Fixed-combination Bimatoprost/Brimonidine/Timolol in Glaucoma: A Randomized, Masked, Controlled, Phase III Study Conducted in Brazil☆

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ABSTRACT

Purpose: Many patients with open-angle glaucoma eventually require >2 medications to lower their intraocular pressure (IOP). Fixed-combination ophthalmic solutions can be advantageous in patients who require multiple medications, but the number of fixed combinations combining 3 complementary IOP-lowering agents remains limited. This study assessed the efficacy and safety of a triple fixed combination (TFC) of bimatoprost 0.01%/brimonidine 0.15%/timolol 0.5% ophthalmic solution in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT), compared with a dual fixed combination (DFC) of brimonidine 0.2%/timolol 0.5%.

Methods: Patients with a baseline IOP of 23−34 mm Hg in both eyes and no history of IOP-lowering procedures were eligible for participation in this multicenter, double-masked, randomized, Phase III study. After washout of previous treatment (if applicable), patients were randomized to receive TFC or DFC twice daily in each eye for 3 months. The primary efficacy variable was the change from baseline in mean IOP in the worse eye at week 12 in the modified intent-to-treat (mITT) population. TFC was superior to DFC if the treatment difference (TFC − DFC) favored TFC at week 12 ($P \leq 0.05$; 2-sample t test). Secondary and sensitivity analyses were also performed. Safety, including adverse events, was assessed at all visits.

Findings: The mITT/safety population included 185 patients (TFC, n = 90; DFC, n = 95). TFC superiority was demonstrated at all postbaseline visits (all, $P < 0.001$) through week 12 (week 12 treatment difference: −2.17 mm Hg; 95% CI, −3.12 to −1.22). While treatment-related conjunctival hyperemia was more frequent with TFC than with DFC (47.8% vs 23.2%; $P < 0.001$), consistent with the additional presence of bimatoprost in TFC, most cases were mild and the numbers of patient discontinuations at week 12 were similar between the TFC and DFC groups (11 [12.2%] vs 7 [7.4%] patients; $P = 0.266$). No unexpected adverse events were reported.

Implications: Compared with DFC, TFC provided superior IOP lowering throughout the primary efficacy period. An acceptable tolerability profile was observed through 12 months of use of TFC, offering an effective therapeutic option in patients with POAG or OHT who require multiple medications to control their IOP. Additional studies are required for the assessment of the long-term effects of TFC. ClinicalTrials.gov identifier: NCT01217606. (*Clin Ther*. 2020;42:263−275) ©

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INTRODUCTION

The importance of controlling intraocular pressure (IOP) in glaucoma has been firmly established.[1–4] It is also well known that many patients require 2 or more medications to reach their target IOP.[5] Accordingly, the mainstay of therapy for primary open-angle glaucoma (POAG) and ocular hypertension (OHT) consists of IOP-lowering agents such as prostaglandin analogues/prostamide, β-blockers, and α_2-adrenergic receptor agonists, which are often used in combination due to their complementary mechanisms of action.[3,6–8]

Many published studies have shown that therapies combining 2 types of hypotensive agents in a single formulation provide greater IOP lowering than do the individual components,[9–15] while potentially lessening adverse events (AEs)[10,16,17] and improving patient adherence to the medication regimen.[3,4,18] Such examples include fixed combinations of bimatoprost/timolol,[19] brimonidine/timolol,[20] and dorzolamide/timolol,[21] which are all well-known dual-combination options. Considering that many medications used as adjunctive monotherapies or in dual fixed combinations are administered 2 or 3 times daily[6,8,22] for maximal effect, as well as data showing that bimatoprost can be formulated for twice-daily use without compromise of its efficacy,[23] a new ophthalmic solution of bimatoprost 0.01%/brimonidine 0.15%/timolol 0.5% (triple fixed combination [TFC]) administered twice daily was developed to incorporate the IOP-lowering power of bimatoprost into a known, dual combination, matching the posology of the dual combination. In a recent study conducted in Mexico and Colombia, TFC administered twice daily provided greater IOP lowering than did the dual fixed combination (DFC) of brimonidine 0.2%/timolol 0.5%,* also administered twice daily, while showing an acceptable tolerability profile at 12 weeks.[24] The study discussed herein was conducted to assess the safety and IOP-lowering efficacy of TFC (compared with DFC) in Brazilian patients with POAG or OHT. In contrast to the previous study, however, data on safety through 12 months of treatment were collected and are presented herein.

* Trademark: Combigan® (Allergan plc, Dublin, Ireland).

