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ORIGINAL RESEARCH

Assessment of the Effectiveness, Tolerability, and Safety of the Preservative-Free Fixed Combination of Timolol, Dorzolamide, and Brimonidine Compared to Separate Therapies in Patients with Glaucoma, a Randomized Controlled Trial

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Purpose: To assess the non-inferiority of a preservative-free fixed combination of timolol, dorzolamide, and brimonidine (TDB-FC /PF) compared to the same fixed combination with preservatives or concomitant therapy for treating patients with uncontrolled primary open-angle glaucoma (POAG).

Patients and Methods: This Phase III study included 80 eyes from 43 patients randomized to receive TDB-FC/PF (preservative-free), TDB-FC (with preservatives), or TDB (triple therapy separately with preservatives) over 90 days. Follow-up visits took place at 2 and 4 weeks, and at 2 and 3 months. A mixed-effects model was used for the analysis. The primary outcome was intraocular pressure (IOP), measured at 9:00 a.m. and 11:00 a.m. Tolerability was assessed using the Ocular Comfort Index (OCI) and by evaluating conjunctival hyperemia and corneal staining. Safety assessments included best-corrected visual acuity, chemosis, visual fields, cup-to-disc ratio, central corneal thickness, and adverse event recording.

Results: After three months of treatment, the mean IOP decreased by 7.7, 8.3, and 8.3 mmHg at 9:00 a.m. and by 9.3, 9.8, and 9.6 mmHg at 11:00 a.m. for TDB-FC/PF, TDB-FC, and TDB, respectively ($p = 0.624$ and 0.753). The TDB-FC group showed a significant increase in conjunctival hyperemia severity at 2 and 4 weeks ($p = 0.044$ and 0.034, respectively). No significant differences were observed among groups for OCI, ocular surface staining, or safety parameters.

Conclusion: TDB-FC/PF effectively lowers IOP and is comparable to preserved fixed combinations or triple therapy in effectiveness. It is well tolerated, has a favorable safety profile, and offers the benefits of preservative-free formulations, which can enhance adherence in patients with POAG who need multiple medications.

Trial Registration: ClinicalTrials.gov identifier, NCT03193333.

Keywords: intraocular pressure, preservative-free fixed combination, ocular surface, ocular tolerability, primary open-angle glaucoma

Introduction

Glaucoma is a degenerative optic nerve disorder marked by the loss of retinal ganglion cells, thinning of the retinal nerve fiber layer, optic disc cupping, and associated visual field loss defects.[1] Primary open-angle glaucoma (POAG) is the most common type of the disease, making up nearly three-quarters of all glaucoma cases worldwide. It is the second leading cause of blindness globally, with an estimated prevalence of about 3.5% among people aged 40–80 years. In 2013, the number of people with glaucoma was estimated to be 64.3 million, rising to 76 million in 2020, and projected

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to increase to 111.8 million by 2040.[2,3] Latin American populations, particularly individuals of Mexican descent, are at higher risk compared to non-Hispanic whites.[4,5]

Although the exact cause of glaucoma is not completely known, elevated intraocular pressure (IOP) is the primary modifiable risk factor for the disease's progression, and lowering it remains the fundamental approach to treatment.[6,7] Monotherapy with prostaglandin analogues or beta-adrenergic blockers is usually the initial treatment; however, many patients require multiple topical treatments to achieve target IOP levels.[8] Due to either insufficient response or tachyphylaxis over time, with a consequent increase in side effects, reduced quality of life, and poor treatment adherence.[9] Fixed combination therapies simplify treatment regimens, potentially improving adherence and reducing exposure to preservatives such as benzalkonium chloride (BAK),[10] which have been associated with ocular surface toxicity and a higher rate of ocular surface disease (OSD).[11,12] The prevalence of OSD among glaucoma patients has been reported to be 30–70%, and the burden of topical therapy is a predictor of corneal staining severity. Some ocular surface issues can worsen when patients are treated with multiple topical glaucoma medications containing preservatives.[13,14]

In Mexico and other Latin American countries, a fixed triple combination of timolol, dorzolamide, and brimonidine is available and may represent a practical option for patients requiring maximal medical therapy.[15–18] There is a gap in the evidence regarding fixed triple combinations, as most previously published studies have focused on dual combinations.[19] Furthermore, limited data are available comparing preservative-free triple combinations with preserved therapies or concomitant regimens, underscoring the relevance of the current work. The aim of this study is to evaluate whether a preservative-free fixed combination of timolol, dorzolamide, and brimonidine is at least as effective as concomitant therapy in patients with uncontrolled primary open-angle glaucoma.

Materials and Methods

Study Design

This was a prospective, multicenter, double-masked, phase III noninferiority trial (ClinicalTrials.gov Identifier: NCT03193333) conducted across eight centers in Mexico and one in Colombia (see Acknowledgments for details). The protocol was conducted according to the principles outlined in the Declaration of Helsinki of 1964, Good Clinical Practice (GCP) guidelines established by the International Council for Harmonization (ICH), and applicable local regulatory requirements. The study included volunteer patients who fulfilled the inclusion criteria and signed informed consent to participate in all procedures. Recruitment took place from September 2017 to October 2024. Lockdown measures during the COVID-19 pandemic temporarily halted study participant recruitment from January 2020 to June 2022; however, these measures did not affect the follow-up of the included patients.

Participants

The included patients were adults over 18 years old with a confirmed diagnosis of POAG that was insufficiently controlled by their existing treatment after at least 2 months of use. After a washout period, the IOP at the baseline visit, conducted at 9:00 a.m., ranged from 21 to 36 mmHg in at least one eye. Furthermore, women of childbearing potential needed to use contraception since pregnancy, breastfeeding, or a high likelihood of childbirth without contraceptive use before enrollment were exclusion factors. Additional criteria for exclusion included an anterior chamber angle of less than 2 on Shaffer's scale, or an optic nerve cup-to-disc ratio exceeding 0.80 in either the horizontal or vertical plane in the targeted eye. Patients were also excluded if they were unable to safely discontinue ocular hypotensive medications during the washout period, if the investigator judged so, had a best-corrected visual acuity (BCVA) worse than 20/200 in either eye, experienced significant central visual field loss in either eye, had a history of ocular trauma within the past six months, a history of cataract surgery or any other intraocular surgery within three months before baseline, or had contraindications to any medication used in the study.

