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APPLICATION NUMBER:

21-764

MEDICAL REVIEW

Deputy Division Director's Review of NDA 21-764

Original New Drug Application

Submission Date: April 27, 2004
Review Completed: February 27, 2005

Deputy Division Director: Wiley A. Chambers, MD

Established Name: Brimonidine tartrate ophthalmic solution

Applicant: Alcon, Inc.
P.O. Box 62
Bosch 69
CH-6331 Hunenberg Switzerland

Pharmacologic Category: Alpha-2 agonist

Proposed Indication: Reduction of intraocular pressure
Dosage Form: Ophthalmic solution
Route of Administration: Topical ocular
NDA Drug Classification: 5S

Table of Contents

I. Recommendations

A. Recommendation on Approvability

NDA 21-764 is recommended for approval for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension following the resolution of the patent infringement suit.

B. Recommendation on Postmarketing Studies and/or Risk Management Steps

No postmarketing studies are recommended. No risk management steps are recommended.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Ocular hypertension is defined as high intraocular pressure (IOP) and may lead to optic nerve head abnormalities and visual field defects. Currently there is no proven direct treatment for optic neuropathy regardless of the initiating cause. Therapy is focused on lowering the intraocular pressure. Presently, five classes of drugs are used to reduce IOP: adrenergic beta-receptor antagonists; cholinergic agonists; adrenergic agonists, carbonic anhydrase inhibitors; and prostaglandin/prostaglandin analogs.

The new drug product proposed in this application is a reformulation of Alphagan P (brimonidine tartrate ophthalmic solution), 0.15%. The application included the results of a clinical bioequivalence study (C-02-49) in which the proposed new drug product demonstrated bioequivalence with Alphagan P.

B. Efficacy

Efficacy is based on the agency's finding of efficacy in NDA 20-613, Alphagan (brimonidine tartrate ophthalmic solution), 0.2% and NDA 21-262, Alphagan P (brimonidine tartrate ophthalmic solution), 0.15%. Study C-02-49 provides a link to Alphagan P through clinical bioequivalence.

C. Safety

Safety is based on the agency's finding of efficacy in NDA 20-613, Alphagan (brimonidine tartrate ophthalmic solution), 0.2% and NDA 21-262, Alphagan P (brimonidine tartrate ophthalmic solution), 0.15%. Study C-02-49 provides a link to Alphagan P through clinical bioequivalence.

D. Dosing, Regimen, and Administration

In the clinical studies evaluating safety, efficacy and bioequivalence, one drop of brimonidine tartrate ophthalmic solution was administered three times daily to the affected eye.

III. Reviews from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

Reviews have been completed from Chemistry/Manufacturing, Non-clinical Pharmacology/Toxicology, Microbiology (sterility assurance), Clinical Pharmacology, and the Division of Drug Marketing, Advertising and Communications (DDMAC). There are no outstanding or unresolved issues from any of the reviews.

IV. Labeling

Labeling is based on the labeling of Alphagan P and includes formulation specific changes.

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/s/

Wiley Chambers
3/1/05 10:28:50 AM
MEDICAL OFFICER

Medical Officer's Clinical Review #2
NDA 21-764

Submission Date:	February 25, 2005
Receipt Date:	February 25, 2005
Review Completed:	February 25, 2005
Reviewer:	Rhea Lloyd, MD Medical Officer
Established Name:	Brimonidine Tartrate Ophthalmic Solution, 0.15%
Proprietary Name:	None
Sponsor:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, TX 76134-2099 (817) 554-4877 Michael E. Pfleger

Submitted:

Final labeling text based on previous review and discussion with the sponsor. The labeling which follows is the sponsor's resubmission dated February 25, 2005.

The sponsor has accepted all labeling changes requested by the agency.

The sponsor also states that there is no new safety information to be reported.

7 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Recommendations:

The submitted package insert labeling is acceptable. The carton and container labels are acceptable with the minor revisions noted.

NDA 21-764, Brimonidine Tartrate Ophthalmic Solution, 0.15% is recommended for approval for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

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/s/

Rhea Lloyd
2/25/05 02:06:13 PM
MEDICAL OFFICER

Wiley Chambers
2/25/05 04:53:31 PM
MEDICAL OFFICER

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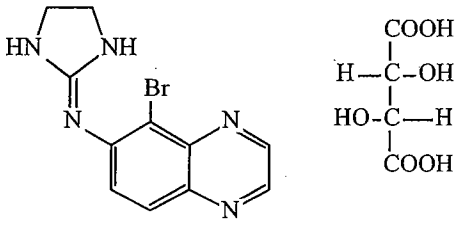
CLINICAL REVIEW

Application Type	NDA
Submission Number	21-764
Submission Code	Original
Letter Date	4/27/2004
Stamp Date	4/28/2004
PDUFA Goal Date	2/28/2005
Reviewer Name	Rhea A. Lloyd, MD
Review Completion Date	11/30/2004
Established Name	Brimonidine Tartrate Ophthalmic Solution, 0.15%
(Proposed) Trade Name	None
Therapeutic Class	Alpha-2 adrenergic agonist
Applicant	Alcon Research, Ltd. 6201 South Freeway Fort Worth, TX 76134-2099 Michael E. Pfleger 817-551-4877
Priority Designation	S

Structure

$C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$



Dosing Regimen

Instill one drop three-times-daily in affected eye

Indication

Reduction of intraocular pressure

Intended Population

Patients with ocular hypertension or open angle glaucoma

Formulation

Ingredient	% w/v
Brimonidine Tartrate	0.15
POLYQUAD (Polyquaternium-1)	0.001
Povidone	
Boric Acid	
Sodium Borate	
Calcium Chloride	
Magnesium Chloride	
Potassium Chloride	
Mannitol	
Sodium Chloride	
NaOH and/or HCl	
Purified Water	

Table of Contents

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Brimonidine Tartrate Ophthalmic Solution, 0.15% with the labeling changes listed in this review is recommended for approval for the reduction of intraocular pressure in patients with open-angle glaucoma and ocular hypertension based upon its proof of bioequivalence with Alphagan® P following resolution of patent infringement suit or 30 months, whichever comes sooner. This application relies upon the agency's findings of safety and efficacy for NDA 20-613, Alphagan®, and NDA 21-262, Alphagan® P. Brimonidine Tartrate Ophthalmic Solution, 0.15% is the same in strength, dosage form and route of administration as Alphagan P.

Brimonidine Tartrate Ophthalmic Solution, 0.15% differs from Alphagan P in that it contains a different preservative, POLYQUAD® 0.001%. The bioequivalence study contained in this application, C-02-49, was required to establish that the change in preservative maintained a similar safety and efficacy profile with Alphagan® P.

The bioequivalence of Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan® P was demonstrated in an adequate and well-controlled study. Statistical significance in the test for equivalence was achieved in that the two-sided, 95% confidence interval for the mean difference in intraocular pressure for treatment groups was within 1.5 mmHg for all intraocular pressure measurement time points and within 1.0 mmHg for the majority of IOP measurement time points.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No postmarketing risk management activity is necessary given the reported event profile of brimonidine tartrate.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are required.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Established Name	Brimonidine Tartrate Ophthalmic Solution, 0.15%
(Proposed) Trade Name	None
Therapeutic Class	Alpha-2 adrenergic agonist

Glaucoma is a common optic neuropathy that is characterized by progressive optic nerve damage. The optic nerve damage results in insidious visual field defects that progress to complete blindness when left untreated. The current standard of practice is to decrease the intraocular pressure with pharmacologic agents that safely and effectively lower intraocular pressure.

Brimonidine tartrate, an alpha-2 agonist, was initially studied as a systemically administered antihypertensive agent. It was not effective. It was subsequently approved for the treatment of patients with open angle glaucoma and ocular hypertension in 1996 as Alphagan (brimonidine tartrate ophthalmic solution, 0.2%) NDA 20-613.

Brimonidine Tartrate Ophthalmic Solution, 0.15% is an alpha-2 agonist which is administered topically. Its proposed indication is the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The application includes a single bioequivalence trial, C-02-49, which randomized 842 subjects. All 842 subjects were included in the overall safety population (subjects with any on-therapy study visits). The study participants were to dose with the study drug three-times-daily for a minimum of six months. The majority of patients, 65%, in each treatment group had greater than six months of exposure to therapy. No other pertinent clinical data sources were used.

1.3.2 Efficacy

Submitted under Section 505 (b)(2) of the Food, Drug, and Cosmetic Act, this application relies upon the proof of safety and efficacy of brimonidine tartrate in NDA 20-613, Alphagan, and NDA 21-262, Alphagan P. The study performed was to compare the safety and efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15%, which uses POLYQUAD 0.001% as a preservative, with Alphagan P (brimonidine tartrate ophthalmic solution), 0.15% in patients with open-angle glaucoma or ocular hypertension.

The study design was prospective, multicenter, randomized, double-masked, parallel group with an active control. In order to establish efficacy and bioequivalence, the mean difference in intraocular pressure between Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P was to be within 1.5 mmHg of a two-sided 95% confidence interval for all intraocular measurement time points and within 1.0 mmHg for the majority of time points at 2, 6 and 12 weeks. Brimonidine Tartrate Ophthalmic Solution, 0.15% demonstrated efficacy and bioequivalence in the study presented in this application.

1.3.3 Safety

The data presented were adequate to assess the safety of Brimonidine Tartrate Ophthalmic Solution, 0.15%. Generally, the adverse events reported were mild to moderate in severity and self-limited. Adverse events were similar between treatment groups and not age dependent.

The most frequent adverse events were associated with allergic conjunctivitis – ocular hyperemia, conjunctivitis, ocular follicles, pruritus. This constellation of symptoms was equally distributed between the treatment groups. No treatment-related serious adverse events were reported. There was one death reported which was not related to treatment.

Brimonidine Tartrate Ophthalmic Solution, 0.15% presents no overall safety concerns not previously seen with the approved product, Alphagan P.

1.3.4 Dosing Regimen and Administration

Brimonidine Tartrate Ophthalmic Solution, 0.15% is dosed one drop three-times-daily in the eye(s) to be treated. This dosing regimen achieves equivalent IOP-lowering with the comparator in this study, Alphagan P.

1.3.5 Drug-Drug Interactions

No drug-drug interaction analyses were performed.

1.3.6 Special Populations

There were no statistically significant differences in demographic data, diagnoses, and baseline intraocular pressures between the treatment groups.

Subgroup analyses did not reveal any differences in safety profile with any specific population i.e., age, race, diagnosis. No studies were performed in pregnant or lactating subjects.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name	Brimonidine Tartrate Ophthalmic Solution, 0.15%
(Proposed) Trade Name	None
Therapeutic Class	Alpha-2 adrenergic agonist
Structure	$C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$
Proposed Indication	the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Formulation

Ingredient	% w/v
Brimonidine Tartrate	0.15
POLYQUAD (Polyquaternium-1)	0.001
Povidone	[redacted]
Boric Acid	[redacted]
Sodium Borate	[redacted]
Calcium Chloride	[redacted]
Magnesium Chloride	[redacted]
Potassium Chloride	[redacted]
Mannitol	[redacted]
Sodium Chloride	[redacted]
NaOH and/or HCl	[redacted]
Purified Water	[redacted]

The active moiety, brimonidine tartrate, is a potent, relatively selective alpha-2-adrenergic agonist.

2.2 Currently Available Treatment for Indications

There are many products of different pharmacologic classes including beta blocking agents, cholinergic medications, carbonic anhydrase inhibitors and prostaglandin analogues marketed for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Within the alpha adrenergic agonist class, Iopidine (apraclonidine ophthalmic solution, 0.5%), brimonidine tartrate ophthalmic solution 0.2% (multiple manufacturers) and Alphagan P are currently marketed.

2.3 Availability of Proposed Active Ingredient in the United States

Brimonidine tartrate, the active moiety, is a potent, relatively selective alpha-2-adrenergic agonist. NDA 20-613, Alphagan, (brimonidine tartrate ophthalmic solution), 0.2% was first approved in 1996 for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and/or ocular hypertension. Alphagan is no longer marketed; however, generic copies of Alphagan are approved and marketed (NDA 76-254, NDA 76-260, NDA 76-372).

Alphagan P, (brimonidine tartrate ophthalmic solution, 0.15%), NDA 21-262, approved in 2000, is the only currently marketed Allergan Alphagan product.

2.4 Important Issues With Pharmacologically Related Products

Alphagan, brimonidine tartrate ophthalmic solution, 0.2%, produced allergic conjunctivitis in a significant percentage of patients. Alphagan P, brimonidine tartrate ophthalmic solution, 0.15%, was developed with both a lower concentration and a different preservative. In Alphagan P, Purite ® (chlorine dioxide) replaced benzalkonium chloride as the preservative.

The applicant has developed Brimonidine Tartrate Ophthalmic Solution, 0.15% as a brimonidine tartrate formulation preserved with Polyquad which maintains an acceptable and comparable tolerability profile to Alphagan P.

2.5 Presubmission Regulatory Activity

The Brimonidine Tartrate Ophthalmic Solution, 0.15% clinical development plan was reviewed with the FDA at an End-of-Phase 2 meeting on January 29, 2003. The purpose of the meeting was to confirm the appropriateness of the clinical study designs, selection of comparative agents and total number of patients to be included in the overall plan.

Pursuant to discussions with the FDA, the Phase 3 clinical plan consisted of a single multicenter, safety and efficacy study (C-02-49). The study was designed as an equivalence trial to compare Brimonidine Tartrate Ophthalmic Solution, 0.15% with Alphagan P both dosed three-times-daily.

Clinical Study C-02-49 was prospectively designed to provide primary efficacy results based on data through the 3-month visit (i.e., at Week 2, Week 6, and Month 3). IOP was assessed at 8 AM, 10 AM, and 5 PM at all study visits. All enrolled patients were to be followed for up to six months. The primary safety data included in the Clinical Study Report for C-02-49 are based on data through the 6-month visit. Patients at selected sites were to be followed for up to 12 months to evaluate endothelial cell counts. Although IOP was assessed at the additional follow-up visits, the primary efficacy conclusions are based on the initial three months. In the report, IOP results at Month 6 are included to provide additional support and confirmation of the primary efficacy findings.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

From the Sterility assurance standpoint, the NDA is recommended for approval.