PATIENTS AND METHODS

Study Design

This multicenter, double-masked, randomized, Phase III study (ClinicalTrials.gov identifier: NCT01217606) was conducted in accordance with the Good Clinical Practice guideline, the Declaration of Helsinki, and applicable local laws in 7 centers in Brazil. The protocol was approved by an institutional review board at each investigational site before study start. The study was conducted between August 2, 2011, and June 30, 2015. All patients provided written informed consent before initiating treatment.

Study Population

Eligible patients were aged ≥18 years with a diagnosis of POAG or OHT requiring bilateral IOP-lowering treatment. At baseline (day 0) hour 0 (8–10 AM), patients had also completed (if applicable) a washout of their previous IOP-lowering therapy (4 days–4 weeks, depending on the medication), and IOP was 23–34 mm Hg in both eyes, with best-corrected visual acuity of ≥20/100 in each eye.

Key exclusion criteria were a known history of nonresponse to previous bimatoprost treatment; known allergy/hypersensitivity to the study medications or their components; contraindication to β-blockers or brimonidine; required long-term use of other ocular medications during the study; functionally significant visual field loss or evidence of progression in the previous year; recent or anticipated change in existing long-term therapy with agents that substantially affect IOP; conjunctival hyperemia >+1.0/mild; history of IOP-lowering procedures; and history of cataract surgery within 6 months of study start.

Study Treatment

At the baseline visit, patients were randomized 1:1 to receive TFC or DFC (with stratification based on

use [yes or no] of systemic β-blockers). An automated system randomly allocated 4-digit numbers to each site; a number was then assigned to each patient in ascending order, without omission or reuse. Patients were instructed to administer 1 drop of study medication in each eye twice daily, ~12 h apart, between 8:30 and 10:30 AM and between 8:30 and 10:30 PM. The study medications were provided in kits of identical appearance, and treatment began in the evening of day 0. On visit days, the morning dose was administered at the investigational site following the hour-0 assessments. An optional masked extension for safety data collection prolonged assigned study treatment from week 12 to month 12 in patients who chose to do so.

Assessments

Following applicable washout of prior IOP-lowering agents, study visits were scheduled at baseline and weeks 1, 2, 4, 8, and 12, at approximately the same time of day. IOP was measured at hours 0 and 2 to assess IOP lowering at the peak and trough of the comparator (DFC) using Goldmann applanation tonometry and a masked, 2-person reading method (in which one person adjusts the dial in a masked fashion and the second person reads and records the value, with no communication between the examiner and recorder that could affect the documented value); 2 consecutive measurements were obtained in each eye, followed by a third measurement at each time point if the between-reading difference was >2 mm Hg. In each patient, the *worse eye* was the eye with the higher IOP at baseline hour 0, or the right eye if both had equal IOP. If a patient's baseline IOP was not available, IOP at the screening visit was used for determining the worse eye prior to the initiation of the study treatment. *Mean IOP* was defined as the mean of the IOP measurements obtained in the worse eye at hours 0 and 2 at each visit.

Outcomes Measures And Analyses

Primary and secondary efficacy analyses were conducted in the modified intent-to-treat (mITT) population (ie, all randomized patients with ≥1 postbaseline efficacy evaluation), with any misrandomized patients analyzed in the treatment group per the randomization scheme. Sensitivity analyses were performed in the per-protocol (PP) population (ie, all randomized patients who received study medication, had no major protocol violations, and completed the treatment or were discontinued due to a lack of efficacy or AEs). The safety population included all patients who received ≥1 dose of study drug and attended ≥1 postbaseline visit; any misrandomized patients were to be analyzed as treated.

The primary efficacy variable was the change from baseline in mean worse-eye IOP at week 12 in the mITT population. The primary efficacy endpoint would be met if, at week 12, TFC provided a greater mean IOP reduction from baseline than did DFC, with a P value of ≤0.05 in a 2-sample t test. Missing data were imputed using the last observation carried forward method, with the exception of baseline values, which were not carried forward.

Secondary efficacy analyses included mean IOP and mean IOP change from baseline at weeks 1, 2, 4, 8, and 12, performed using 2-sample t tests with the last observation carried forward method, as well as mixed-effects model repeated measures (MMRM) on observed values (ie, without imputation for missing data) with unstructured covariance (including subject as random effect and treatment, systemic β-blocker use [yes or no], visit, and a treatment by visit interaction term as factors). Because the mean baseline IOP was found to be 1.0 mm Hg higher in the TFC group than in the DFC group, an analysis of covariance (ANCOVA) of the mean IOP change from baseline was also conducted, with treatment as fixed effect and baseline IOP as covariate. In addition, *post hoc* responder analyses were performed in the mITT population for the evaluation of the percentage of IOP reduction from baseline and mean IOP levels achieved, using observed data.

