These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

20613

NDA 20-613

Alphagan™

(brimonidine tartrate ophthalmic solution) 0.2% Sterile

Allergan

Volume 1 of 1

Joanne Holmes
phone 7-2527
e-mail HolmesJ

NDA 20-613

Allergan, Inc.
Attention: Adelbert L. Stagg, Ph.D.
Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

SEP [illegible] 1996

Dear Dr. Stagg:

Please refer to your August 31, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alphagan™ (brimonidine tartrate ophthalmic solution) 0.2%.

We acknowledge receipt of your amendments dated October 12 and 23, 1995, and February 26, March 1, 18, 22, and 26, April 5, 11, and 25, May 8, 10 (two), 14, 16, June 4, 12 (two), July 16, and August 28, 1996.

This new drug application provides for the indication of lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated August 28, 1996 with the following revision: the first sentence of the Clinical Pharmacology section should be revised into the following two sentences, "ALPHAGAN™ is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing." Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on August 28, 1996, as revised above. Marketing the product with FPL that is not identical to this revised draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-613. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, additional revisions of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, we acknowledge the commitment made during the September 6, 1996, telephone conversation between Peter Kresel (Allergan, Inc.) and Wiley Chambers (FDA). Allergan, Inc., agreed to conduct a Phase 4 study to further evaluate the potential (in at least two

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Joanne Holmes, M.B.A.
Project Manager
(301) 827-2090

Sincerely yours,

MW 9/6/96

Michael Weintraut, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

14. PATENT CERTIFICATION

Because the only patent related to brimonidine for use in ophthalmic products has expired, no patent certifications will be made at this time. A copy of U.S. Patent No. 3,890,319, which covered the active compound brimonidine in Brimonidine Ophthalmic products and expired on 17 June 1992, is provided in this NDA under Section 13, Patent Information.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # NDA 20-613 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-550 Trade (generic) name/dosage form: Alphagan (brimonidine tartrate ophthalmic solution) 0.2% sterile Action: AP (AE) NA

Applicant Allergan Therapeutic Class 15

Indication(s) previously approved none

Pediatric labeling of approved indication(s) is adequate ✓ inadequate ___

Indication in this application lowering IOP in patients with chronic open-angle glaucoma or ocular hypertension

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed. this indication is not prevalent in pediatric patients

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Joanne M Holmes, PM — 8/15/96

Signature of Preparer and Title (PM, CSO, MO, other) — Date

cc: Orig NDA/PLA # 20-613
HFD-550 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

ALLERGAN

2525 Dupont Drive PO Box 19534 Irvine CA 92713-9534 (714) 752-4500

DEBARRMENT CERTIFICATION

REF: Brimonidine Tartrate 0.2% Ophthalmic Solution - NDA 20-613.

Under the provisions of Section 306(k) of the Federal Food, Drug and Cosmetic Act, Allergan, Inc. has made a diligent effort to insure that no individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Act, as referenced above, has provided any services in connection with this application. This effort included identifying all employees of Allergan, Inc. connected with this application and requiring each of them to certify that he or she has not been debarred. This effort also included a requirement that all persons not employed by Allergan, Inc. who provided services in connection with this application certify to us that neither they nor any person employed by them has been disbarred. Relying, in part, on these certifications to us, Allergan, Inc. certifies that it did not and will not use, in any capacity, the services of any individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application.

Peter Kresel

Peter Kresel
Vice President, Global Regulatory Affairs
Allergan, Inc.

8/31/95
Date

Medical Officer's Review NDA 20-613
Original

NDA 20-613 Original	Submission date: 9/7/95, 4/5/96, 6/12/96 Received date: 9/13/95, 4/8/96, 6/14/96 Review date: 7/3/96
Sponsor:	Allergan Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, California 92713-9534
Drug name:	Alphagan
Pharmacologic Category:	Alpha adrenergic receptor agonist
Proposed Indication:	For the reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.
Dosage Form and Route of Administration:	Topical ophthalmic solution.
Submitted:	This application consists of 209 volumes divided into 15 sections. The clinical section consisted of volumes 1.136-1.142. The sponsor has identified 2 Phase III studies as pivotal trials : #A342-103-7831 and #A342-104-7831
Manufacturing Controls:	See Chemist's Review.
Pharmacology:	See Pharmacology and Toxicology Review.
Related Submissions:	IND # NDA#

Clinical Studies Conducted In Support of Brimonidine
for the Reduction of Elevated IOP

Phase	Study Description	Subject Population	Study Number for Reference
1/PK	Clinical Pharmacokinetics	Normal Healthy Volunteers	A342-105-8042 A342-106-7831 A342-119-7831 A342-120-8042
2/PK	Clinical Pharmacokinetics	Normal Healthy Volunteers	PIND-202-7831 A342-115-7831
1	Safety and Comfort/ Dose-titration	Normal Healthy Volunteers	S342-101-7829
1	Safety and Comfort/ Dose-ranging	Normal Healthy Volunteers	S342-107-7831 S342-108-8042 A342-111-8177
1/2	Safety and Comfort	Open-angle glaucoma/ ocular hypertension	S342-109-7829
2	Efficacy and Safety Dose Response	Open-angle glaucoma/ ocular hypertension	A342-110-7831 A342-116-8042 A342-119-7831
3	Efficacy and Safety	Open-angle glaucoma/ ocular hypertension	A342-103-7831 A342-104-7831

Study No.	Investigator	Study Design	Treatment	Dose	Duration	Number of Subjects	Mean Age in Years (Min-Max)	Sex (M/F)	Race* (B/W/O)	Study Conclusion
Early Dose-Tolerance Studies										
S342-101-7829	Laibovitz	Masked Titration	0.02% 0.08% vehicle	One eye Titrated 0.02% qd 0.02% bid 0.08% qd 0.08% bid	4 days	44	30.8 (18-60)	33/11	4/39/1	Brimonidine, at concentrations of 0.02% and 0.08%, is safe and comfortable.
S342-107-7831	Repass	Masked Parallel	0.08% 0.2% vehicle	One eye bid	4 days	50	37.3 (18-72)	38/12	0/47/3	Brimonidine, at concentrations of 0.08% and 0.2%, is safe and comfortable. In addition, brimonidine is more efficacious in lowering intraocular pressure than is vehicle in normal subjects. There is no evidence from this study to conclude that brimonidine 0.08% and 0.2% differ from each other in efficacy.
S342-108-8042	Repass	Masked Parallel	0.5% vehicle	One eye bid	4 days	46	34.7 (19-66)	33/13	0/40/6	Brimonidine, at a concentration of 0.5%, is safe and comfortable. Significantly greater incidences of conjunctival blanching and subjective reports of dry eye were reported with use of brimonidine 0.5% than vehicle. In addition, brimonidine is more efficacious in lowering intraocular pressure than is vehicle in normal subjects.
A342-111-8177	Repass	Masked Parallel	0.35% vehicle	One eye bid	4 days	46	39.0 (19-67)	29/17	0/42/4	Brimonidine, at a concentration of 0.35%, is safe and comfortable. Significantly greater incidences of conjunctival blanching was reported with use of brimonidine 0.35% than vehicle. In addition, brimonidine is more efficacious in lowering intraocular pressure than is vehicle in normal subjects.

Study No.	Investigator	Study Design	Treatment	Dose	Duration	Number of Subjects	Mean Age in Years (Min-Max)	Sex (M/F)	Race* (B/W/O)	Study Conclusions
Short-Term Studies of Therapeutic Response										
S342-109-7829	Repass	Masked Paralled	0.07% 0.08% vehicle	bid	3 days	13	62.3 (34-79)	8/5	0/13/0	Brimonidine, at concentrations of 0.02% and 0.08%, is safe and comfortable. In addition, the results of this study suggests that brimonidine 0.08% is efficacious for the treatment of elevated intraocular pressure. It must be kept in mind, however, that the statistical power of this study was very low, therefore, no firm conclusions can be drawn from this study.
A342-110-7831	Barnebey Choplin Epstein Lewis Repass Robin Zimmerman Van Buskirk	Masked Paralled	0.5% 0.2% 0.08% vehicle	bid	28 days	194	57.2-60.0	94/92	28/145/13	The results of this study demonstrate that twice-daily administered 0.08%, 0.2%, and 0.5% brimonidine are statistically and clinically significantly more efficacious than brimonidine vehicle in lowering elevated intraocular pressure 12 hours post-instillation. Brimonidine 0.2% and 0.5% demonstrated a significantly greater peak ocular hypotensive effect than brimonidine 0.08% or vehicle.

Study No.	Investigator	Study Design	Treatment	Dose	Duration	Number of Subjects	Mean Age in Years (Min-Max)	Sex (M/F)	Race* (B/W/O)	Study Conclusions
Short-Term Studies of Therapeutic Response (Continued)										
A342-115-7831	Robin Nordlund Pasquale Rudikoff Ordman	Masked Crossover	0.5% 0.25% 0.2% vehicle	1/week	5 weeks	26	34.7 (21-60)	24/0	15/9/0	In this acute-dosing study in normal healthy volunteers, no effects on pulmonary function were observed with brimonidine 0.2%, betaxolol suspension 0.25%, timolol 0.5% or vehicle. Brimonidine 0.2%, betaxolol suspension 0.25% and vehicle had no effect on exercise-induced tachycardia whereas timolol was associated with a statistically significant suppression of both exercise and recovery heart rate. The cardiovascular effects of brimonidine upon exercise were limited to a slight suppression of the systolic blood pressure during the recovery period.
A342-116-8042	Repass Walters Sargent	Masked Parallel	0.5% vehicle	bid	8 days	105	49.3 -52.6	30/37	5/53/9	The results of this study suggest that brimonidine 0.5% administered twice-daily in either a regular-tip or micro-tip is equally efficacious in reducing IOP. There were no differences with regard to safety between the two drop sizes.
A342-119-7831	Walters Berg	Masked Parallel	0.2%	bid vs. tid	12 weeks	101	53.0 (26-73)	46/55	11/81/9	Brimonidine 0.2% dosed twice-daily was effective in the lowering of elevated IOP and was well-tolerated in subjects with open-angle glaucoma and/or ocular hypertension. Dosing of brimonidine 0.2% three times per day offers no clinically significant advantage over twice per day dosing.

Studies of Pharmacodynamic Properties										
A342-105-80 42	Flach	Open Probe	0.5%	stet	1 day	4	22.8 (22-24)	4/0	0/3/1	Peak levels of brimonidine in plasma were detected within four hours post-instillation of brimonidine 0.5%. Detectable levels of brimonidine ranged from 3.59 pg/mL to 265.00 pg/mL. No brimonidine was detectable in plasma at 24 hours post-instillation. (The assay method employed has the sensitivity to detect brimonidine in plasma to the lower limit of 2.00 pg/mL).
A342-106-78 31	Plotnik	Open	0.2% 0.2%	bid (young) qd (elderly)	10 day 1 days	7 9	31 (23-39) 70 (65-73)	3/4 3/6	0/6/1 0/9/0	The results showed that ocular doses of 0.2% brimonidine tartrate to elderly and young subjects were well tolerated. The systemic absorption was low but detectable after single and multiple ocular dosing. The mean Cmax was 0.0585 ng/mL after 10 days of repeated dosing. Systemic absorption and elimination of brimonidine in elderly subjects was comparable to that of young adults. Repeated ocular administration did not result in significant changes in brimonidine PK parameters, and there was minimal systemic accumulation following multiple dosing.
A342-120-80 42	Flach	Masked Crossover	0.08% 0.2% 0.5% vehicle	qd	1 day	24 (27 safety analysis)	27.8 (21-35)	24/0	0/22/2	The mean time at which maximum concentrations of brimonidine were found in human plasma (Tmax) occurred at approximately two hours post-dosing (range from 1.7 hours to 3.2 hours). The concentration of brimonidine in plasma declined with an apparent elimination half-life ranging from two to five hours.

PIND-202-7831	Yablonski	Masked Unilateral	0.2%	bid	8 days	21	57.7 (26-78)	13/8	16/5/0	The brimonidine-induced reduction in IOP in humans is associated with a decrease in aqueous flow and an increase in uveoscleral outflow. The decrease in IOP and aqueous flow in the contralateral control eye on day 8 compared to baseline day suggests a mild contralateral effect.

Controlled Clinical Studies:

Study No.	Investigator	Study Design	Treatment	Dose	Duration	Number of Subjects	Mean Age in Years (Min. Max)	Sex (M/F)	(White/ Non-White)
A342-103-7831	Albracht Atlas Barnebey Choplin Craven David/Klemperer Gross Hersh Horwitz Jones Katz Labarta Lamping Levy Perell Rotberg Schuman Siegel Silverstone Sloan Sturm Terry Tortora Wilensky Zimmerman	Double Masked Parallel	0.2% 0.5% Timolol	1 drop	bid	443	62.5 (27.9 - 83.9)	217/ 226	347/96

Controlled Clinical Studies (continued)

Study No.	Investigator	Study Design	Treatment	Dose	Duration	Number of Subjects	Mean Age in Years (Min. Max)	Sex (M/F)	(White/ Non-White)
A342-1 04-7831	Abelson Balazsi/K..sner Beehler Blaydes Brooks Cantor Cooke Crichton Dirks Fichman Foerster Gaasterland Goldberg Hasty LeBlanc Lewis McCulley Melamed Mikelberg Morrison Mundorf Murphy Spirn Stamper Ticho Tingey Trope Walters	Double Masked Parallel	0.2% 0.5% Timolol	1 drop	bid	483	62.7 Brim (28.5-86.4) 61.4 Tim (32.8-83.0)	246/ 237	404/79

APPLICANT'S RATIONALE FOR DOSE AND REGIMEN

A three-day dose-response study (S342-109-7829) was conducted that compared the safety and efficacy of brimonidine 0.02%, 0.08%, and vehicle in 13 subjects with glaucoma or ocular hypertension (S342-109-7831). Subjects were treated twice-daily in both eyes. The results showed a significant difference in mean IOP change from baseline only at one timepoint. At this visit, the 0.08% group had a significantly greater decrease than the vehicle group.

A one-month dose-response study (A342-110-7831) was conducted comparing the safety and efficacy of brimonidine tartrate 0.08%, 0.2%, 0.5%, and vehicle in 194 subjects with open-angle glaucoma or ocular hypertension (A342-116-7831; Derick et al., 1993). Subjects were treated twice-daily in both eyes. Results from this study indicated that all three brimonidine concentrations lowered IOP significantly more than vehicle at all follow-up visits ($p < 0.05$). At days 14, 21, and 28, the 0.5% concentration lowered IOP to the same extent as the 0.2% concentration. The 0.5% concentration, however, was associated with a greater incidence of blurring of vision and foreign body sensation. Incidence of fatigue and/or drowsiness and dry mouth were also higher for this concentration than for either the 0.2% or the 0.08% concentrations. Based on the results of the dose-response study, brimonidine 0.2% was selected for further clinical development in the treatment of open-angle glaucoma and ocular hypertension.

Dosing of brimonidine 0.2% at twice per day (b.i.d.) was compared to three times per day (t.i.d.) in a three-month study (A342-119-7831) to ascertain if more frequent instillation would significantly enhance overall clinical effectiveness (A342-119-7831). One-hundred one patients with glaucoma or ocular hypertension were randomly assigned to the b.i.d. or t.i.d. groups. The data demonstrated that t.i.d. dosing did not enhance overall clinical effectiveness. At morning trough, IOP was reduced approximately 4 mm Hg for both dosing regimens. At the afternoon trough, t.i.d. dosing resulted in a significantly greater reduction in IOP at three hours (3 mm Hg greater with t.i.d. than b.i.d. dosing) and one hour (1.4 mm Hg greater) before the evening dose. The value of this additional decrease is minimal, since a) IOP is generally lowest in the afternoon and evening (Henkind et al., 1973; David et al, 1992), b) both regimens resulted in afternoon trough IOPs of under 20 mm Hg, c) there was not an enhanced IOP reduction at the morning trough, and d) compliance will likely suffer with t.i.d. dosing (Kass et al , 1987). Brimonidine was safe whether dosed b.i.d. or t.i.d. The conclusion from this study was that while t.i.d. dosing was safe, it did not contribute to a clinically significant enhancement of efficacy.

One small, additional study (A342-116-8042) was conducted to ascertain whether a smaller drop size (26 uL) of brimonidine would be as effective as the standard drop size (35 uL) while enhancing the safety profile (A342-110-7831). Sixty-seven patients with glaucoma or ocular hypertension were dosed b.i.d. for seven days. The results showed that the smaller drop size did not enhance the safety profile and therefore, the 35uL drop size was used in all future studies.

Reviewer's Comments: *The applicants rationale for bid dosing is seriously flawed. The morning trough measured was taken in each group 9-12 hours after the evening dose. The equivalence between groups is reflective of the equal amounts of time since the last dose in each group. The difference in the afternoon measurement demonstrates the need for an additional afternoon dose. An occasional missed afternoon dose due to compliance issues is still better than a routinely missed dose because it was not attempted.*

Study Design - Phase III Studies

In the two phase III studies (A342-103-7831 and A342-104-7831), all patients were diagnosed with glaucoma and/or ocular hypertension. Patients were required to meet the following inclusion and exclusion criteria to participate in the study:

Inclusion Criteria: Male or female volunteers, 21 years of age or older, with post-washout IOPs of 23 mm Hg or greater (but less than 35 mm Hg) in each eye at the Hour 0 measurement, and corrected visual acuity of 20/80 (A342-104-7831) or 20/100 (A342-103-7831) English units or better in each eye.

Exclusion Criteria: Existence of any uncontrolled systemic disease; pregnancy, nursing, or childbearing potential (an adult female was considered of childbearing potential unless she was post-menopausal, had her uterus and/or both ovaries removed, or had a bilateral tubal ligation); contraindications to alpha-adrenoceptor agonist therapy such as depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans; contraindications to beta-adrenoceptor antagonist therapy (such as chronic obstructive pulmonary disease, bronchial asthma, heart block more severe than first degree or uncontrolled congestive heart failure); abnormally low or high heart rate or blood pressure for age; known hypersensitivity to any of the ingredients in the study medication, or diagnostic agents used in the study; chronic treatment with any other topical or systemic alpha-adrenoceptor agonist or alpha-adrenoceptor antagonist; alteration of existing chronic therapy with agents which could have a substantial effect on IOP, a substantial effect on the ocular activity of alpha-adrenergic agonists, or substantially interact with alpha-agonists; and treatment with adrenergic-augmenting psychotropic drugs.

Ophthalmic Exclusion Criteria: Corneal abnormalities that would preclude accurate readings with an applanation tonometer, use of contact lenses during the study, any other active ocular disease, dry eye (with confirmation of a Schirmer strip test < 5 mm), Sjogren's syndrome or *keratoconjunctivitis sicca*, required use of other ocular medications during the study, asymmetry of IOP > 5 mm Hg between eyes, visual field loss of 50% or greater or any visual field loss which in the opinion of the investigator was functionally significant, laser or other intraocular surgery within the past six months, and cupping of the optic disc ≥ 0.8 in either eye.

Study Design: Before study medications were dispensed, subjects provided written informed consent. At the prestudy visit (visit 1), an ophthalmic examination consisting of assessments of intraocular pressure (IOP), visual acuity, biomicroscopy, ophthalmoscopy, pupil size, Schirmer tear test, and a visual field were performed to determine a subject's eligibility to participate in the study. Those subjects meeting the initial entry criteria were enrolled into the study and a medical and ophthalmic history was taken. For systemic safety evaluation, heart rate and blood pressure were measured. An ECG was optional at this visit. Blood samples were drawn to evaluate the subject's complete blood count (CBC) and blood chemistry.

The washout period was four days to four weeks depending on the prestudy glaucoma medication that was used. Following washout, all subjects returned for a baseline examination (visit 2, day 0). If no washout period was required, visits 1 and 2 could occur on the same day. At this visit, baseline measurements of IOP, visual acuity, pupil size, heart rate, and blood pressure were taken. Measurements of IOP were taken between 7:30 and 9:30 am (corresponding to trough, 12 hours after treatment-hour 0) and again between 9:30 and 11:30 am (corresponding to peak, two hours after treatment). Biomicroscopy and a Schirmer tear test were performed. Subject comfort was also assessed. Subjects who qualified for entry were randomly assigned to one of the two treatment groups (brimonidine 0.2% or timolol 0.5%). Subjects were instructed to instill the study medication at twelve-hour intervals, between the hours of 7:30 AM and 9:30 AM and between 7:30 PM and 9:30 PM, for a duration of 12 months. Subjects were instructed not to use the morning medication on the day of a scheduled visit.

Subjects returned for follow-up examinations at weeks 1 and 2, and months 1, 2, 3, 6, 9, and 12. At these examinations, efficacy was assessed by evaluating changes from baseline in IOP, visual fields, and cup/disc ratio (month 6 and 12). Ocular safety was assessed by evaluating changes from baseline in visual acuity, pupil size, biomicroscopy, and ocular discomfort. A Schirmer tear test (month 6 and 12) and an ophthalmoscopic examination (month 6 and 12) were also assessed for ocular safety. Systemic safety was assessed by evaluating changes from baseline in heart rate and blood pressure, systemic discomfort, and CBC and blood chemistry (months 6 and 12). Peak (two hours post-instillation) measurements of IOP were taken at week 1 and 2, and at months 1, 3, 6, and 12. Subject comfort was also assessed at all follow-up visits.

Statistical Analysis: One year data from A342-103-7831 and six-month data from A342-104-7831 were analyzed in each respective final report. In this integrated summary, meta-analysis was performed for the combined six-month data from both studies. However, in some tables/graphs, Months 9 and 12 data from A342-103-7831 were also included.

Intraocular pressure was the key variable for both pivotal studies. A p-value less than or equal to 0.05 was considered statistically significant for the main effects and 0.10 for the treatment-by-study interaction effects.

The following table summarizes the study variables and the statistical methods used for their analysis:

Variable	Statistical Method
Age	two-way analysis of variance (ANOVA)[1]
Sex, race distribution, iris color, diagnosis, prestudy history	Cochran-Mantel-Haenszel (CMH) method[2]
IOP	two-way ANOVA; repeated measures analysis
Cup-to-disc ratio	two-way ANOVA; frequency tables for significant changes
Visual fields	shift tables, two-way ANOVA
Drug exposure	frequency tables
Biomicroscopy, ophthalmoscopy, ocular and systemic discomfort, adverse events	frequency tables; Pearson's Chi-square test[3] or Fisher's exact test[4]
Schirmer tear test	two-way ANOVA; frequency tables for significant changes
Visual acuity	frequency tables, CMH method
Pupil size	two-way ANOVA
Heart rate and blood pressure	two-way ANOVA
Laboratory data	two-way ANOVA; shift tables
Analysis of IOP by demographics	two-way ANOVA; analysis of covariance with baseline as a covariate

[1]Milliken and Johnson, 1984; [2]Landis et al., 1978; [3]Snedecor and Cochran, 1980; [4]Brownlee, 1965.

Two major analyses were performed on the two combined studies:

(1) *Preferred Analysis*. Subjects from the efficacy analyzable population were included in this analysis. The preferred analysis was the primary analysis for efficacy.

(2) *Responder Analysis*. Responders were defined as subjects included in the preferred analysis with an IOP reduction of at least 3 mm Hg or greater from baseline at two consecutive visits within the first month of treatment (trough effect, Hour 0 measurement).

Demographics

(All Subjects)

Variable		0.2% Brm	0.5% Tim	All	P-value
Age (Years)	N	221	222	443	
	Mean	62.6	62.5	62.5	0.969
	SD	11.2	10.3	10.7	
	Min	27.9	34.4	27.9	
	Max	83.9	83.4	83.9	
	<45	17 (7.7%)	16 (7.2%)	33(7.4%)	
	45-65	100 (45.2%)	104 (46.8%)	204(46.0%)	
	>65	104 (47.1%)	102 (45.9%)	206(46.5%)	
Sex	Male	100 (45.2%)	117 (52.7%)	217(49.0%)	0.134
	Female	121 (54.8%)	105 (47.3%)	226(51.0%)	
Race	Caucasian	175 (79.2%)	172 (77.5%)	347(78.3%)	0.585
	Hispanic	16 (7.2%)	18 (8.1%)	34(7.7%)	
	Black	26 (11.8%)	25 (11.3%)	51(11.5%)	
	Asian	4 (1.8%)	5 (2.3%)	9(2.0%)	
	Other[b]	0 (0.0%)	2 (0.9%)	2(0.5%)	
Iris Color	Blue	79 (35.7%)	79 (35.6%)	158(35.7%)	0.710
	Green	12 (5.4%)	5 (2.3%)	17(3.8%)	
	Hazel	23 (10.4%)	27 (12.2%)	50(11.3%)	
	Brown	107 (48.4%)	111 (50.0%)	218(49.2%)	
Diagnosis	OAG	137 (62.0%)	138 (62.2%)	275(62.1%)	0.933
	OHT	81 (36.7%)	80 (36.0%)	161(36.3%)	
	OAG/OHT[c]	3 (1.4%)	4 (1.8%)	7(1.6%)	

[b] Other: two Hawaiians
[c] One eye with OAG and the fellow eye with OHT.

Demographics

(Preferred Analysis)

Variable		0.2% Brm	0.5% Tim	All	P-value
Age (Years)	N	186	188	374	0.713
	Mean	62.7	62.2	62.5	
	SD	11.4	10.3	10.9	
	Min	27.9	34.5	27.9	
	Max	83.9	83.4	83.9	
	<45	15 (8.1%)	13 (6.9%)	28(7.5%)	
	45-65	81 (43.5%)	90 (47.9%)	171(45.7%)	
	>65	90 (48.4%)	85 (45.2%)	175(46.8%)	
Sex	Male	84 (45.2%)	103 (54.8%)	187(50.0%)	0.052
	Female	102 (54.8%)	85 (45.2%)	187(50.0%)	
Race	Caucasian	150 (80.6%)	145 (77.1%)	295(78.9%)	0.456
	Hispanic	14 (7.5%)	17 (9.0%)	31(8.3%)	
	Black	18 (9.7%)	21 (11.2%)	39(10.4%)	
	Asian	4 (2.2%)	4 (2.1%)	8(2.1%)	
	Other[b]	0 (0.0%)	1 (0.5%)	1(0.3%)	
Iris Color	Blue	69 (37.1%)	68 (36.2%)	137(36.6%)	0.648
	Green	8 (4.3%)	5 (2.7%)	13(3.5%)	
	Hazel	20 (10.8%)	20 (10.6%)	40(10.7%)	
	Brown	89 (47.8%)	95 (50.5%)	184(49.2%)	
Diagnosis	OAG	115 (61.8%)	118 (62.8%)	233(62.3%)	0.886
	OHT	68 (36.6%)	66 (35.1%)	134(35.8%)	
	OAG/OHT[c]	3 (1.6%)	4 (2.1%)	7(1.9%)	

[b] Other: one Hawaiian
[c] One eye with OAG and the fellow eye with OHT.

Reviewer's Comments: There was no significant differences between the two treatments groups in age, sex, race, iris color, diagnosis distribution, medical or ophthalmic history.

Investigators

Name and Address	Allergan Identification Number	0.2% Brm	0.5% Tim.	Total
Diane Albracht, MD 21675 Redwood Rd Castro Valley, CA 94546	1710	14	17	31
Walter Atlas, MD Nalle Clinic 1350 South Kings Dr Charlotte, NC 28207	1979	13	12	25
Howard Barnebey, MD 901 Boren St, Suite 1030 Seattle, WA 98104	1688	9	10	19
Neil Choplin, MD Naval Hospital of San Diego Dept. of Ophthalmology, Code 69 San Diego, CA 92134	1486	7	9	16
E. Randy Craven, MD Glaucoma Associates 50 E. Harvard, Suite 205 Denver, CO 80210	2027	12	11	23
Robert David, MD Itamar Klemperer, MD Ben-Gurion University of the Negev Soroka Medical Center Beer-Sheva 84101 Israel	0398	14	16	30
Ronald Gross, MD Baylor College of Medicine 6501 Fannin, C529 Houston, TX 77030	1642	3	4	7
Stanley Hersh, MD 1201 W. Main St, Suite 100 Waterbury, CT 06708	1756	1	1	2
Barry Horwitz, MD 8945 Long Point Rd, Suite 111 Houston, TX 77055	1513	19	18	37
Robert Jones, MD 1401 Avocado Ave, Suite 505 Newport Beach, CA 92660	1484	4	4	8

L. Jay Katz, MD Wills Eye Hospital 9th and Walnut St Philadelphia, PA 19107	1960	8	8	16
Larry Labarta, MD study conducted at: 917 Washington Ave Miami Beach, FL 33139 new address: 1034 Alton Rd. Miami Beach, FL 32139	1532	14	15	29
Kathleen Lamping, MD study conducted at: 1611 South Green Rd, Suite 140 South Euclid, OH 44121 new address: 1611 South Green Rd, Suite 144 South Euclid, OH 44121	0654	14	13	27
Norman Levy, MD, PhD Florida Ophthalmic Institute 7106 NW 11th Place, Suite B Gainesville, FL 32605	0619	8	7	15
Howard F. Perell, MD North Arundal Physicians Center 203 Hospital Dr, Suite 306 Glen Burnie, MD 21061	1752	1	1	2
Michael Rotberg, MD Charlotte EENT Associates 1600 E. Third St Charlotte, NC 28204	2037	11	11	22
Joel Schuman, MD New England Eye Center 750 Washington St, Box 450 Boston, MA 02111	2110	5	4	9
Les Siegel, MD Glaucoma Center of Michigan 29201 Telegraph Rd #301 Southfield, MI 48034	1653	5	4	9
David Silverstone, MD 60 Temple St New Haven, CT 06510	0342	6	5	11

Frank Sloan, MD 401 79th Ave North Myrtle Beach, CA 29577	1536	9	8	17
Richard Sturm, MD 200 Hempstead Ave Lynbrook, NY 11563	1587	10	10	20
Stuart Terry, MD South Texas Cataract and Glaucoma Center 215 E. Quincy St, #200 San Antonio, TX 78215	1512	6	6	12
Christopher Tortora, MD Hawaiian Eye Center 606 Kilani Ave Wahiawa, HI 96786	2026	3	4	7
Martin Wax, MD Washington Univ School of Medicine Dept of Ophthalmology, Box 8096 660 S. Euclid Ave St. Louis, MO 63110	2109	7	6	13
Jacob Wilensky, MD University of Illinois at Chicago Dept of Ophthalmology (M/C 648) 1855 West Taylor St Chicago, IL 60612	0296	7	7	14
Thom Zimmerman, MD University of Louisville Kentucky Eye Research 301 East Muhammed Ali Blvd Louisville, KY 40292	0151	11	11	22

Summary of Subject Enrollment and Exit Status

(All Subjects)

Exit Status[a]	0.2% Brm	0.5% Tim	Total
Included in Preferred Analysis[b]			
Enrolled	186	188	374
Completed	115 (61.8%)	154 (81.9%)	269
Terminated - LOE	13 (7.0%)	6 (3.2%)	19
Terminated - AE(Ocular)	30 (16.1%)	3 (1.6%)	33
Terminated - AE(Systemic)	18 (9.7%)	9 (4.8%)	27
Discontinued	14 (7.5%)	17 (9.0%)	31
Excluded from Preferred Analysis			
Enrolled	35	34	69
Completed	4 (11.4%)	13 (38.2%)	17
Terminated - LOE	4 (11.4%)	3 (8.8%)	7
Terminated - AE(Ocular)	2 (5.7%)	0 (0.0%)	2
Terminated - AE(Systemic)	4 (11.4%)	3 (8.8%)	7
Discontinued	21 (60.0%)	15 (44.1%)	36
All Subjects			
Enrolled	221	222	443
Completed	119 (53.8%)	167 (75.2%)	286
Terminated - LOE	17 (7.7%)	9 (4.1%)	26
Terminated - AE(Ocular)	32 (14.5%)	3 (1.4%)	35
Terminated - AE(Systemic)	22 (10.0%)	12 (5.4%)	34
Discontinued	35 (15.8%)	32 (14.4%)	67

[a] LOE=lack of efficacy. AE=adverse event.
[b] Four subjects (0.2% Brm) and one subject (0.5% Tim) were terminated due to both the ocular and systemic AEs. The percentage was calculated based on the actual sample size as the denominator, and did not add up to 100%.

Reviewer's Comments: *Significantly fewer patients in the brimonidine group completed the study and significantly more patients in the brimonidine group were terminated due to ocular adverse events and lack of efficacy as compared to the timolol group.*

EFFICACY RESULTS:

Intraocular Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit
(Hour 0 - Preferred Analysis)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value Treatment	ANOVA P-value Interaction
Baseline	N	186	188	0.662	0.868
	Mean	25.80	25.87		
	SD	2.31	2.81		
	Min	23.00	23.00		
	Max	32.00	34.00		
Week 1	N	171	174	<0.001	0.727
	Mean	-5.32	-6.47		
	SD	2.90	3.00		
	Min	-16.50	-13.50		
	Max	6.00	1.50		
	P-value[b]	<0.001	<0.001		
Week 2[c]	N	63	65	0.030	0.986
	Mean	-4.45	-5.81		
	SD	2.82	2.89		
	Min	-10.00	-12.00		
	Max	2.00	1.50		
	P-value[b]	<0.001	<0.001		
Month 1	N	172	179	<0.001	0.241
	Mean	-4.35	-6.57		
	SD	3.27	2.92		
	Min	-13.50	-16.50		
	Max	11.00	1.00		
	P-value[b]	<0.001	<0.001		
Month 2	N	153	171	<0.001	0.209
	Mean	-4.26	-6.84		
	SD	3.25	3.03		
	Min	-11.50	-15.00		
	Max	11.50	2.50		
	P-value[b]	<0.001	<0.001		
Month 3	N	154	168	<0.001	0.477
	Mean	-4.49	-6.32		
	SD	3.10	3.40		
	Min	-12.00	-16.00		
	Max	3.50	4.00		
	P-value[b]	<0.001	.0.001		
Month 6	N	130	162	<0.001	0.258
	Mean	-3.89	-6.40		
	SD	3.40	3.21		
	Min	-11.00	-15.00		
	Max	6.00	3.50		
	P-value[b]	<0.001	<0.001		
Month 9	N	119	153	<0.001	0.107
	Mean	-4.20	-6.16		
	SD	3.51	3.10		
	Min	-12.50	-14.00		
	Max	6.50	4.00		
	P-value[b]	<0.001	<0.001		
Month 12	N	106	149	<0.001	0.221
	Mean	-3.67	-5.88		
	SD	3.98	3.38		
	Min	-11.50	-16.00		
	Max	8.50	6.50		
	P-value[b]	<0.001	<0.001		

(b) Within-group analysis of changes from baseline using paired t-test.
[c] Twelve out of the 26 investigators used the revised protocol where Week 2 was scheduled.

Intraocular Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit

(Hour 0 - Responder Analysis[a])

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[b] Treatment	Interaction
Baseline	N	124	159	0.431	0.992
	Mean	25.88	26.11		
	SD	2.36	2.90		
	Min	23.00	23.00		
	Max	32.00	34.00		
Week 1	N	113	147	0.017	0.785
	Mean	-6.46	-7.14		
	SD	2.30	2.61		
	Min	-16.50	-13.50		
	Max	-1.00	-2.50		
	P-value[c]	<0.001	<0.001		
Week 2[d]	N	44	55	0.198	0.935
	Mean	-5.85	-6.54		
	SD	2.03	2.44		
	Min	-10.00	-12.00		
	Max	-3.00	-3.00		
	P-value[c]	<0.001	<0.001		
Month 1	N	118	153	<0.001	0.049
	Mean	-5.64	-7.10		
	SD	2.48	2.50		
	Min	-13.50	-15.00		
	Max	5.00	-2.00		
	P-value[c]	<0.001	<0.001		
Month 2	N	106	148	<0.001	0.551
	Mean	-5.09	-7.42		
	SD	3.11	2.70		
	Min	-11.50	-15.00		
	Max	11.50	-1.00		
	P-value[c]	<0.001	<0.001		
Month 3	N	107	145	<0.001	0.523
	Mean	-5.49	-6.84		
	SD	2.64	3.10		
	Min	-12.00	-16.00		
	Max	0.50	0.00		
	P-value[c]	<0.001	<0.001		
Month 6	N	89	141	<0.001	0.276
	Mean	-4.63	-6.80		
	SD	3.53	3.16		
	Min	-11.00	-15.00		
	Max	6.00	3.50		
	P-value[c]	<0.001	<0.001		
Month 9	N	79	132	<0.001	0.043
	Mean	-5.03	-6.67		
	SD	3.41	2.88		
	Min	-12.50	-14.00		
	Max	6.00	4.00		
	P-value[c]	<0.001	<0.001		
Month 12	N	72	127	0.003	0.442
	Mean	-5.03	-6.28		
	SD	3.39	3.37		
	Min	-11.50	-16.00		
	Max	3.50	6.50		
	P-value[c]	<0.001	<0.001		

[a] Responders = Subjects in the preferred analysis with an IOP reduction of at least 3 mm Hg from baseline at two consecutive visits within the first month of treatment.
[b] P-value based on the two-way analysis of variance. Treatment = between-group comparison. Interaction = treatment-by-investigator interaction.
[c] Within-group analysis of changes from baseline using paired t-test
[d] Twelve out of the 26 investigators used the revised protocol where Week 2 was scheduled.

cular Pressure (mm Hg)
95% Confide rval of Between-Group Difference
Changes from Baseline

- Preferred Analysis)

Timepoint	Estimate of Difference[a]	Std Error of Estimate	95% CI of Estimate
Baseline	-0.12	0.271	(-0.65, 0.42)
Week 1	1.19	0.324	(0.55, 1.82)
Week 2[b]	1.24	0.563	(0.13, 2.36)
Month 1	2.21	0.333	(1.55, 2.86)
Month 2	2.65	0.349	(1.97, 3.34)
Month 3	1.87	0.377	(1.13, 2.61)
Month 6	2.52	0.396	(1.74, 3.29)
Month 9	2.13	0.400	(1.34, 2.91)
Month 12	2.27	0.474	(1.34, 3.21)

[a] Estimate was computed for the difference of mean baseline and mean changes from baseline at each scheduled follow-up visit based on the least-squares means by 0.2% Brm group minus 0.5% Tim group.
[b] Twelve out of the 26 investigators used the revised protocol where Week 2 was scheduled.

Intraocular Pressure (mm Hg)
95% Confidence Interval of Between-Group Difference
in Mean Changes from Baseline

(Hour 0 - Responder Analysis[a])

Timepoint	Estimate of Difference[b]	Std Error of Estimate	95% CI of Estimate
Baseline	-0.27	0.345	(-0.95, 0.41)
Week 1	0.82	0.342	(0.15, 1.49)
Week 2[c]	0.67	0.516	(-0.36, 1.69)
Month 1	1.55	0.322	(0.91, 2.18)
Month 2	2.56	0.386	(1.80, 3.32)
Month 3	1.59	0.406	(0.79, 2.39)
Month 6	2.28	0.477	(1.34, 3.22)
Month 9	2.18	0.449	(1.29, 3.06)
Month 12	1.59	0.525	(0.56, 2.63)

[a] Responders = Subjects in the preferred analysis with an IOP reduction of at least 3 mm Hg from baseline at two consecutive visits within the first month of treatment.
[b] Estimate was computed for the difference of mean baseline and mean changes from baseline at each scheduled follow-up visit based on the least-squares means by 0.2% Brm group minus 0.5% Tim group.
[c] Twelve out of the 26 investigators used the revised protocol where Week 2 was scheduled.

Reviewer's Comments:

IOP at trough:

In the prefered analysis mean decreases in IOP from baseline ranged between 3.7 to 5.3 mmHg in the brimonidine group and from 5.8 to 6.8 mmHg in the Timolol group. Mean decreases were statistically significant from baseline in both groups at all visits. Timolol was statistically superior to Brimonidine at all visits. Adjusting the p-value for two interim analysis did not significantly altered these results. (See Biostatistician Review page #5)

In the responder analysis mean decreases from baseline ranged from 4.6 to 6.5 mm Hg in the brimonidine group and from 6.3 to 7.4 mm Hg in the timolol group. Mean decreases from baseline were statistically significant in both treatment groups at all follow-up visits ($p<0.001$). Treatment with timolol resulted in significantly greater decreases compared with brimonidine at months 1 through 12 ($p \leq 0.003$).

