Intraocular Pressure-Lowering Efficacy of Brinzolamide 1%/Timolol 0.5% Fixed Combination Compared with Brinzolamide 1% and Timolol 0.5%

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Purpose: To compare the safety and intraocular pressure (IOP)-lowering efficacy of brinzolamide 1%/timolol 0.5% fixed combination with brinzolamide 1% or timolol 0.5% alone in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Design: Randomized, double-masked, parallel group, multicenter study.

Participants: Five hundred twenty-three patients were randomized to the study treatments.

Methods: Patients with OAG or OHT were recruited to the study. Qualifying eyes had IOPs of 24 to 36 mmHg at 8 AM and 21 to 36 mmHg at 10 AM on 2 eligibility visits after an appropriate washout period from previous treatment. Patients were assigned randomly to either brinzolamide 1%/timolol 0.5%, brinzolamide 1% (Azopt; Alcon Laboratories, Fort Worth, TX), or timolol 0.5%, dosed twice daily and were followed up while receiving therapy for 6 months. At selected sites, additional IOP measurements were performed at 12 PM, 4 PM, and 8 PM during the 2 eligibility visits, at month 3, and at month 6.

Main Outcome Measure: Mean IOP.

Results: Brinzolamide 1%/timolol 0.5% produced statistically significant and clinically relevant reductions from baseline ranging from 8.0 to 8.7 mmHg, which were statistically and clinically superior to that of either brinzolamide 1% (5.1–5.6 mmHg) or timolol 0.5% (5.7–6.9 mmHg). No safety concerns were identified based on an assessment of ocular and cardiovascular parameters and a review of adverse events.

Conclusions: Brinzolamide 1%/timolol 05% is superior in IOP-lowering efficacy to either brinzolamide 1% or timolol 0.5%.

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Although glaucomatous functional damage may be associated with more than one source of neuronal insult, increased intraocular pressure (IOP) is a clear risk factor for the development and progression of the disease.[1,2] Elevated IOP generally is treated medically or by laser, and if these methods fail, surgically. β-Blocking agents are one such class of medications used as initial therapy.[3,4]

β-Adrenergic blocking agents have been used extensively to treat glaucoma and ocular hypertension (OHT) and have gained wide acceptance as standard topical therapy.[3,4] β-Blockers reduce IOP by slowing the rate of aqueous humor formation during waking hours.[5–15] Timolol is approved for the treatment of elevated IOP in patients with open-angle glaucoma (OAG) or OHT.

In the Ocular Hypertension Treatment Study, 40% of the patients receiving treatment for their OHT required 2 medications or more to achieve a 20% decrease in IOP,[2] whereas 75% of the patients in the Collaborative Initial Glaucoma Treatment Study required more than 2 medications to control their IOP adequately over a 5-year period.[16] For many patients, treatment with a β-blocker alone is insufficient in providing long-term control of IOP,[17,18] and these patients eventually require the addition of another IOP-lowering medication such as a carbonic anhydrase inhibitor (CAI) dosed adjunctively to achieve adequate IOP control.[18] Like β-blockers, CAIs also inhibit aqueous humor production[19–21] during waking hours; they also inhibit aqueous production at night.[9,12] Brinzolamide 1% (Azopt; Alcon Laboratories, Fort Worth, TX) is a topical CAI developed by Alcon and shown to be safe and efficacious as both a primary therapy[22] and as an adjunct to timolol 0.5% when dosed either twice daily or 3 times daily.[23,24]

Alcon is developing a fixed combination of timolol 0.5% and brinzolamide 1% to provide practitioners and patients with a means of simplifying treatment when these 2 medications are indicated. The impact of a less complicated

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treatment regimen on patient adherence is beyond the scope of this study, but has been discussed elsewhere.[25–32]

A fixed combination of a CAI and a β-blocker is currently available (dorzolamide 2%/timolol 0.5%); however, the addition of an another, different CAI/β-blocker fixed combination will provide practitioners with a choice in prescribing to meet individual patient needs better.

The present study was designed to demonstrate that the fixed combination of brinzolamide 1%/timolol 0.5% dosed twice daily was superior to either of the component medications alone, each dosed twice daily (i.e., a contribution of elements study). This is an essential standard to meet to achieve registration of the drug with regulatory authorities.

