than Device Dislocations

8.5.1. Specific Potential Safety Issues

Corneal Endothelial cell loss data is presented for Studies GC-009, IDOS-106-EXCH, GC-010 and GC-012. Specular microscopy to assess central corneal endothelial cell density (ECD) was performed at Screening, Month 3, and Month 12 in all study subjects in GC-009, and in subjects at selected sites only in GC-010 and GC-012. For study GC-009, subjects were required to exhibit a minimum ECD dependent on lens status (phakic vs. pseudophakic) and age category. For studies GC-010 and GC-012, there were no such eligibility criteria.

Central Corneal Endothelial Cell Density (cells/mm²) -- 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/mm² and -1.92 [5.9] cells/mm² 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 (%)
Any Post-baseline Visits¹			
N	106	97	100
≥ 30% Loss	1 (0.9)	0	0
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 $\geq 30\%$ 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, where endothelial cell density decreased by $< 2\%$ mean change in the Travoprost Intraocular Implant groups versus 0.05% in 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 $\geq 30\%$ 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 $\geq 30\%$ 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).

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

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)	2332.65 (348.03)
	Min, Max	1277.7, 2906.0
Month 36 (Change from GC-009 Baseline)	n	30
	Mean (SD)	-69.59 (102.75)
	Min, Max	-342.3, 151.0
Baseline Pre-Exchange (Change from GC-009 Baseline)	n	33
	Mean (SD)	-105.30 (120.28)
	Min, Max	-350.3, 286.8
Month 3 Post-Exchange (Change from GC-009 Baseline)	n	33
	Mean (SD)	-145.69 (101.39)
	Min, Max	-406.5, 45.7
Month 12 Post-Exchange (Change from GC-009 Baseline)	n	32
	Mean (SD)	-153.72 (136.34)
	Min, Max	-548.7, 184.8

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	17	G2-TR-063	Severe
GC-010		394	397	G2-TR-063	Mild
GC-010		356	364	G2-TR-063	Mild
GC-010		380	385	G2-TR-063	Mild
GC-010		364	436	G2-TR-063	Moderate
GC-010		473	476	G2-TR-063	Severe
GC-010		360	365	G2-TR-125	Severe
GC-010		10	498	G2-TR-125	Mild
GC-010		950	968	G2-TR-125	Mild
GC-012		39	39	G2-TR-063	Moderate
GC-012		549	553	G2-TR-063	Moderate
GC-012		366	372	G2-TR-125	Moderate
GC-012		55	57	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	43	299	Eye disorders/ Uveitis	G2-TR- 125	Severe
GC-010		44	155	245	Eye disorders/ Iritis	G2-TR- 125	Mild
GC-010		8	42	405	Eye disorders/ Uveitis	G2-TR- 063	Mild
GC-012		24	78	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:

Only 1 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/mm² post-explantation. Pre-explantation specular microscopy images for that eye were not gradable.

Subject (b) (6) ECD has varied from 895 cells/mm² at Week 4, to 1404 cells/mm² at Month 6 to 1095 cells/mm² at Month 12. All other study eyes ECD post-explantation remained relatively stable.

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 data in the study and non-study eye were not collected at Baseline which may limit the interpretation of endothelial cell loss when the device dislocation occurred.

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 (1.0)	4 (1.0)	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)	2 (0.5)
Month 9	n	418	421	417
	Decrease of ≥ 15 letters	5 (1.2)	4 (1.0)	1 (0.2)
Month 12	n	411	415	408
	Decrease of ≥ 15 letters	3 (0.7)	6 (1.4)	1 (0.2)
Overall	n	435	431	432
(Worst Change)¹	Decrease of ≥ 15 letters	14 (3.2)	13 (3.0)	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% or less observed in the Sham/Timolol group at each visit.

8.6. Safety Analyses by Demographic Subgroups

No overall clinical differences in safety have been observed between elderly and other adult subjects in subgroup analyses of adverse events or ocular assessments related to safety.

8.7. Specific Safety Studies/Clinical Trials

No overall clinical differences in safety have been observed as a function of gender, race, ethnicity, and other baseline disease factors (i.e., OAG vs. OHT; baseline mean IOP $\leq$ 25 mmHg vs. $>$ 25 mmHg; number of IOP-lowering medications at Screening = 0 or 1 vs. 2 or 3) in subgroup analyses of adverse events or ocular assessments related to safety.

