CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 218010
Supplement #:	Not applicable (Original-1)
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Indication:	Reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
Applicant:	Glaukos Corporation
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Keywords: double-masked, elevated intraocular pressure, analysis of covariance, noninferiority

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1 EXECUTIVE SUMMARY

The Applicant has developed the Travoprost Intraocular Implants which are designed to release travoprost slowly within eyes for reduction of elevated intraocular pressure (IOP). Two implant models haven been investigated: Model G2-TR-063 (b) (4) and Model G2-TR-125 (b) (4). The Applicant seeks approval of Model G2-TR-125 (iDose® TR) for reduction of elevated IOP in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

The application includes 1-year data of two ongoing 3-year phase 3 trials: GC-010 and GC-012. Study GC-010 and Study CG-012 have almost identical designs. They are multicenter, randomized, double-masked, active-controlled, noninferiority (NI) trials. While Study GC-010 was conducted in the U.S. (92.9%) and Philippines (7.1%), Study GC-012 was conducted in the U.S. (91.1%) and Armenia (8.9%). Both studies compare the efficacy and safety of Models G2-TR-063 and G2-TR-125 to topical Timolol Maleate ophthalmic solution in subjects with OAG or OHT. In each study, eligible subjects were randomized to one of the following three treatment groups:

- G2-TR-063: surgical implant of Model G2-TR-063 followed by placebo eyedrops (1 drop twice daily)
- G2-TR-125: surgical implant of Model G2-TR-125 followed by placebo eyedrops (1 drop twice daily)
- Sham/Timolol: sham surgical procedure followed by Timolol eyedrops (1 drop twice daily)

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

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

Table 1 summarizes the primary analysis results of the primary and key secondary efficacy endpoints. In each study, both G2-TR-063 and G2-TR-125 implant models met the prespecified NI criterion for the primary efficacy endpoint. However, the NI criterion for the key secondary endpoint was met only for the G2-TR-125 group in Study GC-012. The treatment differences (GR-TR implant minus Timolol) in the estimated mean IOP change from baseline ranged from -1.2 to -0.7 mmHg at Day 10, -0.8 to 0.3 mmHg at Week 6, -0.2 to 0.6 mmHg at Month 3, and 0.2 to 1.4 mmHg at Month 12.

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

Table 1: Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, Month 3, and Month 12 (All Randomized Subjects)

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

Abbreviations: ITT = SD = standard deviation, SE = standard error, CI = confidence interval

Source: Table 11 of the SCE. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.

Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

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

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

in the Timolol group. As presented in Table 1, the estimated mean IOP reductions from baseline at Month 12 were also greater in the Timolol group compared with those in the G2-TR implant groups

Regarding safety, the proportion of subjects with adverse events (AEs) was higher in the G2-TR implant groups compared with that in the Timolol group: 49.0% (G2-TR-063), 54.4% (G2-TR-125), and 38.7% (Timolol) in Study GC-010 and 49.2% (G2-TR-063), 44.3% (G2-TR-125), and 38.0% (Timolol) in Study GC-012. The majority of the AEs were mild or moderate. The most commonly reported ocular AE in the study eye in the G2-TR-125 group was iritis. The proportion of subjects with iritis in the G2-TR-125 group was higher than that in the Timolol group: 6.2% vs. 0% in Study GC-010 and 5.1% vs. 0% in Study GC-012. The reviewer defers to the medical reviewer for a comprehensive safety evaluation and for acceptability of the safety profile of G2-TR-125.

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

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Glaucoma is a progressive eye disease characterized by irreversible damage to the optic nerve. It is a leading cause of blindness in the United States. One of the primary risk factors for progression of glaucoma to blindness is elevated intraocular pressure (IOP). Thus, the reduction and control of elevated IOP is one of the main focuses in the treatment of open-angle glaucoma (OAG) and ocular hypertension (OHT).

There are multiple ophthalmic drug products approved for lowering IOP in patients with OAG and OHT. These drug products include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, prostaglandin analogs, and Rho kinase inhibitors.

Travoprost, a prostaglandin analog, is the active ingredient in Travatan®, Travatan Z®, and Izba™ which are topical ophthalmic solutions for the reduction of elevated IOP in patients with OAG or OHT. Multiple generic formulations of travoprost ophthalmic solutions have also been approved.

The Applicant has developed the Travoprost Intraocular Implant, which is a sterile, drug-eluting implant designed to release travoprost slowly within eyes. The Travoprost Intraocular Implant is surgically delivered through a clear corneal incision and anchored in the anterior chamber angle of the eye. The Applicant has evaluated two versions of the implant, Model G2-TR-063 and Model G2-TR-125. Both models have the same formulation comprising of 75 µg of travoprost drug substance. Model G2-TR-063 has (b) (4) while Model G2-TR-125 has (b) (4). The Applicant expects that the Travoprost Intraocular Implant can deliver and maintain more consistent levels of IOP-lowering medication within the eye than currently available topical IOP-lowering treatments.

The Applicant seeks approval of Model G2-TR-125. Model G2-TR-125 is referred to as iDose® TR in the application.

2.1.2 History of Drug Development

Under IND 120995, the Applicant completed a phase 2 study, Study GC-009. At the Type B End-of-Phase (EOP) 2 meeting held on 12/04/2017, the Agency agreed that the clinical data from the phase 2 study provides sufficient support for an expanded investigation of the travoprost implants G2-TR-063 and G2-TR-125 in phase 3 trials. At the meeting, the initial proposal for the design and analysis methods of phase 3 trials was discussed. See the Meeting Minutes for details.

The Applicant currently conducts two similarly designed phase 3 trials: GC-010 and GC-012. The initial protocol and statistical analysis plan (SAP) of Study GC-010 were submitted on

02/02/2018 and reviewed by Dr. Yunfan Deng. The proposed primary efficacy analysis in the SAP was considered acceptable if the number of intercurrent events (IEs) is minimal. Otherwise, Dr. Deng recommended a trimmed mean analysis. See her statistical review for details.

A Type C meeting was held on 06/07/2021 to discuss the ongoing phase 3 trials. At the meeting, the sponsor asked whether the Agency agree that the primary efficacy analyses for the phase 3 studies may be based on either (1) 8AM and 10AM at Day 10, Week 6, and Month 3 visits (a total of 6 timepoints) or (2) 8AM, 10AM, and 4PM at Day 10, Week 6, and Month 3 visits (a total of 9 timepoints as specified in the initial protocol and SAP). The Agency agreed with the proposal (see Question 20a in the Meeting Minutes). Regarding handling of IEs, the Applicant's proposal relying on worse half of subjects was considered acceptable on the condition that the number of subjects with IEs is minimal and balanced between the treatment groups. Otherwise, the Agency recommended a trimmed mean analysis (see Question 20e in the Meeting Minutes). For additional details, see the statistical review by Dr. Solomon Chefo.

A Type B pre-NDA meeting was held on 05/09/2022 to discuss the contents and structure of their planned NDA submission. In the pre-NDA meeting package, the primary efficacy endpoint was defined as "Change from baseline in diurnal IOP in the study eye at 8AM and 10AM at each of Day 10, Week 6, and Month 3 visits (**6 timepoints**)". Regarding the timepoint options (8AM and 10AM vs. 8AM, 10AM, 4PM) for the primary endpoint, the following was the meeting discussion (see Question 1a in the Meeting Minutes):

Meeting Discussion: With respect to the primary endpoint including 6 vs 9 timepoints, the Agency commented that the primary efficacy endpoint should have been determined prior to the start of the study. **The Agency stated that the Sponsor may use 6 or 9 timepoints, but those timepoints need to be selected as soon as possible.**

Source: Meeting discussion under Question 1a in the meeting minutes issued on 05/18/2022.

For additional details of the statistical issues discussed at the pre-NDA meeting, see the statistical review by Dr. Solomon Chefo.

A follow-up pre-NDA meeting was held on 11/29/2022 to further discuss the clinical and statistical portions of the Applicant's planned NDA submission. In general, the Applicant's plan was considered acceptable for submission. The Agency stated that approvability will be a review issue. See the Meeting Minutes for details.

Reviewer Comments:

1. *It appears that no one from the statistical team attended the follow-up pre-NDA meeting held on 11/29/2022. No statistical review of this meeting was found in DARRTS.*
2. *For Study GC-010, the final protocol (Revision # 5 dated 06/06/22) and final SAP (Version 2.0 dated 06/09/2022) were submitted to the Agency on 06/09/2022. For Study GC-012, the final protocol (Revision # 4 dated 07/26/2022) and final SAP (Version 1.0 dated 07/27/2022) were submitted to the Agency on 07/28/2022. In the final protocols and SAPs, the timepoints for the primary efficacy endpoint are specified as 8AM and 10AM at each of Day 10, Week 6, and Month 3 visits (6 timepoints), which is consistent*

with the definition in the pre-NDA meeting package. Note: No statistical reviews of the final protocols and SAPs were found in DARRTS.

3. *The database lock occurred after the finalization of the protocol and SAP. The database lock occurred on 06/10/2022 for Study GC-010 and on 08/12/2022 for Study GC-012.*
4. *Given that the protocols and SAPs were finalized prior to the database lock and the Agency allowed 6 timepoints for the primary endpoint at the pre-NDA meeting on 05/09/2022 ("the Sponsor may use 6 or 9 timepoints"), the reviewer finds the 6 timepoints for the primary endpoint in the final protocols and SAPs acceptable.*

2.1.3 Specific Studies Reviewed

The clinical development program of the Travoprost Intraocular Implant includes the following four studies:

- Study GC-009 (n=270): Phase 2 efficacy and safety study
- Study GC-010 (n=590): Phase 3 efficacy and safety study
- Study GC-012 (n=560): Phase 3 efficacy and safety study
- Study US IDOS-106-EXCH (n=33): Phase 2 safety of the exchange of a Travoprost implant

This statistical review primarily focuses on the two phase 3 studies, Study GC-010 and Study GC-012, which could serve as two adequate and well-controlled trials. A summary of the two studies is presented in Table 2. For a brief summary of the efficacy results from Study GC-009, see Appendix G of this review.

Table 2: Summary of specific studies reviewed

Study ID	**GC-010**	**GC-012**
Design	3-year, randomized, double-masked, active-controlled, noninferiority (NI) study; the submission includes only the first 12-month data, and the studies are ongoing.	
Site	44 sites in the U.S. and 1 site in Philippines	49 sites in the U.S. and 1 site in Armenia
Treatment [1]**/ Sample Size**	G2-TR-063 Implant / 200 G2-TR-125 Implant / 197 Timolol / 193	G2-TR-063 group / 185 G2-TR-125 group / 183 Timolol / 192
Primary Endpoint	Change from baseline [2] in IOP in the study eye at 8AM and 10AM at each of Day 10, Week 6, and Month 3 visits (6 timepoints)	
Key Secondary	Change from baseline in IOP in the study eye at 8AM and 10AM at Month 12 visit	
Study Population	- 18 years of age or older with OAG or OHT - 0 to 2 topical IOP-lowering medications at the time of Screening - 21 mmHg ≤ IOP ≤ 36 mmHg - Best spectacle corrected visual acuity of 20/80 or better - 440 microns ≤ central corneal thickness ≤ 620 microns	

[1] Subjects in the implant groups (G2-TR-063 and G2-TR-125) receive 1 drop of post-operative placebo eyedrops (i.e., artificial tears) twice daily in the study eye. Subjects in the timolol group receive sham surgery followed by 1 drop of post-operative topical Timolol Maleate Ophthalmic Solution 0.5% twice daily in the study eye.
[2] Baseline IOP for 8AM (10AM) is the IOP measure at 8AM (10AM) at the baseline visit.
Source: Reviewer's summary based on the clinical study reports.

2.2 Data Sources

The data sources for this review include protocols, statistical analysis plans (SAPs), clinical study reports (CSRs), the summary of clinical efficacy (SCE), the summary of clinical safety (SCS), and the datasets for the respective studies. The following are the links to the key documents:

- Study GC-010: Protocol, SAP, CSR
- Study GC-012: Protocol, SAP, CSR
- Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS)
- Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS)

In case that the links do not work, the key documents can be found at the following location: \\CDSESUB1\evsprod\NDA218010\0001

The datasets were submitted in the formats of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) in electronic submission. The datasets can be found at the following locations which also include the SAS programming codes used for the CSRs:

- Study GC-010: \\CDSESUB1\evsprod\NDA218010\0001\m5\datasets\gc-010; \\CDSESUB1\evsprod\NDA218010\0004\m5\datasets\gc-010
- Study GC-012: \\CDSESUB1\evsprod\NDA218010\0001\m5\datasets\gc-012

Reviewer Note: The primary efficacy analysis dataset 'ADIOPIMP.xpt' for Study GC-010 was inadvertently not provided in the original NDA submission (eCTD-0001). As a response to our information request regarding this issue, the Applicant submitted this dataset as an amendment (eCTD-0004).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No issues were identified regarding the quality and integrity of the submitted SDTM and ADaM datasets. The datasets were well organized. The Applicant's primary efficacy results were reproduced by the reviewer with minor data manipulation. In general, using SDTM and ADaM datasets, the reviewer was able to conduct the necessary analyses without complex manipulations.

3.2 Evaluation of Efficacy

This section evaluates the efficacy results of Studies GC-010 and GC-012.

3.2.1 Study Design and Endpoints

Studies GC-010 and Study CG-012 have the identical design in terms of the eligibility criteria, study visits, assessments, endpoints, and analysis approaches. Study GC-010 was conducted in the U.S. (92.9%) and Philippines (7.1%) while GC-012 was conducted in the U.S. (91.1%) and Armenia (8.9%).

Both studies are ongoing, 3-year, randomized, double-masked (subject and observer), active-controlled, noninferiority (NI) studies that compare the efficacy and safety of the Travoprost Intraocular Implants (Models G2-TR-063 and G2-TR-125) to topical Timolol Maleate Ophthalmic Solution, USP, 0.5% in subjects with OAG or OHT. In each study, eligible subjects were randomized (1:1:1) to one of the following three treatment groups:

- G2-TR-063: surgical implant of Model G2-TR-063 followed by placebo eyedrops
- G2-TR-125: surgical implant of Model G2-TR-125 followed by placebo eyedrops
- Sham/Timolol: sham surgical procedure followed by Timolol eyedrops

Following the operative visit (implant or sham surgical procedure), all subjects were instructed to instill 1 drop of study medication (placebo or Timolol) twice daily (BID) at approximately 8AM and 8PM in the study eye for 3 years.

Both studies consist of 19 visits over a 3-year period. The screening phase consisted of Visit 1 (screening) and Visit 2 (baseline). The treatment phase consists of Visits 3 (operative Day 0), 4 (Day 1-2), 5 (Day 10), 6 (Week 4), 7 (Week 6), 8 (Month 3), and every three months afterward: Visit 9 (Month 6) to Visit 19 (Month 36).

The protocol-defined primary efficacy endpoint is “change from baseline in IOP in the study eye at 8AM and 10AM at each of Day 10, Week 6, and Month 3 visits (6 timepoints)”. The protocol-defined key secondary endpoint is “change from baseline in IOP in the study eye at 8AM and 10AM at Month 12”.

Other secondary endpoints in the SAP include the following:

- Change from baseline in IOP in the study eye at Months 6 and 9.
- IOP in the study eye at each timepoint through Month 12 for each post-baseline visit.
- % Change from baseline in IOP in the study eye at each timepoint through Month 12 for each post-baseline visit.
- Proportion of subjects achieving at least 20%, 25%, 30%, 35%, or 40% reduction from baseline in study eye IOP for each post-baseline visit and timepoint through Month 12.
- Proportion of subjects achieving study eye IOP reduction of at least 2, 4, 6, 8, 10, or 12 mmHg from baseline for each post-baseline visit and timepoint for each post-baseline visit and timepoint through Month 12.
- Proportion of subjects achieving study eye IOP of at most 24, 22, 20, 18, 16, or 14 mmHg at each post-baseline visit and timepoint through Month 12.

- Proportion of subjects who received rescue medications by visit.
- Number of rescue medication classes by visit.
- Time to the first rescue medication use.

3.2.2 Statistical Methodologies

This section primarily focuses on describing statistical methodologies for analyzing the primary and key secondary efficacy endpoints.