Patients and Methods

This was a multicenter study conducted at 35 sites throughout the United States in accordance with the principles set forth in the Declaration of Helsinki. This double-masked, randomized, parallel group study was designed to demonstrate superiority of brinzolamide 1%/timolol 0.5% dosed twice daily to the individual components brinzolamide 1% and timolol 0.5%. Patients were required to have an IOP of 24 mmHg or more at 8 AM and 21 mmHg or more at 10 AM in at least 1 eye on 2 eligibility visits, after washout of previous ocular hypotensive medications. After randomization, study visits occurred at week 2 (±1 day), month 3 (±7 days), and month 6 (±7 days). At selected sites (8 of 35), additional IOP measurements were obtained at 12 PM, 4 PM, and 8 PM at the eligibility visits and at month 3 and month 6. Patients with IOPs of more than 36 mmHg at any point were excluded from this study. Informed consent was obtained at the screening visit, and patients were assessed for inclusion and exclusion criteria, which included evaluations of visual acuity, blood pressure and pulse, slit-lamp examination results, dilated fundus examination results, gonioscopy results, automated perimetry results, and urine pregnancy test results, if applicable. The minimum period from screening to eligibility visit 1 for treatment-naïve patients was 3 days. For those patients treated with β-blocking agents or prostaglandin analogs, the minimum washout period was 28 days. The study was approved for each study site by an institutional review board, and all patients or their legal representatives read, signed, and dated an institutional review board-approved consent form before undergoing participation in the study. Eligible adult male and female patients, 18 years or older, diagnosed (as documented in the patients' medical records) with OAG (including pseudoexfoliative and pigmentary) or OHT were allowed to participate in the study as long as they met all inclusion and IOP criteria. Key exclusion criteria included: forms of glaucoma other than open angle; ocular trauma or intraocular surgery within the previous 6 months in either eye; ocular infection, ocular inflammation, or ocular laser surgery within the previous 3 months in either eye; any abnormality preventing reliable applanation tonometry; history or current diagnosis of bronchial asthma or severe chronic obstructive pulmonary disease that would preclude the use of a topical β-blocker.

Procedures

Eligible patients were randomized in a 1:1:1 ratio to twice daily dosing with either brinzolamide 1%/timolol 0.5%, brinzolamide 1%, or timolol 0.5%. Although brinzolamide 1% is approved as a thrice daily drug in the United States, it is approved for twice daily or thrice daily use in Europe and other jurisdictions. It also has been shown that the IOP lowering achieved with either twice daily or thrice daily dosing of brinzolamide 1% are statistically and clinically equivalent.[22,33] Study drugs were supplied in opaque white plastic dropper bottles, each labeled with a unique patient number. Patients were instructed to instill 1 drop in each eye at 8 AM and 8 PM except for study visit days, when the morning dose was administered by the study personnel after the 8 AM IOP readings. All IOP measurements were made by Goldmann applanation tonometry using calibrated tonometers (required before screening of first patient) with an operator (operates the tonometer) and reader (reads the value on the tonometer dial). For each eye and time point, the IOP was determined as the average of 2 separate IOP measurements. If the 2 measurements for a given eye differed by more than 4 mmHg, a third measurement was made, with the IOP reported as the average of the 2 most similar measurements. If the 3 measurements differed by equal amounts, all 3 were averaged. The selected 8 AM and +2-hour postdose (approximately 10 AM) IOP measurements were to assess trough and peak ocular hypotensive activity of the study drugs, respectively. Additional IOP measurements (12 PM, 4 PM, and 8 PM at selected sites) during the month 3 and month 6 visits were made to assess the complete diurnal effect.

Visual acuity (logarithm of the minimum angle of resolution units) assessment and slit-lamp examinations were conducted at each study visit. Automated perimetry, dilated fundus, and pachymetry (average of 3 separate readings of central corneal thickness obtained with an ultrasonic pachymeter with a solid tip probe) were conducted before randomization and on study exit. Systolic and diastolic blood pressure and pulse rate were measured at 8 AM and at +2 hours after the 8 AM dose at all visits.