Intraocular Pressure (mm Hg)
Number and Percent of Subjects in Each Change Interval

(Hour 0 - Preferred Analysis)

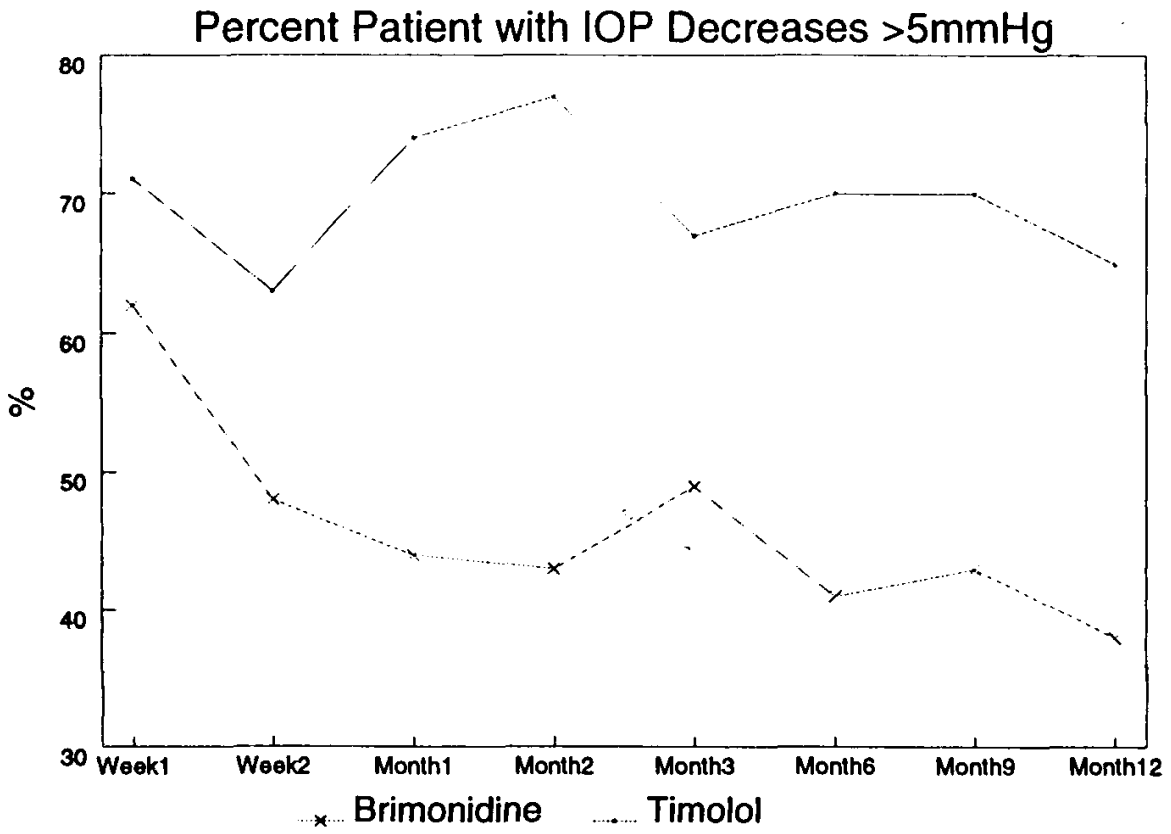
Timepoint	Changes (mm Hg)	0.2% Brm	0.5% Tim
Week 1	<= -5	106 (62.0%)	124 (71.3%)
	> -5 to <= -4	14 (8.2%)	23 (13.2%)
	> -4 to <= -3	19 (11.1%)	9 (5.2%)
	> -3	32 (18.7%)	18 (10.3%)
	Total (N)	171	174
Week 2	<= -5	30 (47.6%)	41 (63.1%)
	> -5 to <= -4	5 (7.9%)	6 (9.2%)
	> -4 to <= -3	10 (15.9%)	10 (15.4%)
	> -3	18 (28.6%)	8 (12.3%)
	Total (N)	63	65
Month 1	<= -5	76 (44.2%)	132 (73.7%)
	> -5 to <= -4	29 (16.9%)	25 (14.0%)
	> -4 to <= -3	23 (13.4%)	8 (4.5%)
	> -3	44 (25.6%)	14 (7.8%)
	Total (N)	172	179
Month 2	<= -5	66 (43.1%)	133 (77.8%)
	> -5 to <= -4	22 (14.4%)	14 (8.2%)
	> -4 to <= -3	23 (15.0%)	8 (4.7%)
	> -3	42 (27.5%)	16 (9.4%)
	Total (N)	153	171
Month 3	<= -5	76 (49.4%)	113 (67.3%)
	> -5 to <= -4	15 (9.7%)	23 (13.7%)
	> -4 to <= -3	18 (11.7%)	11 (6.5%)
	> -3	45 (29.2%)	21 (12.5%)
	Total (N)	154	168
Month 6	<= -5	54 (41.5%)	113 (69.8%)
	> -5 to <= -4	12 (9.2%)	17 (10.5%)
	> -4 to <= -3	13 (10.0%)	14 (8.6%)
	> -3	51 (39.2%)	18 (11.1%)
	Total (N)	130	162
Month 9	<= -5	52 (43.7%)	107 (69.9%)
	> -5 to <= -4	15 (12.6%)	12 (7.8%)
	> -4 to <= -3	18 (15.1%)	12 (7.8%)
	> -3	34 (28.6%)	22 (14.4%)
	Total (N)	119	153
Month 12	<= -5	40 (37.7%)	96 (64.4%)
	> -5 to <= -4	18 (17.0%)	12 (8.1%)
	> -4 to <= -3	5 (4.7%)	16 (10.7%)
	> -3	43 (40.6%)	25 (16.8%)
	Total (N)	106	149

Intraocular Pressure (mm Hg)
Number and Percentage of Subjects in Each Change Interval

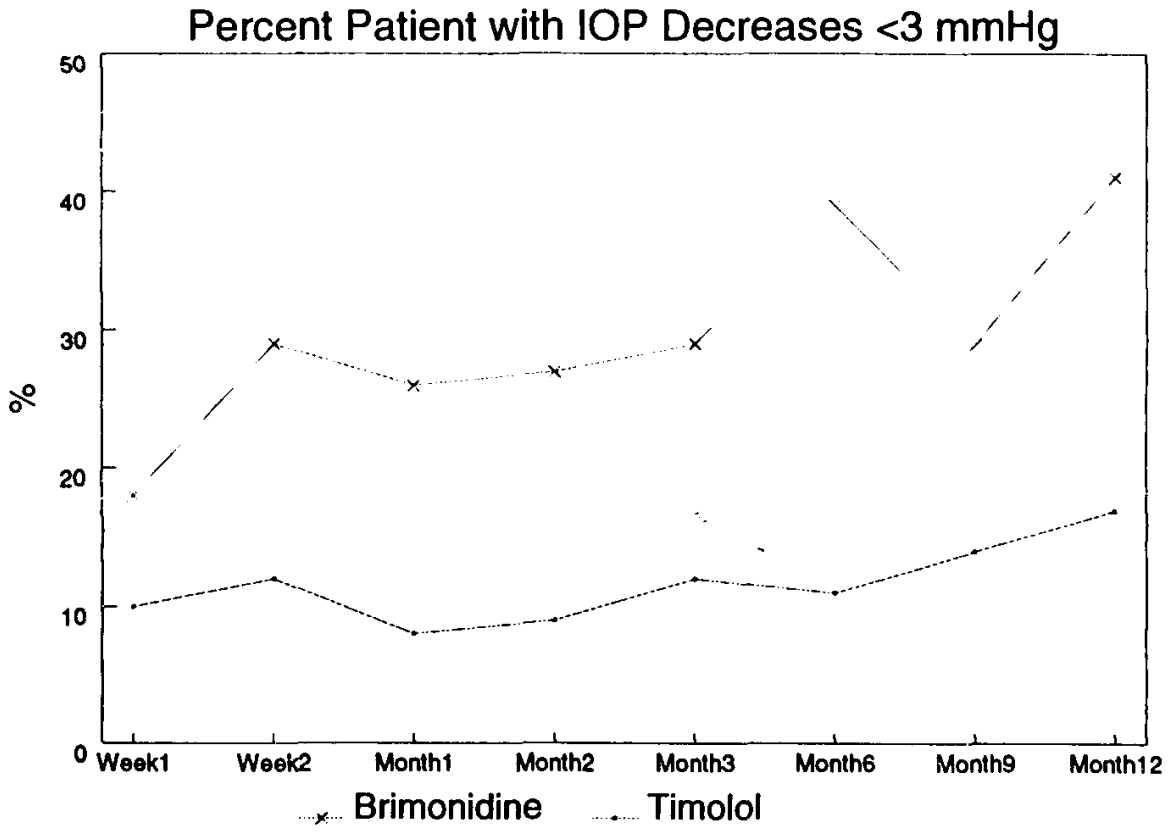
(Hour 0 - Responder Analysis[a])

Timepoint	Changes (mm Hg)	0.2% Brm	0.5% Tim
Week 1	<= -5	90 (79.6%)	118 (80.3%)
	> -5 to <= -4	10 (8.8%)	21 (14.3%)
	> -4 to <= -3	10 (8.8%)	7 (4.8%)
	> -3	3 (2.7%)	1 (0.7%)
	Total (N)	113	147
Week 2[b]	<= -5	30 (68.2%)	41 (74.5%)
	> -5 to <= -4	5 (11.4%)	5 (9.1%)
	> -4 to <= -3	9 (20.5%)	9 (16.4%)
	> -3	0 (0.0%)	0 (0.0%)
	Total (N)	44	55
Month 1	<= -5	71 (60.2%)	126 (82.4%)
	> -5 to <= -4	26 (22.0%)	19 (12.4%)
	> -4 to <= -3	14 (11.9%)	6 (3.9%)
	> -3	7 (5.9%)	2 (1.3%)
	Total (N)	118	153
Month 2	<= -5	58 (54.7%)	127 (85.8%)
	> -5 to <= -4	15 (14.2%)	11 (7.4%)
	> -4 to <= -3	17 (16.0%)	3 (2.0%)
	> -3	16 (15.1%)	7 (4.7%)
	Total (N)	106	148
Month 3	<= -5	65 (60.7%)	109 (75.2%)
	> -5 to <= -4	11 (10.3%)	18 (12.4%)
	> -4 to <= -3	10 (9.3%)	9 (6.2%)
	> -3	21 (19.6%)	9 (6.2%)
	Total (N)	107	145
Month 6	<= -5	48 (53.9%)	108 (76.6%)
	> -5 to <= -4	6 (6.7%)	14 (9.9%)
	> -4 to <= -3	9 (10.1%)	8 (5.7%)
	> -3	26 (29.2%)	11 (7.8%)
	Total (N)	89	141
Month 9	<= -5	44 (55.7%)	101 (76.5%)
	> -5 to <= -4	12 (15.2%)	10 (7.6%)
	> -4 to <= -3	8 (10.1%)	11 (8.3%)
	> -3	15 (19.0%)	10 (7.6%)
	Total (N)	79	132
Month 12	<= -5	37 (51.4%)	90 (70.9%)
	> -5 to <= -4	14 (19.4%)	9 (7.1%)
	> -4 to <= -3	2 (2.8%)	9 (7.1%)
	> -3	19 (26.4%)	19 (15.0%)
	Total (N)	72	127

[a] Responders = Subjects in the preferred analysis with an IOP reduction of at least 3 mm Hg from baseline at two consecutive visits within the first month of treatment.
[b] Twelve out of the 26 investigators used the revised protocol in which Week 2 was scheduled.



Reviewer's Comments: *By month 12, the end of the study, 37.7% (40/106) of the brimonidine-treated subjects and 64.4% (96/149) of thetimolol-treated subjects had IOP decreases greater than or equal to 5 mm Hg. This raises the question of thachyphilaxis.*



Reviewer's Comments: By month 12, the end of the study, 41% (43/106) of the brimonidine-treated subjects compared to 17% (25/149) of the timolol-treated subjects had IOP decreases less than than or equal to 3 mm Hg.

Intraocular Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit

(Hour 2 - Preferred Analysis)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value Treatment	ANOVA P-value Interaction
Baseline	N	185	187	0.966	0.695
	Mean	24.20	24.19		
	SD	3.45	3.35		
	Min	15.00	12.50		
	Max	34.50	34.00		
Week 2[c]	N	62	63	0.033	0.642
	Mean	-6.66	-5.01		
	SD	3.50	3.66		
	Min	-15.50	-12.50		
	Max	1.00	3.00		
	P-value[b]	<0.001	<0.001		
Month 1	N	170	177	0.783	0.653
	Mean	-5.58	-5.86		
	SD	4.31	3.65		
	Min	-14.50	-15.50		
	Max	12.00	7.50		
	P-value[b]	<0.001	<0.001		
Month 3	N	151	171	0.045	0.544
	Mean	-6.41	-5.75		
	SD	3.73	3.83		
	Min	-17.00	-16.00		
	Max	6.50	10.50		
	P-value[b]	<0.001	<0.001		
Month 6	N	134	159	0.673	0.760
	Mean	-5.68	-5.98		
	SD	3.33	3.65		
	Min	-13.50	-16.00		
	Max	6.50	4.50		
	P-value[b]	<0.001	<0.001		
Month 12	N	113	145	0.958	0.312
	Mean	-5.30	-5.61		
	SD	3.79	3.62		
	Min	-13.50	-14.00		
	Max	8.00	4.50		
	P-value[b]	<0.001	<0.001		
Overall[d]		-5.83	-5.60	0.196	0.663

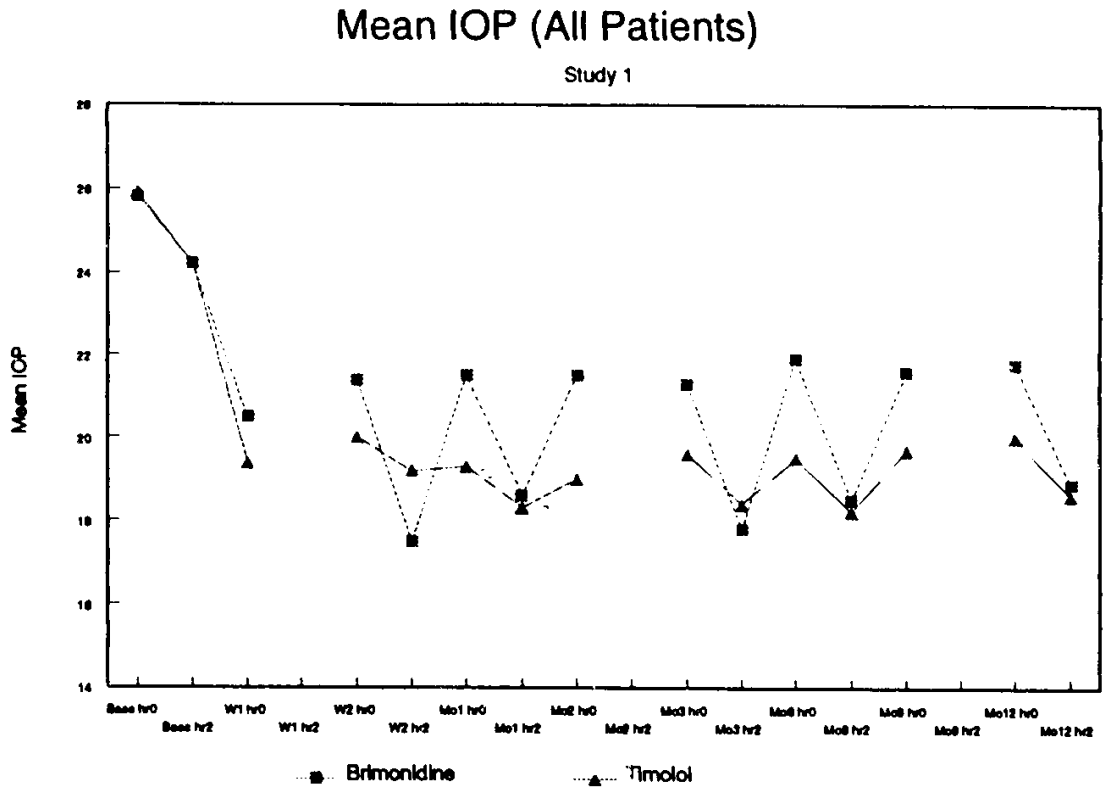
[b] Within-group analysis of changes from baseline using paired t-test.
[c] Twelve out of the 26 investigators used the revised protocol where Week 2 was scheduled.
[d] Least-squares means for IOP changes over the one-year of study. Note that drug-by-time interaction was significant. See Appendix E3 for ANOVA tables.

Intraocular Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit

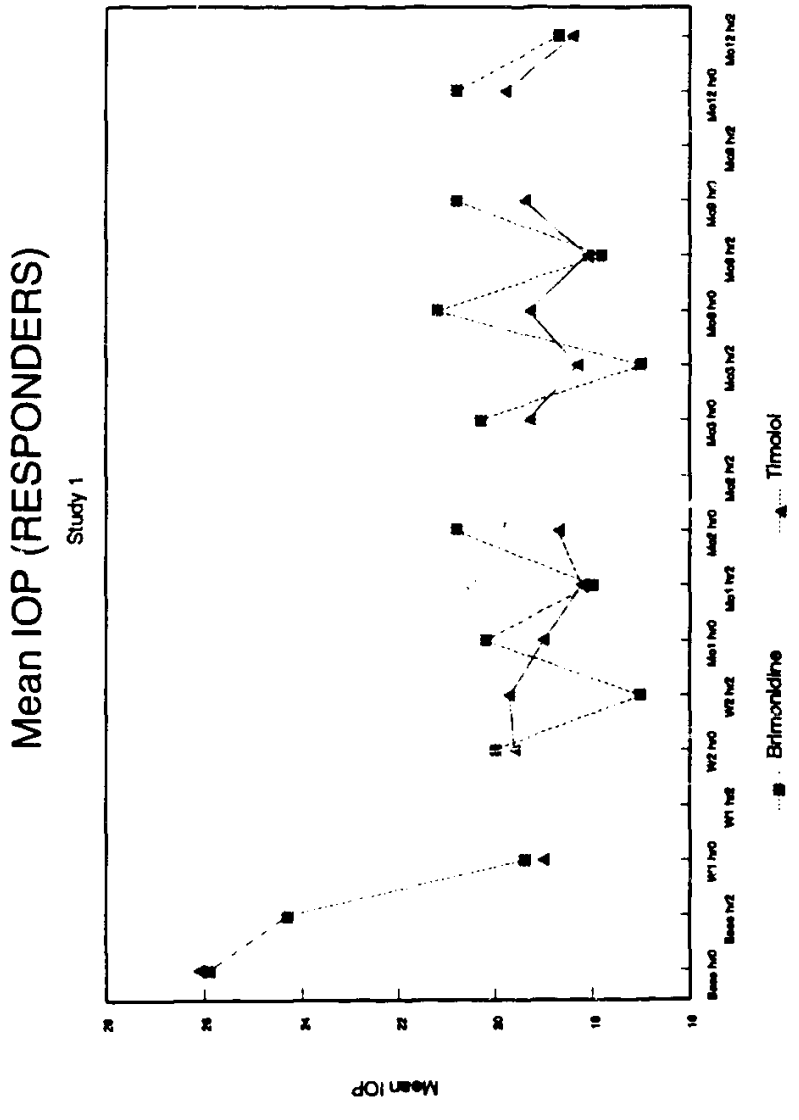
(Hour 2 - Responder Analysis)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value Treatment	Interaction
Baseline	N	123	158	0.504	0.805
	Mean	24.31	24.42		
	SD	3.29	3.37		
	Min	16.00	12.50		
	Max	34.50	34.00		
Week 2[d]	N	43	54	0.017	0.660
	Mean	-7.26	-5.25		
	SD	3.56	3.71		
	Min	-15.50	-12.50		
	Max	1.00	3.00		
	P-value[c]	<0.001	<0.001		
Month 1	N	118	151	0.889	0.624
	Mean	-6.38	-6.23		
	SD	3.55	3.43		
	Min	-14.50	-15.50		
	Max	5.00	7.50		
	P-value[c]	<0.001	<0.001		
Month 3	N	104	148	0.013	0.886
	Mean	-7.27	-6.15		
	SD	3.26	3.66		
	Min	-17.00	-16.00		
	Max	3.50	10.50		
	P-value[c]	<0.001	<0.001		
Month 6	N	91	139	0.865	0.770
	Mean	-6.47	-6.32		
	SD	3.01	3.52		
	Min	-13.50	-16.00		
	Max	2.00	4.50		
	P-value[c]	<0.001	<0.001		
Month 12	N	76	123	0.637	0.692
	Mean	-6.14	-6.06		
	SD	3.45	3.56		
	Min	-13.50	-14.00		
	Max	3.50	4.50		
	P-value[c]	<0.001	<0.001		
Overall[e]		-6.45	-6.11	0.105	0.812

[c] Within-group analysis of changes from baseline using paired t-test.
[d] Twelve out of the 26 investigators used the revised protocol where Week 2 was scheduled.
[e] Least-squares means for IOP changes over the one-year of study. Note that drug-by-time interaction was significant. See Appendix B3 for ANOVA tables.



Reviewer's Comments: *Mean decreases from baseline ranged from 5.3 to 6.7 mm Hg in the brimonidine group and from 5.0 to 6.0 mm Hg in the timolol group. Mean decreases from baseline were statistically significant in both treatment groups at all follow-up visits ($p<0.001$). At week 2 and month 3, brimonidine treatment resulted in greater decreases compared with timolol ($p\leq 0.045$) These differences were not clinically significant. Overall mean decreases from baseline were 5.8 in the brimonidine group and 5.6 in the timolol group.*


Mean IOP (RESPONDERS)
Study 1
Mean IOP
Brimonidine
Timolol

Safety Parameters:

Cup/Disc Ratio
Baseline and Mean Changes from Baseline at Each Scheduled Visit

(Preferred Analysis)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baselin	N	184	188	0.990	0.416
	Mean	0.44	0.44		
	SD	0.17	0.16		
	Min	0.10	0.05		
	Max	0.79	0.72		
Month 6	N	131	165	0.077	0.590
	Mean	0.00	-0.00		
	SD	0.06	0.04		
	Min	-0.30	-0.20		
	Max	0.30	0.15		
	P-value[b]	0.337	0.488		
Month 12	N	111	149	0.755	0.615
	Mean	0.00	0.00		
	SD	0.06	0.05		
	Min	-0.20	-0.15		
	Max	0.20	0.20		
	P-value[b]	0.609	0.677		

Cup-Disc Ratio
Compared to Baseline at Subject's Final Evaluation

(Number of Subjects - Preferred Analysis)

Change from Baseline[a]	0.2% Brm (N=185)	0.5% Tim (N=188)
<=-0.2	2 (1.1%)	2 (1.1%)
>=+0.2	3 (1.6%)	2 (1.1%)

[a] Subjects with the changes of at least 0.2 in one eye or both eyes.

Reviewer's comments: *No significant differences were seen between the brimonidine and timolol treatment groups in mean changes from baseline cup-to-disc ratio values over the 12-month study period.*

Visual Fields: Mean Defects (dB)
Analysis of Changes from Baseline at Month 6

(Preferred Analysis)

Variable	0.2% Brm	0.5% Tim	P-value
Visual Field Change			
N	152	171	0.270[b]
Mean	-1.0	-0.9	
SD	2.4	2.5	
Min	-13.6	-13.9	
Max	9.4	10.9	
Change Interval			
<= -5	7 (4.6%)	4 (2.3%)	0.372[c]
> -5 to <= 5	143 (94.1%)	165 (96.5%)	
> 5	2 (1.3%)	2 (1.2%)	

Reviewer's Comments: *No significant differences were seen between the brimonidine and timolol treatment groups in mean changes from baseline.*

Schirmer Tear Test (mm)
Baseline and Mean Changes from Baseline at Each Scheduled Visit

(All Subjects)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	216	214	0.152	0.981
	Mean	13.24	14.29		
	SD	7.44	7.09		
	Min	1.00	3.00		
	Max	35.00	35.00		
Month 6	N	141	175	0.489	0.344
	Mean	-0.04	-0.81		
	SD	6.75	6.17		
	Min	-27.50	-26.50		
	Max	20.50	20.00		
	P-value[b]	0.940	0.085		
Month 12	N	117	156	0.931	0.285
	Mean	-0.91	-1.28		
	SD	7.40	6.34		
	Min	-25.00	-20.00		
	Max	29.50	19.00		
	P-value[b]	0.184	0.012		

[a] P-value based on the two-way analysis of variance.
Treatment = between-group comparison.
Interaction = treatment-by-investigator interaction.
[b] Within-group analysis of changes from baseline using paired t-test.

Schirmer Test (mm)
Number and Percentage of Subjects with A Clinically Significant[a] Decrease from Baseline at One or More Follow-up Visits

(All Subjects)

Variable	0.2% Brm (N=216)[b]	0.5% Tim (N=214)[b]	P-value[c]
Schirmer Test	38 (17.6%)	46 (21.5%)	0.307

[a] Schirmer test results: (1) baseline < 10 mm and follow-up below 5 mm, or (2) baseline >= 10 mm, follow-up below 10 mm and a decrease from baseline of more than 5 mm.
[b] Sample size of the treatment group.
[c] P-value based on Pearson's Chi-square test.
Note: Some subjects who did not have Visit 2 (baseline) data were not included in the tabulation.

eviewer's Comments: *Schirmer test results, testing for changes in tear secretion, indicate negligible mean changes from baseline in both treatment groups over the 12-month study.*

Visual Acuity
Compared to Baseline at Subject's Final Evaluation
Number of Subjects - All Subjects

(All Subjects)

Changes[a]	0.2% Brm	0.5% Tim	P-value[b]
Worse	13 (5.9%)	21 (9.5%)	0.158
No Change	208 (94.1%)	201 (90.5%)	
Better	0 (0.0%)	0 (0.0%)	
Total	221	222	

[a] Worse = decrease of 2 lines or more
No Change = change between -2 to +2 lines
Better = increase of 2 lines or more
[b] P-value based on Wilcoxon rank-sum test using CMH methods withModified Ridit Scores.
Note: Tabulation was based on the eye with worse change comparing to the fellow eye.

Reviewer's Comments: Comparing final visit visual acuity to baseline, no change in visual acuity occurred in 94.1% (208/221) of subjects in the brimonidine group and 90.5% (201/222) of those in the timolol group. Worsening of visual acuity of two lines or more occurred in 5.9% (13/221) of the subjects in the brimonidine group and 9.5% (21/222) of the subjects in the timolol group. Between-group differences were not significant.

Pupil Size (mm)

Baseline and Mean Changes from Baseline at Each Scheduled Visit (All Subjects)

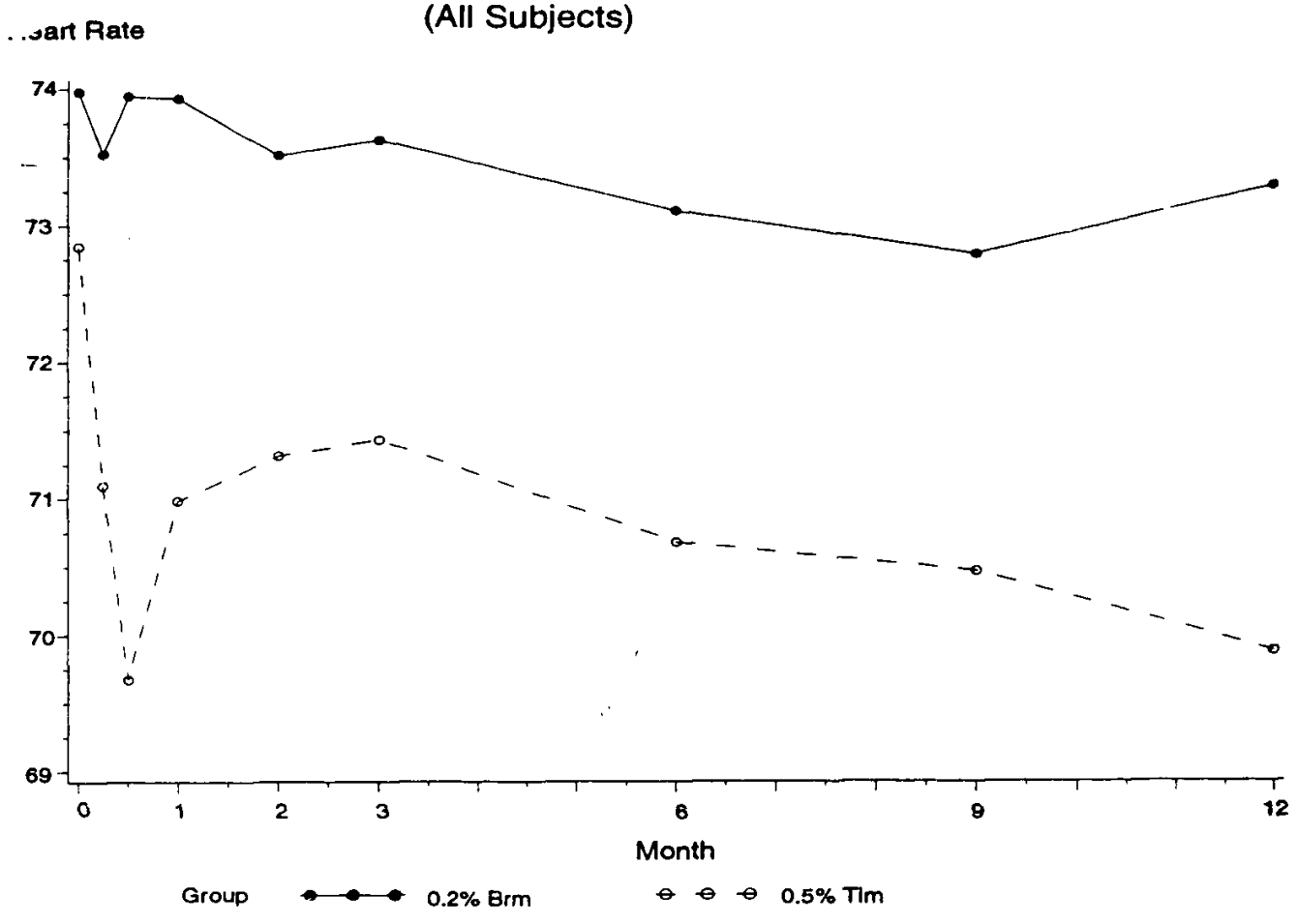
Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	221	222	0.378	0.670
	Mean	3.41	3.49		
	SD	0.95	0.99		
	Min	1.50	2.00		
	Max	8.00	7.00		
Week 1	N	215	218	0.012	0.465
	Mean	-0.22	-0.08		
	SD	0.63	0.60		
	Min	-3.00	-2.00		
	Max	1.50	2.00		
	P-value[b]	<0.001	0.062		
Week 2[c]	N	74	75	0.143	0.371
	Mean	-0.16	0.07		
	SD	0.67	0.71		
	Min	-2.00	-2.00		
	Max	1.00	2.00		
	P-value[b]	0.050	0.417		
Month 1	N	203	211	0.099	0.589
	Mean	-0.13	-0.02		
	SD	0.60	0.66		
	Min	-2.00	-2.50		
	Max	1.50	2.00		
	P-value[b]	0.002	0.594		
Month 2	N	183	197	0.206	0.391
	Mean	-0.16	-0.06		
	SD	0.68	0.69		
	Min	-2.00	-2.00		
	Max	2.50	2.00		
	P-value[b]	0.002	0.244		
Month 3	N	173	192	0.299	0.369
	Mean	-0.16	-0.06		
	SD	0.70	0.61		
	Min	-3.00	-2.00		
	Max	2.00	2.00		
	P-value[b]	0.004	0.201		
Month 6	N	147	183	0.769	0.533
	Mean	-0.14	-0.10		
	SD	0.68	0.75		
	Min	-3.00	-3.00		
	Max	2.00	2.00		
	P-value[b]	0.011	0.062		
Month 9	N	128	172	0.838	0.742
	Mean	-0.18	-0.15		
	SD	0.65	0.72		
	Min	-3.00	-3.00		
	Max	1.00	2.00		
	P-value[b]	0.003	0.007		
Month 12	N	120	168	0.717	0.510
	Mean	-0.16	-0.17		
	SD	0.74	0.87		
	Min	-3.00	-3.00		
	Max	2.00	3.00		
	P-value[b]	0.017	0.010		

Reviewer's Comments: *There is a small decrease in pupil size in the brimonidine group.*

Heart Rate (bpm)
Baseline and Mean Changes from Baseline at Each Scheduled Visit
(All Subjects)

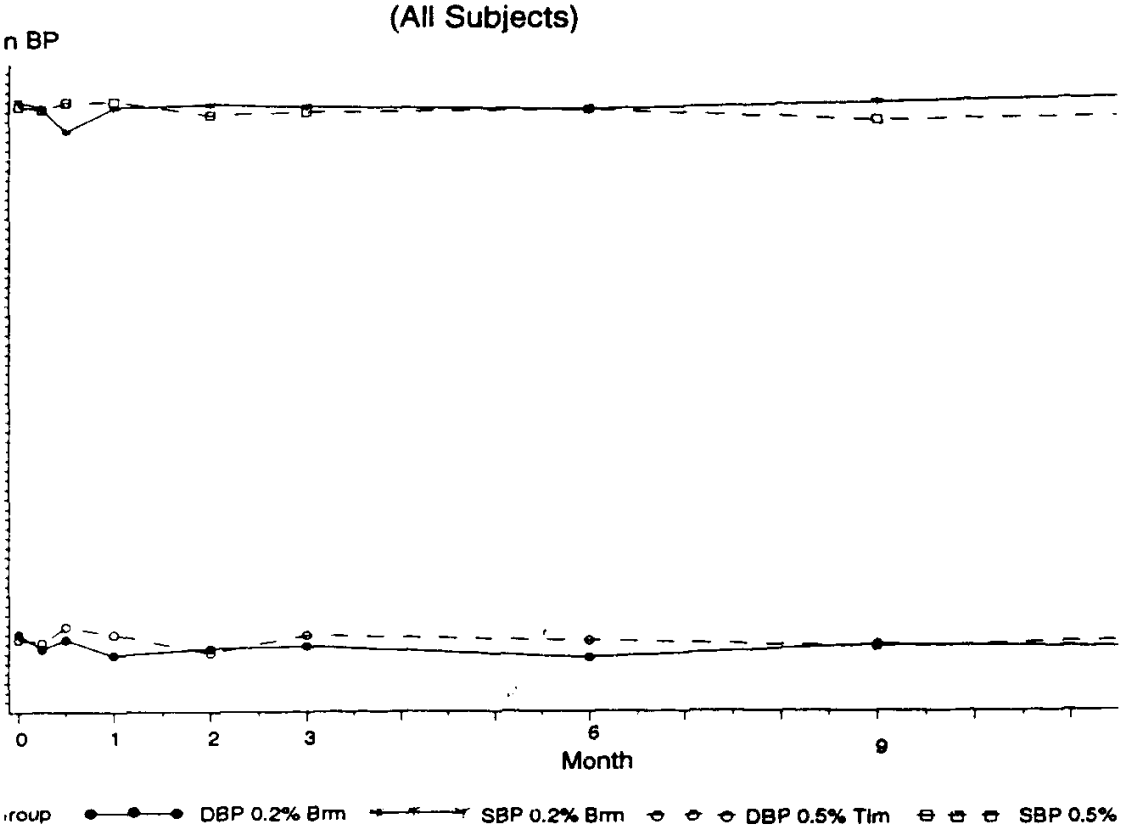
Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	220	222	0.092	0.046
	Mean	73.98	72.85		
	SD	9.20	9.37		
	Min	48.00	48.00		
	Max	98.00	99.00		
Week 1	N	213	218	0.022	0.170
	Mean	-0.28	-1.77		
	SD	8.44	7.50		
	Min	-32.00	-20.00		
	Max	32.00	28.00		
	P-value[b]	0.632	<0.001		
Week 2[c]	N	74	73	0.030	0.344
	Mean	-0.05	-2.97		
	SD	10.05	7.20		
	Min	-30.00	-18.00		
	Max	28.00	28.00		
	P-value[b]	0.963	<0.001		
Month 1	N	200	210	0.005	0.153
	Mean	0.12	-2.06		
	SD	8.79	8.09		
	Min	-32.00	-28.00		
	Max	34.00	20.00		
	P-value[b]	0.853	<0.001		
Month 2	N	182	198	0.004	0.251
	Mean	0.14	-1.89		
	SD	7.24	8.29		
	Min	-18.00	-28.00		
	Max	26.00	24.00		
	P-value[b]	0.791	0.002		
Month 3	N	173	193	0.028	0.731
	Mean	0.12	-1.87		
	SD	8.33	8.17		
	Min	-20.00	-30.00		
	Max	28.00	28.00		
	P-value[b]	0.848	0.002		
Month 6	N	147	184	0.025	0.040
	Mean	-0.59	-2.42		
	SD	8.61	9.03		
	Min	-20.00	-30.00		
	Max	28.00	32.00		
	P-value[b]	0.406	<0.001		
Month 9	N	130	168	0.011	0.041
	Mean	-0.52	-2.57		
	SD	9.96	9.03		
	Min	-26.00	-28.00		
	Max	34.00	24.00		
	P-value[b]	0.550	<0.001		
Month 12	N	119	168	0.009	0.038
	Mean	-0.10	-3.00		
	SD	9.78	10.02		
	Min	-28.00	-33.00		
	Max	26.00	24.00		
	P-value[b]	0.911	<0.001		

Figure 6
Mean Heart Rate (bpm)
(All Subjects)



Reviewer's Comments: *Changes in heart rate with brimonidine treatment were minimal and not clinically significant.*

Figure 7
Mean Blood Pressure (mm Hg)
(All Subjects)



Reviewer's Comments: *No clinically significant differences between both treatment groups.*

Systolic Blood Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit
(All Subjects)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	220	220	0.654	0.240
	Mean	137.07	136.53		
	SD	18.32	17.87		
	Min	100.00	100.00		
	Max	200.00	190.00		
Week 1	N	212	216	0.741	0.241
	Mean	-0.88	-0.59		
	SD	12.80	13.82		
	Min	-48.00	-70.00		
	Max	40.00	40.00		
	P-value[b]	0.319	0.532		
Week 2[c]	N	73	73	0.151	0.210
	Mean	-4.14	0.79		
	SD	14.36	14.08		
	Min	-44.00	-34.00		
	Max	30.00	28.00		
	P-value[b]	0.016	0.631		
Month 1	N	199	207	0.033	0.602
	Mean	-1.61	1.14		
	SD	13.93	14.74		
	Min	-50.00	-40.00		
	Max	55.00	40.00		
	P-value[b]	0.104	0.267		
Month 2	N	182	196	0.808	0.621
	Mean	-0.18	-0.16		
	SD	13.31	14.21		
	Min	-42.00	-40.00		
	Max	43.00	40.00		
	P-value[b]	0.854	0.876		
Month 3	N	173	191	0.548	0.686
	Mean	-0.95	0.19		
	SD	12.69	15.68		
	Min	-40.00	-60.00		
	Max	35.00	46.00		
	P-value[b]	0.327	0.865		
Month 6	N	146	180	0.598	0.163
	Mean	-1.03	0.61		
	SD	15.15	16.81		
	Min	-66.00	-50.00		
	Max	36.00	52.00		
	P-value[b]	0.414	0.629		
Month 9	N	130	169	0.973	0.021
	Mean	-0.35	-0.21		
	SD	14.72	16.28		
	Min	-34.00	-54.00		
	Max	46.00	50.00		
	P-value[b]	0.784	0.869		
Month 12	N	120	166	0.924	0.084
	Mean	0.64	0.46		
	SD	15.88	17.38		
	Min	-44.00	-72.00		
	Max	40.00	42.00		
	P-value[b]	0.659	0.735		

Diastolic Blood Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit
(All Subjects)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	220	220	0.556	0.459
	Mean	82.05	81.47		
	SD	10.12	10.50		
	Min	55.00	50.00		
	Max	130.00	128.00		
Week 1	N	212	216	0.390	0.339
	Mean	-1.73	-0.41		
	SD	8.68	8.71		
	Min	-32.00	-30.00		
	Max	40.00	22.00		
	P-value[b]	0.004	0.493		
Week 2[c]	N	73	73	0.350	0.299
	Mean	-2.23	-0.33		
	SD	8.43	8.65		
	Min	-22.00	-28.00		
	Max	20.00	24.00		
	P-value[b]	0.027	0.746		
Month 1	N	199	207	<0.001	0.714
	Mean	-2.46	0.71		
	SD	9.88	8.77		
	Min	-30.00	-22.00		
	Max	20.00	30.00		
	P-value[b]	<0.001	0.245		
Month 2	N	182	196	0.805	0.691
	Mean	-1.38	-1.15		
	SD	9.57	9.03		
	Min	-34.00	-26.00		
	Max	30.00	24.00		
	P-value[b]	0.054	0.075		
Month 3	N	173	191	0.150	0.519
	Mean	-1.20	0.60		
	SD	8.68	10.98		
	Min	-24.00	-42.00		
	Max	20.00	60.00		
	P-value[b]	0.070	0.449		
Month 6	N	146	180	0.083	0.675
	Mean	-2.23	0.09		
	SD	10.29	10.51		
	Min	-32.00	-32.00		
	Max	25.00	30.00		
	P-value[b]	0.010	0.904		
Month 9	N	130	169	0.790	0.179
	Mean	-0.78	-0.50		
	SD	10.48	10.91		
	Min	-25.00	-30.00		
	Max	34.00	30.00		
	P-value[b]	0.395	0.550		
Month 12	N	120	166	0.345	0.104
	Mean	-0.89	0.40		
	SD	11.09	10.98		
	Min	-30.00	-38.00		
	Max	24.00	30.00		
	P-value[b]	0.380	0.641		

Subjects Treated with Brimonidine
Terminated from the Study Due to Adverse Events
(Incidence Greater than 1%)

Adverse Event	Percent of Subjects	Number of Subjects
Ocular allergic reaction*	7.7%	17/221
Ocular hyperemia	3.1%	7/221
Gastrointestinal symptoms	1.8%	4/221
Dizziness	1.4%	3/221
Ocular irritation	1.4%	3/221
Oral dryness	1.4%	3/221
Somnolence	1.4%	3/221

* Includes subjects with allergic blepharoconjunctivitis, allergic conjunctivitis, and follicular conjunctivitis.