3.2 Animal Pharmacology/Toxicology

From the Pharmacology/Toxicology standpoint, the NDA is recommended for approval with labeling changes included in this review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

All submitted clinical study reports, clinical protocols, and literature reports related to clinical trial, C-02-49 were reviewed. This study was conducted in the United States under IND 64,330 and is evaluated in this Medical Officer's review. This study was to establish bioequivalence with Alphagan P.

The majority of the application was submitted in paper CTD format. Modules 1, 2, and 5 were reviewed in depth.

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

4.2 Table of Clinical Studies

Table 4.2–1. C-02-49, Phase 3, Bioequivalence Study

Study No. Start Date/ End Date	Country	Population Studied	Design	Doses, Frequency of Dosing	Treatment Duration, (not including F/U)	# Pts Treated, Age Range, Mean Age (yrs)	Sex, Race
C-02-49 January 30, 2003 December 18, 2003	USA	Open-angle glaucoma or ocular hypertension	Randomized, multi-center double-masked, active controlled, parallel group	Brimonidine Tartrate Ophthalmic Solution., 0.15% or ALPHAGAN P One drop three times daily (8AM, 3 PM, 10 PM)	3 months (plus 9 month masked extension)	842 417 Brimonidine 0.15% 425 ALPHAGAN P 24 – 91 yrs 62.9 yrs	47.0% Male 53.0% Female 70.5% Caucasian 18.7% Black 0.5% Asian 9.7% Hispanic 0.6% Other

4.3 Review Strategy

This application was submitted in accordance with Sect. 505(b)(2) of the Federal Food, Drug and Cosmetics Act. The application relies on the agency's findings of safety and efficacy for NDA 21-262, Alphagan P (brimonidine tartrate ophthalmic solution), 0.15%, and NDA 20-613, Alphagan (brimonidine tartrate ophthalmic solution, 0.2%). The clinical studies conducted are evaluated to establish bioequivalence of Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P.

The submitted clinical study reports, clinical protocols, and literature reports related to trial C-02-49 were reviewed. The majority of the application was submitted in paper CTD format. Modules 1, 2, and 5 were reviewed in depth.

4.4 Data Quality and Integrity

Case Report Forms for all discontinued subjects in study C-02-49 were reviewed by this medical officer. No concerns were noted.

The Division of Scientific Investigations (DSI) performed an audit of Site No. 2600, David L. Wirta, MD between August 25 and September 4, 2004. The conclusion of the evaluation was that, except for minor deficiencies, Dr. Wirta adhered to the applicable statutory requirements and FDA regulations which govern the conduct of clinical investigations and the protection of human subjects. No deficiencies in the operation of this site that would affect the integrity or the reliability of the data were noted.

4.5 Compliance with Good Clinical Practices

The data were reviewed for consistency with other applications in this class. No special methods were used.

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate. The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Each IRB approved the Informed Consent document and provided a copy to Alcon before study initiation. All patients were completely informed, according to informed consent guidelines, about the pertinent details and purpose of the study. Patients or their legal representatives, read, signed, and dated the consent form before taking part in any study activity. A witness (if applicable) and the individual conducting the informed consent discussion also signed and dated the informed consent form. The investigator kept the original signed copies, and provided the patient with a duplicate copy.

Fifty-eight patients were excluded from the per protocol analysis. The protocol deviations for these patients included the following: 9 patients who did not meet IOP entry criteria, 1 patient

missing baseline IOP data, 2 patients on contraindicated anti-hypertensive medications, 23 patients on steroids, 5 patients who were non-compliant with study medication (including one patient who was enrolled at two investigative sites), and 18 patients who had no on-therapy data. Other protocol deviations were minor and included inconsistency in dosing times, procedures performed slightly outside the specified time window, dosing noncompliance, and changes in concomitant medication.

4.6 Financial Disclosures

The applicant adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

There is no evidence suggesting problems with the integrity of the submitted data.

5 CLINICAL PHARMACOLOGY

The pharmacokinetic and pharmacodynamic properties of brimonidine have been reported in NDA 20-613 and NDA 21-262, as well as in the medical and scientific literature.

Alcon did conduct a well-controlled study, C-03-01, to determine the pharmacokinetics of brimonidine after a single topical ocular administration of Brimonidine Tartrate Ophthalmic Solution, 0.15% or Alphagan P in healthy subjects to support this new drug application for Brimonidine Tartrate Ophthalmic Solution, 0.15%.

Planned comparisons of pharmacokinetic parameters and the systemic exposure to brimonidine after a single topical ocular dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% was compared to the systemic exposure to brimonidine after a single topical ocular dose of Alphagan P using the ratio of the two formulations with respect to geometric means for AUC and C_{max}. This comparison was based on two one-sided 90% confidence limits that were evaluated against a reference range.

Following topical ocular administration, plasma levels are relative low. Comparison of Cmax and AUC data from humans and from toxicology animals at dose levels with no observed adverse effects shows good margins of safety.

5.1 Pharmacokinetics

Table 5.1-1
Mean ± Std (range) Brimonidine Pharmacokinetic Parameters in Healthy Subjects After A Single Bilateral Topical Ocular Dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% or Alphagan P

Pharmacokinetic Parameters	Brimonidine Tartrate Ophthalmic Solution, 0.15% N=14	Alphagan P N=14	Mean Difference Between Treatment Groups N=14	Paired t-test (p-value)
C_{max} (pg/mL)	72.8 ± 18.9 (51.1 – 130)	74.3 ± 25.6 (29.7 – 107)	-1.59 ± 21.1 (-42.9 25.8)	0.7819
Tmax (h)	1.71 ± 0.70 (0.50 – 3.00)	1.65 ± .041 (0.53 – 2.00)	0.07 ± 0.61 (-1.00 – 1.00)	0.6798
AUC_{0-12} (pg*h/mL)	362 ± 89.7 (257 – 594)	362 ± 129 (118 – 529)	0.500± 83.2 (-139 – 139)	0.9824
AUC_{0-inf} (pg*h/mL)	362 ± 89.2 (280 – 601)	373 ± 131 (119 – 545)	2.29 ± 85.5 (-138 – 161)	0.9218
$t_{1/2}$ (h)	2.1 ± 0.6 (1.4 – 3.8)	2.1 ± 0.5 (1.6 – 3.4)	0.1 ± 0.6 (-1.0 – 1.6)	0.6960

5.2 Pharmacodynamics

No studies on human pharmacodynamics were conducted with Brimonidine Tartrate Ophthalmic Solution, 0.15%.

Brimonidine is rapidly absorbed into the eye and has a high affinity for melanin pigmented tissues such as iris-ciliary body, which is the purported site of action for its IOP-lowering effects. Although brimonidine has a relatively high affinity for pigmented tissues, it has been shown to be safe during long term toxicology studies and from actual experience in clinical use.

In vitro studies have shown that the metabolism of brimonidine is similar in rats, monkeys and humans and that the major metabolites are generated by hepatic aldehyde oxidases rather than cytochrome P-450 enzymes. Based on the very low plasma levels in humans following topical ocular administration and the lack of cytochrome P-450 involvement in brimonidine elimination, drug-drug related interactions involving cytochrome P-450 are unlikely.

The primary route of elimination for brimonidine is by metabolism. Studies in rats and monkeys have shown that approximately 60 to 75% of orally or intravenously administered doses are recovered in urine in the form of unconjugated metabolites.

The effect of brimonidine tartrate on the QT interval has not been studied in humans.

5.3 Exposure-Response Relationships

The dose level did not vary with response; therefore, no individual dose response information was obtained.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

6.1.1 Methods

The submitted clinical study reports, clinical protocols, and literature reports related to trial C-02-49 were analyzed in this efficacy review.

The majority of the application was submitted in paper CTD format. Modules 1, 2, and 5 were reviewed in depth.

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

6.1.2 General Discussion of Endpoints

Open-angle glaucoma is characterized clinically by progressive atrophy of the optic nerve head, called cupping. Optic nerve head atrophy is associated with corresponding patterns of visual field loss.

Elevated intraocular pressure is an etiological factor in glaucomatous cupping. Higher intraocular pressure corresponds with a greater frequency of optic nerve damage. Medical therapy for open-angle glaucoma is aimed at lowering the intraocular pressure below a level which is likely to produce further optic nerve damage.

Accordingly, mean intraocular pressure has been the accepted primary endpoint for treatment of open-angle glaucoma or ocular hypertension. To establish equivalence of Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P, the two-sided, 95% confidence interval for the mean difference in intraocular pressure for treatment groups should be within 1.5 mmHg for all intraocular pressure measurement time points and with 1.0 mmHg for the majority of IOP measurement time points.

6.1.3 Study Design - Protocol C-02-49

Title:	A Three-Month, Randomized, Double-Masked, Parallel Group, Primary Therapy Study with a Planned Nine Month Extension of the Safety and IOP-Lowering Efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% Compared to Alphagan P, 0.15% in Patients with Open Angle Glaucoma or Ocular Hypertension
Objective:	To compare the safety and efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% (0.001% polyquaternium-1 as preservative) to that of Alphagan P (brimonidine tartrate ophthalmic solution), 0.15% in patients with open-angle glaucoma or ocular hypertension.
Study Design:	A prospective, randomized, multi-center (66 sites), double masked, parallel group, active controlled trial.
Test Drug Schedule:	One drop of study drug into each study eye three-times-daily at 8 AM (±30 minutes), 3 PM (±30 minutes), and 10 PM (±30 minutes)

Table 6.1.3-1 Table of Investigators

Inv. No.	Principal Investigator (Name and Address)	Dates of Participation MM/DD/YY	Number of Patients	
			Intent to Treat	Per Protocol
2666 [1,2]	Louis Alpern, MD El Paso, TX	1/30/03 - 10/30/03	18	16
2434	Jason Bacharach, MD Petaluma, CA	2/24/03 – 12/12/03	21	21
3414	Charles J. Beischel, MD Charleston, SC	2/18/03 – 11/25/03	11	11
3679	David E. Brodstein,MD Ogden, UT	2/25/03 – 11/07/03	12	12
470	Donald Brotherman, MD Dallas, TX	3/18/03 – 12/02/03	7	7
362 [1,2]	Delmar Caldwell, MD New Orleans, LA	4/14/03 – 12/05/03	7	6
2244 [2]	Moiz M. Carim, MD Reading, PA	3/11/03 – 12/08/03	3	3
842 [1,2]	John Cohen, MD Cincinnati, OH	3/03/03 – 12/15/03	8	8

Inv. No.	Principal Investigator (Name and Address)	Dates of Participation MM/DD/YY	Number of Patients	
			Intent to Treat	Per Protocol
3349	Andrew J. Cottingham, MD San Antonio, TX	3/17/03 – 10/22/03	14	12
1236	E. Randy Craven, MD Littleton, CO	4/3/03 – 10/30/03	5	5
2557	Thomas L. Croley, MD Ocala, FL	2/21/03 – 10/27/03	6	6
2348	Douglas Day, MD Atlanta, GA	2/19/03 – 10/24/03	12	12
1927	Harvey B. DuBiner, MD Morrow, GA	3/10/03 – 12/01/03	13	12
3785	Efraim Duzman, MD Irvine, CA	4/3/03 – 12/10/03	16	15
3511	Lamont Ericson, MD Layton, UT	3/28/03 – 11/25/03	6	6
553[1,2]	Richard M. Evans, MD San Antonio, TX	4/23/03 – 12/6/03	23	22
1928	Joseph G. Feghali, MD Morgantown, WV	3/4/03 – 11/20/03	13	12
2564[1,2]	Robert M. Feldman, MD Houston, TX	2/7/03 – 11/5/03	8	7
3426[4]	Ronald Goldman, MD San Diego, CA	No patients enrolled		
3420[1,2]	Thomas T. Henderson, MD, FACS Austin, TX	4/12/03 – 12/3/03	4	2
3664	Jane Lindell Hughes, MD, FACS San Antonio, TX	3/10/03 – 10/14/03	19	18
2449[2]	Barry Katzman, MD San Diego, CA	3/18/03 – 10/30/03	9	9
784[1,2]	David A. Lee, MD Charleston, SC	3/24/03 – 12/11/03	9	3
3416[1,2]	Steven Litinsky, MD Delray Beach, FL	3/11/03 – 11/21/03	2	2
2302	Douglas Lorenz, DO Henderson, NV	2/25/03 – 11/18/03	14	14
3678[2]	Jeffrey R. Lozier, MD San Diego, CA	2/24/03 – 11/19/03	20	18
2029[2]	Jonathan I. Macy, MD Los Angeles, CA	3/18/03 – 12/02/03	6	4

Inv. No.	Principal Investigator (Name and Address)	Dates of Participation MM/DD/YY	Number of Patients	
			Intent to Treat	Per Protocol
3668	Brian J. McKee, MD Newport News, VA	3/26/03 – 12/04/03	8	8
3397[1,2]	Marlene Moster, MD Philadelphia, PA	4/3/03 – 12/17/03	5	4
3650	Duane J. Nelson, MD Provo, UT	4/3/03 – 10/29/03	3	3
1011[1,2]	Katherine Ochsner, MD Wilmington, NC	2/26/03 – 12/17/03	24	23
2133[1,2]	Silvia Orengo-Nania, MD Houston, TX	4/10/03 – 12/09/03	7	6
3715	Matthew Parsons, MD Provo, UT	3/3/03 – 11/10/03	6	6
3025	Matthew D. Paul, MD Danbury, CT	2/26/03 – 11/7/03	5	5
3627	James H. Peace, MD Inglewood, CA	2/14/03 – 12/10/03	27	26
3720[1,2]	Bernard R. Perez, MD Tampa, FL	4/8/03 – 12/12/03	8	8
3362[2,3] 3858	Anthony Realini, MD Laurie G. Barber, MD Little Rock, AR	3/21/03 – 12/18/03	5	5
2448[1,2]	Ned Reinstein, MD Tulsa, OK	1/30/03 – 12/17/03	21	21
2436	James A. Roberts, MD Largo, FL	3/19/03 – 6/9/03	2	2
648	Alan Lee Robin, MD Baltimore, MD	2/27/03 – 11/21/03	7	7
1393[1,2]	Michael H. Rotberg, MD Charlotte, NC	2/11/03 – 12/9/03	26	23
1806[1,2]	Kenneth Sall, MD Bellflower, CA	2/3/03 – 12/8/03	39	38
3270[1,2]	Paul N. Schacknow, MD, PhD Lake Worth, FL	4/1/03 – 12/2/03	4	4
1939	Howard I. Schenker, MD Rochester, NY	2/11/03 – 12/1/03	27	26
3685	Gail F. Schwartz, MD Baltimore, MD	2/28/03 – 12/15/03	6	6

