

# Intraocular Pressure-lowering Efficacy of Brinzolamide When Added to Travoprost/Timolol Fixed Combination as Adjunctive Therapy

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On behalf of the ADAPT Study Investigator Group

**Purpose:** To compare the efficacy of brinzolamide versus placebo when added to travoprost/timolol fixed combination (TTFC) in uncontrolled patients.

**Patients and Methods:** This was a prospective, double-masked, randomized, placebo-controlled, parallel comparison of ocular hypertensive or primary open-angle glaucoma patients. Patients treated with a prostaglandin-based mono or adjunctive therapy were changed to TTFC qam (every day dosing) for 4 weeks. Patients with an intraocular pressure (IOP) of 19 to 32 mm Hg at 08:00 hours underwent additional measurements at 12:00 and 16:00 hours. Patients were then randomized to either placebo or brinzolamide given twice daily in addition to TTFC. At week 12, patients had their IOP measurements repeated.

**Results:** The per protocol dataset consisting of 78 placebo and 75 brinzolamide-treated patients decreased mean diurnal IOP (mm Hg) as well as IOP at all 3 individual time points ( $P \leq 0.005$ ). Brinzolamide reduced the mean diurnal IOP from  $20.3 \pm 2.0$  to  $17.5 \pm 2.6$ , whereas placebo reduced IOP from  $20.9 \pm 2.7$  to  $19.4 \pm 3.8$ . The mean diurnal IOP was reduced from baseline and for the 08:00 and 16:00 hours time points in the brinzolamide group compared with placebo ( $P \leq 0.014$ ). There were 30 adverse events with placebo and 24 with brinzolamide (intent-to-treat). There was no statistical difference for the side-effect profile observed between the treatment groups ( $P = 0.47$ ).

**Conclusions:** This study suggests that brinzolamide may be safely added to TTFC therapy to provide further significant reduction in IOP patients with ocular hypertensive or primary open-angle glaucoma.

**Key Words:** brinzolamide, travoprost/timolol fixed combination, intraocular pressure, adjunctive therapy, ocular hypertension, primary open-angle glaucoma

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Prostaglandin analogs are the most commonly prescribed medications used to lower the intraocular pressure (IOP) because of their potency and safety in patients with ocular hypertension or open-angle glaucoma.<sup>1</sup> However, in some patients, a second or even a third agent may be required to achieve a desired target IOP to minimize the risk of progressive visual field loss or conversion to glaucoma.<sup>2,3</sup>

Although a prostaglandin is usually prescribed for monotherapy, second-line therapy is most frequently accomplished with a  $\beta$ -blocker, used adjunctively or as a fixed combination product.<sup>1</sup> For third-line therapy, when a prostaglandin and  $\beta$ -blocker combination therapy is inadequate in reaching target IOP, an  $\alpha$ -agonist or a topical carbonic anhydrase inhibitor (CAI) is frequently prescribed.

Brinzolamide (Azopt Alcon Laboratories, Inc, Fort Worth, TX) is a topical CAI which has been shown to provide similar efficacy to dorzolamide with twice or 3 time daily dosing.<sup>4–6</sup> Brinzolamide, however, has demonstrated less stinging than dorzolamide in several clinical trials.<sup>4,7–9</sup> Unfortunately, little information exists on the use of a CAI as third-line therapy, when added to a prostaglandin and  $\beta$ -blocker.

The primary objective of this study was to compare the efficacy of brinzolamide compared with placebo administered twice daily in addition to travoprost/timolol fixed combination (TTFC; DuoTrav, Alcon Laboratories, Inc, Fort Worth, TX), administered once daily in the morning.

## MATERIALS AND METHODS

### Patients

This was a prospective, double-masked, randomized, placebo-controlled, parallel comparison consisting of 15 clinical sites in 6 countries. We included patients who: were at least 18 years of age; had a clinical diagnosis of ocular hypertension, primary open-angle, exfoliation, or pigment dispersion glaucoma in at least one eye (study eye); were treated with a prostaglandin agent alone or in combination with adjunctive drugs in fixed or unfixed combinations for a minimum of 2 weeks at visit 1; demonstrated an IOP

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between 21 and 32 mm Hg inclusive in at least one eye and  $\leq 32$  mm Hg in both eyes at visit 1; had an IOP between 19 and 32 mm Hg inclusive at the 08:00 hours measurement in at least one eye and  $\leq 32$  mm Hg at all time points in both eyes at Visit 2; and had a best corrected visual acuity of 6/30 (20/100 Snellen, 0.7 LogMAR) or better in each eye.

