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ORIGINAL RESEARCH

Travoprost Intracameral Implant Demonstrates Superior IOP Lowering Versus Topical Prostaglandin Analog Monotherapy in Patients with Open-Angle Glaucoma or Ocular Hypertension

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ABSTRACT

Introduction: This study was conducted to analyze and compare the intraocular pressure (IOP) treatment effect of the slow-eluting (SE) travoprost intracameral implant to the IOP treatment effect of topical prostaglandin analog (PGA) monotherapy in a subgroup of subjects who were on pre-study PGA monotherapy prior to enrollment in the two pivotal phase 3 trials of the travoprost intracameral implant.

Methods: A combined study population of 133 subjects from two phase 3 trials, who were on topical PGA monotherapy at screening, subsequently underwent a washout period from their topical PGA, and then were randomized and administered an SE travoprost intracameral implant. The subjects were analyzed for the IOP treatment effects of the pre-study topical PGA monotherapy and the in-study SE travoprost intracameral implant. Paired *t*-tests were used to compare the difference in screening minus post-washout baseline IOP versus month 3 minus post-washout baseline IOP. The IOP-lowering efficacy in eyes administered an SE travoprost intracameral implant was compared to the IOP lowering in the same eyes while on a topical PGA monotherapy prior to study entry.

Results: Pre-study topical PGA monotherapy and the SE travoprost intracameral implant demonstrated IOP treatment effects of –5.76 mmHg and –7.07 mmHg, respectively. The IOP-lowering treatment effect was significantly greater by 1.31 mmHg for the SE travoprost intracameral implant relative to pre-study PGA monotherapy (95% confidence interval: –2.01, –0.60; $P=0.0003$).

Conclusions: The SE travoprost intracameral implant demonstrated superior IOP-lowering treatment effect versus pre-study topical PGA monotherapy with a superiority margin that was both statistically significant and clinically meaningful. The greater IOP reduction from baseline while on the SE implant versus pre-study topical PGA monotherapy may be a reflection of the optimized adherence and continuous elution of PGA therapy into the anterior chamber achieved with the SE travoprost intracameral implant.

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Key Summary Points

Topical intraocular pressure-lowering therapy is associated with poor patient adherence and troublesome side effects.

The slow-eluting travoprost intracameral implant produced clinically relevant and statistically significant greater intraocular pressure treatment effect than subjects' pre-study topical prostaglandin analog monotherapy.

Superior intraocular pressure reduction with the intracameral implant is presumably due to improved patient adherence with an implant.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness in the world [1]. Open-angle glaucoma (OAG) currently affects approximately 53 million people worldwide, with this number expected to increase to 79.8 million in 2040 as the population ages [1]. Lowering intraocular pressure (IOP) is the only treatment available to delay the onset or progression of glaucomatous vision loss [2–6], and medical therapy is the most common initial treatment to lower IOP.

Of the various classes of topical IOP-lowering medications, prostaglandin analogs (PGAs) are the most prescribed pharmacotherapy due to their highly efficacious IOP lowering, overall tolerability, well-established safety profile, and once-daily dosing regimen. However, despite these favorable attributes of PGAs, many patients fail to use their medication as prescribed [7]. If medication *is* being used as prescribed, patients may experience signs and symptoms of ocular surface disease [8, 9], as well as hyperemia, iris color change, eyelash growth/misdirection, and/or orbital fat atrophy [10].

Various drug delivery systems have been developed recently to specifically address the problem of poor patient adherence and the troublesome side effects associated with topical IOP-lowering therapy [11]. The two extended-release pharmaceuticals farthest along in the development pathway are the bimatoprost intracameral implant, an unanchored biodegradable implant containing 10 mcg bimatoprost approved in the US in 2020, and the travoprost intracameral implant, an anchored implant consisting of a titanium implant reservoir with a membrane that controls the sustained release of travoprost approved recently in the US in 2023. Two models of the travoprost implant, fast-eluting (FE-implant) and slow-eluting (SE-implant) models, were evaluated in the phase 2 and 3 trials for the registration of this drug-device combination product; however, approval was only requested for the SE-implant (iDose® TR, travoprost intracameral implant, 75 mcg).