During the treatment period, 14.4% (64/443) of all subjects were terminated from the study because of adverse events. Subjects terminated because of adverse events included 22.6% (50/221) of subjects treated with brimonidine and 6.3% (14/222) treated with timolol. Terminations because of ocular adverse events include 14.5% (32/221) of subjects in the brimonidine group and 1.4% (3/222) of the timolol group. Terminations due to systemic adverse events occurred in 10.0% (22/221) of subjects in the brimonidine group and 5.4% (12/222) of subjects in the timolol group.

ADVERSE EVENTS:

Adverse Events
Number and Percentage of Subjects with at Least One
Severity Grade Increased from Baseline at
One or More Follow-up Visits

(All Subjects)

Finding[a]	0.2% Brm (N=221)	0.5% Tim (N=222)	P-value[b]
Ocular Hyperemia[d]	86 (38.9%)	52 (23.4%)	<0.001
Burning/Stinging	76 (34.4%)	93 (41.9%)	0.104
Oral Dryness	73 (33.0%)	43 (19.4%)	0.001
Blurring	58 (26.2%)	50 (22.5%)	0.362
Fatigue/Drowsiness	44 (19.9%)	38 (17.1%)	0.449
Lens Pathology	43 (19.5%)	50 (22.5%)	0.428
Headache	42 (19.0%)	44 (19.8%)	0.828
Foreign Body Sensation	41 (18.6%)	36 (16.2%)	0.517
Ocular Pruritus	39 (17.6%)	21 (9.5%)	0.012
Fundus Pathology	33 (14.9%)	36 (16.2%)	0.709
Follicles (Conjunctiva)	32 (14.5%)	5 (2.3%)	<0.001
Lid Erythema	32 (14.5%)	16 (7.2%)	0.014
Photophobia	29 (13.1%)	25 (11.3%)	0.549
Lid Edema	28 (12.7%)	7 (3.2%)	<0.001
Lacrimation Disorder	24 (10.9%)	13 (5.9%)	0.057
Conjunctival Edema	24 (10.9%)	13 (5.9%)	0.057
Corneal Staining/Erosion	20 (9.0%)	24 (10.8%)	0.536
Vitreous Pathology	17 (7.7%)	12 (5.4%)	0.331
Ocular Dryness	17 (7.7%)	21 (9.5%)	0.507
Conjunctival Blanching	15 (6.8%)	14 (6.3%)	0.838
Ocular Ache/Pain	14 (6.3%)	11 (5.0%)	0.529
Ocular Irritation	13 (5.9%)	3 (1.4%)	0.011[c]
Allergic Conjunctivitis	13 (5.9%)	0 (0.0%)	<0.001[c]
Ocular Other	13 (5.9%)	9 (4.1%)	N/A
Dizziness	13 (5.9%)	10 (4.5%)	0.513
Upper Respiratory Symptoms	13 (5.9%)	6 (2.7%)	0.099
Lash Debris	12 (5.4%)	10 (4.5%)	0.654
Abnormal Vision	10 (4.5%)	6 (2.7%)	0.304
Gastrointestinal Symptoms	10 (4.5%)	7 (3.2%)	0.452

Crusting (Lid)	9 (4.1%)	8 (3.6%)	0.797
Arcus (Cornea)	9 (4.1%)	3 (1.4%)	0.088[c]
Systemic Other	9 (4.1%)	11 (5.0%)	N/A
Lid Other	8 (3.6%)	10 (4.5%)	N/A
Cornea Other	8 (3.6%)	2 (0.9%)	N/A
Conjunctivitis	7 (3.2%)	1 (0.5%)	0.037[c]
Pinguecula	6 (2.7%)	4 (1.8%)	0.544[c]
Ocular Edema	6 (2.7%)	2 (0.9%)	0.175[c]
Blepharitis	5 (2.3%)	4 (1.8%)	0.751[c]
Hemorrhage (Conjunctiva)	4 (1.8%)	1 (0.5%)	0.216[c]
Discharge (Conjunctiva)	4 (1.8%)	4 (1.8%)	>0.999[c]
Opacity (Cornea)	4 (1.8%)	2 (0.9%)	0.449[c]
Vitreous Floaters	4 (1.8%)	3 (1.4%)	0.724[c]
Muscular Pain	4 (1.8%)	4 (1.8%)	>0.999[c]
Asthenia	4 (1.8%)	2 (0.9%)	0.449[c]
Follicular Conjunctivitis	4 (1.8%)	0 (0.0%)	0.061[c]
Meibomianitis	3 (1.4%)	3 (1.4%)	>0.999[c]
Conjunctiva Other	3 (1.4%)	3 (1.4%)	N/A
Local Iris Atrophy	3 (1.4%)	1 (0.5%)	0.372[c]
Asthenopia (Eyestrain)	3 (1.4%)	5 (2.3%)	0.724[c]
Eyelid Discomfort	3 (1.4%)	2 (0.9%)	0.685[c]
Abnormal Taste	3 (1.4%)	4 (1.8%)	>0.999[c]

Continue...

Chest Pain	3 (1.4%)	2 (0.9%)	0.685[c]
Allergic Blepharoconjunctivitis	3 (1.4%)	0 (0.0%)	0.123[c]
Carcinoma	3 (1.4%)	4 (1.8%)	>0.999[c]
Hypertension	3 (1.4%)	2 (0.9%)	0.685[c]
Corneal Endothel. Changes	3 (1.4%)	6 (2.7%)	0.503[c]
Papillae (Conjunctiva)	1 (0.5%)	6 (2.7%)	0.122[c]
Guttata (Cornea)	1 (0.5%)	3 (1.4%)	0.623[c]
Scar (Cornea)	1 (0.5%)	5 (2.3%)	0.216[c]
Dyspnea	1 (0.5%)	4 (1.8%)	0.372[c]
Influenza	1 (0.5%)	3 (1.4%)	0.623[c]
Cyst (Conjunctiva)	0 (0.0%)	3 (1.4%)	0.248[c]
Tear Film Abnormality	0 (0.0%)	3 (1.4%)	0.248[c]
Depression	0 (0.0%)	3 (1.4%)	0.248[c]
Other[d]	60	53	

[a] Identified from adverse event data, biomicroscopy and pathology data, and/or ocular and systemic symptoms. For a detailed classification, see Appendix D10.
[b] Unless stated otherwise, p-value based on Pearson's Chi-square test.
[c] P-value based on Fisher's exact test.
[d] Findings whose incidence were in less than 1% of the subjects in both treatment groups are grouped together in the 'Other' category. Subjects may report more than one finding in the 'Other' category; thus percentage and p-value are not calculated.

Serious Adverse Events[a]

System	Preferred Term	0.2% Brm (N=221)	0.5% Tim (N=222)
C.N.S.	Cerebrovascular accident	0 (0.00%)	1 (0.45%)
	Dizziness	1 (0.45%)	0 (0.00%)
Cardiovascular	Angina pectoris	1 (0.45%)	1 (0.45%)
	Aortic aneurysm	0 (0.00%)	2 (0.90%)
	Atrial fibrillation	1 (0.45%)	0 (0.00%)
	Bradycardia	1 (0.45%)	0 (0.00%)
	Heart failure	1 (0.45%)	0 (0.00%)
	Hypertension	1 (0.45%)	0 (0.00%)
	Hypotension	1 (0.45%)	0 (0.00%)
	Myocardial infarction	2 (0.90%)	1 (0.45%)
Respiratory	Bronchitis	1 (0.45%)	0 (0.00%)
	Neoplasm benign, lung	1 (0.45%)	0 (0.00%)
Gastrointestinal	Abdominal pain	0 (0.00%)	1 (0.45%)
	Appendicitis	0 (0.00%)	1 (0.45%)
	Neoplasm benign, colon	0 (0.00%)	1 (0.45%)
Genito-Urinary	Kidney failure	0 (0.00%)	1 (0.45%)
	Prostatic disorder	1 (0.45%)	0 (0.00%)
Musculo-Skeletal	Bone fracture, spontaneous	0 (0.00%)	1 (0.45%)
cinoma	Carcinoma, colon	1 (0.45%)	0 (0.00%)
	Carcinoma, gastronitestinal	0 (0.00%)	2 (0.90%)
	Carcinoma, lung	0 (0.00%)	1 (0.45%)
	Carcinoma, mouth	0 (0.00%)	1 (0.45%)
	Carcinoma, prostatic	1 (0.45%)	0 (0.00%)
	Carcinoma, throat	1 (0.45%)	0 (0.00%)
Other	Chest pain	1 (0.45%)	0 (0.00%)
	Death	0 (0.00%)	1 (0.45%)
	Fever	0 (0.00%)	1 (0.45%)
	Hernia	0 (0.00%)	1 (0.45%)

[a] Serious adverse events occured in 5.4% (12/221) of subjects in the 0.2% Brm group and 5.4% (12/222) of subjects in the 0.5% Tim group.

Serious adverse events occurred in 5.4% (12/221) of the subjects treated with brimonidine and 5.4% (12/222) of subjects treated with timolol. None of these events were judged to be treatment associated. Six of the 19 subjects treated with brimonidine and three of the five subjects treated with timolol experiencing serious adverse events were terminated from the study.

2 Pages Purged

Summary and Conclusions:

Brimonidine 0.2% significantly reduced IOP from baseline at every scheduled follow-up visit over the one-year study period when measured at trough and at peak.

2) For the preferred analysis, when IOP was measured at trough, the overall mean decrease from baseline IOP was 4.3 mm Hg.

3) At trough, intraocular pressure reductions with timolol 0.5%, were significantly greater than with brimonidine 0.2% at most scheduled follow-up visits. At peak, decreases with brimonidine were similar to timolol. Similar results were seen in the responder analysis. Adjusting p-values for interim analysis results in only statistically significant differences at week 2.

4) With respect to cup/disc ratio, no significant differences were seen between the brimonidine and timolol treatment groups.

5) Changes in visual field were minimal and clinically insignificant in both groups.

6) Adverse Events:
The most frequently reported ocular adverse events included ocular hyperemia, burning and stinging, blurring, foreign body sensation, ocular pruritus, conjunctival follicles, photophobia, lid edema, ocular allergic reactions, and ocular pruritus.

Non Ocular: The most frequently reported non ocular adverse events were oral dryness, headache, fatigue/drowsiness, upper respiratory symptoms, dizziness, and gastrointestinal symptoms.

7) Ocular Safety

Visual acuity remained unchanged in the majority of the subjects.
Mean pupil size was numerically smaller in the brimonidine group.

Study #2
Study Protocol: A342-104-7831

The long-term safety and ocular hypotensive efficacy of brimonidine tartrate 0.2% in subjects with open-angle glaucoma or ocular hypertension

Demographics

(All Subjects)

Variable		0.2% Brm	0.5% Tim	All	P-value
Age (Years)	N	292	191	483	0.257
	Mean	62.7	61.4	62.2	
	SD	11.1	11.0	11.1	
	Min	28.5	32.8	28.5	
	Max	86.4	83.0	86.4	
	<45	21 (7.2%)	17 (8.9%)	38(7.9%)	
	45-65	134 (45.9%)	91 (47.6%)	225(46.6%)	
	>65	137 (46.9%)	83 (43.5%)	220(45.5%)	
Sex	Male	145 (49.7%)	101 (52.9%)	246(50.9%)	0.471
	Female	147 (50.3%)	90 (47.1%)	237(49.1%)	
Race	Caucasian	242 (82.9%)	162 (84.8%)	404(83.6%)	0.499
	Hispanic	8 (2.7%)	9 (4.7%)	17(3.5%)	
	Black	32 (11.0%)	16 (8.4%)	48(9.9%)	
	Asian	6 (2.1%)	1 (0.5%)	7(1.4%)	
	Other[b]	4 (1.4%)	3 (1.6%)	7(1.4%)	
is Color	Blue	99 (33.9%)	63 (33.0%)	162(33.5%)	0.728
	Green	15 (5.1%)	11 (5.8%)	26(5.4%)	
	Hazel	64 (21.9%)	44 (23.0%)	108(22.4%)	
	Brown	111 (38.0%)	70 (36.6%)	181(37.5%)	
	Other[c]	3 (1.0%)	3 (1.6%)	6(1.2%)	
Diagnosis	OAG	164 (56.2%)	103 (53.9%)	267(55.3%)	0.707
	OHT	115 (39.4%)	81 (42.4%)	196(40.6%)	
	OAG/OHT[d]	13 (4.5%)	7 (3.7%)	20(4.1%)	

[b] Other: Arabic, Yamanit, Irakian and Angloasian.
[c] Other: gray, blue-gray, blue-green, mixed.
[d] One eye with OAG and the fellow eye with OHT.

Reviewer's Comments: *There was no significant difference between the two treatment groups in age, sex, race, iris color, or diagnosis distribution.*

Demographics

(Preferred Analysis)

Variable		0.2% Brm	0.5% Tim	All	P-value
Age (Years)	N	280	183	463	0.216
	Mean	62.9	61.4	62.3	
	SD	11.0	11.2	11.1	
	Min	28.5	32.8	28.5	
	Max	86.4	83.0	86.4	
	<45	19 (6.8%)	17 (9.3%)	36(7.8%)	
	45-65	128 (45.7%)	85 (46.4%)	213(46.0%)	
	>65	133 (47.5%)	81 (44.3%)	214(46.2%)	
Sex	Male	138 (49.3%)	96 (52.5%)	234(50.5%)	0.468
	Female	142 (50.7%)	87 (47.5%)	229(49.5%)	
Race	Caucasian	231 (82.5%)	155 (84.7%)	386(83.4%)	0.432
	Hispanic	8 (2.9%)	9 (4.9%)	17(3.7%)	
	Black	32 (11.4%)	15 (8.2%)	47(10.2%)	
	Asian	6 (2.1%)	1 (0.5%)	7(1.5%)	
	Other[b]	3 (1.1%)	3 (1.6%)	6(1.3%)	
Iris Color	Blue	94 (33.6%)	60 (32.8%)	154(33.3%)	0.811
	Green	13 (4.6%)	10 (5.5%)	23(5.0%)	
	Hazel	64 (22.9%)	42 (23.0%)	106(22.9%)	
	Brown	106 (37.9%)	68 (37.2%)	174(37.6%)	
	Other[c]	3 (1.1%)	3 (1.6%)	6(1.3%)	
Diagnosis	OAG	157 (56.1%)	98 (53.6%)	255(55.1%)	0.799
	OHT	112 (40.0%)	78 (42.6%)	190(41.0%)	
	OAG/OHT[d]	11 (3.9%)	7 (3.8%)	18(3.9%)	

[b] Other: Arabic, Yamanit, Irakian and Angloasian.
[c] Other: gray, blue-gray, blue-green, mixed.
[d] One eye with OAG and the fellow eye with OHT.

Investigators

Name and Address	Allergan Identification Number	0.2% Brm	0.5% Tim.	Total
Mark B. Abelson, MD Ophthalmic Research Assoc. 863 Turnpike Street, Suite 224 North Andover, MA 01845	1584	3	2	5
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ıomas K. Mundorf, MD .resbyterian Medical Tower 1718 East Fourth St., Suite 902 Charlotte, NJ 28204	1485	18	10	28
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Summary of Subject Enrollment and Exit Status

(All Subjects)

Exit Status[a]	0.2% Brm	0.5% Tim	Total
Included in Preferred Analysis[b]			
Enrolled	280	183	463
Completed	209 (74.6%)	165 (90.2%)	374
Terminated - LOE	23 (8.2%)	6 (3.3%)	29
Terminated - AE(Ocular)	26 (9.3%)	1 (0.5%)	27
Terminated - AE(Systemic)	14 (5.0%)	3 (1.6%)	17
Discontinued	10 (3.6%)	8 (4.4%)	18
Excluded from Preferred Analysis			
Enrolled	12	8	20
Completed	1 (8.3%)	2 (25.0%)	3
Terminated - LOE	1 (8.3%)	0 (0.0%)	1
Terminated - AE(Ocular)	1 (8.3%)	0 (0.0%)	1
Discontinued	9 (75.0%)	6 (75.0%)	15
All Subjects			
Enrolled	292	191	483
Completed	210 (71.9%)	167 (87.4%)	377
Terminated - LOE	24 (8.2%)	6 (3.1%)	30
Terminated - AE(Ocular)	27 (9.2%)	1 (0.5%)	28
Terminated - AE(Systemic)	14 (4.8%)	3 (1.6%)	17
Discontinued	19 (6.5%)	14 (7.3%)	33

[a] LOE=lack of efficacy. AE=adverse event.
[b] One subject (0.2% Brm) was terminated due to both an ocular and systemic AE. Another subject (0.2% Brm) was terminated due to LOE and an ocular AE. The percentage was calculated using the actual sample size as the denominator, and did not add up to 100%.

Reviewer's Comments: *Significantly smaller percent of subjects in the brimonidine group completed the study and significantly more subjects were terminated due to lack of effect and ocular adverse events as compared to the timolol group.*

EFFICACY RESULTS:

Intraocular Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit
Study: A342-104
(Hour 0 - Preferred Analysis)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	274	180	0.273	0.178
	Mean	25.96	25.85		
	SD	3.01	2.80		
	Min	22.50	23.00		
	Max	34.50	34.00		
Week 1	N	265	174	<0.001	0.643
	Mean	-4.78	-6.44		
	SD	2.96	3.02		
	Min	-16.50	-17.00		
	Max	4.50	0.50		
	P-value[b]	<0.001	<0.001		
Week 2	N	254	164	<0.001	0.739
	Mean	-4.59	-6.18		
	SD	2.98	3.12		
	Min	-16.00	-15.00		
	Max	4.00	2.50		
	P-value[b]	<0.001	<0.001		
Month 1	N	250	171	<0.001	0.491
	Mean	-3.98	-6.16		
	SD	2.84	3.18		
	Min	-11.50	-14.00		
	Max	8.00	1.50		
	P-value[b]	<0.001	<0.001		
Month 2	N	239	165	<0.001	0.898
	Mean	-4.18	-6.42		
	SD	3.07	3.04		
	Min	-13.50	-14.50		
	Max	3.00	2.50		
	P-value[b]	<0.001	<0.001		
Month 3	N	230	163	<0.001	0.271
	Mean	-4.04	-6.20		
	SD	3.15	2.97		
	Min	-13.50	-14.50		
	Max	5.00	2.50		
	P-value[b]	<0.001	<0.001		
Month 6	N	198	159	<0.001	0.322
	Mean	-3.79	-6.10		
	SD	3.37	3.12		
	Min	-12.50	-15.00		
	Max	7.00	2.50		
	P-value[b]	<0.001	<0.001		

[a] P-value based on the two-way analysis of variance.
Treatment = between-group comparison.
Interaction = treatment-by-investigator interaction.
[b] Within-group analysis of changes from baseline using paired t-test.

ewer's Comments: *IOP at Trough: Mean decreases in IOP ranged from 3.8 to 4.8 . g in the brimonidine group and from 6.1 to 6.4 mmHg in the timolol. Mean decreases from basline were statisticlly significant in both groups at all follow up visits. Timolol was statistically superior at all follow up visits.*

Intraocular Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit
Study: A342-104

(Hour 0 - Responder Analysis[a])

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[b] Treatment	Interaction
Baseline	N	180	154	0.456	0.191
	Mean	26.11	26.10		
	SD	3.03	2.89		
	Min	22.50	23.00		
	Max	34.50	34.00		
Week 1	N	174	148	0.029	0.181
	Mean	-5.92	-6.84		
	SD	2.37	2.81		
	Min	-16.50	-17.00		
	Max	0.50	-1.50		
	P-value[c]	<0.001	<0.001		
Week 2	N	175	147	0.007	0.777
	Mean	-5.90	-6.76		
	SD	2.30	2.66		
	Min	-16.00	-15.00		
	Max	-3.00	-3.00		
	P-value[c]	<0.001	<0.001		
Month 1	N	170	148	<0.001	0.647
	Mean	-4.91	-6.50		
	SD	2.56	3.07		
	Min	-11.50	-14.00		
	Max	2.00	1.00		
	P-value[c]	<0.001	<0.001		
Month 2	N	166	144	<0.001	0.931
	Mean	-5.12	-6.59		
	SD	2.71	3.00		
	Min	-13.50	-14.50		
	Max	1.50	2.50		
	P-value[c]	<0.001	<0.001		
Month 3	N	157	143	<0.001	0.188
	Mean	-4.91	-6.46		
	SD	2.88	2.86		
	Min	-13.50	-14.50		
	Max	2.50	-0.50		
	P-value[c]	<0.001	<0.001		
Month 6	N	139	139	<0.001	0.196
	Mean	-4.44	-6.52		
	SD	3.09	2.87		
	Min	-12.50	-15.00		
	Max	5.00	0.00		
	P-value[c]	<0.001	<0.001		
Overall[d]		-5.14	-6.52	0.957	0.421

[a] Responders = Subjects in the preferred analysis with an IOP reduction of at least 3 mm Hg from baseline at two consecutive visits within the first month of treatment.
[b] P-value based on the two-way analysis of variance.
Treatment = between-group comparison.
Interaction = treatment-by-investigator interaction.
[c] Within-group analysis of changes from baseline using paired t-test.

Intraocular Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit
Study: A342-104

(Hour 2 - Preferred Analysis)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	260	178	0.322	0.971
	Mean	24.75	24.41		
	SD	3.59	3.40		
	Min	15.00	11.00		
	Max	36.00	33.50		
Week 1	N	252	174	0.004	0.818
	Mean	-7.34	-6.31		
	SD	3.71	3.80		
	Min	-19.50	-19.50		
	Max	3.50	7.50		
	P-value[b]	<0.001	<0.001		
Week 2	N	244	162	0.007	0.898
	Mean	-6.97	-6.13		
	SD	3.59	3.53		
	Min	-18.50	-17.00		
	Max	2.00	6.00		
	P-value[b]	<0.001	<0.001		
Month 1	N	236	166	0.101	0.523
	Mean	-6.56	-6.03		
	SD	3.56	3.75		
	Min	-18.50	-16.00		
	Max	2.50	6.50		
	P-value[b]	<0.001	<0.001		
Month 3	N	216	162	0.194	0.801
	Mean	-6.51	-6.07		
	SD	3.71	3.69		
	Min	-21.00	-15.50		
	Max	3.00	5.50		
	P-value[b]	<0.001	<0.001		
Month 6	N	192	156	0.237	0.335
	Mean	-6.15	-5.42		
	SD	3.99	3.77		
	Min	-17.50	-16.00		
	Max	6.00	5.50		
	P-value[b]	<0.001	<0.001		

[a] P-value based on the two-way analysis of variance.
Treatment = between-group comparison.
Interaction = treatment-by-investigator interaction.
[b] Within-group analysis of changes from baseline using paired t-test.

Reviewer's Comments: *IOP at Peak: Mean decreases in IOP ranged from 6.2 to 7.3 mmHg in the brimonidine group and from 5.4 to 6.3 mmHg in the timolol group. Mean decreases from basline were statisticlly significant in both groups at all follow up pts. At weeks 1 and 2 , brimonidine treatment resulted in statistically significant greater decreases in IOP compared to timolol. At months 1, 3, and 6, brimonidine was equivalent to timolol in decreasing IOP.*

Intraocular Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit
Study: A342-104

(Hour 2 - Responder Analysis[a])

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[b] Treatment	Interaction
Baseline	N	170	152	0.446	0.877
	Mean	24.78	24.44		
	SD	3.74	3.55		
	Min	15.00	11.00		
	Max	36.00	33.50		
Week 1	N	167	150	<0.001	0.960
	Mean	-8.00	-6.45		
	SD	3.61	3.90		
	Min	-19.50	-19.50		
	Max	3.50	7.50		
	P-value[c]	<0.001	<0.001		
Week 2	N	166	145	0.001	0.926
	Mean	-7.63	-6.29		
	SD	3.64	3.62		
	Min	-18.50	-17.00		
	Max	2.00	6.00		
	P-value[c]	<0.001	<0.001		
Month 1	N	161	144	0.008	0.432
	Mean	-7.25	-6.06		
	SD	3.62	3.87		
	Min	-18.50	-16.00		
	Max	2.50	6.50		
	P-value[c]	<0.001	<0.001		
Month 3	N	147	142	0.010	0.775
	Mean	-7.30	-6.09		
	SD	3.70	3.77		
	Min	-21.00	-15.50		
	Max	1.50	5.50		
	P-value[c]	<0.001	<0.001		
Month 6	N	134	136	0.179	0.661
	Mean	-6.56	-5.44		
	SD	3.94	3.80		
	Min	-17.50	-16.00		
	Max	6.00	5.50		
	P-value[c]	<0.001	<0.001		

[a] Responders = Subjects in the preferred analysis with an IOP reduction of at least 3 mm Hg from baseline at two consecutive visits within the first month of treatment.
[b] P-value based on the two-way analysis of variance.
Treatment = between-group comparison.
Interaction = treatment-by-investigator interaction.
[c] Within-group analysis of changes from baseline using paired t-test.

Intraocular Pressure (mm Hg)
95% Confidence Interval of Between-Group Difference
in Mean Changes from Baseline

(Hour 0 - Preferred Analysis)

Timepoint	Estimate of Difference[a]	Std Error of Estimate	95% CI of Estimate
Baseline	0.33	0.303	(-0.26, 0.93)
Week 1	1.56	0.311	(0.95, 2.17)
Week 2	1.55	0.330	(0.91, 2.20)
Month 1	2.09	0.311	(1.48, 2.70)
Month 2	2.17	0.334	(1.51, 2.82)
Month 3	2.08	0.332	(1.42, 2.73)
Month 6	2.26	0.367	(1.54, 2.99)

[a] Estimate was computed for the difference of mean baseline and mean changes from baseline at each scheduled follow-up visit based on the least-squares means by 0.2% Brm group minus 0.5% Tim group.

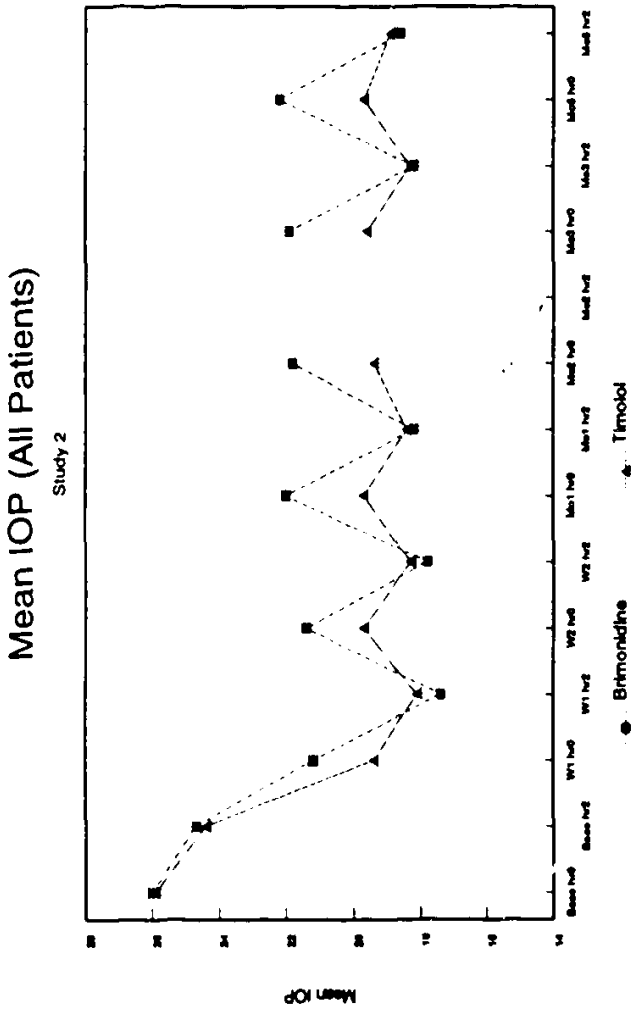
Intraocular Pressure (mm Hg)
95% Confidence Interval of Between-Group Difference
in Mean Changes from Baseline

(Hour 0 - Responder Analysis[a])

Timepoint	Estimate of Difference[b]	Std Error of Estimate	95% CI of Estimate
Baseline	0.26	0.355	(-0.43, 0.96)
Week 1	0.68	0.311	(0.07, 1.29)
Week 2	0.83	0.304	(0.23, 1.43)
Month 1	1.50	0.347	(0.82, 2.18)
Month 2	1.34	0.359	(0.63, 2.04)
Month 3	1.36	0.361	(0.65, 2.07)
Month 6	2.05	0.390	(1.28, 2.82)

[a] Responders = Subjects in the preferred analysis with an IOP reduction of at least 3 mm Hg from baseline at two consecutive visits within the first month of treatment.
[b] Estimate was computed for the difference of mean baseline and mean changes from baseline at each scheduled follow-up visit based on the least-squares means by 0.2% Brm group minus 0.5% Tim group.

6.



Mean IOP (RESPONDERS)
Study 2
Mean IOP
Brimonidine
Timolol

Intraocular Pressure (mm Hg)
Number and Percentage of Subjects in Each Change Interval

(Hour 0 - Preferred Analysis)

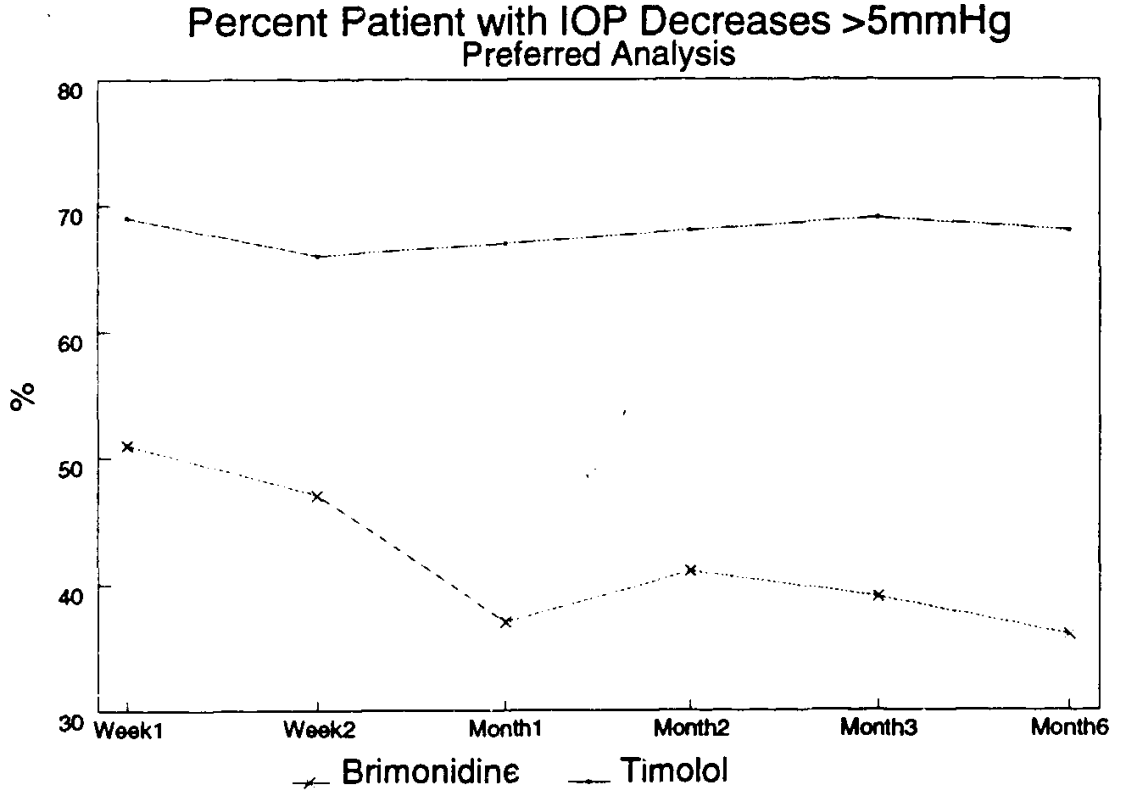
Timepoint	Changes (mm Hg)	0.2% Brm	0.5% Tim
Week 1	<= -5	135 (50.9%)	120 (69.0%)
	> -5 to <= -4	33 (12.5%)	28 (16.1%)
	> -4 to <= -3	40 (15.1%)	11 (6.3%)
	> -3	57 (21.5%)	15 (8.6%)
	Total (N)	265	174
Week 2	<= -5	120 (47.2%)	109 (66.5%)
	> -5 to <= -4	35 (13.8%)	29 (17.7%)
	> -4 to <= -3	33 (13.0%)	11 (6.7%)
	> -3	66 (26.0%)	15 (9.1%)
	Total (N)	254	164
Month 1	<= -5	92 (36.8%)	116 (67.8%)
	> -5 to <= -4	35 (14.0%)	18 (10.5%)
	> -4 to <= -3	40 (16.0%)	15 (8.8%)
	> -3	83 (33.2%)	22 (12.9%)
	Total (N)	250	171
Month 2	<= -5	98 (41.0%)	112 (67.9%)
	> -5 to <= -4	35 (14.6%)	22 (13.3%)
	> -4 to <= -3	30 (12.6%)	13 (7.9%)
	> -3	76 (31.8%)	18 (10.9%)
	Total (N)	239	165
Month 3	<= -5	90 (39.1%)	112 (68.7%)
	> -5 to <= -4	38 (16.5%)	18 (11.0%)
	> -4 to <= -3	28 (12.2%)	14 (8.6%)
	> -3	74 (32.2%)	19 (11.7%)
	Total (N)	230	163
Month 6	<= -5	72 (36.4%)	106 (66.7%)
	> -5 to <= -4	29 (14.6%)	18 (11.3%)
	> -4 to <= -3	27 (13.6%)	13 (8.2%)
	> -3	70 (35.4%)	22 (13.8%)
	Total (N)	198	159

Intraocular Pressure (mm Hg)
Number and Percentage of Subjects in Each Change Interval

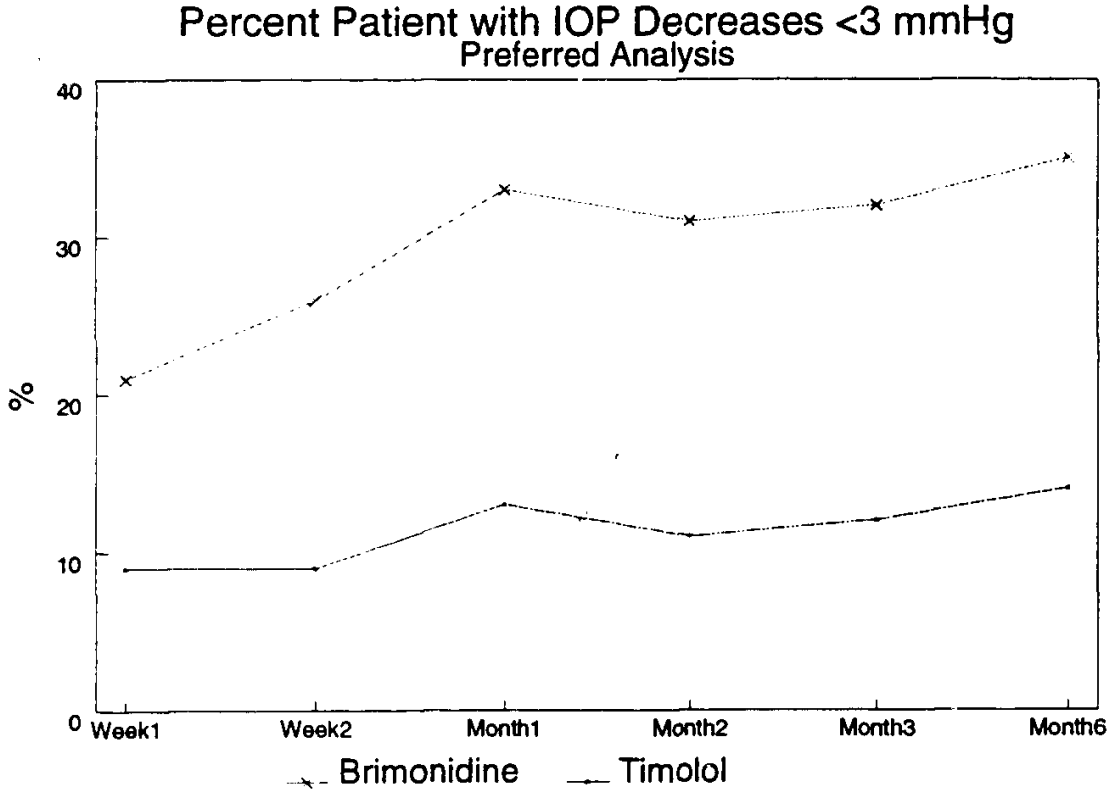
(Hour 0 - Responder Analysis[a])

Timepoint	Changes (mm Hg)	0.2% Brm	0.5% Tim
Week 1	<= -5	118 (67.8%)	109 (73.6%)
	> -5 to <= -4	23 (13.2%)	25 (16.9%)
	> -4 to <= -3	23 (13.2%)	9 (6.1%)
	> -3	10 (5.7%)	5 (3.4%)
	Total (N)	174	148
Week 2	<= -5	113 (64.6%)	108 (73.5%)
	> -5 to <= -4	33 (18.9%)	28 (19.0%)
	> -4 to <= -3	29 (16.6%)	11 (7.5%)
	> -3	0 (0.0%)	0 (0.0%)
	Total (N)	175	147
Month 1	<= -5	84 (49.4%)	104 (70.3%)
	> -5 to <= -4	26 (15.3%)	17 (11.5%)
	> -4 to <= -3	30 (17.6%)	13 (8.8%)
	> -3	30 (17.6%)	14 (9.5%)
	Total (N)	170	148
Month 2	<= -5	89 (53.6%)	100 (69.4%)
	> -5 to <= -4	26 (15.7%)	21 (14.6%)
	> -4 to <= -3	24 (14.5%)	8 (5.6%)
	> -3	27 (16.3%)	15 (10.4%)
	Total (N)	166	144
Month 3	<= -5	76 (48.4%)	102 (71.3%)
	> -5 to <= -4	29 (18.5%)	15 (10.5%)
	> -4 to <= -3	20 (12.7%)	13 (9.1%)
	> -3	32 (20.4%)	13 (9.1%)
	Total (N)	157	143
Month 6	<= -5	60 (43.2%)	100 (71.9%)
	> -5 to <= -4	22 (15.8%)	15 (10.8%)
	> -4 to <= -3	19 (13.7%)	12 (8.6%)
	> -3	38 (27.3%)	12 (8.6%)
	Total (N)	139	139

[a] Responders = Subjects in the preferred analysis with an IOP reduction of at least 3 mm Hg from baseline at two consecutive visits within the first month of treatment.



Reviewer's Comments: *Similar to study #1 there appear to be a decrease in efficacy with time.*


Percent Patient with IOP Decreases <3 mmHg
Preferred Analysis
40
30
20
10
0
%
Week1
Week2
Month1
Month2
Month3
Month6
Brimonidine
Timolol

Safety Parameters:

Cup/Disc Ratio
Baseline and Mean Changes from Baseline at Each Scheduled Visit

(Preferred Analysis)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value Treatment	ANOVA P-value Interaction
Baseline	N	279	183	0.827	0.831
	Mean	0.43	0.42		
	SD	0.17	0.17		
	Min	0.00	0.00		
	Max	0.85	0.75		
Month 6	N	210	160	0.697	0.516
	Mean	-0.00	-0.00		
	SD	0.05	0.05		
	Min	-0.40	-0.20		
	Max	0.10	0.30		
	P-value	0.145	0.851		

Cup-Disc Ratio
Compared to Baseline at Subject's Final Evaluation

(Number of Subjects - Preferred Analysis)

Change from Baseline[a]	0.2% Brm (N=280)	0.5% Tim (N=183)
<=-0.2	3 (1.1%)	1 (0.5%)
>=+0.2	0 (0.0%)	2 (1.1%)

[a] Subjects with the changes of at least 0.2 in one eye or both eyes. No subject had significantly increased in cup-disc ratio in one eye and decreased in the fellow eye.

Reviewer's Comments: *No significant differences were seen between the brimonidine and timolol treatment groups in mean changes from baseline values over the six-month study period. The percentage of subjects with increases or decreases ≥ 0.2 was similar in each of the treatment groups (approximately 1%).*

Visual Fields: Mean Defects (Db)
Analysis of Changes from Baseline

(Preferred Analysis)

Variable	0.2% Brm	0.5% Tim	P-value
Visual Field Change			
N	217	161	
Mean	-0.4	-0.7	0.253
SD	2.4	2.5	
Min	-10.0	-8.7	
Max	9.0	10.1	
Change Interval			
<= -5	9 (4.1%)	7 (4.3%)	
> -5 to <= 5	203 (93.5%)	150 (93.2%)	0.993
> 5	5 (2.3%)	4 (2.5%)	

Reviewer's Comments: *Changes in visual fields were minimal and clinically insignificant in both groups.*

Schirmer Tear Test (mm)
Baseline and Mean Changes from Baseline at Each Scheduled Visit
(All Subjects)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	284	189	0.440	0.943
	Mean	13.46	13.04		
	SD	7.20	7.20		
	Min	3.00	4.00		
	Max	41.25	35.00		
Month 6	N	203	160	0.227	0.203
	Mean	-0.99	0.05		
	SD	7.36	6.76		
	Min	-31.50	-20.50		
	Max	24.00	36.50		
	P-value[b]	0.057	0.919		

Schirmer Test (mm)
Number and Percentage of Subjects with A Clinically Significant[a]
Decrease from Baseline at One or More Follow-up Visits

(All Subjects)

Variable	0.2% Brm (N=284) [b]	0.5% Tim (N=189) [b]	P-value[c]
Schirmer Test	51 (18.0%)	32 (16.9%)	0.774

[a] Schirmer test results: (1) baseline < 10 mm and follow-up below 5 mm, or (2) baseline >= 10 mm, follow-up below 10 mm and a decrease from baseline of more than 5 mm.
[b] Sample size of the treatment group.
[c] P-value based on Pearson's Chi-square test.

