# A 1-Year Study of Brimonidine Twice Daily in Glaucoma and Ocular Hypertension

## *A Controlled, Randomized, Multicenter Clinical Trial*

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**Objective:** Brimonidine tartrate is a highly selective $\alpha_2$-agonist. This study investigates the safety and efficacy of 0.2% brimonidine administered twice daily for 1 year in patients with glaucoma or ocular hypertension.

**Methods:** The study design was a multicenter, double-masked, randomized, parallel-group, active-controlled comparison clinical trial. Subjects instilled 0.2% brimonidine or 0.5% timolol maleate twice daily for 12 months. Subjects were examined at baseline, week 1, and months 1, 2, 3, 6, 9, and 12. A subset of subjects was examined at week 2.

**Results:** Of 443 subjects enrolled in this study, 374 met the entry criteria; 186 received brimonidine and 188 received timolol. Brimonidine-treated subjects showed an overall mean peak reduction in intraocular pressure (IOP) of 6.5 mm Hg; timolol-treated subjects had a mean peak reduction in IOP of 6.1 mm Hg. Brimonidine lowered mean peak IOP significantly more than timolol at week 2 and month 3 ($P<.03$); no significant difference was observed between the groups for this variable at other visits throughout the 1-year course of the study. No evidence of tachyphylaxis was seen in either group. Allergy was seen in 9% of subjects treated with brimonidine. Dry mouth was more common in the brimonidine-treated group than in the timolol-treated group (33.0% vs 19.4%), but complaints of burning and stinging were more common in the timolol-treated group (41.9%) than in the brimonidine-treated patients (28.1%). Headache, fatigue, and drowsiness were similar in the 2 groups. In general, the tolerance to medication was acceptable.

**Conclusions:** Brimonidine is safe and effective in lowering IOP in glaucomatous eyes. Brimonidine provides a sustained long-term ocular hypotensive effect, is well tolerated, and has a low rate of allergic response.

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BRIMONIDINE TARTRATE is a potent α-adrenoceptor agonist with high selectivity for the $\alpha_2$ receptor. It has notably higher affinity for the $\alpha_2$ receptor than does clonidine hydrochloride or apraclonidine hydrochloride.[1] This selectivity and the chemical structure of the drug may provide an advantage for brimonidine over apraclonidine. Apraclonidine has been reported to be effective in lowering intraocular pressure (IOP) in patients with glaucoma and ocular hypertension,[2-5] but its long-term use is limited by allergy and tachyphylaxis.[6-10]

Brimonidine effectively lowers IOP in animal models[11] and in normotensive,[12] glaucomatous, and ocular hypertensive eyes.[13] The 0.5% concentration has been shown to reduce the incidence of IOP spikes after laser trabeculoplasty.[14-16] Brimonidine seems to reduce IOP by a dual mechanism of decreasing inflow and increasing uveoscleral outflow.[17] This study was designed to evaluate the 1-year efficacy and safety of 0.2% brimonidine used twice daily in patients with glaucoma or ocular hypertension.

## RESULTS

### DEMOGRAPHICS

A total of 443 subjects received study medication, with 221 in the brimonidine group and 222 in the timolol group. Of these, 15% of subjects (35/221 for brimonidine; 34/222 for timolol) did not meet entry criteria (reasons included IOP outside of entry range, IOP asymmetry between eyes, inadequate washout period, patient receiving medication that could affect IOP, or patient allergic to timolol), and were not included in the primary efficacy analysis. The remaining 374 subjects met the protocol entry criteria (186 in the brimonidine group and 188 in the timolol group) and were included in the efficacy evaluation. All 443 subjects were included in the analysis of safety.

Sixty-two percent of all subjects in each group had open-angle glaucoma, 36% had ocular hypertension, and 2% had a visual field defect in 1 eye and no field defect in the other. The mean (±SD) age overall was 63±11 years, and the male-female ratio was 50:50. Most subjects were



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## SUBJECTS AND METHODS

### STUDY DESIGN

The study design was a multicenter, double-masked, randomized, parallel-group, active-controlled comparison clinical trial. The clinical protocol received institutional review board approval at each participating site. Subjects instilled 0.2% brimonidine tartrate or 0.5% timolol maleate twice daily for 12 months. Examinations were performed at baseline, week 1, and month 1, 2, 3, 6, 9, and 12. A subset of subjects (40% of all subjects) was evaluated at week 2.

