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Twelve-Month Evaluation of Brimonidine-Purite Versus Brimonidine in Patients With Glaucoma or Ocular Hypertension

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Purpose: To compare the efficacy and safety of brimonidine-Purite (Alphagan; Allergan, Irvine, CA) 0.15% and 0.2% three times daily with brimonidine (Alphagan) 0.2% three times daily in patients with glaucoma or ocular hypertension.

Patients and Methods: In this 12-month, randomized, multicenter, double-masked, parallel-group study, patients were randomly assigned to receive brimonidine-Purite 0.15% (n = 381), brimonidine-Purite 0.2% (n = 383), or brimonidine 0.2% (n = 383) three times daily. Visits were conducted before the study, at baseline, at weeks 2 and 6, and at months 3, 6, 9, and 12. Diurnal intraocular pressure was measured at 8 AM, 10 AM, 3 PM, and 5 PM at baseline, week 6, and at months 3, 6, and 12. Intraocular pressure was also measured at 8 and 10 AM at week 2 and month 9. Safety was evaluated by adverse events and other ocular and systemic measures.

Results: At baseline, mean intraocular pressure was similar in the three treatment groups. During follow-up, there were no statistically significant among-group differences in mean intraocular pressure or mean changes from baseline intraocular pressure (at peak or trough). The difference in mean intraocular pressure between the brimonidine-Purite-0.15% and brimonidine-0.2% treatment group was less than 1 mm Hg at all time points. The relative percent difference in allergic conjunctivitis was 41% lower in the brimonidine-Purite 0.15% group compared with the brimonidine 0.2% group. The comfort and satisfaction rating significantly favored brimonidine-Purite 0.15%.

Conclusions: Over 12-months, brimonidine-Purite 0.15% and 0.2% provided intraocular pressure lowering comparable with brimonidine 0.2% in patients with glaucoma or ocular hypertension. Brimonidine-Purite 0.15% showed the most favorable safety and tolerability profile with a reduced incidence of allergic conjunctivitis and better satisfaction and comfort rating.

Key Words: Benzalkonium chloride—Brimonidine—Glaucoma—Ocular hypertension—Purite.

Since the introduction of brimonidine 0.2% ophthalmic solution (Alphagan; Allergan, Irvine, CA) in 1996, this highly selective α_2-adrenergic agonist has proven to be an effective and safe agent for the long-term management of glaucoma and ocular hypertension.[1] In a randomized, continuous clinical trial, the efficacy of brimonidine 0.2% twice daily was sustained over 4 years and was comparable with the efficacy of timolol 0.5%.[2–6] Additional studies have shown the flexibility of brimonidine 0.2% twice daily as an effective monotherapy, adjunctive, and replacement therapy.[7–9] Brimonidine 0.2% twice daily has become a widely accepted first- and second-line therapy for the long-term management of glaucoma and ocular hypertension.

Studies show that brimonidine 0.2% has a lower risk of systemic adverse events than topical β-blockers.[2,3,7,10,11] In addition, brimonidine 0.2% has a lower

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Members of the Brimonidine-Purite Study Groups 1 and 2 are listed in the Appendix at the end of this article.

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incidence of ocular allergy and shows no cross toxicity compared with apraclonidine (Iopidine; Alcon, Fort Worth, TX).[12] Reports of ocular allergy associated with chronic brimonidine therapy range from 4.2% to 12.7% of patients, depending on the diagnostic criteria and duration of therapy.[1,4,13]

A new formulation of brimonidine ophthalmic solution has been developed to enhance safety and tolerability while maintaining effective intraocular pressure (IOP) reduction. Brimonidine-Purite (Alphagan, Allergan, Irvine, CA) has a different preservative and a lower concentration of active drug than the original brimonidine 0.2% (Alphagan). In the reformulation, the preservative has been changed from benzalkonium chloride (BAK) to Purite. Benzalkonium chloride is the most common antimicrobial preservative used in topical multiuse ophthalmic preparations, including most glaucoma medications.[14,15] It works by denaturing proteins, lysing cytoplasmic membranes, and oxidizing enzymes. At high concentrations, BAK may be more toxic than other preservatives. It can accumulate and remain in ocular tissue for relatively lengthy periods, and may induce cell death in a dose-dependent manner.[16,17] Because glaucoma is a chronic disease and patients may be taking multiple glaucoma medications, these patients may be exposed to high concentrations of BAK with potentially detrimental ocular effects. In contrast, Purite is a stabilized oxychloro complex and oxidative preservative used in Refresh Tears (Allergan, Irvine, CA) artificial eye lubricant and Lens Plus Purite (Allergan, Irvine, CA) Saline.[18–20] When Purite is exposed to light, it is converted to natural tear components (i.e., sodium and chloride ions, oxygen, and water).[21] Purite is a microbicide with a wide spectrum of antimicrobial activity and a very low level of toxicity in mammalian cells.[22]