Safety assessments included AEs, visual acuity, biomicroscopy, ophthalmoscopy, cup/disc ratio, visual field, and vital signs, analyzed without imputation for missing data.

All analyses were generated using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina), and all P values were 2 sided. Unless otherwise noted, categorical variables were analyzed with the Pearson χ^2 test. A sample size of 92 patients per group was determined based on the primary efficacy variable and the assumptions that, at week 12, there was a minimum difference of 1.5 mm Hg in mean IOP change from baseline between treatment groups; an SD value of 3.4 mm Hg (based on data from 2

pivotal studies of DFC, NCT00332384 and NCT00332436); a 2-sided significance level of 0.05; 80% power; and a 10% dropout rate (PASS 2000 software; NCSS LLC, Kaysville, Utah). The optional masked extension period was not powered for efficacy analysis; hence, such an analysis is not included herein.

RESULTS

Patient Disposition And Characteristics

In total, 185 patients were enrolled and included in the mITT and safety populations; 159 (85.9%) completed the week-12 visit. Of 169 patients included in the PP population, 154 (91.1%) completed the week-12 visit. There were no misrandomized patients, and reasons for discontinuation were comparable in the mITT (Figure 1) and PP populations. Demographic and clinical baseline characteristics were similar between populations and between treatment groups (Table I). The majority of patients were white (n = 111; 60.0%) or black (n = 51; 27.6%). Prior to enrollment, the most commonly used IOP-lowering medications were the prostaglandin analogues and β-blockers, and the numbers of patients receiving them were similar between treatment arms.

Efficacy Analyses

The primary efficacy analysis showed that in the mITT population, the mean IOP change from baseline at week 12 was 2.17 mm Hg greater with TFC than DFC ($P < 0.001$), indicating superiority of TFC. Superiority of TFC over DFC was demonstrated at each visit through week 12 (Table II; 2-sample t test), and similar results were obtained in the MMRM analysis as well ($P < 0.001$ at all visits; treatment difference at 12 weeks, −2.20 mm Hg). In