Reviewer's Comments: *Changes in Shirmer test were minimal and clinically insignificant in both groups.*

Visual Acuity
Compared to Baseline at Subject's Final Evaluation

(All Subjects)

Changes[a]	0.2% Brm	0.5% Tim	P-value[b]
Worse	11 (3.8%)	7 (3.7%)	0.900
No Change	280 (95.9%)	184 (96.3%)	
Better	1 (0.3%)	0 (0.0%)	
Total	292	191	

[a] Worse = decrease of 2 lines or more
No Change = change between -2 to +2 lines
Better = increase of 2 lines or more
[b] P-value based on Wilcoxon rank-sum test using CMH methods with

Reviewer's Comments: *Changes in Visual acuity were minimal and clinically insignificant in both groups.*

Pupil Size (mm)
Baseline and Mean Changes from Baseline at Each Scheduled Visit

(All Subjects)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	292	191	0.857	0.471
	Mean	3.38	3.39		
	SD	0.81	0.80		
	Min	1.25	1.00		
	Max	7.50	6.00		
Week 1	N	289	189	0.040	0.556
	Mean	-0.12	-0.00		
	SD	0.65	0.56		
	Min	-4.50	-2.50		
	Max	2.00	1.50		
	P-value[b]	0.002	0.992		
Week 2[c]	N	278	180	0.097	0.290
	Mean	-0.06	0.01		
	SD	0.69	0.64		
	Min	-4.50	-2.50		
	Max	2.50	2.00		
	P-value[b]	0.141	0.807		
Month 1	N	274	184	0.154	0.100
	Mean	-0.01	0.03		
	SD	0.64	0.70		
	Min	-4.50	-2.00		
	Max	2.00	2.00		
	P-value[b]	0.851	0.554		
Month 2	N	263	183	0.082	0.285
	Mean	-0.08	0.02		
	SD	0.64	0.73		
	Min	-4.00	-2.50		
	Max	2.00	3.00		
	P-value[b]	0.055	0.700		
Month 3	N	246	172	0.375	0.042
	Mean	-0.01	-0.01		
	SD	0.67	0.72		
	Min	-4.50	-2.50		
	Max	2.25	3.00		
	P-value[b]	0.760	0.824		
Month 6	N	220	169	0.281	0.524
	Mean	-0.04	0.02		
	SD	0.70	0.73		
	Min	-4.00	-2.00		
	Max	2.00	3.25		
	P-value[b]	0.403	0.744		

[a] P-value based on the two-way analysis of variance.
Treatment = between-group comparison.
Interaction = treatment-by-investigator interaction.
[b] Within-group analysis of changes from baseline using paired t-test.

Reviewer's Comments: *There is a small decrease in pupil size in the brimonidine group.*

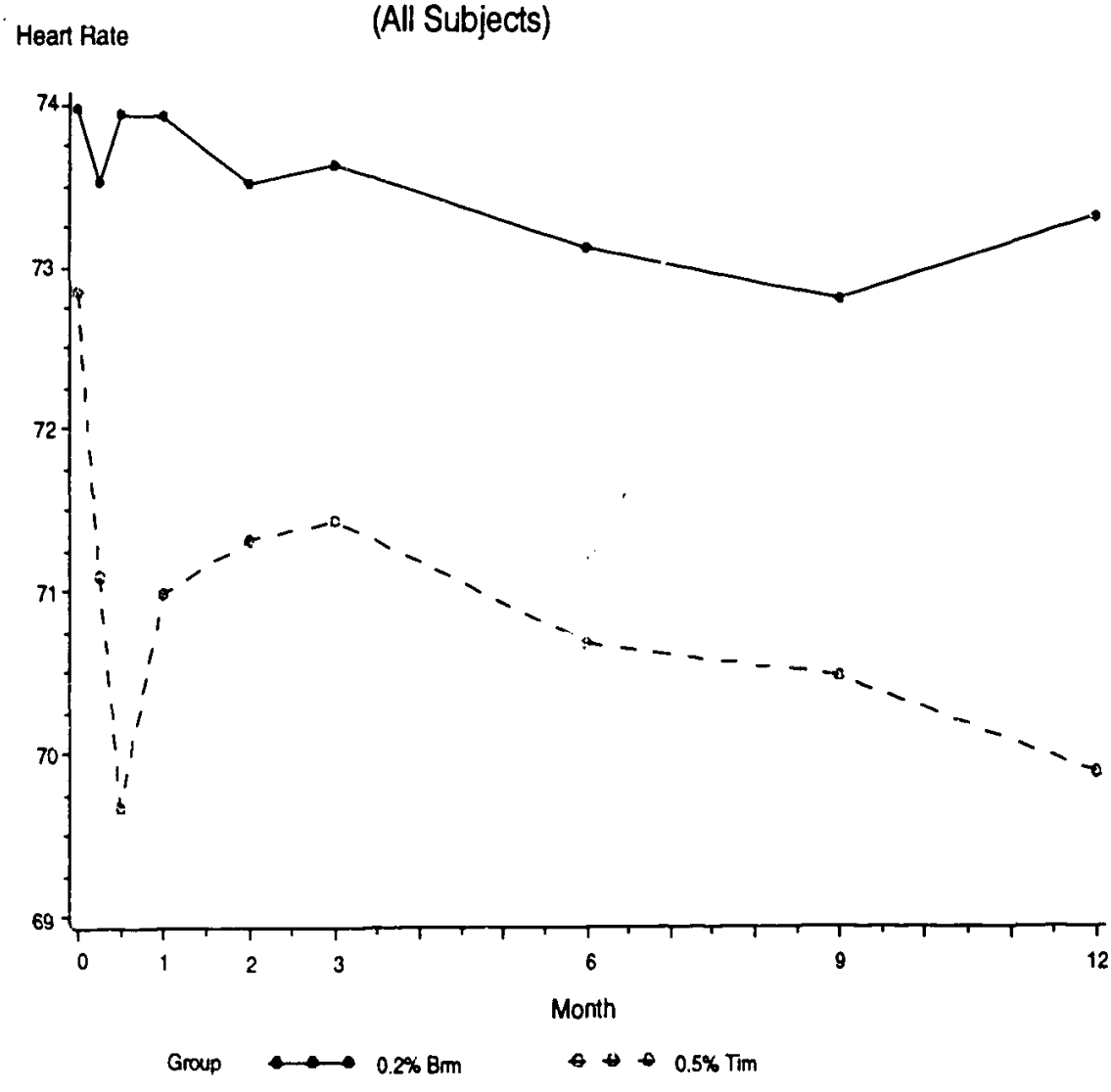
Heart Rate (bpm)
Baseline and Mean Changes from Baseline at Each Scheduled Visit

(All Subjects)

Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value[a] Treatment	Interaction
Baseline	N	292	191	0.276	0.866
	Mean	72.92	72.25		
	SD	9.39	9.98		
	Min	44.00	48.00		
	Max	110.00	100.00		
Week 1	N	287	189	0.059	0.045
	Mean	-0.71	-2.01		
	SD	7.77	8.89		
	Min	-28.00	-24.00		
	Max	30.00	28.00		
	P-value[b]	0.124	0.002		
Week 2	N	[illegible]	180	0.613	0.512
	Mean	-0.87	-1.50		
	SD	9.06	9.55		
	Min	-42.00	-24.00		
	Max	32.00	44.00		
	P-value[b]	0.109	0.036		
Month 1	N	272	183	0.301	0.774
	Mean	-0.64	-1.77		
	SD	9.53	8.57		
	Min	-42.00	-26.00		
	Max	26.00	26.00		
	P-value[b]	0.266	0.006		
Month 2	N	259	182	0.248	0.856
	Mean	-0.51	-1.70		
	SD	10.01	9.66		
	Min	-38.00	-34.00		
	Max	36.00	42.00		
	P-value[b]	0.413	0.018		
Month 3	N	245	172	0.041	0.693
	Mean	-0.20	-2.16		
	SD	9.99	9.13		
	Min	-38.00	-38.00		
	Max	52.00	28.00		
	P-value[b]	0.754	0.002		
Month 6	N	218	167	0.067	0.510
	Mean	-0.30	-2.99		
	SD	9.72	9.64		
	Min	-28.00	-38.00		
	Max	32.00	40.00		
	P-value[b]	0.646	<0.001		

[a] P-value based on the two-way analysis of variance.
Treatment = between-group comparison.
Interaction = treatment-by-investigator interaction.
[b] Within-group analysis of changes from baseline using paired t-test.

Figure 6
Mean Heart Rate (bpm)
(All Subjects)



Reviewer's Comments: *Changes in heart rate with brimonidine treatment were minimal and not clinically significant.*

Systolic Blood Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit

(All Subjects)

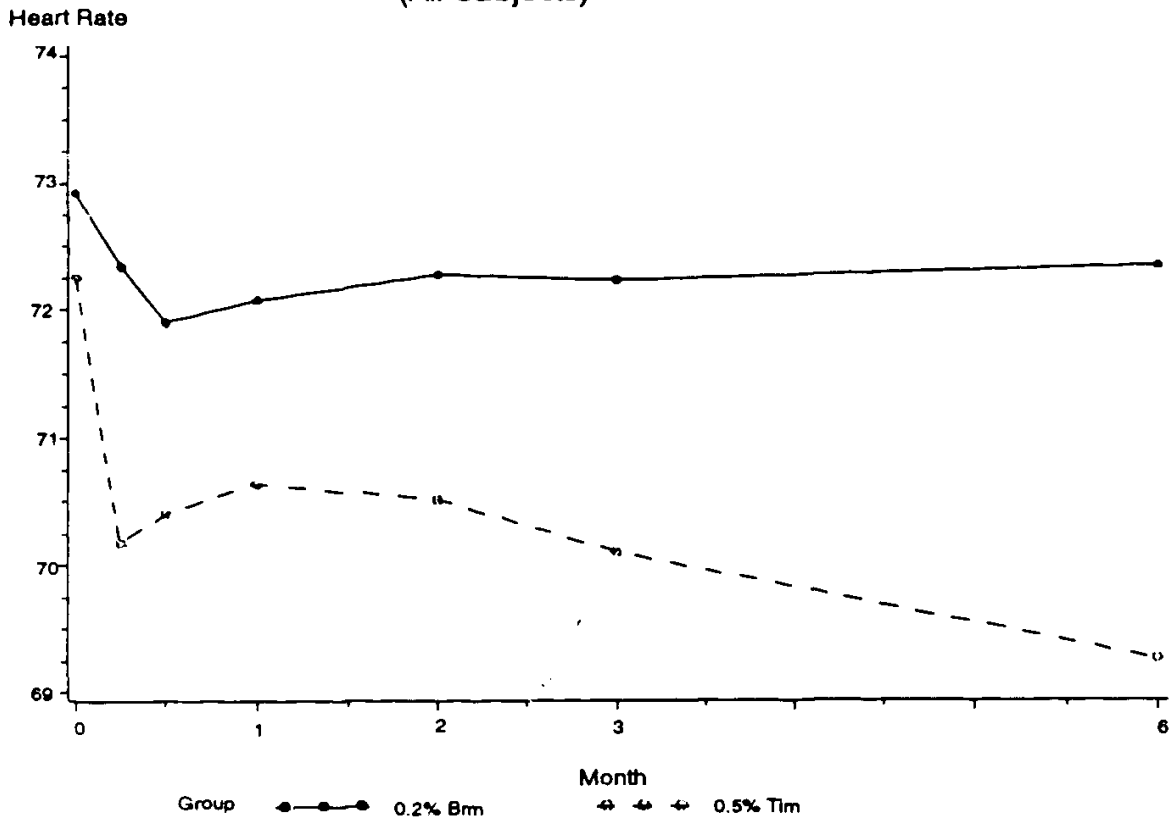
Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value Treatment	ANOVA P-value Interaction
Baseline	N	291	190	0.318	0.5
	Mean	136.93	135.81		
	SD	17.97	17.68		
	Min	90.00	98.00		
	Max	180.00	200.00		
Week 1	N	285	188	0.130	0.463
	Mean	-2.44	-0.95		
	SD	13.97	13.59		
	Min	-52.00	-34.00		
	Max	38.00	40.00		
	P-value	0.004	0.341		
Week 2	N	277	179	0.610	0.841
	Mean	-1.78	-2.94		
	SD	14.39	15.61		
	Min	-48.00	-52.00		
	Max	55.00	70.00		
	P-value	0.040	0.012		
Month 1	N	270	183	0.406	0.925
	Mean	-0.99	-2.63		
	SD	16.12	14.88		
	Min	-40.00	-42.00		
	Max	50.00	50.00		
	P-value	0.316	0.018		
Month 2	N	259	180	0.963	0.579
	Mean	-0.53	-1.37		
	SD	17.05	17.75		
	Min	-54.00	-40.00		
	Max	50.00	70.00		
	P-value	0.621	0.303		
Month 3	N	244	171	0.679	0.087
	Mean	-2.44	-2.64		
	SD	15.48	16.76		
	Min	-50.00	-53.00		
	Max	40.00	60.00		
	P-value	0.014	0.041		
Month 6	N	216	167	0.502	0.694
	Mean	-1.60	-1.44		
	SD	17.76	16.33		
	Min	-46.00	-42.00		
	Max	52.00	60.00		
	P-value	0.186	0.257		

Diastolic Blood Pressure (mm Hg)
Baseline and Mean Changes from Baseline at Each Scheduled Visit

(All Subjects)

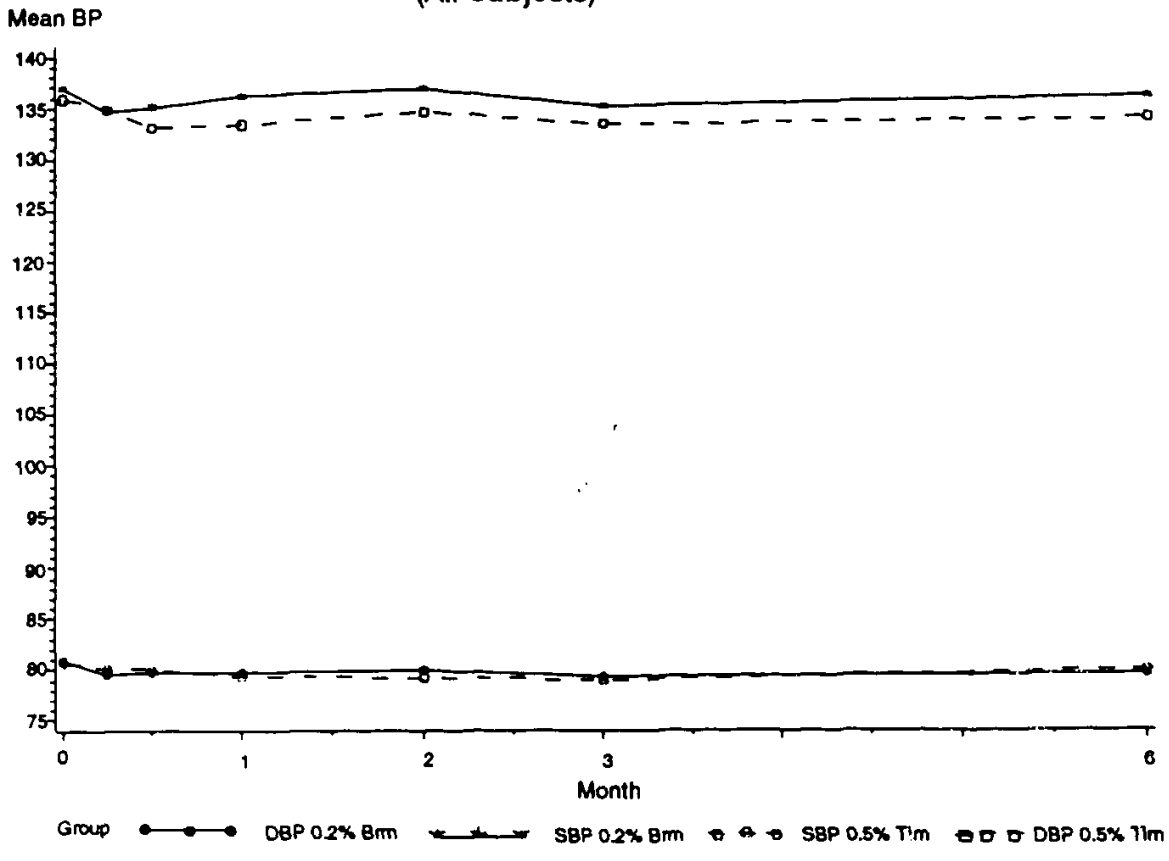
Timepoint		0.2% Brm	0.5% Tim	ANOVA P-value Treatment	ANOVA P-value Interaction
Baseline	N	291	190	0.824	0.089
	Mean	80.87	80.74		
	SD	10.12	10.33		
	Min	54.00	54.00		
	Max	120.00	115.00		
Week 1	N	285	188	0.313	0.044
	Mean	-1.24	-0.66		
	SD	8.35	8.09		
	Min	-30.00	-24.00		
	Max	20.00	28.00		
	P-value	0.013	0.265		
Week 2	N	277	179	0.768	0.098
	Mean	-0.99	-0.70		
	SD	9.17	9.55		
	Min	-30.00	-26.00		
	Max	28.00	36.00		
	P-value[b]	0.074	0.325		
Month 1	N	270	183	0.642	0.246
	Mean	-1.16	-1.56		
	SD	8.63	9.23		
	Min	-26.00	-30.00		
	Max	30.00	30.00		
	P-value[b]	0.029	0.023		
Month 2	N	259	180	0.644	0.166
	Mean	-0.75	-1.50		
	SD	9.14	9.31		
	Min	-34.00	-26.00		
	Max	25.00	24.00		
	P-value[b]	0.191	0.032		
Month 3	N	244	171	0.315	0.399
	Mean	-1.41	-1.99		
	SD	9.60	10.37		
	Min	-30.00	-25.00		
	Max	30.00	40.00		
	P-value[b]	0.023	0.013		
Month 6	N	216	167	0.548	0.661
	Mean	-1.40	-0.59		
	SD	9.86	10.06		
	Min	-35.00	-25.00		
	Max	20.00	36.00		
	P-value	0.038	0.452		

Figure 6
Mean Heart Rate (bpm)
(All Subjects)



Reviewer's Comments: Changes in heart rate with brimonidine treatment were minimal and not clinically significant.

Figure 7
Mean Blood Pressure (mm Hg)
(All Subjects)



Reviewer's Comments: *Changes in blood pressure with brimonidine treatment were minimal and not clinically significant.*

Adverse Events
Number and Percentage of Subjects with at Least One Severity Grade Increased from Baseline at One or More Follow-up Visits
Excluding Findings Related to Ocular Allergic Reaction[a]

(All Subjects)

Finding	0.2% Brm (N=292)	0.5% Tim (N=191)	P-value[b]
Oral Dryness	81 (27.7%)	21 (11.0%)	<0.001
Ocular Hyperemia[d]	68 (23.3%)	43 (22.5%)	0.843
Burning/Stinging	61 (20.9%)	75 (39.3%)	<0.001
Headache	54 (18.5%)	34 (17.8%)	0.847
Foreign Body Sensation	53 (18.2%)	26 (13.6%)	0.187
Blurring	41 (14.0%)	33 (17.3%)	0.334
Lens Pathology	39 (13.4%)	28 (14.7%)	0.685
Fatigue/Drowsiness	37 (12.7%)	18 (9.4%)	0.272
Ocular Allergic Reaction[e]	29 (9.9%)	1 (0.5%)	<0.001[c]
Ocular Pruritus	25 (8.6%)	15 (7.9%)	0.782
Follicles (Conjunctiva)	22 (7.5%)	7 (3.7%)	0.080
Corneal Staining/Erosion	21 (7.2%)	20 (10.5%)	0.206
Ocular Ache/Pain	19 (6.5%)	5 (2.6%)	0.054
Photophobia	19 (6.5%)	11 (5.8%)	0.739
Ocular Dryness	18 (6.2%)	16 (8.4%)	0.353
Upper Respiratory Symptoms	17 (5.8%)	11 (5.8%)	0.977
Fundus Pathology	16 (5.5%)	13 (6.8%)	0.548
Lacrimation Disorder	16 (5.5%)	5 (2.6%)	0.132
Dizziness	14 (4.8%)	5 (2.6%)	0.229
Blepharitis	12 (4.1%)	4 (2.1%)	0.302[c]
Systemic Other	11 (3.8%)	6 (3.1%)	N/A
Lid Erythema	10 (3.4%)	3 (1.6%)	0.262[c]
Asthenia	9 (3.1%)	3 (1.6%)	0.379[c]
Conjunctival Edema	9 (3.1%)	9 (4.7%)	0.355
Gastrointestinal Symptoms	8 (2.7%)	6 (3.1%)	0.797
Lash Debris	7 (2.4%)	2 (1.0%)	0.493[c]
Ocular Other	7 (2.4%)	4 (2.1%)	N/A
Photophobia	19 (6.5%)	11 (5.8%)	0.739
Ocular Dryness	18 (6.2%)	16 (8.4%)	0.353
Upper Respiratory Symptoms	17 (5.8%)	11 (5.8%)	0.977
Fundus Pathology	16 (5.5%)	13 (6.8%)	0.548
Lacrimation Disorder	16 (5.5%)	5 (2.6%)	0.132
Dizziness	14 (4.8%)	5 (2.6%)	0.229
Blepharitis	12 (4.1%)	4 (2.1%)	0.302[c]
Systemic Other	11 (3.8%)	6 (3.1%)	N/A
Lid Erythema	10 (3.4%)	3 (1.6%)	0.262[c]
Asthenia	9 (3.1%)	3 (1.6%)	0.379[c]
Conjunctival Edema	9 (3.1%)	9 (4.7%)	0.355

Gastrointestinal Symptoms	8 (2.7%)	6 (3.1%)	0.797
Lash Debris	7 (2.4%)	2 (1.0%)	0.493[c]
Ocular Other	7 (2.4%)	4 (2.1%)	N/A
Muscular Pain	7 (2.4%)	3 (1.6%)	0.747[c]
Insomnia	7 (2.4%)	1 (0.5%)	0.155[c]
Opacity (Cornea)	6 (2.1%)	1 (0.5%)	0.253[c]
Cornea Other	6 (2.1%)	2 (1.0%)	N/A
Abnormal Vision	6 (2.1%)	5 (2.6%)	0.685
Ocular Irritation	6 (2.1%)	2 (1.0%)	0.488[c]
Corneal Endothel. Changes	6 (2.1%)	4 (2.1%)	>0.999[c]
Crusting (Lid)	5 (1.7%)	1 (0.5%)	0.410[c]
Meibomianitis	5 (1.7%)	5 (2.6%)	0.494
Dermatochalasis	5 (1.7%)	2 (1.0%)	0.709[c]
Pinguecula	5 (1.7%)	3 (1.6%)	>0.999[c]
Conjunctiva Other	5 (1.7%)	2 (1.0%)	N/A
Lid Edema	5 (1.7%)	3 (1.6%)	>0.999[c]
Endothel. Pigment	4 (1.4%)	4 (2.1%)	0.718[c]
Scar (Cornea)	4 (1.4%)	4 (2.1%)	0.718[c]
Vitreous Pathology	4 (1.4%)	1 (0.5%)	0.653[c]
Asthenopia (Eyestrain)	4 (1.4%)	2 (1.0%)	>0.999[c]
Lid Other	3 (1.0%)	0 (0.0%)	N/A
Hemorrhage (Conjunctiva)	3 (1.0%)	2 (1.0%)	>0.999[c]
Abnormal Taste	3 (1.0%)	1 (0.5%)	>0.999[c]
Influenza	3 (1.0%)	1 (0.5%)	>0.999[c]
Arthralgia	3 (1.0%)	0 (0.0%)	0.281[c]
Anterior Chamber Cells	3 (1.0%)	1 (0.5%)	>0.999[c]
Papillae (Conjunctiva)	2 (0.7%)	3 (1.6%)	0.389[c]
Other[d]	59	36	

[a] The following findings have been removed for subjects having an Ocular Allergic Reaction: Lid Erythema, Lid Edema, Ocular Hyperemia, Conjunctival Edema, Burning/Stinging, Blurring, F.B.S., Conjunctivitis, Blepharitis, Crusting (Lid), Lash Debris, Discharge (Conjunctiva), Follicles (Conjunctiva), Papillae (Conjunctiva), Follicles; Papillae (Conjunctiva), Edema+Papillae (Conjunctiva), Ocular Pruritus, Ocular Irritation, Eyelid Discomfort, Ocular Edema, and Lacrimation Disorder
[b] Unless stated otherwise, p-value based on Pearson's Chi-square test.
[c] P-value based on Fisher's exact test.
Note: Adverse events occurred in 87% (254/292) of subjects in the 0.2% Brm group and 82% (156/191) of subjects in the 0.5% Tim group.

Serious Adverse Events[a]

System	Preferred Term	0.2% Brm (N=292)	0.5% Tim (N=191)
Neurological	Dizziness	1 (0.34%)	0 (0.00%)
	Migraine	1 (0.34%)	0 (0.00%)
Cardiovascular	Myocardial infarction	1 (0.34%)	0 (0.00%)
Respiratory	Influenza	1 (0.34%)	0 (0.00%)
Gastrointestinal	Bowel abscess	0 (0.00%)	1 (0.52%)
	Upper gastrointestinal bleeding	1 (0.34%)	0 (0.00%)
Carcinoma	Carcinoma, prostatic	1 (0.34%)	0 (0.00%)

[a] Serious adverse events occured in 1.7% (5/292) of subjects in the 0.2% Brm group and 0.5% (1/191) of subjects in the 0.5% Tim group.

2 Pages Purged

Summary and Conclusions:

'ficacy:

Brimonidine 0.2% reduced IOP at every scheduled follow-up visit over the six-month study period.

2) At trough, IOP reductions with timolol 0.5%, were significantly greater than with brimonidine 0.2% at all scheduled follow-up visits. At peak, decreases with brimonidine were similar to timolol.

3) There was a decrease in efficacy over time in the brimonidine group.

Safety:

4) The most common adverse events occurring with brimonidine treatment were oral dryness, ocular hyperemia, burning/stinging, headache,foreign body sensationBlurring, fatigue/drowsiness and ocular allergic reactions. Oral dryness was more frequent with brimonidine treatment.

5) Ocular allergic reactions occurred in 9.9% of the subjects treated with brimonidine.

6) The most common cause for subject termination due to adverse events with brimonidine treatment was ocular allergic reaction (7.2%).

7) Changes in heart rate and blood pressure with brimonidine treatment were minimal and not clinically significant.

8) With respect to cup/disc ratio, no significant differences were seen between the brimonidine and timolol treatment groups.

9) Changes in visual fields were minimal and clinically insignificant in both groups.

:udy #3 (Only the efficacy data is presented)
342-119-7831

STUDY OBJECTIVE:

The objective of this study was to compare the safety and efficacy of twice-daily (b.i.d.) versus three-times-daily (t.i.d.) brimonidine 0.2%, in subjects with open-angle glaucoma or ocular hypertension.

STUDY DESIGN:

This study was a randomized, double-masked, parallel comparison of brimonidine 0.2% b.i.d. vs. brimonidine 0.2% t.i.d. The study was three months in duration, and consisted of eight visits during the study period.

STUDY POPULATION:

One hundred one subjects with open angle glaucoma or ocular hypertension who had no contraindications to the use of ocular alpha-adrenoceptor agonist therapy were enrolled into this study.

STUDY MEDICATION:

The study evaluated two treatment groups: brimonidine 0.2% administered twice-daily (b.i.d.) versus brimonidine 0.2% administered three times daily (t.i.d.).

STUDY METHODS:

During the first visit (Visit 1), the subject's medical and ophthalmological history was recorded and written informed consent was obtained from each subject. Intraocular pressure (IOP) and pupil size were assessed. Biomicroscopy, ophthalmoscopy, Schirmer tear test, visual acuity and visual field examinations were performed. Heart rate and blood pressure were also recorded for each subject.

Following Visit 1 there was a washout period of 0-30 days, depending upon pre-study medication. Each subject returned after the washout period for baseline assessments (Visit 2). A biomicroscopic examination was performed, as well as assessments of visual acuity, pupil size, Schirmer tear test, heart rate, blood pressure, and subject comfort. Baseline diurnal measurements of IOP, heart rate, and blood pressure were also recorded at 9-10:00 a.m. (Hour 2), 11 a.m. -12:00 p.m. (Hour 4), 2-3:00 p.m. (Hour 7), 4-5:00 p.m. (Hour 9), and 6 -7:00 p.m. (Hour 11). Blood plasma was also collected at Hours 0, 7, and 11 from 40 of the 101 subjects in this study. Blood samples were collected to determine the plasma concentration levels of brimonidine tartrate in subjects on the t.i.d. dosing regimen versus the b.i.d. dosing regimen.

After the 6:00-7:00 p.m. (Hour 11) measurements, subjects received three bottles of medication to take home. Depending upon which group the subject was randomized into, the bottle labeled "afternoon drops" contained either brimonidine 0.2% or the vehicle.

Subjects were instructed to instill one drop into each eye from the bottle labeled "morning drops"

between 7:00 and 9:00 AM; one drop in each eye from the bottle labeled "afternoon drops" between 2:00 and 3:00 PM, and one drop in each eye from the bottle labeled "evening drops" between 10 p.m. and 12 a.m.

Subjects returned the next day (Day 1) for administration of medication and diurnal measurements. Upon arrival, a biomicroscopic examination was performed as well as assessments of IOP, pupil size, visual acuity, heart rate, blood pressure, and subject comfort. Medications were then administered to each subject. Intraocular pressure, pupil size, blood pressure, heart rate, and subject comfort were measured again at Hour 2, 4, 7, 9, and 11). The measurements recorded at the Hour 7 timepoint were done before the afternoon medication was instilled.

Subjects returned at Weeks 1, 3, 6, and 8. Biomicroscopy, IOP, pupil size, visual acuity, heart rate, blood pressure and subject comfort were recorded at each visit. Blood plasma was collected at Hour 0 at Weeks 3, 6, and 8 from the same 45 subjects that had their plasma collected at Day 0. At Week 6, IOP, subject comfort, heart rate and blood pressure were again recorded at Hour 2, 4, 7, 9, and 11. Blood plasma was also be collected at Hour 0, 7, and 11 on the same subjects that had their plasma collected at previous visits. All measurements at Hour 7 were recorded prior to the instillation of the afternoon medication.

At Week 12, subjects returned for a final visit. Upon arrival, subjects had IOP, pupil size, biomicroscopy, visual acuity, visual field, heart rate, blood pressure, and comfort assessed. IOP, subject comfort, heart rate, and blood pressure were again recorded at Hour 2, 4, 7, and 9. Blood plasma was also collected at Hour 0, 7, and 11 on most of the same subjects that had their plasma collected at previous visits. All measurements at Hour 7 were recorded prior to the instillation of the afternoon medication. At Hour 11, biomicroscopy and ophthalmoscopy examinations will be performed as well as measurements of IOP, pupil size, Schirmer tear test, visual acuity, heart rate, blood pressure, and subject comfort. After the completion of the Hour 11 measurements, subjects were then considered to have successfully completed the study.

RESULTS:

Demographic
(Preferred Analysis)

	B.I.D.	T.I.D.	P-value*
Age			
N	48	48	0.556
Mean	53.3	52.4	
SD	11.0	11.7	
Min	33	26	
Max	73	72	
Sex			
Male	18 (38%)	26 (54%)	0.107
Female	30 (63%)	22 (46%)	
Race			
Caucasian	35 (73%)	41 (85%)	0.200
Hispanic	6 (13%)	2 (4%)	
Black	6 (13%)	5 (10%)	
Asian	1 (2%)	0 (0%)	
Iris Color			
Blue	10 (21%)	13 (27%)	0.697
Green	1 (2%)	0 (0%)	
Hazel	10 (21%)	8 (17%)	
Brown	27 (56%)	27 (56%)	
Diagnosis			
OAG	18 (38%)	17 (35%)	>0.999
OHT	30 (63%)	31 (65%)	

* Between-group comparisons.

Reviewer's Comments: There were no significant differences between the two groups.

Summary of Subjects Enrollment And Exit Status

	B.I.D.	T.I.D.	Total
Evaluable Subjects (included in preferred analysis)	48	48	96
Discontinued	1*	0	1
Terminated			
Lack of efficacy	0	0	0
Underirable side effects	0	2	2
Completed	47	46	93
Unevaluable Subjects# (excluded from preferred analysis)	2	3	5
Discontinued	2	3	5
Terminated			
Lack of efficacy	0	0	0
Underirable side effects	0	0	0
Completed	0	0	0
Total Enrolled	50	51	101
Discontinued	3	3	6
Terminated			
Lack of efficacy	0	0	0
Underirable side effects	0	2	2
Completed	47	46	93

* Subject 1634-139 had the examination at Hour 0 of Visit 8 and then discontinued from the study. Diurnal examinations were missing.

\# Subjects who did not meet protocol entry criteria.

Discontinued And Terminated Subjects

Exit Status	Group	Subject	Visit	Exit Reason
Discontinued	B.I.D.	1634-139	8.00	Other reason (viral conjunctivitis)
		1972-202	4.00	Concurrent use of alpha agonist.
		1972-209	4.00	Pt was on amitriptyline antidepressant.
Discontinued	T.I.D.	1634-129	4.00	Progression of VF loss
		1634-158	4.00	Uncontrolled CV disease
		1972-217	5.01	Child bearing potential
Terminated	T.I.D.	1634-134*	4.00	Undesirable side effects
		1972-201#	6.01	Undesirable side effects

*1634-134: terminated due due to amnesia (forgetfulness), increased appetite,oral dryness, foreign body sensation, somnolence (drowsiness, brain fatigue).

#1972-201: terminated due to somnolence (tired), cojunctivitis, ocular pruritis,discharge

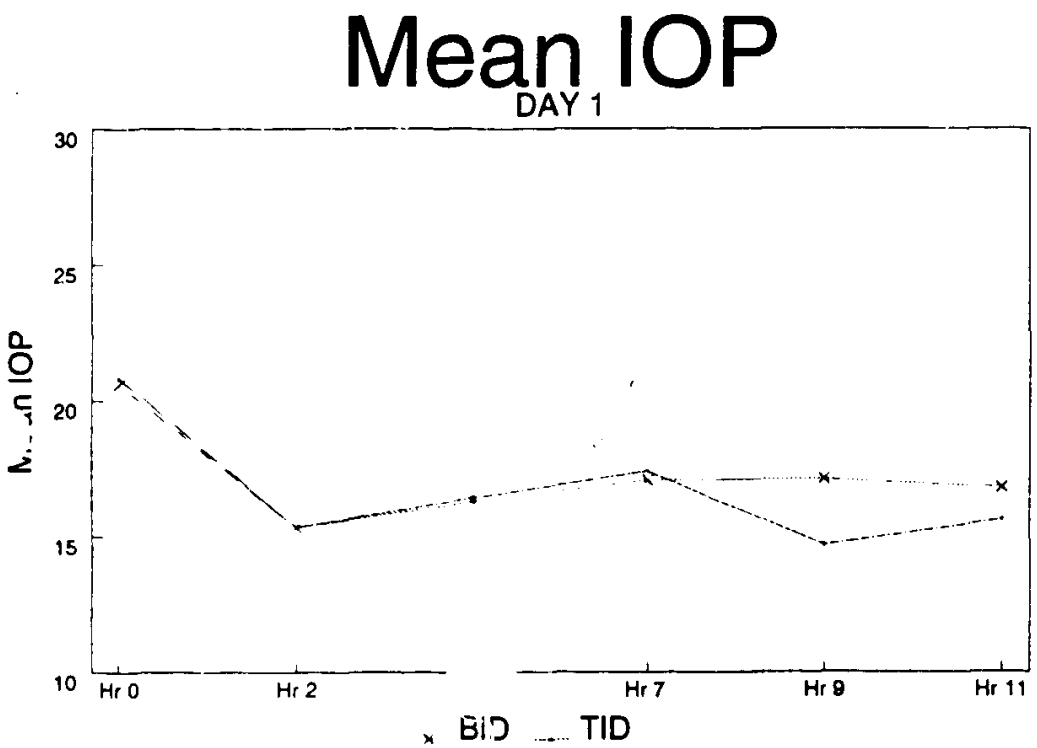
Intraocular Pressure (mm Hg)
Baseline and Mean Changes from Baseline

Visit		B.I.D.	T.I.D.	P-value*
2 (Day 0)	N	48	48	0.893
	Mean	25.78	25.76	
	SD	2.26	3.21	
	Min	23.00	23.00	
	Max	33.00	35.00	
3 (Day 1)	N	48	48	0 904
	Mean	-5.19	-4.94	
	SD	3.77	3.70	
	Min	-17.50	-14.50	
	Max	3.00	4.50	
	P-value^	<0.001	<0.001	
4 (Wk 1)	N	47	48	0.607
	Mean	-4.14	-4.38	
	SD	3.25	3.52	
	Min	-13.00	-14.00	
	Max	2.50	3.00	
	P-value^	<0.001	<0.001	
5 (Wk 3)	N	48	47	0.925
	Mean	-3.45	-3.21	
	SD	3.23	3.47	
	Min	-12.00	-12.50	
	Max	1.50	4.00	
	P-value^	<0.001	<0.001	
6 (Wk 6)	N	48	46	0.543
	Mean	-3.48	-2.83	
	SD	3.52	3.26	
	Min	-12.00	-12.00	
	Max	3.00	3.00	
	P-value^	<0.001	<0.001	
7 (Wk 8)	N	46	45	0.848
	Mean	-3.35	-3.39	
	SD	3.17	3.42	
	Min	-11 50	-12.00	
	Max	4.00	5.00	
	P-value^	<0.001	<0.001	
8 (Wk 12)	N	48	46	0.288
	Mean	-3.36	-3.97	
	SD	3.31	3.56	
	Min	-9.50	-12.00	
	Max	7.50	5.00	
	P-value^	<0.001	<0.001	
Overall^		-3.63	-3.67	0.955

Baseline Intraocular Pressure (mm Hg)
(Diurnal Examination at Visit 2)

Hour#		B.I.D.	T.I.D.	P-value*
0	N	48	48	0.893
	Mean	25.78	25.76	
	SD	2.26	3.21	
	Min	23.00	23.00	
	Max	33.00	35.00	
2	N	48	48	0.604
	Mean	23.54	23.41	
	SD	3.62	4.25	
	Min	17.00	16.00	
	Max	32.50	39.00	
4	N	48	48	0.715
	Mean	23.86	23.85	
	SD	3.85	3.90	
	Min	16.50	17.00	
	Max	34.50	33.50	
7	N	48	48	0.532
	Mean	21.57	22.11	
	SD	2.94	3.82	
	Min	14.50	15.50	
	Max	29.00	33.50	
9	N	48	48	0.388
	Mean	22.28	22.02	
	SD	2.83	3.55	
	Min	17.00	16.00	
	Max	28.50	30.50	
11	N	48	48	0.427
	Mean	22.39	22.15	
	SD	2.90	3.10	
	Min	16.50	17.00	
	Max	30.00	29.00	

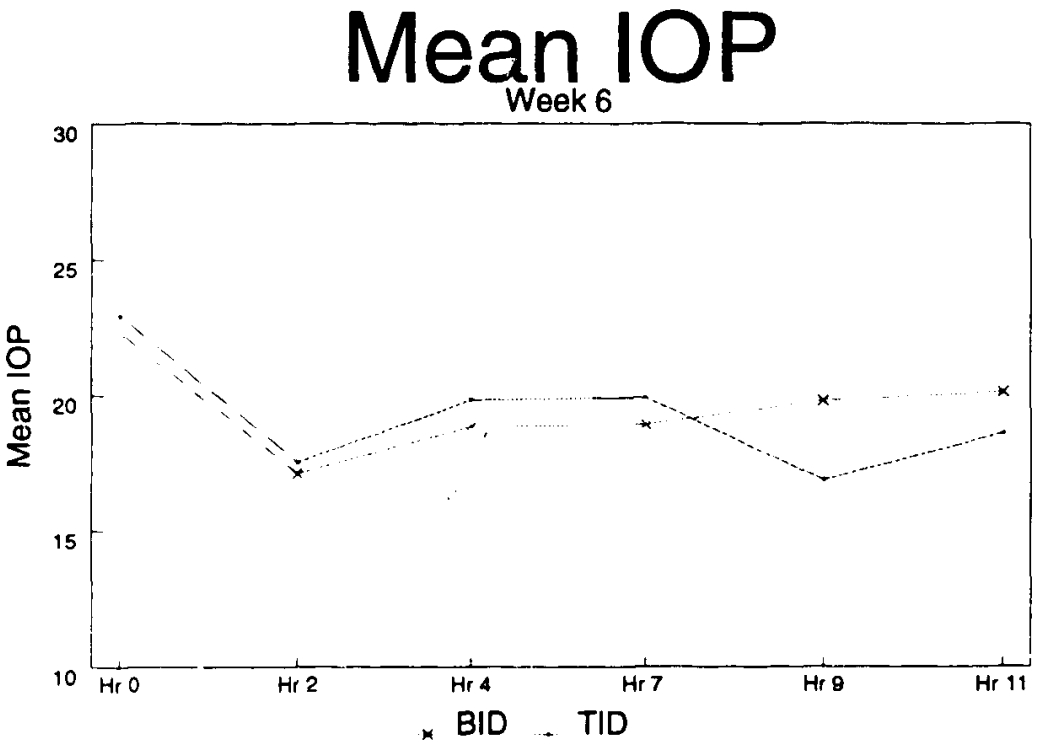
Each timepoint of Visit 2 is the baseline for the diurnal examination.
* Between-group comparisons. Treatment-by-investigator interaction was significant at Hour 9 (p=0.053) and Hour 11 (p=0.097).