Treatment and Evaluations

Participants were evaluated for eligibility during a screening visit scheduled between 5 and 28 days before baseline, during which their medical and ocular histories were recorded. All screened patients started a washout period, the length of which was determined by the type of ocular hypotensive medication they used. Washout periods were defined as ≥ 5 days for topical cholinergic agonists and oral or topical carbonic anhydrase inhibitors, ≥ 14 days for α-adrenergic agonists, and ≥ 28 days for prostaglandin analogues and β-adrenergic blockers. For patients on combination therapies, the most extended washout period among the individual components was applied. Eligible patients were enrolled at the baseline visit. The patients were randomized to receive either the fixed combination of 0.5% timolol, 2% dorzolamide, 0.2% brimonidine preservative-free eye drops (n= 26, Krytantek Ofteno® PF, Laboratorios Sophia, S.A. de C.V., Jalisco, Mexico [TDB-FC/PF group]), or fixed combination of 0.5% timolol, 2% dorzolamide, 0.2% brimonidine (n= 25, Krytantek Ofteno®, Laboratorios Sophia, S.A. de C.V., Jalisco, Mexico [TDB-FC group]), or the concomitant triple therapy (n=29 [TDB group]) of 0.5% timolol (Imot Ofteno®, Laboratorios Sophia, S.A. de C.V., Jalisco, Mexico), 2% dorzolamide (Trusopt®, Merck Sharp & Dohme Corp., NJ, USA), and 0.2% brimonidine (Alphagan®, Allergan, Inc., Dublin, Ireland). To maintain double-blinding and standardize posology, participants in the TDB-FC/PF and TDB-FC groups received two placebo bottles. Treatments were administered twice daily, at 9:00 a.m. and 9:00 p.m., for three months, with a 5-minute interval between each drop. The study drug was discontinued if either the principal investigator or the patient determined that ongoing treatment was not in the patient's best interest, if the assigned treatment proved ineffective (defined as a 20% reduction in IOP from baseline), or if female patients became pregnant.

Outcome Variables

Efficacy was assessed by monitoring IOP from baseline through day 90 (three months). Measurements were taken by a masked investigator at consistent times during each follow-up visit, specifically at 9:00 a.m. (before the morning dose) and 11:00 a.m. (two hours after the morning dose). Tolerability was assessed using the Ocular Comfort Index (OCI) questionnaire,[20,21] conjunctival hyperemia grading (Efron scale),[22] and corneal fluorescein staining to detect epithelial defects (Oxford scale).[23] Safety variables included BCVA, chemosis, and visual fields assessed by computerized perimetry.[24,25] Cup-to-disc ratio, central corneal thickness determined by pachymetry,[26] and the incidence of adverse events.[27,28] Follow-up visits were scheduled at weeks 2 and 4, and at months 2 and 3 after therapy initiation.

Statistical Analysis

Statistical analyses were conducted using the R statistical software (The R Foundation for Statistical Computing; http://www.R-project.org). Unless otherwise specified, data are presented as mean ± standard deviation (SD). Before starting the study, an equation for continuous quantitative variables in clinical trials was used to determine that a minimum of 17 eyes per group would be necessary to detect a difference of at least 2.0 mmHg in mean controlled IOP among treatments, assuming a significance level of 0.05 and statistical power of 0.80.[15,29] Analyses of the primary and secondary outcomes were conducted in the intention-to-treat (ITT) population, which included all patients who underwent randomization and received treatment. Statistical analyses employed a mixed-effects model that accounted for repeated observations within groups and intra-patient correlation to avoid overestimating significance, especially since some patients contributed data from both eyes.[30] Noninferiority was established if the upper bound of the two-sided 95% confidence interval (CI) for the estimated mean difference in IOP change was below the predefined margin of 2.0 mmHg. Categorical variables were analyzed using p × q contingency tables, with differences assessed through Pearson's Chi-square test. All statistical analyses performed in this study had a threshold of $p < 0.05$.

Results

A total of 48 patients were screened, and 80 eyes from 43 patients (13 males and 30 females) were randomized (both eyes from 37 patients and one eye from six patients), with a mean age of 63.7 ± 14.4 years. Eight patients (15 eyes) discontinued participation before day 106 (safety call), conforming to the ITT population (see Figure 1). The mean deviation (MD) from Visual Field tests was −3.87 ± 3.12 for the TDB-FC/PF, −7.85 ± 6.43 for the TDB-FC group, and −2.15 ± 3.09 for the TDB group ($p < 0.0001$). For the pattern standard deviation, the values were 3.68 ± 2.35, 6.47 ± 3.69, and 2.98 ± 2.34, respectively ($p < 0.0001$). These were the

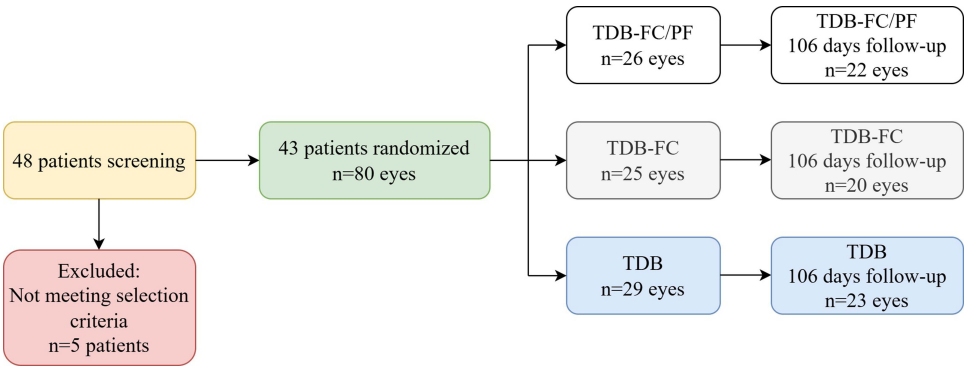

Figure 1 Current diagram of patients enrolled in the study.

only variables that initially demonstrated a statistically significant difference between the groups. Demographics and baseline characteristics are summarized in Table 1. Treatment adherence ranged from 85% to 100% throughout the study, with no significant differences observed among groups (factor group, p = 0.632) or across visits (factor visit, p = 0.087).