Primary estimand

The following is the description of the primary estimand in the SAP:

1. Population: ITT population including all randomized subjects. Subjects with open-angle glaucoma or ocular hypertension defined through enrollment criteria. A key aspect of eligibility is that subjects must have mean diurnal IOP $\geq$ 21 mm Hg and $\leq$ 36 mm Hg at the baseline visit.
2. Variable (endpoint): Change from baseline in IOP at 8AM and 10AM at each of Day 10, Week 6, and Month 3 visits (6 timepoints).
3. Intercurrent events: the following categories are potential intercurrent events for this study, which could be related to study treatment and require an adjustment to the imputation strategy for the efficacy analyses:
    - Premature discontinuation from the study due to adverse event or lack of efficacy
    - Taking rescue medication for the study eye
    - Having concurrent procedure for the study eye post-baseline
    - In the investigational treatment groups:
        - Failure to implant device
        - Failure to implant device in the correct ocular region
        - Explant of investigational product
4. Population-level summary parameter: difference in mean change from baseline IOP between treatment groups for evaluating of non-inferiority.

Source: Section 2.1 of the SAPs for Studies GC-010 and GC-012

Reviewer Comments:

1. *The description of the primary estimand in the SAP is incomplete as it does not describe how to handle the intercurrent events (IEs) in the primary estimand.*
2. *Compared to the estimand in the draft SAP in the pre-NDA meeting package, the following IEs were added to the estimand in the final SAP:*

    - In the investigational treatment groups:
        - Failure to implant device
        - Failure to implant device in the correct ocular region
        - Explant of investigational product

    Note that these additional IEs (related to implant procedure) only apply to the investigational treatment groups. However, the reviewer has no major concern about this given the following:

- *In the planned approach for handling IEs, outcomes of subjects with IEs are treated as bad outcomes (see the next subsection of this review). Thus, inclusion of such IEs (related to implant procedure) only in the investigational treatment groups is not likely to favor the investigational treatment groups.*
- *The number of patients with such IEs related to implant procedure is minimal:*
  - *Study GC-010: only 1 patient in the G2-TR-063 group had "failure to implant". The number of patients with "explant of investigational product" was 7 in the G2-TR-063 group and 3 in the G2-TR-125 group. However, all of them were due to adverse events (AEs) and they were considered as the premature treatment discontinuation due to AEs in terms of IE category.*
  - *Study GC-012: No subject had "failure to implant" or "failure to implant device in the correct ocular region". The number of patients with "explant of investigational product" was 2 in the G2-TR-063 group and 2 in the G2-TR-125 group. However, all of them were due to adverse events (AEs) and they were considered as the premature treatment discontinuation due to AEs in terms of IE category.*

Testing procedure for primary and key secondary endpoints

Per the SAPs, the primary and key secondary endpoints are sequentially tested in the following order:

1. Testing NI of G2-TR-125 to Timolol for the primary efficacy endpoint
2. Testing NI of G2-TR-063 to Timolol for the primary efficacy endpoint
3. Testing NI of G2-TR-125 to Timolol for the key secondary efficacy endpoint
4. Testing NI of G2-TR-063 to Timolol for the key secondary efficacy endpoint

The SAP-defined criteria for NI are as follows:

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

Reviewer Notes:

1. *The Agency agreed with the NI criterion for the primary efficacy endpoint (see Question 20b in the Meeting Minutes of the Type C meeting held on 06/07/2021). However, the reviewer was not able to find any agreement from the Agency with the NI criterion for the key secondary endpoint.*
2. *The NI margin of 1.5 mmHg (for all 6 timepoints) and the NI margin of 1 mmHg (for half or more of the 6 timepoints) are clinical NI margins. The reviewer is not aware of data to statistically support these NI margins. For NI or equivalence trials for IOP reduction, the*

Division of Ophthalmology has accepted an NI margin of 1.5 mmHg to be met at all time points and 1.0 mmHg to be met at the majority of time points.

Primary analysis method for primary and key secondary endpoints

The SAP-defined primary analysis method is an analysis of covariance (ANCOVA) model including treatment and time-matched baseline IOP as a covariate. The ANCOVA model is fitted for each timepoint separately.

Handling of intercurrent events

The primary method for handling intercurrent events and missing data is referred to as the "Worse-Half" method in the SAP. The following are excerpts from the SAP regarding this method:

- **Worse-Half Method**

1) For subjects who have missing IOP but no intercurrent events after treatment administration, we will assume the missing data are Missing At Random (MAR), i.e., the dropout reasons are unrelated to treatment. Multiple Imputation (MI) techniques (Monte Carlo Markov Chain [MCMC]) will be used to impute the missing data from the randomized treatment group. Each timepoint within each visit will be modeled separately. The variables to be included in the imputation model: treatment group, timepoint-matched baseline IOP value, and IOP measure. The sample SAS code is as the following for each timepoint at each visit:

proc mi data = *in1* seed = 813951 out = *out1*;
mcmc initial = em;
var *trt01pn baseline aval*;
run;

where

-*in1* is the input dataset
-*out1* is the output dataset
-*trt01pn* is the treatment group variable in numeric format
-*baseline* is the baseline IOP for the given timepoint
-*aval* is the IOP measure

2) Intercurrent events after treatment administration include dropout due to AE or lack of efficacy, taking rescue medications or having a concurrent procedure in the study eye, etc. As the dropout reason may be related to treatment, we will handle this kind of missing data as Missing Not At Random (MNAR). Missing data for each treatment and timepoint will be imputed using the MI MCMC method on the worse half of subjects. For each treatment group and timepoint the worse half of subjects will be those subjects having IOP reductions from baseline that are less than the median IOP reduction for that treatment group and timepoint. The MI MCMC model will be similar to 1) described above, with seed = 906197.

3) The following are the detailed steps:

For each timepoint at each visit:

- Step 1: Create Dataset 1: For Subjects with IOP data that are MAR, impute missing data with MI – MCMC including all subjects without intercurrent events, 50 imputed datasets will be generated with seed = 813951. (Dataset 1)
- Step 2: Set IOP values to missing for subjects with an intercurrent event at the visit.
- Step 3: Determine the median change from baseline for subjects with non-missing IOP values by treatment group. Keep the worse half of the subjects (i.e., subjects with IOP reductions from baseline that are less than the median value).
- Step 4: Create Dataset 2: For subjects with intercurrent events, impute the missing data with MI – MCMC using the worse half of the subjects, 50 imputed datasets will be generated with seed = 906197. (Dataset 2)
- Step 5: Combine the two datasets together, perform the statistical test to the combined data.
- Step 6: Use SAS procedure proc mianalyze to get the final parameter estimates.

Worse-half method will be the primary approach for analysis of primary and secondary efficacy endpoints.

Source: Section 6.1.3 of the SAPs

Reviewer Comments:

1. *The Agency agreed with the multiple imputation (MI) approach #1 for imputing purely missing values (but no IEs). See Question 20d in the Meeting Minutes of the Type C meeting held on 06/07/2021.*
2. *Regarding the approach #2 above (handling of intercurrent events relying on the worse half of subjects), the Agency considered it acceptable on the condition that "the number of subjects with intercurrent events (IEs) are minimal and balanced between the treatment groups". If the number of subjects with IEs are more than minimal and/or unbalanced, the Agency recommended a trimmed mean analysis. See Question 20e in the Meeting Minutes of the Type C meeting held on 06/07/2021.*
3. *Section 6.1.3 of the SAPs defines a trimmed mean analysis as a sensitivity analysis. The SAPs prespecify the proportion of data that will be trimmed, which depends on the rate of subjects with IEs or missing values. See Appendix C of this review for details.*
4. *In the reviewer's understanding, the target primary estimand appears to be close to an estimand using a composite strategy that assigns bad outcomes for subjects with IEs using the worse half of subjects. The reviewer finds the primary estimand acceptable given the following:*
    a. *The number of subjects with IEs is well-balanced across the treatment groups (see Table 7 of this review).*

b. The results of the primary estimand are consistent with those of multiple supportive analyses. See below for description of the supportive analyses.

Supportive analyses

The SAPs specify the following supportive analyses:

1. ANCOVA on per-protocol set: this is the same as the primary efficacy analysis except that the analysis set is the per-protocol set.
2. ANCOVA with accounting for rescue medication at the study level: this is the same as the primary efficacy analysis except handling of rescue medication. In this supportive analysis, visits after the first use of rescue medications are considered as visits with intercurrent events. Consequently, data collected after the first use of rescue mediations are discarded. Of note, in the primary analysis, whether or not on rescue medication is determined separately for each visit.
3. A trimmed mean analysis (see Appendix C for details)
4. ANCOVA on observed data: the primary ANCOVA model is performed on the observed data with no imputation of missing data and no special handling of IEs.
5. ANCOVA with LOCF: the primary ANCOVA model is performed with the last observation carried forward (LOCF) for imputing missing data and no special handling of IEs
6. A tipping point analysis (see Appendix F for details)

3.2.3 Subject Disposition, Demographic, and Baseline Characteristics

Subject disposition and primary reasons for study discontinuation are summarized in Table 3. Seven subjects (1%) in Study GC-010 and 3 subjects (<1%) in Study GC-012 discontinued the study prior to or at Month 3. In Study GC-010, two subjects in the Timolol group died prior to Month 3 due to cardiopulmonary arrest (on Day 10) and COVID-19 (on Day 22). In Study GC-012, no subjects died prior to Month 3 in Study GC-012.

Table 3: Subject Disposition (ITT Population), n (%)

	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
Discontinued prior to or at Month 3						
Yes	2 (1.0)	1 (<1)	4 (2.1)	1 (<1)	0	2 (1.0)
No	198 (99.0)	196 (99.5)	189 (97.9)	184 (99.5)	183 (100.0)	190 (99.0)
Discontinuation reason						
Withdrawal [1]	1 (<1)	0	0	1 (<1)	0	1 (<1)
Adverse Event	0	0	2 (1.0)	0	0	1 (<1)
Death	0	0	2 (1.0)	0	0	0
Investigator [2]	1 (<1)	0	0	0	0	0
Lost to Follow-Up	0	1 (<1)	0	0	0	0
Discontinued prior to						

or at Month 12						
Yes	8 (4.0)	4 (2.0)	10 (5.2)	7 (3.8)	2 (1.1)	9 (4.7)
No	192 (96.0)	193 (98.0)	183 (94.8)	178 (96.2)	181 (98.9)	183 (95.3)
Discontinuation reason						
Withdrawal [1]	4 (2.0)	1 (<1)	2 (1.0)	4 (2.2)	0	1 (<1)
Adverse Event	2 (1.0)	1 (<1)	2 (1.0)	0	0	3 (1.6)
Death	1 (<1)	0	4 (2.1)	1 (<1)	1 (<1)	2 (1.0)
Investigator [2]	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)
Lost to Follow-Up	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (1.0)

Abbreviations: ITT = intention-to-treat population

[1] Withdrawal = Consent Withdrawal; [2] Investigator = Investigator Decision

Source: Table 7 of the CSR for each study. Reproduced by the reviewer based on the dataset adsl.xpt;

Baseline demographic characteristics are summarized in Table 4. In general, the demographic characteristics were well balanced across the treatment groups in both studies. The mean age was 63.6 years in GC-010 and 63.0 years in GC-012. In both studies, the proportions of males and females were similar. The majority of subjects were enrolled in the U.S. (92.9% in GC-010 and 91.1% in GC-012). The majority of subjects were of White race (66.3% in GC-010 and 83.4% in GC-012). The majority of subjects were not of Hispanic or Latino ethnicity (93.2% in GC-010 and 82.7% in GC-012).

Table 4: Baseline Demographics (ITT Population)

	Phase 3 GC-010			**Phase 3 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**
Age, years						
Mean	63.8	63.2	63.8	63.1	61.9	63.9
SD	11.52	12.61	11.39	11.81	12.79	12.08
Median	64.0	66.0	65.0	65.0	63.0	65.0
Min, Max	22.0, 86.0	24.0, 89.0	28.0, 94.0	29.0, 87.0	22.0, 88.0	21.0, 86.0
Age Group, n (%)						
18 to < 65	102 (51.0)	91 (46.2)	93 (48.2)	92 (49.7)	100 (54.6)	93 (48.4)
>= 65	98 (49.0)	106 (53.8)	100 (51.8)	93 (50.3)	83 (45.4)	99 (51.6)
Sex, n (%)						
Female	109 (54.5)	99 (50.3)	108 (56.0)	88 (47.6)	88 (48.1)	105 (54.7)
Male	91 (45.5)	98 (49.7)	85 (44.0)	97 (52.4)	95 (51.9)	87 (45.3)
Race, n (%) [1]						
White	143 (71.5)	120 (60.9)	128 (66.3)	150 (81.1)	155 (84.7)	162 (84.4)
Black	38 (19.0)	50 (25.4)	41 (21.2)	26 (14.1)	22 (12.0)	20 (10.4)
Asian	15 (7.5)	19 (9.6)	16 (8.3)	1 (<1)	2 (1.1)	2 (1.0)
Indian	0	0	2 (1.0)	3 (1.6)	2 (1.1)	2 (1.0)
Hawaiian	1 (<1)	0	0	0	0	0
Multi-Racial	0	0	0	1 (<1)	0	1 (<1)
Unknown	0	1 (<1)	1 (<1)	4 (2.2)	2 (1.1)	5 (2.6)
Other	3 (1.5)	7 (3.6)	5 (2.6)	0	0	0
Ethnicity, n (%) [2]						
Not Hispanic	191 (95.5)	179 (90.9)	180 (93.3)	153 (82.7)	157 (85.8)	153 (79.7)
Hispanic	9 (4.5)	15 (7.6)	10 (5.2)	30 (16.2)	25 (13.7)	39 (20.3)
Unknown	0	3 (1.5)	3 (1.6)	2 (1.1)	1 (<1)	0
Region, n (%)						

U.S.	186 (93.0)	183 (92.9)	179 (92.7)	168 (90.8)	167 (91.3)	175 (91.1)
Philippines	14 (7.0)	14 (7.1)	14 (7.3)	0	0	0
Armenia	0	0	0	17 (9.2)	16 (8.7)	17 (8.9)

Abbreviations: ITT = intention-to-treat population, SD = standard deviation

[1] Black = Black or African American, Indian = American Indian or Alaska Native, Hawaiian = Native Hawaiian or Other Pacific Islander

[2] Not Hispanic = Not Hispanic or Latino, Hispanic = Hispanic or Latino

Source: Table 9 of the CSR for each study. Reproduced by the reviewer based on the dataset adsl.xpt;

Baseline disease and ocular characteristics are summarized in Table 5. In general, the disease type (OAG or OHT) and mean diurnal IOP were well balanced across the treatment groups in both studies. The majority of the study eyes had OAG (86.8% in GC-010 79.1% in GC-012). The mean baseline diurnal IOP was 24.11 mmHg in GC-010 and 24.27 mmHg in GC-012. The majority of subjects had brown iris (57.1% in GC-010 55.71% in GC-012).

Table 5: Baseline Disease and Ocular Characteristics for Study Eye (ITT Population)

	Phase 3 GC-010			**Phase 3 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**
Disease Type						
OAG	175 (87.5)	170 (86.3)	167 (86.5)	149 (80.5)	139 (76.0)	155 (80.7)
OHT	25 (12.5)	27 (13.7)	26 (13.5)	36 (19.5)	44 (24.0)	37 (19.3)
Mean Diurnal IOP						
Mean	24.2	24.0	24.1	24.4	24.1	24.3
SD	2.78	2.81	2.68	3.21	2.81	2.99
Median	23.3	23.3	23.5	23.5	23.3	23.5
Min, Max	21.0, 33.0	21.0, 33.7	21.0, 34.7	21.0, 36.0	21.0, 34.7	21.0, 35.2
Mean Diurnal IOP, n (%)						
≤ 25 mmHg	141 (70.5)	141 (71.6)	138 (71.5)	129 (69.7)	135 (73.8)	133 (69.3)
> 25 mmHg	59 (29.5)	56 (28.4)	55 (28.5)	56 (30.3)	48 (26.2)	59 (30.7)
Iris Color, n (%)						
Blue	57 (28.5)	41 (20.8)	55 (28.5)	40 (21.6)	48 (26.2)	51 (26.6)
Brown	109 (54.5)	122 (61.9)	106 (54.9)	102 (55.1)	100 (54.6)	110 (57.3)
Green	7 (3.5)	7 (3.6)	7 (3.6)	6 (3.2)	9 (4.9)	9 (4.7)
Hazel	26 (13.0)	27 (13.7)	25 (13.0)	35 (18.9)	25 (13.7)	21 (10.9)
Other	1 (<1)	0	0	2 (1.1)	1 (<1)	1 (<1)

Abbreviations: ITT = intention-to-treat population, OAG = open-angle glaucoma, OHT = ocular hypertension, SD = standard deviation

Source: Table 10 of the CSR for each study. This table was produced by the reviewer based on the adsl.xpt dataset.