Inv. No.	Principal Investigator (Name and Address)	Dates of Participation MM/DD/YY	Number of Patients	
			Intent to Treat	Per Protocol
1238[2]	Stephen V. Scoper, MD Norfolk, VA	2/14/03 – 12/16/03	22	20
731	Elizabeth D. Sharpe, MD Mt. Pleasant, SC	2/3/03 – 12/1/03	21	19
1611[1,2]	Mark B. Sherwood, MD Gainesville, FL	3/12/03 – 11/20/03	17	17
3346	Philip (Lee) Shettle, DO Largo, FL	2/25/03 – 10/8/03	7	7
589	Robert L. Shields, MD Denver, CO	4/1/03 – 11/11/03	1	1
1002[1,2]	Charles Shrader, MD Wichita, KS	2/27/03 – 12/9/03	10	10
271[1,2]	Robert H. Stewart, MD Houston, TX	2/4/03 – 11/19/03	25	25
2631[4]	William Colby Stewart, MD Cookeville, TN	No patients enrolled		
2247	Richard T. Sturm, MD Lynnbrook, NY	2/20/03 – 10/02/03	9	9
1455[1,2]	Joseph Tauber, MD Kansas City, MO	4/28/03 – 8/7/03	1	1
2353[1,2]	George C. Thorne, MD Austin, TX	2/20/03 – 12/4/03	25	25
3665	Jean H. Tibbetts, MD Bangor, ME	2/25/03 – 11/24/03	26	26
3505	Gail Torkildsen, MD North Andover, MA	4/12/03 – 12/13/03	20	20
1007[1,2]	Thomas Walters, MD Austin, TX	5/9/03 – 12/15/03	29	29
1913[2]	Jeffrey Wasserstrom, MD La Mesa, CA	3/11/03 – 12/2/03	9	9
394	Mark J. Weiss, MD Tulsa, OK	2/7/03 – 11/12/03	16	16
3016[4]	Stephen Whiteside, MD Temple, TX	No patients enrolled		
1909[1,2]	Jess Whitson, MD Dallas, TX	4/10/03 – 12/12/03	6	6
2128	Robert D. Williams, MD Louisville, KY	2/7/03 – 11/21/03	23	21

Inv. No.	Principal Investigator (Name and Address)	Dates of Participation MM/DD/YY	Number of Patients	
			Intent to Treat	Per Protocol
2600[1,2]	David L. Wirta, MD Newport Beach, CA	2/20/03 – 12/16/03	38	36

1. Denotes investigative sites where endothelial cell photography was performed.
2. Denotes investigative sites that were extended to 12 months.
3. Laurie Barber, MD took over as principal investigator from Anthony Realini, MD on June 6, 2003.
4. IRB approval was obtained for these investigators; however, no patients were enrolled.
5. Dates of participation reflect the date of the first patient screened through the last patient to complete the Month 6 Visit.

Reviewer's Comments:
It is preferred that at least ten patients per treatment arm per clinical site be randomized to allow for an investigator interaction analysis.

The principal investigator at one site changed during the trial. Investigator 3362 – Anthony Realini, MD was replaced by Investigator 3858 – Laurie Barber, MD.

Study Design

Inclusion Criteria

Patients had to meet the following criteria to be eligible for enrollment:

1. Patients of any race, two years of age or older and of either sex, diagnosed with open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension.
2. Patients must have satisfied the following IOP entry criteria in at least one eye:
    a. For each qualifying eye, the mean IOP at 8AM at both Eligibility 1 and 2 Visits must have been from 22 to 36 mmHg.
    b. The mean IOP was the average of two IOP measurements in the same eye.
    c. The mean IOP in either eye at any timepoint must not have been greater than 36 mmHg at the Eligibility 1 and 2 Visits.
    d. The same eye had to qualify at both Eligibility Visits.

Exclusion Criteria

Patients were excluded from participation according to the following criteria:

1. Forms of glaucoma other than open-angle glaucoma (with or without a pigment dispersion or pseudoexfoliation component) or ocular hypertension.
2. Therapy with an investigational agent within 30 days of the Eligibility 1 Visit.
3. History of active, severe, unstable or uncontrolled cardiovascular (e.g. coronary insufficiency, hypertension), cerebrovascular (e.g. cerebral insufficiency), hepatic, or renal disease that precluded the safe administration of a topical alpha-agonist.
4. History of chronic or recurrent severe inflammatory eye disease (i.e. scleritis, uveitis) in either eye.
5. History of ocular trauma or intraocular surgery within the past six months in either eye.
6. History of ocular infection, ocular inflammation, or ocular laser surgery within the past three months in either eye.
7. History of clinically significant or progressive retinal disease such as retinal degeneration, diabetic retinopathy, or retinal detachment in either eye.
8. History of any severe ocular pathology (including severe dry eye) that precluded the administration of a topical alpha-agonist.

9. History of severe or serious hypersensitivity to any alpha adrenergic receptor agonist drug, or to any components of either of the study medications. A list of formulation components present in the study medications was included in the Clinical Investigator's Brochure.
10. Any abnormality preventing reliable applanation tonometry of either eye.
11. Best-corrected visual acuity worse than 0.6 logMAR score in either eye.
12. Angle grade less than Grade 2 in either eye.
13. Patients with a cup/disc ratio greater than 0.80 in either eye.
14. Patients with severe central field loss in either eye. Severe central field loss is defined as a sensitivity of $\leq$ 10dB in at least two of the four visual field test points closest to the point of fixation.
15. Contraindications to pupil dilation.
16. Patients who could not safely discontinue use of all IOP-lowering ocular medication(s) for a minimum period of 5 days $\pm$ 1 day to 28 days $\pm$ 1 day. The Investigator assessed the minimum washout period based on the class of the patient's current IOP-lowering medication.
17. Patients who could not safely discontinue all glucocorticoid medications administered by any route are excluded from participation in this study. Patients must have been washed out of chronic glucocorticoid medications for at least four weeks; or intermittent glucocorticoid therapy for at least two weeks prior to the Eligibility 1 Visit, and must have been able to remain off these medications for the duration of the study.
18. Use of any additional topical or systemic ocular hypotensive medication during the study.
19. Current or anticipated treatment with any psychotropic drugs that augment adrenergic response (e.g., desipramine, amitriptyline).
20. Contraindications to brimonidine therapy, such as concurrent use of monoamine oxidase (MAO) inhibitor therapy.
21. Patients with less than 30 days stable dosing regimen before the Screening Visit of any medications or substances that may affect IOP administered by any route and used on a chronic basis. These may include, but were not limited to, the following:
    a. Sympathomimetic agents
    b. Antimuscarinic agents

c. Antihistamines

d. Phenothiazines

e. Beta-adrenergic blocking agents

f. Calcium channel blockers

g. Angiotensin converting enzyme inhibitors

h. Cardiac glycosides

Note: Patients must have been on a stable dosing regimen of these medications for at least 30 days prior to the Screening Visit and must not have changed the dosing regimen during the eligibility period. Any change in dosage or addition of such medication(s) during the study was documented in the patient's chart.

22. History or other evidence of severe illness or any other conditions which would have made the patient, in the opinion of the Investigator, unsuitable for the study.
23. Additionally, the Alcon Medical Monitor may have declared any patient ineligible for a valid medical reason.

Study Plan

Table 6.1.3-2 Study Phases

Treatment Group	Study Phase	
	Phase I	**Phase II**
	(Screening / Eligibility Phase)	(Treatment Phase)
	Screening and Eligibility 1 & 2 Visits	Week 2, Week 6, & Month 3 Visits STUDY EXTENSION (Month 6 Visit) or (Month 6, Month 9 & Month 12 Visits)
Brimonidine Tartrate Ophthalmic Solution, 0.15 %	No Dosing (washout)	Brimonidine Tartrate Ophthalmic solution, 0.15%, TID, 8 AM (± 30 minutes), 3 PM (± 30 minutes) and 10 PM (±30 minutes)
Alphagan P	No Dosing (washout)	Alphagan P TID, 8 AM (± 30 minutes), 3 PM (± 30 minutes) and 10 PM (±30 minutes)

Phase I, the off-therapy phase of the study, consisted of a Screening Visit, drug washout, followed by two Eligibility Visits. Potential subjects went through the informed consent process and a screening examination. Subjects taking ocular hypotensive medications and who qualified for participation in the study at the screening visit were asked to discontinue these medications. The Investigator evaluated the minimum washout period based on the class of the patient's current IOP-lowering medication, Table 6.1.3-3. The Investigator was permitted to extend the washout period. To minimize the potential risk to the patient due to IOP elevation, the Investigator could substitute the patient's current medication with one requiring a shorter washout period.

Patients continued to the treatment phase of the study if they met all inclusion and exclusion criteria, including the following IOP criteria in at least one eye:

- For each qualifying eye, the mean IOP must have been from 22 to 36 mmHg at 8 AM at both Eligibility 1 and 2 Visits.
- The mean IOP was defined as the average of two IOP measurements in the same eye at a given timepoint. If the first two measurements differed by more than 4 mmHg, a third measurement must be performed. Calculate the mean IOP from the two IOP measurements that are closest in number.
- The mean IOP in either eye at any time point during the Eligibility 1 and 2 Visits must not be greater than 36 mmHg.

Table 6.1.3-3 Ocular Hypotensive Medication Washout Schedule

Ocular Hypotensive Medication		**Washout Period *– Screening to Eligibility1 Visit**
Generic Name	**Trade Name**	
No ocular hypotensive medication		3 days ± 1 day
Miotics and carbonic anhydrase inhibitors (CAIs)		5 days ± 1 day
Pilocarpine	PILOPINE HS, ISOPTO CARPINE, PILOCAR	
Carbachol	ISOPTO CARBACHOL	
Acetazolamide	DIAMOX	
Methazolamide	NEPTAZANE	
Dorzolamide HCl	TRUSOPT	
Brinzolamide	AZOPT	
Alpha and alpha/beta agonists		14 days ± 1 day
Epinephrine	EPINAL,EPPY/N, EPIFRIN, GLAUCON	
Dipivefrin	PROPINE	
Apraclonidine	IOPIDINE	
Brimonidine	ALPHAGAN P	
Beta-agonists, prostaglandins, and combination drugs (use longest washout period of individual components)		28 days ± 1 day
Betaxolol	BETOPTIC-S	
Timolol	TIMOPTIC, TIMOPTIC-XE, BETIMOL, TIMOLOL GEL-FORMING SOLUTION	
Carteolol	OCUPRESS	
Metipranolol	OPTIPRANOLOL	
Levobunolol	BETAGAN	
Latanoprost	XALATAN	
Travoprost	TRAVATAN	
Bimatoprost	LUMIGAN	
Unoprostone Isopropyl	RESCULA	
Dorzolamide HCl / Timolol maleate	COSOPT	

- The washout period of longest duration was used when the patient was taking multiple ocular hypotensive medications form more than one class.

The treatment phase, Phase II, was randomized and double-masked. Study visits are at Week 2, Week 6, Month 3 and Month 6. The study included a three month extension to assess safety and a nine month extension to assess endothelial cell count.

After completing Eligibility 2 examination, qualified patients were randomized to Brimonidine Tartrate Ophthalmic Solution, 0.15% or Alphagan P three-times-daily at 8 AM (±30 minutes), 3 PM (±30 minutes), and 10 PM (±30 minutes). At sites performing the endothelial cell assessments the masked medication was dosed for 12 months. Although IOP was measured for 6 months, the primary efficacy conclusions were based on the initial three months. (See Table 6.1.3-5 Study Flow Chart).

Patients were instructed by the investigator/staff to follow all protocol guidelines and the dosing regimen. The time of last drug instillation prior to the 8 AM visit was recorded. To ensure compliance, the 8 AM dosing on study visit days was performed by the study staff. Because the 8 AM IOP measure was a trough IOP, if the patient had not dosed the previous evening or had taken the 8 AM dose, the visit was rescheduled.

Study Medications and Masking
All study medications were supplied in identical opaque 5 ml [redacted] bottles which were labeled with the appropriate patient number.

Table 6.1.3-4 Study Medications

Test Article	Lot Numbers	Formulation Identification Numbers
Brimonidine Tartrate Ophthalmic Solution, 0.15 %	02-50045-1	104110
Alphagan® P	02-500448-1	104368
Alphagan® P	03-500473-1	104368
Alphagan® P	03-500501-1	104368

Efficacy Analysis

The primary efficacy parameter was the mean IOP in the patient's worse eye measured at the 8AM, 10 AM and 5 PM time points. Study visits were scheduled for Week 2, Week 6, and Month 3 for primary efficacy. The patient's worse eye was considered in the analysis. The worse eye was defined as follows:

- The eye with the higher intraocular pressure at 8 AM, averaged across two eligibility visits. If both eyes were equal, then
- The eye with the higher intraocular pressure at 10 AM, averaged across the two eligibility visits. If both eyes were equal, then
- The eye with the higher intraocular pressure at 5 PM, averaged across the two eligibility visits. If both eyes were equal, then the right eye was selected for analysis.

The primary efficacy endpoint was the test of equivalence. A 95% confidence interval for the treatment group difference was constructed based on the analysis of variance at each visit and time point. Primary inference for the test of equivalence was based on the per protocol data set. In order to demonstrate equivalence, all of the confidence limits had to be within ± 1.5 mmHg, the margin of clinical relevance, and the majority had to be within ± 1.0 mm Hg.