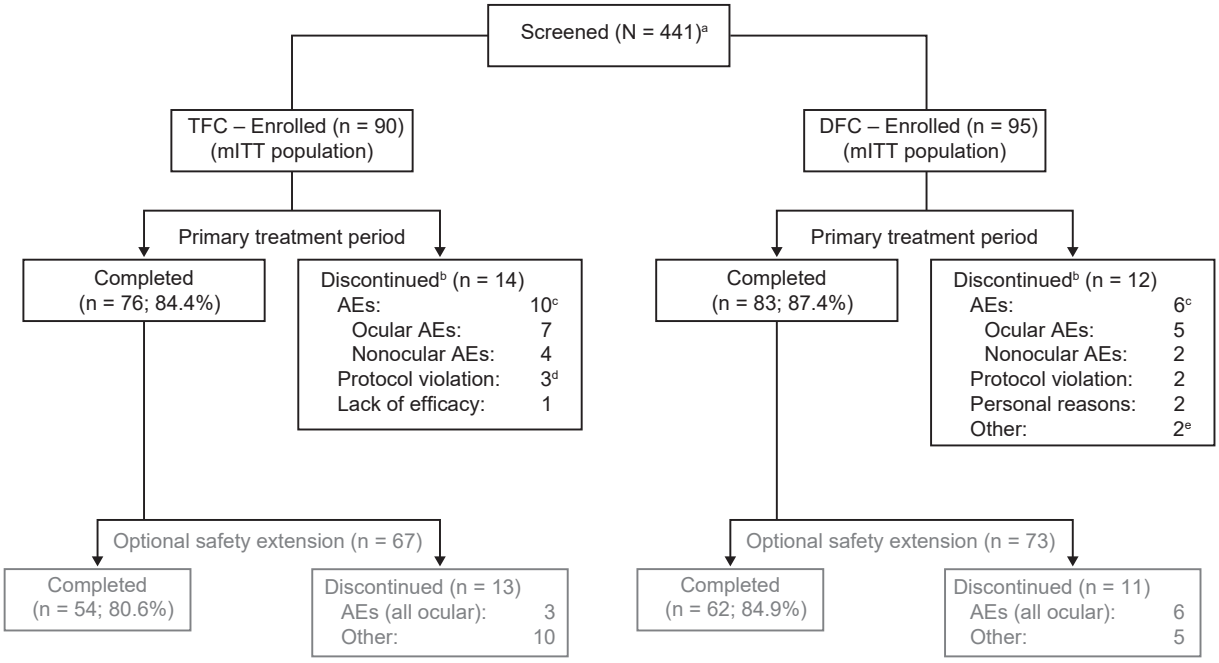

Figure 1. Patient disposition. The modified intent-to-treat (mITT) population included all randomized patients with ≥1 postbaseline efficacy evaluation. [a]A total of 256 patients failed screening, including 223 who did not meet the eligibility criteria; a reason was not provided for 33 patients. [b]An additional 2 patients in the triple fixed-combination (TFC) group and 4 patients in the dual fixed-combination (DFC) group had adverse events (AEs) leading to discontinuation after the week-12 visit and did not enroll in the optional masked extension. [c]One patient in each group discontinued due to both ocular and nonocular AEs. [d]One patient was enrolled despite meeting exclusion criteria, and discontinued after 1 week of treatment. [e]One patient had elevated IOP; 1 had normal IOP after discontinuing the study drug following a serious AE (Achilles tendon rupture, considered not treatment related).

the PP population, the treatment difference also favored TFC over DFC at all visits ($P < 0.001$), reaching −2.11 mm Hg and −2.26 mm Hg at week 12 in the 2-sample t test and MMRM analysis, respectively.

Although mean baseline IOP was higher in the TFC group than in the DFC group in both the mITT (25.4 [2.9] vs 24.4 [2.6] mm Hg; $P = 0.015$) and PP (25.5 [3.0] vs 24.5 [2.7] mm Hg; $P = 0.024$) populations, the mean IOP remained statistically significantly lower in the TFC group at all postbaseline visits through week 12 (Table III). An ANCOVA model that adjusted for baseline IOP in those populations also demonstrated that TFC produced statistically significantly greater mean IOP changes from baseline than did DFC at all visits; at week 12, the treatment differences were −1.50 mm Hg ($P < 0.001$) and −1.42 mm Hg ($P = 0.005$) in the mITT and PP populations, respectively.

In a responder analysis in which the magnitude of IOP lowering in each treatment group was assessed, the proportions of patients who achieved high (≥30%, ≥40%, and ≥50%) percentages of IOP lowering from baseline after 12 weeks of treatment were statistically significantly greater in the TFC group (85.5%, 57.9%, and 25.0%) than in the DFC group

Table I. Patient demographic and clinical characteristics at baseline (modified intent-to-treat population*). Data are given as no. (%) of patients unless otherwise noted.

Characteristic	TFC (n = 90)	DFC (n = 95)	P
Age			
Mean (SD), y	59.7 (10.5)	61.3 (8.5)	0.253
≤65 y	68 (75.6)	62 (65.3)	
Female	53 (58.9)	63 (66.3)	0.296
Diagnosis†			0.556
POAG	61 (67.8)	68 (71.6)	
OHT	26 (28.9)	26 (27.4)	
OHT, POAG	3 (3.3)	1 (1.1)	
Use of systemic β-blocker	19 (21.1)	21 (22.1)	0.870
Use of prior IOP-lowering therapy requiring washout	74 (82.2)	79 (83.2)	—

DFC = dual fixed combination; IOP = intraocular pressure; OHT = ocular hypertension; POAG = primary open-angle glaucoma; TFC = triple fixed combination.
*The modified intent-to-treat population included all randomized patients with ≥1 postbaseline efficacy evaluation.
† Refers to patients with POAG in both eyes, OHT in both eyes or OHT in 1 eye and POAG in the other eye, respectively.

Table II. Mean changes from baseline in IOP (modified intent-to-treat population*; 2-sample t test). Data are given as mm Hg.

Visit	ΔIOP, Mean (SD)		Between-Treatment Difference† (95% CI)	P
	TFC (n = 90)	DFC (n = 95)		
Week 1	−11.63 (3.06) (n = 82)	−8.13 (2.97) (n = 91)	−3.50 (−4.40 to −2.59)	<0.001
Week 2	−11.20 (3.29) (n = 84)	−8.28 (3.08) (n = 92)	−2.93 (−3.87 to −1.98)	<0.001
Week 4	−10.85 (3.18) (n = 85)	−8.53 (3.23) (n = 93)	−2.32 (−3.27 to −1.37)	<0.001
Week 8	−10.44 (3.11) (n = 85)	−8.07 (3.52) (n = 93)	−2.36 (−3.35 to −1.38)	<0.001
Week 12‡	−10.45 (3.18) (n = 85)	−8.28 (3.26) (n = 93)	−2.17 (−3.12 to −1.22)	<0.001

DFC = dual fixed combination; IOP = intraocular pressure; TFC = triple fixed combination.
*The modified intent-to-treat population included all randomized patients with ≥1 postbaseline efficacy evaluation.
† Negative values indicate greater IOP lowering with TFC than DFC.
‡ Primary efficacy variable.