The 0.2% concentration of brimonidine was selected for long-term evaluation after a 1-month dose-response study that showed similar efficacy to the 0.5% concentration.[13] A twice-daily regimen of brimonidine was chosen because this frequency was shown to be as effective as a 3-times daily regimen.[18]

### PATIENT SELECTION

Adults with primary open-angle glaucoma or ocular hypertension who gave written informed consent to participate and were receiving no more than 2 ocular hypotensive agents were recruited for this study. After appropriate washout of prestudy ocular hypotensive medications (including a 4-week washout of β-blockers), subjects were required to have untreated IOP of 23 mm Hg or more and less than 35 mm Hg in each eye, and best-corrected visual acuity of 20/100 or better in each eye. Patients were evenly randomized in a masked fashion to the 2 treatment groups.

The systemic exclusion criteria included uncontrolled systemic disease, pregnancy or childbearing potential, contraindications to α-adrenoceptor agonist or β-adrenoceptor antagonist therapy, abnormally low heart rate or blood pressure for age, and known hypersensitivity to any ingredients in the study medication. Other exclusion criteria included long-term treatment with any other topical or systemic α-adrenoceptor agonist or antagonist, alteration during the study of existing long-term therapy that could have a substantial effect on IOP or ocular activity of the study drugs, treatment with adrenergic-augmenting psychotropic drugs, and participation in a current or recent (past 30 days) research study.

Ophthalmic exclusion criteria were corneal abnormalities that would interfere with tonometry, wearing of contact lenses, active ocular disease, dry eye, Sjögren syndrome, keratitis sicca, required use of other ocular medications, asymmetry of IOP between eyes of more than 5 mm Hg, extensive visual field loss, laser treatment or ocular surgery within the past 6 months, and optic nerve–head cup:disc ratio of 0.8 or more in either eye. Subjects who met these entry criteria were included in the primary (per-protocol) efficacy analysis. All subjects who received study medication were evaluated in the safety analysis.

### EFFICACY AND SAFETY VARIABLES

The primary efficacy variable was IOP. Intraocular pressure was measured in millimeters of mercury using applanation tonometry affixed to a slit-lamp. Cup:disc ratios (recorded as 0.0-0.9) and visual fields (using Humphrey program 30-2 or Octopus program 32) were secondary efficacy variables.

Patients were monitored for signs and symptoms of adverse events, ocular and general discomfort, and other ocular and systemic safety factors. At each visit, patients were asked specifically about any discomfort, whether ocular (burning or stinging, blurring, foreign body sensation, or photophobia) or general (headache, dry mouth, or fatigue or drowsiness). Adverse events were graded for severity (trace, mild, moderate, or severe) and assessed for relation to the study treatment. Symptoms of ocular dis-

white (79%), with blue, green, or hazel iris color (51%). No significant between-group differences were seen in age, race, sex, iris color, diagnosis, prestudy history, or baseline values for any variable.

### INTRAOCULAR PRESSURE

The mean peak IOP change from baseline was measured 2 hours after dosing in both groups. Intraocular pressures were similar between treatment groups at baseline (brimonidine, 24.8 mm Hg; timolol, 24.6 mm Hg) ($P=.70$). Mean peak IOP decreases from baseline were statistically significant in both treatment groups at all follow-up visits ($P<.001$) and ranged from 5.9 to 7.0 mm Hg for brimonidine subjects and 5.2 to 6.3 mm Hg for timolol subjects (**Figure 1**). Overall, brimonidine subjects showed a mean 6.5 mm Hg IOP reduction at peak, and timolol subjects had a mean 6.1 mm Hg IOP decrease with no significant difference between the 2 groups. There was no evidence of tachyphylaxis and no significant correlation between iris color and IOP lowering effect in either group.