We hypothesized that due to the optimized adherence and continuous elution of travoprost into the anterior chamber with the SE travoprost intracameral implant, the IOP reductions with the implant would be greater than that while on topical PGA therapy. This analysis compared the IOP-lowering effect of the SE travoprost intracameral implant to the IOP-lowering effect of topical PGA therapy in a subgroup of subjects who were on pre-study PGA monotherapy prior to enrollment in the two pivotal phase 3 trials of the travoprost intracameral implant.

METHODS

Study Design and Setting

This was a subgroup analysis of data from two phase 3 trials (GC-010 and GC-012, ClinicalTrials.gov, NCT03519386 and NCT03868124, respectively), which were prospective, randomized, double-masked, active-controlled pivotal safety and efficacy trials conducted to support the registration of the travoprost

intracameral implant for the reduction of IOP in patients with OAG or ocular hypertension (OHT). The trials were conducted in a total of 95 clinical sites in the USA, Armenia, and the Philippines. Both trials adhered to the tenets of the Declaration of Helsinki and were conducted in conformance with the International Conference on Harmonization good clinical practice and local laws and regulations. Institutional Review Board/Independent Ethics Committee approval was obtained for each site and all subjects provided written informed consent prior to participation.

Study procedures and the safety and efficacy results of these trials have been presented previously [12, 13]. In brief, adult subjects with OAG or OHT on zero to three IOP-lowering medications at screening, and mean diurnal IOP ≥ 21 mmHg (based on 8:00 a.m., 10:00 a.m., and 4:00 p.m. measurements) and IOP of ≤ 36 mmHg at each of these three diurnal time points at baseline following washout from prior IOP-lowering medication (4 weeks for PGAs), if applicable, were randomized to receive one of two models of the travoprost intracameral implant (slow-eluting or fast-eluting) or timolol maleate ophthalmic solution, 0.5% twice daily (BID). For masking purposes, subjects randomized to the travoprost implants received an artificial tear ophthalmic solution BID, and subjects randomized to timolol 0.5% BID underwent a sham surgical procedure. In both trials, one eye of each subject was randomized.

At screening, IOP could be measured at any time of day, whereas at baseline, day 10, week 6, and month 3, IOP was measured at 8:00 a.m. (± 30 min), 10:00 a.m. (± 30 min), and 4:00 p.m. (± 30 min). At all visits, IOP was measured by two observers. Observer 1 (unmasked to treatment) looked through the slit lamp and turned the dial, with the readings being masked. Observer 2 (masked to treatment) recorded the IOP readings. Each time IOP was measured, two measurements were taken and recorded unless they differed by more than 2 mmHg, in which case a third measurement was taken and recorded.

The primary efficacy objective for the trials was to demonstrate that the mean change from baseline in diurnal IOP in the study eye was not inferior to the mean change from baseline in diurnal IOP in the timolol 0.5% BID group at 8:00 a.m. and 10:00 a.m. at each of the day 10, week 6, and month 3 visits (six time points).

The objective of the current analysis was to compare the IOP-lowering treatment effects of the pre-study topical PGA monotherapy and the in-study SE travoprost intracameral implant. The treatment effect for the pre-study topical PGA monotherapy was determined as a difference between IOP while on a pre-study topical PGA collected at the screening visit and the post-washout IOP collected at the baseline visit. The treatment effect of the SE travoprost intracameral implant was determined as described previously as a difference between IOP at month 3 and the post-washout baseline IOP.

Participants

The study population consisted of all randomized subjects who received one of the two models of the travoprost intracameral implant (plus artificial tears ophthalmic solution BID for masking purposes) or timolol maleate ophthalmic solution, 0.5% BID (plus sham surgical procedure for masking purposes). Subjects who were on topical PGA monotherapy at screening and who were randomized to the SE travoprost intracameral implant were selected from the combined study population of the two trials for the current analysis.