Statistical Methods

If only 1 of a patient's eyes was dosed, the dosed eye was selected for analysis. If both eyes were dosed, the worse eye was selected for analysis. The worse eye was the eye with the higher IOP at 8 AM averaged across the 2 eligibility visits. If both eyes were equal, the eye with the higher IOP at 10 AM across the 2 eligibility visits was selected. If both eyes were equal at 8 AM and 10 AM, than the right eye was selected for analysis. Hypothesis tests were performed using a repeated measures analysis of variance model. The model included the IOP assessments from week 2 and months 3 and 6 at the 8 AM and 10 AM time points. Analysis of other parameters was conducted using analysis of variance, *t* tests, chi-square tests, or Fisher exact tests, as appropriate, depending on the variable being analyzed.

Analyses were conducted using 2 data sets, intent to treat (ITT) and per protocol. The ITT data included all patients who received study medication and underwent at least 1 examination while receiving therapy. The per protocol data set included all ITT patients who satisfied all inclusion and exclusion criteria. In addition, only those data points that satisfied protocol criteria were included in the per protocol set. In the ITT data set, the last observation was carried forward to impute missing IOP values.

The primary statistical objective of this study was to demonstrate that the IOP-lowering efficacy of brinzolamide 1%/timolol 0.5% ophthalmic suspension, dosed twice daily at 8 AM and 8 PM, was superior to either brinzolamide 1% dosed twice daily or timolol 0.5% ophthalmic solution dosed twice daily in patients with OAG or OHT. The primary inference for this study was mean IOP at month 6 (8 AM and 10 AM). Hommel's procedure[34] was used to control for multiplicity across the 4 comparisons (brinzolamide 1%/timolol 0.5% ophthalmic suspension vs each of its 2 components for the 2 time points at month 6) under consideration for primary efficacy. Superiority was declared if all 4 comparisons were statistically significant, favoring brinzolamide 1%/timolol 0.5% ophthalmic suspension, when controlled for multiplicity. All

other comparisons among groups and for the additional time points were carried out to provide supportive efficacy for this study.

Results

Demographics

Of the 523 patients enrolled, 477 completed the study and 46 discontinued before completion. Table 1 contains the patient demographics by treatment group. The number of discontinued patients per treatment group and the reasons for discontinuation are given in Table 2 (available at http://aaojournal.org). Six patients (brinzolamide/timolol, n = 3; brinzolamide 1%, n = 1; and timolol 0.5%, n = 2) were excluded from the ITT analysis because they discontinued the study prior to the first scheduled examination while receiving therapy.

Mean Intraocular Pressure and Changes from Baseline

The mean baseline IOPs for the 3 treatment groups were not statistically different. Mean IOPs for the 3 treatment groups for all visits at the 8 AM and +2-hour (10 AM) postdose time points are presented in Figure 1 and Table 3 (Table 3 available at http://aaojournal.org). The fixed combination was significantly superior at all visits and time points (Table 3, available at http://aaojournal.org). Mean IOP reductions from baseline for brinzolamide 1%/timolol 0.5% were clinically relevant and statistically superior at all times compared with those for brinzolamide 1% or timolol 0.5%. The IOP reductions ranged from 8.0 to 8.7 mmHg for brinzolamide 1%/timolol 0.5%, from 5.7 to 6.9 mmHg for timolol 0.5%, and from 5.1 to 5.6 mmHg for brinzolamide 1% (Table 4). Relative response to treatment can be assessed by comparison of the percentage of patients in each of the treatment groups to reach a threshold IOP (i.e., less than 18 mmHg) at each of the time points. Although this is a somewhat arbitrary target for clinical practice, it is less so in a clinical study such as this where the patient population is more homogeneous and defined, that is, in terms of entry IOP (24–36 mmHg at 8 AM), cup-to-disc ratio (not more than 0.8), and visual acuity (not worse than 0.6 logarithm of minimum angle of resolution units). When evaluating the 8 AM and +2-hour (10 AM) IOPs for those patients completing the month 6 visit, up to 58% of patients in the brinzolamide 1%/timolol 0.5% group achieved at least 1 IOP measurement of 18 mmHg or less at the +2-hour (10 AM) postdose time point compared with 26% of patients in the brinzolamide 1% group and 38% of patients in the timolol 0.5% group (Table 5, available at http://aaojournal.org).