We excluded patients: with presence of other primary or secondary glaucomas not listed above; presence of narrow angles with complete or partial closure in either eye; with any abnormality preventing reliable applanation tonometry in study eye(s); any opacity or patient uncooperativeness that restricted adequate examination of the ocular fundus or anterior chamber of the study eye(s); with concurrent conjunctivitis, keratitis, or uveitis in either eye; with intraocular conventional surgery or laser surgery in study eye(s)  $< 3$  months before visit 1; who were women of childbearing potential; any clinically significant, serious, or severe medical or psychiatric condition; who had participated in any other investigational study within 30 days before visit 1; with known medical history of allergy or sensitivity to any components of the preparations to be used in this trial (ie, sulfa or benzalkonium chloride allergy); with concomitant administration of an oral CAI; prescribed systemic hypertension medications known to affect the IOP which were not stable for  $\geq 30$  days before visit 1 or an anticipated change in the dosage during the course of the study; with a history of bronchial asthma or chronic obstructive pulmonary disease that would preclude the safe administration of a topical  $\beta$ -blocker; with a history of, or at risk for, uveitis or cystoid macular edema; with a history of ocular herpes simplex, Fuch's corneal dystrophy, moderate-to-severe corneal guttata, low endothelial cell count by slit lamp biomicroscopy; or contact lens use.

## Procedures

Patients first signed an Ethics Committee approved informed consent form. This trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00382226). Patients who were being treated with a prostaglandin agent alone or in combination with an adjunctive medicine as a fixed or unfixed combination, and who had an IOP between 21 and 32 mm Hg inclusive at 08:00 hours, underwent a screening examination at week 4 (visit 1) including: medical and ocular history, automated full threshold perimetry by the investigator's preferred perimeter and software program, and dilated ocular examinations. At this visit, as well as at all other visits, Goldmann applanation tonometry, distance Snellen visual acuity at 6 meters, and slit lamp biomicroscopy were performed.

Patients who met the inclusion and exclusion criteria were changed from their current therapy to TTFC combination dosed each morning for 4 weeks and returned for the day 0 (visit 2) baseline examinations. Patients eligible for randomization were those with an IOP between 19 and 32 mm Hg inclusive at 08:00 hours. They then underwent baseline mean diurnal IOP testing at 12:00 and 16:00 hours after the 08:00 hours IOP measurement. Qualified patients were randomized to receive brinzolamide or placebo (brinzolamide vehicle), each given one drop to the study eye(s) at 08:00 and 20:00 hours, in addition to the fixed combination. Patients were instructed to separate the instillations of glaucoma medicines by at least 5 minutes.<sup>10</sup>

Patients returned at week 4 (visit 3) at 16:00 hours for an IOP measurement and safety evaluation. At week 12 (visit 4) patients had their 08:00 hours IOP measured. After

morning dosing of TTFC combination and the masked study medicine (5 min apart), the efficacy of mean diurnal IOP was measured. Patients then were exited from the study barring any unresolved, clinically significant, related or possibly related adverse events.

Study medication (brinzolamide and placebo) was packaged especially for this study by the sponsor in exactly identical containers, labeled appropriately for the trial. The placebo for this study was the vehicle for commercially available brinzolamide. The TTFC combination was supplied in open label packaging suitable for the trial.

## Statistics

PRN Pharmaceutical Research Network, LLC analyzed the data. All data analyses were 2 sided and had an  $\alpha$ -level of 0.05. The per protocol analysis was used primarily to evaluate treatment groups for this study. The statistical package used for all analyses was SAS (SAS Institute, Inc, Cary, NC).

The primary efficacy variable, mean diurnal IOP, was analyzed by a linear repeated measures of analysis model.<sup>11</sup> A SD of 3.5 mm Hg was assumed.<sup>12</sup> This study provided an 80% power that a 1.5 mm Hg difference could be excluded between the groups if at least 80 patients in each arm completed the study. Diurnal IOP was defined as the average of the 3 individual diurnal time points.