(57.8%, 34.9%, and 7.2%) (Figure 2A). The proportions of patients who achieved low (≤13, ≤14, and ≤16 mm Hg) levels of IOP with treatment were numerically greater with TFC than with DFC (28.9% vs 15.7%, 36.8% vs 22.9%, and 71.1% vs 55.4%, respectively). However, the difference between treatment groups reached statistical significance only in the IOP ≤16 mm Hg analysis ($P = 0.049$) (Figure 2B).

Safety Evaluation

Through completion of the week-12 visit, treatment-related AEs were reported in 65 of 90 and in 51 of 95 patients receiving TFC and DFC, respectively (72.2% vs 53.7%; $P = 0.009$); most were ocular and mild, and none were serious. The most common treatment-related AE, conjunctival hyperemia, was reported by statistically significantly more patients receiving TFC compared with DFC (47.8% vs 23.2%; $P < 0.001$), as was eye pruritus (12.2% vs 4.2%; $P = 0.046$) (Table IV). However, the numbers of patient discontinuations at week 12 due to treatment-related AEs were similar between the TFC and DFC groups (11 [12.2%] vs 7 [7.4%]; $P = 0.266$).

Results were similar when the masked-extension safety data were included in the analysis (Table V); over the entire 12 months of data collection, 74 (82.2%) and 62 (65.3%) patients reported treatment-related AEs with TFC and DFC ($P = 0.009$), which included 72 (80.0%) and 59 (62.1%) patients with treatment-related ocular AEs, respectively ($P = 0.007$). As expected, conjunctival hyperemia was the most common treatment-related AE and was observed in more patients receiving TFC compared with DFC (53.3% vs 29.5%; $P = 0.001$). More patients also reported eye irritation (TFC, 12.2% vs DFC, 3.2%; $P = 0.020$). However, the numbers of patient discontinuations at month 12 due to treatment-related AEs were similar between the TFC and DFC treatment groups (13 [14.4%] vs 12 [12.6%]; $P = 0.718$). No treatment-related, clinically meaningful changes from baseline or statistically significant differences between groups were found in terms of best-corrected visual acuity, cup/disc ratio, ophthalmoscopy, visual field, and vital signs.

Table III. Mean IOP at each visit (modified intent-to-treat population).* Data are given as mm Hg.

Visit	IOP, Mean (SD)		Between-Treatment Difference† (95% CI)	*P*
	TFC (n = 90)	DFC (n = 95)		
Baseline	25.4 (2.9) (n = 90)	24.4 (2.6) (n = 95)	+0.99 (+0.19 to +1.79)	0.015
Week 1	13.8 (2.9) (n = 82)	16.2 (2.9) (n = 91)	−2.46 (−3.33 to −1.59)	<0.001
Week 2	14.3 (2.9) (n = 82)	16.2 (2.7) (n = 87)	−1.94 (−2.78 to −1.09)	<0.001
Week 4	14.7 (2.9) (n = 82)	15.8 (3.0) (n = 88)	−1.25 (−2.13 to −0.37)	0.005
Week 8	15.1 (3.0) (n = 75)	16.3 (3.5) (n = 87)	−1.34 (−2.37 to −0.32)	0.011
Week 12	15.0 (2.9) (n = 76)	16.0 (3.0) (n = 83)	−1.12 (−2.03 to −0.21)	0.016

DFC = dual fixed combination; IOP = intraocular pressure; TFC = triple fixed combination.
* Mixed-effects model repeated measures. The modified intent-to-treat population included all randomized patients with ≥1 postbaseline efficacy evaluation.
† Negative values indicate greater IOP lowering with TFC than DFC.

DISCUSSION

In this study, the IOP-lowering effect of TFC was found to be superior to that of DFC at all postbaseline visits through 12 weeks of treatment. These results are in line with other reports showing that fixed combinations containing 3 complementary hypotensive agents provide greater IOP lowering than dual combinations in patients with elevated IOP.[24–26] Evidence of a more robust response to TFC (compared with DFC) was also demonstrated in responder analyses, with a larger percentage of patients in the TFC treatment group experiencing a greater reduction in IOP at 12 weeks. The masked extension was optional and performed to provide an understanding of AEs over a longer term; it was not powered for efficacy purposes. However, IOP-