Outcomes and Statistical Analysis

Since IOP measurements at screening could be performed at any time of day, whereas IOP measurements at baseline, day 10, week 6, and month 3 were required to be performed at 8:00 a.m. (± 30 min), 10:00 a.m. (± 30 min), and 4:00 p.m. (± 30 min), the IOP at screening was mapped to the closest IOP time point (i.e., 8:00 a.m., 10:00 a.m., or 4:00 p.m.). Therefore, all IOP analyses are based on a single time point.

IOP treatment effect in eyes administered an SE travoprost intracameral implant was compared to the IOP treatment effect (i.e., the difference in IOP at screening while on a pre-study PGA and IOP at the post-washout baseline) in the same eyes

that were on a topical PGA monotherapy prior to study entry.

Paired *t*-tests were used to compare the difference of screening minus post-washout baseline IOP versus month 3 minus post-washout baseline IOP, using the baseline and month 3 time-consistent measures to screening. Two-sided 95% *t*-distribution confidence intervals and a two-sided *P*-value were reported. SAS version 9.4 was used for the analysis.

IOP analyses were performed on the intent-to-treat population which included all subjects who were randomized, with subjects analyzed according to their original treatment assignment, regardless of actual treatment received. For the evaluation of adverse events, analyses were performed on the safety population, which included all subjects who were randomized and received study treatment, with subjects analyzed according to the actual treatment received.

RESULTS

Demographics and Baseline Characteristics

In the phase 3 study GC-010, 590 subjects were randomized in a 1:1:1 treatment allocation to receive the SE travoprost implant, FE travoprost implant, or timolol 0.5% BID in the study eye. Similarly, in the phase 3 study GC-012, 560 subjects were randomized in a 1:1:1 treatment allocation to receive the SE implant, FE implant, or timolol 0.5% BID in the study eye. Of the 380 subjects across the two trials who were randomized to the SE implant and in the intent-to-treat population, 133 were on topical PGA monotherapy at screening.

Demographic data and baseline ocular characteristics for the 133 subjects are provided in Table 1. The mean age was 63.59 years. Mean (standard deviation, SD) IOP was 18.09 (3.29) mmHg at the screening visit and 23.86 (3.23) mmHg at baseline following washout from pre-study PGA monotherapy.

Efficacy

Mean IOP at Screening, Baseline, and Month 3

Of the 133 subjects who were on PGA monotherapy at screening, 125 were included in the month 3 analysis (six had been prescribed additional IOP-lowering medication and were removed from the month 3 analysis, and two had missing month 3 data). The mean (SD) IOP while on pre-study topical PGA monotherapy was 18.00 (3.20) mmHg (collected at the screening visit) as shown in Fig. 1. Mean IOP at a post-washout baseline was 23.76 (3.25) mmHg (collected at the baseline visit after washout from pre-study topical PGA monotherapy). The mean IOP while on SE travoprost intracameral implant at month 3 was 16.69 (4.13) mmHg.

Comparison of Pre-study PGA Monotherapy to Travoprost Intracameral Implant Monotherapy

The mean (SD) IOP-lowering treatment effect while on pre-study PGA monotherapy was 5.76 (3.43) mmHg and the mean (SD) IOP-lowering treatment effect while on the SE travoprost intracameral implant was 7.07 (4.27) mmHg. The magnitude of the treatment effect was significantly greater by 1.31 (3.97) mmHg in the same eyes while on the SE travoprost intracameral implant compared to pre-study PGA (95% CI –2.01, –0.60; $P=0.0003$) (Table 2, Fig. 2).

A similar trend of greater IOP-lowering treatment effect while on the SE travoprost intracameral implant compared to pre-study PGA was shown regardless of pre-study PGA (Table 2). For all pre-study PGAs other than latanoprost, treatment groups were too small to provide meaningful analyses.