3.2.4 Results and Conclusions

Section 3.2.4.1 provides efficacy results for the primary and key secondary efficacy endpoints. Section 3.2.4.2 presents the efficacy results for change from baseline in IOP at Months 6 and 9. The reviewer's efficacy conclusion is provided in Section 3.2.4.3.

3.2.4.1 Change from Baseline in IOP at Day 10, Week 6, Month 3, and Month 12

Primary Analysis

Table 6 presents the primary analysis results of the primary and key secondary endpoints. In each study, both G2-TR-063 and G2-TR-125 groups met the NI criterion for the primary efficacy endpoint (i.e., the upper limit of 95% CI for the treatment difference is < 1.5 mmHg for all 6 timepoints and < 1 mmHg for at least half of the 6 timepoints). For the key secondary endpoint (change from baseline at Month 12), only G2-TR-125 in Study GC-010 met the prespecified NI criterion (i.e., the upper limit of 95% CI for the treatment difference is < 1.5 for both 8am and 10am). In Study GC-012, both G2-TR-063 and G2-TR-125 groups failed to meet the prespecified NI criteria.

Table 6: Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, Month 3, and Month 12 (ITT Population, Worse-Half Method for Handling Intercurrent Events and Missing Data)

	GC-010			GC-012		
	G2-TR-063	**G2-TR-125**	**Timolol**	**G2-TR-063**	**G2-TR-125**	**Timolol**
Baseline IOP						
8AM						
N	200	197	193	185	183	192
Mean (SD)	24.7 (3.4)	24.4 (3.2)	24.7 (3.5)	24.7 (4.0)	24.6 (3.5)	24.7 (3.7)
Min, Max	17.0, 35.0	17.0, 36.0	17.0, 35.0	17.5, 38.0	16.0, 36.0	16.5, 37.5
10AM						
N	200	197	193	185	183	192
Mean (SD)	24.3 (3.3)	24.1 (3.3)	24.0 (3.1)	24.3 (3.6)	24.1 (3.2)	24.2 (3.3)
Min, Max	19.0, 34.0	19.0, 35.5	17.5, 34.0	17.0, 38.5	18.5, 35.0	18.0, 35.5
Change from Baseline						
Day 10 8AM						
N	200	197	192	184	182	190
Mean (SD)	-8.5 (4.1)	-8.4 (4.1)	-7.8 (3.6)	-8.4 (4.7)	-8.6 (4.3)	-7.2 (4.0)
Min, Max	-23.0, 2.5	-21.0, 9.0	-19.5, 1.0	-20.5, 2.5	-20.0, 4.0	-17.5, 5.0
LS mean (SE)	-8.4 (0.2)	-8.5 (0.2)	-7.7 (0.2)	-8.3 (0.3)	-8.4 (0.3)	-7.2 (0.3)
Difference (CI)	**-0.7 (-1.4, -0.1)**	**-0.8 (-1.5, -0.1)**		**-1.1 (-1.8, -0.4)**	**-1.2 (-2.0, -0.5)**	
Day 10 10AM						
N	200	197	192	184	182	190
Mean (SD)	-8.5 (4.0)	-8.5 (4.4)	-7.1 (3.5)	-8.3 (3.9)	-8.5 (4.0)	-7.1 (3.8)
Min, Max	-20.0, 4.5	-19.5, 11.0	-18.0, 1.5	-19.0, 3.5	-20.5, 0.0	-17.0, 4.0
LS mean (SE)	-8.4 (0.2)	-8.4 (0.2)	-7.2 (0.2)	-8.2 (0.2)	-8.3 (0.2)	-7.1 (0.2)
Difference (CI)	**-1.2 (-1.8, -0.5)**	**-1.2 (-1.9, -0.6)**		**-1.1 (-1.8, -0.4)**	**-1.2 (-1.9, -0.5)**	
Week 6 8AM						
N	196	191	187	180	179	187
Mean (SD)	-7.4 (4.0)	-7.2 (4.0)	-7.3 (3.9)	-7.1 (4.7)	-7.3 (4.3)	-7.3 (4.0)
Min, Max	-24.0, 5.5	-17.5, 7.5	-19.0, 2.0	-20.5, 6.5	-19.0, 5.0	-19.5, 4.5
LS mean (SE)	-7.3 (0.2)	-7.3 (0.2)	-7.1 (0.2)	-6.8 (0.3)	-7.2 (0.3)	-7.2 (0.3)
Difference (CI)	**-0.3 (-0.9, 0.4)**	**-0.2 (-0.9, 0.5)**		**0.3 (-0.4, 1.1)**	**-0.0 (-0.8, 0.7)**	
Week 6 10AM						
N	197	192	187	180	178	188
Mean (SD)	-7.7 (4.0)	-7.7 (3.9)	-7.0 (3.7)	-7.3 (4.3)	-7.0 (4.3)	-7.3 (3.8)
Min, Max	-20.5, 14.0	-18.0, 4.5	-18.0, 3.0	-18.0, 9.5	-19.5, 5.0	-18.0, 1.5
LS mean (SE)	-7.6 (0.2)	-7.6 (0.2)	-6.9 (0.2)	-6.9 (0.3)	-6.8 (0.3)	-7.2 (0.2)
Difference (CI)	**-0.7 (-1.4, -0.1)**	**-0.8 (-1.4, -0.1)**		**0.2 (-0.5, 0.9)**	**0.3 (-0.4, 1.0)**	
Month 3 8AM						
N	197	191	187	180	180	188
Mean (SD)	-6.9 (3.9)	-6.6 (4.2)	-7.0 (4.0)	-6.7 (4.5)	-6.8 (4.4)	-7.2 (4.2)
Min, Max	-19.5, 5.5	-15.0, 16.0	-20.5, 3.5	-19.0, 4.0	-19.5, 3.0	-20.5, 5.0
LS mean (SE)	-6.6 (0.3)	-6.6 (0.3)	-6.7 (0.3)	-6.3 (0.3)	-6.7 (0.3)	-6.8 (0.3)

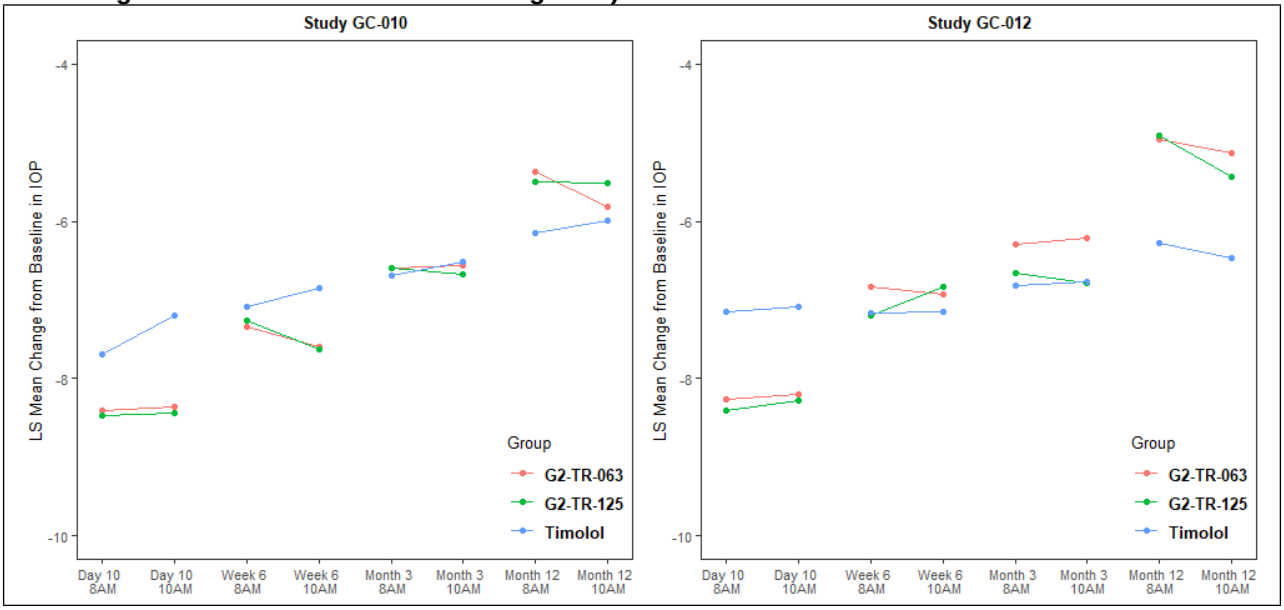
	GC-010			GC-012		
	G2-TR-063	**G2-TR-125**	**Timolol**	**G2-TR-063**	**G2-TR-125**	**Timolol**
Difference (CI)	**0.1 (-0.6, 0.8)**	**0.1 (-0.6, 0.8)**		**0.5 (-0.2, 1.3)**	**0.2 (-0.6, 0.9)**	
Month 3 10AM						
N	197	191	187	180	180	188
Mean (SD)	-6.9 (3.9)	-6.8 (4.1)	-6.9 (3.8)	-6.5 (4.2)	-7.0 (4.1)	-7.1 (4.2)
Min, Max	-18.5, 4.5	-18.0, 13.5	-18.5, 8.0	-19.0, 7.0	-19.5, 4.0	-19.0, 2.5
LS mean (SE)	-6.6 (0.3)	-6.7 (0.3)	-6.5 (0.3)	-6.2 (0.3)	-6.8 (0.3)	-6.8 (0.3)
Difference (CI)	**-0.0 (-0.8, 0.7)**	**-0.2 (-0.9, 0.6)**		**0.6 (-0.2, 1.3)**	**-0.0 (-0.8, 0.7)**	
Month 12 8AM						
N	186	190	182	175	175	176
Mean (SD)	-5.7 (4.3)	-5.5 (4.2)	-7.0 (4.0)	-5.9 (4.4)	-5.3 (4.4)	-6.8 (4.1)
Min, Max	-18.0, 10.0	-14.0, 7.0	-20.0, 2.5	-20.5, 2.5	-20.5, 6.0	-24.5, 2.5
LS mean (SE)	-5.4 (0.3)	-5.5 (0.3)	-6.1 (0.3)	-5.0 (0.3)	-4.9 (0.3)	-6.3 (0.3)
Difference (CI)	**0.8 (0.0, 1.6)**	**0.6 (-0.1, 1.4)**		**1.3 (0.5, 2.1)**	**1.4 (0.6, 2.1)**	
Month 12 10AM						
N	186	190	182	175	175	177
Mean (SD)	-6.2 (4.1)	-5.8 (4.0)	-6.7 (3.7)	-5.9 (4.3)	-5.7 (4.3)	-6.8 (4.1)
Min, Max	-19.0, 11.0	-15.0, 4.0	-20.5, 0.5	-21.5, 8.0	-19.0, 5.0	-22.5, 6.0
LS mean (SE)	-5.8 (0.3)	-5.5 (0.3)	-6.0 (0.3)	-5.1 (0.3)	-5.4 (0.3)	-6.5 (0.3)
Difference (CI)	**0.2 (-0.5, 0.9)**	**0.5 (-0.2, 1.2)**		**1.3 (0.5, 2.1)**	**1.0 (0.3, 1.8)**	

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

Figure 1 depicts the estimated mean change from baseline in IOP over time. At Day 10, the estimated mean IOP reduction was numerically greater in both G2-TR-063 (red line) and G2-TR-125 (green line) groups compared to that in the Timolol group (blue line) in both studies. At Month 3 in Study GC-10, the mean IOP reduction was similar across the three treatment groups. At Month 3 in Study GC-12, the mean IOP reduction was smaller in the G2-TR-063 (red line) compared to that in the G2-TR-125 (green line) and Timolol (blue line) groups. At Month 12, both G2-TR-063 (red line) and G2-TR-125 (green line) groups showed numerically smaller IOP reduction compared to that in the Timolol group (blue line) in both studies.

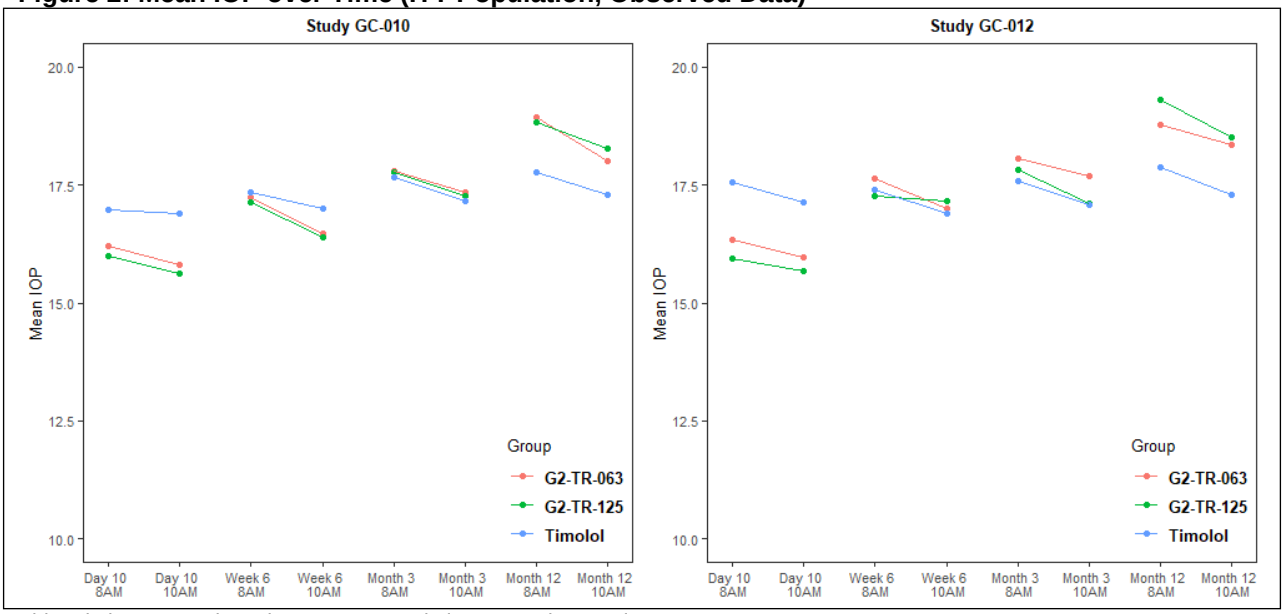
Figure 2 depicts the observed mean IOP over time by treatment group. The mean IOP at each time point is the sample mean of the observed data with no imputation and no special handling of IEs. The overall pattern in the mean IOP is similar to that in the mean change from baseline in IOP in Figure 1. At Day 10, the mean IOP in both G2-TR-063 (red line) and G2-TR-125 (green line) groups were lower than that in the Timolol group (blue line). At Week 6 and Month 3, the mean IOP becomes similar across the 3 treatment groups. At Month 12, both G2-TR-063 (red line) and G2-TR-125 (green line) groups showed higher mean IOP compared to that in the Timolol group (blue line) in both studies.

Figure 1: LS Mean Change from Baseline in IOP over Time (ITT Population, Worse-Half Method for Handling Intercurrent Events and Missing Data)



Abbreviations: ITT = intention-to-treat population, IOP = intraocular pressure
Source: Figure 1 of the SCE. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.
Note: LS mean changes were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

Figure 2: Mean IOP over Time (ITT Population, Observed Data)



Abbreviations: ITT = intention-to-treat population, IOP = intraocular pressure
Source: This table was produced by the reviewer using the dataset adiopimp.xpt for each study.
Note: LS mean changes were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

Table 7 presents the number of imputed IOP values in the primary efficacy analysis. The proportion of imputed IOP values ranges from 1% to 5% at Day 10, 4% to 11% at Week 6, 8% to 12% at Month 3, and 21% to 30% at Month 12. The rows of “Missing”, “Rescue Med”, and

"Other IEs" in the table present the number of imputed IOP values due to missing, use of rescue IOP-lowering medications, and other intercurrent events, respectively. The majority of imputations were due to use of rescue IOP-lowering medications: 0% to 1% at Day 10, 2% to 5% at Week 6, 4 to 7% at Month 3, and 16% to 22% at Month 12.