Intraocular pressure at hour 0 (morning trough, 12 hours after the evening drug instillation) showed mean decreases from similar baseline values (26 mm Hg) ranging from 3.7 to 5.3 mm Hg in the brimonidine group, and from 5.8 to 6.8 mm Hg in the timolol group. Mean decreases from baseline values were statistically significant in both treatment groups at all follow-up visits ($P<.001$). Both brimonidine and timolol subjects showed a sustained therapeutic effect during the 12-month period. Trough IOP reductions were significantly greater for timolol subjects than brimonidine subjects during the study ($P<.03$). Overall mean decreases from baseline at trough were 4.3 mm Hg in the brimonidine group and 6.3 mm Hg in the timolol group. As with the peak effect, no IOP drift was seen in the timolol- or brimonidine-treated subjects at trough. Both drugs showed a sustained therapeutic effect at peak and trough during the 1-year follow-up.

An additional efficacy analysis was performed in which all subjects who received medication were included (including the 15% of subjects who did not meet the entry criteria). This analysis showed similar findings with the primary analysis.



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comfort were evaluated on a 0- to 3-point scale (0=none, 1=mild, 2=moderate, and 3=severe) at all visits.

Biomicroscopic evaluation was performed at each visit without pupillary dilation, using the same 0- to 3-point scale. Direct and indirect ophthalmoscopy was used to evaluate the fundus and optic nerve head. The Schirmer tear test was performed at baseline and at months 6 and 12 using standard Schirmer strips. The strips were inserted into the conjunctival sac near the inner angle for 5 minutes, following the administration of 1 drop (about 20 µL) of topical anesthetic. Visual acuity was measured with a Snellen chart and pupil size with a pupillometer or millimeter ruler.

Heart rate and blood pressure were measured at each visit with patients in a resting position. Blood samples were obtained at baseline and at months 6 and 12 for assessment of hematologic and blood chemistry values.

### STATISTICAL ANALYSIS

Intraocular pressure was the key efficacy variable. Because subjects were treated bilaterally, average values from both eyes were used in the analysis. Data were analyzed using the 2-way analysis of variance (ANOVA) with fixed effects for treatment, investigator, and treatment-by-investigator interaction.[19] Within each treatment group, mean changes from baseline at each follow-up visit were analyzed using a paired Student *t* test.[20] Overall mean changes from baseline were analyzed using the ANOVA for repeated measures.[19]

The study was designed as an active-control equivalence trial. Thus, in addition to test for superiority, test for equivalence in efficacy was applied. The two 1-sided hypotheses for equivalence were tested by constructing a 95% confidence interval for the between-group difference in mean IOP changes from baseline. Other than IOP, the continuous variables were analyzed using 2-way ANOVA. The ordinal categorical variables were analyzed using Cochran-Mantel-Haenszel methods with modified ridit scores.[21] Nominal variables were analyzed using the Fisher exact test, the Pearson $\chi^2$ test, or Cochran-Mantel-Haenszel methods with table scores. All hypothesis tests were 2-sided. A *P* value of .05 or less was considered significant for main effects and .10 for the treatment-by-investigator interaction effects.

For visual fields, mean defect values were analyzed based on the eye with the worse changes from baseline compared with its fellow eye. Investigators were asked to assess whether visual fields had changed from baseline. Baseline values and mean changes from baseline were summarized with descriptive statistics and compared between the 2 treatment groups using the ANOVA. The changes from baseline in mean defect values were also tabulated in 3 categories: −5 decibels (dB) or less, −5 or more to 5 dB or more, and more than 5 dB. The distributions were analyzed using the Cochran-Mantel-Haenszel method with modified ridit scores.

In addition, a secondary visual field analysis was conducted on a subset of patients in whom visual fields were performed using the full threshold strategy of Program 30-2 of the Humphrey Field Analyzer (Humphrey Instruments, San Leandro, Calif) at baseline, 6 months, and 12 months. Data collected included mean deviation, short-term fluctuation, corrected-pattern SD, and reliability indexes.[22] Data were averaged for the 2 eyes. Changes over time were assessed using the glaucoma change probability plot of STATAC II (Humphrey Instruments). This software identifies points in the most recent field that show improvement or worsening compared with the first 2 examinations taken together as baseline, and calculates the change in mean deviation from baseline to the most recent field. The number of points that showed worsening or improvement in a manner expected in less than 5% of a stable glaucoma population were counted from the printout. Finally, the series of visual fields was objectively examined by 1 of us (N.T.C.), looking for the development of a new scotomata or for deepening or broadening of scotomata present on the initial examination.