Relative Contributions of the 8:00 a.m., 10:00 a.m., and 4:00 p.m. IOP Values to the Overall IOP-Lowering Treatment Effect

Since IOP measurements at screening could be performed at any time of day, whereas IOP

Table 1 Subject demographics and baseline characteristics

		SE travoprost intracameral implant ***N*** **= 133**
Age (years)	Mean (SD)	63.59 (12.58)
	Minimum, maximum	24, 87
Age category *n* (%)	≥ 18 years to < 65 years	60 (45.1%)
	≥ 65 years	73 (54.9%)
Sex *n* (%)	Male	65 (48.9%)
	Female	68 (51.1%)
Race *n* (%)	Asian	4 (3.0%)
	Black or African American	29 (21.8%)
	White	97 (72.9%)
	Other	2 (1.5%)
	Unknown	1 (0.8%)
Ethnicity *n* (%)	Hispanic or Latino	15 (11.3%)
	Not Hispanic or Latino	117 (88.0%)
	Unknown	1 (0.8%)
Type of disease *n* (%)	Open-angle glaucoma	114 (85.7%)
	Ocular hypertension	19 (14.3%)
Screening IOP (mmHg)	Mean (SD)	18.09 (3.29)
Pre-study PGA *n* (%)	Latanoprost	73 (54.9%)
	Bimatoprost	29 (21.8%)
	Travoprost	16 (12.0%)
	Latanoprostene bunod	9 (6.8%)
	Tafluprost	6 (4.5%)

IOP intraocular pressure, *PGA* prostaglandin analog, *SD* standard deviation, *SE* slow-eluting

measurements at baseline and month 3 were required to be performed at 8:00 a.m. (±30 min), 10:00 a.m. (±30 min), and 4:00 p.m. (±30 min), the IOP at screening was mapped to the closest IOP time point (i.e., 8:00 a.m., 10:00 a.m., or 4:00 p.m.), and the IOP treatment effect values are shown in Table 2.

Similar trends were observed in these analyses performed on the subgroups of subjects whose screening IOP measurement was performed closest to 8:00 a.m. ($n = 19$), closest to 10:00 a.m. ($n = 55$), and closest to 4:00 p.m. ($n = 51$); differences achieved significance in the larger subgroups (i.e., $P = 0.0173$ for the 10:00 a.m. subgroup and $P = 0.0207$ for the 4:00 p.m. subgroup).

The lack of a meaningful difference in outcome based on IOP measurement time point

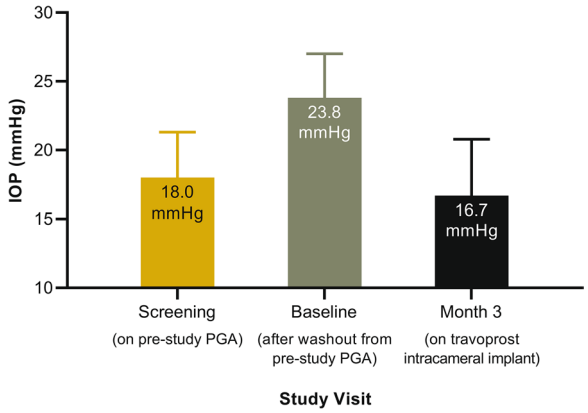

Fig.1 Mean IOP at screening (while subjects were on their pre-study PGA monotherapy), baseline (after washout from pre-study PGA monotherapy), and at month 3 (after administration of the slow-eluting travoprost intracameral implant). Error bars represent standard deviation. *IOP* intraocular pressure, *PGA* prostaglandin analog

validated the approach of comparing the IOP at screening to the closest single time point IOP at baseline and month 3.

IOP-Lowering Treatment Effect at Screening, Baseline, Day 10, Week 6, and Month 3

Mean (SD) IOP in the combined study population of 133 subjects from two phase 3 trials, who were on topical PGA monotherapy at screening is shown in Fig. 3.