Table 7: Number of Imputed IOP Values in Primary Efficacy Analysis

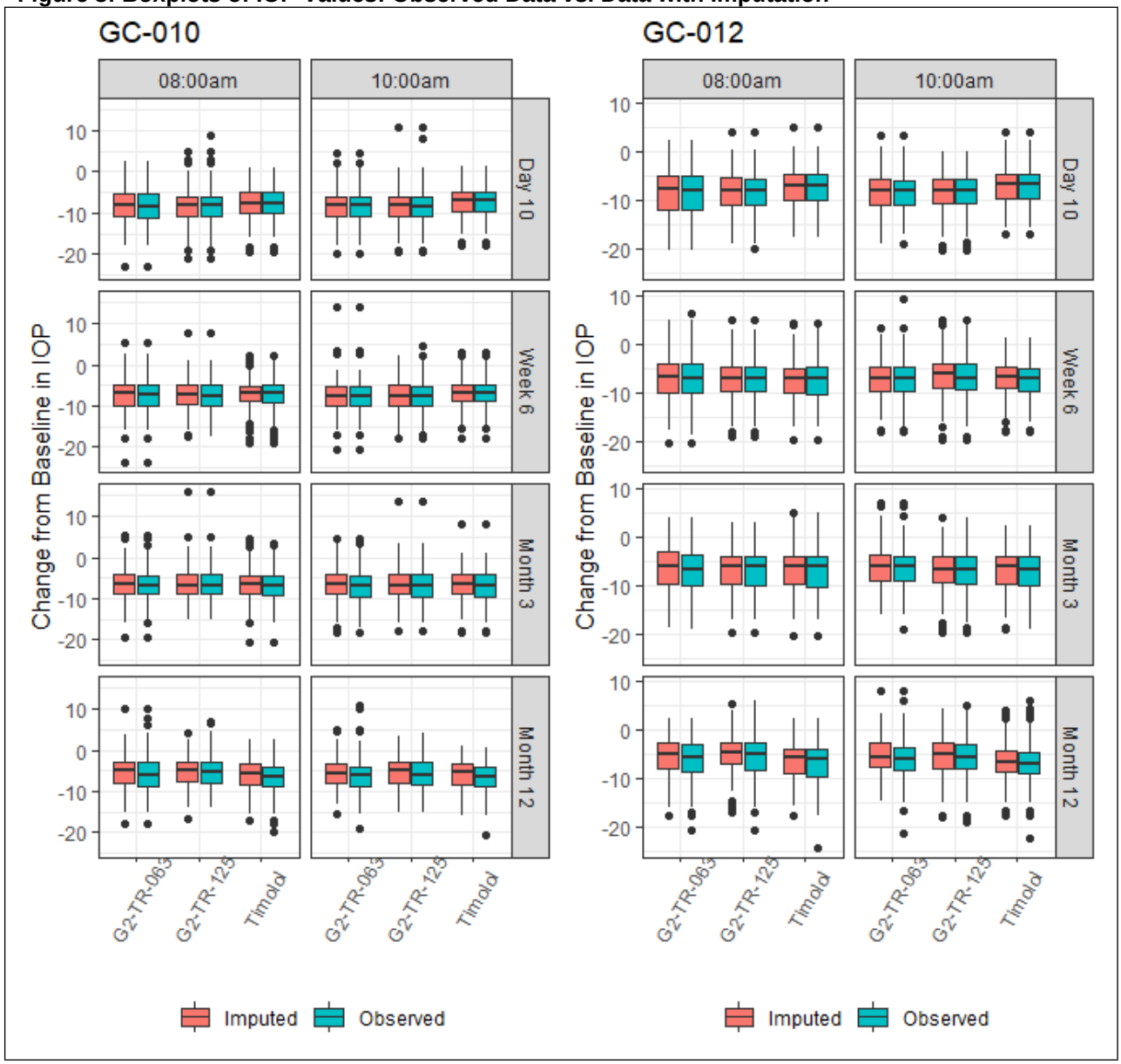
	GC-010			GC-012		
	G2-TR-063 N=200	G2-TR-125 N=197	Timolol N=193	G2-TR-063 N=185	G2-TR-125 N=183	Timolol N=192
Day 10 8AM						
Not Imputed	197 (98.5)	193 (98.0)	192 (99.5)	178 (96.2)	175 (95.6)	190 (99.0)
Missing	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Rescue Med	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)
Other IEs	2 (1.0)	3 (1.5)	0 (0.0)	5 (2.7)	5 (2.7)	0 (0.0)
Day 10 10AM						
Not Imputed	197 (98.5)	193 (98.0)	192 (99.5)	178 (96.2)	175 (95.6)	190 (99.0)
Missing	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Rescue Med	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)
Other IEs	2 (1.0)	3 (1.5)	0 (0.0)	5 (2.7)	5 (2.7)	0 (0.0)
Week 6 8AM						
Not Imputed	188 (94.0)	184 (93.4)	180 (93.3)	165 (89.2)	169 (92.3)	180 (93.8)
Missing	2 (1.0)	4 (2.0)	5 (2.6)	5 (2.7)	4 (2.2)	4 (2.1)
Rescue Med	6 (3.0)	3 (1.5)	6 (3.1)	9 (4.9)	4 (2.2)	7 (3.6)
Other IEs	2 (1.0)	4 (2.0)	1 (0.5)	6 (3.2)	6 (3.3)	0 (0.0)
Week 6 10AM						
Not Imputed	189 (94.5)	185 (93.9)	181 (93.8)	165 (89.2)	168 (91.8)	181 (94.3)
Missing	1 (0.5)	3 (1.5)	4 (2.1)	5 (2.7)	5 (2.7)	3 (1.6)
Rescue Med	6 (3.0)	3 (1.5)	6 (3.1)	9 (4.9)	4 (2.2)	7 (3.6)
Other IEs	2 (1.0)	4 (2.0)	1 (0.5)	6 (3.2)	6 (3.3)	0 (0.0)
Month 3 8AM						
Not Imputed	184 (92.0)	180 (91.4)	174 (90.2)	163 (88.1)	167 (91.3)	177 (92.2)
Missing	0 (0.0)	4 (2.0)	4 (2.1)	3 (1.6)	2 (1.1)	3 (1.6)
Rescue Med	10 (5.0)	8 (4.1)	13 (6.7)	12 (6.5)	8 (4.4)	10 (5.2)
Other IEs	3 (1.5)	3 (1.5)	0 (0.0)	5 (2.7)	5 (2.7)	1 (0.5)
Month 3 10AM						
Not Imputed	184 (92.0)	180 (91.4)	174 (90.2)	163 (88.1)	167 (91.3)	177 (92.2)
Missing	0 (0.0)	4 (2.0)	4 (2.1)	3 (1.6)	2 (1.1)	3 (1.6)
Rescue Med	10 (5.0)	8 (4.1)	13 (6.7)	12 (6.5)	8 (4.4)	10 (5.2)
Other IEs	3 (1.5)	3 (1.5)	0 (0.0)	5 (2.7)	5 (2.7)	1 (0.5)
Month 12 8AM						
Not Imputed	140 (70.0)	148 (75.1)	148 (76.7)	131 (70.8)	136 (74.3)	151 (78.6)
Missing	9 (4.5)	3 (1.5)	9 (4.7)	7 (3.8)	7 (3.8)	12 (6.2)
Rescue Med	43 (21.5)	36 (18.3)	31 (16.1)	38 (20.5)	32 (17.5)	23 (12.0)
Other IEs	3 (1.5)	6 (3.0)	3 (1.6)	6 (3.2)	7 (3.8)	2 (1.0)
Month 12 10AM						
Not Imputed	140 (70.0)	148 (75.1)	148 (76.7)	131 (70.8)	136 (74.3)	152 (79.2)
Missing	9 (4.5)	3 (1.5)	9 (4.7)	7 (3.8)	7 (3.8)	11 (5.7)

	GC-010			GC-012		
	G2-TR-063 N=200	G2-TR-125 N=197	Timolol N=193	G2-TR-063 N=185	G2-TR-125 N=183	Timolol N=192
Rescue Med	43 (21.5)	36 (18.3)	31 (16.1)	38 (20.5)	32 (17.5)	23 (12.0)
Other IEs	3 (1.5)	6 (3.0)	3 (1.6)	6 (3.2)	7 (3.8)	2 (1.0)

Abbreviations: Rescue Med = use of additional IOP-lowering medication; Other ICEs = Other intercurrent events which are premature study discontinuation, concurrent procedure, failure to implant device, failure to implant device in the correct region, and explant of investigational product.

To investigate the impact of imputed IOP values on the primary efficacy analysis, Figure 3 compares the following two distributions at each timepoint: (1) distribution of observed IOP values with no imputation and no handling of IEs (green in the figure) vs. (2) distribution of IOP values with imputations used in the primary analysis (red in the figure). As the imputation technique for the primary analysis relied on the worse-half patients, the median (black horizontal line in each box) of the IOP data with imputations tends to be higher than the median of the observed IOP data. However, the reviewer does not find any notable or remarkable difference between the two distributions at the timepoints from Day 10 to Month 3. Th reviewer does not find any pattern indicating that the imputation approach in the primary analysis notably favored the Travoprost Intraocular Implant groups.

Figure 3: Boxplots of IOP Values: Observed Data vs. Data with Imputation



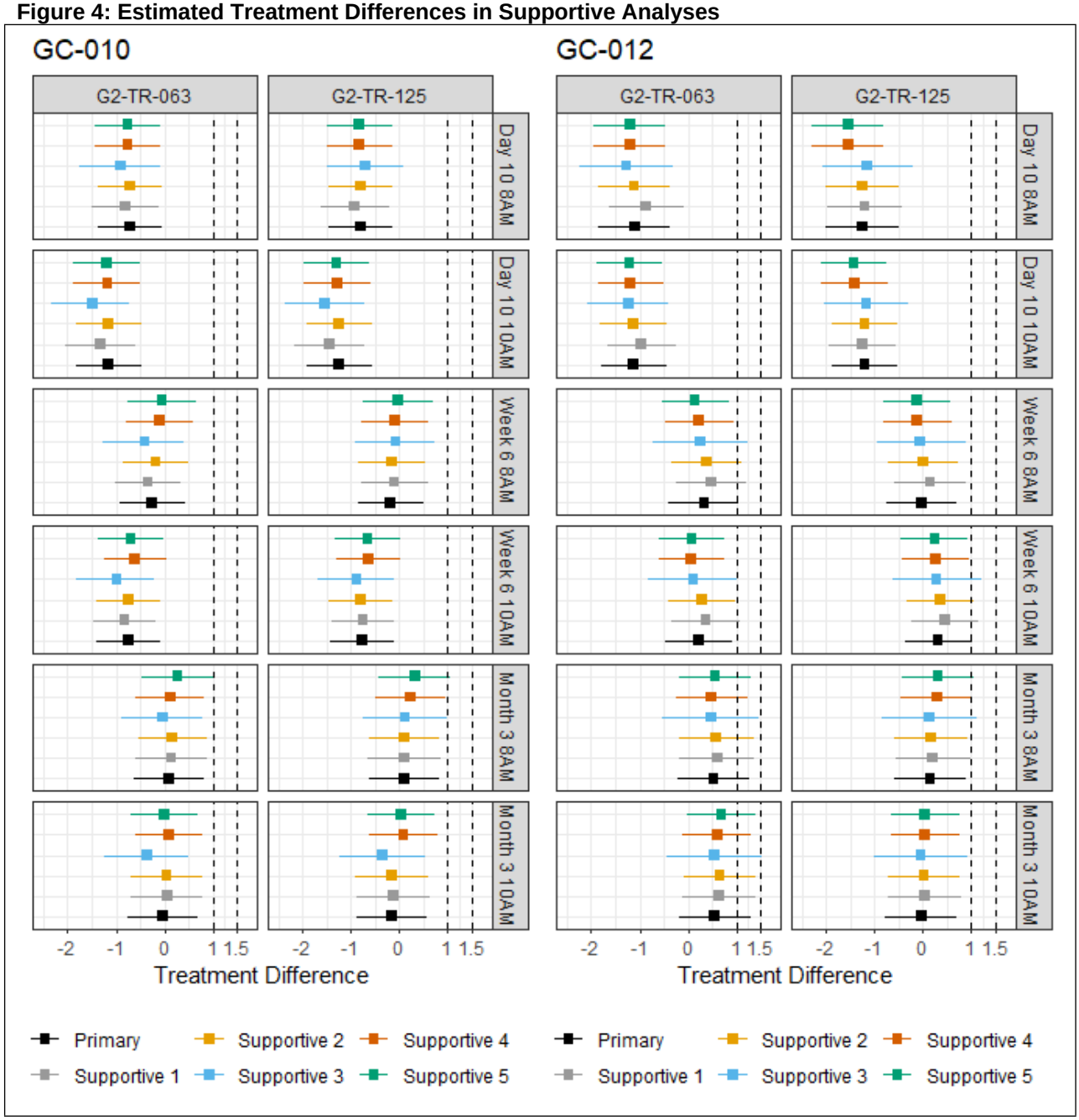
Abbreviations: IOP = intraocular pressure
Source: This table was produced by the reviewer using the datasets adiopimp.xpt and adiop.xpt for each study.
Note: The "Imputed" (red) and "Observed" (green) boxes present the distribution of IOP values without imputation and distribution of IOP values with imputation, respectively.

Supportive Analyses

Figure 4 depicts the results of the supportive analyses described in Section 3.2.2 of this review. The supportive analyses in the figure are as follows: (1) "Supportive 1": ANCOVA on per-protocol set, (2) "Supportive 2": ANCOVA with accounting for rescue medication at study level, (3) "Supportive 3": trimmed mean analysis (20% of data were trimmed), (4) "Supportive 4": ANCOVA on observed data, and (5) "Supportive 5": ANCOVA with LOCF for missing data. See Appendices A to E for details of the numerical results of these supportive analyses. In general, the estimated treatment differences from the supportive analyses are well aligned with

the estimated treatment differences from the primary analyses. In most supportive analyses, the NI conclusion for the primary efficacy endpoint remains the same (i.e., both implant groups met the pre-defined NI criterion for the primary efficacy endpoint in both studies; see Table 8).

Figure 4: Estimated Treatment Differences in Supportive Analyses



Source: This table was produced by the reviewer using the datasets adiopimp.xpt and adiop.xpt for each study.
Note: The "Primary" represents the estimated treatment difference (implant group – Timolol group) and 95% CI at each timepoint in the primary efficacy analyses. The other lines present the estimated treatment difference in the following supportive analyses: (1) "Supportive 1": ANCOVA on per-protocol set, (2) "Supportive 2": ANCOVA with accounting for rescue medication at study level, (3) "Supportive 3": trimmed mean analysis (20% of data were trimmed), (4) "Supportive 4": ANCOVA on observed data, and (5) "Supportive 5": ANCOVA with LOCF for missing data.

Table 8: Summary Table of Noninferiority Results from Supportive Analyses of Primary Endpoint

	GC-010		GC-012	
	G2-TR-063 vs. Timolol	G2-TR-125 vs. Timolol	G2-TR-063 vs. Timolol	G2-TR-125 vs. Timolol
Met NI criterion for primary efficacy endpoint?				
Supportive 1	Yes	Yes	No	Yes
Supportive 2	Yes	Yes	Yes	Yes
Supportive 3	Yes	Yes	Yes	Yes
Supportive 4	Yes	Yes	Yes	Yes
Supportive 5	Yes	Yes	Yes	Yes

Source: Table 16 of the CSRs. This table was produced by the reviewer using the datasets adiopimp.xpt and adiop.xpt.
Note: (1) "Supportive 1": ANCOVA on per-protocol set, (2) "Supportive 2": ANCOVA with accounting for rescue medication at study level, (3) "Supportive 3": trimmed mean analysis (20% of data were trimmed), (4) "Supportive 4": ANCOVA on observed data, and (5) "Supportive 5": ANCOVA with LOCF for missing data.