8.8. Additional Safety Explorations

8.8.1. Human Reproduction and Pregnancy

Subjects who were pregnant or planning to become pregnant during the course of the clinical trials were excluded from participation. In addition, a pregnancy test was performed at the baseline visit to confirm that the subject was not pregnant at the time of surgery.

8.8.2. Pediatrics and Assessment of Effects on Growth

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.

8.9. Safety in the Postmarket Setting

Not applicable; the Travoprost Intraocular Implant has not been marketed in any country.

8.10. 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 $\geq$ 30% reduction in endothelial cell density in the Travoprost Intraocular Implant groups; the Agency considers a corneal endothelial cell loss of $\geq$ 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 $\geq$ 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/mm² 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 $\geq 3\%$ of Subjects

The most common adverse events occurring in $\geq 3\%$ of subjects in any treatment group were intraocular pressure increased, iritis, dry eye, and visual field defect reported in the following percentage of subjects in the G2-TR-125 implant group, G2-TR-063 implant group, and Timolol group, respectively:

- Intraocular pressure increased: 4.4% (19/432); 6.7% (29/436); 2.3% (10/435)
- Iritis: 5.1% (22/432); 2.5% (11/436); 0% (0/435)
- Dry eye: 2.8% (12/432); 3.4% (15/436); 2.3% (10/435)
- Visual field defect: 3.0% (13/432); 2.3% (10/436); 1.1% (5/435)

9. Advisory Committee Meeting and Other External Consultations

There were no issues raised during the review of this application that were thought to benefit from an Advisory Committee meeting.

10. Labeling Recommendations

See CDTL memo for final labeling.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategies are recommended.

12. Postmarketing Requirements and Commitments

None.

13. Appendices

120-Day Safety Update

The 120-day Safety Update Report was submitted June 14, 2023. There has been no new safety information affecting the risks associated with the Travoprost Intraocular Implant based on the analysis of additional long-term safety information (i.e., safety data of approximately 12 months from the ongoing trials GC 010 and GC 012) that warrants a change to the Contraindications, Warnings and Precautions or Adverse Reactions sections of the proposed Prescribing Information.

Month 24 endothelial cell density (ECD) data are now available for 12, 12, and 8 subjects in the G2-TR-063, G2-TR-125, and Sham/Timolol treatment groups in GC-010, and for 11, 9, and 11 subjects in the G2-TR-063, G2-TR-125, and Sham/Timolol treatment groups in GC-012.

Reviewer's Comments:

Given the sensitivity of endothelial cell loss as a safety parameter and the endothelial cell loss demonstrated through Month 12 in clinical trials GC-010 and GC-012; the change from baseline and % change from baseline in ECD values for GC-010 and GC-012 are presented at Month 24 in the following table.

GC-010 and GC-012 Central Endothelial Cell Density (cells/mm²) – Change from Baseline and Percent Change from Baseline by Visit for Study Eye (Safety Analysis Set [Endothelial Cell Subset])

	GC-010			GC-012		
Visit	G2-TR-063 Implant (N = 26)	G2-TR-125 Implant (N = 20)	Timolol (N = 20)	G2-TR-063 Implant (N = 29)	G2-TR-125 Implant (N = 25)	Timolol (N = 33)
Baseline						
n	26	20	20	29	25	33
Mean	2231 (493)	2404 (472)	2445 (282)	2490 (308)	2493 (350)	2432 (402)
Min, Max	1207,2990	1533,3076	1800,3091	1631,3200	1729,3040	1541,3028
Month 3, CFB						
N	26	20	18	29	24	31
Mean	-49 (94)	-42 (83)	-29 (126)	-31 (117)	-55 (106)	11 (70)
Min, Max	-270.5, 71.9	-261.0, 113.3	-428.5, 113.5	-531.5, 92.5	-339.6, 61.2	-122.5, 161.5
Month 3, % CFB						
N	26	20	18	29	24	31
Mean (SD)	-2.69 (5.78)	-1.93 (4.37)	-0.96 (5.04)	-1.34 (4.84)	-2.06 (3.81)	0.48 (2.99)
Min, Max	-22.4, 5.0	-17.0, 4.5	-16.5, 5.3	-22.0, 3.3	-12.6, 2.2	-4.9, 7.9
Month 12, CFB						
N	24	20	18	28	23	30
Mean (SD)	-56 (131)	-54 (98)	41 (66)	-65 (115)	-79 (123)	9 (124)
Min, Max	-417, 173	-288, 107	-102, 143	-564, 41	-359, 65	-148, 517