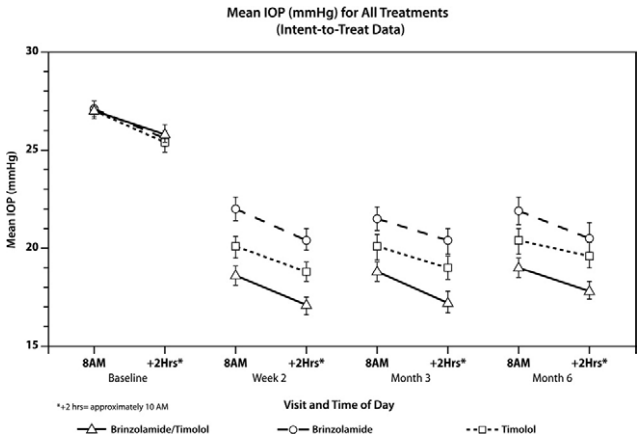

Figure 1. Graph showing mean intraocular pressure (IOP; mmHg) for all treatments (intent-to-treat data).

Table 1. Patient Demographics (Intent-to-Treat Data)

	Total		Brinzolamide/ Timolol		Brinzolamide		Timolol		
	No.	%	*No.*	%	*No.*	%	*No.*	%	**P Value***
Total	517	100.0	171	100.0	173	100.0	173	100.0	
Age (yrs)									
<65	286	55.3	94	55.0	96	55.5	96	55.5	0.9937
≥65	231	44.7	77	45.0	77	44.5	77	44.5	
Gender									
Male	221	42.7	80	46.8	74	42.8	67	38.7	0.3198
Female	296	57.3	91	53.2	99	57.2	106	61.3	
Race									
American Indian or Alaska native	1	0.2	1	0.6	0	0.0	0	0.0	0.5821
Asian	7	1.4	3	1.8	1	0.6	3	1.7	
Black	96	18.6	28	16.4	31	17.9	37	21.4	
Multiracial	1	0.2	0	0.0	1	0.6	0	0.0	
Other	3	0.6	0	0.0	1	0.6	2	1.2	
White	409	79.1	139	81.3	139	80.3	131	75.7	
Diagnosis									
Ocular hypertension	189	36.6	63	36.8	65	37.6	61	35.3	0.3004
Open-angle glaucoma with pigment dispersion	10	1.9	5	2.9	1	0.6	4	2.3	
Open-angle glaucoma with pseudoexfoliation	7	1.4	3	1.8	0	0.0	4	2.3	
Open-angle glaucoma	311	60.2	100	58.5	107	61.8	104	60.1	
Central corneal thickness, mean (SD)									
Baseline (μm)			570 (40)		560 (40)		570 (40)		

SD = standard deviation.
**P* value from chi-square or Fisher exact test.

Table 4. Mean Intraocular Pressure (mmHg) Change from Baseline (Intent-to-Treat Data)

	Baseline*		Week 2		Month 3		Month 6	
	8 AM	+2 Hours†	8 AM	+2 Hours	8 AM	+2 Hours	8 AM	+2 Hours
Brinzolamide/timolol								
Mean	27.1	25.8	−8.4	−8.7	−8.3	−8.7	−8.1	−8.0
Standard deviation	2.7	3.0	3.5	3.6	3.8	3.9	3.7	3.7
No.	171	171	170	170	171	171	171	171
P value	—	—	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Upper 95% CI	27.5	26.2	−7.9	−8.2	−7.8	−8.1	−7.6	−7.5
Lower 95% CI	26.7	25.4	−9.0	−9.3	−8.8	−9.2	−8.6	−8.5
Azopt								
Mean	27.1	25.6	−5.1	−5.2	−5.6	−5.3	−5.2	−5.1
Standard deviation	2.6	2.8	3.1	3.1	3.4	3.4	3.9	3.9
No.	173	173	172	172	173	173	173	173
P value	—	—	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Upper 95% CI	27.5	26.0	−4.6	−4.7	−5.1	−4.7	−4.7	−4.5
Lower 95% CI	26.7	25.2	−5.6	−5.7	−6.1	−5.8	−5.7	−5.6
Timolol								
Mean	27.0	25.4	−6.9	−6.6	−6.9	−6.4	−6.6	−5.7
Standard deviation	2.5	2.9	3.3	2.7	3.6	3.5	3.5	3.6
No.	173	173	173	173	173	173	173	173
P value	—	—	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Upper 95% CI	27.4	25.8	−6.4	−6.1	−6.4	−5.9	−6.1	−5.2
Lower 95% CI	26.6	25.0	−7.4	−7.1	−7.4	−6.9	−7.1	−6.3