Table 6.1.3-5 STUDY FLOW CHART

Activity	Screen	Eligibility 1			Eligibility 2			Week 2 ±1 day			Week 6 ±3 days			Month 3 ±3 days			Month 6 ±3 days			Month 9 ±3 days			Month 12 ±3 days or Early Discontinue		
		8 AM	10 AM	5 PM	8 AM	10 AM	5 PM	8 AM	10 AM	5 PM	8 AM	10 AM	5 PM	8 AM	10 AM	5 PM	8 AM	10 AM	5 PM	8 AM	10 AM	5 PM	8 AM	10 AM	5 PM
Informed consent	X																								
Demographics	X																								
Medical History	X																								
Inclusion/Exclusion	X																								
Change in Health/ Meds		X			X			X			X			X			X			X			X		
Urine Pregnancy Test [1]	X													X			X						X		
Pulse / BP	X	X			X			X			X			X			X			X			X		
Visual Acuity [2]	X	X			X			X			X			X			X			X			X		
Slit lamp [3]	X	X			X			X			X			X			X			X			X		
IOP [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated Fundus [5]	X																		X						X
Gonioscopy	X																								
Automated Perimetry [6]	X																X						X		
Endothelial Cell Density [9]					X												X						X		
Pachymetry [8]					X												X						X		
D/C Current Glaucoma Meds	X																								
Dispense Study Medications [7]							X			X			X			X			X			X			
Adverse Events								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Study Medications																			X[10]						X
Exit Patient																			X[10]						X

[1] Urine pregnancy test kits (redacted) are provided for the study. The Investigator, study staff, and patient should follow the manufacturer's procedure in the package insert for this product; [2] Best Corrected logMAR scale; [3] Ocular Signs will be assessed at each visit by (redacted) according to the grading criteria outlined in the Definition of Terms (redacted)

Subject Disposition and Demographics

Table 6.1.3-6 Subject Disposition

	Number of Subjects		
	Brimonidine 0.15% N (%)	Alphagan P N (%)	Total N (%)
Randomized	417 (49.5)	425 (50.5)	842
Discontinued prematurely	95 (22.8)	92 (21.6)	187 (22.2)
Safety Population received study medication	417 (100.0)	425 (100.0)	842 (100.0)
Intent-to-treat Population ≥ 1 on therapy study visit	408 (97.8)	416 (97.9)	824 (97.9)
Per Protocol Population No on-therapy study visits or protocol violation	387 (92.8)	397 (93.4)	784 (92.8)
Excluded from PP Population	30 (7.2)	28 (6.6)	58 (6.9)

Of the 842 randomized patients, 18 discontinued the study prior to collection of any on-therapy study visit data. Therefore, 824 patients were included in the ITT analysis. Fifty-eight patients were excluded from the per protocol analysis: the 18 patients with no on-therapy study visit data, and 40 patients due to protocol violations. The violations included use of steroids (n=23), non-qualifying IOP (n=9), non-compliance (n=5), use of contraindicated anti-hypertensive medications (n=2), and missing baseline IOP data (n=1).

Table 6.1.3-7 Patients Discontinued from Study

Investigator Number	Patient Number	Treatment	Reason Discontinued
271	1705	Alphagan P	Protocol violation - Did not meet entry criteria
	1709	Alphagan P	AE – Pain; Tearing; Burning; Blurred vision; Foreign body sensation
	1710	Brimonidine 0.15%	AE – Pain; Red eyes
	1714	Brimonidine 0.15%	AE – Tearing
	1716	Brimonidine 0.15%	AE – Red eyes
	1718	Alphagan P	AE – Eye pain
	1719	Alphagan P	AE – Eye soreness
362	201	Brimonidine 0.15%	Patient decision – Change in work schedule
	202	Alphagan P	AE – Drowsiness
	205	Brimonidine 0.15%	AE – Allergic conjunctivitis

Investigator Number	Patient Number	Treatment	Reason Discontinued
394	6704	Brimonidine 0.15%	AE – Allergic conjunctivitis
	6705	Brimonidine 0.15%	AE – Allergic conjunctivitis
	6707	Alphagan P	AE – Allergic conjunctivitis
	6713	Alphagan P	AE – Allergic conjunctivitis
	6714	Brimonidine 0.15%	AE – Allergic conjunctivitis
553	505	Brimonidine 0.15%	AE – Itching; redness; tearing; fatigue; body aches
	518*	Brimonidine 0.15%	Noncompliance
	520	Alphagan P	Inadequate control of IOP
648	5803	Alphagan P	AE – Topical allergy
	5804	Brimonidine 0.15%	AE – Itching, redness
731	6203	Alphagan P	Inadequate control of IOP
	6207	Brimonidine 0.15%	AE – Ocular allergic reaction
	6208	Alphagan P	AE – Ocular allergic reaction
	6211	Alphagan P	AE – Ocular allergic reaction
	6214	Brimonidine 0.15%	Inadequate control of IOP
	6215	Alphagan P	AE – Ocular redness
	6218	Brimonidine 0.15%	AE – Ocular redness; conjunctival follicles; ocular itching
	6219	Alphagan P	Inadequate control of IOP
784	802	Alphagan P	AE – Conjunctival inflammation
	803	Brimonidine 0.15%	AE – Allergic conjunctivitis; drowsiness
	806	Alphagan P	AE – Hyperemia; blepharitis
842	403	Brimonidine 0.15%	AE – Terminal liver cancer
	406	Alphagan P	Patient decision – Family emergency; Had to leave town for extended time.
842	407	Alphagan P	AE – Contact dermatitis; allergic conjunctivitis
1002	1602	Alphagan P	AE – Follicular conjunctivitis
	1605	Alphagan P	AE – Follicular conjunctivitis
	1608	Brimonidine 0.15%	AE – Follicular conjunctivitis
1007	2114	Alphagan P	Inadequate control of IOP
	2122	Alphagan P	AE – Blepharoconjunctivitis
	2126	Alphagan P	AE – Watery eyes; Red eyes
1011	2602	Alphagan P	Inadequate control of IOP
	2608	Brimonidine 0.15%	AE – Allergic conjunctivitis
	2609	Brimonidine 0.15%	AE – Follicular conjunctivitis
	2611	Alphagan P	AE – Allergic conjunctivitis
	2612	Brimonidine 0.15%	AE – Ocular allergic reaction; subepithelial corneal opacities

Investigator Number	Patient Number	Treatment	Reason Discontinued
	2614	Brimonidine 0.15%	AE – Ocular allergic reaction
	2615	Brimonidine 0.15%	AE – Hyperemia; Itching; Conjunctival follicles
	2619	Brimonidine 0.15%	AE – Follicular conjunctivitis
	2621	Brimonidine 0.15%	Inadequate control of IOP
	2623	Alphagan P	AE – Allergic blepharoconjunctivitis
	2624	Alphagan P	Inadequate control of IOP
1236	4105	Brimonidine 0.15%	AE – Ocular allergic reaction
1238	6105	Brimonidine 0.15%	Protocol violation – Did not meet inclusion/exclusion criteria
	6110	Brimonidine 0.15%	Patient decision – No explanation sited.
	6113	Brimonidine 0.15%	AE – Lowering of blood pressure
	6116	Alphagan P	AE – Ocular allergic reaction
	6123	Brimonidine 0.15%	AE – Acute follicular conjunctivitis
1393	1301	Brimonidine 0.15%	AE – Ocular allergic reaction
	1302	Alphagan P	AE – Ocular allergic reaction
	1309	Brimonidine 0.15%	AE – Ocular allergic reaction
	1311	Alphagan P	Protocol violation – Did not meet inclusion/exclusion criteria
	1312	Brimonidine 0.15%	AE – Ocular allergic reaction
	1313	Alphagan P	Protocol violation – Did not meet inclusion/exclusion criteria
	1314	Brimonidine 0.15%	AE – Conjunctivitis
	1315	Brimonidine 0.15%	AE – Allergic conjunctivitis
	1320	Alphagan P	Patient decision – Unable to attend study visits
1455	1901	Alphagan P	AE – Allergic conjunctivitis
1611	2402	Alphagan P	AE – Fatigue; Dry mouth
	2403	Brimonidine 0.15%	AE – Dry mouth; Allergic reaction
	2408	Brimonidine 0.15%	Inadequate control of IOP
	2410	Alphagan P	AE – Allergic conjunctivitis
	2412	Brimonidine 0.15%	AE – Allergic conjunctivitis
1806	1401	Alphagan P	Inadequate control of IOP
	1406	Brimonidine 0.15%	AE – Allergic conjunctivitis
	1407	Alphagan P	AE – Diarrhea; Dizziness
	1408	Brimonidine 0.15%	Patient decision – No explanation sited
	1410	Alphagan P	AE – Allergic conjunctivitis
	1411	Brimonidine 0.15%	Patient decision – No explanation sited
	1415	Alphagan P	AE – Allergic conjunctivitis

Investigator Number	Patient Number	Treatment	Reason Discontinued
	1416	Alphagan P	Inadequate control of IOP
	1418	Brimonidine 0.15%	Inadequate control of IOP
	1420	Alphagan P	Inadequate control of IOP
	1423	Alphagan P	Inadequate control of IOP
	1425	Brimonidine 0.15%	Patient decision – Refused to comply with visit schedule. Withdrew consent.
	1426	Alphagan P	Inadequate control of IOP
	1431	Brimonidine 0.15%	Lost to follow up
	1433	Brimonidine 0.15%	Inadequate control of IOP
1913	2801	Brimonidine 0.15%	AE – Allergic conjunctivitis
	2802	Alphagan P	AE – Allergic conjunctivitis
	2805	Alphagan P	AE – Allergic conjunctivitis
1927	4408	Alphagan P	AE – Hyperemia
	4409	Brimonidine 0.15%	AE – Allergic conjunctivitis; Decrease in visual acuity
1928	4604	Alphagan P	AE – Ocular allergic reaction; Headache
	4605	Brimonidine 0.15%	AE – Follicular conjunctivitis
	4607	Alphagan P	AE – Follicular conjunctivitis
1939	5904	Alphagan P	Inadequate control of IOP
	5910	Brimonidine 0.15%	AE – Allergic conjunctivitis
	5912	Alphagan P	AE – Allergic conjunctivitis
	5921	Alphagan P	AE – Allergic conjunctivitis
2029	903	Brimonidine 0.15%	Non-compliance
2128	6803	Brimonidine 0.15%	Inadequate control of IOP
	6804	Brimonidine 0.15%	Inadequate control of IOP
	6805	Brimonidine 0.15%	AE – Ocular allergic reaction
	6813	Alphagan P	AE – Ocular allergic reaction
2128	6816	Brimonidine 0.15%	Inadequate control of IOP
	6817	Alphagan P	Inadequate control of IOP
2133	1003	Brimonidine 0.15%	AE – Allergic conjunctivitis
	1004	Brimonidine 0.15%	Protocol violation – Did not meet inclusion/exclusion criteria
2247	6504	Brimonidine 0.15%	Inadequate control of IOP
	6508	Brimonidine 0.15%	AE – Allergic conjunctivitis
	6509	Brimonidine 0.15%	Inadequate control of IOP
2302	5005	Brimonidine 0.15%	AE – Allergic conjunctivitis
	5006	Brimonidine 0.15%	AE – Allergic reaction
	5007	Alphagan P	Inadequate control of IOP
	5011	Alphagan P	AE – Eyelids inflamed
2348	4308	Alphagan P	Inadequate control of IOP

Investigator Number	Patient Number	Treatment	Reason Discontinued
2353	2002	Alphagan P	AE – Ocular allergic reaction
	2005	Alphagan P	AE – Ocular allergic reaction
	2008	Brimonidine 0.15%	AE – Ocular allergic reaction; Acute posterior vitreous detachment
	2016	Brimonidine 0.15%	Inadequate control of IOP
	2019	Brimonidine 0.15%	Inadequate control of IOP
	2020	Alphagan P	Inadequate control of IOP
	2022	Alphagan P	Serious AE – Fractured pelvis (hospital would not allow study medication.)
	2025	Brimonidine 0.15%	AE – Ocular allergy
2434	3503	Alphagan P	Protocol violation – Did not meet inclusion/exclusion criteria
	3511	Alphagan P	AE – Allergic blepharoconjunctivitis
	3514	Alphagan P	AE – Allergic follicular conjunctivitis
2436	5701	Brimonidine 0.15%	AE – Itching; Conjunctival injection
	5702	Alphagan P	AE – Conjunctival injection
2448	1203	Alphagan P	AE – Allergic conjunctivitis
	1206	Brimonidine 0.15%	AE – Allergic conjunctivitis
	1211	Alphagan P	AE – Ophthalmic infection; Ophthalmic allergic reaction
	1220	Alphagan P	AE – Allergic conjunctivitis
	1221	Brimonidine 0.15%	AE – Follicular conjunctivitis
2564	601	Alphagan P	Protocol violation – Did not meet inclusion/exclusion criteria
	602	Alphagan P	Protocol violation – Did not meet inclusion/exclusion criteria
	603	Brimonidine 0.15%	Patient decision – Noncompliance
	606	Brimonidine 0.15%	Inadequate control of IOP
	607	Alphagan P	AE – Allergic reaction; follicles
2600	2303	Brimonidine 0.15%	AE – Allergic conjunctivitis; Lower eyelid dermatitis
	2304	Brimonidine 0.15%	Patient decision – No reason sited.
	2306	Brimonidine 0.15%	AE – Allergic conjunctivitis
	2307	Alphagan P	AE – Allergic conjunctivitis
	2311	Alphagan P	AE – Conjunctival hyperemia
	2315	Brimonidine 0.15%	AE – Allergic conjunctivitis
	2321	Brimonidine 0.15%	AE – Allergic conjunctivitis
	2325	Alphagan P	Lost to follow up
	2332	Brimonidine 0.15%	AE – Eye pain
	2336	Alphagan P	AE – Allergic conjunctivitis
	2337	Brimonidine 0.15%	AE – Allergic conjunctivitis