Visit	GC-010			GC-012		
	G2-TR-063 Implant (N = 26)	G2-TR-125 Implant (N = 20)	Timolol (N = 20)	G2-TR-063 Implant (N = 29)	G2-TR-125 Implant (N = 25)	Timolol (N = 33)
Month 12, % CFB						
N	24	20	18	28	23	30
Mean (SD)	-3.29 (8.40)	-2.65 (5.12)	1.73 (2.92)	-2.79 (4.94)	-3.07 (4.81)	0.45 (5.42)
Min, Max	-34.5, 7.2	-18.8, 3.7	-4.4, 7.1	-23.3, 1.6	-14.6, 3.0	-7.2, 22.0
Month 24, CFB						
N	12	12	8	11	9	11
Mean (SD)	-149 (187)	-121 (94)	3 (87)	-126 (192)	-158 (144)	-11 (107)
Min, Max	-631,-8	-317,-2	-152,97	-671,17	-499,-29	-121,241
Month 24, % CFB						
N	12	12	8	11	9	11
Mean (SD)	-8.67 (14.6)	-5.92 (5.6)	0.06 (3.5)	-5.01 (8.0)	-6.09 (5.3)	-0.08 (5.4)
Min, Max	-52.2, -0.4	-20.6, -0.1	-6.1, 3.7	-27.8, 0.7	-18.6, -1.2	-5.3, 11.9

Source: 120-Day Safety Update, Table 7. GC-010 Table 14.3-10.1 and GC-010 14.3-10.2; GC-012 Table 14.3-10.1 and GC-012 14.3-10.2

CFB = change from baseline; Min = minimum; Max = maximum; SD = standard deviation

In GC-010 for those subjects for whom Month 24 data are available, the mean change from baseline in central ECD was -121.31 cells/mm² (-5.9%) in the G2-TR-125 implant group (n=12) and -148.56 cells/mm² (-8.7%) in the G2-TR-063 implant group (n=12). The change from baseline in the Sham/Timolol group (n=8) was 3.01 cells/mm², corresponding to $< 1\%$ change from the mean baseline measured values.

In GC-012 for those subjects for whom Month 24 data are available, the mean change from baseline in central ECD was -157.57 cells/mm² (-6.1%) in the G2-TR-125 implant group (n=9) and -125.60 cells/mm² (-5.0%) in the G2-TR-063 implant group (n=11). The change from baseline in the Sham/Timolol group (n=11) was -11.41 cells/mm², corresponding to $< 1\%$ change from the mean baseline measured values.

Reviewer's Comments:

In both trials the control group had $< 1\%$ change from the mean baseline measured values of endothelial cell loss, while in the treatment groups loss ranged from -5.0% (n=11) to -8.7% (n=12). The sample size is small, but at Month 24 greater endothelial loss continued in the treatment groups compared to the control group.

Given this additional data, approval continues to be recommended for iDose TR (G2-TR-125 (b) (4) implant). The 120 Day Safety Update Data continues to support single use only with subsequent removal of the implant at Month 3 or more of iDose TR (G2-TR-125, (b) (4) implant).

13.1. 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: <u>96</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>15</u>		
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: <u>0</u> Significant payments of other sorts: <u>2 (Stock options 50K)</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator: <u> </u> Sponsor of covered study: <u>0</u>		
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) <u> </u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 2: 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.

Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

(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.
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Clinical Review of NDA 218010

Martin P. Nevitt, M.D., M.P.H.

iDose TR (travoprost intraocular implant), 75 µg

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.

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RHEA A LLOYD
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Placed into DARRTS for Martin Nevitt, MD.

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