In addition to the change in preservative, brimonidine-Purite 0.15% contains 25% less active drug than original brimonidine 0.2%. Animal studies suggest that brimonidine tartrate has enhanced ocular bioavailability when formulated as brimonidine-Purite.[23] In addition, 0.15% is the lowest effective concentration tested, which attains the desired therapeutic effect.[24] Therefore, the new formulation of brimonidine may provide an improved safety and tolerability profile with comparable efficacy.

The objective of this study was to evaluate the safety and efficacy of brimonidine-Purite 0.15% and 0.2% compared with brimonidine 0.2%. The results represent the pooled analyses of two identically designed clinical trials. All three study medications were administered three times daily for 1 year in patients with glaucoma or ocular hypertension. Although brimonidine twice daily has been shown to be as effective as three-times-daily brimonidine,[24,25] the three-times-a-day dosage was selected for this study to satisfy US regulatory requirements.

PATIENTS AND METHODS

Study Design

Two identically designed, 12-month, double-masked, randomized, parallel-group studies were conducted at 44 sites across the United States. The results presented here are from the analyses of pooled data from these two clinical trials. The studies were conducted in accordance with Institutional Review Board and Informed Consent Regulations. Each investigator obtained appropriate review board approval before study initiation. All patients gave their written consent before participating in any study-related activities. Patients who were treated with ocular hypotensive medications before study entry were required to undergo a washout period ranging from 4 to 28 days, depending on the medication taken. This washout eliminated any potential residual effects of previous therapy.

Patients were randomly assigned to receive brimonidine-Purite 0.15% (n = 381), brimonidine-Purite 0.2% (n = 383), brimonidine 0.2% (n = 383) three times daily in the morning (7:30–8:30 AM), in the midafternoon (2:30–3:30 PM), and in the evening (9:30–10:30 PM). Scheduled visits occurred before study, at baseline, at weeks 2 and 6, and at months 3, 6, 9, and 12.

Criteria

Key inclusion criteria included an age of 18 years or older with a diagnosis of glaucoma (primary open angle, pseudoexfoliative, pigment dispersion, chronic angle closure with a patent peripheral iridectomy/iridotomy for at least 3 months) or ocular hypertension (IOP $\geq$ 22 mm Hg, $\leq$ 34 mm Hg in each eye after washout, with between-eye IOP asymmetry $\leq$ 5 mm Hg), likelihood to be controlled on monotherapy, negative pregnancy test for women of childbearing potential, and best corrected visual acuity of 20/100 or better.

Key exclusion criteria included uncontrolled systemic disease, other active ocular disease, abnormally low or high blood pressure or heart rate, anticipated alteration of existing chronic therapy with agents that could substantially affect IOP, use of ocular medication other than periodic use of artificial tears, and functionally significant visual field loss.

Efficacy Variables

The primary efficacy variable was IOP. Diurnal IOP was measured at approximately 8 AM (before the morning drop), 10 AM, 3 PM (before the afternoon drop), and 5 PM at baseline, week 6, and at months 3, 6, and 12. The IOP was also measured at approximately 8 AM (before the morning drop) and 10 AM at week 2 and month 9.

Other efficacy variables included clinical success as evaluated by the investigator (regardless of whether a physician recommended continuation of study medication for the patient), subject satisfaction evaluation, and subject comfort evaluation using standardized scales.

Other measures that were evaluated included adverse events, visual acuity, cup/disc ratio, biomicroscopy, ophthalmoscopy, visual fields, heart rate, and systolic and diastolic blood pressure. The severity of adverse events was assessed based on the following guidelines: mild (awareness of sign or symptom, but easily tolerated), moderate (discomfort enough to cause interference with usual activity) and severe (incapacitating or unable to work or perform usual activities).