Efficacy

Intraocular Pressure

IOP was measured at 9:00 a.m. and again 2 hours later at each visit. At 9:00 a.m., the IOP reduction from baseline was similar across all groups, with no significant differences among them (p = 0.624). IOP decreased by 7.8 mmHg (95% CI, −8.49 to −7.14), 7.8 mmHg (95% CI, −8.50 to −7.14), 8.3 mmHg (95% CI, −8.96 to −7.56), and 7.9 mmHg (95% CI, −8.62 to −7.20) after 2 weeks, 4 weeks, 2 months, and 3 months of treatment, respectively (p < 0.0001). Figure 2a illustrates the reduction in IOP across the groups.

Table 1 Demographics and Baseline Characteristics for Each Group

		TDB-FC/PF	TDB-FC	TDB
No. of patients		14	14	15
No. of eyes		26	25	29
Age, years		62.9 ± 14.5	68.6 ± 11.4	59.8 ± 16.2
Nationality	Mexican	8 (57.1)	9 (64.3)	12 (80)
	Colombian	5 (35.7)	5 (35.7)	3 (20)
	American	1 (7.1)	0 (0)	0 (0)
BMI, kg/m^2		27.4 ± 6.0	27.0 ± 3.7	26.8 ± 4.0
Incidence of comorbidities, n (%)		9 (64.3)	7 (50)	13 (86.7)
IOP at 9:00 a.m., mmHg		26.2 ± 3.8	24.0 ± 2.8	23.7 ± 1.8
IOP at 11:00 a.m., mmHg		24.5 ± 4.5	22.6 ± 3.3	23.0 ± 1.7
Visual field, MD (dB)		−3.87 ± 3.12	−7.85 ± 6.43*	−2.15 ± 3.09
PSD		3.68 ± 2.35	6.47 ± 3.69*	2.98 ± 2.34
CCT, µm		538 ± 32.7	538 ± 49.2	542 ± 52.7
BCVA, LogMAR		0.65 ± 0.41	0.69 ± 0.39	0.75 ± 0.37
Cup-to-disc ratio		0.65 ± 0.09	0.67 ± 0.14	0.65 ± 0.14
OCI score		30.4 ± 15.9	34.4 ± 7.6	35.1 ± 11.8

Notes: One-way ANOVA showed p > 0.05 for all comparisons, except for visual fields and PSD, TDB-FC < TDB-FC/PF and TDB, where *p < 0.0001.

Abbreviations: BCVA, best corrected visual acuity; BMI, body mass index; CCT, central corneal thickness; IOP, intraocular pressure; MD, mean deviation; OCI, ocular comfort index; PSD, pattern standard deviation; TDB, concomitant triple therapy of timolol, dorzolamide, and brimonidine; TDB-FC, fixed combination of timolol, dorzolamide, and brimonidine; TDB-FC/PF, fixed combination of timolol, dorzolamide, and brimonidine preservative-free.

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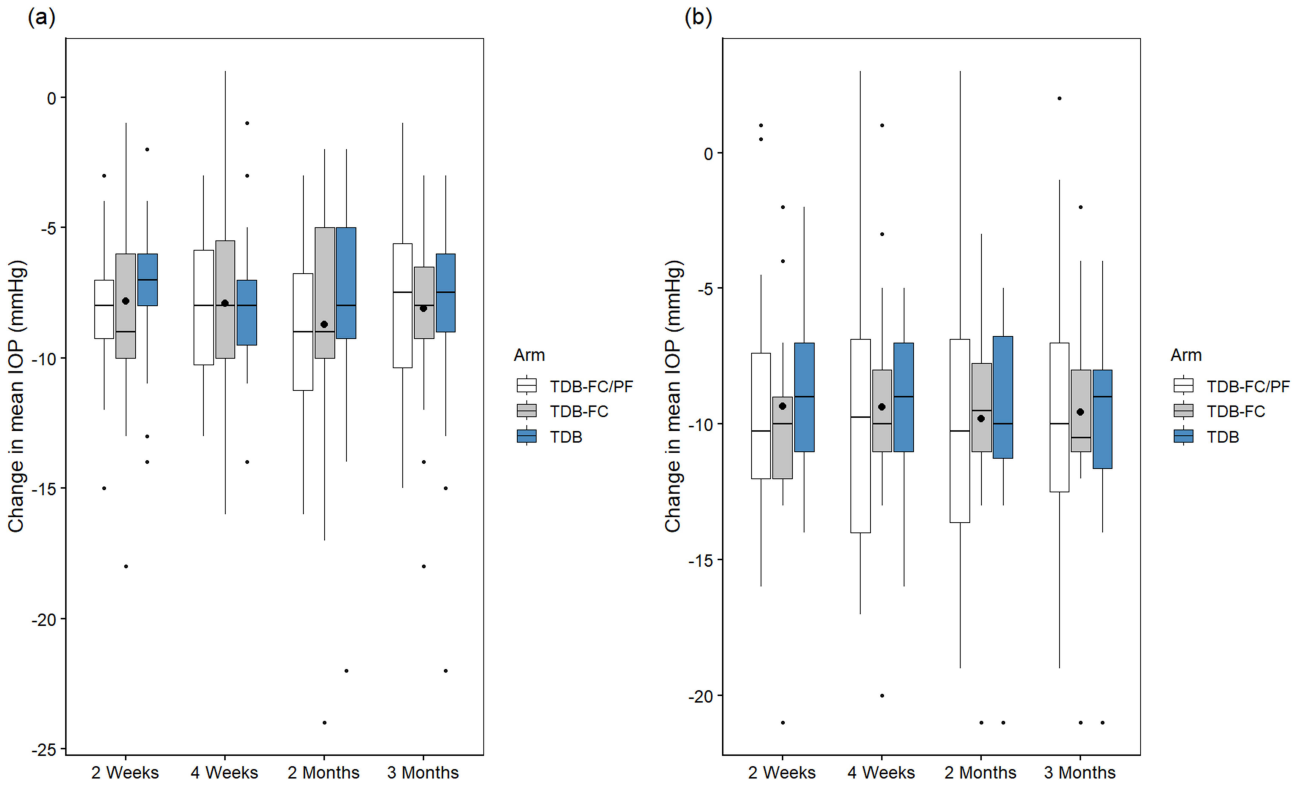

Figure 2 Comparison of changes in mean intraocular pressure (IOP) among treatments from baseline versus each visit, at 9:00 a.m. (**a**) and 11:00 a.m. (**b**). The full circle indicates the mean, while a small circle outside the box represents the outliers.