## SECONDARY EFFICACY VARIABLES

No significant within-group or between-group change was seen in cup:disc ratio or visual fields during the study. As evaluated by the clinical investigators, visual fields were completely unchanged, or within 5 dB of baseline values in 95% of patients in each treatment group, 4% improved and 1% worsened. An additional visual field analysis was performed on a subset of patients in whom complete Humphrey 30-2 visual field data were collected (total, 188 subjects; 77 receiving brimonidine and 111 receiving timolol).[22] In this subanalysis, the mean deviation, short-term fluctuation, and corrected pattern SD did not differ between the 2 groups in any variable at any examination. Similarly, the difference in the change in each index from baseline to the third examination was not statistically different between the groups. There was no statistically significant difference in the net change in points worsening or improving from baseline to final examination between the 2 groups and no statistically significant difference in mean deviation change. Finally, 23 (20.7%) of 111 subjects treated with timolol were judged to have subjectively worsened in the 1-year period. Seventeen (22%) of the 77 subjects in the brimonidine group were similarly judged to have worsened. The difference was not statistically significant ($c^2$=0.0; *P*=.97).

## OCULAR SAFETY

### Schirmer Tear Test

Of patients randomized to the brimonidine and timolol groups, 17.6% (38/216) and 21.5% (46/214), respectively, experienced a clinically significant decrease from baseline defined as (1) baseline less than 10 mm and follow-up below 5 mm, or (2) baseline 10 mm or more and follow-up below 10 mm and a decrease from baseline of more than 5 mm in Schirmer tear test results. The between-group difference was not significant. Overall, the mean changes from baseline were negligible in both treatment groups during the 12-month study period.



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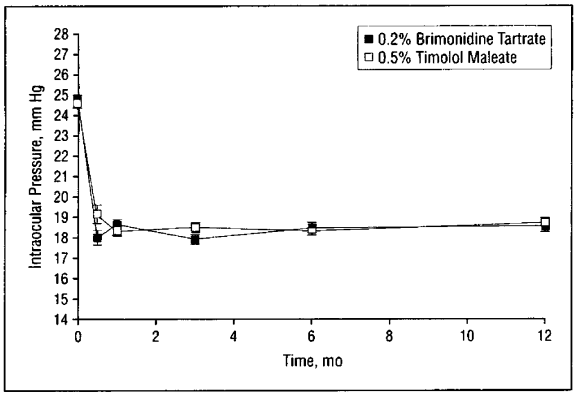


**Figure 1.** *The peak mean change in intraocular pressure from baseline occurs at hour 2 after dosing in the brimonidine- and timolol-treated groups. Vertical bars represent 1 SE. Overall, at peak, no significant difference in IOP-lowering efficacy was seen between brimonidine and timolol. There was no evidence of tachyphylaxis throughout the 1-year course of the study.*

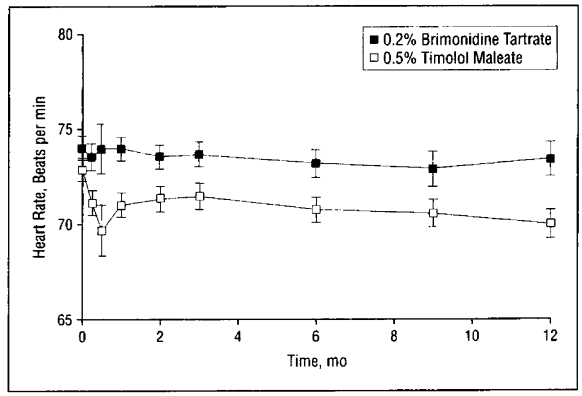


**Figure 2.** *A statistically significant mean reduction in heart rate is seen in the timolol-treated group, ranging from 1.7 to 3.0 beats per minute compared with baseline. No significant change in heart rate is seen with brimonidine. Vertical bars represent 1 SE.*

### Visual Acuity

Comparing final-visit visual acuity with baseline, no change in visual acuity occurred in 94.1% (208/221) of subjects in the brimonidine group and 90.5% (201/222) of those in the timolol group. Worsening of visual acuity of 2 lines or more occurred in 5.9% (13/221) of the patients in the brimonidine group and 9.5% (21/222) of those in the timolol group. The between-group difference was not significant. These findings were assumed not to be drug-related and may have been associated with the progression of cataracts, which can be expected considering the demographic profile of this patient population.