CI = confidence interval.
Estimates are based on least squares means using repeated measures analysis of variance. Baseline estimates were obtained from a separate model. *P* values and CIs were based on repeated measures analysis of variance. *P* value is associated with hypothesis test of each least squares mean against 0.
*Baseline is the average of the 2 eligibility visits if both values were not missing; otherwise, the nonmissing value of the 2 visits was used.
†Approximately 10 AM.

For those patients in the subset completing the diurnal IOP assessments, up to 57% of patients in the brinzolamide 1%/timolol 0.5% group achieved at least 1 IOP of 18 mmHg or less at 8 hours (4 PM) after the 8 AM dose at month 6 compared with 30% of patients in the brinzolamide group and 26% of patients in the timolol 0.5% group (Table 5, available at http://aaojournal.org).

Safety Evaluation

The evaluation of safety was conducted in 523 adult and elderly patients (26–90 years of age) who were randomized into the study and received at least 1 dose of study drug. Twenty-one patients discontinued the study because of an adverse event, which included 5 patients reporting a serious adverse event and 12 patients who discontinued the study because of a treatment-related adverse event (Table 2, available at http://aaojournal.org). Four of the serious adverse events resulting in a patient discontinuation were not related to therapy; one, decompensation of chronic obstructive pulmonary disease, for a patient randomized to the brinzolamide/timolol combination was assessed as being related to therapy.

Table 6 summarizes all treatment-related adverse events reported during the study. Patients treated with either brinzolamide 1%/timolol 0.5% or brinzolamide 1% reported a 3.4% and 2.9% incidence of blurred vision, respectively, versus 0.6% in patients with exposure to timolol 0.5% alone. Blurred vision did not represent a safety issue to the patients. Dysgeusia, a common adverse reaction for CAIs, was reported previously in approximately 5% of dorzolamide 2%-treated patients and in 5% to 10% of brinzolamide 1%-treated patients. In this study, it was reported at a similar incidence in patients treated with brinzolamide 1% alone (4.6%) but was markedly lower with the fixed combination (1.1%) or timolol 0.5% (0.6%), indicating that the fixed combination produces less taste perversion than brinzolamide 1% alone. Ocular burning and punctate keratitis were reported at a similar incidence in patients treated with either brinzolamide 1%/timolol 0.5% or timolol 0.5%. Ocular stinging and conjunctival hyperemia were reported at a similar incidence in all 3 treatment groups. All other adverse drug reactions reported in patients within each of the 3 treatment groups occurred at an incidence of 1.1% or less. A review of adverse events revealed no safety issues based on an assessment of incidence, onset date, duration, relationship to therapy, and impact on continuing participation in the study.

No safety issues were identified based on an analysis of change from baseline for visual acuity (best-corrected logarithm of the minimum angle of resolution units), ocular sign parameters (eyelids and conjunctiva, cornea, iris and anterior chamber, lens), pachymetry, visual fields, dilated fundus parameters (vitreous, retina and macula and choroid, optic nerve), including cup-to-disc ratio and cardiovascular parameters (pulse and blood pressure).