In the TDB-FC/PF group, the mean baseline of IOP at 9:00 a.m. was 26.2 ± 3.8 mmHg, which significantly decreased to 19.0 ± 4.4 mmHg after three months of treatment, representing a mean reduction of 7.7 ± 3.8 mmHg (29 ± 13%). For the TDB-FC group, IOP decreased from 24.0 ± 2.8 mmHg to 15.8 ± 2.7 mmHg, indicating a reduction of 8.3 ± 3.5 mmHg (34 ± 12%). Lastly, in the TDB group, IOP decreased from 23.7 ± 1.8 mmHg to 16.0 ± 3.3 mmHg, a decrease of 8.3 ± 4.1 mmHg (35 ± 18%), all p-values < 0.0001.

At 11:00 a.m. (two hours after the morning dose), the reduction in IOP from baseline was similar across all groups, with no significant differences among them (p = 0.753). The IOP decreased by 9.3 mmHg (95% CI, −9.99 to −8.65), 9.2 mmHg (95% CI, −9.93 to −8.58), 9.5 mmHg (95% CI, −10.19 to −8.79), and 9.4 mmHg (95% CI, −10.08 to −8.67) after 2 weeks, 4 weeks, 2 months, and 3 months of treatment, respectively (p < 0.0001). Figure 2b illustrates the reduction in IOP across the groups.

Following the changes in each treatment group, the mean baseline for the TDB-FC/PF group was 24.5 ± 4.5 mmHg, which significantly decreased to 15.2 ± 2.3 mmHg after three months of treatment, representing a mean reduction of 9.3 ± 4.8 mmHg (36 ± 16%). In the TDB-FC group, the IOP decreased from 22.6 ± 3.3 mmHg to 12.7 ± 2.2 mmHg, indicating a reduction of 9.8 ± 3.8 mmHg (42 ± 12%). Finally, in the TDB group, the IOP decreased from 23.0 ± 1.7 mmHg to 14.2 ± 2.2 mmHg, representing a 9.6 ± 3.4 mmHg (39 ± 10%) decrease, all p-values < 0.0001.

The estimated mean differences among groups at 9:00 were −0.99 mmHg and −0.48 mmHg (versus TDB-FC and TDB, respectively), while at 11:00 they were −0.57 mmHg and 0.48 mmHg. These differences were neither statistically significant nor clinically relevant. The upper bound of the 95% CI around the estimated means remained well below the allowed noninferiority limit of 2.0 mmHg.

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Tolerability

Ocular Comfort Index Questionnaire

The OCI score did not change significantly from baseline to the final visit in any treatment group (visit factor, p = 0.155). No differences among groups were observed at baseline, where the average scores were 30.4 ± 15.9 (min = 0, max = 51.4), 34.4 ± 7.6 (min = 24.6, max = 46.8), and 35.1 ± 11.8 (min = 15.9, max = 51.4) for the TDB-FC/PF, TDB-FC, and TDB groups, respectively. At the final visit, OCI scores were 29.4 ± 12.0 (min = 0, max = 44.1) for the TDB-FC/PF group, 29.2 ± 12.4 (min = 0, max = 48.4) for the TDB-FC group, and 29.4 ± 13.4 (min = 0, max = 45.2) for the TDB group (factor group; p = 0.722), as shown in Table 2.

Conjunctival Hyperemia

At baseline, 30.8% (8/26), 28% (7/25), and 48.3% (14/29) of eyes exhibited grade 0 (normal) conjunctival hyperemia in the TDB-FC/PF, TDB-FC, and TDB groups, respectively. After two weeks of treatment, conjunctival hyperemia was slightly reduced in the TDB-FC/PF and TDB groups, with 33.3% (8/24) and 60% (15/25) of eyes achieving grade 0, respectively. In contrast, the TDB-FC group showed an increasing trend, with only 20.8% (5/24) of eyes achieving grade 0 (p = 0.044). After four weeks of treatment, the proportion of eyes achieving grade 0 was 66.7% (16/24) in the TDB-FC /PF group, 31.8% (7/22) in the TDB-FC group, and 52% (13/25) in the TDB group (p = 0.034). Similar trends were observed at two and three months, with 63.6% (14/22), 35% (7/20), and 56.5% (13/23) of participants, respectively. No significant differences were observed among groups at baseline, 2 months, and 3 months (Chi-square, p-values: 0.425, 0.059, and 0.059, respectively). One eye assigned to the TDB-FC group exhibited severe conjunctival hyperemia from week 4 through month 3; meanwhile, the TDB-FC/PF and TDB groups showed only normal-to-mild conjunctival hyperemia throughout the study, as depicted in Figure 3.

Corneal Fluorescein Staining (CFS)

Compared with baseline, a slight reduction in the proportion of eyes with grade 0 cases was observed in all groups after two weeks of treatment. The TDB-FC/PF group experienced a decrease in grade 0 cases from 61.5% (16/26) to 54.2% (13/24), the TDB-FC group decreased from 64% (16/25) to 54.2% (13/24), and the TDB group experienced a drop from 65.5% (19/29) to 48% (12/25). After four weeks, the TDB-FC/PF group improved to 70.8% of cases (17/24) rated as grade 0. For the TDB group, 56% (14/25) were assigned a grade of 0, while the TDB-FC group saw a slight reduction, with 36.4% (8/22) of cases graded as 0. Similar findings were noted after 2 and 3 months, with 68.2% (15/22), 40% (8/20), and 52.2% (12/23) of cases achieving a grade of 0 for TDB-FC/PF, TDB-FC, and TDB, respectively. No significant differences were observed among groups at any time (Chi-square test, p-values: 0.198, 0.800, 0.098, 0.314, and 0.313 at baseline, 2 and 4 weeks, and 2 and 3 months, respectively), see Figure 4.

Table 2 Change from Baseline at 3-Month Follow-Up Visit

	TDB-FC/PF	TDB-FC	TDB	p-value
IOP at 9:00 a.m.	−7.7 ± 3.8	−8.3 ± 3.5	−8.3 ± 4.1	0.624
IOP at 11:00 a.m.	−9.3 ± 4.8	−9.8 ± 3.8	−9.6 ± 3.4	0.753
Visual field, MD (dB)	−4.07 ± 4.87	−7.10 ± 3.79*	−3.93 ± 2.73	< 0.001
PSD	3.18 ± 1.99	6.32 ± 3.67*	4.02 ± 2.63	< 0.0001
CCT	541 ± 37.5	550 ± 24.8	552 ± 53.0	0.724
BCVA, LogMAR	0.92 ± 0.99	0.63 ± 0.39	0.85 ± 0.31	0.420
Cup-to-disc ratio	0.61 ± 0.14	0.70 ± 0.09	0.66 ± 0.13	0.165
OCI score	29.4 ± 12.0	29.2 ± 12.4	29.4 ± 13.4	0.722

Notes: All values are reported as mean ± standard deviation, using a mixed-effects model. *Indicates statistical significance: for MD, TDB-FC < TDB-FC/PF, and TDB, p< 0.001; for PSD, TDB-FC > TDB-FC/PF and TDB, p < 0.0001.