### Pupil Size

Mean changes in pupil size ranged from −0.13 to −0.22 mm with brimonidine and from 0.07 to −0.17 mm with timolol in this study. No clinically significant differences were observed between the treatment groups throughout the follow-up.

## SYSTEMIC SAFETY

### Heart Rate

No significant change in heart rate was seen with brimonidine, but a statistically significant mean reduction in heart rate was seen in the timolol group, ranging from 1.7 to 3.0 beats per minute compared with baseline (**Figure 2**). This decrease with timolol was statistically significantly higher than the mean changes seen in the brimonidine group at most of the follow-up visits.

### Blood Pressure

Some mean changes in systolic and diastolic blood pressure were seen in both treatment groups. These changes were statistically but not clinically significant. No clinically significant differences were observed between the treatment groups.

### Laboratory Analysis

Although there were several statistically significant changes from baseline in hematologic and blood chemistry variables in both groups, these changes were not clinically significant or associated with adverse events. Several shifts were observed in blood lipid values for both treatments, but these shifts were in both directions and were not reflected in the mean laboratory values. A statistically significant mean increase from baseline in serum glucose levels of approximately 10% occurred in the brimonidine group at 12 months. This change is not considered to be clinically significant because the samples were from nonfasting subjects, and because the change did not differ statistically from that occurring with timolol.

### Adverse Events

The **Table** gives the adverse events seen for the timolol and brimonidine groups, with their incidence and the percentage of subjects terminated from the study due to an adverse event. Information about occurrence and severity of adverse events was actively elicited from the patients at each visit.

Overall, the number of patients with adverse events was similar between the 2 treatment groups (191 of 221 subjects for brimonidine and 181 of 222 subjects for timolol). The most commonly reported adverse events in both groups were burning and stinging, dry mouth, blurring, fatigue and drowsiness, headache, foreign body sensation, ocular pruritus, and photophobia. Dry mouth and allergic reaction were reported significantly more often in patients receiving brimonidine ($P<.001$); burning and stinging was reported significantly more often in patients receiving timolol ($P=.002$).

Allergy (allergic conjunctivitis, allergic blepharoconjunctivitis, and follicular conjunctivitis) was seen in 9% of subjects treated with brimonidine and caused discontinuation of the drug in 7.2%. No timolol-treated subjects experienced allergy, and few were terminated from the study for any reason; this may be because most subjects in each treatment group were treated with a topical β-blocker just before washout for this study, and a se-



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**Adverse Events for Timolol and Brimonidine Treatment Groups***

| Adverse Events† | 0.2% Brimonidine Tartrate (n=221) | | 0.5% Timolol Maleate (n=222) | | |
|---|---|---|---|---|---|
| | Overall % | Exited Study % | Overall % | Exited Study % | P |
| Ocular | | | | | |
| Allergy‡ | 9.0 | 7.2 | 0.0 | 0.0 | <.001 |
| Blurring | 22.2 | 1.8 | 22.5 | <1.0 | .93 |
| Burning/stinging | 28.1 | <1.0 | 41.9 | <1.0 | .002 |
| Conjunctival follicles | 8.1 | 0.0 | 2.3 | 0.0 | .005 |
| Foreign body sensation | 15.4 | <1.0 | 16.2 | 0.0 | .81 |
| Hyperemia | 30.3 | 2.3 | 23.4 | 0.0 | .10 |
| Lid erythema | 10.4 | 0.0 | 7.2 | 0.0 | .24 |
| Ocular pruritus | 12.2 | 0.0 | 9.5 | 0.0 | .35 |
| Photophobia | 11.3 | 0.0 | 11.3 | 0.0 | .99 |
| Systemic | | | | | |
| Dry mouth | 33.0 | 1.4 | 19.4 | <1.0 | .001 |
| Fatigue/drowsiness | 19.9 | 2.7 | 17.1 | 0.0 | .45 |
| Headache | 19.0 | <1.0 | 19.8 | <1.0 | .83 |