Demographics and adverse events were evaluated using a  $\chi^2$  or Fisher exact test as appropriate.<sup>11</sup> Adverse events were listed separately for ocular and systemic events. Funduscopy, visual field, and slit lamp parameters were not statistically evaluated.

Serious adverse events were listed with the investigators assessment of its relationship to the study medicine. Discontinued patients (after visit 2) were listed by the associated reason and study medicine.

## RESULTS

### Patients

We enrolled 163 patients in this study, and the per protocol dataset had 78 in the placebo arm and 75 in the brinzolamide arm. Table 1 shows the disposition of patients in this study. Patient characteristics between the 2 groups are shown in Table 2. There was no statistical difference between the treatment groups for any analyzed characteristic ( $P > 0.05$ ).

**TABLE 1.** Patient Disposition

	Patients (%)		
	Placebo	Brinzolamide	Total
Screened patients			203
Intent-to-treat analysis	84 (100)	79 (100)	163 (100)
Per protocol analysis	78 (93)	75 (95)	153 (94)
Patients excluded from per protocol analysis	6 (7)	4 (5)	10 (6)
Incomplete intraocular pressure data	2 (1)	0 (0)	2 (1)
Withdrawals	4 (3)	4 (4)	8 (6)
Adverse events	2 (1)	1 (1)	3 (2)
Administrative error	1 (1)	0 (0)	1 (1)
Lost to follow up	0 (0)	1 (1)	1 (1)
Ran out of study drug	0 (0)	2 (2)	2 (1)
Lack of efficacy	1 (1)	0 (0)	1 (1)

**TABLE 2.** Patient Characteristics – Per Protocol

Variable	Value	Patients (%)			P
		Placebo (N = 78)	Brinzolamide (N = 75)	Total (N = 153)	
Sex	Female	53 (68)	42 (56)	95 (62)	0.13
	Male	25 (32)	33 (44)	58 (38)	
Age (y)	< 56	14 (18)	12 (16)	26 (17)	0.08
	56-65	25 (32)	16 (22)	41 (28)	
	66-75	28 (36)	23 (31)	51 (33)	
Race	> 75	11 (14)	23 (31)	34 (22)	1.00
	White	75 (96)	75 (100)	150 (98)	
	Other	3 (4)	0 (0)	3 (2)	
Iris color	Brown	46 (59)	42 (56)	88 (58)	0.77
	Blue	14 (18)	17 (23)	31 (20)	
	Hazel	12 (15)	8 (11)	20 (13)	
	Green	5 (6)	5 (7)	10 (7)	
	Other	1 (1)	3 (4)	4 (3)	
Past medical history	Arterial hypertension	45 (58)	41 (55)	88 (56)	0.44
	Diabetes	12 (15)	15 (20)	27 (18)	
	Hypercholesterolemia	19 (24)	12 (16)	31 (20)	
Past ophthalmic medical history	Cataract	14 (18)	13 (17)	27 (18)	0.95
	Exfoliation glaucoma	7 (9)	8 (11)	15 (10)	
	Conjunctival hyperemia	3 (4)	3 (4)	6 (4)	
Past ophthalmic surgical history	Trabeculectomy	15 (19)	9 (12)	24 (16)	0.14
	Trabeculoplasty	6 (8)	9 (12)	15 (10)	
	Phacoemulsification	4 (5)	9 (12)	13 (8)	
Past ophthalmic medication history	Prostaglandin	64 (82)	59 (79)	123 (80)	0.79
	β-Blocker/prostaglandin	15 (19)	15 (20)	30 (20)	
	β-Blocker	14 (18)	7 (9)	21 (14)	
	CAI	4 (5)	6 (8)	10 (6)	
	β-Blocker/CAI	5 (6)	4 (5)	9 (6)	
	β-Blocker/α-agonist	1 (1)	1 (1)	2 (1)	
Concomitant systemic medications	ACE inhibitor	15 (19)	23 (31)	38 (25)	0.19
	Statin	17 (22)	11 (15)	28 (18)	
	β-Blocker	13 (17)	10 (13)	23 (15)	

ACE indicates angiotensin converting enzyme; CAI, carbonic anhydrase inhibitor.