Abbreviations: BCVA, best corrected visual acuity; CCT, central corneal thickness; IOP, intraocular pressure; MD, mean deviation; OCI, ocular comfort index; PSD, pattern standard deviation; TDB, concomitant triple therapy of timolol, dorzolamide, and brimonidine; TDB-FC, fixed combination of timolol, dorzolamide, and brimonidine; TDB-FC/PF, fixed combination of timolol, dorzolamide, and brimonidine preservative-free.

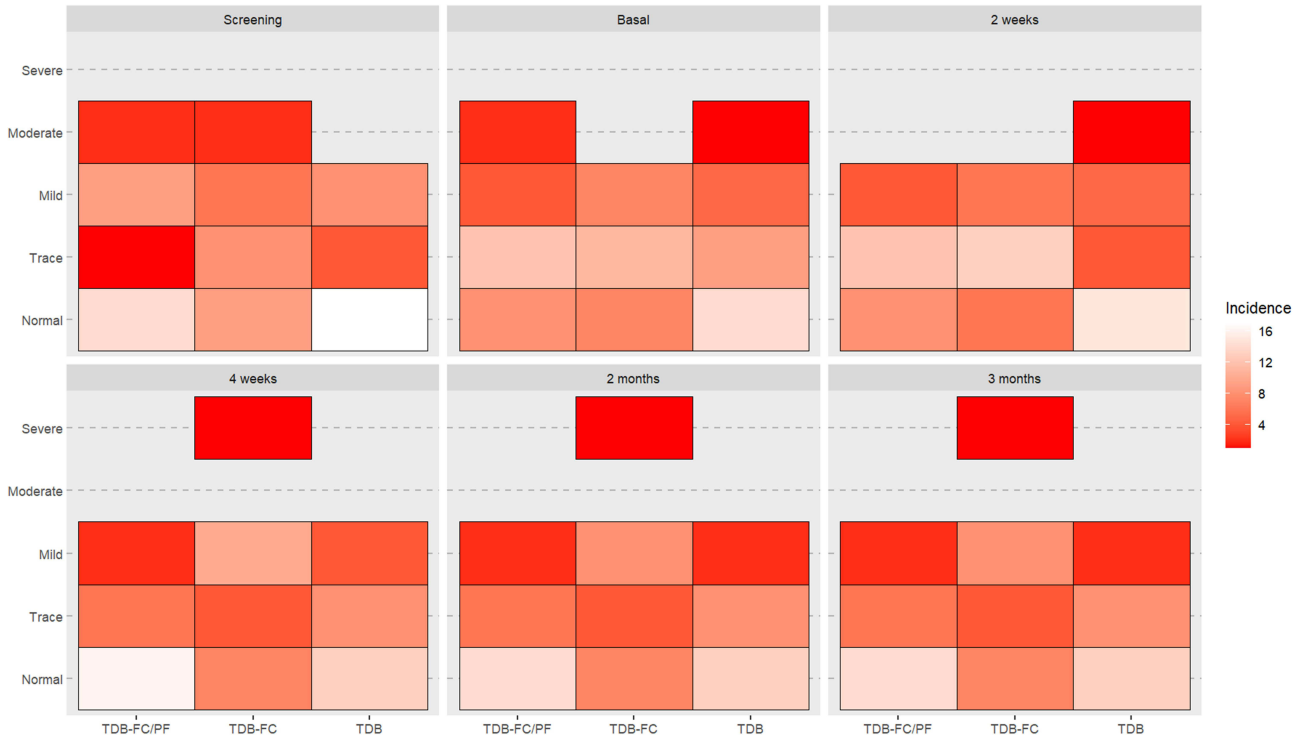

Figure 3 Incidence and severity of conjunctival hyperemia. The figure shows the number of cases (eyes). The TDB-FC group showed an increase in severity grading at 2 and 4 weeks of treatment (p-values: 0.044 and 0.034) compared with the TDB-FC/PF and TDB groups.