Statistical Analysis

The primary variables of analysis for efficacy were mean IOP and the mean change in IOP from baseline. These IOP data were analyzed using both the intent-to-treat with last observation carried forward and per-protocol populations. The per-protocol population consisted of observed cases. Only patients who met the protocol entry criteria, had no major protocol violations, received study medication, and had at least one follow-up visit were included in the per-protocol analysis, and only data from visits within specified time windows were included. Decisions for per-protocol exclusions were made before unmasking of the treatment groups for analysis. Safety data were analyzed using the intent-to-treat population. For comparison of treatment efficacy, both noninferiority and a two-sided paired *t* test for superiority were performed. Noninferiority criteria were set by the US Food and Drug Administration. Criteria were tested by constructing a two-sided 95% confidence interval for the between-group difference between experimental drug and brimonidine in mean IOP. If the upper limit of 95% confidence interval at all time points did not exceed 1.5 mm Hg, brimonidine-Purite was considered at least as effective as brimonidine.

Nominal categorical data such as sex and race were analyzed by the Cochran-Mantel-Haenszel method and continuous variables such as age and blood pressure were analyzed using a two-way analysis of variance with factors of treatment group and investigator site. Adverse events were analyzed using the Pearson χ^2 test or Fisher exact test. Ordinal categorical variables such as comfort and safety data were analyzed using the stratum (investigator site) adjusted Kruskal-Wallis and Wilcoxon rank-sum test.

RESULTS

Subject Demographics

The demographics and clinical characteristics of patients taking brimonidine-Purite 0.15% three times daily, brimonidine-Purite 0.2% three times daily, and brimonidine 0.2% three times daily are summarized in Table 1. No significant between-group differences were noted in baseline demographics, which included mean patient age, gender, race, and iris color.

Efficacy

Criteria for the per-protocol analysis were met by 97.9% (1,123 of 1,147) of patients (brimonidine-Purite 0.15%, 97.6% [372 of 381 patients]; brimonidine-Purite 0.2%, 97.9% [375 of 383 patients]; brimonidine 0.2%, 98.2% [376 of 383 patients]) and 92% of all data points were included with a similar distribution across the treatments. Twenty-four patients did not meet the entry criteria as defined in the study protocol and were excluded from the efficacy analysis. Other key reasons for patient data exclusions from the per-protocol analysis included use of excluded medications during the study, inappropriate instillation of study medications, and visits occurring outside of visit windows. There was no significant difference in the IOP results between the intent-to-treat and per-protocol analyses, and the per-protocol results are presented. The conclusions drawn from either intent-to-treat or per-protocol populations were the same.

Overall IOP Efficacy

At baseline, mean IOP was similar across the three treatment groups at each time point. Baseline mean IOP at 10 AM was 23.6 mm Hg (with an approximate SD of 3.2 mm Hg). Baseline mean IOP at 8 AM was 24.9 mm Hg (with an approximate SD of 2.7 mm Hg) (Fig. 1 and 2). Over the next 12 months, the difference in mean IOP at 10 AM (morning peak) (Fig. 1) and 8 AM (morning trough) (Fig. 2) between brimonidine-Purite 0.15% and brimonidine 0.2% was less than or equal to 0.4 mm Hg.

The mean IOP for each group was within 1 mm Hg of

TABLE 1. *Demographics and clinical characteristics of patients on brimonidine-Purite 0.15%, brimonidine-Purite 0.2%, and brimonidine 0.2%*

	Brimonidine-Purite 0.15% (n = 381)		Brimonidine-Purite 0.2% (n = 383)		Brimonidine 0.2% (n = 383)		Total (n = 1147)		
Variable	No.	(%)	No.	(%)	No.	(%)	No.	(%)	P
Age (years)									0.460
Mean	63.4		63.8		62.7		63.3		
SD	12.8		12.1		12.6		12.5		
Min	22.4		25.4		25.2		22.4		
Max	88.8		90.4		93.4		93.4		
Median	64.7		65.8		64.2		64.7		
Sex									0.845
Male	169	44.4%	162	42.3%	167	43.6%	498	43.4%	
Female	212	55.6%	221	57.7%	236	56.4%	649	56.6%	
Race									0.377
Caucasian	303	79.5%	298	77.8%	305	79.6%	906	79.0%	
Black	48	12.6%	59	15.4%	47	12.3%	154	13.4%	
Asian	2	0.5%	1	0.3%	3	0.8%	6	0.5%	
Hispanic	28	7.3%	23	6.0%	26	6.8%	77	6.7%	
Other	0	0.0%	2	0.5%	2	0.5%	4	0.3%	
Iris color									0.468
Blue	113	29.7%	108	28.2%	111	29.0%	332	28.9%	
Brown	179	47.0%	196	51.2%	183	47.8%	558	48.6%	
Green	23	6.0%	18	4.7%	18	4.7%	59	5.1%	
Hazel	59	15.5%	58	15.1%	68	17.8%	185	16.1%	
Other	7	1.8%	3	0.8%	3	0.8%	13	1.1%	

the mean IOP in the other groups at all visits and all time points, showing comparable IOP-lowering capabilities.