Mean IOP
DAY 1
30
25
20
15
10
Hr 0
Hr 2
Hr 7
Hr 9
Hr 11
BID
TID

Mean Changes in Intraocular Pressure (mm Hg)
(Diurnal Examination at Visit 6)

Hour#		B.I.D.	T.I.D.	P-value*
0	N	48	46	0.543
	Mean	-3.48	-2.83	
	SD	3.52	3.26	
	Min	-12.00	-12.00	
	Max	3.00	3.00	
	P-value^	<0.001	<0.001	
2	N	48	46	0.476
	Mean	-6.43	-5.89	
	SD	3.41	4.04	
	Min	-17.00	-16.00	
	Max	0.50	2.00	
	P-value^	<0.001	<0.001	
4	N	48	45	0.232
	Mean	-5.01	-4.03	
	SD	4.10	3.98	
	Min	-16.00	-15.00	
	Max	4.00	3.00	
	P-value^	<0.001	<0.001	
7	N	48	46	0.648
	Mean	-2.67	-2.20	
	SD	2.56	3.37	
	Min	-7.00	-12.00	
	Max	3.50	4.50	
	P-value^	<0.001	<0.001	
9	N	47	46	0.001
	Mean	-2.49	-5.15	
	SD	2.89	4.15	
	Min	-10.00	-12.50	
	Max	4.00	9.00	
	P-value^	<0.001	<0.001	
11	N	47	46	0.021
	Mean	-2.29	-3.57	
	SD	2.65	2.62	
	Min	-9.50	-9.00	
	Max	4.00	2.50	
	P-value^	<0.001	<0.001	

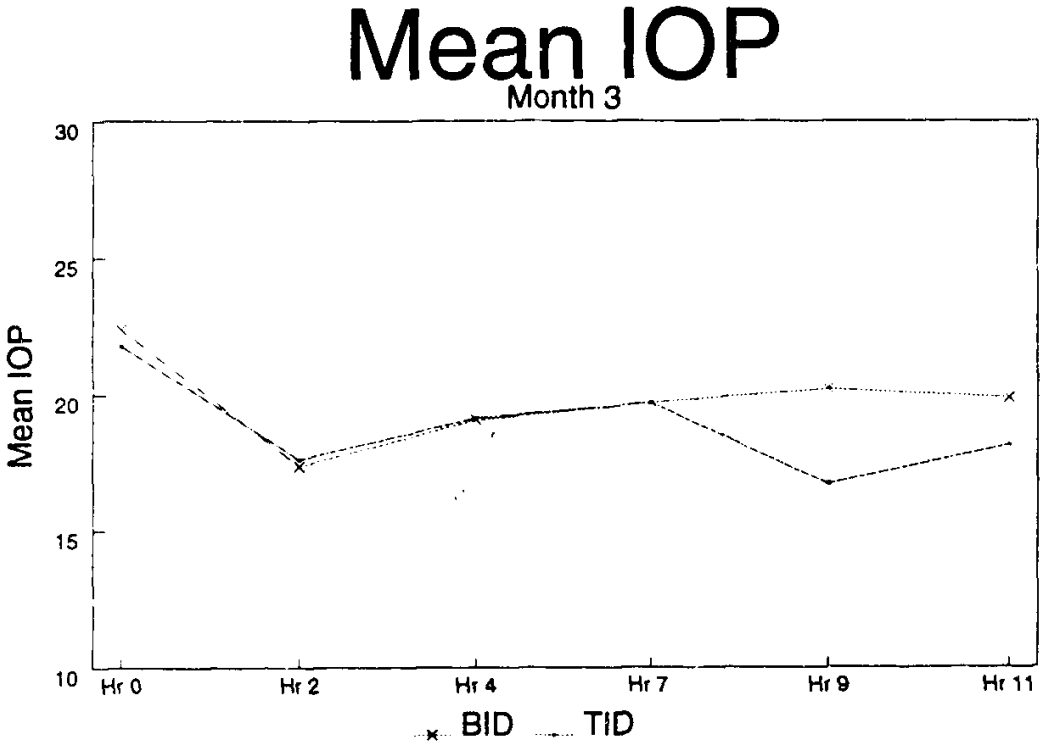
Mean changes from baseline (the corresponding timepoint of Visit 2).
* Between-group comparisons. Treatment-by-investigator interaction was not significant at any timepoint, p > 0.10.
^ Within-group analysis of changes from baseline.


Mean IOP
Week 6
Mean IOP
30
25
20
15
10
Hr 0
Hr 2
Hr 4
Hr 7
Hr 9
Hr 11
BID
TID

Mean Changes in Intraocular Pressure (mm Hg)
(Diurnal Examination at Visit 8)

Hour#		B.I.D.	T.I.D.	P-value*
0	N	48	46	0.288
	Mean	-3.36	-3.97	
	SD	3.30	3.56	
	Min	-9.50	-12.00	
	Max	7.50	5.00	
	P-value^	<0.001	<0.001	
2	N	47	46	0.528
	Mean	-6.17	-5.80	
	SD	4.03	4.29	
	Min	-15.00	-17.00	
	Max	2.00	-0.50	
	P-value^	<0.001	<0.001	
4	N	47	46	0.501
	Mean	-4.81	-4.27	
	SD	3.75	3.46	
	Min	-14.50	-13.00	
	Max	5.50	1.00	
	P-value^	<0.001	<0.001	
7	N	47	46	0.363
	Mean	-1.87	-2.42	
	SD	2.98	3.55	
	Min	-9.00	-14.50	
	Max	5.00	4.00	
	P-value^	<0.001	<0.001	
9	N	47	45	<0.001
	Mean	-2.07	-5.31	
	SD	3.05	3.80	
	Min	-10.00	-12.00	
	Max	3.50	2.00	
	P-value^	<0.001	<0.001	
11	N	47	46	0.020
	Mean	-2.51	-4.01	
	SD	3.18	2.77	
	Min	-9.00	-9.50	
	Max	6.00	2.00	
	P-value^	<0.001	<0.001	

Mean changes from baseline (the corresponding timepoint of Visit 2).
* Between-group comparisons. Treatment-by-investigator interaction was not significant at any timepoint, p > 0.10.
^ Within-group analysis of changes from baseline.

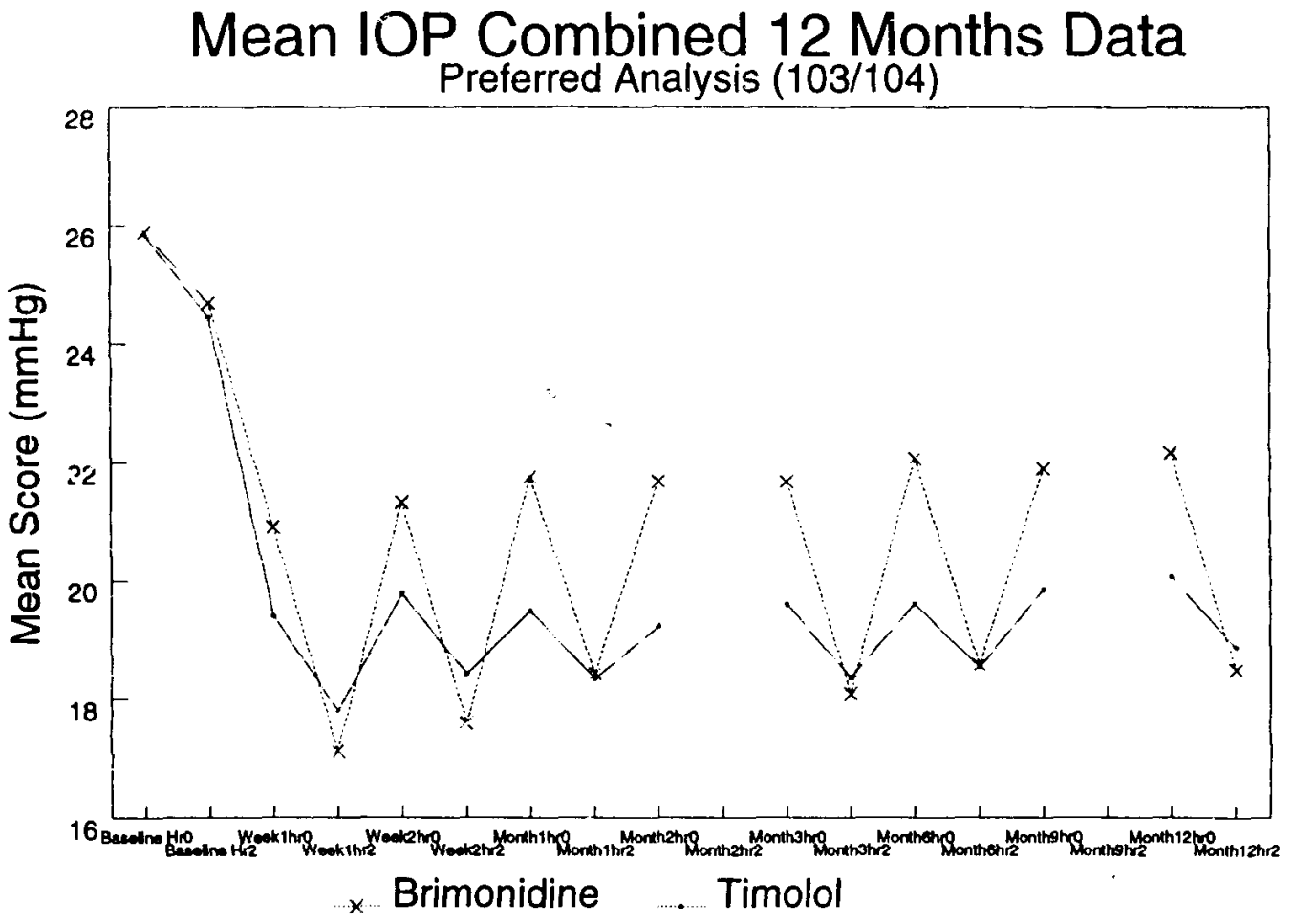

Mean IOP
Month 3
30
25
20
15
10
Mean IOP
Hr 0
Hr 2
Hr 4
Hr 7
Hr 9
Hr 11
BID
TID

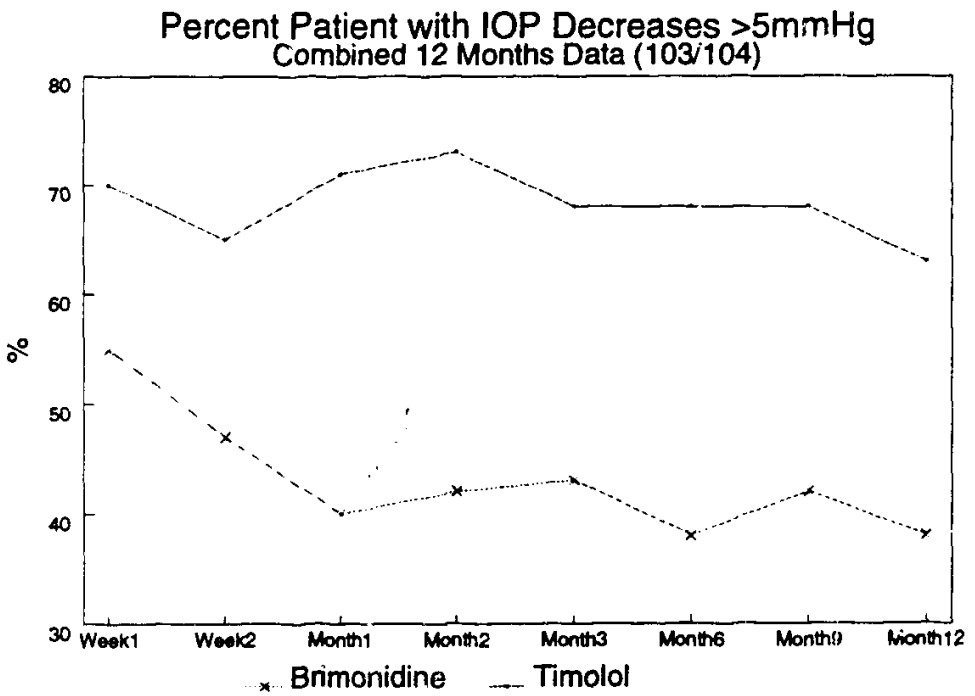
Summary and conclusions:

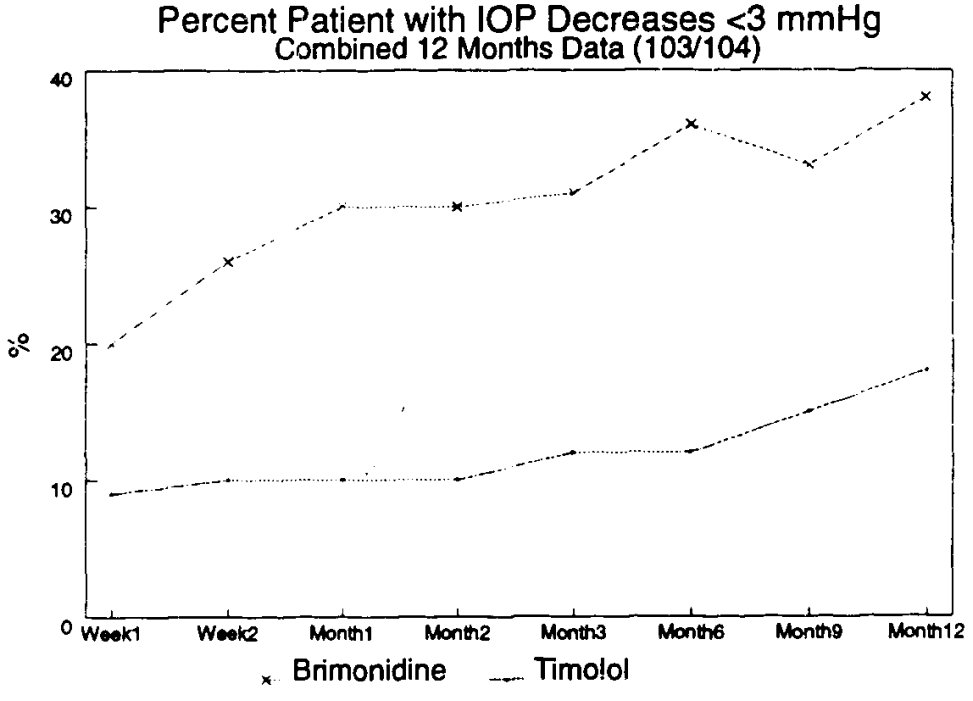
1) Mean decreases from baseline ranged from 3.4 to 5.2 mm Hg in the b.i.d. group, and from 2.8 to 4.9 mm Hg in the t.i.d. group.

2) On all diurnal visits (Day 1, Week 6, and Week 12) both treatment groups showed a statistically significant within-group decrease from baseline in mean IOP at each timepoint of diurnal examination. There were statistically significant differences favoring t.i.d. treatment between groups at Hour 9 for the Day 1 visit, and at Hours 9 and 11 for the Weeks 6 and 12 visits ($p \leq 0.021$). At hour 9 at weeks 6 and 12, the mean difference was approximately 3.0 mm Hg.

Integrated Graphical Summary: Based on Combined Data from Studies A342-103 and A342-104 (12 months Data)




Percent Patient with IOP Decreases >5mmHg
Combined 12 Months Data (103/104)
80
70
60
50
40
30
%
Week1
Week2
Month1
Month2
Month3
Month6
Month9
Month12
Brimonidine
Timolol


Percent Patient with IOP Decreases <3 mmHg
Combined 12 Months Data (103/104)
40
30
20
10
0
%
Week1
Week2
Month1
Month2
Month3
Month6
Month9
Month12
Brimonidine
Timolol

Summary of Adverse Events
Excluding Findings Related to Ocular Allergic Reaction[a]
Combined Data from Studies A342-103 and A342-104

Finding	0.2% Brm (N=513)	0.5% Tim (N=413)	P-value[b]
Oral Dryness	160 (31.2%)	69 (16.7%)	<0.001
Ocular Hyperemia[d]	147 (28.7%)	104 (25.2%)	0.237
Burning/Stinging	133 (25.9%)	180 (43.6%)	<0.001
Lens Pathology	101 (19.7%)	105 (25.4%)	0.037
Headache	97 (18.9%)	83 (20.1%)	0.650
Blurring	96 (18.7%)	93 (22.5%)	0.153
Foreign Body Sensation	95 (18.5%)	69 (16.7%)	0.473
Fatigue/Drowsiness	84 (16.4%)	62 (15.0%)	0.572
Follicles (Conjunctiva)	65 (12.7%)	23 (5.6%)	<0.001
Ocular Allergic Reaction[e]	65 (12.7%)	1 (0.2%)	<0.001[c]
Fundus Pathology	64 (12.5%)	58 (14.0%)	0.483
Ocular Pruritus	57 (11.1%)	42 (10.2%)	0.645
Corneal Staining/Erosion	47 (9.2%)	48 (11.6%)	0.220
Photophobia	47 (9.2%)	42 (10.2%)	0.605
Lid Erythema	43 (8.4%)	22 (5.3%)	0.070
Ocular Ache/Pain	37 (7.2%)	18 (4.4%)	0.068
Ocular Dryness	37 (7.2%)	40 (9.7%)	0.176
Lacrimation Disorder	36 (7.0%)	21 (5.1%)	0.224
Upper Respiratory Symptoms	35 (6.8%)	21 (5.1%)	0.270
Lid Edema	34 (6.6%)	13 (3.1%)	0.016
Conjunctival Edema	33 (6.4%)	26 (6.3%)	0.932
Dizziness	28 (5.5%)	15 (3.6%)	0.189
Vitreous Pathology	27 (5.3%)	19 (4.6%)	0.645
Systemic Other	26 (5.1%)	25 (6.1%)	0.514
Ocular Other	22 (4.3%)	19 (4.6%)	0.819
Blepharitis	20 (3.9%)	12 (2.9%)	0.411
Lash Debris	19 (3.7%)	13 (3.1%)	0.645
Ocular Irritation	18 (3.5%)	6 (1.5%)	0.050
Gastrointestinal Symptoms	18 (3.5%)	14 (3.4%)	0.922
Asthenia	18 (3.5%)	7 (1.7%)	0.090
Conjunctival Blanching	18 (3.5%)	16 (3.9%)	0.769
Abnormal Vision	17 (3.3%)	15 (3.6%)	0.792
Cornea Other	16 (3.1%)	5 (1.2%)	0.053
Muscular Pain	16 (3.1%)	10 (2.4%)	0.523
Lid Other	14 (2.7%)	12 (2.9%)	0.872
Pinguecula	13 (2.5%)	8 (1.9%)	0.544
Crusting (Lid)	12 (2.3%)	9 (2.2%)	0.871
Conjunctiva Other	11 (2.1%)	5 (1.2%)	0.278
Opacity (Cornea)	11 (2.1%)	3 (0.7%)	0.104[c]
Meibomianitis	10 (1.9%)	10 (2.4%)	0.623
Dermatochalasis	10 (1.9%)	5 (1.2%)	0.376
Arcus (Cornea)	10 (1.9%)	4 (1.0%)	0.284[c]
Corneal Endothel. Changes	10 (1.9%)	10 (2.4%)	0.623
Hemorrhage (Conjunctiva)	8 (1.6%)	3 (0.7%)	0.362[c]
Asthenopia (Eyestrain)	8 (1.6%)	8 (1.9%)	0.661
Abnormal Taste	8 (1.6%)	5 (1.2%)	0.654
Insomnia	8 (1.6%)	3 (0.7%)	0.362[c]
Discharge (Conjunctiva)	7 (1.4%)	7 (1.7%)	0.682
Papillae (Conjunctiva)	7 (1.4%)	9 (2.2%)	0.344
Conjunctivitis	7 (1.4%)	2 (0.5%)	0.313[c]
Endothel. Pigment	6 (1.2%)	6 (1.5%)	0.705
Scar (Cornea)	6 (1.2%)	11 (2.7%)	0.092
Vitreous Floaters	5 (1.0%)	5 (1.2%)	0.730
Chest Pain	5 (1.0%)	3 (0.7%)	0.738[c]
Carcinoma	5 (1.0%)	5 (1.2%)	0.730
Anterior Chamber Cells	5 (1.0%)	3 (0.7%)	0.738[c]
Trichiasis	4 (0.8%)	0 (0.0%)	0.133[c]
Anterior Chamber Other	4 (0.8%)	1 (0.2%)	0.388[c]
Eyelid Discomfort	4 (0.8%)	2 (0.5%)	0.697[c]
Ocular Edema	4 (0.8%)	3 (0.7%)	>0.999[c]
Depression	4 (0.8%)	5 (1.2%)	0.523[c]
Systemic Allergies	4 (0.8%)	2 (0.5%)	0.697[c]
Influenza	4 (0.8%)	4 (1.0%)	>0.999[c]
Hypertension	4 (0.8%)	2 (0.5%)	0.697[c]
Myocardial Infarction	4 (0.8%)	1 (0.2%)	0.388[c]
Cyst (Lid)	3 (0.6%)	1 (0.2%)	0.633[c]
Ectropion	3 (0.6%)	0 (0.0%)	0.258[c]
Pterygium	3 (0.6%)	4 (1.0%)	0.706[c]
Pannus (Cornea)	3 (0.6%)	2 (0.5%)	>0.999[c]

Local Iris Atrophy	3 (0.6%)	2 (0.5%)	>0.999[c]
Anxiety	3 (0.6%)	2 (0.5%)	>0.999[c]
Fever	3 (0.6%)	1 (0.2%)	0.633[c]
Palpitations	3 (0.6%)	2 (0.5%)	>0.999[c]
Pruritus (Skin)	3 (0.6%)	2 (0.5%)	>0.999[c]
Angina Pectoris	3 (0.6%)	2 (0.5%)	>0.999[c]
Renal Calculus	3 (0.6%)	1 (0.2%)	0.633[c]
Arthralgia	3 (0.6%)	0 (0.0%)	0.258[c]
Bronchitis	3 (0.6%)	2 (0.5%)	>0.999[c]
Anterior Chamber Post. Synechiae	3 (0.6%)	0 (0.0%)	0.258[c]
Blepharoptosis	2 (0.4%)	1 (0.2%)	>0.999[c]
Chalazion	2 (0.4%)	4 (1.0%)	0.416[c]
Skin Disorder (Lid)	2 (0.4%)	1 (0.2%)	>0.999[c]
Cyst (Conjunctiva)	2 (0.4%)	3 (0.7%)	0.661[c]
Guttata (Cornea)	2 (0.4%)	5 (1.2%)	0.252[c]
Anterior Basement Membrane Dystrophy	2 (0.4%)	1 (0.2%)	>0.999[c]
Diplopia	2 (0.4%)	0 (0.0%)	0.505[c]
Nasal Dryness	2 (0.4%)	4 (1.0%)	0.416[c]
Dyspnea	2 (0.4%)	6 (1.5%)	0.149[c]
Skin Disorder	2 (0.4%)	2 (0.5%)	>0.999[c]
Syncope	2 (0.4%)	2 (0.5%)	>0.999[c]
Bone Fracture	2 (0.4%)	2 (0.5%)	>0.999[c]
Death	2 (0.4%)	2 (0.5%)	>0.999[c]
Edema (Peripheral)	2 (0.4%)	0 (0.0%)	0.505[c]
Districhiasis	1 (0.2%)	0 (0.0%)	>0.999[c]
Hordeolum	1 (0.2%)	3 (0.7%)	0.329[c]
Rosacea (Lid)	1 (0.2%)	0 (0.0%)	>0.999[c]
Verruca (Lid)	1 (0.2%)	0 (0.0%)	>0.999[c]
Papillae (Lid)	1 (0.2%)	1 (0.2%)	>0.999[c]
Follicles;Injection (Conjunctiva)	1 (0.2%)	1 (0.2%)	>0.999[c]
Pigment (Conjunctiva)	1 (0.2%)	2 (0.5%)	0.589[c]
Follicles;Papillae (Conjunctiva)	1 (0.2%)	1 (0.2%)	>0.999[c]
Conjunctiva Edema + Papillae (Conjunctiva)	1 (0.2%)	0 (0.0%)	>0.999[c]
Periph. Iridectomy	1 (0.2%)	1 (0.2%)	>0.999[c]
Ocular Allergic Symptoms	1 (0.2%)	1 (0.2%)	>0.999[c]
Improved Vision	1 (0.2%)	1 (0.2%)	>0.999[c]
Bell's Palsy	1 (0.2%)	0 (0.0%)	>0.999[c]
Arteriosclerosis	1 (0.2%)	0 (0.0%)	>0.999[c]
Allergic Reaction (Urticaria)	1 (0.2%)	1 (0.2%)	>0.999[c]
Asthma	1 (0.2%)	3 (0.7%)	0.329[c]
Bradycardia	1 (0.2%)	1 (0.2%)	>0.999[c]
Cerebral Ischemia	1 (0.2%)	3 (0.7%)	0.329[c]
Emotional Lability	1 (0.2%)	0 (0.0%)	>0.999[c]
Ocular Hemorrhage	1 (0.2%)	0 (0.0%)	>0.999[c]
Hyperglycemia	1 (0.2%)	1 (0.2%)	>0.999[c]
Hypesthesia	1 (0.2%)	1 (0.2%)	>0.999[c]
Intraocular Pressure	1 (0.2%)	0 (0.0%)	>0.999[c]
Migraine	1 (0.2%)	2 (0.5%)	0.589[c]
Myasthenia	1 (0.2%)	1 (0.2%)	>0.999[c]
Tachycardia	1 (0.2%)	1 (0.2%)	>0.999[c]
Upper Gastrointestinal Bleeding	1 (0.2%)	0 (0.0%)	>0.999[c]
Viral Conjunctivitis	1 (0.2%)	1 (0.2%)	>0.999[c]
Atrial Fibrillation	1 (0.2%)	0 (0.0%)	>0.999[c]
Diabetes Mellitus	1 (0.2%)	0 (0.0%)	>0.999[c]
Gout	1 (0.2%)	0 (0.0%)	>0.999[c]
Heart Failure	1 (0.2%)	0 (0.0%)	>0.999[c]
Hernia	1 (0.2%)	1 (0.2%)	>0.999[c]
Hypotension	1 (0.2%)	0 (0.0%)	>0.999[c]
Keratitis (Chemical)	1 (0.2%)	0 (0.0%)	>0.999[c]
Malaise	1 (0.2%)	0 (0.0%)	>0.999[c]
Neoplasm	1 (0.2%)	1 (0.2%)	>0.999[c]
Palsy	1 (0.2%)	0 (0.0%)	>0.999[c]
Prostatic Disorder	1 (0.2%)	0 (0.0%)	>0.999[c]
Urinary Retention	1 (0.2%)	1 (0.2%)	>0.999[c]
Visual Field Defect	1 (0.2%)	1 (0.2%)	>0.999[c]
Arthritis	1 (0.2%)	0 (0.0%)	>0.999[c]
Deep Thrombophlebitis	1 (0.2%)	0 (0.0%)	>0.999[c]
Corneal Edema	1 (0.2%)	2 (0.5%)	0.589[c]
Skin Nevus (Lid)	0 (0.0%)	1 (0.2%)	0.446[c]
Tear Film Abnormality	0 (0.0%)	3 (0.7%)	0.088[c]

Ulcer (Cornea)	0 (0.0%)	2 (0.5%)	0.199[c]
Concentration Difficulty	0 (0.0%)	2 (0.5%)	0.199[c]
Memory Loss	0 (0.0%)	1 (0.2%)	0.446[c]
Impotency	0 (0.0%)	1 (0.2%)	0.446[c]
Tenosynovitis	0 (0.0%)	1 (0.2%)	0.446[c]
Bowel Abscess	0 (0.0%)	1 (0.2%)	0.446[c]
Scleritis	0 (0.0%)	1 (0.2%)	0.446[c]
Aortic Aneurysm	0 (0.0%)	3 (0.7%)	0.088[c]
Appendicitis	0 (0.0%)	1 (0.2%)	0.446[c]
Cerebrovascular Accident	0 (0.0%)	1 (0.2%)	0.446[c]
Kidney Failure	0 (0.0%)	2 (0.5%)	0.199[c]
Pain (eyelid)	0 (0.0%)	1 (0.2%)	0.446[c]
Rhinitis	0 (0.0%)	1 (0.2%)	0.446[c]
Bursitis	0 (0.0%)	1 (0.2%)	0.446[c]
Anterior Chamber Flare	0 (0.0%)	1 (0.2%)	0.446[c]

[a] The following findings have been removed for subjects having an Ocular Allergic Reaction: Lid Erythema, Lid Edema, Ocular Hyperemia Lid Edema, Ocular Hyperemia, Conjunctival Edema, Burning/Stinging, Blurring, F.B.S., Conjunctivitis, Blepharitis, Crusting (Lid), Lash Debris, Discharge (Conjunctiva), Follicles (Conjunctiva), Papillae (Conjunctiva), Follicles; Papillae (Conjunctiva), Edema+Papillae (Conjunctiva), Ocular Pruritus, Ocular Irritation, Eyelid Discomfort, Ocular Edema, and Lacrimation Disorder.
[b] Unless stated otherwise, p-value based on Pearson's Chi-square test.
[c] P-value based on Fisher's exact test.
[d] Includes Conjunctival Erythema/Hyperemia.
[e] Includes Allergic Blepharitis, Allergic Blepharoconjunctivitis, Allergic Conjunctivitis, Allergic Reaction (Ocular), and Follicular Conjunctivitis.

Integrated subgroup analysis:

Based on the combined data from studies 103 and 104 IOP changes were analized by demographic variables; age group (<45, 45-65, >65 years), sex (male vs female), race (white vs non white) and iris color (dark vs light). Comparing brimonidine to timolol the results of the subgroup analysis were similar to those in the overall preferred analysis. Within the brimonidine group mean IOP changes were compared between the categories for age, sex, race and iris color. No clinically significant differences were found.

5 Pages
Purged

Regulatory Recommendation: NDA 20-613, Alphagan Ophthalmic Solution is recommended for approval for lowering intraocular pressure in patients with open angle glaucoma and ocular hypertension with the above revised labeling.

Jose A. Carreras, M.D.
Ophthalmology Medical Officer

cc: NDA 20-613
HFD-550
HFD-550/Chem/Tso
HFD-550/Pharm/Conrad
HFD-550/ProjManager/Holmes
HFD-550/Acting Director/Chambers MAC 8/25/96

Medical Officer's Review NDA 20-613
Amendment

NDA 20-613 Amendment	Submission date: Review date:	8/28/96 8/28/96
Sponsor:	Allergan Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, California 92715-1599	
Drug name:	Alphagan	
Pharmacologic Category:	Alpha adrenergic receptor agonist	
Proposed Indication:	For the reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.	
Dosage Form and Route of Administration:	Topical ophthalmic solution.	
Submitted:	Draft Labeling	

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Regulatory Recommendation: NDA 20-613, Alphagan Ophthalmic Solution is recommended for approval for lowering intraocular pressure in patients with open angle glaucoma and ocular hypertension with the above labeling.

for

Jose A. Carreras, M.D.
Ophthalmology Medical Officer

cc: NDA 20-613
HFD-550
HFD-550/Chem/Tso
HFD-550/Pharm/Conrad
HFD-550/ProjManager/Holmes
HFD-550/Acting Director/Chambers mae 8/29/96

STATISTICAL REVIEW AND EVALUATION

JAN 30 1996

NDA#/Drug class:	20-613/1S
Applicant:	Allergan Inc.
Name of Drug:	Alphagan (brimonidine tartrate 0.2% ophthalmic solution)
Documents Reviewed:	Volumes 1.1, 1.59-1.69, dated August 31, 1995, and data on disks provided by the sponsor
Type of Report:	Statistical
Indication:	Single therapy for chronic use for IOP in patients with open-angle glaucoma or ocular hypertension.
Medical Officer:	Tony Carreras, M.D., HFD-540

I. Introduction

The applicant has submitted two studies (protocols A342-103-7831 and A342-104-7831) as pivotal evidence to support the claim that brimonidine tartrate 0.2% ophthalmic solution is safe and effective in the treatment of elevated intraocular pressure (IOP). Throughout the review, the terms "Study 103", and "study 104" refer to protocols A342-103-7831 and A342-104-7831, respectively. The treatment name abbreviations brimonidine and timolol refer to brimonidine tartrate 0.2% sterile ophthalmic solution and timolol maleate 0.5% sterile ophthalmic solution, respectively.

Two studies, 103 and 104, were identical in design with the exception of duration, randomization method and interim analyses. The objective of these two studies was to determine the long-term safety and ocular hypotensive efficacy of brimonidine administered twice-daily in subjects with open-angle glaucoma or ocular hypertension. Timolol maleate 0.5%, a marketed treatment for glaucoma with a known ability to lower IOP, served as the active control. Change in IOP from baseline was a primary efficacy endpoint.

II. Study Design, Study Population, and Statistical Methods

Studies 103 and 104 were multicenter, randomized, parallel comparison, active controlled trials. Study 103 had duration one year and study 104 had duration 6

months. Each study had two treatment arms (brimonidine and timolol). Study 103 had assignment of qualified subjects at each center to masked treatment groups in randomized blocks of four. Study 104 had assignment of qualified subjects at each center to masked treatment groups randomized in a 3 to 2 ratio, brimonidine and timolol, respectively. Dosage was one drop administered in each eye twice daily. Visit schedule in Study 103 was the following: Prestudy, day 0 (baseline), weeks 1, 2 (at new sites), months 1, 2, 3, 6, 9, and 12. Visit schedule in Study 104 was the following: Prestudy, day 0 (baseline), weeks 1, 2, months 1, 2 , 3, and 6.

REVIEWER COMMENTS: ***The protocol did not specify time window for clinic visits.***

In study 103, two interim analyses were performed but the applicant did not apply a P-value adjustment. It is the opinion of this reviewer that a P-value adjustment for two interim analyses should be applied to the efficacy analyses. Thus, in study 103, a P-value adjustment using the method of O'Brien and Fleming * will be applied, using a significance level of 0.047. Correspondingly, in study 103, adjusted 95.5% confidence intervals will be used to evaluate equivalence between brimonidine and timolol.

Inclusion Criteria: Male or female subjects (females not of child-bearing potential), 21 years of age or older, with primary open-angle glaucoma (OAG) or ocular hypertension (OHT) in each eye (subjects who were either newly diagnosed or who were currently receiving no more than two glaucoma drugs were considered eligible); visit 2 post-washout IOP of 23 mmHg or greater, but less than 35 mm Hg, in each eye; corrected visual acuity (VA) of 20/100 or better in each eye.

Exclusion Criteria: Any uncontrolled systemic disease; female volunteers who were pregnant, nursing, or of childbearing potential; any contraindications to alpha-adrenoceptor agonist or antagonist therapy and some other. For more details on the exclusion criteria please see the medical officer report.

Procedures at each visit: Following a washout period, all subjects returned for a baseline examination (day 0) when baseline measurement of IOP, visual acuity, pupil size, heart rate, and blood pressure were taken. Measurements of IOP were taken between 7:30 AM and 9:30 AM (corresponding to hour 0) and again between 9:30 AM and 11:30 AM (corresponding to hour 2). Biomicroscopy and Schrimer tear test were performed. Subject comfort was also assessed. Subjects who qualified for entry (i.e., IOP> = 23 mmHg and < 35 mmHg at hour 0) were

* [illegible] Geller and S. Pocock, Interim Analyses in Randomized Clinical Trials: Ramifications and Guidelines for Practitioners Biometrics, 43 pp 213-223, 1987

randomly assigned to one of the two treatment groups. Subjects were instructed to instill the study medication at 12 hour intervals, between the hours of 7:30AM and 9:30 AM and between 7:30 PM and 9:30 PM for the duration of the study. Subjects were instructed not to use the morning medication the day of a scheduled visit.

In Study 103, subjects returned for follow-up examinations at Week 1 and Months 1, 2, 3, 6, 9, and 12. Subjects at new sites had an additional visit at Week 2. Hour 0 measurements of IOP were taken at each visit. Hour 2 (post-instillation) measurements of IOP were taken at Week 2 (for new sites) and at Months 1, 3, 6 and 12.

In Study 104, subjects returned for follow-up examinations at Weeks 1, 2, and Months 1, 2, 3, and 6. Hour 0 measurements of IOP were taken at each follow-up visit. Hour 2 (post-instillation) measurements of IOP were taken at Weeks 1 and 2, and at Months 1, 3, and 6. Subject comfort was also assessed at all follow-up visits

Throughout the study, subjects were monitored for signs and symptoms of adverse events, ocular and general discomforts. Any adverse event occurring during the study was recorded by the investigator, graded for severity (trace, mild, moderate, or severe), and assessed for relationship to the study treatment.

STATISTICAL METHODS:

This reviewer used the following three population/strategies:

(1) *Preferred analysis* was the primary efficacy analysis which included all evaluable patients. A patient was deemed evaluable if he/she met the protocol entry criteria, and had data from at least one follow-up visit.

(2) *Last observation carried forward (LOCF)* analysis used all evaluable patients. The last observation for subjects who were terminated due to lack of efficacy was carried forward in the analysis of the scheduled visits as planned according to the protocol. The LOCF efficacy analyses were performed to evaluate the consistency and robustness of the results.

(3) *Intent-to-treat (ITT) analysis* included all subjects who received study medication. Efficacy and safety analyses were performed. The results of the ITT efficacy analysis were compared with those of the preferred analysis to support consistency and robustness of the results. The ITT safety analysis was the primary analysis for the safety profile of the studies.

The following definitions were used for subject disposition:

Completed - Disposition category for subjects who completed the treatment period (12 months in Study 103 and 6 months in Study 104).

Terminated - Disposition category for subjects who exited early from the study because of lack of efficacy or adverse events, whether or not these were judged to be treatment-related.

Excluded from the Preferred analysis - Subjects who were removed from the study due to improper study entry (e.g., should not have been enrolled in the study because of significant deviation from protocol-specified procedures for efficacy and/or baseline values that were determined to be clinically unacceptable by the investigator).

Discontinued - Disposition category for subjects who exited early from the study for reasons unrelated to the use of study medication.

Each study was designed as a multicenter study with at least ten subjects per group at each site. For the purpose of analysis where investigator and treatment-by-investigator interaction effects were involved, sites with fewer than 10 subjects per group were combined to form a single site or combined with larger sites by geographical proximity.

The categorical data for demographics were analyzed using the CMH method stratifying by investigator. Subject age was analyzed using the two-way ANOVA.

Frequency distributions were compared between the two treatment groups using Chi-square test. If there was a sufficiently large number of incidence observed at each visit, the frequency distributions were compared between the two treatment groups using the CMH method stratifying by investigator. The Breslow-Day test for homogeneity of the odds ratios was used to test the consistency of the response across investigators.

Since subjects were treated bilaterally, average values from both eyes were calculated for each subject as follows: the change (or percent change) from baseline was calculated separately for each eye, then an average was taken of the changes in both eye.

Efficacy IOP was the key efficacy variable. The null hypothesis was that there was no difference between the two treatment groups in mean IOP changes from baseline. The alternative hypothesis was that there was a difference between groups.

Within group analysis of changes from baseline was also performed for each treatment group. In this analysis, the null hypothesis of no change from baseline was tested against the two-sided alternative hypothesis that there was a change. In study 104, a P-value less than or equal to 0.05 was considered to be statistically significant for main effects. In study 103, to adjust for two interim analyses, a P-value less than or equal to 0.045 was considered to be statistically significant for main effects. A P-value less than or equal to 0.10 was considered to be statistically significant for drug-by-investigator interactions. For the key efficacy variable at hour 0 (trough) and hour 2 (peak), IOP, mean changes from baseline at each follow-up visit were compared between the two treatment groups via the two-way ANOVA (PROC GLM) with fixed effects for treatment, investigator, and treatment-by-investigator interaction. For the hour 2 analysis, baseline values were taken from data from hour 2 of visit 2 (pretreatment). Within each treatment group, mean changes from baseline and mean percent changes from baseline at each follow-up visit were analyzed using a paired t-test. Overall mean IOP changes and overall mean percent changes from baseline were analyzed via analysis of variance for repeated measures (PROC MIXED). The mixed model was used with fixed effects of treatment and study site for the repeated measures over 12 months in Study 103 (over 6 months in Study 104).