*In both groups, more than 50% had been treated before study with a topical β-blocker.
†Data reflect events with an incidence of 10% and greater or those with a significant between-group difference. Lens and fundus abnormalities, which occurred in greater than 10% of patients, were excluded as the incidence was similar in both groups and assumed not to be drug related.
‡Allergic conjunctivitis, allergic blepharoconjunctivitis, follicular conjunctivitis.

lection bias may exist for these subjects that would account for the low numbers of subjects in the timolol group who left the study early because of side effects.

## COMMENT

This multicenter, double-masked, randomized, parallel-group, active-controlled comparison clinical trial shows the safety and efficacy of brimonidine in the management of subjects with elevated IOP and glaucoma. Peak IOP reduction was similar for brimonidine and timolol. In the timolol group, the mean change from baseline in trough IOP was similar to that seen at peak measurements. The trough decrease in the brimonidine group was somewhat less than its peak effect. A sustained reduction in peak and trough IOP for the 1-year duration of the study was seen for brimonidine and timolol. Overall, in this study, 95% of visual fields were judged by the clinical investigators to be unchanged from baseline, with a similar distribution between the treatment groups. The subanalysis on visual fields showed no statistically significant difference between the treatment groups. In subjects in whom visual fields were judged to have subjectively worsened, there is insufficient information to differentiate among the multiple factors that may influence the apparent worsening of the visual field. Longer periods of observation will be necessary to determine whether any visual field changes will occur in the long-term treatment of glaucoma with brimonidine that are irrespective of IOP control.

As in previous studies,[20] brimonidine did not reduce heart rate, which is a common effect associated with topical β-blocker use and has been confirmed in this study. In addition, the effect brimonidine had on blood pressure was of no clinical significance.

We found a low incidence of adverse events overall, even though subjects were explicitly questioned about the potential side effects. There was more burning and stinging in the timolol group than in the brimonidine group, but allergy and dry mouth were more frequent among brimonidine subjects than timolol subjects. Although fatigue and drowsiness and headache have been observed with other α-agonists, the incidence of these complaints in this study was similar in the brimonidine and timolol groups. The first report of allergy in the brimonidine group in this study did not occur until day 44.

It is important to discriminate between mild side effects and those that require that the subject be terminated from the study. In this context, this study was biased in favor of timolol, in that most of the subjects in each treatment group had been tolerating a β-blocker just before enrollment. This preselected population may explain why adverse events typically associated with β-blocker therapy were less prominent in the timolol-treated group.

Several advantages of brimonidine over other topical α-agonists may be inferred from this study. The allergy rate seen in this 1-year study for brimonidine (9%) was much lower than that reported in the literature for apraclonidine (ranging from 20%-48% with 1% apraclonidine[8,10] and 14%-36% with the 0.5% concentration).[7,8,23,24] No tachyphylaxis was seen with brimonidine during the 1-year follow-up of this investigation; apraclonidine has been reported to lose potency over time.[2,10] Brimonidine, in this study, was effective as a twice-daily drug, and mydriasis and eyelid retraction, commonly seen with apraclonidine,[3] were not seen in this study.

Brimonidine seems to offer several advantages over existing glaucoma medications and may be appropriate for first-line therapy in many patients. Nordlund et al[25] have shown a safety profile superior to timolol, with no effect of brimonidine on exercise-induced tachycardia. In the present study, unlike timolol, brimonidine had no effect on heart rate, and the effect on systemic blood pressure was not clinically significant. Moreover, reduction in IOP was similar to timolol. Based on this profile, there may be subgroups of patients, especially those receiving a systemic β-blocker, who may not respond well to a topical β-blocker;



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or persons with cardiopulmonary disease, for whom brimonidine would be an obvious drug of first choice.

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