The Applicant also conducted a tipping point analysis. In the tipping point analysis, a shift parameter starting at 0 mmHg and increasing by 0.1 mmHg was added to the imputed values for subjects in the G2-TR implant groups. The addition of the shift parameter to the imputed values makes the data less favorable to the G2-TR implant groups. The ANCOVA model in the primary efficacy analysis was repeated with different values of the shift parameter until the tipping point (a value of the shift parameter at which he G2-TR implant groups no longer met the NI criterion) was reached. The tipping points identified in these analyses were as follows:

- Tipping point for G2-TR-063: 7.2 mmHg in GC-010 and 2.5 mmHg in GC-012.
- Tipping point for G2-TR-125: 6.1 mmHg in GC-010 and 6.3 mmHg in GC-012

The tipping points (6.1 mmHg and 6.3 mmHg) for the G2-TR-125 group appear to be large given that change from baseline in IOP was < 6.0 mmHg for the majority of subjects (> 99% at all 6 timepoints) in both studies. The large magnitude of the tipping points supports the robustness of NI conclusion of G2-TR-125 over Timolol. For additional details of the tipping point analysis, see Appendix F of this review.

For the key secondary endpoint, similar supportive analyses (except the tipping point analysis) were conducted. The G2-TR implant groups did not meet the NI criterion for the key secondary endpoint in all supportive analyses except the following case: G2-TR-125 group in the "Supportive 2" analysis. The numerical results of the supportive analyses for the key secondary endpoint can be found in Appendices A to E of this review.

3.2.4.2 Change from Baseline in IOP at Month 6 and Month 9

Table 9 presents the mean change from baseline in IOP at Months 6 and 9. Unlike the visits included in the primary and key secondary endpoints, the Months 6 and 9 visits measured IOP at a single timepoint (either 8AM, 10AM, or 4PM). The observed mean IOP reduction from baseline was greater in the Timolol group at both Month 6 and Month 9 in both studies.

Table 9: Change from Baseline in IOP at Month 6 and Month 9 (ITT Population, Observed Data)

	GC-010			GC-012		
	G2-TR-063	G2-TR-125	Timolol	G2-TR-063	G2-TR-125	Timolol

	GC-010			GC-012		
	G2-TR-063	**G2-TR-125**	**Timolol**	**G2-TR-063**	**G2-TR-125**	**Timolol**
Month 6						
N	194	192	189	180	178	182
08 AM	61	60	51	49	52	64
10 AM	101	93	102	100	100	84
04 PM	32	39	36	31	26	34
Mean (SD)	-5.8 (4.4)	-5.8 (4.4)	-6.4 (4.1)	-5.6 (4.7)	-5.6 (4.3)	-6.7 (4.2)
Min, Max	-16.0, 13.0	-16.0, 18.0	-18.0, 4.0	-17.5, 5.5	-18.0, 5.0	-20.5, 5.0
LS mean (SE)	**-5.7 (0.3)**	**-5.8 (0.3)**	**-6.4 (0.3)**	**-5.6 (0.3)**	**-5.7 (0.3)**	**-6.7 (0.3)**
Difference (95% CI)	0.7 (-0.0, 1.5)	0.6 (-0.1, 1.4)		1.2 (0.4, 1.9)	1.0 (0.3, 1.8)	
Month 9						
N	193	190	186	175	179	182
08 AM	67	65	54	52	60	62
10 AM	92	95	96	90	87	90
04 PM	34	30	36	33	32	30
Mean (SD)	-5.8 (4.1)	-5.9 (4.7)	-6.5 (3.9)	-5.5 (4.4)	-5.3 (4.5)	-6.7 (4.3)
Min, Max	-18.5, 6.5	-16.0, 15.0	-18.5, 10.0	-18.0, 4.5	-18.0, 14.0	-19.0, 4.0
LS mean (SE)	**-5.8 (0.3)**	**-5.9 (0.3)**	**-6.5 (0.3)**	**-5.5 (0.3)**	**-5.3 (0.3)**	**-6.8 (0.3)**
Difference (95% CI)	0.7 (-0.1, 1.4)	0.6 (-0.2, 1.3)		1.3 (0.5, 2.1)	1.5 (0.7, 2.3)	

Abbreviations: ITT = intention-to-treat population, SD = standard deviation, SE = standard error, CI = confidence interval
Source: Table 14.2-3.2 of the SCE. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.
Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

3.2.4.3 Efficacy Conclusion

The two pivotal studies demonstrated noninferiority of the two G2-TR implant models (G2-TR-063 and G2-TR-125) over the Timolol for the primary efficacy endpoint: change from baseline in IOP at 8AM and 10AM at Day 10, Week 6, and Month 3. The estimated mean IOP reduction at Day 10 was greater in the G2-TR implant groups compared to that in the Timolol group. The estimated mean IOP reduction at Week 6 and Month 3 was comparable across the treatment groups. However, the estimated mean IOP reduction at Months 6, 9, and 12 was greater in the Timolol group compared to that in the G2-TR implant groups. The two pivotal studies do not provide adequate evidence for NI of G2-TR implants over Timolol beyond 3 months.

3.3 Evaluation of Safety

In this section, high-level summaries of adverse events within 12 months are provided; see the FDA medical review for a comprehensive safety evaluation.

3.3.1 Summary of Adverse Events

Table 10 presents the number (%) of subjects with adverse events (AEs). For both studies, the proportion of subjects with AEs was higher in the G2-TR implant groups compared with that in the Timolol group: (1) 49.0% (G2-TR-063), 54.4% (G2-TR-125), and 38.7% (Timolol) in Study GC-010 and (2) 49.2% (G2-TR-063), 44.3% (G2-TR-125), and 38.0% (Timolol) in Study GC-

012. The majority of the AEs were mild or moderate. The proportion of subjects with serious AEs (SAEs) was comparable across the treatment groups: (1) 7.0% (G2-TR-063), 6.2% (G2-TR-125), and 5.2% (Timolol) in Study GC-010 and (2) 3.8% (G2-TR-063), 6.0% (G2-TR-125), and 5.2% (Timolol) in Study GC-012.

Table 10: Number (%) of Subjects with Adverse Events within 12 months (Safety Analysis Set)

	GC-010			GC-012		
	G2-TR-063 Implant N=200	G2-TR-125 Implant N=195	Sham/ Timolol N=194	G2-TR-063 Implant N=185	G2-TR-125 Implant N=183	Sham/ Timolol N=192
Adverse Events (AEs)	98 (49.0)	106 (54.4)	75 (38.7)	91 (49.2)	81 (44.3)	73 (38.0)
AEs in Study Eye	68 (34.0)	77 (39.5)	39 (20.1)	70 (37.8)	58 (31.7)	34 (17.7)
Related to Treatment	35 (17.5)	41 (21.0)	5 (2.6)	39 (21.1)	29 (15.8)	4 (2.1)
Maximum Severity						
Mild	43 (21.5)	50 (25.6)	25 (12.9)	41 (22.2)	40 (21.9)	24 (12.5)
Moderate	21 (10.5)	21 (10.8)	14 (7.2)	26 (14.1)	18 (9.8)	8 (4.2)
Severe	4 (2.0)	6 (3.1)	0	3 (1.6)	0	2 (1.0)
AEs in Non-Study Eye [1]	65 (32.5)	54 (27.7)	54 (27.8)	56 (30.3)	45 (24.6)	54 (28.1)
Related to Treatment	1 (<1)	2 (1.0)	0	0	1 (<1)	0
Mild	32 (16.0)	28 (14.4)	25 (12.9)	30 (16.2)	21 (11.5)	30 (15.6)
Moderate	22 (11.0)	17 (8.7)	21 (10.8)	19 (10.3)	15 (8.2)	16 (8.3)
Severe	11 (5.5)	9 (4.6)	8 (4.1)	7 (3.8)	9 (4.9)	8 (4.2)
Serious AEs (SAEs)	14 (7.0)	12 (6.2)	10 (5.2)	7 (3.8)	11 (6.0)	10 (5.2)
SAEs in Study Eye	1 (<1)	3 (1.5)	0	0	0	0
SAEs in Non-Study Eye	13 (6.5)	9 (4.6)	10 (5.2)	7 (3.8)	11 (6.0)	10 (5.2)
Death	2 (1.0)	0	4 (2.1)	1 (<1)	1 (<1)	2 (1.0)

Abbreviations: AE = adverse event, SAE = serious adverse event,

[1] AEs in Non-Study Eye include (1) AEs in non-study eye and (2) non-ocular AEs.

Source: Table 27 of the CSR for each study. This table was produced by the reviewer based on the adae.xpt dataset.

Table 11 presents the most commonly reported ocular AEs in the study eye (in ≥ 3% of subjects in each treatment group in either of the two studies). The most commonly reported ocular AE in the study eye in the G2-TR-125 group was iritis. The proportion of subjects with iritis in the G2-TR-125 group was higher than that in the Timolol group: 6.2% vs. 0% in Study GC-010 and 5.1% vs. 0% in Study GC-012.

Table 11: Adverse Events in Study Eye for at Least 3% of Subjects in Any Treatment Group (Safety Analysis Set)

	GC-010			GC-012		
MedDRA Organ Class Preferred Term	G2-TR-063 Implant N=200	G2-TR-125 Implant N=195	Sham/ Timolol N=194	G2-TR-063 Implant N=185	G2-TR-125 Implant N=183	Sham/ Timolol N=192
Eye disorders						
Cataract	3 (1.5)	7 (3.6)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Conjun hyperaemia [1]	0 (0.0)	0 (0.0)	0 (0.0)	9 (4.5)	4 (2.1)	1 (0.5)
Dry eye	6 (3.0)	7 (3.6)	3 (1.5)	8 (4.0)	5 (2.6)	7 (3.6)
Eye pain	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	8 (4.1)	0 (0.0)
Iritis	1 (0.5)	12 (6.2)	0 (0.0)	7 (3.5)	10 (5.1)	0 (0.0)

Ocular hyperaemia	9 (4.5)	5 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Punctate keratitis	6 (3.0)	3 (1.5)	5 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Visual acuity reduced	2 (1.0)	9 (4.6)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations						
IOP Increased	15 (7.5)	9 (4.6)	4 (2.1)	12 (6.0)	10 (5.1)	5 (2.6)
Nervous system disorders						
Visual field defect	6 (3.0)	6 (3.1)	2 (1.0)	4 (2.0)	7 (3.6)	2 (1.0)

Abbreviations: IOP = intraocular pressure.
[1] Conjunctival hyperaemia.
Source: Table 28 of the CSR for each study. This table was produced by the reviewer based on the adae.xpt dataset.

3.3.2 Safety Conclusion

For both studies, the proportion of subjects with AEs was higher in the G2-TR implant groups compared to that in the Timolol group. Regarding the acceptability of the safety profile, the reviewer defers to the Clinical review team.

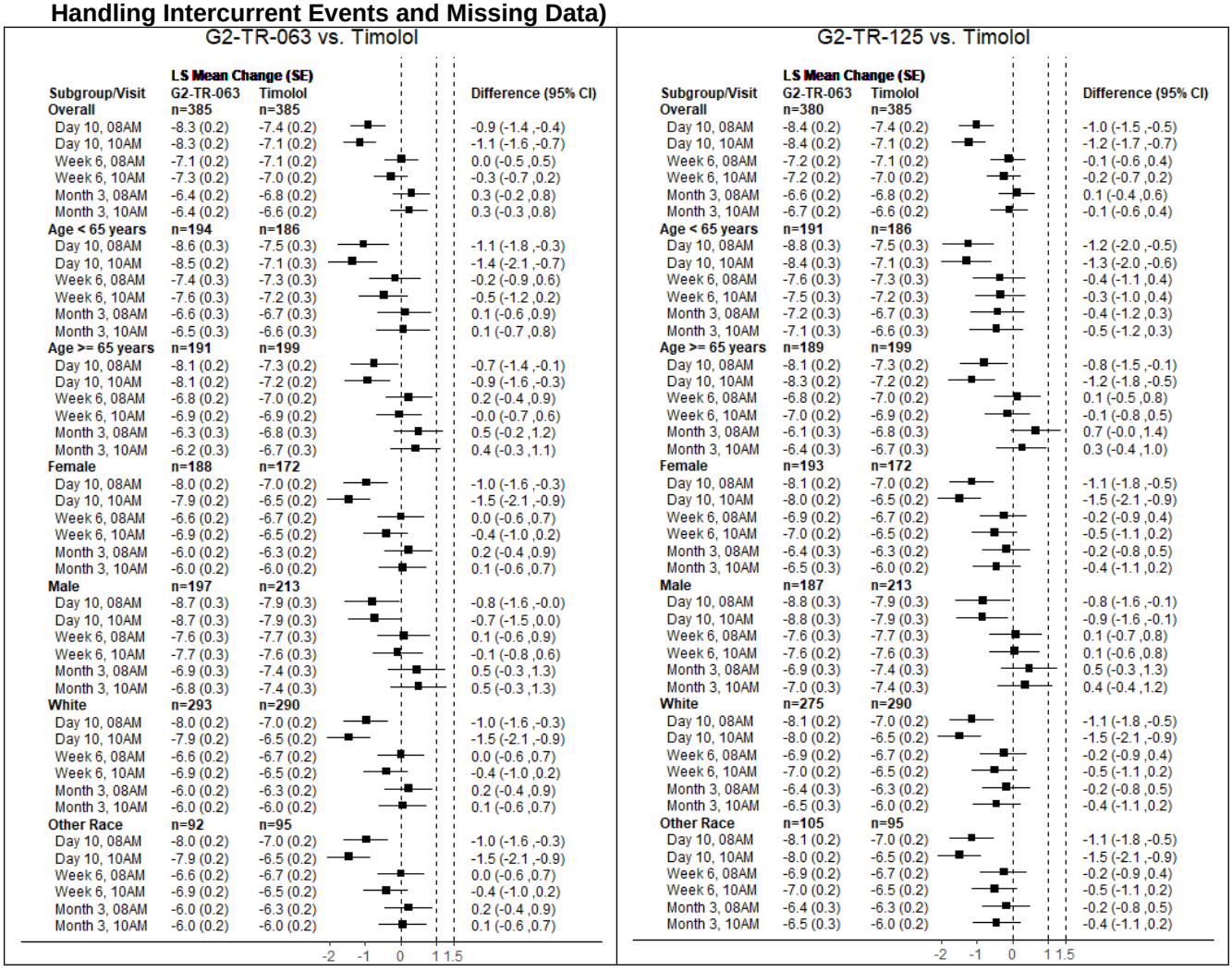
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Considering that the phase 3 studies had almost identical designs and showed consistent efficacy conclusion, the subgroup analyses were performed on the pooled data from Studies GC-010 and GC-12.

Figure 5 shows the subgroup results by age, gender, or race. In the overall population, the estimated mean IOP changes ranged from -6.4 to -8.3 mmHg in the G2-TR-063 group, -6.6 to -8.4 mmHg in the G2-TR-125 group, and -6.6 to -7.4 mmHg in the Timolol group. At Day 10, the magnitude of the IOP reduction was greater in the G2-TR implant groups compared to the Timolol group. At Week 6 and Month 3, the magnitude of the IOP reduction was comparable across the three treatment groups. Similar ranges of IOP reductions and similar patterns over time were observed in all subgroups by age, gender, and race. The two G2-TR implant groups met the NI criterion in all subgroups by age, gender, and race.

Figure 6 shows the subgroup results by disease type (OAG or OHT), baseline IOP (≤ 25 mmHg or >25 mmHg), or country (U.S. or other). The disease type subgroups (OAG or OHT) showed similar ranges of IOP reductions and similar patterns over time to those in the overall populations. In the subgroup of subjects with baseline IOP ≤ 25 mmHg, the magnitude of the estimated mean IOP changes tends to be lower (-5.7 to -7.5 mmHg) compared to that of the overall population. On the other hand, the subgroup of subjects with baseline IOP > 25 mmHg showed larger mean IOP reductions (-8.0 to -10.7 mmHg). The patterns over time in the subgroups by baseline IOP were similar to that in the overall population. The U.S. subgroup showed similar ranges of IOP reductions and similar patterns over time to those in the overall populations. The G2-TR-125 group met the NI criterion in all subgroups by disease type, baseline, and country except the subgroup of “Other Countries”. The 95% CIs for the estimated treatment differences in the “Other Countries” subgroup are wider due to relatively small sample size (about 30 per arm in the pooled dataset).