The mean (SD) IOP-lowering treatment effect while on pre-study PGA monotherapy was 5.77 (3.46) mmHg while on the SE travoprost intracameral implant. The IOP-lowering treatment effects were 8.16 (4.11) mmHg at day 10, 7.13 (4.01) mmHg at week 6, and 7.07 (4.27) mmHg at month 3, treatment effects which were 2.36 mmHg, 1.43 mmHg, and 1.31 mmHg greater ($P \leq 0.0003$) than the IOP-lowering treatment effect of the pre-study topical PGA monotherapy.

Safety

Treatment-emergent adverse events were reported in the study eye of 30.3% of subjects during the 3-month period following administration of the SE travoprost intracameral implant, with most adverse events being mild and transient in nature. The most frequently reported adverse events were reduced visual acuity, iritis, and increases in IOP; these events were observed in < 6% of subjects.

DISCUSSION

Analysis of IOP data following topical IOP-lowering medication washout was used in this work to determine the IOP-lowering effect of pre-study topical PGA monotherapy. This methodology has been suggested as a means to better reflect the real-world scenario and assess the real-world efficacy of topical PGA pharmacotherapy, which is likely diminished by patients' low adherence to their prescribed IOP-lowering medication [14]. Applying this methodology to data from two large, well-controlled phase 3 trials of travoprost intracameral implant, the treatment effect of the pre-study topical PGA monotherapy was determined to be 5.76 mmHg from a 23.76 mmHg baseline. The IOP reduction at month 3 while on PGA monotherapy with the travoprost intracameral implant was 7.07 mmHg. The statistically significantly greater IOP reduction while on the travoprost implant may reflect the enhanced IOP-lowering that can be achieved by a treatment modality that provides continuous intracameral elution of travoprost and, importantly, is independent of patient adherence. The 1.31 mmHg greater reduction in IOP with the travoprost implant is also clinically relevant; the Early Manifest Glaucoma Trial concluded that for each 1 mmHg of IOP reduction from baseline in the first 3 months of treatment, there was an approximately 10% reduction in visual field loss [15]. An IOP lowering intracameral implant circumvents the issue of medication adherence, the absence of which is a well-known risk factor for glaucomatous progression [16–19].

Additional benefits associated with the travoprost intracameral implant include avoiding ocular surface disease associated with preservatives in topical medications [8, 9], avoiding conjunctival inflammation which raises the failure risk of future glaucoma filtering surgeries, if needed [20–22], and avoiding the difficulty

Table 2 IOP-lowering treatment effect at month 3 for the overall population, by time-matched IOP measurement, and by pre-study PGA

	n	IOP-lowering treatment effect mean (SD) mmHg		Difference in treatment effect mean (SD) mmHg [95% CI; *P*-value]
		Pre-study PGA	SE travoprost intracameral implant	
Overall population	125	−5.76 (3.43)	−7.07 (4.27)	−1.31 (3.97) [−2.01, −0.60; *P* = 0.0003]
By time-matched IOP measurement				
8:00 a.m Time-matched	19	−5.50 (3.17)	−6.37 (2.52)	−0.87 (2.71) [−2.18, 0.44; *P* = 0.1798]
10:00 a.m Time-matched	55	−5.65 (3.62)	−7.14 (5.03)	−1.49 (4.50) [−2.71, −0.27; *P* = 0.0173]
4:00 p.m Time-matched	51	−5.98 (3.38)	−7.25 (3.94)	−1.27 (3.80) [−2.35, −0.20; *P* = 0.0207]
By pre-study PGA				
Latanoprost	69	−5.68 (3.27)	−7.26 (3.93)	−1.58 (3.60) [−2.45, −0.71; *P* = 0.0005]
Bimatoprost	27	−6.11 (3.91)	−7.13 (3.50)	−1.02 (3.50) [−2.40, 0.37; *P* = 0.1427]
Travoprost	15	−4.90 (3.60)	−5.17 (6.62)	−0.27 (5.81) [−3.49, 2.95; *P* = 0.8615]
Latanoprostene bunod	8	−5.75 (3.34)	−6.06 (2.96)	−0.31 (2.45) [−2.36, 1.73; *P* = 0.7288]
Tafluprost	6	−7.25 (3.17)	−10.67 (4.00)	−3.42 (6.06) [−9.78, 2.94; *P* = 0.2259]