Brimonidine-Purite 0.15% Versus Brimonidine 0.2%

There were no statistically significant differences in diurnal mean IOP measurements between brimonidine-Purite 0.15% and brimonidine 0.2%, except at the 5-PM time point at month 3 (P = 0.046) where the mean IOP difference was 0.5 mm Hg in favor of brimonidine 0.2%. There were no statistically significant differences in the mean changes from baseline in diurnal IOP measurements, except for the 10-AM time point at week 2 (P = 0.015), the 5-PM time point at month 3 (P = 0.010), and the 5-PM time point at month 6 (P = 0.004). The mean

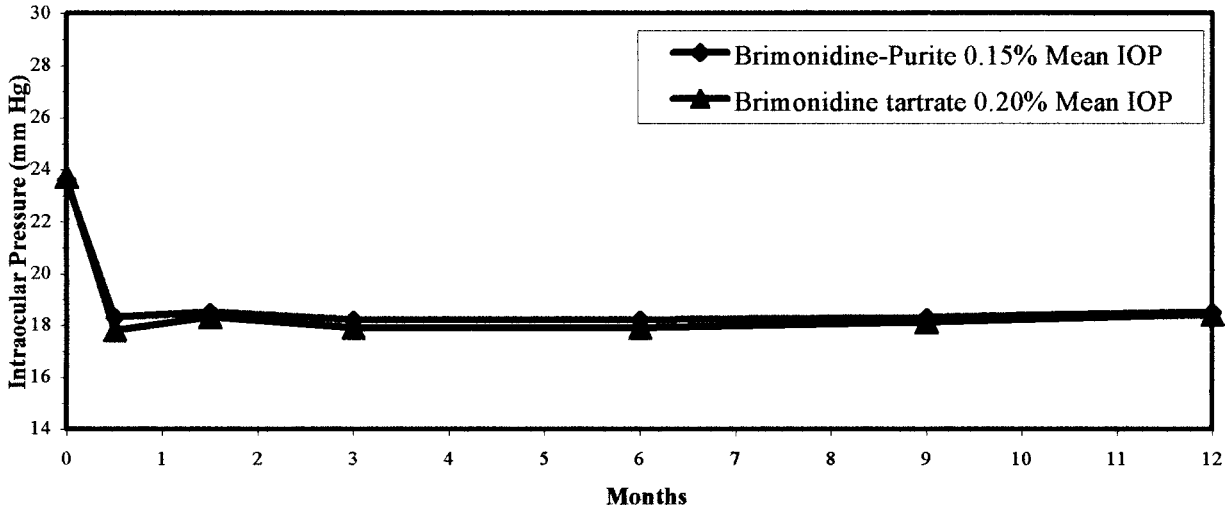

FIG. 1. Efficacy graph at 10 AM (peak) showing mean intraocular pressure of patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15% and brimonidine 0.2% (Alphagan). The difference in mean intraocular pressure between the treatment groups was less than or equal to 0.4 mm Hg at all time points. All standard errors were less than 0.180.