Notice that for a hypertensive treatment, change from baseline is a negative number (for example, if IOP is 23 mmHg at baseline and IOP is 18 mmHg at a follow-up visit, then change from baseline is -5 mmHg). The regulatory definition of equivalence states that two treatments are considered equivalent if the confidence interval includes zero and the absolute value of the difference between mean changes from baseline does not exceed 1.5 mmHg. Since we want the new drug not to be much worse than the marketed one, for the negative numbers this means that the upper bound of the confidence interval should not exceed 1.5 mmHg.

In study 104, the 95% confidence interval (two-sided) was used to test the equivalence between the two treatment groups regarding mean IOP changes from baseline at each follow-up visit. If the 95% confidence interval for the difference in the mean IOP reduction between brimonidine and timolol included 0 and its upper bound did not exceed 1.5 mm Hg, then brimonidine was considered to be equivalent to timolol.

In study 103, since the adjusted P-value of 0.045 was used, the reviewer employed an adjusted 95.5% confidence interval to evaluate equivalence between brimonidine and timolol. If the 95.5% confidence interval for the difference in the mean IOP reduction between brimonidine and timolol included 0 and its upper bound did not exceed 1.5 mm Hg, then brimonidine was considered to be equivalent to timolol.

Safety All subjects who received study medication, were included in the safety analysis. Frequency distributions were generated for the number and percent of subjects who had reported adverse events plus any findings with at least one severity grade increased from baseline. The frequency distributions were compared between the two treatment groups using Chi-square test or Fisher's exact test.

III. Results

Study 103

STUDY POPULATION AND SUBJECT DISPOSITION

Table 1 presents demographic characteristics of all subjects enrolled in Study 103. Of the 443 subjects, 221 were in the brimonidine group and 222 were in the timolol group. Ages ranged from 28 to 84 years, with mean age of 63 years. The majority of subjects in both treatment groups were Caucasians. As can be seen from Table 1, there was no significant difference ($P>0.1$) between the two treatment groups in age, sex, race, iris color, or diagnosis distribution. There were also no significant differences between the two treatment groups in any of the medical or ophthalmic history variables evaluated ($P\geq 0.2$).

Table 1. Demographics of all Patients in Study 001

		Brimonidine N = 221	Timolol N = 222	P-value*
Age (years)	Mean	62.6	62.5	1.0
	<45	17 (8%)	16 (7%)	
	45-65	100 (45%)	104 (47%)	
	>65	104 (47%)	102 (46%)	
Sex	Male	100 (45%)	117 (53%)	0.1
	Female	121 (55%)	105 (47%)	
Race	White	175 (79%)	172 (78%)	0.6
	Non-white	46 (21%)	50 (23%)	
Iris Color	Dark	107 (48%)	111 (50%)	0.7
	Light	114 (52%)	111 (50%)	
Diagnosis	OAG	137 (62%)	138 (62%)	0.9
	OHT	81 (37%)	80 (36%)	
	OAG/OHT§	3 (1%)	4 (2%)	

* P-values for between-group comparisons. Age was analyzed by two-way ANOVA. Sex, race, iris color and diagnosis were analyzed by CMH method. Treatment-by-investigator interactions were not significant (P>0.2).
§ One eye with OAG and the fellow eye with OHT.

The disposition of study subjects is summarized in Table 2. As can be seen from Table 2, in both ITT and in the Preferred analysis populations, significantly (P<0.001) fewer subjects in the brimonidine group completed the study and significantly more subjects in the brimonidine group were terminated due to ocular adverse events as compared to the timolol group (P<0.001).

Table 2. Summary of Subject Enrollment and Exit Status, Study 103

Exit Status *	Brimonidine	Timolol	P-value§
Included in Preferred Analysis#			
Enrolled	186	188	
Completed	115 (62%)	154 (82%)	<0.001
Terminated - LOE	13 (7%)	6 (3%)	0.09
Terminated - AE (Ocular)	30 (16%)	3 (2%)	<0.001
Terminated - AE (Systemic)	18 (10%)	9 (5%)	0.07
Discontinued	14 (8%)	17 (9%)	0.6
Excluded from Preferred Analysis			
Enrolled	35	34	
Completed	4 (11%)	13 (38%)	0.01
Terminated - LOE	4 (11%)	3 (9%)	0.7
Terminated - AE (Ocular)	2 (6%)	0 (0%)	0.2
Terminated - AE (Systemic)	4 (11%)	3 (9%)	0.7
Discontinued	21 (60%)	15 (44%)	0.2
ITT population (All Subjects)			
Enrolled	221	222	
Completed	119 (54%)	167 (75%)	<0.001
Terminated - LOE	17 (8%)	9 (4%)	0.1
Terminated - AE (Ocular)	32 (15%)	3 (1%)	<0.001
Terminated - AE (Systemic)	22 (10%)	12 (5%)	0.07
Discontinued	35 (16%)	32 (14%)	0.7

* LOE = Lack of efficacy. AE = Adverse event.

§ P-value for between-group comparisons in the Chi-square test.

Four subjects on Brimonidine and one subject on Timolol were terminated due to both the ocular and systemic AEs. The percentage was calculated based on the actual sample size as the denominator, and did not add up to 100%.

EFFICACY

Of the 443 subjects enrolled in the study, 374 (84%) were included in the Preferred efficacy analysis and in the LOCF efficacy analysis (186 on brimonidine and 188 on timolol). Nineteen subjects were terminated due to lack of efficacy (LOE) and were carried forward.

Trough (hour 0) The Preferred analysis of mean change from baseline in IOP at

trough is presented in Table 3. As can be seen from Table 3, mean decreases in IOP from baseline in Study 103 ranged from 3.7 to 5.3 mm Hg in the brimonidine group and from 5.8 to 6.8 mmHg in the timolol group. Mean decreases from baseline were statistically significant in both treatment groups at all follow-up visits ($P<0.001$). Timolol was statistically superior to brimonidine at all follow-up visits ($P\leq 0.03$).

Treatment-by-investigator interaction was not significant ($P\geq 0.11$) at all follow-up visits. Overall mean decreases from baseline were 4.3 mmHg in the brimonidine group and 6.3 mmHg in the timolol group ($P<0.001$).

The results of the Preferred analysis of mean percent change from baseline at trough were similar to those of mean change from baseline.

Peak (hour 2): The Preferred analysis of mean change from baseline in IOP in Study 103 is presented in Table 4. As can be seen from Table 4, mean decreases from baseline ranged from 5.3 to 6.7 mmHg in the brimonidine group and from 5.0 to 6.0 mmHg in the timolol group. Mean decreases from baseline were statistically significant in both groups at all follow-up visits ($P<0.001$). At Week 2, brimonidine treatment resulted in significantly greater decreases compared with timolol ($P=0.03$). At Months 1, 3, 6 and 12, brimonidine was equivalent to timolol in decreasing IOP ($P\geq 0.045$ and the upper bounds in the adjusted 95.5% confidence intervals were less than 1.1 mmHg).

The LOCF analysis produced results that were similar to those from the Preferred analysis except that at peak brimonidine produced significantly greater IOP reduction ($P<0.03$) than timolol only at Week 2, and therefore at peak, brimonidine and timolol were equivalent: ($P>0.2$) at Months 1, 3, 6 and 12.

The ITT efficacy analysis included all 448 enrolled patients and was consistent with the Preferred analysis except the following: at peak the between-group differences in mean change from baseline IOP were no longer significant at Week 2 and Month 3, i.e. at peak brimonidine and timolol were equivalent ($P>0.2$) at all visits (Week 2 and Months 1, 3, 6, and 12).

Table 3. Baseline and Mean IOP Changes from Baseline at Each Follow-up Visit in Study 103. (Trough - Preferred Analysis)

Timepoint		Brimonidine	Timolol	P-value*	Difference¿	95.5% CI**
Baseline	N	186	188	0.7	-0.12	(-0.67, 0.43)
	Mean	25.80	25.37			
Week 1	N	171	174	<0.001	1.19	(0.54, 1.84)
	Mean	-5.32	-6.47			
	P-value§	<0.001	<0.001			
Week 2†	N	63	65	0.030	1.24	(0.10, 2.38)
	Mean	-4.45	-5.81			
	P-value§	<0.001	<0.001			
Month 1	N	172	179	<0.001	2.21	(1.54, 2.88)
	Mean	-4.35	-6.57			
	P-value§	<0.001	<0.001			
Month 2	N	153	171	<0.001	2.65	(1.95, 3.35)
	Mean	-4.26	-6.84			
	P-value§	<0.001	<0.001			
Month 3	N	154	168	<0.001	1.87	(1.11, 2.63)
	Mean	-4.49	-6.32			
	P-value§	<0.001	<0.001			
Month 6	N	130	162	<0.001	2.52	(1.72, 3.31)
	Mean	-3.89	-6.40			
	P-value§	<0.001	<0.001			
Month 9	N	119	153	<0.001	2.13	(1.32, 2.93)
	Mean	-4.20	-6.18			
	P-value§	<0.001	<0.001			
Month 12	N	106	149	<0.001	2.27	(1.32, 3.23)
	Mean	-3.67	-5.88			
	P-value§	<0.001	<0.001			

* P-value based on the two-way ANOVA.

§ Within-group analysis of changes from baseline using paired t-test.

† Twelve of the 26 investigators had the revised protocol with Week 2 scheduled.

¿ Estimate was computed for the difference of mean baseline and mean changes from baseline at each scheduled follow-up visit based on the least-squares means by brimonidine group minus timolol group.

** To adjust for two interim analyses, 95.5% confidence intervals were used.

Table 4. Baseline and Mean IOP Changes from Baseline at Each Follow-up Visit in Study 103. (Peak - Preferred Analysis)

Time point		Brimonidine	Timolol	P-value*	Difference‡	95.5% CI**
Baseline	N	185	187	1.0	0.02	(-0.71, 0.75)
	Mean	24.20	24.19			
Week 2#	N	62	63	0.03	-1.57	(-3.05, -0.09)
	Mean	-6.66	-5.01			
	P-value§	<0.001	<0.001			
Month 1	N	170	177	0.8	0.12	(-0.76, 1.00)
	Mean	-5.58	-5.86			
	P-value§	<0.001	<0.001			
Month 3	N	151	171	0.045	-0.90	(-1.79, 0.00)
	Mean	-6.41	-5.75			
	P-value§	<0.001	<0.001			
Month 6	N	134	159	0.7	0.18	(-0.68, 1.05)
	Mean	-5.68	-5.98			
	P-value§	<0.001	<0.001			
Month 12	N	113	145	1.0	0.03	(-0.94, 0.99)
	Mean	-5.30	-5.61			
	P-value§	<0.001	<0.001			

* P-value based on the two-way ANOVA.

§ Within-group analysis of changes from baseline using paired t-test.

\# Twelve of the 26 investigators had the revised protocol with Week 2 scheduled.

‡ Estimate was computed for the difference of mean baseline and mean changes from baseline at each scheduled follow-up visit based on the least-squares means by brimonidine group minus timolol group.

** To adjust for two interim analyses, 95.5% confidence interval were used.

SAFETY

Data collected for the safety evaluation included adverse event reports; ocular safety variables including the symptoms of ocular discomfort, biomicroscopy and ophthalmoscopy, Schirmer tear test results, visual acuity, and pupil size; and systemic safety variables including the symptoms of systemic discomfort, heart rate, systolic and diastolic blood pressure, and laboratory data (hematology and blood chemistry).

Exposure to Treatment Patients instilled brimonidine or timolol twice daily to both eyes for up to one year. Total 221 subjects received brimonidine and 222 subjects received timolol for at least one day. The longest exposure of at least 12 months was experienced by 124 subject on brimonidine and 167 subjects on timolol.

Adverse Events Analysis of adverse events was primary safety analysis. Ocular and systemic adverse events (including adverse events reports, discomfort data and biomicroscopic and ophthalmoscopic findings) occurred in 86% (191/221) of subjects in the brimonidine group and in 82% (181/222) of subjects in the timolol group. The most common adverse events are summarized in Table 5.

Table 5. Adverse Events. Number and Percentage of Subjects in Study 103 with at Least One Severity Grade Increased from Baseline at One or More Follow-up Visits.

Finding	Brimonidine	Timolol	P-value*
Oral Dryness	73 (33%)	43 (19%)	0.001
Ocular Hyperemia	67 (30%)	52 (23%)	0.1
Burning Stinging	62 (28%)	93 (42%)	0.002
Blurring	49 (22%)	50 (23%)	0.9
Fatigue Drowsiness	44 (20%)	38 (17%)	0.5
Lens Pathology	43 (20%)	50 (23%)	0.4
Headache	42 (19%)	44 (20%)	0.8
Foreign Body Sensation	34 (15%)	36 (16%)	0.8
Fundus Pathology	33 (15%)	36 (16%)	0.7
Ocular Pruritus	27 (12%)	21 (10%)	0.4
Photophobia	25 (11%)	25 (11%)	1.0
Lid Erythema	23 (10%)	16 (7%)	0.2
Ocular Allergic Reaction	20 (9%)	0 (0%)	<0.001#
Corneal Staining/Erosion	20 (9%)	24 (11%)	0.5
Follicles (Conjunctiva)	18 (8%)	5 (2%)	0.005

* Unless stated otherwise, P-value based on Pearson's Chi-square test.
\# P-value based on Fisher's exact test.

As can be seen from Table 5, the most common adverse events in the brimonidine group were oral dryness, ocular hyperemia, burning/stinging, blurring, and fatigue/drowsiness. Among all adverse events, significant differences between the treatment groups were noted only for four: oral dryness, ocular allergic reaction, and conjunctival follicles were significantly more frequent in the brimonidine group ($P<0.005$) and burning stinging was significantly more frequent in the timolol group ($P=0.002$).

None of the serious adverse events occurring in 5.4% (12/221) of the subjects treated with brimonidine and 5.4 (12/222) of the subjects treated with timolol were judged to be treatment associated. There were no laboratory adverse events.

Termination Due to Adverse Events. During the treatment period, 14% (64/443) of all subjects were terminated from the study because of adverse events. Subjects terminated because of adverse events included 23% (50/221) of subjects treated with brimonidine and 6% (14/222) treated with timolol ($P<0.001$). Ocular adverse events resulted in the termination of 8% (35/443) of all subjects. Terminations because of ocular adverse events included 15% (32/221) of subjects in the brimonidine group and 1% (3/222) of the timolol group ($P<0.001$, Table 2). The most frequent causes of terminations due to adverse events in the brimonidine group were ocular allergic reaction and ocular hyperemia. Terminations due to systemic adverse events occurred in the 8% (34/443) of all subjects. Terminations due to systemic events occurred in 10% (22/221) of subjects in the brimonidine group and in 5% (12/222) of subjects in the timolol group ($P=0.07$, Table 2).

REVIEWER CONCLUSIONS: ***Using the adjusted P-value of 0.045 in Study 103, in the Preferred efficacy analyses of IOP reductions at trough, brimonidine was statistically inferior to timolol at all follow-up visits ($P=0.03$ at Week 2 and $P<0.001$ at other follow-up visits). At peak, brimonidine was equivalent to timolol in IOP reductions at Months 1, 3, 6 and 12 ($P \leq 0.045$ and the upper bound in the adjusted 95.5% confidence interval less than 1.1 mmHg) and at Week 2 brimonidine was statistically superior to timolol ($P=0.03$). The LOCF and ITT efficacy analyses produced results that were similar to those from the Preferred analyses.***

Safety analysis of Study 103 demonstrated that brimonidine was statistically inferior to timolol relative to occurrence of oral dryness, ocular allergic reaction, and conjunctival follicles ($P \leq 0.005$). Brimonidine was statistically superior to timolol in the occurrence of burning/stinging ($P=0.002$). Brimonidine and timolol were comparable in occurrence of other common adverse events. Brimonidine was statistically inferior to timolol in the termination rate due to ocular adverse events ($P<0.001$).

Study 104

STUDY P[illegible]N AND SUBJECT DISPOSITION

Table 6 presents demographic characteristics of all subjects enrolled in Study 104. Of the 483 subjects, 292 were in the brimonidine group and 191 were in the timolol group. Ages ranged from 28.5 to 86.4 years, with a mean age of 62.2 years. The majority of subjects in both treatment groups were Caucasians. As can be seen from Table 6, there was no significant difference (P>0.3) between the two treatment groups in age, sex, race, iris color, or diagnosis distribution.

Table 6. Demographics of all Patients in Study 104

		Brimonidine N=292	Timolol N=191	P-value*
Age (years)	Mean	62.7	61.4	0.3
	<45	21 (7%)	17 (9%)	
	45-65	134 (46%)	91 (48%)	
	>65	137 (47%)	83 (44%)	
Sex	Male	145 (50%)	101 (53%)	0.5
	Female	147 (50%)	90 (47%)	
Race	White	242 (83%)	162 (85%)	0.5
	Non-white	50 (17%)	29 (15%)	
Iris Color	Dark	111 (38%)	70 (37%)	0.7
	Light	181 (62%)	121 (63%)	
Diagnosis	OAG	164 (56%)	103 (54%)	0.7
	OHT	115 (39%)	81 (42%)	
	OAG/OHT§	13 (5%)	7 (4%)	

* P-values for between-group comparisons. Age was analyzed by two-way ANOVA. Sex, race, iris color and diagnosis were analyzed by CMH method. Treatment-by-investigator interactions were not significant (P>0.1).
§ One eye with OAG and the fellow eye with OHT.

The disposition of study subjects is summarized in Table 7. As can be seen from Table 7, in both ITT and in the Preferred analysis populations, significantly smaller percent of subjects in the brimonidine group completed the study (P<0.001) and

significantly greater percent of subjects in the brimonidine group was terminated due to ocular adverse events ($P<0.001$) or lack of efficacy ($P\leq 0.03$) as compared to the timolol group.

Table 7. Summary of Subject Enrollment and Exit Status, Study 104

Exit Status *	Brimonidine	Timolol	P-value§
Included in Preferred Analysis#			
Enrolled	280	183	
Completed	209 (75%)	165 (90%)	<0.001
Terminated - LOE	23 (8%)	6 (3%)	0.03
Terminated - AE (Ocular)	26 (9%)	1 (1%)	<0.001
Terminated - AE (Systemic)	14 (5%)	3 (2%)	0.06
Discontinued	10 (4%)	8 (4%)	0.7
Excluded from Preferred Analysis			
Enrolled	12	8	
Completed	1 (8%)	2 (25%)	0.3
Terminated - LOE	1 (8%)	0 (0%)	0.4
Terminated - AE (Ocular)	1 (8%)	0 (0%)	0.4
Discontinued	9 (75%)	6 (75%)	1.0
ITT population (All Subjects)			
Enrolled	292	191	
Completed	210 (72%)	167 (87%)	<0.001
Terminated - LOE	24 (8%)	6 (3%)	0.02
Terminated - AE (Ocular)	27 (9%)	1 (<1%)	<0.001
Terminated - AE (Systemic)	14 (5%)	3 (2%)	0.06
Discontinued	19 (7%)	14 (7%)	0.7

* LOE = Lack of efficacy. AE = Adverse event.

§ P-value for between-group comparisons in the Chi-square test.

One subjects on brimonidine was terminated due to both an ocular and systemic AE. Another subject on brimonidine was terminated due to LOE and an ocular AE. The percentage was calculated based on the actual sample size as the denominator, and did not add up to 100%.

EFFICACY

Of the 483 subjects enrolled in the study, 463 (96%) were included in the Preferred efficacy analysis and in the LOCF efficacy analysis (280 on brimonidine and 183 on timolol). Twenty nine (29) subjects were terminated due to lack of efficacy (LOE) and 26 subjects were carried forward because three were terminated

at the last visit.

Trough (hour 0) The Preferred analysis of mean change from baseline in IOP at trough is presented in Table 8.

Table 8. Baseline and Mean IOP Changes from Baseline at Each Follow-up Visit in Study 104. (Trough - Preferred Analysis)

Timepoint		Brimonidine	Timolol	P-value*	Difference¶	95% CI
Baseline	N	274	180	0.3	0.3	(-0.26, 0.93)
	Mean	25.96	25.85			
Week 1	N	265	174	<0.001	1.56	(0.95, 2.17)
	Mean	-4.78	-6.44			
	P-value§	<0.001	<0.001			
Week 2	N	254	164	<0.001	1.55	(0.91, 2.20)
	Mean	-4.59	-6.18			
	P-value§	<0.001	<0.001			
Month 1	N	250	171	<0.001	2.09	(1.48, 2.70)
	Mean	-3.98	-6.16			
	P-value§	<0.001	<0.001			
Month 2	N	239	165	<0.001	2.17	(1.51, 2.82)
	Mean	-4.18	-6.42			
	P-value§	<0.001	<0.001			
Month 3	N	230	163	<0.001	2.08	(1.42, 2.73)
	Mean	-4.04	-6.20			
	P-value§	<0.001	<0.001			
Month 6	N	198	159	<0.001	2.26	(1.54, 2.99)
	Mean	-3.79	-6.10			
	P-value§	<0.001	<0.001			

* P-value based on the two-way ANOVA.

§ Within-group analysis of changes from baseline using paired t-test.

¶ Estimate was computed for the difference of mean baseline and mean changes from baseline at each scheduled follow-up visit based on the least-squares means by brimonidine group minus timolol group.

As can be seen from Table 8, mean decreases in IOP from baseline in Study 104 ranged from 3.8 to 4.8 mm Hg in the brimonidine group and from 6.1 to 6.4 mmHg

in the timolol group. Mean decreases from baseline were statistically significant in both treatment groups at all follow-up visits ($P<0.001$). Timolol was statistically superior to brimonidine at all follow-up visits ($P\leq 0.001$).

Treatment-by-investigator interaction was not significant ($P\geq 0.18$) at all follow-up visits. Overall mean decreases from baseline were 4.1 mmHg in the brimonidine group and 6.1 mmHg in the timolol group ($P=0.004$).

The results of the Preferred analysis of mean percent change from baseline at trough were similar to those of mean change from baseline.

Peak (hour 2) The Preferred analysis of mean change from baseline in IOP in Study 104 is presented in Table 9. As can be seen from Table 9, mean decreases from baseline ranged from 6.2 to 7.3 mmHg in the brimonidine group and from 5.4 to 6.3 mmHg in the timolol group. Mean decreases from baseline were statistically significant in both groups at all follow-up visits ($P<0.001$). At Weeks 1 and 2, brimonidine treatment resulted in significantly greater decreases compared with timolol ($P\leq 0.007$). At Months 1, 3, and 6, brimonidine was equivalent to timolol in decreasing IOP ($P>0.1$ and the upper bounds in the 95% confidence intervals were less than 0.4 mmHg).

The LOCF analysis produced results that were similar to those from the Preferred analysis.

The ITT efficacy analysis included all 443 enrolled patients and was consistent with the Preferred analysis.

Table 9. Baseline and Mean IOP Changes from Baseline at Each Follow-up Visit in Study 104 (Peak - Preferred Analysis)						
Timepoint		Brimonidine	Timolol	P-value*	Difference¶	95% CI
Baseline	N	260	178	0.32	0.37	(-0.36, 1.10)
	Mean	24.75	24.41			
Week 1	N	252	174	0.004	-1.15	(-1.92, -0.38)
	Mean	-7.34	-6.31			
	P-value§	<0.001	<0.001			
Week 2	N	244	162	0.007	-1.04	(-1.80, -0.29)
	Mean	-6.97	-6.13			
	P-value§	<0.001	<0.001			
Month 1	N	236	166	0.1	-0.63	(-1.38, 0.12)
	Mean	-6.56	-6.03			
	P-value§	<0.001	<0.001			
Month 3	N	216	162	0.2	-0.53	(-1.33, 0.27)
	Mean	-6.51	-6.07			
	P-value§	<0.001	<0.001			
Month 6	N	192	156	0.2	-0.50	(-1.34, 0.33)
	Mean	-6.15	-5.42			
	P-value§	<0.001	<0.001			

* P-value based on the two-way ANOVA.

§ Within-group analysis of changes from baseline using paired t-test.

¶ Estimate was computed for the difference of mean baseline and mean changes from baseline at each scheduled follow-up visit based on the least-squares means by brimonidine group minus timolol group.

SAFETY

Data collected for the safety evaluation included adverse event reports; ocular safety variables including the symptoms of ocular discomfort, biomicroscopy and ophthalmoscopy, Schrimer tear test results, visual acuity, and pupil size; and systemic safety variables including the symptoms of systemic discomfort, heart rate, systolic and diastolic blood pressure, and laboratory data (hematology and blood chemistry).

Exposure to Treatment Patients instilled brimonidine or timolol twice daily to both eyes for up to 6 months. Total 292 subjects received brimonidine and 191 subjects

received timolol for at least one day. The longest exposure of at least 6 months was experienced by 227 subject on brimonidine and 171 subjects on timolol.

Adverse Events Analysis of adverse events was primary safety analysis. Ocular and systemic adverse events (including adverse events reports, discomfort data and biomicroscopic and ophthalmoscopic findings) occurred in 87% (254/292) of subjects in the brimonidine group and in 82% (156/191) of subjects in the timolol group. The most common adverse events are summarized in Table 10.

Table 10. Adverse Events in Study 104. Number and Percentage of Subjects with at Least One Severity Grade Increased from Baseline at One or More Follow-up Visits.

Finding	Brimonidine	Timolol	P-value*
Oral Dryness	81 (28%)	21 (11%)	<0.001
Ocular Hyperemia	68 (23%)	43 (23%)	0.8
Burning/Stinging	61 (21%)	75 (39%)	<0.001
Headache	54 (19%)	34 (18%)	0.8
Foreign Body Sensation	53 (18%)	26 (14%)	0.2
Blurring	41 (14%)	33 (17%)	0.3
Lens Pathology	39 (13%)	28 (15%)	0.7
Fatigue/Drowsiness	37 (13%)	18 (9%)	0.3
Ocular Allergic Reaction#	29 (10%)	1 (0.5%)	<0.001
Ocular Pruritus	257 (9%)	15 (8%)	0.8
Follicles (Conjunctiva)	22 (8%)	7 (4%)	0.08
Corneal Staining/Erosion	21 (7%)	20 (11%)	0.2
Ocular Ache/Pain	19 (7%)	5 (3%)	0.054
Photophobia	19 (7%)	11 (6%)	0.7
Ocular Dryness	18 (6%)	16 (8%)	0.4

* Unless stated otherwise, P-value based on Person's Chi-square test.
\# P-value based on Fisher's exact test.

As can be seen from Table 10, the five most common adverse events in the brimonidine group were oral dryness, ocular hyperemia, burning/stinging, headache, and foreign body sensation. Among all adverse events, significant differences ($P<0.001$) between the treatment groups were noted only for three: oral dryness and ocular allergic reaction were significantly more frequent in the brimonidine group and burning/stinging was significantly more frequent in the timolol group.

None of the serious adverse events occurring in 1.7% (5/292) of the subjects treated with brimonidine and 1% (1/191) of subjects treated with timolol were judged to be treatment associated.

Termination Due to Adverse Events. During the six-month treatment period, 9% (44/483) of all subjects were terminated from the study because of adverse events. Subjects terminated because of adverse events included 14% (40/292) of subjects treated with brimonidine and 2% (4/191) treated with timolol. This difference was statistically significant with $P<0.001$. Ocular adverse events resulted in the termination of 6% (28/483) of all subjects. Terminations because of ocular adverse events include 9% (27/292) of subjects in the brimonidine group and <1% (1/191) of the timolol group ($P<0.001$, Table 7). Terminations due to systemic adverse events occurred in 4% (17/483) of all subjects. Terminations due to systemic events occurred in 5% (14/292) of subjects in the brimonidine group and in 2% (3/191) of subjects in the timolol group (0.06, Table 7). The most frequent causes of terminations due to adverse events in the brimonidine group were ocular allergic reaction, asthenia, headache, and oral dryness.

REVIEWER CONCLUSIONS: ***In Study 104, in the Preferred analyses of IOP changes from baseline at trough, brimonidine was statistically inferior to timolol ($P<0.001$) at all follow-up visits. At peak, brimonidine was equivalent to timolol at Months 1, 3, and 6 ($P>0.1$ and the upper bound of the 95% confidence interval less than 0.4 mmHg) and brimonidine was statistically superior to timolol at Weeks 1 and 2 ($P\leq 0.007$). Significantly more subjects in the brimonidine group were terminated due to lack of efficacy ($P=0.03$) than in the timolol group. The LOCF and ITT efficacy analyses produced results that were similar to those from the Preferred analyses.***

Safety analysis of Study 104 demonstrated that brimonidine was statistically inferior to timolol relative to occurrence of oral dryness and ocular allergic reaction ($P\leq 0.001$). Brimonidine was statistically superior to timolol in the occurrence of burning/stinging ($P<0.001$). Brimonidine and timolol were comparable in occurrence of other common adverse events ($P>0.05$). Brimonidine was statistically inferior to timolol in the termination rate due to ocular adverse events ($P<0.001$).

Integrated Subgroup Analysis

Based on the combined data from Studies 103 and 104, mean IOP changes from baseline were analyzed by demographic variables: age group (<45 years, 45-65 years, >65 years), sex (male vs. female), race (white vs. non-white), and iris color (dark vs. light). Comparing brimonidine to timolol, the results of the subgroup analysis were similar to those in the overall Preferred analysis: timolol was statistically more effective than brimonidine at lowering IOP. Within the brimonidine group, mean IOP changes were compared between the categories for age, sex, race, and iris color. No significant differences in mean IOP changes from baseline were found except for the analysis by age at Month 2 (P=0.03).

IV. SUMMARY AND CONCLUSIONS (Which may be conveyed to the Sponsor)

Since two interim analyses were performed in study 103, the reviewer used an adjusted P-value of 0.045. In study 103, in the Preferred efficacy analyses of IOP reductions at trough, brimonidine was statistically inferior to timolol at all follow-up visits (P=0.03 at Week 2 and P<0.001 at other follow-up visits). At peak, brimonidine was equivalent to timolol in IOP reductions at Months 1, 3, 6 and 12 (P < 0.045 and the upper bound in the adjusted 95.5% confidence interval less than 1.1 mmHg) and at Week 2 brimonidine was statistically superior to timolol (P=0.03). The LOCF and ITT efficacy analyses produced results that were similar to those from the Preferred analyses.

In Study 104, in the Preferred analyses of IOP changes from baseline at trough, brimonidine was statistically inferior to timolol (P<0.001) at all follow-up visits. At peak, brimonidine was equivalent to timolol at Months 1, 3, and 6 (P>0.1 and the upper bound of the 95% confidence interval less than 0.4 mmHg) and brimonidine was statistically superior to timolol at Weeks 1 and 2 (P<0.007). Significantly more subjects in the brimonidine group were terminated due to lack of efficacy (P=0.03) than in the timolol group. The LOCF and ITT efficacy analyses produced results that were similar to those from the Preferred analyses.

Integrated subgroup analysis of studies 103 and 104 supported the results of the efficacy analyses of these studies.

Safety analyses of both studies 103 and 104 demonstrated that brimonidine was statistically inferior to timolol relative to occurrence of oral dryness and ocular allergic reaction (P<0.001). In study 103, brimonidine was also inferior to timolol relative to occurrence of conjunctival follicles. In both studies 103 and 104, brimonidine was statistically superior to timolol in the occurrence of burning/stinging (P≤ 0.002). Brimonidine and timolol were comparable in occurrence of other common adverse events. In both studies, brimonidine was

statistically inferior to timolol in the termination rate due to ocular adverse events ($P<0.001$).

RECOMMENDED REGULATORY ACTION: ***Studies 103 and 104 provide sufficient statistical evidence to indicate that brimonidine 0.2% b.i.d. is inferior to timolol 0.5% b.i.d. with respect to long term efficacy and safety. So, this reviewer does not recommend approval of brimonidine 0.2% b.i.d. as a first-line monotherapy for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension. However, brimonidine 0.2% b.i.d. may be useful for patients in which timolol is contraindicated. This is a matter for the clinical judgement of the reviewing medical division.***

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cc: 20-613
Archival NDA ~~20-524~~
HFD-540
HFD-540/Mr. Cross
HFD-540/Dr. Wilkin
HFD-540/Dr. Chambers
HFD-540/Dr. Carreras
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan

JAN 30 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-613

Submission Date: August 31, 1995

Product: Brimonidine Tartrate 0.2% Ophthalmic Solution (ALPHAGAN®)
Chemical Name: [5-bromo-6-(2-imidazolidinylideneamino)quinoxaline L-tartrate]

Sponsor: Allergan, Inc.,
Irvine, CA

Type of Submission: Original New Drug Application

OCPB Reviewer: Philip M. Colangelo, Pharm.D., Ph.D.

I. SYNOPSIS

The sponsor submitted the results from a total of 80 animal, human, and analytical studies to support this NDA for brimonidine tartrate 0.2% ophthalmic solution. Of these studies, 4 *in vivo* human pharmacokinetic/pharmacodynamic studies and 5 *in vitro* studies of the distribution and metabolism of brimonidine were reviewed. The *in vivo* human studies have adequately addressed (1) the absorption, metabolism, and elimination of brimonidine following a radioactive oral dose; (2) systemic plasma pharmacokinetics and dose proportionality following single ocular doses above and below the targeted dose for this application (i.e., 0.08%, 0.2%, 0.5%); and (3) multiple ocular dose plasma pharmacokinetics in young healthy subjects and single ocular dose plasma pharmacokinetics in elderly subjects using the 0.2% solution. The sponsor has also attempted pharmacokinetic/pharmacodynamic analyses after single and multiple ocular doses (0.2%) in young volunteers and after a single ocular dose (0.2%) in elderly subjects. In addition, plasma brimonidine concentrations after multiple ocular doses of 0.2% were evaluated over a 12 week period in patients with either open angle glaucoma or ocular hypertension.

The *in vitro* studies addressed human plasma protein binding, blood to plasma partitioning, and hepatic metabolism using human liver microsomes and liver slices.

II. RECOMMENDATION

The information contained in the Human Pharmacokinetics and Bioavailability Section of NDA 20-613 is acceptable for meeting the requirements of 21 CFR 320.21 and the Clinical Pharmacology labeling under 21 CFR 201.57 provided that Comments 1 through 4 are adequately addressed by the sponsor. Comments 5 through 11 are for

general information pur, oses and may be conveyed to the sponsor.

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Appendix 1 - Review of Pharmacokinetic/Pharmacodynamic Studies:

1. Study (^{14}C-Brimonidine ADME Study)
2. Protocol A342-120-8042 (PK - Single Dose Escalation)
3. Protocol A342-106-7831 (PK/PD - Single/Multiple Dose; Young/Elderly)
4. Protocol A342-119-783: (PK - Tid *vs.* Bid Dosing in Patients)
5. Protocol PK-1991-RSCH-015-AGN 190342 (*In Vitro* Plasma Protein Binding)
6. Protocol PK-94-P009 (*In Vivo* Plasma Protein Binding)
7. Protocol PK-1992-RSCH-023-AGN 190342-LF (Blood:Plasma Partitioning)
8. Protocol PK-1990-RSCH-013-AGN 190342 (*In Vitro* Metabolism)
9. Protocol PK-95-021 (*In Vitro/In Vivo* Metabolite Identification)

Appendix 2 (Included With Review):

Proposed Labeling

Appendix 2 List (Available Upon Request):

Protocol A342-120-8042:
- Assay Amendment
- Plasma Brimonidine Concentrations

Protocol A342-106-7831:
- Plasma Brimonidine Concentrations
- Pharmacodynamic Measures
- PK/PD Modeling Parameters

Protocol A342-119-7831:
- Plasma Brimonidine Concentrations

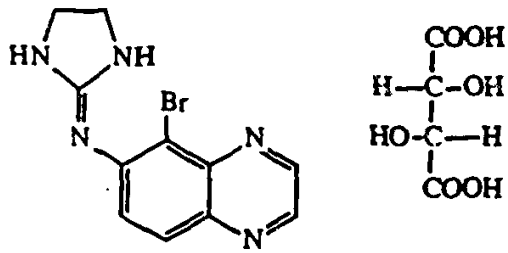
III. BACKGROUND

Brimonidine tartrate (AGN 190342-LF) is a potent and selective α_2-adrenergic receptor agonist. It is intended to be used as first-line, single-agent therapy for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) and/or ocular hypertension (OHT). The IOP reducing effects apparently are the result of suppression of aqueous humor production and from enhanced uveoscleral outflow. According to the sponsor, the ocular hypotensive effects in rabbits are mediated through stimulation of peripheral α_2-adrenoreceptors whereas the ocular hypotensive and cardiovascular effects (i.e., blood pressure reduction) in primates are mediated by an imidazoline receptor in the brain. The marketed product will be a 0.2% ophthalmic solution of brimonidine tartrate and the recommended dose will be one drop instilled into the affected eye(s) twice daily (every 12 hours). The sponsor has studied the safety and efficacy of this regimen for up to 12 months in two pivotal clinical trials (Protocols A342-103-7831 and A342-104-7831).

IV. DRUG CHARACTERISTICS AND FORMULATION

A. Physical/Chemical Characteristics

1. Structure



AGN 190342-LF
Brimonidine tartrate

2. Molecular Formula: $C_{15}H_{16}N_5O_6Br$

3. Molecular Weight: 442.24

4. pK_a: 7.78 ± 0.05

B. Dosage Formulation

The formulation of the product proposed in this NDA (i.e., 0.2% ophthalmic solution) is Formula No. 7831X. This formulation was used in 3 of the 4 human pharmacokinetic studies that were reviewed (i.e., Protocols A342-120, A342-106, and A342-119) and in the two pivotal safety and efficacy studies (i.e., A342-103 and A342-104). The table below gives the composition of the final product and a representative batch (140L) for Formula No. 7831X.

Ingredient	Percent (w/v)	mg/mL	Composition for a 140 liter batch

Drug product stability of Formulation No. 7831X has been tested with respect to brimonidine tartrate, benzalkonium chloride, osmolality, pH, physical appearance, preservative effectiveness, sterility, brimonidine tartrate related substances, and water loss. Of these factors, water loss was found to be the limiting parameter for determination of expiration dating for the 0.2% ophthalmic solution. Fill volumes of 10ml and 15 ml have been shown to be chemically and physically stable for at least 30 months at or below 25°C, while 6 ml fill volumes (physician samples only) are stable for 24 months. The sponsor proposed a 36-month expiration date on the 10 and 15 ml capacity bottles and a 24-month expiration on the 6 ml physician sample bottles when stored at or below 25°C.

V. PHARMACOKINETICS/PHARMACODYNAMICS STUDY SUMMARIES

A. Pharmacokinetics

1. Protocol No. A342-120-8042: "Systemic Drug Absorption Following a Single Eyedrop of 0.08%, 0.2%, and 0.5% Brimonidine Tartrate to Healthy Human Subjects" (Report No. PK-1992-034)

This study evaluated the pharmacokinetics and dose proportionality of brimonidine plasma concentrations following single doses of 0.08%, 0.2%, and 0.5% into each eye using a randomized, double-blind, 3-way crossover design in 24 young healthy male subjects. Following instillation of a single 0.2% dose of brimonidine tartrate into each eye, quantifiable brimonidine plasma concentrations in the pg/ml range were observed at 0.5 hours, with maximum concentrations (mean ~50 pg/ml) occurring at ~1-2 hrs. The mean AUC(0-12) was estimated to be 241 pg.hr/ml after the 0.2% dose. Brimonidine plasma concentrations were less than 2 pg/ml by ~12 hrs after the 0.2% dose. Values of apparent T½ were given for each subject rather than for each dose and the overall mean apparent T½ was 3.26 hrs (range from 1.77 to 5.00 hrs). The intersubject variability (i.e., %CV) for Cmax and AUC was high, i.e., ~50% for all three doses, and was even higher for Tmax, ranging between ~51% and ~88% and suggested that absorption of brimonidine from the eye may be a variable process.

Although the increases in AUC and Cmax appeared to be nearly linear as the dose strength increased from 0.08% to 0.2% to 0.5%, the increases in AUC (log-transformed and dose normalized) was proportional between 0.08% and 0.2%, and not between 0.2% and 0.5% or 0.08% and 0.5% (i.e, less than proportional in both cases). The increases in Cmax (log-transformed and dose normalized) between the three dose levels was less than proportional.

2. Protocol No. A342-119-7831: "A Comparison of the Safety and Efficacy (and Pharmacokinetics) of Twice Daily vs. Three Times Daily Administration of Brimonidine 0.2% in Subjects with Open Angle Glaucoma or Ocular Hypertension" (Report No. PK-1993-074)

This study evaluated the efficacy, safety, and plasma concentrations of brimonidine after either bid or tid treatment with 0.2% into each eye (one drop) for 12 weeks using a randomized, double blind, parallel groups design in 96 patients with either OAG or OHT. Plasma brimonidine concentrations were determined in 47 of the 96 patients before the morning dose (i.e., trough) at weeks 3, 6, 8, and 12, and also at 7 and 11 hrs after the morning dose on weeks 6 and 12. Steady-state trough (i.e., predose) plasma brimonidine plasma concentrations appeared to be attained by 3 weeks of multiple bid or tid dosing. Mean trough plasma levels were similar between the two dosing groups at weeks 3, 6, 8, and 12 and ranged between ~11 and ~16 pg/ml. The mean 7-hour postdose levels at weeks 6 and 12 were also similar between and within the groups and ranged between ~15 and ~17 pg/ml. However, mean concentrations at 11 hours postdose (i.e., 4 hours after the second dose) at weeks 6 and 12 were ~9-fold higher for the tid group (~40 pg/ml) compared to the bid (~4.5 pg/ml) group. The between patient variability in plasma concentrations for both groups was high (i.e., CV ~50-120%) across all time intervals.