Figure 5: Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, and Month 3 by Age Subgroups, Sex Subgroups, and Race Subgroups (Pooled ITT Population, Worse-Half Method for Handling Intercurrent Events and Missing Data)

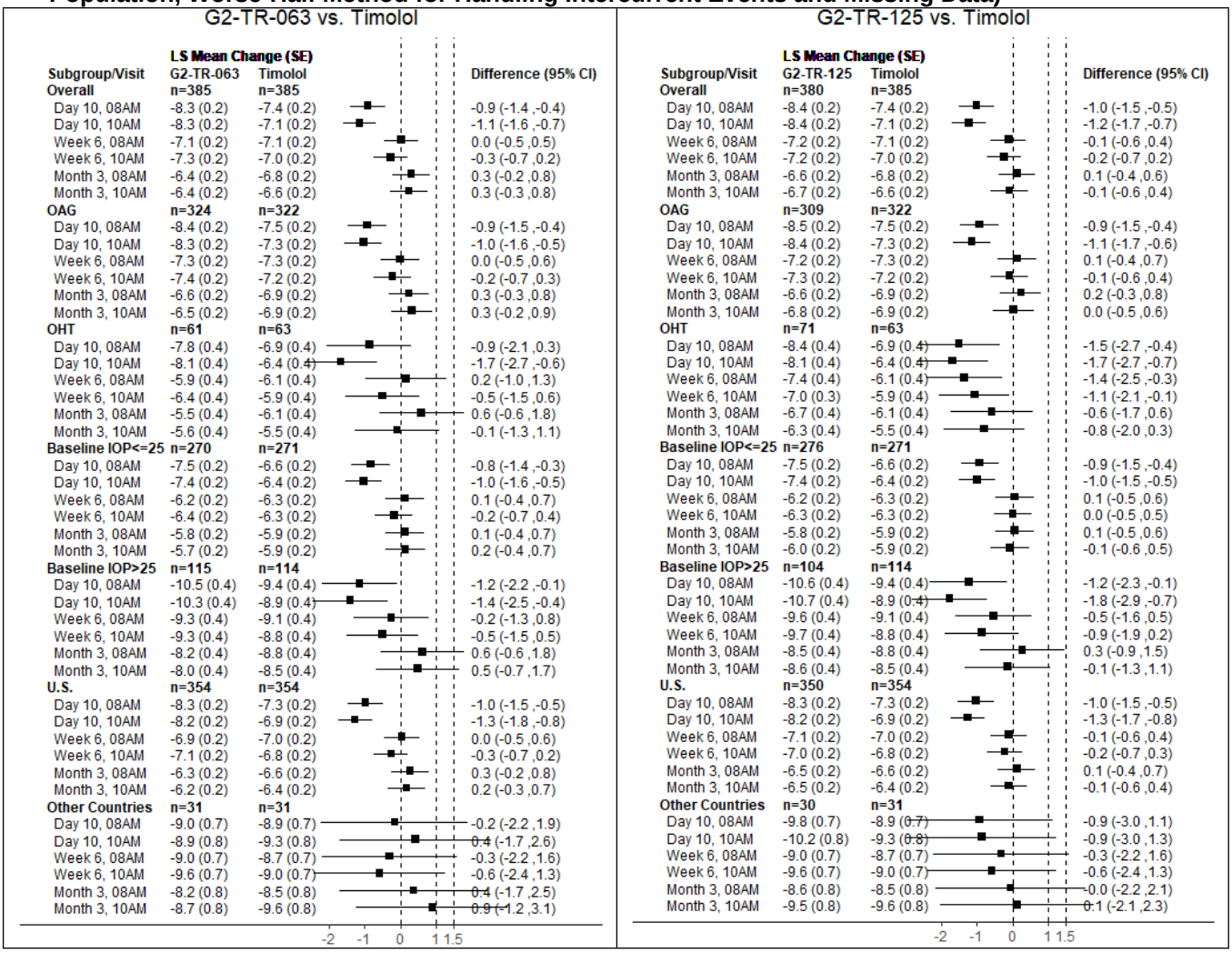


Abbreviations: ITT = intention-to-treat population, SE = standard error, CI = confidence interval, LS = least square.

Source: Figure 5 of the ISE. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.

Note: Difference (95% CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

Figure 6: Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, and Month 3 by Disease Type Subgroups, Baseline IOP Subgroups, and Country Subgroups (Pooled ITT Population, Worse-Half Method for Handling Intercurrent Events and Missing Data)



Abbreviations: ITT = intention-to-treat population, SE = standard error, CI = confidence interval, LS = least square.
Source: Figure 5 of the ISE. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.
Note: Difference (95% CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The reviewer found no major statistical issues.

5.2 Collective Evidence

The Applicant seeks approval of iDose® TR (G2-TR-125) for reduction of elevated IOP in patients with OAG or OHT. Efficacy and safety of G2-TR-125 were evaluated in the two pivotal studies, Study GC-010 and Study GC-012.

In terms of IOP reduction up to three months, the two pivotal studies demonstrated NI of G2-TR-125 over Timolol. The G2-TR-125 group met the prespecified NI criterion for the primary efficacy endpoint, change from baseline in IOP in the study eye at 8AM and 10AM at each of Day 10, Week 6, and Month 3. The treatment difference (G2-TR-125 - Timolol) in the estimated mean IOP change from baseline at Day 10 ranged from -0.8 [95% CI: (-1.5, -0.1)] to -1.2 [95% CI: (-2.0, -0.5)], which favor the G2-TR-125 group. The mean IOP changes from baseline at Week 6 and Month 3 were comparable between the G2-TR-125 and Timolol groups. The treatment difference at Week 6 ranged from -0.8 [95% CI: (-1.4, -0.1)] to 0.3 [95% CI: (-0.4, 1.0)]. The treatment difference at Month 3 ranged from -0.2 [95% CI: (-0.9, -0.6)] to 0.2 [95% CI: (-0.6, 0.9)].

In terms of efficacy beyond three months, the two pivotal studies do not provide sufficient evidence for demonstrating NI of G2-TR-125 over Timolol. The estimated mean IOP reductions from baseline at Months 6 and 9 were greater in the Timolol group compared with those in the G2-TR implant groups: -5.9 to -5.3 mmHg in the G2-TR implant groups vs. -6.7 to -6.4 mmHg in the Timolol group. In Study GC-012, the G2-TR-125 group failed to meet the NI criterion for the key secondary endpoint, change from baseline in IOP at 8AM and 10AM at Month 12. The treatment difference (G2-TR-125 - Timolol) in the estimated mean IOP change from baseline at Month 12 ranged from 0.5 [95% CI: (-0.2, -1.2)] to 1.4 [95% CI: (0.6, 2.1)], which favor the Timolol group.

In terms of the AE profile, the proportion of subjects with adverse events (AEs) was higher in the G2-TR-125 group compared with that in the Timolol group: 54.4% vs. 38.7% in Study GC-010 and 44.3% (G2-TR-125) vs. 38.0% in Study GC-012. The most commonly reported ocular AE in the study eye in the G2-TR-125 group was iritis. The proportion of subjects with iritis in the G2-TR-125 group was higher than that in the Timolol group: 6.2% vs. 0% in Study GC-010 and 5.1% vs. 0% in Study GC-012.

5.3 Conclusions and Recommendations

Study GC-010 and Study GC-012 demonstrated that the iDose® TR (G2-TR-125) was noninferior to Timolol up to three months in reducing elevated IOP in patients with OAG or OHT. The reviewer recommends approval of iDose® TR.

5.4 Labeling Recommendations

The reviewer recommends limiting the indication up to three months as the Application does not provide adequate evidence to support efficacy beyond 3 months. The reviewer finds Section 14 of the proposed labeling (see below) acceptable.

(b) (4)

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

APPENDICES

Appendix A. Supportive Analysis 1

Supportive Analysis 1 is the same as the primary efficacy analysis except that the analysis set is the per-protocol set. Table 12 presents the results of Supportive Analysis 1.

Table 12: Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, Month 3, and Month 12 (Per-Protocol Set, Worse-Half Method for Handling Intercurrent Events and Missing Data)

	GC-010			GC-012		
	G2-TR-063 N=200	G2-TR-125 N=197	Timolol N=193	G2-TR-063 N=185	G2-TR-125 N=183	Timolol N=192
Day 10 8AM						
LS mean (SE)	-8.5 (0.2)	-8.6 (0.3)	-7.7 (0.3)	-8.1 (0.3)	-8.4 (0.3)	-7.2 (0.3)
Difference (CI)	-0.8 (-1.5, -0.1)	-0.9 (-1.6, -0.2)		-0.9 (-1.6, -0.1)	-1.2 (-2.0, -0.4)	
Day 10 10AM						
LS mean (SE)	-8.4 (0.3)	-8.5 (0.3)	-7.1 (0.3)	-8.0 (0.3)	-8.3 (0.3)	-7.1 (0.2)
Difference (CI)	-1.3 (-2.0, -0.6)	-1.4 (-2.2, -0.7)		-1.0 (-1.7, -0.3)	-1.2 (-1.9, -0.5)	
Week 6 8AM						
LS mean (SE)	-7.4 (0.2)	-7.2 (0.2)	-7.1 (0.3)	-6.8 (0.3)	-7.1 (0.3)	-7.3 (0.3)
Difference (CI)	-0.3 (-1.0, 0.3)	-0.1 (-0.8, 0.6)		0.5 (-0.3, 1.2)	0.2 (-0.6, 0.9)	
Week 6 10AM						
LS mean (SE)	-7.7 (0.2)	-7.6 (0.2)	-6.9 (0.2)	-6.9 (0.3)	-6.8 (0.3)	-7.3 (0.3)
Difference (CI)	-0.8 (-1.5, -0.2)	-0.7 (-1.4, -0.1)		0.4 (-0.3, 1.1)	0.5 (-0.2, 1.2)	
Month 3 8AM						
LS mean (SE)	-6.5 (0.3)	-6.6 (0.3)	-6.7 (0.3)	-6.2 (0.3)	-6.6 (0.3)	-6.8 (0.3)
Difference (CI)	0.1 (-0.6, 0.9)	0.1 (-0.6, 0.9)		0.6 (-0.2, 1.4)	0.2 (-0.6, 1.0)	
Month 3 10AM						
LS mean (SE)	-6.5 (0.3)	-6.6 (0.3)	-6.5 (0.3)	-6.2 (0.3)	-6.8 (0.3)	-6.8 (0.3)
Difference (CI)	0.1 (-0.7, 0.8)	-0.1 (-0.9, 0.6)		0.6 (-0.1, 1.4)	0.0 (-0.7, 0.8)	
Month 12 8AM						
LS mean (SE)	-5.3 (0.3)	-5.5 (0.3)	-6.2 (0.3)	-5.0 (0.3)	-4.9 (0.3)	-6.3 (0.3)
Difference (CI)	0.9 (0.1, 1.7)	0.7 (-0.0, 1.5)		1.3 (0.5, 2.1)	1.4 (0.6, 2.2)	
Month 12 10AM						
LS mean (SE)	-5.8 (0.3)	-5.4 (0.3)	-6.1 (0.3)	-5.1 (0.3)	-5.4 (0.3)	-6.5 (0.3)
Difference (CI)	0.3 (-0.4, 1.0)	0.6 (-0.1, 1.3)		1.4 (0.6, 2.2)	1.1 (0.3, 1.9)	

Abbreviations: LS = least square, SE = standard error, CI = confidence interval
Source: Table 14.2-1.2 of the CSR. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.
Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

Appendix B. Supportive Analysis 2

Supportive Analysis 2 is the same as the primary efficacy analysis except the handling of intercurrent event of rescue medication use. In the primary efficacy analysis, whether or not on rescue medication was determined separately at the visit level (i.e., a patient was considered on rescue medication at a specific visit if the patient received a rescue medication within a certain

window of the visit). In Supportive Analysis 2, visits after the first recue medications are considered as visits on rescue medications. Table 13 presents the results.

Table 13: Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, Month 3, and Month 12 (ITT Population, Worse-Half Method for Handling Intercurrent Events and Missing Data, Rescue Medications at Study Level)

	GC-010			GC-012		
	G2-TR-063 N=200	G2-TR-125 N=197	Timolol N=193	G2-TR-063 N=185	G2-TR-125 N=183	Timolol N=192
Day 10 8AM						
LS mean (SE)	-8.4 (0.2)	-8.5 (0.2)	-7.7 (0.2)	-8.3 (0.3)	-8.4 (0.3)	-7.2 (0.3)
Difference (CI)	-0.7 (-1.4, -0.1)	-0.8 (-1.5, -0.1)		-1.1 (-1.9, -0.4)	-1.2 (-2.0, -0.5)	
Day 10 10AM						
LS mean (SE)	-8.4 (0.2)	-8.4 (0.2)	-7.2 (0.2)	-8.3 (0.3)	-8.4 (0.3)	-7.2 (0.3)
Difference (CI)	-1.2 (-1.8, -0.5)	-1.2 (-1.9, -0.6)		-1.1 (-1.9, -0.4)	-1.2 (-2.0, -0.5)	
Week 6 8AM						
LS mean (SE)	-7.3 (0.2)	-7.3 (0.2)	-7.1 (0.2)	-6.8 (0.3)	-7.2 (0.3)	-7.2 (0.3)
Difference (CI)	-0.2 (-0.9, 0.5)	-0.2 (-0.8, 0.5)		0.4 (-0.4, 1.1)	0.0 (-0.7, 0.7)	
Week 6 10AM						
LS mean (SE)	-7.6 (0.2)	-7.7 (0.2)	-6.9 (0.2)	-6.9 (0.3)	-6.8 (0.3)	-7.2 (0.2)
Difference (CI)	-0.7 (-1.4, -0.1)	-0.8 (-1.5, -0.1)		0.3 (-0.4, 1.0)	0.4 (-0.3, 1.1)	
Month 3 8AM						
LS mean (SE)	-6.6 (0.3)	-6.6 (0.3)	-6.7 (0.3)	-6.2 (0.3)	-6.7 (0.3)	-6.8 (0.3)
Difference (CI)	0.2 (-0.5, 0.9)	0.1 (-0.6, 0.8)		0.6 (-0.2, 1.4)	0.2 (-0.6, 0.9)	
Month 3 10AM						
LS mean (SE)	-6.5 (0.3)	-6.7 (0.3)	-6.6 (0.3)	-6.1 (0.3)	-6.7 (0.3)	-6.8 (0.3)
Difference (CI)	0.0 (-0.7, 0.8)	-0.2 (-0.9, 0.6)		0.7 (-0.1, 1.4)	0.0 (-0.7, 0.8)	
Month 12 8AM						
LS mean (SE)	-5.3 (0.3)	-5.5 (0.3)	-6.1 (0.3)	-4.9 (0.3)	-5.0 (0.3)	-6.4 (0.3)
Difference (CI)	0.8 (0.0, 1.6)	0.6 (-0.2, 1.3)		1.5 (0.7, 2.3)	1.4 (0.6, 2.1)	
Month 12 10AM						
LS mean (SE)	-5.8 (0.3)	-5.6 (0.3)	-6.0 (0.3)	-5.0 (0.3)	-5.4 (0.3)	-6.5 (0.3)
Difference (CI)	0.2 (-0.6, 0.9)	0.4 (-0.3, 1.1)		1.5 (0.7, 2.3)	1.1 (0.3, 1.8)	

Abbreviations: ITT = intent-to-treat, LS = least square, SE = standard error, CI = confidence interval
Source: Table 14.2-1.3.1 of the CSR. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.
Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

Appendix C. Supportive Analysis 3

Supportive Analysis 3 is a trimmed mean analysis (https://pubmed.ncbi.nlm.nih.gov/27523396/). The Agency recommended a trimmed mean analysis for the two pivotal studies. In principle, a trimmed mean analysis treats missing data and data at or after intercurrent events as bad outcomes and trims equal proportions of the worst observations from each treatment arm. The treatment comparison is based on means of the remaining better outcomes. The following are the SAP-defined steps to perform a trimmed mean analysis:

Trimmed Mean Approach:

- Trimmed Means will be applied separately to the pairwise testing of G2-TR-063 vs timolol and G2-TR-125 vs timolol.
- Trimming criteria: subjects who have intercurrent events defined in Section 5.6. Subjects with missing IOP data will also be trimmed.
- Subjects meeting trimming criteria above (i.e., must be trimmed subjects) are always ranked the worst. Rank the data based on change from baseline IOP value.
- The proportion of data trimmed from each treatment group in the trimmed means analysis will be dependent on the maximum pooled rate of subjects meeting trimming criteria between G2-TR-063 & timolol and G2-TR-125 & timolol using the following:

Maximum Pooled Rate of Subjects Meeting Trimming Criteria (%)	Data Trimmed (%)
≤ 5%	10%
> 5% to ≤ 10%	20%
> 10% to ≤ 15%	30%
> 15% to ≤ 20%	40%
> 20% to ≤ 25%	50%

For calculating which data to trim, subjects with intercurrent events will be included as the worst observations in the treatment group. After trimming is done, the trimmed means of the change from baseline values and the difference in trimmed means between the two treatment groups is calculated to find an observed treatment effect. To determine the 95% CI and p-value, 5000 permutations of the untrimmed data will be run, and the trimming methodology will be repeated, using the same trimming %. The permutation p-value for the difference in trimmed means will be determined by dividing the number of permutations that result in an effect size greater than or equal to the observed effect size + 1 (to account for the observed data) by the number of permutations + 1 (to account for the observed data). The 95% CI of the difference in trimmed means will be calculated through adding the 2.5 and 97.5 percentiles of the permutation distribution of the difference in trimmed means to the observed difference in trimmed means.