CI confidence interval, *IOP* intraocular pressure, *PGA* prostaglandin analog, *SD* standard deviation, *SE* slow-eluting

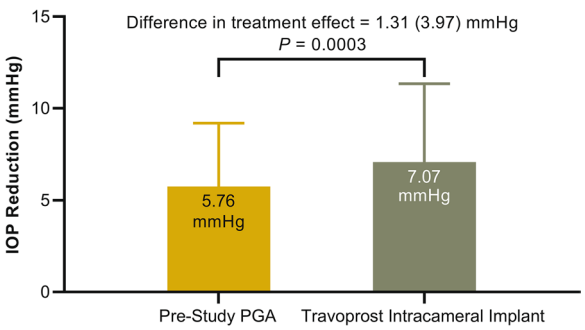

Fig. 2 IOP-lowering treatment effect and treatment effect difference. Error bars represent standard deviation. *IOP* intraocular pressure, *PGA* prostaglandin analog

with multiple or complicated dosing regimens and the struggle with accurate drop administration, particularly in the elderly or those with decreased manual dexterity and/or poor eyesight [23].

The 5.76 mmHg IOP increase post-washout from PGA monotherapy observed in the current analysis is similar to the 5.7 mmHg washout IOP observed in a previous analysis of 705 subjects on IOP-lowering monotherapy, of which 78.3% were on a topical PGA [14], and who had a post-washout baseline mean IOP of approximately 24.5 mmHg [24, 25]. In both analyses, subjects underwent a 4-week washout

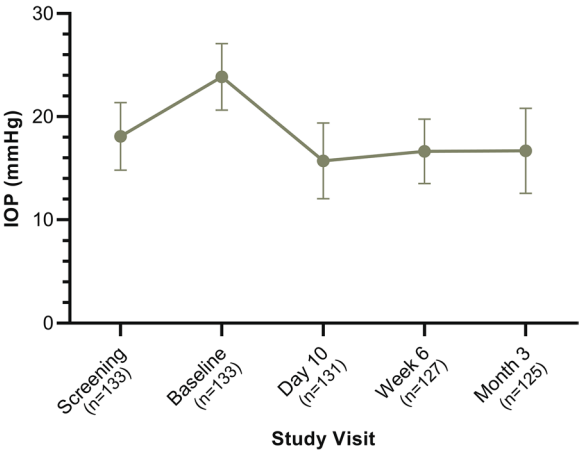

Fig. 3 Mean IOP for all subjects randomized to the slow-eluting travoprost intracameral implant who had been on a pre-study PGA monotherapy at screening. Since IOP was assessed at a single time point at the screening visit and at three time points (8:00 a.m., 10:00 a.m., *and* 4:00 p.m.) at the baseline, day 10, week 6, and month 3 visits, the IOP data at baseline, day 10, week 6, and month 3 are those from the time point (8:00 a.m., 10:00 a.m., *or* 4:00 p.m.) closest to that at which IOP was measured at screening. Error bars represent standard deviation. *IOP* intraocular pressure, *PGA* prostaglandin analog

for PGAs and had a post-washout baseline IOP of approximately 24 mmHg.

A limitation of the current study is that subjects were on a variety of pre-study PGAs, not just travoprost. However, the IOP reduction with bimatoprost, latanoprost, and travoprost has been shown to be comparable [26], and conversely, the IOP elevation following washout of individual medications within the PGA class has been shown to be comparable [14, 27]. In addition, our analysis demonstrated a greater IOP reduction while on the SE travoprost intracameral implant regardless of pre-study PGA. Another limitation is that the washout from PGAs was only 4 weeks. Lingering IOP effects of an insufficient washout may prevent the observation of a true unmedicated baseline IOP. However, a 4-week washout is the most common duration for pre-study PGAs in glaucoma clinical trials [28], and IOP has been demonstrated to return to its untreated baseline approximately 4 weeks after discontinuing latanoprost, the most commonly used pre-study PGA in this analysis [29].