The reductions in IOP from baseline values for the two groups were not significantly different at the morning trough at weeks 3, 6, 8, and 12, but were significantly different at 9 and 11 hours after morning dosing at weeks 6 and 12.

B. Pharmacokinetic/Pharmacodynamic Studies (PK/PD Analyses)

3. Protocol No. A342-106-7831: "An Evaluation of the Accumulation of Brimonidine in Plasma Following Single and Multiple Topical Dosing of 0.2% Brimonidine Tartrate in Normal Subjects" (Report No. PK-95-042)

This open-label study was designed to: (1) compare the plasma pharmacokinetics (noncompartmental) of brimonidine following single (Day 1) vs multiple bid doses for 10 days (Day10) in young healthy male and female subjects (n=7); (2) compare the plasma pharmacokinetics (noncompartmental) of brimonidine in the same young (n=7) vs elderly subjects (n=9) following single doses (Day 1); (3) assess the effect of brimonidine on intraocular pressure (IOP), heart rate (HR), systolic and diastolic blood pressures (SBP and DBP) following single and multiple ocular dose administration; and (4) examine the relationships between plasma brimonidine concentrations and systemic effects following single and multiple ocular dose administration using compartmental PK/PD modeling.

Non-Compartmental PK:
On average, plasma brimonidine concentrations following ocular instillation were below 60pg/ml in both young and elderly groups after single doses and after multiple doses in young subjects. Maximum plasma concentrations were attained within 2 hours in both groups and elimination appeared to be rapid, as evidenced by an apparent T½ of 2-3 hours. Plasma drug levels fell below the LOQ (2 pg/ml) at 24 hrs postdose following either single or multiple dose administration to all young subjects and single dose

administration to all elderly subjects.

Twice daily ocular instillation of 0.2% brimonidine tartrate solution to young subjects for 10 days resulted in greater systemic exposure to brimonidine as compared to a single dose (mean Day 10 Cmax and AUC(0-12): 58.5 pg/ml and 308.5 pg.hr/ml; mean Day 1 estimates: 41.4 pg/ml and 227.9 pg.hr/ml). Plasma brimonidine concentrations by the tenth day of multiple dosing were ~40% higher than those after single dosing (accumulation factor 1.36). However, no significant differences were detected in any of the pharmacokinetic parameters resulting from single and multiple doses to the young subjects. Steady-state plasma concentrations following multiple doses did not appear to be attained over the 10-day study duration in the young subjects. Inspection of the mean predose levels on Days 7, 9, and 10 revealed that the Day 9 mean concentration was ~26% lower than that on Day 7, and the Day 10 mean predose drug concentration was ~70% lower than that on Day 9. Further evidence for the lack of attainment of steady-state was afforded by the number of individual predose concentrations that fell below the LOQ (i.e., 2 pg/ml) on Days 7, 9, and 10. The pharmacokinetic estimates determined in this study after single dose administration were consistent with those obtained from Study A342-120-8042 after a single 0.2% dose to young subjects.

Systemic exposure to brimonidine following single ocular dose administration in the elderly subjects was greater when compared to that in the young subjects. The mean Cmax and mean AUC(0-12) estimates (52.4 pg/ml and 308.3 pg.hr/ml) were increased by ~30-35% when compared to those of the younger subjects. Mean Tmax and mean apparent T½ were each ~2.5 hrs for the elderly subjects. There were no significant differences detected in any of the pharmacokinetic parameters between the elderly and young groups.

Pharmacodynamic Measurements:
Decreases in SBP, DBP, and IOP at various timepoints during the study were observed after single and multiple doses in young subjects, however, the reductions appeared to be greater after multiple dosing. The elderly subjects appeared to show greater pharmacodynamic effects with respect to the reductions in SBP, DBP, and IOP than the young subjects after single dose instillation. No consistent changes in HR were observed for either of the two groups.

Compartmental Pharmacokinetic/Pharmacodynamic Modeling:
PK/PD modeling of the mean change in HR with brimonidine plasma concentrations resulted in very poor fits of the predicted and observed HR changes, and no relationship was apparent with plasma brimonidine concentrations in either young or elderly subjects. Some association between the reduction in SBP and DBP and plasma drug concentrations was observed for the young and elderly groups, and the model fits were marginal, but improved over that for HR. In general, the occurrence of maximal changes in SBP and DBP lagged behind the occurrence of brimonidine Cmax. No clear relationship was apparent between the reduction in IOP and mean brimonidine plasma concentrations in young or elderly subjects, except that the occurrence of the mean

maximal reduction in IOP was consistent with the occurrence of brimonidine Cmax. Better PK/PD model fits of the IOP data were obtained for the elderly subjects compared to the young subjects. The poor PK/PD relationship for IOP changes may have been due to the limited sampling schedule of IOP measurements and that systemic plasma drug concentrations were used to model the IOP reducing effect in the eye.

C. Metabolism

4. Pfizer Study: "The Drug Kinetics of UK-14,304 in Man Following Oral Administration"

This study was conducted by while brimonidine was being developed as an oral hypertensive agent. It was designed to investigate the systemic absorption, metabolism, and elimination of radiolabeled (^{14}C) brimonidine following oral administration of 0.5mg capsules (10.7 µCi/capsule) to two healthy male volunteers. Oral absorption of brimonidine was rapid with maximum plasma radioactivity (Cmax) achieved within 1-2 hours postdose for both subjects (4.1 and 4.8 ng-eq/ml, respectively). Drug related material was rapidly eliminated in the urine as evidenced by a ~20-fold decrease in plasma radioactivity at 12 hrs postdose and no parent drug related material detected in plasma in the 1 hour postdose samples. Approximately 88% and 86% of the administered dose was recovered in urine and feces by 120 hours, with most of the radioactivity excreted in the urine (77% and 71%) and the remaining portion excreted in the feces. The TLC analysis of the urine collected from both subjects at the 2-4 hour postdose interval showed only a small proportion of the dose was excreted as unchanged drug related material (not able to quantify with results provided). In addition to rapid oral absorption, these results suggested that brimonidine was also rapidly and extensively metabolized. No qualitative or quantitative metabolite analysis was performed by the sponsor in this study.

D. In Vitro Studies

The sponsor conducted two plasma protein binding studies (one *in vitro*, one *in vivo*) and one blood to plasma partitioning study in animals and man. The *in vitro* binding of ^{14}C-brimonidine to plasma proteins of mice, rats, dogs, monkeys, and humans, using equilibrium dialysis, was low (i.e., <35%) for all species tested. In particular, the binding of the drug to human plasma proteins was ~21% (unbound fraction ~79%). Brimonidine plasma protein binding was linear (i.e., concentration independent) for all species over the concentration range studied from ~0.2-200 ng/ml. The results from the *in vivo* protein binding studies in the same species were in agreement with the *in vitro* results. Specifically, the mean *in vivo* unbound fraction for human plasma was ~71% over a brimonidine concentration range from 90-121 pg/ml. The *in vitro* blood to plasma (B/P) ratios were determined for mice, rats, monkeys, and humans using ^{14}C-brimonidine.

For human blood, B/P ratios ranged from 1.12-1.31 using concentrations from 7.07-707 ng/ml and indicated comparable distribution of brimonidine between blood and plasma.

The metabolism of brimonidine was evaluated and its metabolites identified in two *in vitro* studies, one using human and animal (rat, dog, monkey) liver microsomes and the other using human liver slices, rat lung slices, and urine from rats after single dose oral administration. The results indicated that brimonidine was extensively metabolized in all species to a number of metabolites, i.e., rat lung slices: 4; human microsomes: 6, rat and monkey microsomes: 8; human liver slices: 11; and rat urine: 14. The metabolic pattern in the human microsomes was qualitatively similar to that of monkey and rat homogenates, but different to that of dog liver. The two major pathways of brimonidine metabolism appeared to be (1) alpha-carbon oxidation of the quinaxoline moiety, which may be mediated by cytosolic liver aldehyde oxidase, with subsequent glucuronide conjugation, and (2) oxidative cleavage of the imidazoline ring, which may be mediated by CYP450. The metabolic activity appeared to be the highest for human and rat liver microsomes, followed by monkey, and lowest in dog homogenates.

VI. PROPOSED LABELING

A copy of the proposed labeling is provided as **Appendix 2**.

VII. COMMENTS (TO BE SENT TO SPONSOR)

A. Protocol No. A342-106-7831/Report PK-95-042:

1. The sponsor claimed that steady-state plasma brimonidine concentrations were attained by Day 7 of multiple dosing in young subjects. However, inspection of the mean predose levels on Days 7, 9, and 10 revealed that the Day 9 mean concentration was ~26% lower than that on Day 7, and the Day 10 mean predose drug concentration was ~70% lower than that on Day 9. Thus, it appears that steady-state was not attained for this study, and this is further supported by the number of individual predose concentrations that fell below the LOQ (i.e., 2 pg/ml) on Days 7, 9, and 10. In addition, it is not clear why the Day 10 predose concentrations listed in Table 9 are different from those listed in Table 3 at 216.00 hours (i.e., the predose concentrations on Day 10). It is recommended that the sponsor change the assessment of steady-state to indicate that steady-state brimonidine concentrations were not attained with twice daily dosing over the 10 day period of the study, and resolve the discrepancy between Table 9 and Table 3 in the report.

B. Protocol No. A342-119-7831/Report PK-1993-074:

2. Although the sponsor stated that significant differences between the sexes were to be determined statistically, no results of the gender analyses were reported with respect to the plasma concentration or IOP data. It is recommended that the sponsor provide such results.

C. Proposed Labeling:

3. On page 9, under Pharmacokinetics, the following statement was made: "In humans, systemic metabolism of brimonidine is extensive; *brimonidine does not accumulate*". Since an accumulation ratio of 1.36 was determined after 10 days of bid dosing in healthy subjects (Study A342-106-7831), it is recommended that the latter portion of this statement be clarified to reflect this, i.e., that accumulation of brimonidine in plasma following bid administration for 10 days was observed to be ~35-40% in healthy young subjects.

4. On page 9, under Pharmacokinetics, the statement: "It is metabolized primarily by the liver" should be clarified/expanded upon to reflect the results from *in vitro* studies with human microsomes indicating that the drug is extensively metabolized to at least 6 metabolites and a description of what the major metabolic pathways are.

VIII. GENERAL COMMENTS

A. Protocol No. A342-120-8042/Report PK-1992-034:

5. Rather than a "representative" plot for one subject (i.e., #110), it is suggested that the sponsor provide plots comparing the mean brimonidine plasma concentrations *vs* time for all three dose strengths on (1) rectilinear and (2) semilogarithmic scales in future submissions. Error bars representing either the standard deviation or standard error of the mean should be included if possible.

6. It is not clear why the sponsor chose to set all postdose plasma concentrations that fell below the LOQ to 1 pg/ml (i.e., one-half the LOQ) instead of to 0 pg/ml. For future submissions, it is suggested that some justification for this procedure be provided or that these values be changed to 0 pg/ml.

7. In Table IV, the apparent T½ values are provided for each subject based on either single or mean values for all treatments with quantifiable plasma concentrations in the terminal phase. For future submissons, it is suggested that the sponsor provide individual apparent T½ values, with summary statistics, for each dose level rather than a single value for each subject. Although the sponsor noted that the estimation of apparent Ke (and therefore apparent T½) was not possible in 16 out of 24 subjects

receiving the 0.08% strength, it is more appropriate to provide individual estimates of apparent T½ according to the dosage strength for those subjects in whom estimates are possible. In this way more meaningful comparisons of the pharmacokinetics between dose groups can be made.

8. It is suggested that the sponsor correct the typographical errors occurring in the tables of final plasma concentration data in Appendix I of Report No. PK-1992-034 (pages 83-020 to 83-031). In addition, for subject 116, it was noted that the concentration at 2.5 hrs after the 0.2% dose was reported by the bioanalytical lab to be 19.1 pg/ml, but a value of 18.1 pg/ml was incorrectly typed into the final tables of Appendix I and this incorrect value was used in the pharmacokinetic analysis. The correct value of 19.1 pg/ml should be used. Also, it is not clear why values of 1 pg/ml (i.e., one-half the LOQ) were assigned to postdose plasma concentrations that the bioanalytical lab reported as "not reportable" (i.e., NR) for several subjects. For future submissions, it is suggested that justification for this latter procedure be provided or that these values be reported as NR.

B. Protocol No. A342-106-7831/Report PK-95-042:

9. In the PK report (PK-95-042), it was claimed that the plasma concentration-time data were adequately described by either a monoexponential model with first-order input or a biexponential model with zero-order input, where adequacy of the fit was described with respect to the correlation coefficient (r). In addition to the r values, it is suggested that for future submissions, the sponsor provide either plots of the predicted vs observed plasma concentration data or provide the residual data (i.e., predicted conc. - observed conc.) so that a better assessment of the fit of the data may be determined.

10. In the PK report (PK-95-034), the PK/PD modeling was apparently performed using the concentration-effect link model to obtain estimates of Ce (effect compartment concentration) and keo (transfer rate constant from plasma to the effect compartment). While this model is appropriate to describe the potential relationships between the known systemic HR and BP lowering effects and plasma concentrations, it may not be appropriate to describe the IOP reducing effects since the drug is instilled directly into the effect compartment (i.e., the eye) and then distributes from the effect compartment to the plasma. Thus, it appears that Ce may be a better predictor of changes in IOP. For future submissions, it is suggested that the Ce estimates be provided along with the other PD parameters (i.e., Emax, EC50, keo, correlation coefficient) and any potential relationship(s) between brimonidine Ce and IOP reduction also be examined.

C. Protocol No. A342-119-7831/Report PK-1993-074:

11. It was pointed out by the sponsor that plasma samples below the LOQ were set at one-half the LOQ (i.e., at 1 pg/ml). In future submissions, it is recommended that a rationale for why this was done be provided or that these values be set to 0 pg/ml.

Philip M. Colangelo 1/30/96
Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

FT and RD signed by Frank Pelsor, Pharm.D., Team Leader 1/30/96

Biopharm Day: 01/29/96; **Attendees:** D. Bashaw, J. Hunt, L. Lesko, M. Mehta, F. Pelsor

cc: NDA 20-613, HFD-540(Review), HFD-880 (Fleischer, Pelsor, Colangelo), HFD 860 (Malinowski), HFD-340 (Viswanathan), Drug file, Chron. file, Review, FOI (HFD-19)

APPENDIX 1:

PHARMACOKINETIC/PHARMACODYNAMIC STUDIES

1. **Pfizer Study:** "The Drug Kinetics of UK-14,304 in Man Following Oral Administration"

Volume: 82

Pages: 82-048 to 82-061

Investigator & Location:

Study Date: June, 1975

OBJECTIVE:
To investigate the systemic absorption, metabolism, and elimination of radiolabeled brimonidine following oral administration to two healthy male volunteers.

FORMULATIONS:
Radiolabeled Brimonidine Tartrate - radiochemically pure ^{14}C-brimonidine (UK-14,304) capsules 0.5 mg (Lot #291-1); 10.7 µCi/capsule

METHODS:
After an overnight fast, an oral dose of the radiolabeled formulation was administered to two healthy male subjects (0.18 µCi; 0.0083 mg/kg for 60 kg body weight). Measurements of blood pressure and heart rate were taken predose and up to 24 hours postdose. Plasma and saliva samples were collected at 0 (predose), 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose for measurement of drug related radioactivity. Urine and feces were also collected over a period of 5 days postdose. Radioactivity in all matrices was determined by liquid scintillation counting (LSC). Parent drug and metabolites in plasma and urine were characterized by thin layer chromatography (TLC) using silica plates.

RESULTS:
Systolic and diastolic blood pressures decreased from predose levels in Subject 1 within 1 hour postdose and remained lower up to 24 hours postdose, while in Subject 2, there was no decrease in blood pressure (Table 1). The blood pressure in Subject 2 at 24 hours postdose returned to its predose level, whereas in Subject 1, it remained lower than its predose level. Heart rates in either subject were not affected.

Concentrations of drug related material in plasma and saliva are provided in Tables 2 and 3, and excretion data for urine and feces are given in Tables 4 and 5. Maximum plasma radioactivity (Cmax) was achieved within 1-2 hours postdose for both subjects at 4.1 and 4.8 ng-eq/ml for Subjects 1 and 2, respectively (Table 2). Drug related radioactivity in plasma declined to 0.2-0.3 ng-eq/ml at 12 hours postdose (~20-fold decrease) and no unchanged drug related material in plasma was detectable by TLC analysis in the 1 hour postdose samples. Very little drug related radioactivity was detected in saliva and the saliva/plasma ratio was in the range from ~0.2-0.4 (Table 3).

As shown in Tables 4 and 5, 88% and 86% of the administered dose was recovered in urine and feces by 120 hours for Subjects 1 and 2, respectively, with most of the radioactivity excreted in the urine (77% and ~71%) and the remaining portion excreted in the feces. Approximately 60-70% of the radioactivity was excreted in the urine in the first 8 hours following dosing. The TLC analysis of the urine collected from both subjects at the 2-4 hour postdose interval showed only a small proportion of the dose was excreted as unchanged drug related material (not able to quantify with results provided).

REVIEWERS CONCLUSIONS:
The results suggested that oral absorption of brimonidine was rapid and that drug related material was rapidly eliminated in the urine. Since no unchanged drug was able to be detected in plasma (i.e., at 1 hour postdose) and urine (i.e., at 2-4 hours postdose), this indicated that brimonidine was also rapidly and extensively metabolized.

No qualitative or quantative metabolite analysis was performed by the sponsor in this study.

5 Pages Purged

2. Protocol No. A342-120-8042: "Systemic Drug Absorption Following a Single Eyedrop of 0.08%, 0.2%, and 0.5% Brimonidine Tartrate to Healthy Human Subjects" **(Report No. PK-1992-034)**

Volume: 83

Pages: 83-001 to 83-056

Investigator & Location:

Study Dates: July 31, 1991 - October 30, 1991

OBJECTIVE:
To evaluate the systemic absorption of brimonidine and examine the dose proportionality of brimonidine plasma concentrations following ocular instillation of 0.08%, 0.2%, and 0.5% brimonidine tartrate in healthy male volunteers.

FORMULATIONS:
Brimonidine Tartrate (AGN 190342-LF) Ophthalmic Solutions -

(i) 0.08% - Formulation No. 7830X; Lot No. 09600; Batch Size L
(ii) 0.2% - Formulation No. 7831X; Lot No. 09601B; Batch Size L
(iii) 0.5% - Formulation No. 8042X; Lot No. 09544A; Batch Size L

Analysis of the three ophthalmic solutions yielded brimonidine tartrate concentrations of 0.078%, 0.194%, and 0.498%, respectively.

STUDY POPULATION:
24 healthy male subjects 21 years of age and older (mean age 28 years). A prestudy screen was conducted on all subjects which included an eye examination consisting of evaluation of IOP, visual acuity, biomicroscopy, and ophthalmoscopy. For inclusion into the study, all subjects must have corrected visual acuity equal to or better than 20/20 in each eye and intraocular pressure (IOP) ≤21 mm Hg.

METHODS:
The study was a randomized, double-blind, crossover design with a washout period of at least 7 days between treatments. Following a 10 hour fast before dosing, a single drop (35 μl) of brimonidine tartrate solution of either 0.08%, 0.2%, or 0.5% was instilled into each eye on three separate occasions. Meals were provided at 1, 3, and 8 hours after dosing. Plasma samples for the determination of brominidine concentrations were collected at 0 (predose), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, and 24 hours postdose. Heart rate, blood pressure, general and ocular comfort were monitored at 2, 12, and 24 hours after each of the three doses. An eye examination was also performed at 24 hours after each dose which included assessment of visual acuity,

biomicroscopy, and non-dilated ophthalmoscopy.

ASSAY:

DATA ANALYSIS:

Pharmacokinetic:
Cmax: maximum brimonidine plasma concentration obtained directly from the concentration-time data;
Tmax: time of first occurrence of Cmax;
AUC(0-12): area under the plasma concentration-time curve estimated by linear trapezoidal approximation;
AUC(0-inf): AUC(0-12) + C_{12hr}/Ke;
Ke: apparent elimination rate constant obtained by linear least squares regression

analysis of the log-linear portion of the concentration-time curve (i.e., last 3 to 6 timepoints between 5 to 12 hours postdose); only treatments with concentrations above the LOQ in the terminal phase were used to estimate Ke;
Apparent T½: 0.693/Ke

Statistical:
Linear regression analysis was used to evaluate the dose-dependency of AUC and Cmax. A standard ANOVA for crossover design was performed for log-transformed, dose-normalized AUC and Cmax, and untransformed Tmax data. Between group comparisons were performed by constructing 100(1-2α)% confidence intervals for log-transformed, dose-normalized AUC and Cmax, and untransformed Tmax, with α set at 0.05 (i.e., Westlake 90% confidence intervals). Dose proportionality was based on bioequivalency criteria, which was set between the limits of 0.8 and 1.2 for the 90% CI of the AUC and Cmax ratios.

*Comments/Notes:
The sponsor noted that all predose (i.e., 0 hr) plasma concentrations were set at 0pg/ml since 61 out of 72 predose samples yielded concentrations <2pg/ml (LOQ) and 9 predose samples were <5pg/ml. However, it was also pointed out by the sponsor, without any explanation, that plasma samples beyond 0 hr that were below the LOQ were set at one-half the LOQ (i.e., at 1pg/ml). This occurred primarily for the 0.08% dose strength from the 10 to 24-hour postdose timepoints. Recalculation of the AUC(0-12) using 0 pg/ml instead of 1 pg/ml did not appear to significantly affect the AUC estimates.

The bioequivalency acceptance criteria for log-transformed AUC and Cmax should be set between 0.8 and 1.25, instead of 0.8 and 1.2.

RESULTS:
The individual plasma brimonidine concentrations following instillation of 0.08%, 0.2%, and 0.5% brimonidine tartrate into each eye are provided in **Appendix 2**. In general, plasma concentrations following instillation of 0.2% were below 2 pg/ml (LOQ) at 12 to 24 hours postdose. The individual estimates and descriptive statistics of the pharmacokinetic parameters are given in Tables I through V. In Figure 2, the relationships between mean AUC(0-12), AUC(0-inf) and dose are shown, and Figure 3 illustrates the relationship between mean Cmax and dose. The mean increases in both AUC and Cmax with dose appeared to be linear (r^2 >0.99). The mean Cmax after instillation of 0.2% was 46.5 pg/ml and mean AUC(0-12) was 241 pg.hr/ml. Mean Tmax for the 0.2% strength was at 1.65 hrs (range 0.5 to 3.5 hrs) and was the shortest of all three doses. In Table IV, values of apparent T½ are given for each subject rather than for each dose; the overall mean apparent T½ was 3.26 hrs (range from 1.77 to 5.00 hrs). The intersubject variability (i.e., %CV) for Cmax and AUC was quite high, i.e., ~50% for all three doses, and was even higher for Tmax, ranging between ~51% and ~88%.

The results of the statistical analyses are provided in Tables VI through IX. The ANOVA

in Table IX detected statistically significant treatment differences in Tmax (p = 0.006), AUC(0-12) and AUC(0-inf) (p = 0.026 for both); no significant carryover or period effects were detected for any of the parameters tested. In Table VIII, the between group comparisons in assessing dose proportionality of systemic exposure are summarized. The 90% confidence intervals for dose-normalized AUC(0-12) indicate bioequivalence between the 0.08% and 0.2% doses (0.812, 1.188), but not between 0.08% and 0.5% or 0.2% and 0.5%. The same results occurred for dose-normalized AUC(0-inf). The between group analysis for dose-normalized Cmax indicated bioinequivalence for all three dose levels. Statistically significant differences were detected in Tmax between the 0.08% and 0.2% (p = 0.006) and 0.08% and 0.5% (p = 0.035) doses, but not between 0.2% and 0.5% (p = 0.491).

REVIEWERS CONCLUSIONS:
Following instillation of a single 0.2% dose of brimonidine tartrate into each eye, quantifiable brimonidine plasma concentrations in the pg/ml range are observed at 0.5 hours, with maximum concentrations (mean 40-50 pg/ml) occurring at ~1-2 hrs. Brimonidine concentrations in plasma were less than 2 pg/ml by ~12 hrs after the 0.2% dose.

The relatively high degree of intersubject variability observed in the pharmacokinetic parameters across all three dose levels suggested that absorption of brimonidine from the eye was a variable process.

Although the increases in AUC and Cmax appeared to be nearly linear as the dose strength increased from 0.08% to 0.2% to 0.5%, the increases in AUC was dose proprotional only between 0.08% and 0.2%, and not between 0.2% and 0.5% or 0.08% and 0.5% (i.e, less than proportional in both cases). The increases in Cmax between the three dose levels was less than dose proportional.

5 Pages
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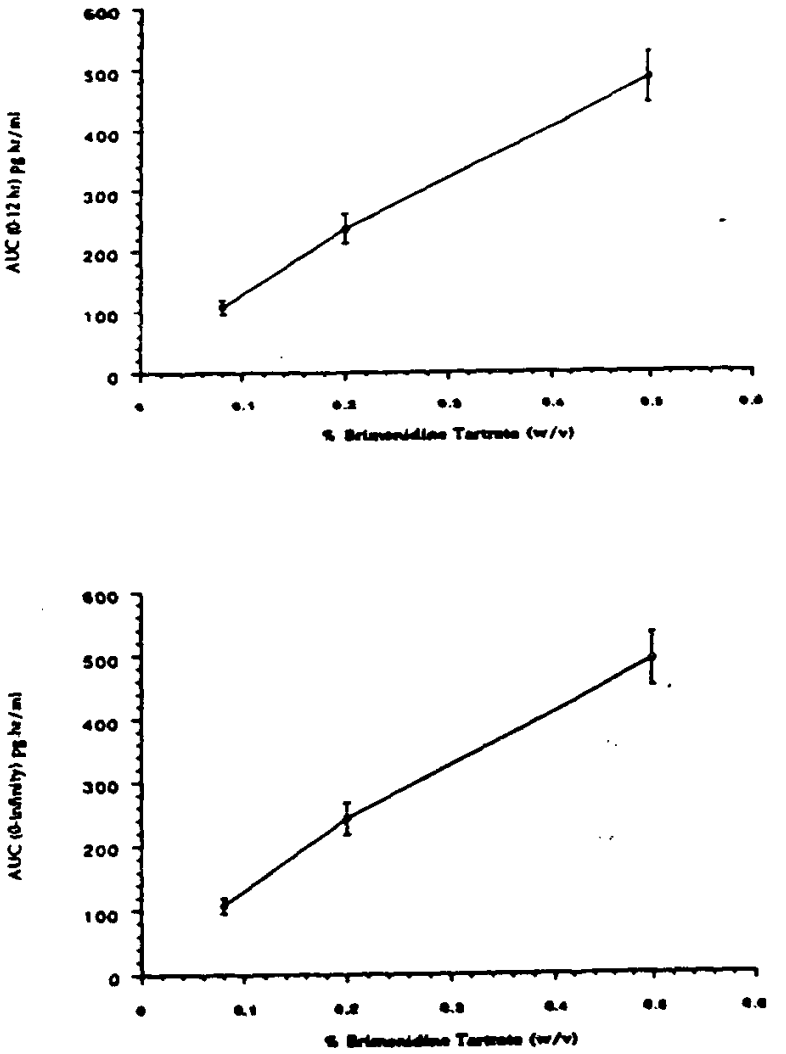

Figure 2

Relationship between AUC of Brimonidine and Dosing Strength After a Single Instillation of One Eyedrop of 0.08%, 0.20% and 0.50% Brimonidine Tartrate Solution to Both Eyes of Human Subjects (Mean ± SEM, n = 24)

R-1990-2154 p 48

83 017

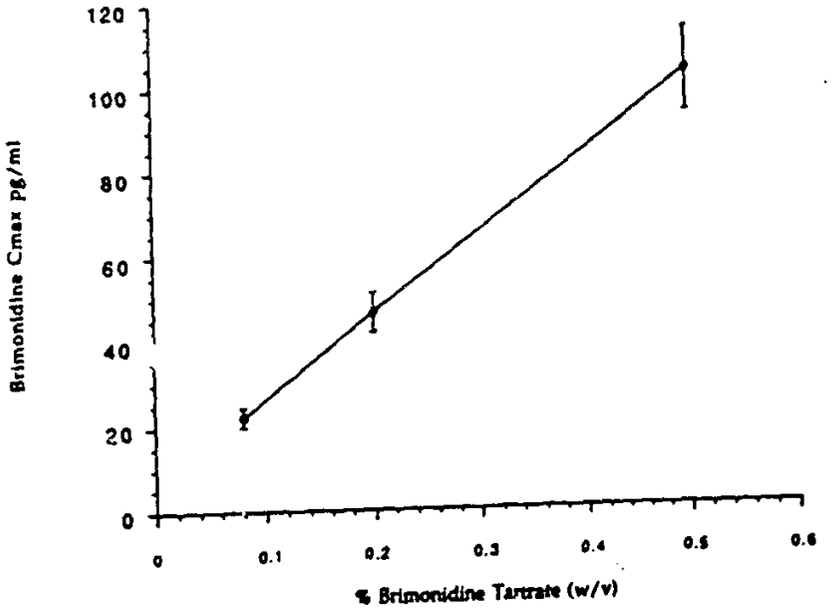

Figure 3

Relationship between Cmax of Brimonidine in Plasma and Dosing Strength After a Single Instillation of One Eyedrop of Brimonidine Tartrate to Both Eyes of Human Subjects (Mean ± SEM, n = 24)

R-1990-2154, p 49

Table VI

Dose-Normalized Pharmacokinetic Parameters (Cmax and AUC) After a Single Ophthalmic Dose of 0.08%, 0.20% and 0.50% Brimonidine Tartrate Solutions to Human Subjects

Dose-Normalized Variable	Statitistics	0.08%	0.20%	0.50%
Cmax (pg/ml)	N	24	24	24
	Mean	284.66	239.45	206.27
	SD	138.47	117.57	97.74
	Min	60.77	78.77	68.88
	Max	614.10	541.24	475.90
AUC (0-12 hr) pg.hr/ml	N	24	24	24
	Mean	1377.03	1242.40	978.33
	SD	714.03	626.90	411.59
	Min	275.64	419.59	449.80
	Max	2615.38	2855.67	2022.09
AUC (0-∞) pg.hr/ml	N	24	24	24
	Mean	1387.50	1253.24	987.28
	SD	719.67	632.21	415.08
	Min	283.33	427.32	455.82
	Max	2628.21	2881.44	2046.18

Dose-normalized for Cmax and AUC using the raw data divided by 0.078, 0.194 and 0.498 for group 0.08%, 0.20% and 0.50%, respectively.

Reference 9 (Biostatistical analysis)

83 012

Table VII

Log Transformation of Dose-Normalized Pharmacokinetic Parameters (Cmax and AUC) After a Single Ophthalmic Dose of 0.08%, 0.20% and 0.50% Brimonidine Tartrate Solutions to Healthy Human Subjects

Dose-Normalized Variable	Statitistics	0.08%	0.20%	0.50%
Cmax (pg/ml)	N	24	24	24
	Mean	5.51	5.35	5.22
	SD	0.58	0.52	0.47
	Min	4.11	4.37	4.23
	Max	6.42	6.29	6.17
AUC (0-12 hr) pg.hr/ml	N	24	24	24
	Mean	7.07	6.99	6.80
	SD	0.60	0.54	0.42
	Min	5.62	6.04	6.11
	Max	6.42	7.96	7.61
AUC (0-∞) pg.hr/ml	N	24	24	24
	Mean	7.08	7.00	6.81
	SD	0.60	0.54	0.42
	Min	5.65	6.06	6.12
	Max	7.87	7.97	7.62

Reference 9 (Biostatistical analysis)

S3 013

Table VIII

Summary of Between-Group Comparisons of Cmax and AUC After a Single Ophthalmic Dose of 0.08%, 0.20% and 0.50% Brimonidine Tartrate Solutions to Human Subjects

Variable *a*	Comparison	Estimate of Difference*b*	Lower Limit 90% Confidence Interval *c*	Upper limit 90% Confidence Interval c	P value *b*
Tmax	0.08% vs 0.20%	1.540	0.637	2.442	0.006
	0.08% vs 0.50%	1.167	0.764	2.569	0.035
	0.20% vs 0.50%	-0.373	-1.276	0.530	0.491
Cmax	0.08% vs 0.20%	1.171	0.742	1.258	0.150
	0.08% vs 0.50%	1.335	0.651	1.349	0.010
	0.20% vs 0.50%	1.140	0.762	1.238	0.230
AUC 0-12 hr	0.08% vs 0.20%	1.091	0.812	1.188	0.402
	0.08% vs 0.50%	1.312	0.673	1.327	0.007
	0.20% vs 0.50%	1.211	0.730	1.238	0.052
AUC (0-∞)	0.08% vs 0.20%	1.083	0.813	1.187	0.404
	0.08% vs 0.50%	1.311	0.674	1.326	0.007
	0.20% vs 0.50%	1.210	0.730	1.270	0.051

a Tmax was not dose-normalized. Cmax and AUC data were dose-normalized and log transformed before estimating the ratios for two treatments.

b Difference of marginal means between the treatment groups. P-values for the analysis of differences in Tmax of two groups significantly different from zero and ratio of Cmax or AUC of two groups significantly different from one.

c For Cmax and AUC, bioequivalency was based on 90% confidence interval. Treatments are bioequivalent if the lower limit is greater than 0.8 and the upper limit is less than 1.2

Table IX

Analysis of Variance for Crossover Study After a Single Ophthalmic Dose of 0.08%, 0.20% and 0.50% Brimonidine Tartrate Solutions to Healthy Human Subjects Plasma Pharmacokinetic Parameters

Parameter	Source of Variation	DF	SS	MS	F	P-value
Tmax	Subject	23	60.211			
	-Carryover	2	1.826	0.913	1.05	0.367
	-Error	21	18.243	0.869		
	Treatment	2	39.076	19.538	5.73	0.006
	Carryover	2	9.048	4.524	1.33	0.277
	Period	2	9.725	4.863	1.43	0.252
	Error Within	42	143.313	3.412		
Log Cmax (Dose-Normalized)	Subject	23	12.859			
	-Carryover	2	0.519	0.559	0.36	0.702
	-Error	21	3.767	0.259		
	Treatment	2	0.887	0.179	3.05	0.143
	Carryover	2	0.010	0.005	2.47	0.097
	Period	2	0.172	0.086	0.59	0.558
	Error Within	42	6.109	0.145		
Log AUC (0-12 hr) (Dose-Normalized)	Subject	23	14.144			
	-Carryover	2	0.422	0.211	1.03	0.373
	-Error	21	4.292	0.204		
	Treatment	2	0.902	0.451	3.99	0.026
	Carryover	2	0.066	0.033	0.29	0.748
	Period	2	0.252	0.126	1.12	0.337
	Error Within	42	4.742	0.113		
Log AUC (0-∞) (Dose-Normalized)	Subject	23	14.067			
	-Carryover	2	0.264	0.132	1.04	0.373
	-Error	21	4.268	0.203		
	Treatment	2	0.897	0.449	4.00	0.026
	Carryover	2	0.066	0.033	0.29	0.747
	Period	2	0.253	0.126	1.13	0.333
	Error Within	42	4.711	0.112		

Reference 9 (Biostatistical Analysis)

3. **Protocol No. A342-106-7831**: "An Evaluation of the Accumulation of Brimonidine in Plasma Following Single and Multiple Topical Dosing of 0.2% Brimonidine Tartrate in Normal Subjects" **(Report No. PK-95-042)**

Volume: 85

Pages: 85-001 to 85-460

Investigator & Location:

Study Dates: November 5, 1994 - November 15, 1994

OBJECTIVES:
(i) To evaluate the systemic pharmacokinetics and accumulation potential of brimonidine following single and multiple ocular dose administration in healthy young subjects.
(ii) To evaluate the systemic pharmacokinetics of brimonidine in elderly (≥65 yrs) versus young (21-40 yrs) subjects following a single ocular dose administration.
(iii) To assess the effect of brimonidine on intraocular pressure (IOP), heart rate (HR), and blood pressure (BP) following single and multiple ocular dose administration.
(iv) To examine the relationships between plasma brimonidine concentrations and systemic effects following single and multiple ocular dose administration.

FORMULATION:
Brimonidine Tartrate (AGN 190342-LF) 0.2% Ophthalmic Solution - 10 mL bottle; Formulation No. 7831X; Lot No. 09960A; Expiration Date: December, 1994; Batch Size 2.5 L

STUDY POPULATION:
A total of 16 healthy subjects participated: 7 young healthy male (N = 3) and female (N = 4) subjects 24 to 49 years of age (mean age 31 years), and 9 healthy elderly male (N = 3) and female (N = 6) subjects 65 to 73 years of age (mean age 70 years). A prestudy screen was conducted on all subjects which included an eye examination consisting of evaluation of IOP, visual acuity, biomicroscopy, and ophthalmoscopy. Each subject must have corrected visual acuity equal to or better than 20/20 in each eye and intraocular pressure (IOP) between 12 and 21 mm Hg (ie., 12≤IOP≤21 mm Hg) with no asymmetry in IOP of >5 mm Hg between eyes. Any female subjects who were pregnant, nursing, planning a pregnancy, or not using a reliable form of birth control were excluded from participating in the study.

METHODS:
This was an open-label, comparative study evaluating brimonidine tartrate 0.2%

ophthalmic solution for one or ten days. Two age groups, one young and one elderly, were studied and two comparisons were made: (1) between the single and multiple dose systemic pharmacokinetics of brimonidine in young subjects, and (2) between the single dose systemic pharmacokinetics of bromonidine in the young versus elderly subjects.

One drop (35 μl) of brominidine tartrate solution 0.2% was instilled into each eye of both young and elderly subjects on Day 1 of dosing. Ocular doses were repeated on Days 2 through 9 only for the young subjects, i.e., one drop into each eye twice daily, once in the morning and once in the evening, between 7:00 am/pm and 9:00 am/pm. The morning dose was instilled by a qualified staff member during clinic visits on Days 2, 7, 9, and 10 and no evening dose was instilled on Day 10. Plasma samples for the determination of brimonidine concentrations were collected at 0 (predose), 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours postdose on Days 1 (both groups) and 10 (young group). Predose plasma samples were also collected on Days 7 and 9 from the young subjects. Predose measurements of HR, BP, IOP, and general and ocular comfort were recorded on Days 1, 2, 7, 9, and 10, and at 2, 12, 16, and 24 hours postdose on Days 1 and 10.

ASSAY:

DATA ANALYSIS:

Non-Compartmental Pharmacokinetics:
Cmax - maximum brimonidine plasma concentration obtained directly from the concentration-time data;
Tmax - time of first occurrence of Cmax;
AUC(0-12) - area under the plasma concentration-time curve from 0 to 12 hours postdose estimated by linear trapezoidal approximation;
AUC(0-tlast) - area under the plasma concentration-time curve from 0 to the last quantifiable concentration at time, t, estimated by linear trapezoidal approximation;
AUC(0-inf) - AUC(0-tlast) + C_{last}/Ke, where C_{last} is the last quantifiable concentration;
Ke - apparent elimination rate constant obtained by linear least squares regression analysis of the log-linear portion of the concentration-time curve; only treatments with concentrations above the LOQ in the terminal phase were used to estimate Ke;
Apparent T½ - 0.693/Ke;
Accumulation Factor - Day 10 AUC(0-12)/Day 1 AUC(0-12)

Compartmental Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling:
The potential relationships between brimonidine plasma concentrations and changes in heart rate (HR), systolic and diastolic blood pressures (SBP and DBP) and intraocular pressure (IOP) from baseline (BL) following single and multiple ocular dose administration were evaluated using PK/PD modeling techniques.

A monoexponential model with first-order input or a biexponential model with zero-order input were used to fit the brimonidine plasma concentration (Cp) data and obtain parameter estimates of Cp, ka, and Kel (monoexponential model) or R, S, alpha, and beta (biexponential model). These parameter estimates were then used to determine the concentration in the effect compartment (Ce) and keo (transfer rate constant from plasma to effect site) using the concentration-effect link model. The Ce values were then used in the Emax model to estimate the pharmacodynamic parameters: E (predicted effect), Emax, and EC50, i.e., E = Emax*Ce/(EC50 + Ce).

The effect measurements taken at several timepoints postdose were subtracted from their respective baseline or predose measurements (i.e., at 0 hr) and reductions were recorded as positive values and increases recorded as negative values. All increases were converted to 0 for PK/PD curve fitting.

Statistical:
An ANOVA was performed for the paired comparison of the pharmacokinetic parameters following single and multiple ocular dosing in the young subjects, and for the unpaired comparison between the young and elderly groups following single dose administration. The level of significance was set at $p < 0.05$.