Investigator Number	Patient Number	Treatment	Reason Discontinued
2666	104	Brimonidine 0.15%	Protocol violation – Did not meet inclusion/exclusion criteria
	108	Brimonidine 0.15%	Protocol violation – Did not meet inclusion/exclusion criteria
	118	Alphagan P	Patient decision – Unable to attend study visits
3270	1501	Alphagan P	AE – Allergic conjunctivitis
	1502	Alphagan P	AE – Hyperemia; Periorbital erythema; Itching
3349	4002*	Alphagan P	Noncompliance
	4009	Alphagan P	Protocol violation – Patient taking excluded medication.
	4010	Brimonidine 0.15%	AE – Ocular allergic reaction
3362	1104	Brimonidine 0.15%	AE – Fatigue; Listlessness
3414	3603	Brimonidine 0.15%	Inadequate control of IOP
3420	7103	Brimonidine 0.15%	AE – Allergic conjunctivitis
	7104	Brimonidine 0.15%	AE – Conjunctival follicles; Conjunctival injection
3505	6911	Alphagan P	Lost to follow up
	6917	Brimonidine 0.15%	AE – Ocular allergy
3627	5619	Alphagan P	Non-compliance
3664	4703	Brimonidine 0.15%	AE – Allergic conjunctivitis
	4704	Brimonidine 0.15%	AE – Punctate keratitis
	4711	Alphagan P	AE – Allergic conjunctivitis
	4718	Alphagan P	AE – Allergic conjunctivitis; Red eyes
3665	6608	Brimonidine 0.15%	AE – Ocular allergic response
	6610	Brimonidine 0.15%	Serious AE – Death, unrelated
	6617	Brimonidine 0.15%	AE – Ocular allergic response
	6619	Alphagan P	AE – Allergic conjunctivitis
3668	5203	Brimonidine 0.15%	AE – Blepharoconjunctivitis
3678	5105	Alphagan P	AE – Allergic blepharoconjunctivitis
	5107	Brimonidine 0.15%	AE – Allergic blepharoconjunctivitis
3679	3806	Alphagan P	AE – Contact dermatitis
3715	5401	Brimonidine 0.15%	Inadequate control of IOP
	5404	Alphagan P	Inadequate control of IOP
	5406	Alphagan P	Lost to follow up
3720	7206	Alphagan P	AE – Decrease in visual acuity; Allergic conjunctivitis
3785	7001	Brimonidine 0.15%	AE – Redness; Itching
	7005	Alphagan P	AE – Low blood pressure; Generalized weakness

Investigator Number	Patient Number	Treatment	Reason Discontinued
	7007	Alphagan P	Inadequate control of IOP
	7013	Brimonidine 0.15%	AE – Hyperemia
	7014	Alphagan P	Inadequate control of IOP
	7018	Brimonidine 0.15%	AE – Dry mouth; Chest congestion

One patient (*) was enrolled at two investigational sites (Investigator 553, Patient 518 and Investigator 3349, Patient 4002). The patient was discontinued when this protocol violation was discovered. Both patient records were retained in the intent-to-treat and safety data sets. No adjustment for correlation was attempted since the impact on the ITT analysis of including both patient records is negligible.

Reviewer's Comments:
A total of 187 patients (22% of randomized patients) were discontinued from the study prior to completion largely because of adverse events.

Similar numbers of patients discontinued from both treatment groups - Brimonidine 0.15%, 95; Alphagan P, 92.

Table 6.1.3-8 Demographic Statistics by Treatment Group
Intent-to-Treat Patients

	Brimonidine 0.15%		Alphagan P		
	N	%	N	%	p-value[a]
Total	408	49.5	416	50.5	
Age					
<65 years [b]	214	52.5	214	51.4	0.7720
≥65 years	194	47.5	202	48.6	
Age (≥ 65 years)					
≥65- <75 years	131	67.5	131	64.9	0.5726
≥75- <85 years	58	29.9	62	30.7	
≥85- <95 years	5	2.6	9	4.5	
≥95 years	0	0.0	0	0.0	
Gender					
Male	190	46.6	197	47.4	0.8209
Female	218	53.4	219	52.6	
Race					
Caucasian	289	70.8	292	70.2	0.9231
Black	76	18.6	78	18.8	
Asian	1	0.2	3	0.7	
Hispanic	40	9.8	40	9.6	
Other	2	0.5	3	0.7	
Iris Color					
Brown	216	52.9	227	54.6	0.8771
Hazel	54	13.2	61	14.7	
Green	15	3.7	14	3.4	
Blue	119	29.2	109	26.2	
Grey	4	1.0	5	1.2	
Diagnosis					
Ocular Hypertension	158	38.7	155	37.3	0.4034
Open-Angle Glaucoma	240	58.8	255	61.3	
Pigmentary Glaucoma	5	1.2	5	1.2	
Pseudoexfoliation Glaucoma	5	1.2	1	0.2	

[a] p-value from chi-square or Fisher's exact test.
[b] Although the study protocol allowed patients age 2 years and older, the minimum age for an enrolled patient was 24 years.

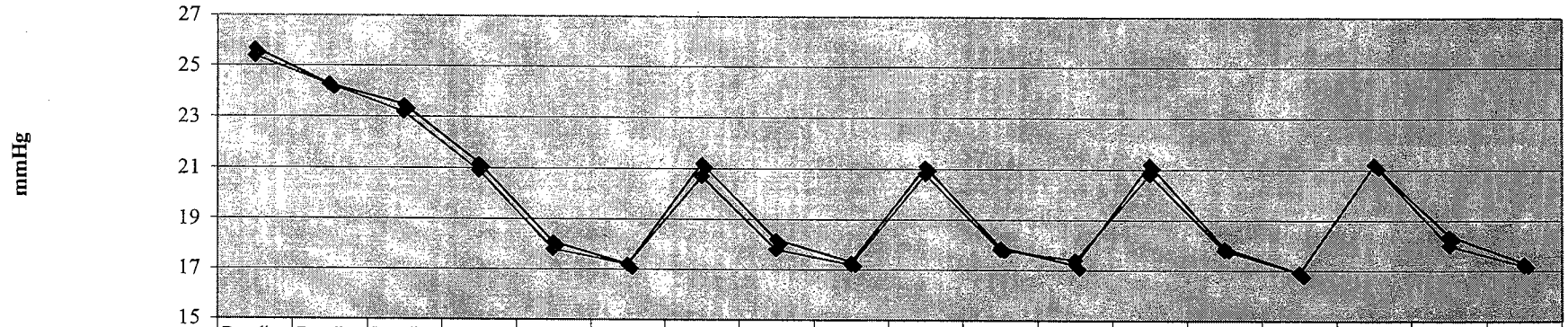
Reviewer's Comments:
There was no significant difference in the baseline demographics between the treatment groups.

6.1.4 Efficacy Findings

This application relies upon safety and efficacy established for NDA 20-613, Alphagan, and NDA 21-262, Alphagan P. This study was to establish bioequivalence of Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P.

Chart 6.1.4-1

Mean IOP Comparison of
Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P - ITT

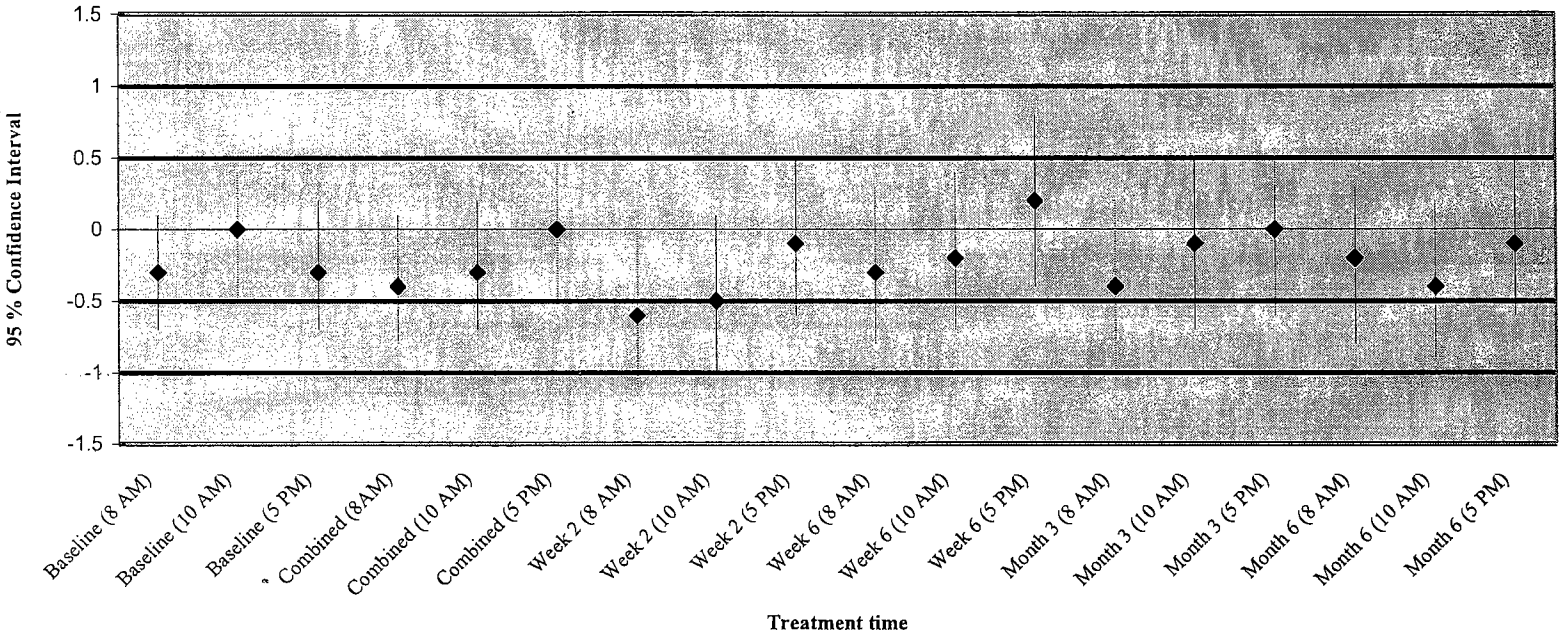


	Baseline (8 AM)	Baseline (10 AM)	Baseline (5 PM)	Comb (8AM)	Comb (10AM)	Comb (5PM)	Week 2 (8 AM)	Week 2 (10 AM)	Week 2 (5 PM)	Week 6 (8 AM)	Week 6 (10 AM)	Week 6 (5 PM)	Month 3 (8 AM)	Month 3 (10 AM)	Month 3 (5 PM)	Month 6 (8 AM)	Month 6 (10 AM)	Month 6 (5 PM)
Brimonidine 0.15%	25.4	24.3	23.2	20.9	17.8	17.2	20.7	17.8	17.2	20.8	17.8	17.4	20.8	17.8	16.9	21.2	18	17.2
Alphagan P	25.7	24.3	23.5	21.2	18.1	17.2	21.2	18.2	17.3	21.1	17.9	17.2	21.2	17.9	16.9	21.2	18.4	17.3

Reviewer's Comments:
The difference between the IOP lowering effect of Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P was not clinically relevant. The difference was not statistically significant at 8 of the 9 time points from baseline through Month 3.

Chart 6.1.4-2

95% Confidence Intervals of the IOP Mean Difference Between
Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P

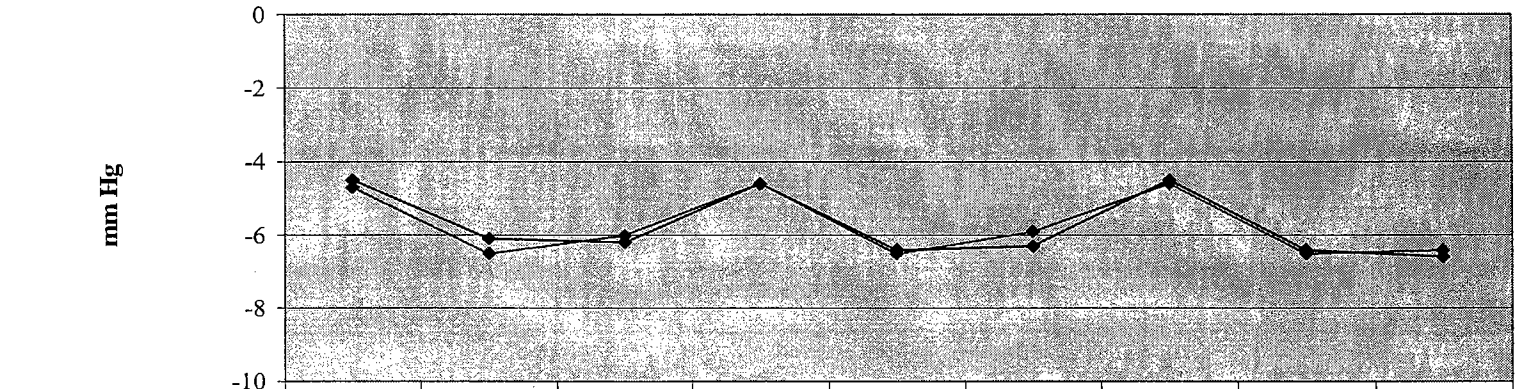


Reviewer's Comments:

The 95% confidence limits on the mean difference in IOP lowering ability between the Brimonidine Tartrate 0.15% group and the Alphagan P group are less than 1.5 mmHg for all time points, and less than 1.0 mmHg for 8 of 9 time points from baseline through Month 3.

Table 6.1.4-3

Mean IOP Change From Baseline
Intent-to-Treat Data



	Week 2, 8 AM	Week 2, 10 AM	Week 2, 5 PM	Week 6, 8 AM	Week 6, 10 AM	Week 6, 5 PM	Month 3, 8 AM	Month 3, 10 AM	Month 3, 5 PM
Brimonidine 0.15%	-4.7	-6.5	-6	-4.6	-6.5	-5.9	-4.6	-6.5	-6.4
Alphagan P	-4.5	-6.1	-6.2	-4.6	-6.4	-6.3	-4.5	-6.4	-6.6

Treatment Time

Reviewer's Comment:

There was no significant difference (p=0.8939) in IOP lowering ability between Brimonidine Tartrate Ophthalmic Solution 0.15% and Alphagan P.

6.1.5 Clinical Microbiology

This is not an antimicrobial. Not applicable.