Another limitation is that the use of IOP as an outcome measure for estimating adherence may be problematic due to diurnal variations in IOP. However, while IOP was measured at a single time point at the pre-study visit, it was measured at three time points (8:00 a.m., 10:00 a.m., and 4:00 p.m.) while on study, and a subgroup analysis demonstrated the same trend (i.e., a greater IOP-lowering treatment effect while on the travoprost intracameral implant compared to that while on pre-study PGA) in subjects in whom screening IOP was measured closest to 8:00 a.m., 10:00 a.m., or 4:00 p.m.

CONCLUSION

The study provides compelling results on the statistically significant and clinically relevant superiority in the IOP-lowering treatment effect with the travoprost intracameral implant compared with the IOP-lowering treatment effect of pre-study topical PGA monotherapy. The analysis demonstrates that the travoprost intracameral implant resulted in greater IOP reduction than subjects' prior topical PGA monotherapy, presumably because it removes the factor of patient adherence with dosing.

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Authorship. All authors whose names appear on the manuscript have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; drafted the work or revised it critically for important intellectual content; approved the version to be published; and agreed to be accountable for all aspects of the

work in ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved.

Author Contributions. Conception and design: Long V. Doan, Kerry G. Stephens, L. Jay Katz; Data collection: Jason Bacharach, Long V. Doan, Kerry G. Stephens; Analysis and interpretation: Dale W. Usner, Angela C. Kothe, Tomas Navratil; Writing and editing: Angela C. Kothe, Dale W. Usner, Jason Bacharach, L. Jay Katz, Tomas Navratil.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Jason Bacharach is a consultant/advisor for Glaukos Corporation and Allergan, Inc., has received research funding from Glaukos Corporation, and has received lecture fees/honoraria from Allergan, Inc. Long V. Doan, Kerry G. Stephens, Angela C. Kothe, L. Jay Katz and Tomas Navratil are employees of Glaukos Corporation and may hold stock and/or stock options. Dale W. Usner was an employee of Glaukos Corporation at the time this analysis was conducted and held stock and/or stock options, and is currently a consultant for Glaukos Corporation.

Ethical Approval. Human Subjects: Human subjects were included in these trials. The trials were registered at ClinicalTrials.gov (NCT03519386 and NCT03868124) and were performed in accordance with the tenets of the Declaration of Helsinki of 1964 and its later amendments, and with approval of the relevant Institutional Review Board/Independent Ethics Committee (for GC-010: WCG Institutional Review Board, Puyallup, Washington [reference number 20180735] or Wills Eye Hospital Institutional Review Board, Philadelphia, Pennsylvania [reference number 18–763] for sites in the USA, and St. Cabrini Medical Center—Asian Eye Institute Ethics Review Committee, Makati City, Philippines [reference number 2018–023] for the single site in the Philippines; for GC-012: WCG Institutional Review Board, Puyallup, Washington [reference number 20181794] for sites in the USA and the Ethics Committee of Ophthalmological Center named after S.V. Malayan, Yerevan, Armenia [approved on January 16, 2020] for the single site in Armenia). All subjects provided informed consent to participate in the study.

REFERENCES

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121:2081–90.

2. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7, the relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000;130:429–40.

3. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M; Early Manifest Glaucoma Trial

Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268–79.

4. Anderson DR; Normal Tension Glaucoma Study. Collaborative normal tension glaucoma study. Curr Opin Ophthalmol. 2003;14:86–90.

5. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701–13.

6. Garaway-Heath DF, Crabb DP, Bunce D, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomized, multicentre, placebo-controlled trial. Lancet. 2015;385:1295–304.

7. Nordstrom BL, Friedman DS, Mozaffari E, et al. Persistence and adherence with topical glaucoma therapy. Am J Ophthalmol. 2005;140:598–606.