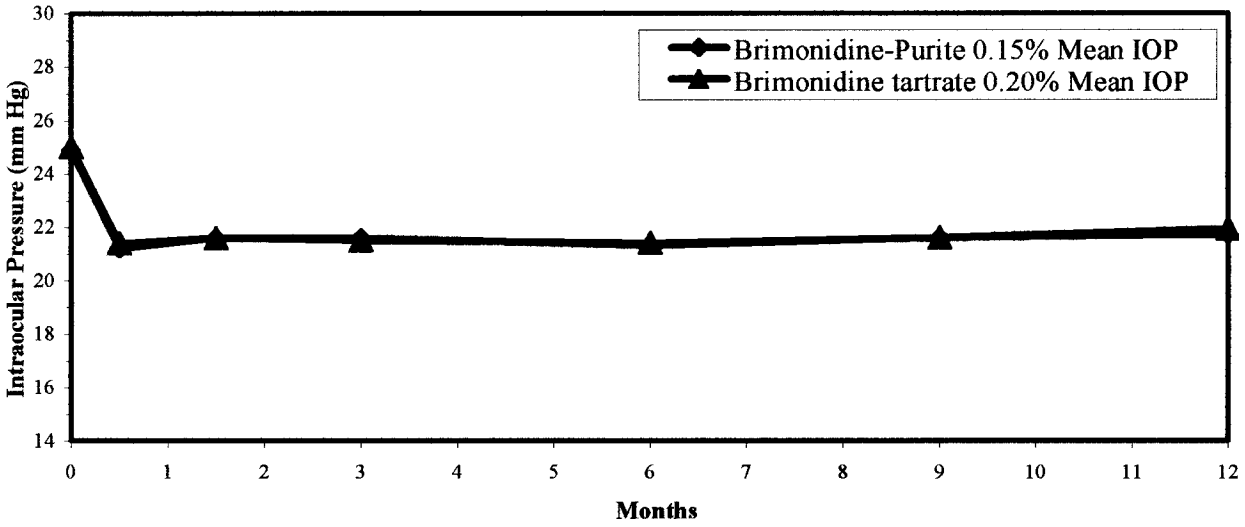

FIG. 2. Efficacy graph at 8 AM (trough) showing mean intraocular pressure of patients with glaucoma or ocular hypertension during 12-month treatment with brimonidine-Purite 0.15% and brimonidine 0.2% (Alphagan). All standard errors were less than 0.211.

change from baseline IOP difference was 0.6, 0.7, and 0.9 mm Hg, respectively favoring brimonidine 0.2%. The noninferiority criteria were satisfied because 40/40 of the upper limits of 95% confidence intervals were less than or equal to 1.5 mm Hg, with 36/40 less than or equal to 1.0 mm Hg (mean IOP and mean change from baseline IOP), showing that brimonidine-Purite 0.15% was comparable in efficacy with brimonidine 0.2%.

Brimonidine-Purite 0.15% Versus Brimonidine-Purite 0.2%

There were no statistically significant differences observed in mean IOP or mean changes from baseline in diurnal IOP measurements between brimonidine-Purite 0.15% and brimonidine-Purite 0.2%, except at the 5-PM time point at month 3 ($P = 0.027$, mean IOP), the 10-AM time point at month 9 ($P = 0.009$, mean IOP), and the 10-AM time point at month 12 ($P = 0.011$, mean IOP). The mean IOP difference was 0.6, 0.8, and 0.8 mm Hg, respectively, favoring brimonidine-Purite 0.2%. The noninferiority criteria were satisfied because 40/40 of the upper limits of 95% confidence intervals were less than or equal to 1.5 mm Hg, with 35/40 less than or equal to 1.0 mm Hg (mean IOP and mean changes from baseline IOP), showing that brimonidine-Purite 0.15% was comparable in efficacy with brimonidine-Purite 0.2%.

Brimonidine-Purite 0.2% Versus Brimonidine 0.2%

In the comparison of brimonidine-Purite 0.2% and brimonidine 0.2%, there were no statistically significant differences observed in mean IOP or mean changes from baseline in diurnal IOP measurements except for the 10-AM time point at month 9 ($P = 0.045$, mean IOP), the 10-AM time point at month 12 ($P = 0.018$, mean IOP), and the 5-PM time point at month 12 ($P = 0.041$, mean IOP). The average difference in mean IOP and mean changes from baseline in IOP difference was −0.6, −0.8, and −0.7 mm Hg, respectively, favoring brimonidine-Purite 0.2%. The only measurement favoring brimonidine 0.2% was at the 10-AM time point at month 6 (mean change from baseline IOP difference of 0.7 mm Hg, $P = 0.019$). The noninferiority criteria were satisfied because 40/40 of the upper limits of the 95% confidence intervals were less than or equal to 1.5 mm Hg, with 37/40 less than or equal to 1.0 mm Hg (mean IOP and mean changes from baseline IOP), showing that brimonidine-Purite 0.2% was comparable in efficacy with brimonidine 0.2%.

Safety

The following results were analyzed as intent-to-treat, and all data points were considered. Throughout the study, patients were monitored for signs and symptoms of adverse events (Table 2). Investigators rated the majority of adverse events as mild or moderate in severity. The overall frequency of treatment-related adverse events reported was fewer in the brimonidine-Purite 0.15% than with brimonidine-Purite 0.2% or brimonidine 0.2%. There was a lower incidence rate of allergic conjunctivitis, conjunctival hyperemia, and oral dryness favoring brimonidine-Purite 0.15% compared

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