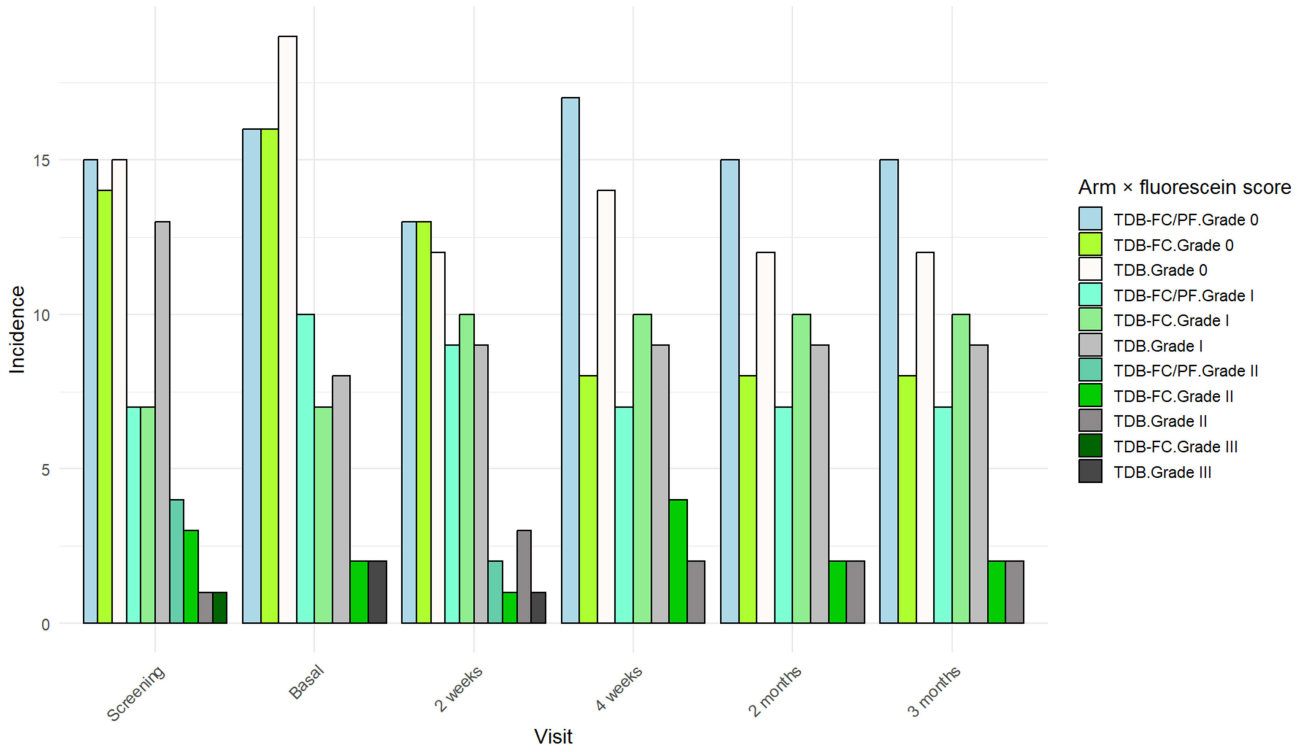

Figure 4 Incidence of fluorescein staining grading on the Oxford scale. The figure illustrates the cases (eyes) in each grading group from 0 to III. In TDB-FC/PF, only grades 0 to II were observed, with no significant differences among groups.

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Safety

Best-Corrected Visual Acuity (BCVA)

BCVA, assessed using the logarithm of the minimum angle of resolution (LogMAR), did not change significantly from baseline to the final visit in any treatment group (factor visit, p = 0.240). At baseline, mean BCVA values were 0.65 ± 0.41 for the TDB-FC /PF group, 0.69 ± 0.39 for the TDB-FC group, and 0.75 ± 0.37 for the TDB group, with no significant differences among them. At the final visit, BCVA was 0.92 ± 0.99 for the TDB-FC/PF group, 0.63 ± 0.39 for the TDB-FC group, and 0.85 ± 0.31 for the TDB group, with no significant differences among the groups (factor group; p = 0.420), as shown in Table 2.

Chemosis

No notable differences in chemosis incidence were seen across groups during the study. Initially, two cases were reported in each group, but these were not statistically significant (p = 1.000). In the TDB-FC/PF group, these cases, corresponding to the same patients, persisted from the screening to the final visit.

Visual Fields, Cup-to-Disc Ratio, and Central Corneal Thickness

Mean deviation (MD) from visual field testing did not change significantly from baseline to the final visit within any group. Baseline values were −3.87 ± 3.12, −7.85 ± 6.43, and −2.15 ± 3.09 for TDB-FC/PF, TDB-FC, and TDB, respectively. At the final visit, values were −4.07 ± 4.87 for TDB-FC/PF, −7.10 ± 3.79 for TDB-FC, and −3.93 ± 2.73 for TDB, with significant differences among groups (factor group; p < 0.001), as shown in Table 2. Post hoc analysis revealed that the MD values of the TDB-FC group differed significantly from those in the TDB-FC/PF group (p < 0.001; 95% CI, −5.66 to −1.44) and the TDB group (p < 0.0001; 95% CI, 2.53 to 6.60). However, no significant effect was observed for the factor visit (p = 0.471). The interaction between factors was not significant (group × visit day; p = 0.335).

The cup-to-disc ratio remained largely unchanged from baseline to the final visit across all groups (factor visit, p = 0.974). There were no significant differences between groups at the start (refer to Table 1). The final ratios were 0.61 ± 0.14 for TDB-FC/PF, 0.70 ± 0.09 for TDB-FC, and 0.66 ± 0.13 for TDB, with no notable differences among the groups (factor group, p = 0.165); see Table 2.

Central corneal thickness (CCT) did not change significantly from baseline to the final visit in any of the groups (factor visit, p = 0.259). The final CCT values were 541 ± 37.5 µm, 550 ± 24.8 µm, and 552 ± 53.0 µm for the TDB-FC /PF, TDB-FC, and TDB groups, respectively, with no significant differences between groups (factor group, p = 0.724). These results are presented in Table 2.

Adverse Events

A total of fifty-three adverse events (AEs) were reported by 65.1% (28/43) of the patients during the study. Of these, 54.7% were classified as expected AEs. Additionally, 50.9% of AEs were related to the study treatments, with 10%, 14.3%, and 10% classified as unexpected in the TDB-FC/PF, TDB-FC, and TDB groups, respectively (p = 0.572). Regarding causality assessment, 15.1% of AEs were considered possible, 47.2% probable or likely, and 37.7% unlikely. In the TDB-FC/PF group, one severe AE (hypertonic bladder) was reported. In contrast, in the TDB-FC group, two severe AEs were documented (eye irritation and one acute coronary syndrome). The eye irritation in the TDB-FC group was classified as related to the study treatment with possible causality. The most frequently reported related AEs were eye irritation (48.1%), followed by ocular hyperemia (14.8%) and eye pruritus (7.41%), with no significant differences among groups (p = 0.389). A summary of the AEs is displayed in Table 3.

Table 3 Adverse Events (53 AE/28 Patients)

	TDB-FC/PF	TDB-FC	TDB	Total
Patients with AE, n (%)	9 (64.3)	9 (64.3)	10 (66.7)	28 (65.1)
Total-AE, n (%)	22 (41.5)	16 (30.2)	15 (28.9)	53 (100)
Unexpected / Expected-AE, n (%)	13 (59.1) / 9 (40.9)	7 (43.8) / 9 (56.2)	9 (60) / 6 (40)	29 (54.7) / 24 (45.3)

(*Continued*)

Table 3 (Continued).