8. Baudouin C. Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. Acta Ophthalmol. 2008;86:716–26.

9. Stalmans I, Lemij H, Clarke J, et al. Signs and symptoms of ocular surface disease: the reason for patient dissatisfaction with glaucoma treatments. Clin Ophthalmol. 2020;14:3675–80.

10. Tapply I, Broadway DC. Improving adherence to topical medication in patients with glaucoma. Patient Prefer Adherence. 2021;15:1477–89.

11. Cvenkel B, Kolko M. Devices and treatments to address low adherence in glaucoma patients: a narrative review. J Clin Med. 2023;12:151–71.

12. Katz LJ, Sarkisian SR, Voskanyan LA, et al. Results of the prospective, randomized, controlled, multicenter phase 3 trials of the travoprost intraocular implant versus topical timolol. Invest Ophthalmol Vis Sci. 2023;64:4296.

13. Sarkisian SR, Ang RE, Lee AM, et al. Travoprost intracameral implant for open-angle glaucoma or ocular hypertension: 12-month results of a randomized, double-masked trial. Ophthalmol Ther. 2024;13(4):995–1014.

14. Johnson TV, Jampel HD. Intraocular pressure following prerandomization glaucoma medication washout in the HORIZON and COMPASS trials. Am J Ophthalmol. 2020;216:110–20.

15. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2003;121:48–56.

16. Rossi GC, Pasinetti GM, Scudeller L, et al. Do adherence rates and glaucomatous visual field progression correlate? Eur J Ophthalmol. 2011;21:410–4.

17. Newman-Casey PA, Niziol LM, Gillespie BW, et al. The association between medication adherence and visual field progression in the collaborative initial glaucoma treatment study. Ophthalmology. 2020;127:477–83.

18. Shu Y-H, Wu J, Luong T, Mattox C, Fang EN, Lee BL, Jones JP, Campbell J, Shih V, Zhao C, Fong D. Topical medication adherence and visual field progression in open-angle glaucoma: analysis of a large US health care system. J Glaucoma. 2021;30:1047–55.

19. Rajanala AP, Prager AJ, Park MS, et al. Association of the effectiveness of eye drop self-instillation and glaucoma progression. J Glaucoma. 2022;31(3):156–9.

20. Broadway DC, Grierson I, Stürmer J, et al. Reversal of topical antiglaucoma medication effects on the conjunctiva. Ophthalmology. 1996;114:262–7.

21. Broadway DC, Chang LP. Trabeculectomy, risk factors for failure and the preoperative state of the conjunctiva. J Glaucoma. 2001;10(3):237–49.

22. Boimer C, Birt CM. Preservative exposure and surgical outcomes in glaucoma patients: the PESO study. J Glaucoma. 2013;22:730–5.

23. Kholdebarin R, Campbell RJ, Jin Y-P, et al. Multicenter study of compliance and drop administration in glaucoma. Can J Ophthalmol. 2008;43(4):454–61.

24. Samuelson TW, Chang DF, Marquis R, et al. A Schlemm canal microstent for intraocular pressure reduction in primary open-angle glaucoma and cataract: the HORIZON study. Ophthalmology. 2019;126(1):29–37.

25. Vold S, Ahmed II, Craven ER, et al. Two-year COMPASS trial results: supraciliary microstenting with phacoemulsification in patients with open-angle glaucoma and cataracts. Ophthalmology. 2016;123(10):2103–12.

26. Parrish RK, Palmberg P, Sheu W-P, XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol. 2003;135(5):688–703.

27. Jampel HD, Chon BH, Stamper R, et al. Effectiveness of intraocular pressure-lowering medication determined by washout. JAMA Ophthalmol. 2014;132(4):390–5.

28. Diaconita V, Quinn M, Jamal D, et al. Washout duration of prostaglandin analogues: a systematic review and meta-analysis. J Ophthalmol. 2018. https://doi.org/10.1155/2018/3190684.

29. Stewart WC, Holmes KT, Johnson MA. Washout periods for brimonidine 0.2% and latanoprost 0.005%. Am J Ophthalmol. 2001;131(6):798–9.