Discussion

Because monotherapy frequently is inadequate in controlling the IOP of patients with OAG or OHT,[2,6] practitioners may administer multiple ocular medications to patients. Doing so increases the risk of patient noncompliance, the possibility of adverse side effects, and exposure to preservatives.[25–30] Development of a fixed combination of 2 different IOP-lowering medications may provide nearly the efficacy of the individual components used concomitantly, while providing patients with the advantages and convenience of a single bottle.[31,32] To show that treatment with the fixed com-

Table 6. All Adverse Events Related to Therapy: Overall Safety Population

Coded Adverse Event	Brinzolamide/ Timolol (n = 174)		Brinzolamide (n = 174)		Timolol (n = 175)	
	No.	%	*No.*	%	*No.*	%
Eye disorders						
Blurred vision	6	3.4	5	2.9	1	0.6
Eye irritation (burning)	5	2.9	2	1.1	6	3.4
Punctate keratitis	3	1.7	1	0.6	3	1.7
Reduced visual acuity					1	0.6
Eye pain (stinging)	2	1.1	1	0.6	2	1.1
Conjunctival hyperemia	2	1.1	2	1.1	1	0.6
Dry eye			1	0.6	1	0.6
Eye pruritus	2	1.1	1	0.6		
Foreign body sensation in eyes	1	0.6	1	0.6	1	0.6
Ocular hyperemia	1	0.6	1	0.6		
Eye discharge			1	0.6		
Corneal epithelium disorder	1	0.6				
Photophobia			1	0.6	1	0.6
Eyelid edema			1	0.6	1	0.6
Lacrimation increased					2	1.1
Conjunctival edema					1	0.6
Cardiac disorders						
Bradycardia					2	1.1
Gastrointestinal disorders						
Nausea			2	1.1		
Vomiting			1	0.6		
Cardiovascular						
Blood pressure decreased	2	1.1				
Heart rate decreased					1	0.6
Nervous system disorders						
Dysgeusia	2	1.1	8	4.6	1	0.6
Headache			1	0.6		
Sinus headache					1	0.6
Respiratory, thoracic, and mediastinal disorders						
Dyspnea					1	0.6
Pharyngolaryngeal pain	1	0.6	1	0.6		
Chronic obstructive pulmonary disease	1	0.6				
Wheezing					1	0.6
Skin and subcutaneous disorder						
Periorbital edema			1	0.6		

Brinzolamide = brinzolamide 10 mg/ml eye drops, suspension; brinzolamide/timolol = brinzolamide 10 mg/ml + timolol 5 mg/ml eye drops, suspension; timolol = timolol 5 mg/ml eye drops, solution.

bination results in better adherence and thus to better IOP control than treatment with the unfixed combination, it is necessary to include a concomitant administration treatment group (i.e., one in which patients received both timolol and brinzolamide, but in separate bottles) in the study. Although this would be of great interest, this was not the objective of the present study, which was to demonstrate superior IOP reductions for the fixed combination versus the individual components. In the present study, a fixed combination of brinzolamide 1%/timolol 0.5% was found to be superior in IOP-lowering efficacy in patients with OAG or OHT compared with either brinzolamide 1% or timolol 0.5% each dosed twice daily.

Brinzolamide 1%/timolol 0.5% was found to produce statistically significant and clinically relevant greater reductions in IOP from baseline as compared with brinzolamide 1% and with timolol 0.5% over 6 months of therapy. The greatest IOP-lowering effect measured for the combination was found to be at the +2-hour (approximately 10 AM) postdose measurement, with mean IOP reductions from baseline across all 6 on-therapy assessment times ranging from 8.0 to 8.7 mmHg or 29.6% to 33.5%, respectively, as compared with 5.1 to 5.6 mmHg (18.9% to 20.8%) for the brinzolamide 1% group and 5.7 to 6.9 mmHg (22.8% to 26.1%) for the timolol 0.5% group (Table 4). Among the patients enrolled at selected sites where additional IOP measurements were performed at 12 PM, 4 PM, and 8 PM, mean IOP reductions from baseline across these additional 6 on-therapy assessment times ranged from 5.9 to 7.2 mmHg (8 PM, month 6; 12 PM, month 3, respectively) for the combination, 3.0 to 4.9 mmHg (8 PM, month 6; 12 PM, months 3 and 6 , respectively) for the brinzolamide 1% group, and 3.3 to 5.2 mmHg (8 PM, month 6; 12 PM, month 6, respectively) for the timolol 0.5% group (Table 7, available at http://aaojournal.org).

Overall, no safety issues beyond those known for topical β-blockers and CAIs were identified in a population of adult and elderly patients with OAG or OHT administered brin-

zolamide 1%/timolol 0.5% suspension twice daily for 6 months. In addition, the adverse drug reaction profile observed in patients with exposure to the fixed combination is consistent with previous clinical trial experience involving the individual components.