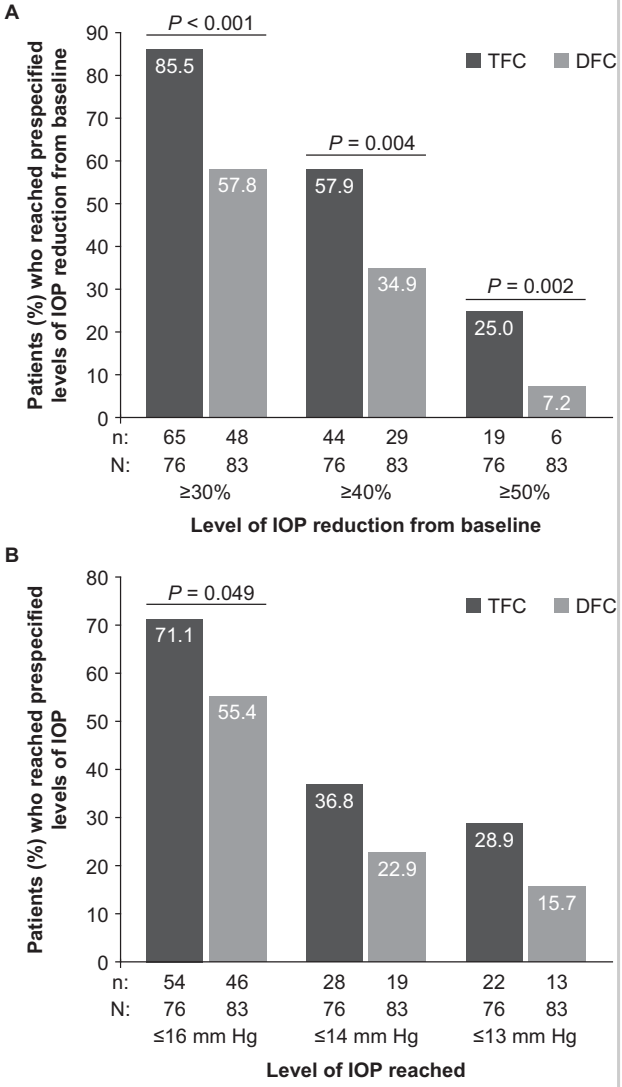

Figure 2. Percentages of patients achieving prespecified levels of intraocular pressure (IOP) reduction from baseline (top panel) and IOP (bottom panel) at week 12. Statistical significance was determined using the Fisher exact test. DFC = dual fixed combination; TFC = triple fixed combination.

lowering data collected during that period were supportive of the statistically significant difference in efficacy favoring TFC during the powered portion of the study. The between-treatment difference was −1.9 mm Hg (95% CI, −3.0 to −0.9; $P < 0.001$) at months 6 and 9, and −1.6 mm Hg (95% CI, −2.7 to −0.4; $P \leq 0.007$) at month 12 in the mITT population, with similar (and numerically greater) results in the PP population ($P \leq 0.017$).

The 3 active ingredients in TFC are known to reduce IOP via complementary mechanisms of action, and the current fixed combination requires the administration of only 1 drop from the same bottle of ophthalmic solution twice per day. The same 3-drug regimen used as concurrent monotherapies requires up to 6 administrations of drops from 3 different bottles per day, and 3 or more administrations from multiple bottles per day if dual fixed combinations are available. The need for using multiple bottles of different medications per day increases treatment burden for the patient. The multiple drops also increase exposure to benzalkonium chloride (BAK), a frequently used preservative that can cause ophthalmic discomfort, especially in patients who are sensitive to the compound.[3,27,28] Combining the 3 active ingredients into TFC allows simplification of the treatment regimen, while maintaining the active ingredients at the same or lower concentrations than when the individual monotherapy formulations, or DFC and bimatoprost, are administered concurrently, and reduces exposure to BAK by 50%−75%. Twice-daily administration of TFC exposes a patient to 100 ppm of BAK (50 ppm per dose), compared with up to 400 ppm with separate administrations of bimatoprost 0.01%* (200 ppm BAK), timolol 0.5% (50−100 ppm BAK), and BAK-free brimonidine 0.15%.†

The clinical relevance of a 3-agent medication such as TFC is further highlighted when considering that up to 80% of patients with glaucoma may struggle with adherence to their medication regimen because of the inconvenience associated with multiple eye drop instillation,[29–33] among other factors. Patients have also been shown to be less adherent with their first medication drop when a second medication drop is added,[18,34,35] suggesting that adding a third drop could reduce adherence even more. The rationale for developing TFC was thus based on a perceived need for a product that effectively lowers IOP in patients with uncontrolled POAG or OHT, while reducing the

* Trademark: Lumigan® (Allergan).

† Trademark: Alphagan® P (Allergan).

Table IV. Treatment-related adverse events (AEs) reported by 2+ patients in at least 1 group through week 12. Data are given as no. (%) of patients.