This approach will be repeated separately for each timepoint for the Day 10, Week 6, and Month 3 visits. The same % trim will be used for all analysis. A permutation dataset will be output using seed: 61702.

Trimmed mean method will be the secondary approach for sensitivity analysis of primary efficacy endpoints.

Source: Section 6.1.3 of the SAP.

Table 14 presents the number (proportion) of patients who had IEs or missing data. According to the pre-specification for the proportion of data trimmed, the worst 20% of data were trimmed from each treatment group for the primary endpoint. The maximum pooled rate among the 6 timepoints of the primary endpoint was 8.8% in Study GC-010 and 9.5% in Study GC-012. For the key secondary endpoint of Month 12, the worst 50% of data were trimmed from each

treatment group. The maximum pooled rate among the 2 timepoints at Month 12 was 26.1% and 25.4% in Studies GC-010 and GC-12, respectively.

Table 14: Number of Subjects who Had IEs or Missing Data (ITT Population), n (%)

	GC-010				GC-012			
	G2-TR-063 N=200	G2-TR-125 N=197	Timolol N=193	All N=590	G2-TR-063 N=185	G2-TR-125 N=183	Timolol N=192	All N=560
Day 10								
8AM	3 (1.5)	4 (2.0)	1 (0.5)	8 (1.4)	7 (3.8)	8 (4.4)	2 (1.0)	17 (3.0)
10AM	3 (1.5)	4 (2.0)	1 (0.5)	8 (1.4)	7 (3.8)	8 (4.4)	2 (1.0)	17 (3.0)
Week 6								
8AM	12 (6.0)	13 (6.6)	13 (6.7)	38 (6.4)	20 (10.8)	14 (7.7)	12 (6.2)	46 (8.2)
10AM	11 (5.5)	12 (6.1)	12 (6.2)	35 (5.9)	20 (10.8)	15 (8.2)	11 (5.7)	46 (8.2)
Month 3								
8AM	16 (8.0)	17 (8.6)	19 (9.8)	52 (8.8)	22 (11.9)	16 (8.7)	15 (7.8)	53 (9.5)
10AM	16 (8.0)	17 (8.6)	19 (9.8)	52 (8.8)	22 (11.9)	16 (8.7)	15 (7.8)	53 (9.5)
Month 12								
8AM	60 (30.0)	49 (24.9)	45 (23.3)	154 (26.1)	54 (29.2)	47 (25.7)	41 (21.4)	142 (25.4)
10AM	60 (30.0)	49 (24.9)	45 (23.3)	154 (26.1)	54 (29.2)	47 (25.7)	40 (20.8)	141 (25.2)

Abbreviations: ITT = intent-to-treat, IEs = intercurrent events
Source: This table was produced by the reviewer using the dataset adiopimp.xpt for each study.

Table 15 presents the results of the trimmed mean analysis relying on the remaining 80% of the data for the primary endpoint and the remaining 50% of the data for the key secondary endpoint. Of note, the CIs for the treatment differences in Table 15 are slightly different from the CIs reported in the CSRs because the reviewer's trimmed mean analysis was conducted on R while the Applicant's trimmed mean analysis was conducted on SAS. However, the numerical differences between them are negligible and do not alter the NI conclusion for the primary efficacy endpoint.

Table 15: Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, Month 3, and Month 12 (ITT Population, Trimmed Mean Analysis)

	GC-010			GC-012		
	G2-TR-063 N=200	G2-TR-125 N=197	Timolol N=193	G2-TR-063 N=185	G2-TR-125 N=183	Timolol N=192
Day 10 8AM						
Mean (SD)	-9.8 (3.3)	-9.6 (3.0)	-8.9 (2.9)	-9.7 (3.9)	-9.6 (3.5)	-8.5 (3.2)
Difference (CI)	-0.9 (-1.8, -0.1)	-0.7 (-1.5, 0.1)		-1.3 (-2.2, -0.3)	-1.2 (-2.1, -0.2)	
Day 10 10AM						
LS mean (SE)	-9.8 (3.1)	-9.8 (3.2)	-8.3 (2.8)	-9.5 (3.1)	-9.4 (3.4)	-8.2 (3.2)
Difference (CI)	-1.5 (-2.3, -0.7)	-1.5 (-2.3, -0.7)		-1.2 (-2.1, -0.4)	-1.2 (-2.0, -0.3)	
Week 6 8AM						
Mean (SD)	-8.6 (3.3)	-8.2 (3.1)	-8.2 (3.1)	-8.0 (3.8)	-8.3 (3.5)	-8.2 (3.3)
Difference (CI)	-0.4 (-1.3, 0.4)	-0.1 (-0.9, 0.7)		0.2 (-0.7, 1.2)	-0.1 (-0.9, 0.9)	
Week 6 10AM						
Mean (SD)	-8.8 (3.1)	-8.7 (3.1)	-7.8 (2.9)	-8.0 (3.4)	-7.9 (3.6)	-8.1 (3.2)
Difference (CI)	-1.0 (-1.8, -0.2)	-0.9 (-1.7, -0.1)		0.1 (-0.8, 1.0)	0.3 (-0.6, 1.2)	
Month 3 8AM						
Mean (SD)	-7.8 (3.0)	-7.6 (3.0)	-7.8 (3.2)	-7.4 (3.9)	-7.7 (3.7)	-7.9 (3.7)
Difference (CI)	-0.0 (-0.9, 0.8)	0.1 (-0.7, 1.0)		0.5 (-0.5, 1.5)	0.1 (-0.9, 1.1)	
Month 3 10AM						

Mean (SD)	-7.8 (3.1)	-7.8 (3.2)	-7.5 (3.3)	-7.2 (3.5)	-7.8 (3.6)	-7.8 (3.7)
Difference (CI)	-0.4 (-1.3, 0.5)	-0.3 (-1.2, 0.5)		0.5 (-0.4, 1.5)	-0.0 (-1.0, 0.9)	
Month 12 8AM						
Mean (SD)	-8.0 (2.8)	-8.1 (2.7)	-8.7 (2.7)	-7.7 (3.1)	-7.5 (3.1)	-8.7 (2.9)
Difference (CI)	0.7 (-0.4, 1.7)	0.6 (-0.5, 1.7)		1.1 (-0.1, 2.3)	1.2 (0.1, 2.4)	
Month 12 10AM						
Mean (SD)	-8.1 (2.4)	-8.1 (2.9)	-8.2 (2.4)	-7.7 (2.7)	-8.0 (3.2)	-8.9 (2.6)
Difference (CI)	0.1 (-0.9, 1.0)	0.1 (-1.0, 1.1)		1.1 (0.1, 2.3)	0.9 (-0.1, 2.0)	

Abbreviations: ITT = intent-to-treat, LS = least square, SE = standard error, CI = confidence interval
Source: Tables 14.2-1.4 and 14.2-2.3 of the CSR. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.
Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by a trimmed mean analysis. The worst 20% (50%) of data including missing data and data with intercurrent events were trimmed from each treatment group for the primary (key secondary) endpoint. The 95% CIs were computed using a permutation approach with 5000 permutations.

Appendix D. Supportive Analysis 4

Supportive Analysis 4 is the same as the primary efficacy analysis except the handling of missing data and intercurrent events. The primary ANCOVA model was performed on the observed data with no imputation of missing data and no special handling of intercurrent events. Table 16 presents the results.

Table 16: Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, Month 3, and Month 12 (ITT Population, Observed Data)

	GC-010			GC-012		
	G2-TR-063 N=200	G2-TR-125 N=197	Timolol N=193	G2-TR-063 N=185	G2-TR-125 N=183	Timolol N=192
Day 10 8AM						
LS mean (SE)	-8.4 (0.2)	-8.5 (0.2)	-7.7 (0.2)	-8.4 (0.3)	-8.7 (0.3)	-7.2 (0.3)
Difference (CI)	-0.8 (-1.4, -0.1)	-0.8 (-1.5, -0.1)		-1.2 (-1.9, -0.5)	-1.5 (-2.3, -0.8)	
Day 10 10AM						
LS mean (SE)	-8.4 (0.2)	-8.5 (0.2)	-7.2 (0.3)	-8.3 (0.2)	-8.5 (0.2)	-7.1 (0.2)
Difference (CI)	-1.2 (-1.9, -0.5)	-1.3 (-2.0, -0.6)		-1.2 (-1.9, -0.5)	-1.4 (-2.1, -0.7)	
Week 6 8AM						
LS mean (SE)	-7.3 (0.2)	-7.3 (0.2)	-7.2 (0.2)	-7.1 (0.3)	-7.4 (0.3)	-7.3 (0.3)
Difference (CI)	-0.1 (-0.8, 0.6)	-0.1 (-0.8, 0.6)		0.2 (-0.5, 0.9)	-0.1 (-0.8, 0.6)	
Week 6 10AM						
LS mean (SE)	-7.7 (0.2)	-7.7 (0.2)	-7.0 (0.2)	-7.2 (0.2)	-7.0 (0.2)	-7.3 (0.2)
Difference (CI)	-0.6 (-1.3, 0.0)	-0.6 (-1.3, 0.0)		0.1 (-0.6, 0.8)	0.3 (-0.4, 1.0)	
Month 3 8AM						
LS mean (SE)	-6.8 (0.3)	-6.7 (0.3)	-7.0 (0.3)	-6.6 (0.3)	-6.8 (0.3)	-7.1 (0.3)
Difference (CI)	0.1 (-0.6, 0.8)	0.2 (-0.5, 0.9)		0.5 (-0.3, 1.2)	0.3 (-0.4, 1.0)	
Month 3 10AM						
LS mean (SE)	-6.8 (0.2)	-6.8 (0.2)	-6.9 (0.3)	-6.5 (0.3)	-7.1 (0.3)	-7.1 (0.3)
Difference (CI)	0.1 (-0.6, 0.8)	0.1 (-0.6, 0.8)		0.6 (-0.1, 1.3)	0.1 (-0.7, 0.8)	
Month 12 8AM						
LS mean (SE)	-5.7 (0.3)	-5.6 (0.3)	-6.9 (0.3)	-5.9 (0.3)	-5.3 (0.3)	-6.8 (0.3)
Difference (CI)	1.2 (0.4, 1.9)	1.2 (0.5, 2.0)		0.9 (0.1, 1.7)	1.4 (0.7, 2.2)	

Month 12 10AM						
LS mean (SE)	-6.1 (0.3)	-5.8 (0.3)	-6.8 (0.3)	-5.8 (0.3)	-5.7 (0.3)	-6.9 (0.3)
Difference (CI)	0.6 (-0.1, 1.3)	1.0 (0.2, 1.7)		1.0 (0.3, 1.8)	1.2 (0.4, 2.0)	

Abbreviations: ITT = intent-to-treat, LS = least square, SE = standard error, CI = confidence interval
Source: Table 14.2-1.6 of the CSR. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.
Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

Appendix E. Supportive Analysis 5

Supportive Analysis 5 is the same as the primary efficacy analysis except the handling of missing data and intercurrent events. The primary ANCOVA model was performed with the last observation carried forward (LOCF) for imputing missing data and no special handling of intercurrent events. Table 17 presents the results.

Table 17: Change from Baseline in IOP at 8AM and 10AM at Day 10, Week 6, Month 3, and Month 12 (ITT Population, LOCF for Missing Data)

	GC-010			GC-012		
	G2-TR-063 N=200	**G2-TR-125 N=197**	**Timolol N=193**	**G2-TR-063 N=185**	**G2-TR-125 N=183**	**Timolol N=192**
Day 10 8AM						
LS mean (SE)	-8.4 (0.2)	-8.5 (0.2)	-7.7 (0.2)	-8.4 (0.3)	-8.7 (0.3)	-7.2 (0.3)
Difference (CI)	-0.8 (-1.4, -0.1)	-0.8 (-1.5, -0.1)		-1.2 (-1.9, -0.5)	-1.5 (-2.3, -0.8)	
Day 10 10AM						
LS mean (SE)	-8.4 (0.2)	-8.5 (0.2)	-7.2 (0.2)	-8.3 (0.2)	-8.5 (0.2)	-7.1 (0.2)
Difference (CI)	-1.2 (-1.9, -0.5)	-1.3 (-2.0, -0.6)		-1.2 (-1.9, -0.5)	-1.4 (-2.1, -0.7)	
Week 6 8AM						
LS mean (SE)	-7.3 (0.3)	-7.3 (0.3)	-7.3 (0.3)	-7.1 (0.3)	-7.4 (0.3)	-7.3 (0.2)
Difference (CI)	-0.0 (-0.8, 0.7)	-0.0 (-0.7, 0.7)		0.1 (-0.5, 0.8)	-0.1 (-0.8, 0.6)	
Week 6 10AM						
LS mean (SE)	-7.7 (0.2)	-7.7 (0.2)	-7.0 (0.2)	-7.2 (0.2)	-7.1 (0.3)	-7.3 (0.2)
Difference (CI)	-0.7 (-1.4, -0.0)	-0.7 (-1.3, 0.0)		0.1 (-0.6, 0.8)	0.2 (-0.4, 0.9)	
Month 3 8AM						
LS mean (SE)	-6.7 (0.3)	-6.7 (0.3)	-7.0 (0.3)	-6.6 (0.3)	-6.8 (0.3)	-7.1 (0.3)
Difference (CI)	0.3 (-0.5, 1.0)	0.3 (-0.4, 1.1)		0.6 (-0.2, 1.3)	0.3 (-0.4, 1.0)	
Month 3 10AM						
LS mean (SE)	-6.8 (0.3)	-6.8 (0.3)	-6.8 (0.3)	-6.5 (0.3)	-7.1 (0.3)	-7.1 (0.3)
Difference (CI)	0.0 (-0.7, 0.7)	0.0 (-0.7, 0.7)		0.7 (-0.0, 1.4)	0.0 (-0.7, 0.8)	
Month 12 8AM						
LS mean (SE)	-5.7 (0.3)	-5.5 (0.3)	-6.9 (0.3)	-5.8 (0.3)	-5.4 (0.3)	-7.0 (0.3)
Difference (CI)	1.2 (0.5, 2.0)	1.4 (0.7, 2.2)		1.2 (0.4, 1.9)	1.6 (0.8, 2.3)	
Month 12 10AM						
LS mean (SE)	-6.1 (0.3)	-5.7 (0.3)	-6.8 (0.3)	-5.8 (0.3)	-5.8 (0.3)	-7.0 (0.3)
Difference (CI)	0.7 (-0.1, 1.4)	1.1 (0.4, 1.8)		1.3 (0.5, 2.0)	1.3 (0.5, 2.0)	

Abbreviations: ITT = intent-to-treat, LS = least square, SE = standard error, CI = confidence interval, LOCF = last observation carried forward.
Source: Table 14.2-1.7 of the CSR. This table was produced by the reviewer using the dataset adiopimp.xpt for each study.

Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean change from baseline. They were estimated by fitting the ANCOVA model separately for each timepoint. The ANCOVA model included treatment and time-matched baseline IOP.