This study showed that the use of brinzolamide 1%/timolol 0.5% fixed combination is statistically and clinically significantly superior in IOP lowering to either timolol 0.5% or brinzolamide 1% dosed twice daily while providing a similar safety profile to the individual components.

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The Brinzolamide 1%/Timolol 0.5% Study Group

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Table 2. Discontinued Patients by Treatment Group

	Brinzolamide/ Timolol (n = 174)		Brinzolamide (n = 174)		Timolol (n = 175)		Total (n = 523)	
	No.	%	*No.*	%	*No.*	%	*No.*	%
Total	13	7.5	20	11.5	13	7.4	46	8.8
Inadequate control of IOP	1	0.6	14	8.0	3	1.7	18	3.4
Adverse event	8	4.6	3	1.7	6	3.4	17	3.3
Decision unrelated to an adverse event	1	0.6	0	0.0	0	0.0	1	0.2
Lost to follow-up	0	0.0	1	0.6	2	1.1	3	0.6
Protocol noncompliance	0	0.0	1	0.6	1	0.6	2	0.4
Other	3*	1.7	1†	0.6	1‡	0.6	5	1.0

IOP = intraocular pressure.
*Patient did not meet IOP criteria at second eligibility visit, patient using excluded medication, patient unavailable because of being admitted to a long-term psychiatric facility.
†Principle investigator's decision because of added medications.
‡Patient moved out of state.

Table 3. Comparison of Mean Intraocular Pressure (mmHg) between Treatment Groups (Intent-to-Treat Data)

	Baseline*		Week 2		Month 3		Month 6	
	8 AM	+2 Hours†	8 AM	+2 Hours	8 AM	+2 Hours	8 AM	+2 Hours
Brinzolamide/timolol								
Mean	27.1	25.8	18.6	17.1	18.8	17.2	19.0	17.8
Standard deviation	2.7	3.0	3.3	3.1	3.5	3.4	3.5	3.3
No.	171	171	170	170	171	171	171	171
Brinzolamide								
Mean	27.1	25.6	22.0	20.4	21.5	20.4	21.9	20.5
Standard deviation	2.6	2.8	4.0	3.7	4.2	4.1	4.6	4.8
No.	173	173	172	172	173	173	173	173
Difference in mean IOP	0.0	0.2	−3.3	−3.3	−2.7	−3.2	−2.9	−2.7
P value	0.9816	0.4492	<0.0001	<0.0001	<0.0001	<0.0001	≤0.0002‡	≤0.0002‡
Brinzolamide/timolol								
Mean	27.1	25.8	18.6	17.1	18.8	17.2	19.0	17.8
Standard deviation	2.7	3.0	3.3	3.1	3.5	3.4	3.5	3.3
No.	171	171	170	170	171	171	171	171
Timolol								
Mean	27.0	25.4	20.1	18.8	20.1	19.0	20.4	19.6
Standard deviation	2.5	2.9	3.9	3.6	4.4	4.2	4.3	4.5
No.	173	173	173	173	173	173	173	173
Difference in Mean IOP	0.1	0.5	−1.4	−1.7	−1.3	−1.8	−1.4	−1.8
P value	0.6784	0.1192	0.0008	<0.0001	0.0031	<0.0001	0.0011‡	≤0.0002‡

IOP = intraocular pressure.
Estimates were based on least squares means using repeated measures analysis of variance. Baseline estimates were obtained from a separate model.
*Baseline is the average of the 2 eligibility visits if both values were not missing; otherwise the nonmissing value of the 2 visits was used.
†Approximately 10 AM.
‡*P* values are adjusted for multiplicity using Hommel's method.