6.1.6 Efficacy Conclusions

The clinical study, C-02-49, did demonstrate statistical significance for the primary efficacy endpoint, the test of the equivalence of Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P. The mean difference in intraocular pressure of Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P was within 1.5 mmHg of a two-sided 95% confidence interval for all intraocular measurement time points and within 1.0 mmHg for 8 of 9 time points through the Month 3 Visit.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Eight hundred and forty-two subjects, 24 to 91 years of age, were randomized to receive one drop of the assigned test article three-times-daily. All of these subjects were included in the safety data set: 417 with exposure to Brimonidine 0.15%, and 425 with exposure to Alphagan P. All study medication was dosed in both eyes unless a potential safety concern was evident in the opinion of the investigator. No imputation for missing values due to patient discontinuation or missed visits was performed in the safety data set.

Safety data was collected for patients through the Month 6 visit (minimum) or up to the exit visit for patients who discontinued prior to or after Month 6. The patient who was enrolled at two different sites had two different patient numbers and received Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P during the study. This patient is counted twice in the analysis of safety data.

Adverse events in the overall safety population were mild to moderate, often resolved without treatment, were not age dependent, and were similar between treatment groups. The most frequently reported adverse event in either group was ocular hyperemia. One hundred and twenty two patients discontinued study participation due to adverse events. The most frequent events resulting in discontinuations included signs and/or symptoms of an ocular allergic reaction (i.e., conjunctivitis, ocular hyperemia, conjunctival follicles, pruritus, etc.), per Alcon, no treatment-related serious adverse events were identified during the study in either treatment group. Twenty patients had serious, non-fatal adverse events reported during this study.

7.1.1 Deaths

One death was reported during the study. A 72 year old patient in the Brimonidine 0.15% treatment group died following a hospital admission for pneumonia (Pt. 6610, Investigator 3665).

Reviewer's Comments:
This death appears to be unrelated to therapy.

7.1.2 Other Serious Adverse Events

Table 7.1.2-1 Other Serious Adverse Events

Investigator / Patient	Age	Treatment	Adverse Event	Outcome
2434 / 3521	82	Brimonidine 0.15%	Infection	Resolved w/ Tx
3664 / 4706	79	Brimonidine 0.15%	Chest Pain	Resolved w/ Tx
2434 / 3521	82	Brimonidine 0.15%	Colostomy transfer/ Hernia repair	Resolved w/ Tx
3346 / 6305	71	Brimonidine 0.15%	L. knee replacement	Resolved w/ Tx
3665 / 6606	82	Brimonidine 0.15%	Total knee replacement	Resolved w/ Tx
2564 / 604	66	Brimonidine 0.15%	Cardiovascular Disease	Resolved w/ Tx
2128 / 6808	65	Brimonidine 0.15%	Heart Failure	Resolved w/ Tx
2600 / 2304	85	Brimonidine 0.15%	Cholangitis	Resolved w/ Tx
2448 / 1215	68	Brimonidine 0.15%	Joint Disease	Resolved w/ Tx
2434 / 3519	80	Brimonidine 0.15%	Neuralgia	Continued Tx
3665 / 6610	72	Brimonidine 0.15%	Pneumonia	Patient died
3346 / 6304	62	Alphagan P	Allergic reaction to non-study drug	Resolved w/ Tx
1927 / 4415	55	Alphagan P	Chest Pain	Resolved w/ Tx
1011 / 2602	81	Alphagan P	Abdominal Aortic Aneurysm Repair	Resolved w/ Tx
1611 / 2414	73	Alphagan P	Angina Pectoris	Resolved w/ Tx
2353 / 2015	73	Alphagan P	Anomaly Vascular	Resolved w/ Tx
1393 / 1320	71	Alphagan P	Cerebrovascular Accident	Continued Tx
2600 / 2316	69	Alphagan P	Coronary Artery Disease	Continued Tx
3270 /1502	76	Alphagan P	Myocardial Infarct	Resolved w/ Tx
3362 / 1102	65	Alphagan P	Cholecystectomy	Resolved w/ Tx
3270 / 1502	76	Alphagan P	Stomach ulcer hemorrhage	Resolved w/ Tx
2353 / 2022	87	Alphagan P	Spontaneous Bone Fracture	Continued Tx
3678 / 5117	67	Alphagan P	Neuralgia	Continued Tx

Reviewer's Comments:
Serious adverse events were reported for 2.4% (20/842) of patients – 2.2% in the Brimonidine 0.15% group and 2.6% in the Alphagan P group.

7.1.3 Dropouts and Other Significant Adverse Events

The case report forms of all subjects who discontinued study participation were evaluated.

7.1.3.1 Overall profile of dropouts.

Table 7.1.3.1-1 Overall Reasons for Discontinuation

Reason for discontinuation	Brimonidine 0.15% N=417		Alphagan P N=425	
	N	%	N	%
Total	95	22.8	92	21.6
Inadequate Control of IOP	15	3.6	19	4.4
Adverse Event	65	15.6	57	13.4
Patient Decision	7	1.7	3	0.7
Lost to Follow-Up	1	0.2	3	0.7
Noncompliance	2	0.5	2	0.5
Other	5	1.2	8	1.9

Reviewer's Comments:
The case report forms for patients discontinued due to patient decision, loss to follow-up, and noncompliance were reviewed to identify any additional, unreported adverse events. No other adverse events were noted.

The reasons for discontinuation were similar between treatment groups, p=0.8022.

7.1.3.2 Adverse events associated with dropouts

The adverse event that caused the largest number of discontinuations was conjunctivitis, Brimonidine 0.15%, 24 (5.8%) and Alphagan P, 22(5.2%). Allergic conjunctivitis resulted in the second largest number of patient discontinuations - 16 (3.8%) in the Brimonidine 0.15% group and 11 (2.6%) in the Alphagan P group.

7.1.3.3 Other significant adverse events

There were no other significant adverse events observed in this study.

7.1.4 Other Search Strategies

No other search strategies were used to analyze adverse events.

7.1.5 Common Adverse Events

In the overall safety population, adverse events were experienced by four hundred ninety-eight (59.1%) of the patients participating in the study. Similar numbers of patients belonged to each

treatment group, Brimonidine 0.15%, 58.5%, and Alphagan P, 59.8%. There were no clinically relevant or statistically significant differences in the incidence of adverse events based on treatment group, age or any other patient demographic.

7.1.5.1 Eliciting adverse events data in the development program

The protocol adequately defined an adverse event. Each investigator evaluated study participants for adverse events, volunteered and elicited, at each intraocular pressure check on each study visit. An Adverse Event Form was completed to document a description of the event, onset, severity, treatment required, outcome, and relatedness to the use of the study medication. Checklists were not used.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The study utilized the MedDRA preferred terms for adverse event recording. The terms were sufficiently descriptive to assess adverse events expected to be experienced by the study population.

7.1.5.3 Incidence of common adverse events

Table 7.1.5.3-1 Frequency and Incidence of Adverse Events for ≥ 1% of Patients - Overall Safety Population

Coded Adverse Event	Brimonidine, 0.15% N=417		Alphagan P N=425	
OCULAR	**N**	**%**	**N**	**%**
Hyperemia Eye	51	12.2	36	8.5
Conjunctivitis	32	7.7	34	8.0
Allergic Reaction	22	5.3	16	3.8
Follicles Conjunctival	19	4.6	14	3.3
Visual Acuity Decrease	15	3.6	14	3.3
Pruritus Eye	18	4.3	13	3.1
Vision Blurred	9	2.2	10	2.4
Foreign Body Sensation	8	1.9	11	2.6
Discomfort Eye	9	2.2	9	2.1
Dry Eye	4	1.0	12	2.8
Pain Eye	7	1.7	4	0.9
Tearing	6	1.4	5	1.2
Blepharoconjunctivitis	4	1.0	6	1.4
Cataract	5	1.2	5	1.2
Vitreous Disease	3	0.7	6	1.4
Lid Disease	6	1.4	3	0.7
Staining Corneal	4	1.0	2	0.5
Keratitis	4	1.0	2	0.5
Vitreous Detachment	4	1.0	1	0.2
NON-OCULAR	**N**	**%**	**N**	**%**
Hypertension	22	5.3	25	5.9
Dry Mouth	13	3.1	10	2.4
Hypercholesterolemia	12	2.9	5	1.2
Arthritis	6	1.4	10	2.4
Infection	8	1.9	6	1.4
Headache	6	1.4	8	1.9
Allergy	6	1.4	8	1.9
Hypotension	7	1.7	6	1.4
Arthralgia	7	1.7	4	0.9
Sinusitis	5	1.2	7	1.6
Fatigue	5	1.2	6	1.4
Anxiety	3	0.7	6	1.4
Cold Syndrome	5	1.2	5	1.2
Diabetes Mellitus	5	1.2	4	0.9
Bone Fracture Spontaneous	2	0.5	5	1.2
Insomnia	2	0.5	5	1.2
Bronchitis	1	0.2	5	1.2
Urinary Tract Infection	1	0.2	5	1.2
GI Disturbance	4	1.0	4	0.9
Joint Disease	4	1.0	2	0.5
Osteoporosis	4	1.0	2	0.5
Somnolence	4	1.0	1	0.2
Chest Pain	4	1.0	1	0.2

Reviewer's Comments:
The most frequent ocular adverse events resulted in the most patient discontinuations.

7.1.5.4 Common adverse event tables

Refer to Section 7.1.5.3 Incidence of Common Adverse Events.

7.1.5.5 Identifying common and drug-related adverse events

The most common adverse events are those associated with allergic conjunctivitis. These signs include ocular hyperemia, conjunctivitis, allergic reaction and conjunctival follicles. The allergic response was related to exposure. These findings are consistent with the published literature and clinical practice.

7.1.5.6 Additional analyses and explorations

Adverse events associated with allergic conjunctivitis were most frequently seen and most frequently resulted in discontinuation. No relationship to dose or demographic characteristics influenced adverse event occurrence. Additional analyses were performed on these adverse events for both treatment groups.

Table 7.1.5.6-1 Characteristics of Adverse Events Resulting in Patient Discontinuation

	Brimonidine 0.15%	**Alphagan P**
	N = 65[d]	**N = 57[e]**
Onset Day of Adverse Event[b]	85.0	64.9
Day of Discontinuation	106.6	84.1
Duration of Adverse Event[c]	35.3	24.1

All values are in days (mean) following randomization.
[a]A patient could have more than one adverse event that resulted in patient discontinuation.
[b]For each patient, the earliest onset day for any adverse event resulting in discontinuation was used in the calculation.
[c]For each patient, the longest duration for any adverse event resulting in discontinuation was used in the calculation.
[d]Adverse event duration not available for Patients 403, 1206 and 7104.
[e]Adverse event duration not available for Patients 806, 1302, and 2802.

Reviewer's Comments:
Patients in the Brimonidine 0.15% group had a later onset day of adverse event and later day of discontinuation due to an adverse event although there were more events in the Brimonidine 0.15% group.

Several investigators performed rechallenge tests to confirm a relationship between an adverse event and the study drug. In all cases presented in the application, the rechallenge was done using the same dose of study drug, not a reduced dose.

Of the twenty-eight patients rechallenged with Brimonidine 0.15% (N=16) and Alphagan P (N=12), all had positive recurrences. The results were similar between both treatment groups. Thus, although patient discontinuations due to adverse events were high, the incidence of patients discontinuing study participation was similar in both treatment groups, and most of the discontinuations were due to signs and/or symptoms of an ocular allergic reaction.

7.1.6 Less Common Adverse Events

The overall safety population was not sufficiently large to identify rare events of significant concern.

7.1.7 Laboratory Findings

No clinical laboratory evaluations were performed in this study.

7.1.8 Vital Signs

Cardiovascular parameters (resting pulse and blood pressure) were measured at the Eligibility 2 Visit at 8 AM and at each subsequent visit at 8 AM. Measurements were taken after the patient had been seated quietly for at least five minutes. Clinically relevant changes from baseline were to be identified and reported as an adverse event. All cardiovascular measurements which met the following criteria were queried:

- Pulse: ± 20 beat per minute (BPM) change from baseline
- Systolic blood pressure: ± 30 mmHg change from baseline
- Diastolic blood pressure: ± 20 mmHg change from baseline

7.1.8.1 Overview of vital signs testing in the development program

Refer to Section 7.1.8

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable to this study.

7.1.8.3 Standard analyses and explorations of vital signs data

Sixty five adverse events were reported for the cardiovascular parameters of pulse and blood pressure. These adverse events were coded bradycardia (3), tachycardia (2), hypotension (13) and hypertension (47).

Table 7.1.8.3-3 Pulse Rate (BPM) by Visit Day Overall Safety Population Baseline through Month 6 Data

Treatment		Baseline	Week 2	Week 6	Month 3	Month 6
Brimonidine 0.15%	Mean	71.8	70.3	70.9	70.6	70.5
	Std	10.5	10.4	10.7	10.1	9.5
	N	417	404	397	372	338
	Min	38.0	42.0	33.0	35.0	35.0
	Max	112.0	107.0	118.0	99.0	98.0
Alphagan P	Mean	71.5	71.6	71.7	70.8	71.5
	Std	9.8	10.5	11.0	10.3	10.6
	N	424	416	397	374	339
	Min	48.0	46.0	43.0	47.0	48.0
	Max	102.0	115.0	110.0	106.0	114.0

Reviewer's Comment:
There was no clinically relevant difference between the mean pulse rate for the Brimonidine, 0.15% group and the Alphagan P group.

Table 7.1.8.3-5 Systolic Blood Pressure (mmHg) by Visit Day - Overall Safety Population Baseline through Month 6 Data

Treatment		Baseline	Week 2	Week 6	Month 3	Month 6
Brimonidine 0.15%	Mean	132.6	133.2	132.7	132.0	133.3
	Std	14.8	15.2	15.0	14.7	14.6
	N	417	405	398	371	338
	Min	90.0	89.0	100.0	100.0	77.0
	Max	180.0	198.0	182.0	180.0	188.0
Alphagan P	Mean	132.0	133.0	133.2	133.0	133.5
	Std	15.7	15.8	16.1	16.3	16.0
	N	425	417	398	377	339
	Min	80.0	96.0	94.0	97.0	90.0
	Max	197.0	217.0	197.0	200.0	213.0

mmHg=millimeters of mercury

Reviewer's Comment:
There was no clinically relevant difference between the mean systolic blood pressure for the Brimonidine, 0.15% group and the Alphagan P group.