**IOP**

The results for the IOP levels are shown in Table 3 and Figure 1. Brinzolamide and placebo decreased IOP from baseline for the mean diurnal IOP and all 3 individual time points ( $P \leq 0.005$ ). In patients randomized to the brinzolamide treatment group the IOP levels for the mean diurnal IOP and at all 3 individual time points were reduced when compared with patients randomized to the placebo treatment group ( $P \leq 0.017$ ).

The IOP reductions from baseline are shown in Table 4 and Figure 2. The brinzolamide treatment group had reduced IOP levels from baseline when compared with placebo for the mean diurnal IOP as well

as the 08:00 and 16:00 hours time points ( $P \leq 0.014$ ). However, the 12:00 hours time point was not significant ( $P = 0.054$ ).

**Safety**

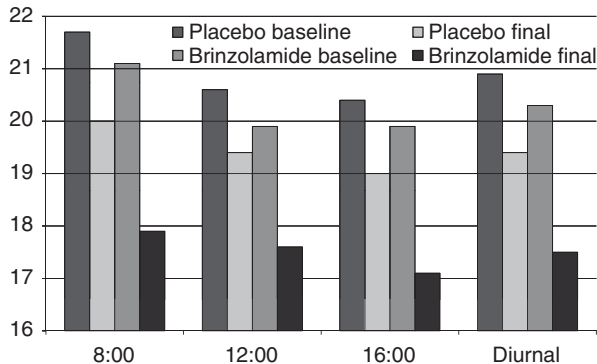
Systemic and ocular adverse events with an incident of greater than 1% are shown in Table 5. In total, there were 30 adverse events in the placebo treatment group and 24 in the brinzolamide treatment group. There was no statistical difference for the side-effect profile between the treatment groups ( $P = 0.47$ ).

There were 2 serious adverse events during the study, both in the placebo treatment group. One patient was

**TABLE 3.** Mean Intraocular Pressures at Baseline (Week 0) and Final Visit (Week 12) – Per Protocol

Time (h)	mm Hg ± SD						P*
	Placebo (N = 78)			Brinzolamide (N = 75)			
	Baseline	Week 12	P	Baseline	Week 12	P	
08:00	21.7 ± 2.4	20.0 ± 3.8	< 0.001	21.1 ± 2.1	17.9 ± 3.2	< 0.001	0.002
12:00	20.6 ± 3.4	19.4 ± 4.6	0.005	19.9 ± 2.6	17.6 ± 2.9	< 0.001	0.011
16:00	20.4 ± 3.4	19.0 ± 4.3	< 0.001	19.9 ± 2.9	17.1 ± 2.8	< 0.001	0.017
Diurnal	20.9 ± 2.7	19.4 ± 3.8	< 0.001	20.3 ± 2.0	17.5 ± 2.6	< 0.001	0.003

\*Between treatments.



**FIGURE 1.** Intraocular pressure (mm Hg) results by time (h) and mean diurnal for baseline and treatment with placebo and brinzolamide.

hospitalized for cardiac stent surgery and the other for bilateral knee replacements. These serious adverse events were not believed to be related to the trial medicine by the investigators.

There were 2 adverse events that lead to discontinuation in the placebo group; one for itching and one for lid darkening. In contrast, there was one adverse event that led to discontinuation in the brinzolamide group (mild anterior uveitis).

**DISCUSSION**

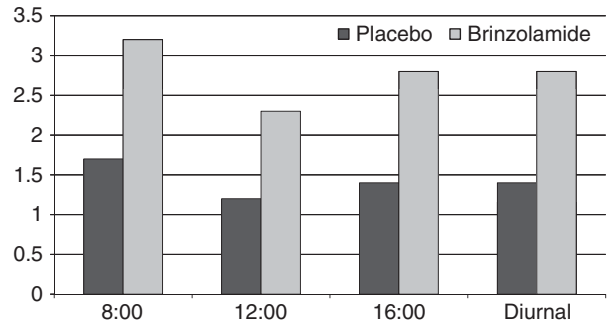
There is little information in the literature from clinical trials assessing 3-drug therapy in glaucoma patients.<sup>13</sup> The few studies available have indicated an average IOP reduction of 16% with the addition of a third drug including: latanoprost, pilocarpine, timolol, brimonidine, brinzolamide, and dorzolamide.<sup>8,14-17</sup>

In addition, little previous data are available about adding brinzolamide to prostaglandin-based 2-drug therapy, specifically. However, prior studies have shown beneficial additive effects of brinzolamide to prostaglandins alone.<sup>18-20</sup> It is reasonable to expect that brinzolamide may show even further IOP-lowering effects when added to prostaglandin/timolol therapy as a third-line treatment. The purpose of this study was to evaluate the additive IOP-lowering effect of adding either brinzolamide or placebo to TTFC combination in patients who need further IOP control after treatment with TTFC combination alone.