AE[*,†]	TFC (n = 90)	DFC (n = 95)	P[‡]
Conjunctival hyperemia	43 (47.8)	22 (23.2)	<0.001[§]
Punctate keratitis	11 (12.2)	10 (10.5)	0.716[§]
Eye pruritus	11 (12.2)	4 (4.2)	0.046[§]
Eye irritation	9 (10.0)	3 (3.2)	0.059[§]
Conjunctival follicles	6 (6.7)	9 (9.5)	0.484[§]
Erythema of eyelid	6 (6.7)	5 (5.3)	0.687[§]
Eye allergy	5 (5.6)	2 (2.1)	0.268
Somnolence	4 (4.4)	2 (2.1)	0.434
Blepharal pigmentation	4 (4.4)	1 (1.1)	0.202
Meibomianitis	3 (3.3)	3 (3.2)	>0.999
Dry eye	3 (3.3)	1 (1.1)	0.358
Foreign body sensation in eyes	3 (3.3)	1 (1.1)	0.358
Hypertrichosis	3 (3.3)	1 (1.1)	0.358
Blepharitis	3 (3.3)	0	0.113
Ocular discomfort	3 (3.3)	0	0.113
Eyelid edema	2 (2.2)	1 (1.1)	0.613
Skin hyperpigmentation	2 (2.2)	0	0.235
Conjunctival edema	0	2 (2.1)	0.498
Eyelid pruritus	0	2 (2.1)	0.498

DFC = dual fixed combination; TFC = triple fixed combination.

[*] By Medical Dictionary for Regulatory Activities preferred term.

[†] One serious treatment-unrelated AE was reported (Achilles tendon rupture, DFC group). Severe treatment-related AEs included conjunctival hyperemia, eye allergy, and ocular discomfort in the TFC group (n = 1 each), and conjunctival hyperemia, conjunctival follicles, and drug hypersensitivity in the DFC group (n = 1 each). Severe treatment-unrelated AEs included influenza and cough (n = 1 each, TFC group), as well as subcapsular cataract (n = 1, DFC group).

[‡] Based on the Fisher exact test unless otherwise noted.

[§] Based on the Pearson x2 test.

Table V. Treatment-related adverse events (AEs) reported by 2+ patients in at least 1 group through month 12. Data are given as no. (%) of patients.

AE[*,†]	TFC (n = 90)	DFC (n = 95)	P[‡]
Conjunctival hyperemia	48 (53.3)	28 (29.5)	0.001[§]
Punctate keratitis	18 (20.0)	14 (14.7)	0.344[§]
Eye pruritus	12 (13.3)	6 (6.3)	0.107[§]
Eye irritation	11 (12.2)	3 (3.2)	0.020[§]
Conjunctival follicles	6 (6.7)	12 (12.6)	0.171[§]
Erythema of eyelid	6 (6.7)	6 (6.7)	0.923[§]
Eye allergy	6 (6.7)	5 (5.3)	0.687[§]
Meibomianitis	6 (6.7)	4 (4.2)	0.528
Blepharal pigmentation	6 (6.7)	1 (1.1)	0.059
Hypertrichosis	5 (5.6)	2 (2.1)	0.268
Blepharitis	4 (4.4)	2 (2.1)	0.434
Somnolence	4 (4.4)	2 (2.1)	0.434
Dry eye	3 (3.3)	2 (2.1)	0.676
Foreign body sensation in eyes	3 (3.3)	1 (1.1)	0.358
Ocular discomfort	3 (3.3)	0	0.113
Eyelid edema	2 (2.2)	3 (3.2)	>0.999
Growth of eyelash	2 (2.2)	1 (1.1)	0.613
Lacrimation increased	2 (2.2)	1 (1.1)	0.613
Eye pain	2 (2.2)	0	0.235
Lacrimal disorder	2 (2.2)	0	0.235
Skin hyperpigmentation	2 (2.2)	0	0.235
Visual field defect	2 (2.2)	0	0.235
Conjunctival edema	1 (1.1)	3 (3.2)	0.621
Dry mouth	1 (1.1)	2 (2.1)	>0.999
Eyelid pruritus	0	2 (2.1)	0.498
Pinguecula	0	2 (2.1)	0.498

DFC = dual fixed combination; TFC = triple fixed combination.

[*] By Medical Dictionary for Regulatory Activities preferred term.

[†] Between the end of the primary study period (12 weeks) and study end (12 months), 1 additional serious treatment-unrelated AE was reported (rotator cuff syndrome, TFC group). Additional severe treatment-related AEs included congenital trichomegaly, conjunctival hyperemia, and eye irritation (n = 1 each) in the TFC group. Additional severe treatment-unrelated AEs included exostosis and spinal osteoarthritis (n = 1 each) in the TFC group, and retinal hemorrhage (n = 1) in the DFC group.

[‡] Based on the Fisher exact test unless otherwise noted.