Table 7.1.8.3-4 Systolic Blood Pressure (mmHg) Change from Baseline to Any Visit – Overall Safety Population

Baseline through Month 6 Data

		Increase										Decrease							
	Total	>30 mmHg		21 to 30 mmHg		11 to 20 mmHg		1 to 10 mmHg		No Change		1 to 10 mmHg		11 to 20 mmHg		21 to 30 mmHg		>30 mmHg	
Treatment	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	**839**	**41**	**4.9**	**89**	**10.6**	**189**	**22.5**	**162**	**19.3**	**1**	**0.1**	**102**	**12.2**	**149**	**17.8**	**69**	**8.2**	**37**	**4.4**
Brimonidine 0.15%	**415[a]**	**21**	**5.1**	**46**	**11.1**	**87**	**21.0**	**72**	**17.3**	**0**	**0**	**52**	**12.5**	**83**	**20.0**	**37**	**8.9**	**17**	**4.1**
18 to 64 years	216	5	2.3	21	9.7	45	20.8	41	19.0	0	0	34	15.7	45	20.8	17	7.9	8	3.7
65 years	199	16	8.0	25	12.6	42	21.1	31	15.6	0	0	18	9.0	38	19.1	20	10.1	9	4.5
Alphagan P	**424[b]**	**20**	**4.7**	**43**	**10.1**	**102**	**24.1**	**90**	**21.2**	**1**	**0.2**	**50**	**11.8**	**66**	**15.6**	**32**	**7.5**	**20**	**4.7**
18 to 64 years	218	5	2.3	17	7.8	57	26.1	56	25.7	0	0	30	13.8	37	17.0	10	4.6	6	2.8
65 years	206	15	7.3	26	12.6	45	21.8	34	16.5	1	0.5	20	9.7	29	14.1	22	10.7	14	6.8

[a] 2 patients had missing baseline or follow-up systolic blood pressure data.
[b] 1 patient had missing baseline or follow-up systolic blood pressure data.
"To any visit" is representative of the worst case scenario and is defined as the visit with the maximum change (increase or decrease) in systolic blood pressure from baseline to any scheduled or unscheduled visit. If the patient experiences both an increase and a decrease of the same magnitude, the magnitude of the increase is used in this table

Reviewer's Comment:
Although the analysis of systolic blood pressure showed a statistically significant increase ($p<0.05$) for the Alphagan P group, the magnitude of the change was small (+1.8 mmHg) and not clinically relevant.

No safety concerns were found regarding systolic blood pressure for the overall safety population or any subpopulation.

Table 7.1.8.3-5 Diastolic Blood Pressure (mmHg) by Visit Day – Overall Safety Population Baseline through Month 6 Data

Treatment		Baseline	Week 2	Week 6	Month 3	Month 6
Brimonidine 0.15%	Mean	76.9	76.9	76.9	76.5	77.2
	Std	9.3	9.7	9.6	9.6	8.7
	N	417	404	398	371	338
	Min	50.0	48.0	46.0	38.0	51.0
	Max	101.0	109.0	109.0	99.0	97.0
Alphagan P	Mean	77.4	77.9	77.7	78.0	78.6
	Std	8.8	9.2	9.5	9.1	9.4
	N	425	417	398	377	339
	Min	51.0	49.0	51.0	50.0	51.0
	Max	105.0	108.0	112.0	107.0	114.0

Reviewer's Comment:
No clinically relevant mean changes in diastolic blood pressure were noted at any time point for the overall safety population.

Table 7.1.8.3-6 Diastolic Blood Pressure (mmHg) Change From Baseline to Any Visit – Overall Safety Population Baseline through Month 6 Data

		Increase										Decrease							
	Total	>30 mmHg		21 to 30 mmHg		11 to 20 mmHg		1 to 10 mmHg		No Change		1 to 10 mmHg		11 to 20 mmHg		21 to 30 mmHg		>30 mmHg	
Treatment	**N**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total	**839**	**2**	**0.2**	**28**	**3.3**	**159**	**19.0**	**243**	**29.0**	**5**	**0.6**	**226**	**26.9**	**152**	**18.1**	**23**	**2.7**	**1**	**0.1**
Brimonidine 0.15%	**415**[a]	**0**	**0**	**15**	**3.6**	**69**	**16.6**	**120**	**28.9**	**3**	**0.7**	**116**	**28.0**	**80**	**19.3**	**11**	**2.7**	**1**	**0.2**
18 to 64 years	216	0	0	4	1.9	31	14.4	68	31.5	3	1.4	66	30.6	41	19.0	3	1.4	0	0
65 years	199	0	0	11	5.5	38	19.1	52	26.1	0	0	50	25.1	39	19.6	8	4.0	1	0.5
Alphagan P	**424**[b]	**2**	**0.5**	**13**	**3.1**	**90**	**21.2**	**123**	**29.0**	**2**	**0.5**	**110**	**25.9**	**72**	**17.0**	**12**	**2.8**	**0**	**0**
18 to 64 years	218	1	0.5	7	3.2	40	18.3	71	32.6	0	0	58	26.6	37	17.0	4	1.8	0	0
65 years	206	1	0.5	6	2.9	50	24.3	52	25.2	2	1.0	52	25.2	35	17.0	8	3.9	0	0

2 patients had missing baseline or follow-up diastolic blood pressure data.
1 patient had missing baseline or follow-up diastolic blood pressure data.
"To any visit" is representative of the worst case scenario and is defined as the visit with the maximum change (increase or decrease) in diastolic blood pressure from baseline to any scheduled or unscheduled visit. If the patient experiences both an increase and a decrease of the same magnitude, the magnitude of the increase is used in this table

Reviewer's Comment:

Although a statistically significant change in diastolic blood pressure was noted in the Alphagan P group, the magnitude of this change was small (+1.0 mmHg) and not clinically relevant.

No statistically significant treatment group differences were noted when comparing the treatment groups.

No safety concerns were identified based on changes in diastolic blood pressure for the overall safety population or any subpopulation.

7.1.8.4 Additional analyses and explorations

No additional analyses and explorations were performed.

7.1.8.5 Electrocardiograms (ECGs)

Brimonidine tartrate has had no electrocardiographic effects noted in previous studies or current use. Electrocardiograms were not obtained during the development plan for this product.

7.1.9 Immunogenicity

Not applicable. Drug product is not likely to induce immunogenic changes.

7.1.10 Human Carcinogenicity

Not applicable. Brimonidine tartrate did not have positive genotoxicity or animal carcinogenicity findings to warrant a systematic assessment of all human tumors reported during drug development.

7.1.11 Special Safety Studies

Safety analysis was based on an evaluation of other safety parameters, as well, which included visual acuity (best corrected logMAR), ocular signs (cornea, iris/anterior chamber, lens, eyelids/conjunctiva), dilated fundus parameters (vitreous, retina/macula/choroid, optic nerve, cup/disc ration), automated perimetry, pachymetry, endothelial cell density, and cardiovascular parameters (pulse rate, systolic blood pressure, and diastolic blood pressure).

7.1.11.1 Visual Acuity

Best corrected visual acuity was measured in logMAR values at Baseline (Eligibility Visit 2) and at each subsequent visit. The maximum change in visual acuity for the worst eye in each patient (either the right or left eye which had the greatest decrease in visual acuity) was calculated as the change in logMAR lines (0.1 unit = 1 logMAR line) from baseline. Clinically relevant changes in visual acuity were defined as a decrease of three or more logMAR lines from baseline and are presented in the table below.

Table 7.1.11.1-1 Clinically Relevant logMAR Visual Acuity Decrease from Baseline Baseline through Month 6 Data

		Exit Visit		Any Visit	
	Total	3 Line Decrease		3 Line Decrease	
Treatment	**N**	**N**	**%**	**N**	**%**
Total	**834**	**16**	**1.9**	**28**	**3.4**
Brimonidine 0.15%	**414[a]**	**9**	**2.2**	**15**	**3.6**
Adults (18 to 64 years)	215	4	1.9	7	3.3
Elderly (65 years or older)	199	5	2.5	8	4.0
Alphagan P	**420[b]**	**7**	**1.7**	**13**	**3.1**
Adults (18 to 64 years)	217	4	1.8	7	3.2
Elderly (65 years or older)	203	3	1.5	6	3.0

p=0.5934 (Exit visit) from Chi-Square test.
p=0.6721 (Any visit) from Chi-Square test.
[a] 3 patients had missing baseline or follow-up visual acuity data.
[b] 5 patients had missing baseline or follow-up visual acuity data.
Clinically relevant decrease in visual acuity is defined as 0.3 logMAR line decrease from baseline to exit visit or to any visit for either eye compared to the same eye at baseline.
To "any visit" is representative of the worst case scenario and is defined as the visit with the maximum change in visual acuity for either eye from baseline to any scheduled or unscheduled visit.

Reviewer's Comment:
No clinically or statistically significant differences were found between treatment groups when change in visual acuity was measured to the Exit Visit, p=0.5934, or to Any Visit, p=0.6721.

Table 7.1.12.1-2 logMAR Visual Acuity Change from Baseline to Any Visit
Baseline through Month 6 Data

		Increase						No		Decrease					
	Total	3 Line		2 Line		1 Line		Change		1 Line		2 Line		3 Line	
Treatment	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	**834**	**0**	**0.0**	**1**	**0.1**	**12**	**1.4**	**384**	**46.0**	**307**	**36.8**	**102**	**12.2**	**28**	**3.4**
Brimonidine 0.15%	**414[a]**	**0**	**0.0**	**1**	**0.2**	**7**	**1.7**	**196**	**47.3**	**143**	**34.5**	**52**	**12.6**	**15**	**3.6**
Adults (18 to 64 years)	215	0	0.0	1	0.5	3	1.4	103	47.9	75	34.9	26	12.1	7	3.3
Elderly (65 years or older)	199	0	0.0	0	0.0	4	2.0	93	46.7	68	34.2	26	13.1	8	4.0
Alphagan P	**420[b]**	**0**	**0.0**	**0**	**0.0**	**5**	**1.2**	**188**	**44.8**	**164**	**39.0**	**50**	**11.9**	**13**	**3.1**
Adults (18 to 64 years)	217	0	0.0	0	0.0	2	0.9	105	48.4	75	34.6	28	12.9	7	3.2
Elderly (65 years or older)	203	0	0.0	0	0.0	3	1.5	83	40.9	89	43.8	22	10.8	6	3.0

p=0.5073 from Cochran-Mantel-Haenszel test.
[a] 3 patients had missing baseline or follow-up visual acuity data.
[b] 5 patients had missing baseline or follow-up visual acuity data.
To "any visit" is representative of the worst case scenario and is defined as the visit with the maximum change in visual acuity for either eye from baseline to any scheduled or unscheduled visit.

Reviewer's Comment:
No clinically or statistically significant differences were observed when comparing the range of visual acuity changes measured to the Exit Visit, p=0.1714, or to Any Visit, p=0.5073.

7.1.11.2 Ocular Signs

An assessment of ocular signs was made at the Eligibility Visit 2 and each subsequent visit. Clinically relevant changes in ocular signs were defined as an increase of one or more units from baseline.

Table 7.1.11.2-1 Clinically Relevant Increase in Ocular Signs from Baseline to Any Visit Baseline through Month 6 Data

				Iris/Anterior Chamber				Eyelids/ Conjunctiva	
	Total	Cornea				Lens			
Treatment	**N**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total	**840**	**25**	**3.0**	**1**	**0.1**	**10**	**1.2**	**187**	**22.3**
Brimonidine 0.15%	**416[a]**	**15**	**3.6**	**0**	**0.0**	**3**	**0.7**	**103**	**24.8**
Adults (18 to 64 years)	216	8	3.7	0	0.0	0	0.0	55	25.5
Elderly (65 years or older)	200	7	3.5	0	0.0	3	1.5	48	24.0
Alphagan P	**424[b]**	**10**	**2.4**	**1**	**0.2**	**7**	**1.7**	**84**	**19.8**
Adults (18 to 64 years)	218	3	1.4	1	0.5	2	0.9	47	21.6
Elderly (65 years or older)	206	7	3.4	0	0.0	5	2.4	37	18.0

p=0.2875 (cornea) from Chi-Square test.
p=1.0 (iris/anterior chamber) from Fisher's Exact test.
p=0.3410 (lens) from Fisher's Exact test.
p=0.0848 (eyelids/conjunctiva) from Chi-Square test.
[a] 1 patient had missing baseline or follow-up ocular signs data.
[b] 1 patient had missing baseline or follow-up ocular signs data.
To any visit is representative of the worst case scenario and is defined as the visit with the maximum change in ocular signs for either eye from baseline to any scheduled or unscheduled visit.

Each clinically relevant change in ocular signs from baseline in the overall safety population was mild to moderate in intensity and resolved with or without treatment. Most of the occurrences that resulted in study discontinuation were due to eyelid/conjunctiva signs and/or symptoms related to an ocular allergic reaction. The number of discontinuations was similar between treatment groups.

Reviewer's Comments:
No statistically significant differences between treatment groups were noted for any ocular signs parameter.

7.1.11.3 Dilated Fundus Examination

An assessment of dilated fundus parameters (vitreous, retina/macula/choroid, optic nerve) was made at Screening Visit and at Exit Visit. Clinically relevant changes in dilated fundus parameters were defined as an increase of one or more units from baseline.

Table 7.1.11.3-1
Clinically Relevant Increase in Fundus Parameters from Baseline to Any Visit
Baseline through Month 6 Data

		Retina/Macula/ Choroid		Optic Nerve		Vitreous	
Treatment	**Total N**	**N**	**%**	**N**	**%**	**N**	**%**
Total	**817**	**4**	**0.5**	**2**	**0.2**	**2**	**0.2**
Brimonidine 0.15%	**402[a]**	**3**	**0.7**	**1**	**0.2**	**0**	**0.0**
Adults (18 to 64 years)	209	3	1.4	1	0.5	0	0.0
Elderly (65 years or older)	193	0	0.0	0	0.0	0	0.0
Alphagan P	**415[b]**	**1**	**0.2**	**1**	**0.2**	**2**	**0.5**
Adults (18 to 64 years)	214	0	0.0	0	0.0	2	0.9
Elderly (65 years or older)	201	1	0.5	1	0.5	0	0.0

p=0.3663 (retina/macula/choroid) from Fisher's Exact test.
p=1.0 (optic nerve) from Fisher's Exact test.
p=0.4995 (vitreous) from Fisher's Exact test.
[a] 15 patients had missing baseline or follow-up fundus data.
[b] 10 patients had missing baseline or follow-up fundus data.
To any visit is representative of the worst case scenario and is defined as the visit with the maximum change in fundus parameter for either eye from baseline to any scheduled or unscheduled visit.