The results of this study showed that patients in the brinzolamide group had a reduced mean diurnal IOP and at all 3 time points from baseline ( $P < 0.001$ ). Placebo also reduced the mean diurnal IOP and all 3 individual time points from baseline ( $P \leq 0.005$ ). However, compared with placebo, brinzolamide reduced the mean diurnal IOP as

**TABLE 4.** Mean Intraocular Pressures Reductions From Baseline in the Brinzolamide and Placebo Treatment Groups (Weeks 0-12) – Per Protocol

Time (h)	mm Hg ± SD		P
	Placebo (N = 78)	Brinzolamide (N = 75)	
08:00	1.7 ± 2.7	3.2 ± 3.1	0.001
12:00	1.2 ± 3.7	2.3 ± 3.1	0.054
16:00	1.4 ± 3.6	2.8 ± 3.3	0.014
Diurnal	1.4 ± 2.7	2.8 ± 2.5	0.002



**FIGURE 2.** Mean intraocular pressure (mm Hg) reductions by time (hours) and mean diurnal for baseline and treatment with placebo and brinzolamide.

well as the mean IOP at the 08:00 and 16:00 hours time points.

These data are important because they add to the small group of prior studies noted above which indicate that a third medication can be added to a prior fixed combination therapy to achieve a significant reduction in the IOP.

The difference in the IOP reduction by the addition of brinzolamide was approximately 1.1 to 1.5 mm Hg (approximately 6% to 9%) compared with placebo. The decrease in IOP in this study was not as great as those observed typically after monotherapy.<sup>21-23</sup> This may be because the treatment with timolol in the fixed combination, by initially reducing the aqueous production, may have prevented the additional aqueous suppressant, like brinzolamide, from providing the same additional decrease to aqueous inflow. Nonetheless, the reduction in IOP associated with brinzolamide in this study may be clinically important in selected cases because of prior evidence which showed that a further 1 mm Hg decrease in pressure may help inhibit either the onset of glaucoma in ocular hypertension patients or the progression of open-angle glaucoma.<sup>24-26</sup>

There were no major safety concerns in this study as both treatments were generally well tolerated. No statistically significant differences in the adverse event profile existed between treatments. Only 2 serious adverse events

**TABLE 5.** Adverse Events With an Incidence of >1% – Intent-to-treat

Event	Patients (%)			P
	Placebo (N = 84)	Brinzolamide (N = 79)	Total (N = 163)	
Conjunctival hyperemia	3 (4)	7 (10)	10 (6)	0.47
Eyelashes (darker/longer)	4 (5)	3 (4)	7 (5)	
Cataract	5 (6)	0 (0)	5 (4)	
Blurring	4 (4)	1 (1)	5 (4)	
Superficial punctate keratitis	2 (2)	3 (3)	5 (4)	
Conjunctival redness	2 (2)	1 (1)	3 (3)	
Reduced visual acuity	0 (0)	3 (4)	3 (3)	
Itching	3 (4)	0 (0)	3 (3)	

occurred, both in the placebo group, and were not believed to be related to the treatment. Three patients were discontinued for an adverse event, none of which was sight threatening.

This placebo-controlled study suggests that brinzolamide may be generally safely added to prior TTFC combination therapy and a further statistically significant reduction in mean diurnal IOP can be achieved in patients with ocular hypertension or primary open-angle glaucoma.

This study did not evaluate the long-term outcomes of vision or costs by using brinzolamide as a third medication versus other forms of medical or surgical therapy. Further research is needed to help clarify the benefit of using a third medication to help prevent the progression of visual field loss in ocular hypertension or open-angle glaucoma patients.

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