	TDB-FC/PF	TDB-FC	TDB	Total
Causality term, n (%)				
Possible	3 (13.6)	3 (18.8)	2 (13.3)	8 (15.1)
Probable or likely	9 (40.9)	6 (37.5)	10 (66.7)	25 (47.2)
Unlikely	10 (45.5)	7 (43.8)	3 (20)	20 (37.7)
Severity, n (%)				
Mild	9 (40.9)	9 (56.2)	12 (80)	30 (56.6)
Moderate	12 (54.5)	5 (31.2)	3 (20)	20 (37.7)
Severe	1 (4.6)	2 (12.5)	0 (0)	3 (5.7)
Related AE, n				
Drug ineffective	0	1	0	1
Dysgeusia	0	0	1	1
Eye irritation	5	4	4	9
Eye pain	0	0	1	1
Eye pruritus	1	0	1	2
Hypersensitivity	0	0	1	1
Lacrimation increased	0	0	1	1
Ocular hyperemia	2	1	1	4
Punctate keratitis	1	0	0	1
Vertigo	1	0	0	1
Vision blurred	0	1	0	1
Total-related AE, n (%)	10 (45.5)	7 (43.8)	10 (66.7)	27 (50.9)

Discussion

Several potential benefits have been described of using fixed combination (FC) medications compared with using the individual components separately, such as a reduction in the total number of drops and preservatives instilled daily, cost savings, improved tolerability and treatment adherence, and avoidance of the washout effect resulting from rapid instillation of multiple drops. Efforts to develop effective FC glaucoma medications date back several decades, and many of these commonly paired drug combinations have been approved by various regulatory agencies in different countries, achieving widespread clinical acceptance.[19]

On the other hand, numerous studies have confirmed that prolonged use of anti-glaucomatous eye drops, especially those containing BAK, can cause or worsen ocular surface injury, reducing patient compliance with treatment. BAK has been studied over the last few decades and has consistently demonstrated toxicity at concentrations between 0.005 and 0.02% in experimental and clinical studies.[31–33] Generally, patients with glaucoma require long-term treatment with topical medications that demonstrate good efficacy and adequate tolerability; therefore, preservation of ocular tissues remains a key priority in glaucoma management.[32] Today, there are alternative strategies to prevent patients from being chronically exposed to the toxic effects of preservatives, including preservative-free medications.[32] This approach improves adherence and provides a higher quality of life and better long-term outcomes for the glaucoma patient.[34]

Our study did not specifically target patients with co-existing OSD, such as chronic dry eye, nor was it designed to show statistical differences in tolerability. However, the findings showed that the preservative-free fixed combination was well-tolerated and offered a favorable safety profile, thereby improving adherence among patients with POAG who require multiple medications. In this multicenter randomized clinical trial, our findings demonstrated that the preservative-free fixed combination of timolol, dorzolamide, and brimonidine (TDB-FC/PF) is non-inferior to the preservative-containing fixed combination (TDB-FC) and the concomitant therapy (TDB) in reducing and controlling IOP in patients with POAG with uncontrolled IOP. Patients treated with TDB-FC/PF experienced a mean decrease of 7.7 mmHg after 90 days, with an OCI score similar to baseline. This suggests that the treatment was well-tolerated, with non-severe conjunctival hyperemia and a safety profile comparable to that of other therapies, in concordance with previous studies using fixed topical combinations in glaucomatous patients.[35,36] Overall, TDB-FC/PF was non-inferior to TDB-FC or the

TDB group in terms of IOP reduction during the three-month follow-up. According to results from the Early Manifest Glaucoma Trial, a 25% reduction in IOP from baseline has been shown to slow the progression of POAG.[37]

In our study, this threshold was exceeded in all treatment groups. At the 11:00 a.m. measurement, the TDB-FC group achieved a 42% reduction, while the TDB-FC/PF and TDB groups achieved reductions of 36% and 39%, respectively. Although the TDB group showed a slightly higher IOP reduction, the difference was not clinically meaningful and remained within the predefined non-inferiority margin. Notably, the TDB-FC/PF group, despite a somewhat lower reduction (36%), achieved a clinically effective outcome. Given its preservative-free formulation, it may be particularly advantageous for patients with preservative intolerance, such as those with dry eye syndrome or ocular surface disease, further supporting its role as a robust and well-tolerated therapeutic option.

Our results are consistent with those reported by Baiza et al, who compared the efficacy and safety of FC of timolol maleate 0.5%/dorzolamide 2%/brimonidine tartrate 0.2% versus an ophthalmic FC of 0.5% timolol/dorzolamide 2% in patients with open-angle glaucoma and ocular hypertension for 180 days. At the three- and six-month follow-ups, the triple combination achieved a 42.3% reduction in IOP, compared with 28.8% and 28.4% in the dual therapy group.[17] However, in a separate study by Baiza-Durán et al, the triple fixed combination of timolol 0.5%, brimonidine 0.2%, and dorzolamide 2% resulted in a 27.4% IOP reduction at 8:00 a.m. and a 22.5% reduction at 4:00 p.m. after 90 days of treatment, indicating a somewhat lower, yet clinically significant, effect depending on the time of measurement.[15] In contrast, a more recent study conducted in Bolivia reported a lower IOP reduction of 24.6% after one year of treatment following a switch from a fixed combination of timolol 0.5%/dorzolamide 2% (TD-FC) to a triple fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (TDB-FC) in patients with intermediate-stage glaucoma. Differences in patient populations, baseline IOP, treatment duration, and the timing of IOP measurements may help explain this variability. Nevertheless, our findings, with a 36% reduction in IOP observed over just three months of treatment with the preservative-free triple fixed combination (TDB-FC/PF), support its strong and rapid IOP-lowering efficacy. Recent efforts have focused on developing fixed triple-combination therapies to simplify treatment regimens and enhance IOP control in glaucoma. For example, Menon et al evaluated a triple fixed combination of bimatoprost 0.01%, brimonidine 0.15%, and timolol 0.5% in patients with suboptimal IOP control on dual therapy. After 12 weeks of treatment, the mean diurnal IOP reduction was approximately 4.0 mmHg, which corresponds to a 17.4% decrease from baseline. Their findings demonstrated that such formulations are feasible, well-tolerated, and potentially beneficial in real-world clinical practice.[38] Although the active ingredients and concentrations differ from those in our study, this work underscores the growing interest in triple fixed combinations as a strategy to improve therapeutic outcomes in glaucoma management. The development and use of FC therapies have reduced preservative-related side effects that negatively impact patient adherence to treatment and have decreased the washout effect after multiple instillations.[32,39] In several clinical studies, the PF formulations showed less severe signs and symptoms of OSD and performed adequately in terms of IOP control compared to preservative-containing formulations.[40,41] Therefore, enhancing adherence is crucial not only for efficacy but also for cost-effectiveness.