Appendix F. Supportive Analysis 6 (Tipping Point Analysis)

The Applicant conducted a tipping point analysis for the primary efficacy endpoint. In the Applicant's tipping point analysis, a non-negative shift parameter starting at 0 and increasing by 0.1 mmHg were added to the imputed values for subjects in the G2-TR implant groups. The addition of the shifting parameter makes the analysis results less favorable to the G2-TR implant groups. A tipping point is defined as the value of the shift parameter at which the G2-TR implant groups no longer met the NI criterion for the primary efficacy endpoint. The following are the SAP-defined steps to perform the tipping analysis:

Implementing the tipping point approach will include the following steps:

1. Set the IOP values as missing for subjects with intercurrent events at visit level.
2. A multiple imputation step with SAS PROC MI – MCMC performed on the IOP data for the ITT subjects at each timepoint and visit, similar to Step 1 described in Section 6.1.3. The missing data are filled in 50 times to generate 50 complete data sets, with seed = 501107.
3. For Timolol group assumed MAR, no shift will be added on the imputed IOP values. For the G2-TR treatment groups assumed MNAR, a shift parameter will be added to the imputed IOP values. The shift starts at 0 and will be increased in a repeated process until the treatment effect is no longer statistically non-inferior to Timolol at 0.05 level in step 5, i.e., the upper limit of two-sided 95% CI $\geq$ 1.5 mmHg.
4. The 50 complete data sets are analyzed by using ANCOVA model similar to the primary analysis to estimate the treatment differences and corresponding 95% CI.
5. The results from the 50 complete data sets are combined using SAS PROC MIANALYZE, which combines the estimates.
6. Repeat Steps 4 to 6 with different values of the shift parameter until the tipping point is reached. Repeat for each timepoint and each visit

Source: Section 6.1.6 of the SAP.

Tipping Point for G2-TR-125

The tipping point for the G2-TR-125 group was reached at the shift parameter of 6.1 mmHg in Study GC-010 and at the shift parameter of 6.3 mmHg in Study GC-012. At the tipping points, the upper limit of the 95% CI of the treatment difference (G2-TR-125 minus Timolol) was < 1.5 mmHg for 5 of 6 timepoints. For details of the estimated treatment differences in these tipping point analyses, see Table 14.2-1.5 of the CSR.

Tipping Point for G2-TR-063

The tipping point for the G2-TR-063 group was reached at the shift parameter of 7.2 mmHg in Study GC-010 and at the shift parameter of 2.5 mmHg in Study GC-012. At the tipping points, the upper limit of the 95% CI of the treatment difference (G2-TR-125 minus Timolol) was < 1.5

mmHg for 5 of 6 timepoints. For details of the estimated treatment differences in these tipping point analyses, see Table 14.2-1.5 of the CSR.

Appendix G. Study GC-009

Study Design and Endpoint

Study GC-009 was conducted in the U.S. (90.9%) and Philippines (9.1%). This study was a completed, phase 2, 3-year, randomized, double-masked (subject and observer), active-controlled, NI study that compare the efficacy and safety of the Travoprost Intraocular Implant (Models G2-TR-063 and G2-TR-125) to topical Timolol Maleate Ophthalmic Solution, USP, 0.5% in subjects with OAG or OHT. In each study, eligible subjects were randomized (1:1:1) to one of the following three treatment groups:

- G2-TR-063: surgical implant of Model G2-TR-063 followed by placebo eyedrops
- G2-TR-125: surgical implant of Model G2-TR-125 followed by placebo eyedrops
- Sham/Timolol: sham surgical procedure followed by Timolol eyedrops

Following the operative visit (implant or sham surgical procedure), all subjects were instructed to instill 1 drop of study medication (placebo or Timolol) twice daily (BID) at approximately 8AM and 8PM in the study eye for 3 years.

Both studies consist of 19 visits over a 3-year period. The screening phase consisted of Visit 1 (screening) and Visit 2 (baseline). The treatment phase consists of Visit 3 (operative Day 0) and Visits 4 (Day 1-2), 5 (Day 10), 6 (Week 4), 7 (Week 6), 8 (Month 3), and every three months afterward: Visit 9 [Month 6] to Visit 19 [Month 36].

The primary efficacy endpoint defined in the SAP is “the diurnal IOP in the study eye at 8AM, 10AM, and 4PM at each of Day 10, Week 6, and Month 3 visits (9 timepoints)”. For each of the G2-TR-063 group and G2-TR-125 group, the SAP-defined criteria for NI are as follows:

- “The upper limit of the 2-sided 95% confidence interval for the difference in the mean IOP is <1.5 mmHg at each of the 9 post-baseline timepoints and is < 1 mmHg at the 5 or more of the 9 post-baseline timepoints”.

The secondary efficacy endpoints include the following:

- Standard IOP (measured at 8:00 AM) in the study eye at Months 6, 9, and 12.
- Change from baseline in IOP in the study eye at each timepoint through Month 12 for each post-baseline visit.

For further details of the study design, see the protocol.

Statistical Methodologies

The description of the primary estimand in the SAP is the same as one in Studies GC-010 and GC-012 except the following:

- Population-level summary parameter: **difference in post-baseline IOP means** between treatment groups for evaluating of non-inferiority.
- IEs related to the implant procedure (failure, incorrect region, or explant) are not considered.

The primary analysis method is a two-sample t-test at each time point. The CIs for the treatment differences are estimated from the two-sample t-test distribution. The SAP planned to perform the primary analysis on the intent-to-treat (ITT) population (defined as all randomized subjects) without any imputation for missing data. The SAP prespecifies multiple sensitivity analyses including (1) LOCF for imputation, (2) "Worse-Half" method for imputation similar to the one for Studies GC-010 and GC-012, and (3) trimmed mean method.

Subject Disposition, n (%)

Subject disposition and primary reasons for study discontinuation are summarized in Table 18. No one discontinued prior to or at Month 3. Four subjects discontinued the study prior to or at Month 12: two due to consent withdrawal and two due to adverse event

Table 18: Subject Disposition in GC-009 (ITT Population), n (%)

	G2-TR-063 Implant N=51	G2-TR-125 Implant N=54	Sham/Timolol N=49
Discontinued prior to or at Month 3			
No	51 (100.0)	54 (100.0)	49 (100.0)
Discontinued prior to or at Month 12			
Yes	2 (3.9)	1 (1.9)	1 (2.0)
No	49 (96.1)	53 (98.1)	48 (98.0)
Discontinuation reason			
Withdrawal	1 (2.0)	1 (1.9)	0
Adverse Event	1 (2.0)	0	1 (2.0)
Discontinued prior to or at Month 36			
Yes	7 (13.7)	8 (14.8)	4 (8.2)
No	44 (86.3)	46 (85.2)	45 (91.8)
Discontinuation reason			
Withdrawal	3 (5.9)	4 (7.4)	0
Adverse Event	1 (2.0)	0	1 (2.0)
Death	0	2 (3.7)	0
Investigator Decision	1 (2.0)	1 (1.9)	1 (2.0)
Lost to Follow-Up	1 (2.0)	1 (1.9)	2 (4.1)
Other	1 (2.0)	0	0

Abbreviations: ITT = intention-to-treat population
Source: Table 7 of the CSR. This table was produced by the reviewer based on the dataset adsl.xpt;

Baseline Demographics and Characteristics

Baseline demographic characteristics are summarized in Table 19. In general, the demographic characteristics were well balanced across the treatment groups. The mean age was 62.7 years. The proportions of males and females were similar. The majority of subjects were enrolled in the

U.S. (90.9%). The majority of subjects were of White race (77.3%). The majority of subjects were not of Hispanic or Latino ethnicity (94.8%).

Table 19: Baseline Demographics in GC-009 (ITT Population)

	G2-TR-063 Implant N=51	G2-TR-125 Implant N=54	Sham/Timolol N=49
Age, years			
Mean (SD)	63.9 (9.80)	61.4 (13.88)	63.0 (12.61)
Median	63.0	64.0	65.0
IQR	56.0, 71.0	53.0, 69.0	58.0, 71.0
Min, Max	40.0, 86.0	18.0, 86.0	23.0, 86.0
Age Group, n (%)			
18 to <65	28 (54.9)	30 (55.6)	24 (49.0)
65 ≥	23 (45.1)	24 (44.4)	25 (51.0)
Sex, n (%)			
Female	27 (52.9)	25 (46.3)	29 (59.2)
Male	24 (47.1)	29 (53.7)	20 (40.8)
Race, n (%) [1]			
White	41 (80.4)	41 (75.9)	37 (75.5)
Black	6 (11.8)	8 (14.8)	5 (10.2)
Asian	4 (7.8)	5 (9.3)	6 (12.2)
Unknown	0	0	1 (2.0)
Ethnicity, n (%) [2]			
Not Hispanic	47 (92.2)	53 (98.1)	46 (93.9)
Hispanic	4 (7.8)	1 (1.9)	3 (6.1)
Region, n (%)			
U.S.	47 (92.2)	49 (90.7)	44 (89.8)
Philippines	4 (7.8)	5 (9.3)	5 (10.2)

Abbreviations: ITT = intention-to-treat population, SD = standard deviation

[1] Black = Black or African American

[2] Not Hispanic = Not Hispanic or Latino, Hispanic = Hispanic or Latino

Source: Table 9 of the CSR for each study. Reproduced by the reviewer based on the dataset adsl.xpt;

Baseline disease and ocular characteristics are summarized in Table 20. In general, the disease type (OAG or OHT) and mean diurnal IOP were well balanced between G2-TR implant groups and Timolol group. The majority of the study eyes had OAG (79.9%). The mean baseline diurnal IOP was 24.98 mmHg. The majority of subjects had brown iris (44.2%).

Table 20: Baseline Disease and Ocular Characteristics for Study Eye in GC-009 (ITT Population)

	G2-TR-063 Implant N=51	G2-TR-125 Implant N=54	Sham/Timolol N=49
Disease Type			
OAG	38 (74.5)	45 (83.3)	40 (81.6)
OHT	13 (25.5)	9 (16.7)	9 (18.4)
Mean Diurnal IOP			
Mean (SD)	25.4 (3.55)	24.8 (3.94)	24.8 (3.01)
Median	24.7	23.7	24.2
Min, Max	21.0, 34.5	21.0, 35.8	21.2, 33.8
Baseline Mean Diurnal IOP Group, n (%)			
≤ 25 mmHg	29 (56.9)	37 (68.5)	31 (63.3)
> 25 mmHg	22 (43.1)	17 (31.5)	18 (36.7)

Iris Color, n (%)			
Blue	12 (23.5)	20 (37.0)	14 (28.6)
Brown	24 (47.1)	20 (37.0)	24 (49.0)
Green	1 (2.0)	0	0
Hazel	11 (21.6)	12 (22.2)	10 (20.4)
Other	1 (2.0)	1 (1.9)	1 (2.0)
Missing	2 (3.9)	1 (1.9)	0

Abbreviations: ITT = intention-to-treat population, OAG = open-angle glaucoma, OHT = ocular hypertension, SD = standard deviation

Source: Table 10 of the CSR for each study. This table was produced by the reviewer based on the adsl.xpt dataset.

Primary Efficacy Results

Table 21 presents the primary efficacy results. Neither G2-TR-063 nor G2-TR-125 met the NI criteria (i.e., the upper limit of 95% CI for the difference is < 1.5 for all 9 timepoints and <1 for at least 5 of the 9 timepoints). The results are numerically in favor of G2-TR-063 and G2-TR-125 at Day 10 and Week 6 while the results are numerically in favor of the Timolol at Month 3.

Table 21: IOP at 8AM, 10AM, and 4PM at Baseline, Day 10, Week 6, and Month 3 (ITT Population)

	G2-TR-063	G2-TR-125	Timolol
Baseline 8AM			
N	51	54	49
Mean (SD)	26.36 (4.94)	25.27 (4.71)	25.34 (3.89)
Min, Max	19.00, 38.00	18.00, 40.00	20.00, 38.50
Baseline 10AM			
N	51	54	49
Mean (SD)	25.38 (4.23)	25.04 (4.23)	25.00 (3.14)
Min, Max	18.50, 36.50	18.00, 36.00	21.00, 33.50
Baseline 4PM			
N	51	54	49
Mean (SD)	24.29 (3.60)	24.17 (4.10)	23.95 (3.39)
Min, Max	18.00, 36.00	19.00, 36.00	19.00, 35.00
Day 10 8AM			
N	51	54	49
Mean (SD)	17.58 (4.38)	17.28 (4.29)	17.98 (3.05)
Min, Max	9.00, 29.00	10.00, 32.00	11.50, 26.00
Difference (CI)	**-0.40 (-1.90, 1.09)**	**-0.70 (-2.15, 0.74)**	
Day 10 10AM			
N	51	54	49
Mean (SD)	16.78 (4.40)	16.99 (4.09)	17.35 (2.92)
Min, Max	10.00, 30.00	10.50, 32.50	11.00, 24.00
Difference (CI)	**-0.56 (-2.04, 0.92)**	**-0.36 (-1.74, 1.03)**	
Day 10 4PM			
N	51	54	49
Mean (SD)	16.44 (3.33)	16.19 (3.15)	17.40 (2.87)
Min, Max	10.00, 24.50	9.50, 26.00	11.50, 26.00
Difference (CI)	**-0.96 (-2.19, 0.28)**	**-1.21 (-2.39, -0.04)**	
Week 6 8AM			
N	51	54	49
Mean (SD)	17.89 (4.28)	17.26 (3.91)	18.15 (4.04)
Min, Max	10.50, 33.50	11.00, 34.00	13.00, 33.00
Difference (CI)	**-0.26 (-1.91, 1.39)**	**-0.89 (-2.45, 0.66)**	
Week 6 10AM			
N	51	54	49
Mean (SD)	17.25 (3.57)	16.69 (3.96)	16.83 (3.69)
Min, Max	11.50, 30.50	8.00, 26.00	12.00, 28.00
Difference (CI)	**0.42 (-1.02, 1.86)**	**-0.13 (-1.63, 1.36)**	
Week 6 4PM			

	G2-TR-063	G2-TR-125	Timolol
N	51	54	49
Mean (SD)	16.72 (3.52)	16.53 (3.89)	16.99 (3.00)
Min, Max	10.00, 29.50	9.50, 30.00	11.50, 25.50
Difference (CI)	**-0.27 (-1.57, 1.02)**	**-0.46 (-1.81, 0.89)**	
Month 3 8AM			
N	51	54	49
Mean (SD)	18.71 (4.09)	18.05 (5.07)	17.46 (3.02)
Min, Max	10.00, 29.00	10.00, 44.00	12.00, 24.50
Difference (CI)	**1.25 (-0.18, 2.67)**	**0.59 (-1.03, 2.20)**	
Month 3 10AM			
N	51	54	49
Mean (SD)	16.81 (3.16)	17.54 (4.68)	16.58 (2.91)
Min, Max	12.00, 24.00	11.00, 41.00	10.50, 24.00
Difference (CI)	**0.23 (-0.97, 1.44)**	**0.96 (-0.56, 2.47)**	
Month 3 4PM			
N	51	54	49
Mean (SD)	16.69 (3.30)	16.52 (4.61)	16.45 (2.85)
Min, Max	11.00, 25.00	9.50, 35.00	9.50, 23.50
Difference (CI)	**0.24 (-0.99, 1.46)**	**0.07 (-1.42, 1.56)**	

Abbreviation: SD (Standard Deviation), CI (95% Confidence Interval).
Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean IOP.
Source: Table 13 of CSR. This table was reproduced by the reviewer using the dataset adiop.xpt

IOP at Months 6 and 9

Table 22 presents IOP at Months 6 and 9. Unlike the visits included in the primary and key secondary endpoints, Months 6 and 9 measured IOP at a single timepoint of 8AM. The observed mean IOP was greater in the Timolol group at both Month 6 and Month 9 in both studies. The mean IOPs at Months 6 and 9 were similar between the G2-TR-125 and Timolol groups. The mean IOPs at Months 6 and 9 in the G2-TR-063 group was higher than the Timolol group.

Table 22: Mean IOP at Months 6 and 9 (ITT Population)

	G2-TR-063	G2-TR-125	Timolol
Month 6, 8AM			
N	51	53	49
Mean (SD)	18.8 (3.6)	17.8 (3.2)	17.8 (4.4)
Min, Max	12.0, 27.5	12.0, 28.0	10.5, 39.5
Difference (CI)	1.0 (-0.6, 2.6)	0.0 (-1.5, 1.5)	
Month 9, 8AM			
N	49	54	49
Mean (SD)	18.9 (3.5)	17.8 (3.9)	17.4 (3.1)
Min, Max	13.0, 27.5	10.0, 30.0	10.0, 27.0
Difference (CI)	1.5 (0.2, 2.8)	0.4 (-1.0, 1.8)	

Abbreviation: SD (Standard Deviation), CI (95% Confidence Interval).
Note: Difference (CI) is the difference (95% CI) against the Timolol group in the mean IOP.
Source: Table 24 of CSR. This table was reproduced by the reviewer using the dataset adiop.xpt

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I concur.