Table 5. Frequency and Percent of Patients Who Achieved Target Intraocular Pressure of Less than 18 mmHg (Intent-to-Treat Data)

	Week 2		Month 3					Month 6				
	8 AM	+2 Hours*	8 AM	+2 Hours	12 PM	4 PM	8 PM	8 AM	+2 Hours	12 PM	4 PM	8 PM
Brinzolamide/timolol												
Total	170	170	171	171	60	60	59	171	171	60	60	59
No.	64	91	57	99	31	37	32	59	70	29	34	28
%	37.6	53.5	33.3	57.9	51.7	61.7	54.2	34.5	40.9	48.3	56.7	47.5
Brinzolamide												
Total	172	172	173	173	57	57	57	173	173	57	57	57
No.	14	40	25	44	11	11	13	28	45	14	17	12
%	8.1	23.3	14.5	25.4	19.3	19.3	22.8	16.2	26.0	24.6	29.8	21.1
Timolol												
Total	173	173	173	173	57	57	57	173	173	57	57	57
No.	39	66	43	56	15	16	20	43	62	20	15	19
%	22.5	38.2	24.9	32.4	26.3	28.1	35.1	24.9	35.8	35.1	26.3	33.3
P value†	<0.0001	<0.0001	0.0002	<0.0001	0.0004	<0.0001	0.002	0.0005	0.0123	0.0274	0.001	0.011

8 AM and +2 hours include data from all study sites. 12 PM, 4 PM, and 8 PM data from the subset of study sites where these additional time points were collected.
*Approximately 10 AM.
†*P* value from chi-square or Fisher exact test.

Table 7. Descriptive Statistics for Intraocular Pressure (mmHg) at Selected Sites Where Intraocular Pressure Was Measured at Additional Time Points* (Intent-to-Treat Data)

	Baseline†					Week 2		Month 3					Month 6				
	AM		PM			AM		AM		PM			AM		PM		
	8	+2 Hours‡	12	4	8	8	+2 Hours	8	+2 Hours	12	4	8	8	+2 Hours	12	4	8
Brinzolamide/timolol																	
Mean	26.6	25.3	24.5	24.0	23.5	18.4	17.1	19.0	17.3	17.3	17.0	16.9	18.8	17.8	17.8	17.5	17.5
Standard deviation	2.2	2.4	2.9	2.6	2.6	3.6	3.3	3.9	3.8	3.7	3.6	3.1	3.6	3.6	3.5	3.8	3.3
No.	60	60	60	60	60	60	60	60	60	60	60	59	60	60	60	60	59
Minimum	24	21	19	18	18	10	10	10	9	9	10	8	10	8	10	8	9
Maximum	33	31	33	30	30	26	25	26	29	30	31	24	28	29	30	31	24
Brinzolamide																	
Mean	27.2	25.6	24.9	23.8	23.8	22.4	20.9	21.8	20.7	19.8	19.7	19.9	22.0	20.1	19.8	20.3	20.5
Standard deviation	2.4	2.6	3.1	3.3	3.5	4.2	3.7	4.1	4.1	3.3	3.0	3.8	4.5	4.9	4.1	4.5	3.9
No.	59	59	59	59	59	59	59	59	59	57	57	57	59	59	57	57	57
Minimum	24	21	19	18	18	13	13	12	14	12	13	11	15	11	12	10	14
Maximum	34	34	34	32	33	34	33	34	34	30	31	32	34	34	33	32	34
Timolol																	
Mean	26.7	25.4	24.5	23.8	23.3	20.5	19.1	20.2	19.3	19.6	19.4	19.2	20.5	19.4	19.3	20.3	20.0
Standard deviation	2.0	2.7	2.4	2.5	2.7	4.3	3.6	4.4	3.7	4.4	3.8	4.0	4.6	3.9	4.0	5.2	4.8
No.	58	58	58	58	58	58	58	58	58	57	57	57	58	58	57	57	57
Minimum	24	21	21	18	17	12	11	10	8	8	12	12	12	11	13	12	11
Maximum	33	33	31	31	32	35	31	34	32	38	34	35	31	28	28	45	37

Brinzolamide = brinzolamide 10 mg/ml eye drops, suspension; brinzolamide/timolol = brinzolamide 10 mg/ml + timolol 5 mg/ml eye drops, suspension; maximum = the largest observation in the sample; minimum = the smallest observation in the sample; timolol = timolol 5 mg/ml eye drops, solution.
*Additional time points: 12 PM, 4 PM, and 8 PM.
†Baseline is the average of the 2 eligibility visits if both values were not missing; otherwise, the nonmissing value of the 2 visits was used.
‡Approximately 10 AM.