In general, the side effects associated with topical glaucoma medications fall into three categories: those related to mild or transient discomfort, those associated with cosmetic changes, and those related to safety concerns. Many topical medications are associated with transient and bothersome side effects that may not pose a significant safety risk.[42] In our study, 50.9% of adverse events were treatment-related. In the TDB-FC group, one serious adverse event (ocular irritation) was related to the study treatment. Similar to previously reported studies with treatments containing all or some of the same active ingredients.[15,43] We found that the most frequently reported related AEs were eye irritation (48.1% of subjects), followed by conjunctival hyperemia (14.8%) and eye pruritus (7.4%), with no significant differences between groups.

Prospective observational studies of patients under treatment with topical therapy for glaucoma have demonstrated significantly higher rates of signs and symptoms of dry eye compared to the general population.[44,45] For example, brimonidine has previously been shown to have possible local toxicity, causing follicular conjunctivitis and conjunctival hyperemia in up to 30% of patients. Furthermore, the low pH of carbonic anhydrase inhibitors, such as dorzolamide, may also be associated with ocular surface damage.[33] In addition, the association of allergy induced by topical antiglaucoma

treatment has been described mainly in the conjunctiva and periorbital region, manifesting as conjunctival hyperemia, chemosis, eyelid edema, itching, or periorbital eczema.[46]

In our study, despite the relatively high incidence of drug-related adverse events, these were mostly mild, and we did not find data suggestive of allergy in the participants. Only one subject in the TDB-FC group voluntarily withdrew from the study after experiencing ocular irritation. The adverse event reported by the patient was not associated with clinical signs, such as conjunctival hyperemia, chemosis, or corneal staining, during the ophthalmological examination. Conversely, no subjects in the TDB-FC/PF or TDB groups discontinued their participation in the study related to the presence of drug-related adverse events. Regarding other safety variables, as in other studies,[47,48] the difference in mean baseline visual field deviation between groups could be attributed to the inclusion of patients with glaucoma at various stages. However, there were no changes in either group regarding BCVA, chemosis, visual fields, cup-to-disc ratio, or central corneal thickness. Although a higher percentage of patients with grade 0 for both conjunctival hyperemia and fluorescein staining was observed in the TDB-FC/PF group, the difference between the groups was not statistically significant.

TDB-FC/PF and TDB groups showed only normal-to-mild conjunctival hyperemia from week 4 through the end of the study, demonstrating the favorable tolerability profile of this preservative-free fixed combination, which is essential for long-term glaucoma management. Variations in conjunctival hyperemia and fluorescein staining among treatment groups could be linked to the pH level in the TDB-FC group. For optimal comfort, the pH of ophthalmic medications and the ocular surface should ideally be between 6.6 and 7.8, resembling that of natural tears. Any deviations can lead to irritation, increased tearing, and discomfort.[49–51] Therefore, the differences in pH across treatments might account for the variations in conjunctival hyperemia and fluorescein staining, rather than disparities in the drug molecules themselves.[49]

The sponsor's decision to terminate this study early was due solely to a prolonged recruitment period that prevented the planned number of participants from being reached in a reasonable timeframe. It is essential to emphasize that this decision was not made due to safety concerns or adverse events that compromised the integrity of the study subjects. All procedures were conducted in accordance with current ethical and regulatory guidelines, and participant safety was a top priority at all times.

The main limitation of this study was the small sample size. This may be too small to accurately assess the efficacy and safety of this FC of hypotensive medications. Although a sample size calculation was estimated before the study began, this was done with the understanding that each patient could contribute one eye to the study. However, recruitment was challenging due to strict inclusion criteria, lockdown restrictions during the COVID-19 pandemic, and other factors. Several patients entered the trial with both eyes. However, data from both eyes can be analyzed by treating eyes as a "within-subjects" factor.[30] A statistical approach was used in the data analysis. While noninferiority was demonstrated at 3 months, to prevent overestimating significance, intra-patient correlation was accounted for in the statistical analysis.[30,52,53] Finally, it's crucial to consider that this short follow-up period may limit long-term safety monitoring, disease progression monitoring, and sustained adherence, so long-term studies would be advisable.

Conclusion

In summary, TDB-FC/PF presents a favorable safety profile and adequate hypotensive efficacy by demonstrating non-inferiority to TDB-FC or TDB, offering the inherent benefits of preservative-free ophthalmic solutions and the potential to improve patient adherence by simplifying the treatment dosing, constituting a good alternative for patients with POAG who require multiple medications to achieve IOP control.

Abbreviations

BCVA, best corrected visual acuity; CCT, central corneal thickness; CFS, corneal fluorescein staining; IOP, intraocular pressure; OCI, ocular comfort index; POAG, primary open-angle glaucoma; TDB, concomitant triple therapy of timolol, dorzolamide, and brimonidine; TDB-FC, fixed combination of timolol, dorzolamide, and brimonidine; TDB-FC/PF, fixed combination of timolol, dorzolamide, and brimonidine preservative-free.

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Data Sharing Statement

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

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The study protocol and informed consent form were approved by their respective Institutional Review Boards, chosen by the principal investigator or research center as follow: *Centro Hospitalario Vicor, S.A. de C.V., CHG Hospitales, Instituto Jalisciense de Investigación Clínica S.A. de C.V., RM Pharma Specialist, Investigación Biomédica para el Desarrollo de Fármacos S.A. de C.V.*, and *Fundación Oftalmológica Nacional*.

PRO-122 versus concomitant therapy in subjects with uncontrolled primary open-angle glaucoma (PRO-122LATAM), NCT3193333, was conducted in accordance with the principles of the Declaration of Helsinki (1964), the ICH guidelines, and current local legislation. The Original Study Group comprised members from eight sites in Mexico and one in Colombia, where the trial was conducted: Aris Vision Institute de Guadalajara, S.C., Fundación Oftalmológica Nacional, Consultorio Dr. Chávez, RM Pharma Specialist S.A. de C.V., IIMET Investigación e Innovación en Medicina Traslacional, Consultorio de Medicina Especializada, Catarata y Glaucoma de Occidente S.A. de C.V., Retina Center, and Consultorio Dr. Collado.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr Sandra Belalcazar reports personal fees from Abbvie, outside the submitted work. Dr Andrea Tornero-Jimenez, Dr Claudia Mejia-Morales, Dr Oscar Olvera-Montaño, and Dr Patricia Muñoz-Villegas are employees of Laboratorios Sophia. The authors report no other conflicts of interest in this work.

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