[§] Based on the Pearson x2 test.

burden of treatment and potentially improving adherence to treatment.[3] The effectiveness of fixed-combination products such as once-daily TFC should not, however, undermine the importance of adherence, and clinicians should counsel their patients regularly on the merit of using their medications as prescribed.

Brimonidine and bimatoprost are both known to cause hyperemia,[6,7] and the greater prevalence of treatment-related conjunctival hyperemia observed with TFC was expected based on the addition of bimatoprost to the formulation. However, TFC did not raise any new, previously unknown safety concerns, and discontinuation rates were similar between groups. In fact, in a *post hoc* analysis of hyperemia reported through week 12 in the current study, it was found that, regardless of relationship to treatment, the overwhelming majority of reports in the TFC group were mild to moderate in severity (45 of 46; 97.8%); most of these cases (34 of 45; 75.6%) were mild. Results were similar in the DFC group, with a high prevalence of mild reports (20 of 22; 90.9%). One patient in each treatment group reported severe hyperemia, suggesting that the addition of bimatoprost to the combination formulation did not lead to additional severe findings. It is worth noting that the prevalence of conjunctival hyperemia observed with TFC is similar to that reported with bimatoprost 0.03% monotherapy,[36–42] which has been used worldwide for over 18 years. It also appears to be consistent with that of other, newer IOP-lowering treatments that contain 2 or fewer medications (eg, 47%–53% with netarsudil[‡] monotherapy[43,44] and 59% with fixed-combination netarsudil/latanoprost.[§,44] Fixed-combination netarsudil/latanoprost was recently approved by the United States Food and Drug Administration.[45]

In addition to being a preservative, BAK is a well-known enhancer of corneal penetration,[46–48] and preclinical investigations have demonstrated greater ocular bioavailability and pharmacokinetics of bimatoprost 0.01% when the concentration of BAK was raised from 50 to 200 ppm,[49] supporting the development of 0.01% bimatoprost as an alternative to the original 0.03% formulation, with similar efficacy at a lower drug concentration. Preclinical studies have also shown that bimatoprost drug exposure is similar in target ocular tissues of animals treated with bimatoprost 0.01% (preserved with 200 ppm BAK) once or twice daily, as well as bimatoprost 0.01% in a fixed combination (preserved with 100 ppm BAK) instilled once or twice daily.[23] Similarly, twice-daily administration of preservative-free bimatoprost 0.01% was shown to provide IOP lowering similar to that with once-daily administration in Phase II studies,[50] supporting the use of TFC administered twice daily. In a Phase III study that compared the efficacy and safety of bimatoprost 0.01% (preserved with 200 ppm BAK) and bimatoprost 0.03% (preserved with 50 ppm BAK), both formulations were shown to provide equivalent IOP lowering over 12 months.[51] Taken together, these findings suggest that the treatment regimen of a bimatoprost-containing ophthalmic solution could be manipulated through changes in the concentrations of bimatoprost and BAK. In this case, the combination of a lower concentration of both bimatoprost and BAK allows TFC to be instilled twice daily; the flexibility in administration afforded by reformulating to a twice-daily drop permits the unique combination of bimatoprost with medications requiring twice-daily instillation into one fixed-dose combination, maintaining the substantial IOP-lowering efficacy expected of the 3 components used concurrently, with an acceptable tolerability profile.

Potential study limitations included the fact that the study was not powered for efficacy analysis following week 12. However, the IOP lowering observed during the extension was supportive of the primary efficacy findings. The statistically significant difference in baseline IOP between treatment groups should also be considered, as it could have led to greater IOP lowering from baseline in the TFC group. However, an ANCOVA model that adjusted for baseline IOP in those populations confirmed that TFC produced statistically significantly greater mean IOP changes from baseline than DFC at all visits. Additional studies are required to assess the long-term efficacy of TFC.

‡ Trademark: Rhopressa® (Aerie Pharmaceuticals Inc, Durham, North Carolina).

§ Trademark: Roclatan™ (Aerie Pharmaceuticals).

CONCLUSIONS

In this double-masked, randomized, multicenter, Phase III study of 185 patients in Brazil, TFC provided clinically and statistically significantly superior IOP-lowering efficacy than did DFC at week 12 and the primary efficacy endpoint of the study was met ($P < 0.001$). TFC also exhibited clinically and statistically significantly greater IOP-lowering efficacy than DFC at all other postbaseline visits through 12 weeks of treatment (all, $P < 0.001$). In addition, TFC caused no unexpected AEs or marked worsening of expected AEs arising from the combination of these 3 medications into 1 ophthalmic solution. The results presented herein support the use of TFC as an effective, convenient therapeutic option for substantial IOP lowering in patients with elevated IOP due to POAG or OHT who require multiple hypotensive agents.

DISCLOSURES

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