Reviewer's Comments:
No statistically significant differences between treatment groups were noted for any dilated fundus parameter.

7.1.11.4 Cup/Disc Ratio

An assessment of cup/disc ratio was made at the Screening Visit and at Exit Visit. Clinically relevant changes in cup/disc ratio, in the Investigator's opinion, were reported as adverse events.

In the overall safety population, one subject, in the Brimonidine 0.15% treatment group experienced a clinically relevant change in the cup/disc ratio. No subject in the Alphagan P treatment group experienced a similar change.

No safety concerns were noted based on a review of the cup/disc data.

7.1.11.5 Visual Fields

An assessment of visual field examinations was performed at Screening Visit and at the Exit Visit. Clinically relevant changes in the visual field, in the opinion of the study investigator, were reported as adverse events.

One subject in the Brimonidine 0.15% group and two subjects in the Alphagan P group were assessed to have worsening of their visual field examinations. These events were reported as mild, continuing without treatment and did not require the subjects to discontinue study participation.

No safety concerns were raised by the review of the visual field examinations in the overall safety population.

7.1.11.6 Corneal Thickness

An assessment of corneal thickness was performed at Eligibility Visit 2 (8 AM) and Exit Visit at selected sites following the IOP measurements. Analyses for the overall safety population, the adult (18-64y) and elderly (≥ 65y) were performed.

Table 7.1.11.6-1 Corneal Thickness Change from Baseline

Treatment		CORNEAL THICKNESS CHANGE (mm)					
		Overall Safety		Age 18-64 years		Age ≥ 65 years	
		Baseline	Change at Month 6	Baseline	Change at Month 6	Baseline	Change at Month 6
Brimonidine 0.15%	Mean	0.5652	0.0027	0.5675	0.0025	0.5625	0.0029
	Std	0.0374	0.0145	0.0381	0.0144	0.0367	0.0147
	N	317	296	167	159	150	137
	Min	0.4615	-0.0540	0.4615	-0.0540	0.4900	-0.0525
	Max	0.6830	0.0700	0.6600	0.0700	0.6830	0.0635
Alphagan P	Mean	0.5670	0.0017	0.5701	0.0019	0.5635	0.0015
	Std	0.0407	0.0157	0.0406	0.0164	0.0406	0.0151
	N	321	301	169	159	152	142
	Min	0.4080	-0.0940	0.4680	-0.0940	0.4080	-0.0590
	Max	0.6965	0.0715	0.6830	0.0575	0.6965	0.0715
		P=0.4334*		P=0.7367*		P=0.4276*	

* One way analysis of variance, change from baseline.

Reviewer's Comment:
No statistically significant treatment group differences were noted for any of these populations.

No safety concerns were identified with regard to change in corneal thickness.

7.1.11.7 Endothelial Cell Density

An assessment of endothelial cell density was performed at selected sites at Eligibility Visit 2, (8AM), and at Exit Visit. The change in endothelial cell density from baseline to Month 6 was statistically insignificant, p=0.2119.

Table 7.1.11.7-1 Endothelial Cell Density Change from Baseline

Treatment		ENDOTHELIAL CELL DENSITY CHANGE (cells/mm^2)					
		Overall Safety		Age 18-64 years		Age ≥ 65 years	
		Baseline	Change at Month 6	Baseline	Change at Month 6	Baseline	Change at Month 6
Brimonidine 0.15%	Mean	2413	54.7	2483	70.4	2333	35.9
	Std	394.3	192.8	343.8	225.7	433.6	143.5
	N	180	173	96	94	84	79
	Min	575.5	-598	1253	-312	575.5	-598
	Max	3446	1663	3446	1663	3072	732.5
Alphagan P	Mean	2395	24.0	2497	34.9	2279	11.3
	Std	463.9	256.6	402.9	326.5	503.2	135.1
	N	181	170	97	92	84	78
	Min	767.5	-1663	1075	-1663	767.5	-409
	Max	3738	1501	3738	1501	3431	556.0
		P=0.2119*		P=0.3885*		P=0.2689*	

Reviewer's Comment:
No statistically significant or clinically relevant treatment group differences were found in any of the above populations.

No safety concerns were identified regarding endothelial cell density for either treatment group.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

7.1.13 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. There was no inadvertent exposure to the drug product in pregnant women during drug development.

7.1.14 Assessment of Effect on Growth

The intended population of study C-02-49 included enrollment of individuals age 2 and older. Study participants were aged 24 - 91. This application contains no pediatric data.

7.1.15 Overdose Experience

This drug has no overdose potential and no studies were performed.

7.1.16 Postmarketing Experience

Spontaneous adverse event reports for brimonidine tartrate, have produced no new signals or trends. Adverse events thought to be associated with brimonidine tartrate generally are mild and resolve without sequelae.

7.2 Adequacy of Patient Exposure and Safety Assessments

Submitted under Section 505(b)(2) of the Food, Drug and Cosmetic Act, this application relies on the agency's findings in NDA 20-613, Alphagan®, and NDA 21-262, Alphagan® P for demonstration of the safety of brimonidine tartrate. In order to link safety for Brimonidine Tartrate Ophthalmic Solution, 0.15%, which is preserved with polyquaternium 0.001%, study C-02-49 was performed.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The submitted clinical study reports, clinical protocols, and literature reports related to trial C-02-49 were analyzed in this efficacy review. Proposed draft labeling and Case Report Forms for discontinued subjects in C-02-49 were provided and reviewed.

See Section 4.2 for the table of clinical studies.

All patients were treated with brimonidine three times daily.

Table 7.2.1 Duration of Exposure to Study Drug - Overall Safety Population Baseline through Month 6 Data

Treatment	Total N	1 to 15 days N	%	16 to 45 days N	%	46 to 90 days N	%	91 to 180 days N	%	>180 days* N	%
Total	**840**	**24**	**2.9**	**37**	**4.4**	**30**	**3.6**	**201**	**23.9**	**548**	**65.2**
Brimonidine 0.15%	416[a]	11	2.6	15	3.6	16	3.8	103	24.8	271	65.1
Alphagan P	424[b]	13	3.1	22	5.2	14	3.3	98	23.1	277	65.3

p-value = 0.8989 - Cochran-Mantel-Haenszel rank scores test
[a]1 patient (#1425) had no record of Exit treatment use.
[b]1 patient (#6911) had no record of Exit treatment use.
*The Month 6 visit extended beyond 180 days for many patients.

For those patients randomized to receive Brimonidine 0.15%, the mean exposure was 163.7 days, the median was 182 days, and the longest duration of exposure was 219 days. For patients randomized to receive Alphagan P, the mean exposure was 160.5 days, the median was 182 days, and the longest duration of exposure was 219 days.

Reviewer's Comments:
The extent of exposure was similar between the treatment groups, and there were no clinically relevant demographic differences observed between the treatment groups.

No clinically relevant differences within or between treatment groups were noted in the duration of exposure to study drug with the greatest percentage patients having greater than 180 days of exposure to therapy.

7.2.1.1 Study type – See Section 4.2.

7.2.1.2 Demographics

Refer to Table 6.1.3-8 Demographic Statistics by Treatment Group

Reviewer's Comments:
There are no remarkable differences between treatment groups in baseline demographic characteristics.

Subgroup analyses did not reveal any differences in the primary efficacy endpoint between males and females. The safety profiles seen in males and females, including the types and rates of adverse events, are similar.

7.2.1.3 Extent of exposure (dose/duration) – See Table 7.2.1

Reviewer's Comment:
More than 96% of subjects had at least 90 days of exposure to the study drug. The majority of subjects had more than 6 months of exposure to the study drug.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

7.2.2.1 Other studies

There are no other studies that were used to evaluate safety.

7.2.2.2 Postmarketing experience

No postmarketing data were used to evaluate safety.

7.2.2.3 Literature

The applicant's literature search was complete, including important issues of safety and efficacy.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience was adequate.

The clinical study presented in this application, C-02-49, was to establish bioequivalence of Brimonidine Tartrate Ophthalmic Solution, 0.15% with polyquaternium-1 as preservative, to Alphagan P, the currently marketed product. An adequate number subjects from relevant demographic groups were exposed to this formulation to assess for potential risks. The study design, randomized, double blind, parallel groups and an active control was appropriate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable. There was no special animal or in vitro testing performed. Refer to the Pharmacology/Toxicology review for additional details.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing and monitoring of study subjects was adequate to elicit adverse events.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance and interaction were not performed due to the negligible systemic absorption of Brimonidine Tartrate Ophthalmic Solution, 0.15%.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant made adequate efforts to detect specific adverse events. Given the experience with the currently marketed forms of this drug product and published literature, no further studies are recommended.

7.2.8 Assessment of Quality and Completeness of Data

The data presented was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted the four-month safety update dated August 25, 2004, and received on August 26, 2004. This submission also included the revised draft package insert which accounted for the additional safety data.

A total of four hundred and thirty one (431) subjects had exposure to Brimonidine 0.15%. Overall, eight-hundred and forty-two subjects were evaluable for safety data.

Three patients experienced fatal adverse events, two with exposure to Brimonidine 0.15% (encephalopathy, pneumonia) and one with exposure to Alphagan P (carcinoma, GI) during the study. All deaths were assessed to be unrelated to therapy. Twenty nine patients experienced serious, non-fatal adverse events.

Review of the entire twelve months of safety data from protocol C-02-49 demonstrates that Brimonidine, 0.15% administered three-times-daily is safe in patients with ocular hypertension or open-angle glaucoma. Review of the adverse events and assessment of the ocular and cardiovascular parameters demonstrates that Brimonidine 0.15% exhibits a safety profile similar to Alphagan P.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Refer to Section 7.1.5.3 through Section 7.1.5.6 for a detailed discussion of important drug-related adverse events.

7.4 General Methodology

Refer to Section 7.1.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable. Data was not pooled across studies to estimate or compare incidence.

7.4.1.1 Pooled data vs. individual study data

Not applicable. Data was not pooled across studies to estimate or compare incidence.

7.4.1.2 Combining data

Not applicable. Data was not pooled across studies to estimate or compare incidence.

7.4.2 Explorations for Predictive Factors

A detailed discussion of the adverse events is given in Sections 7.1.1 through Section 7.1.5. The only predictive factor for a drug-related adverse event identified was prior exposure to brimonidine tartrate.

7.4.3 Causality Determination

A constellation of symptoms which represent an ocular allergic reaction (ocular hyperemia, conjunctival follicles, pruritus, etc.) have been shown to occur in patients exposed to brimonidine tartrate.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Brimonidine Tartrate Ophthalmic Solution, 0.15% will be dosed one drop three-times-daily in the eye to be treated. This dosing regimen is the same regimen as that of Alphagan P, the approved comparator. Using this regimen, Brimonidine Tartrate Ophthalmic Solution, 0.15% achieves equivalent safety and IOP lowering effect with Alphagan P.

8.2 Drug-Drug Interactions

No important drug-drug interactions have been identified.

8.3 Special Populations

Subgroup analyses did not reveal any differences in the primary efficacy endpoint between males and females. The safety profiles seen in males and females, including the types and rates of adverse events, are similar.

No populations have been identified for which dosing special considerations need to be made.

8.4 Pediatrics

The applicant requested a waiver of the pediatric study requirements for this original new drug application. The waiver was requested because: (1) The safety and effectiveness of brimonidine tartrate ophthalmic solution, 0.2 % has been studied in pediatric glaucoma patients age 2 to 7 years. This information is contained in the approved labeling for Alphagan, Alphagan P and Brimonidine Tartrate Ophthalmic Solution, 0.2%; and (2) Brimonidine tartrate is not recommended for use in patients under the age of 2 years.

8.5 Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting will be held regarding this application.

8.6 Literature Review

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

8.7 Postmarketing Risk Management Plan

Not applicable. The applicant did not submit a postmarketing risk management plan.

8.8 Other Relevant Materials

Comments received from DDMAC and the Office of Drug Safety have been incorporated in the labeling review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The application relies on the proof of safety and efficacy from the agency's prior findings for NDA 20-613, Alphagan, and NDA 21-262, Alphagan P. The applicant has shown that Brimonidine Tartrate Ophthalmic Solution, 0.15% is bioequivalent to Alphagan P.

9.2 Recommendation on Regulatory Action

The application is recommended for approval with the labeling changes listed in this review.

9.3 Recommendation on Postmarketing Actions

No postmarketing risk management activities are recommended.

9.3.1 Risk Management Activity

No postmarketing risk management activity is recommended.

9.3.2 Required Phase 4 Commitments

Not applicable. No required Phase 4 commitments are applicable.

9.3.3 Other Phase 4 Requests

Not applicable. No Phase 4 requests will be made.

9.4 Labeling Review

See the Appendix for the medical officers labeling review. The applicant has not submitted a trade name. The drug product will be marketed using the established name. No Medication Guide or Patient Package Insert has been proposed or is necessary for this product.

9.5 Comments to Applicant

No comments pertaining to specific deficiencies.

10 APPENDICES

10.1 Review of Individual Study Reports

Refer to Sections 4, 6 and 7 of this review. This application contains only one clinical study.

10.2 Line-by-Line Labeling Review

The reviewer's additions are noted by underline and deletions are noted by.

Brimonidine Tartrate Ophthalmic Solution, 0.15%

Reviewer's Comment:
The sponsor has not submitted a trade name.

4 Page(s) Withheld

____ Trade Secret / Confidential

X Draft Labeling

____ Deliberative Process

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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2/22/05 12:24:42 PM
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