RESULTS:

Non-Compartmental Pharmacokinetics:
The mean plasma brimonidine concentration-time data for the young and elderly groups and following single (Day 1) and multiple (Day 10) ocular dosing for the young group are plotted in Figures 1 through 4. The individual plasma concentration data, including the predose ("trough") levels, are provided in **Appendix 2** (Tables 2, 3, 4, and 9). Brimonidine concentrations were below the LOQ (2 pg/ml) at 24 hrs postdose following either single or multiple dose administration to all young subjects and single dose administration to all elderly subjects. On average, plasma concentrations were below 60 pg/ml for both groups and for both single and multiple dosing. Predose levels were quantifiable for 2 of 7 young subjects on Day 7 (mean 6.2 pg/ml, CV 219%), 4 of 7 young subjects on Day 9 (mean 4.6 pg/ml, CV 169%), and 3 of 7 young subjects on Day 10 (mean 3.7 pg/ml, CV 208%). As Figure 1 illustrates, mean plasma brimonidine concentrations following single ocular administration were greater for the elderly subjects in the first 8 hours postdose. Figure 3 illustrates that mean concentrations in young subjects were higher after multiple versus single doses, indicating that brominidine accumulated in the plasma by Day 10.

The non-compartmental pharmacokinetic parameters are provided in Tables 5 to 7, and the statistical results are given in Table 8. Mean Cmax and AUC(0-12) on Day 10 (58.5 pg/ml and 308.5 pg.hr/ml) were increased from the Day 1 estimates (41.4 pg/ml and 227.9 pg.hr/ml) by ~40% in the young subjects. The AUC(0-inf) estimate on Day 1 was 281.3 pg.hr/ml. Mean Tmax was ~2 hrs and mean apparent T½ was ~3 hrs on Days 1 and 10. The accumulation factor between Days 1 and 10 was 1.36. As indicated in Table 8, no statistically significant differences were detected in any of the pharmacokinetic parameters between single and multiple ocular administration in the young subjects. For the elderly subjects the mean Cmax estimate (52.4 pg/ml) was increased by ~30% and mean AUC(0-12) and AUC (0-inf) values (308.3 and 337.2 pg.hr/ml, respectively) were increased by ~35% and ~20% when compared to those of the younger subjects. Mean Tmax and mean apparent T½ were each ~2.5 hrs on Day 1 for the elderly subjects. No statistically significant differences were detected in any of the pharmacokinetic parameters between the young and elderly groups (Table 8).

Pharmacodynamic Measurements:
The mean changes in HR, SBP, DBP, and IOP from baseline (BL) are plotted as a function of time in Figures 5 through 8 for the young subjects (i.e., single vs multiple dosing) and in Figures 9 through 12 for the young vs elderly subjects (i.e., single dose), with the individual and mean effect data provided in **Appendix 2** (Tables 13 through 25).

For the young subjects, changes in HR were variable, fluctuating above and below baseline, after either single or multiple dosing. On average, HR was maximally decreased from between 4 to 6 hours after either single or multiple dosing which lagged behind Tmax for brimonidine. Heart rate appeared to be decreased to a greater extent after multiple dosing, but was increased above baseline under both conditions at 12

hours postdose. Systolic and diastolic blood pressures were both decreased for up to 12 hours postdose following single or multiple doses, and the reduction in SBP and DBP appeared to be greater after multiple dosing. Decreases in IOP were observed following both single and multiple dose administration. IOP was maximally decreased by 4 mm Hg after multiple dosing and by 3 mm Hg after a single dose at 2 hours postdose, in concert with brimonidine Tmax. The IOP returned to baseline after the dose on Day 1, but remained reduced at 24 hours following the dose on Day 10.

For the elderly subjects, the changes in HR fluctuated above and below baseline, with the reduction in HR less pronounced than that for the young subjects following single dose administration. Both SBP and DBP were decreased to a greater extent in the elderly subjects, with maximal decreases occurring within the first 4 hours postdose. Both SBP and DBP remained below baseline for the elderly subjects over the entire 24-hour period. The reduction in IOP was, on average, greater for the elderly subjects. The mean maximal reduction in IOP was 5 mm Hg in the elderly subjects occurring at 2 hours postdose. IOP remained reduced for up to 16 hours postdose and then returned to baseline values for both elderly and young subjects at 24 hours after single dosing.

Compartmental Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling:
The pharmacokinetic model parameters are provided in **Appendix 2** (Tables 10 through 12) for all subjects. For the 7 subjects in the young group, the biexponential model with zero-order input was used to describe the brimonidine plasma concentration data for 3 subjects after single dosing and for 5 subjects after multiple dosing. The monoexponential model with first-order input was used for the remaining subjects after single (i.e., 4 subjects) and multiple (i.e., 2 subjects) dosing. For the 9 subjects in the elderly group, the biexponential model with zero-order input was used to describe the brimonidine plasma concentration data for 7 subjects after single dosing and the monoexponential model with first-order input was used for the remaining 2 subjects. The correlation coefficients (r values) were the only measures of the fit of the PK data provided by the sponsor, i.e., no residual data (predicted conc. - observed conc.) or plots of predicted vs observed conc. were provided. The r values ranged between 0.930 and 0.993 for the young subjects and from 0.976 to 0.993 for the elderly subjects.

The resulting pharmacodynamic parameters from the PK/PD modeling of HR, SBP, DBP, and IOP are also provided in **Appendix 2** (Tables 26 through 37) for all subjects. The correlation coefficients were the only measures of the fit of the PK/PD models provided and no estimates of Ce, the concentration in the effect compartment, were provided. The sponsor noted that r values of 0.400 or greater was considered an adequate indication that the PD response was, at least partially, related to the observed plasma brimonidine concentrations. The mean changes from baseline in HR, SBP, DBP, and IOP following single and multiple doses are plotted as a function of the respective mean brimonidine plasma concentrations in the young and elderly subjects in Figures 13 through 21.

For HR changes in the young and elderly subjects (Figures 13 to 15), there appeared to be no consistent relationship with plasma concentrations, and this was supported by the

poor fits of the PK/PD model for HR, with r values ranging from 0.000 to 0.926 for the young subjects and from 0.051 to 0.591 for the elderly subjects. The EC50 estimates ranged from ~4 to several thousand-fold higher than the observed brimonidine Cmax.

For mean changes in SBP and DBP, there appeared to be some trend for a reduction in both as mean plasma concentrations increased in the young and elderly subjects (Figures 16 to 18). However, the fits of the PK/PD models were generally poor and the r values ranged from 0.000 to 0.890 for the young subjects following either single and multiple doses and from 0.000 to 0.796 for the elderly subjects. The mean EC50 values for SBP and DBP in both the young and elderly subjects ranged from ~10 to ~2000-fold higher than the observed plasma Cmax.

For mean changes in IOP, no clear relationship was apparent between the reduction in IOP and mean brimonidine plasma concentrations in young or elderly subjects (Figures 19 to 21), except that the occurrence of the mean maximal reduction in IOP was consistent with the occurrence of brimonidine Cmax. For the young subjects, r values for the PK/PD fit of the IOP model ranged from 0.000 to 0.922 following either single and multiple doses, and the EC50 values were, on average, ~1500 to ~2000-fold higher than the observed Cmax. Better fits of the IOP data were obtained for the elderly subjects, as r values ranged from 0.552 to 0.997 and the EC50 values varied from 1 pg/ml to 2863 pg/ml (mean EC50 390 pg/ml, CV 242%).

REVIEWERS CONCLUSIONS:
On average, plasma brimonidine concentrations following ocular instillation were below 60pg/ml in both young and elderly groups after single doses and after multiple doses in young subjects. Maximum plasma concentrations were attained within 2 hours in both groups and elimination appeared to be rapid, as evidenced by an apparent T½ of 2-3 hours. Plasma drug levels fell below the LOQ (2 pg/ml) at 24 hrs postdose following either single or multiple dose administration to all young subjects and single dose administration to all elderly subjects.

Twice daily ocular instillation of 0.2% brimonidine tartrate solution to young subjects for 10 days resulted in slightly greater systemic exposure to brimonidine in plasma as compared to a single dose. Plasma brimonidine concentrations by the tenth day of multiple dosing were ~40% higher than those after single dosing (accumulation factor 1.36). However, no significant differences were detected in any of the pharmacokinetic parameters resulting from single and multiple doses to the young subjects. Due to the rapid apparent elimination, steady-state plasma concentrations following multiple doses were not attained over the 10-day duration of the study in the young subjects. The pharmacokinetic estimates determined in this study after single dose administration were consistent with those obtained from Study A342-120-8042 after a single 0.2% dose to young subjects.

Systemic exposure to brimonidine following single ocular dose administration in the elderly subjects was greater when compared to that in the young subjects, but no significant differences were detected in any of the pharmacokinetic parameters between

the elderly and young groups.

Decreases in SBP, DBP, and IOP at various timepoints during the study were observed after single and multiple doses in young subjects, however, the reductions appeared to be greater after multiple dosing. The elderly subjects appeared to show greater pharmacodynamic effects with respect to the reductions in SBP, DBP, and IOP than the young subjects after single dose instillation. No consistent changes in HR were observed for either of the two groups.

Pharmacokinetic/Pharmacodynamic modeling of the mean change in HR with brimonidine plasma concentrations resulted in very poor fits of the predicted and observed HR changes, and no relationship was apparent with plasma brimonidine concentrations in either young or elderly subjects. Some association between the reduction in SBP and DBP and plasma drug concentrations was observed for the young and elderly groups, and the model fits were marginal, but improved over that for HR. In general, the occurrence of maximal changes in SBP and DBP lagged behind the occurrence of brimonidine Cmax. No clear relationship was apparent between the reduction in IOP and mean brimonidine plasma concentrations in young or elderly subjects, except that the occurrence of the mean maximal reduction in IOP was consistent with the occurrence of brimonidine Cmax. Better PK/PD model fits of the IOP data were obtained for the elderly subjects compared to the young subjects. The poor PK/PD relationship for IOP changes may have been due to the limited sampling schedule of IOP measurements and that systemic plasma drug concentrations were used to model the IOP reducing effect in the eye.

Figure 1

Mean (S.E.M.) Plasma Brimonidine Concentrations Versus Time

Day 1 – Linear Scale

60

Figure 2

Mean Plasma Brimonidine Concentrations Versus Time

Day 1 – Semi-Logarithmic Scale

61

Figure 3

Mean (S.E.M.) Plasma Brimonidine Concentrations Versus Time

Young Subjects – Linear Scale

62

Figure 4

Mean Plasma Brimonidine Concentrations Versus Time

Young Subjects – Semi-Logarithmic Scale

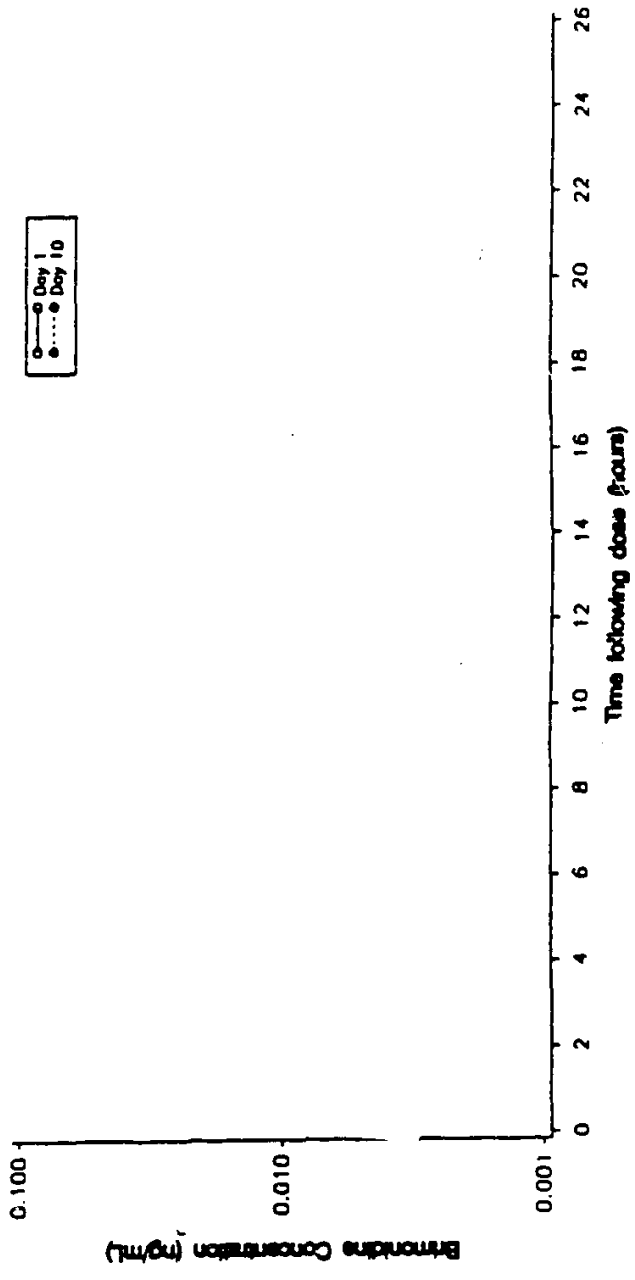

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Table 5

Individual and mean non-compartmental pharmacokinetic parameters for concentrations of brimonidine in plasma after one instillation of a 0.2% brimonidine tartrate solution in each eye of young (21-40 years of age) human volunteers

Subject Number	Parameters						
	Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-12) ng*hr/mL	AUC(0-inf) ng*hr/mL	Kel 1/hr	T 1/2el hr
1							
2							
3							
4							
5							
6							
10							
Mean	0.0413	2.36	0.2512	0.2279	0.2811	0.2751	3.19
S.D.	0.0088	1.03	0.0886	0.0660	0.1215	0.1228	1.84
C.V.(%)	21.4126	43.67	35.2540	28.8871	43.2016	44.6005	57.64
S.E.M.	0.0233	0.39	0.0335	0.0242	0.0458	0.0464	0.70
N	7.0000	7.00	7.0000	7.0000	7.0000	7.0000	7.00
Minimum	0.0273	1.00	0.1286	0.1239	0.1381	0.1161	1.73
Maximum	0.0503	4.00	0.3674	0.2952	0.4848	0.4006	5.97
Harmonic Mean	.	1.95	.	0.1239	.	.	.

Table 6

Individual and mean non-compartmental pharmacokinetic parameters for concentrations of brimonidine in plasma on Day 10 after multiple instillations of a 0.2% brimonidine tartrate solution twice daily in each eye of young (21-40 years of age) human volunteers for 10 days

Subject Number	Parameters				
	Cmax ng/mL	Tmax hr	AUC(0-12) ng*hr/mL	Kel = 1/Kel 1/hr	hr
1					
2					
3					
4					
5					
6					
10					
Mean	0.0585	2.21	0.3085	0.3064	2.72
S.D.	0.0299	0.57	0.1021	0.1101	1.44
C.V.(%)	51.1276	25.60	46.0522	35.9442	60.37
S.E.M.	0.0113	0.21	0.0537	0.0416	0.62
N	7.0000	7.00	7.0000	7.0000	7.00
Minimum	0.0323	1.50	0.1433	0.1092	1.48
Maximum	0.1040	3.00	0.5399	0.4691	6.35
Harmonic Mean		2.08	0.1423		

Table 7

Individual and mean non-compartmental pharmacokinetic parameters for concentrations of brimonidine in plasma after one instillation of a 0.2% brimonidine tartrate solution in each eye of elderly (65 years of age or older) human volunteers

Subject Number	Parameters						
	Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-12) ng*hr/mL	AUC(0-inf) ng-hr/mL	Kel * 1/2el 1/hr	hr
Mean	0.0524	2.50	0.3243	0.3083	0.3372	0.2891	2.47
S.D.	0.0341	1.03	0.2202	0.2012	0.3230	0.0539	0.45
C.V.(%)	65.0452	41.23	67.8797	65.8944	66.1365	18.6337	18.09
S.E.M.	0.0114	0.34	0.0734	0.0677	0.0761	0.0180	0.15
n	9.0000	9.00	9.0000	9.0000	9.0000	9.0000	9.00
Minimum	0.0102	1.00	0.0419	0.0419	0.0481	0.2099	1.80
Maximum	0.1110	4.00	0.6604	0.6287	0.6715	0.3844	3.30
Harmonic Mean	.	2.09	.	0.1860	.	.	.

Table 8

Summary of statistical analysis of non-compartmental pharmacokinetic parameters

Parameter	Young subjects — Mean (s.d.) Day 1	Young subjects — Mean (s.d.) Day 10	Elderly subjects Day 1	P-value Day 1 vs. Day 10	P-value Young vs. Elderly
Cmax (ng/mL)	0.0413 (0.0068)	0.0585 (0.0299)	0.0524 (0.0341)	0.1606	0.4181
Tmax (hr)	2.36 (1.03)	2.21 (0.57)	2.50 (1.03)	0.6016	0.7872
AUC(0-t) (ng*hr/mL)	0.2512 (0.0886)		0.3243 (0.2200)		0.4243
AUC(0-12) (ng*hr/mL)	0.2279 (0.0640)	0.3085 (0.1421)	0.3083 (0.2032)	0.1423	0.3329
AUC(0-inf) (ng*hr/mL)	0.2813 (0.1215)		0.3372 (0.2230)		0.5615
Kel (1/hr)	0.2753 (0.1228)	0.3064 (0.1101)	0.2891 (0.0539)	0.5214	0.7653
$T_{1/2el}$ (hr)	3.19 (1.84)	2.72 (1.44)	2.47 (0.65)	0.4845	0.2712
Accumulation Factor		1.36 (0.55)			

Day 1 vs. Day 10 = p-value of analysis of variance test comparing young subjects Day 1 values to Day 10 values

Young vs. Elderly = p-value of analysis of variance test comparing young subjects Day 1 values to elderly subjects Day 1 values

Accumulation Factor = Day 10 AUC(0-12) / Day 1 AUC(0-12)

Figure 5

Young - Mean HR Changes Day 1 vs Day 10

Figure 6

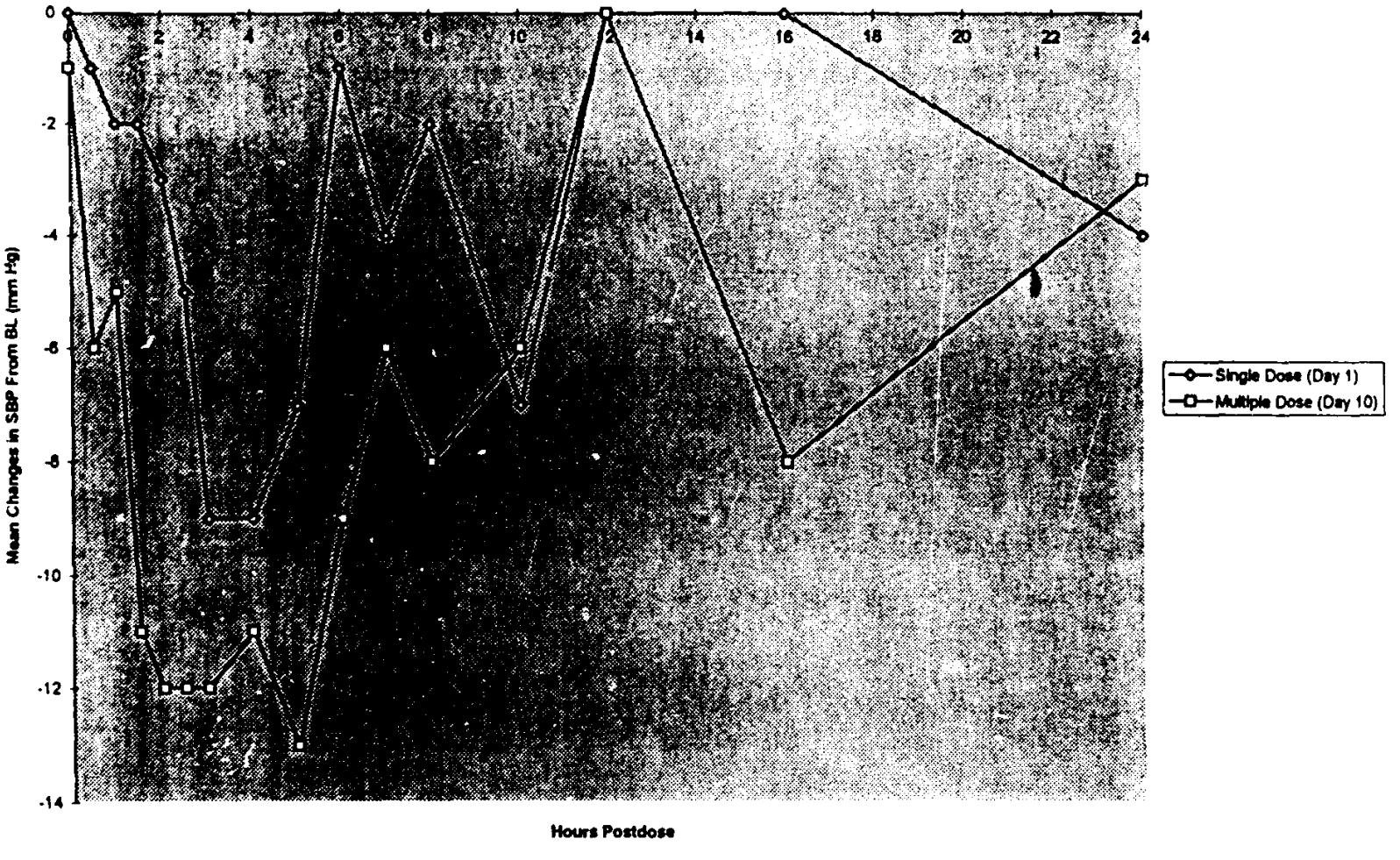


Figure 7

Young - Mean DBP Changes Day 1 vs Day 10

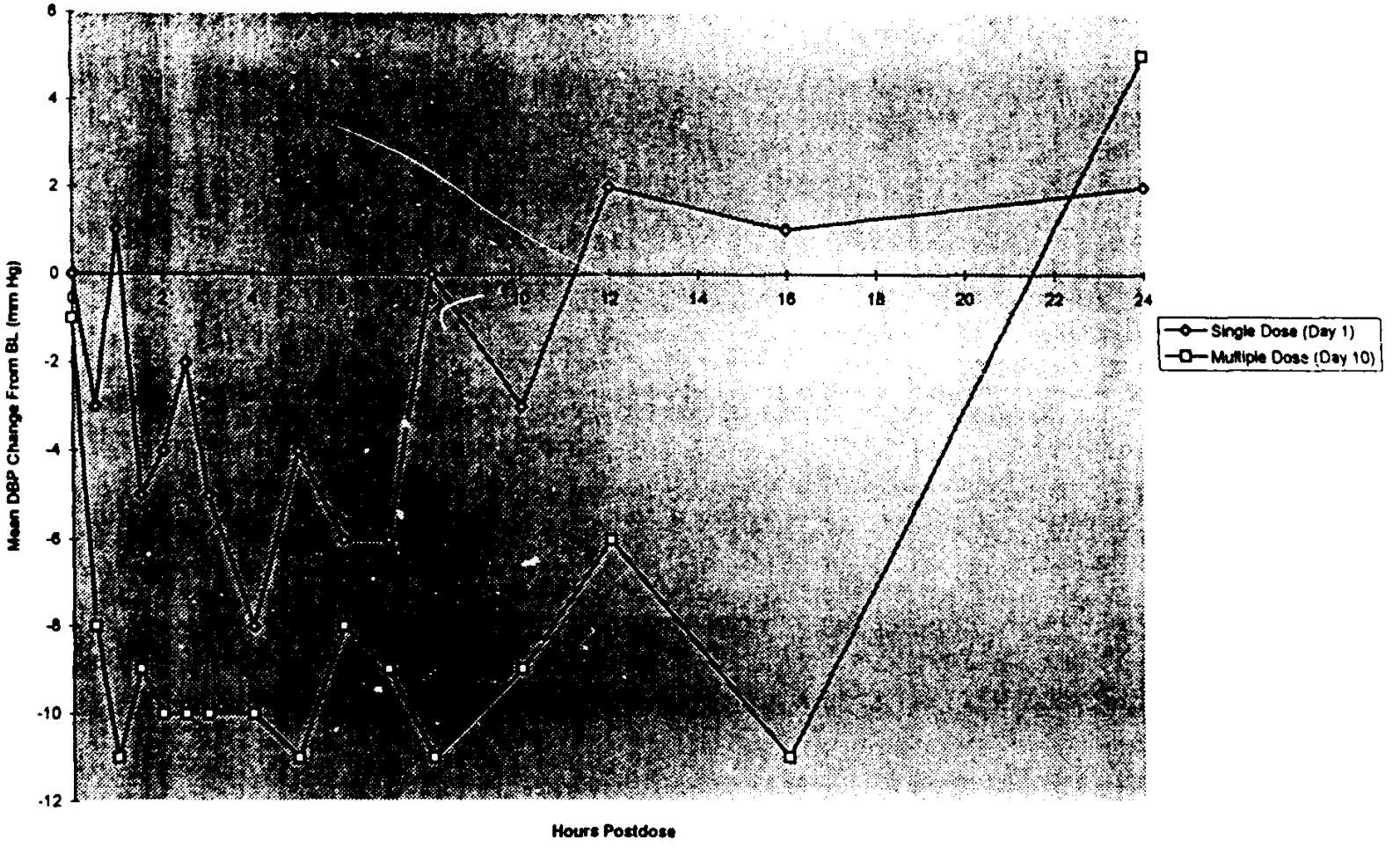


Figure 8

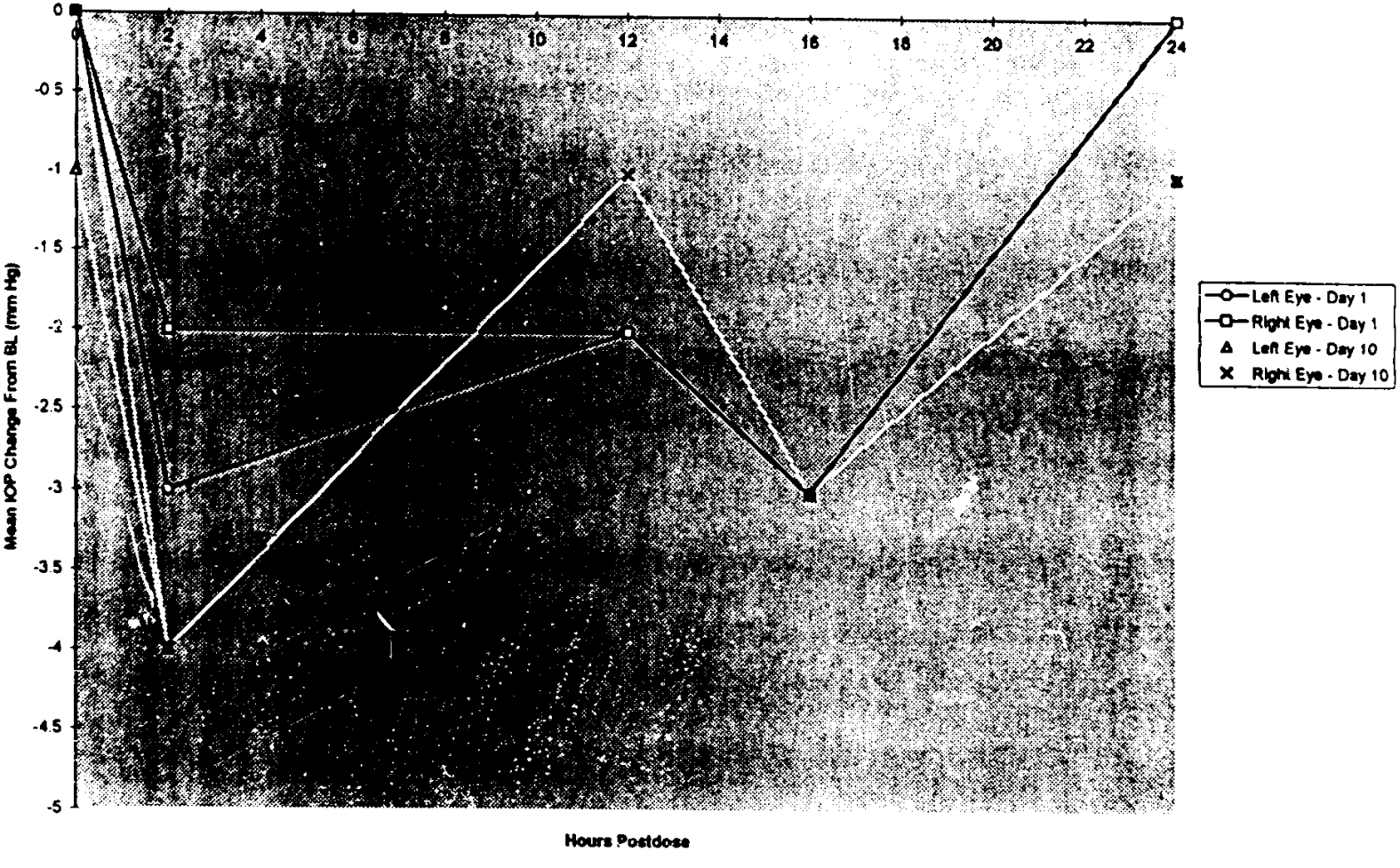


Figure 9

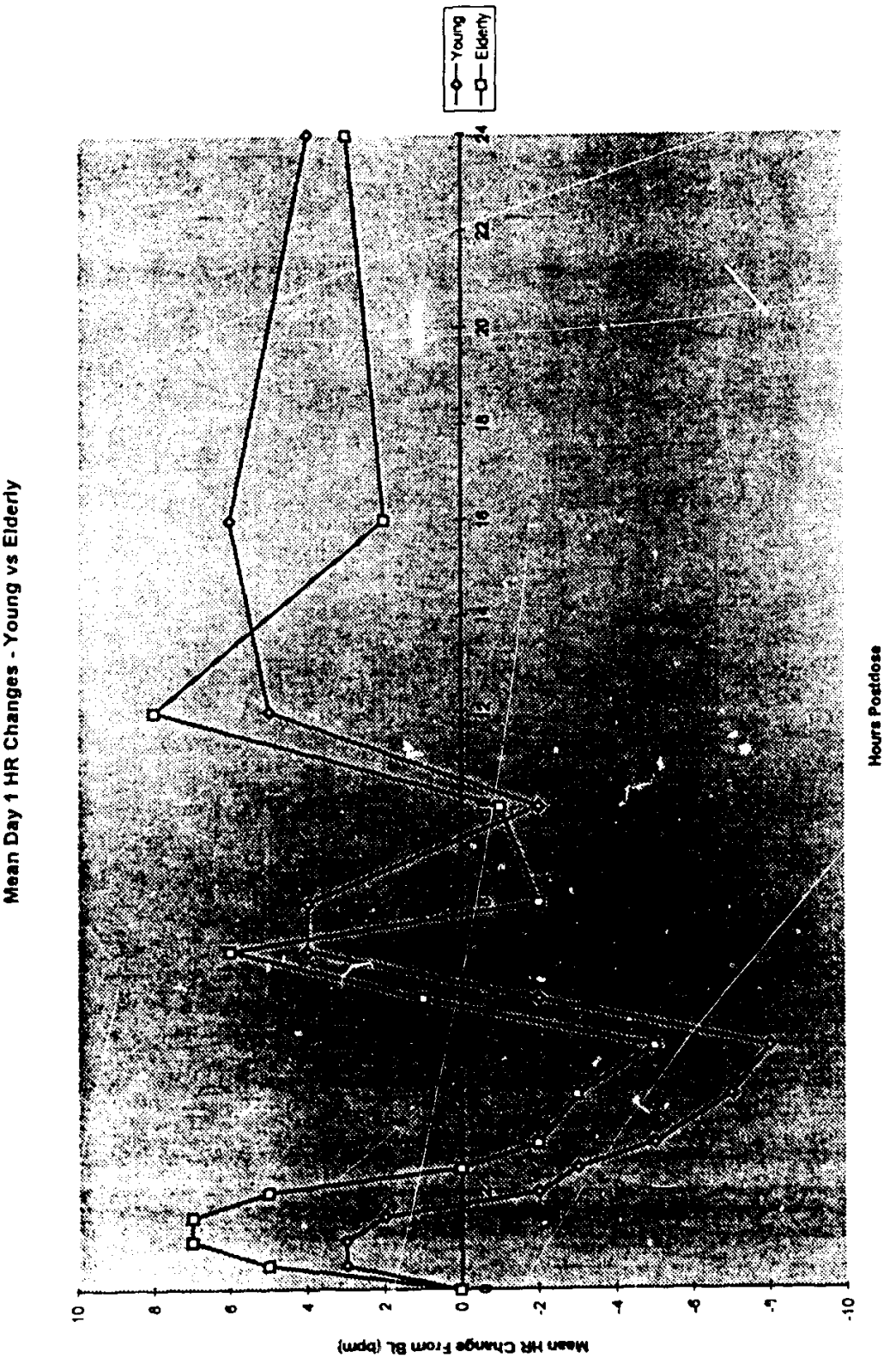

Mean Day 1 HR Changes - Young vs Elderly
Young
Elderly
Mean HR Change From BL (bpm)
10
8
6
4
2
0
-2
-4
-6
-8
-10
Hours Postdose
0
2
4
6
8
10
12
14
16
18
20
22
24

Figure 10

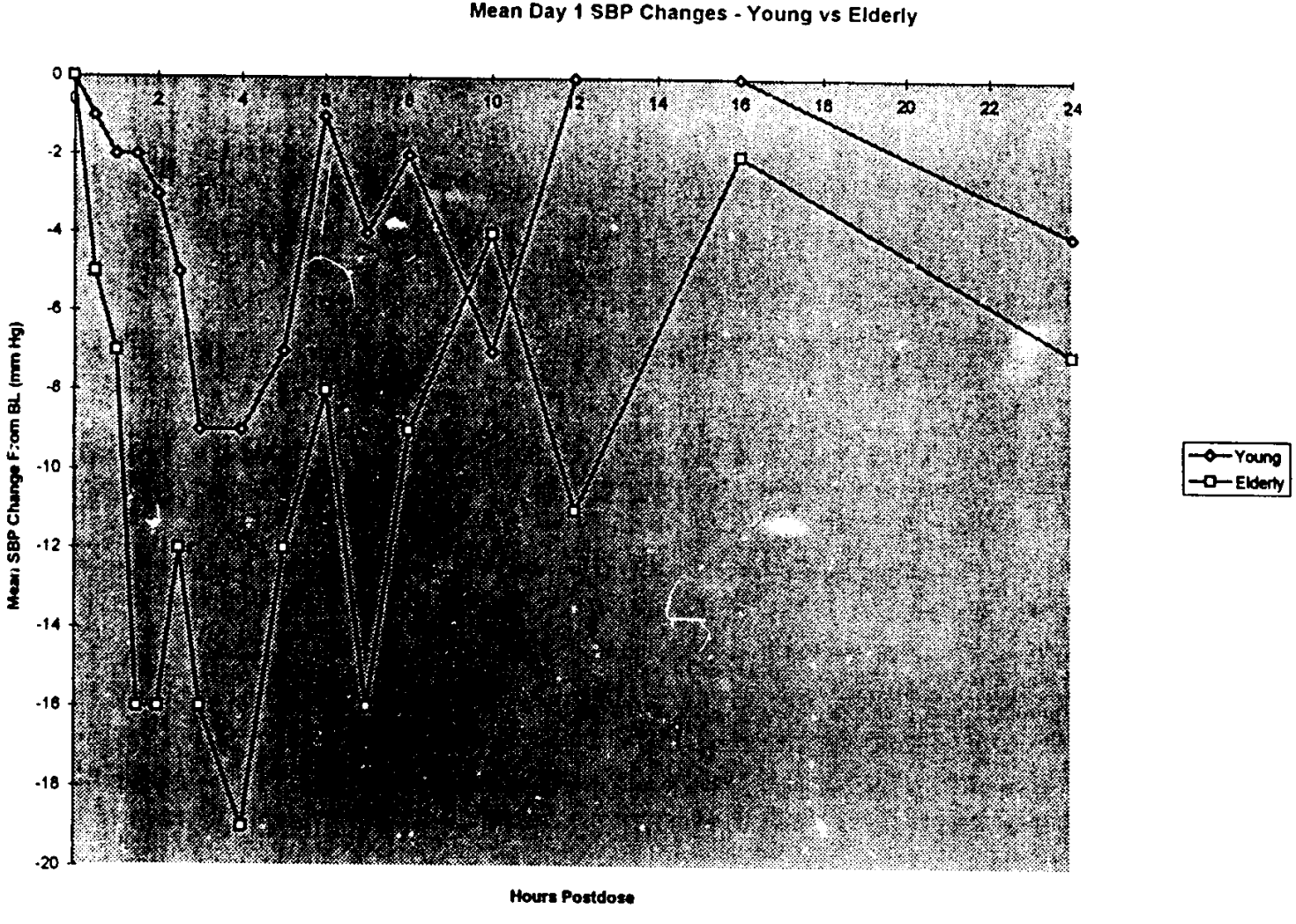


Figure 11

Mean Day 1 DBP Changes - Young vs Elderly

Figure 12

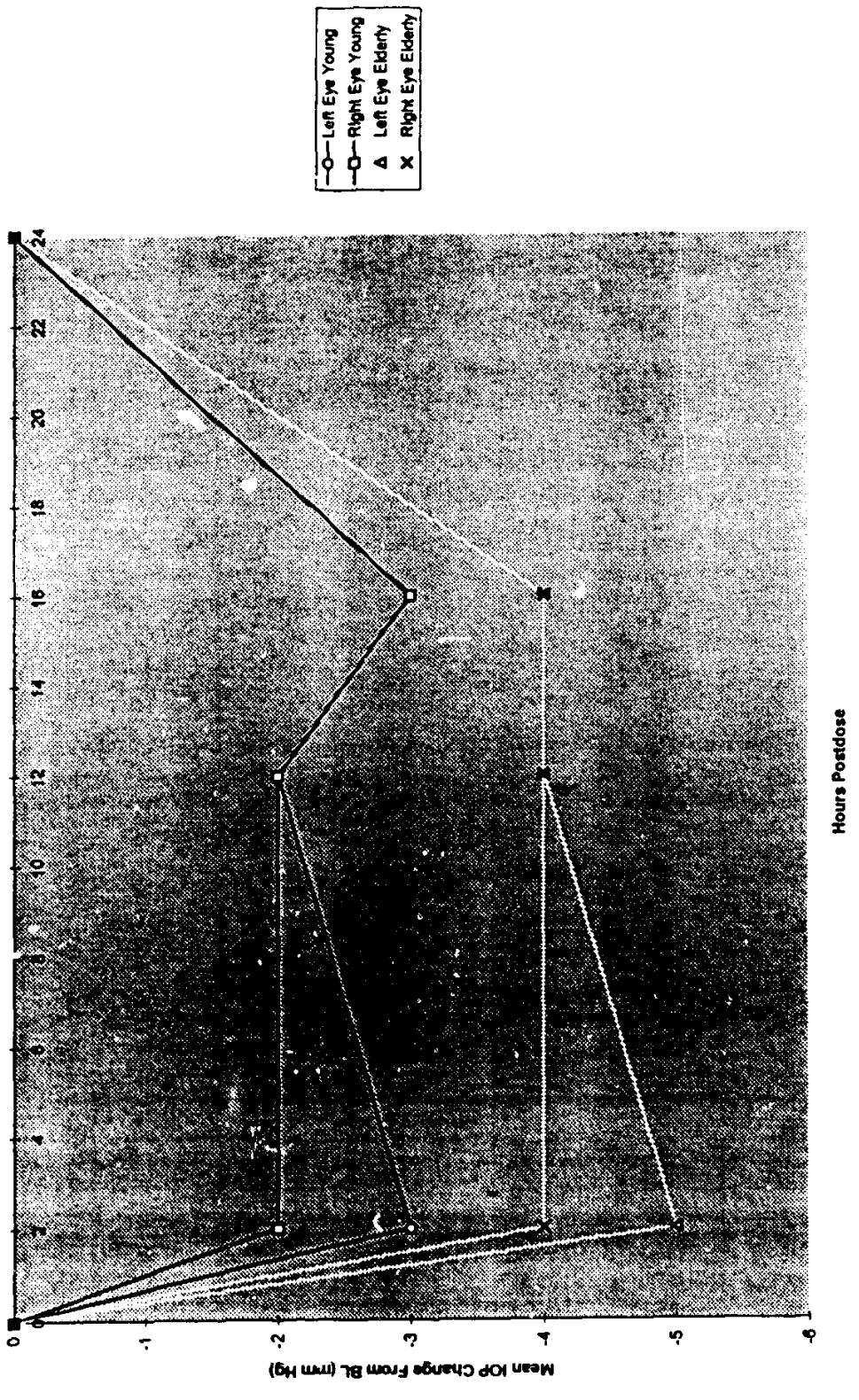

Mean Day 1 IOP Changes - Young vs Elderly
Left Eye Young
Right Eye Young
Left Eye Elderly
Right Eye Elderly
Mean IOP Change From BL (mm Hg)
Hours Postdose
0
-1
-2
-3
-4
-5
-6
2
4
6
8
10
12
14
16
18
20
22
24

Figure 13

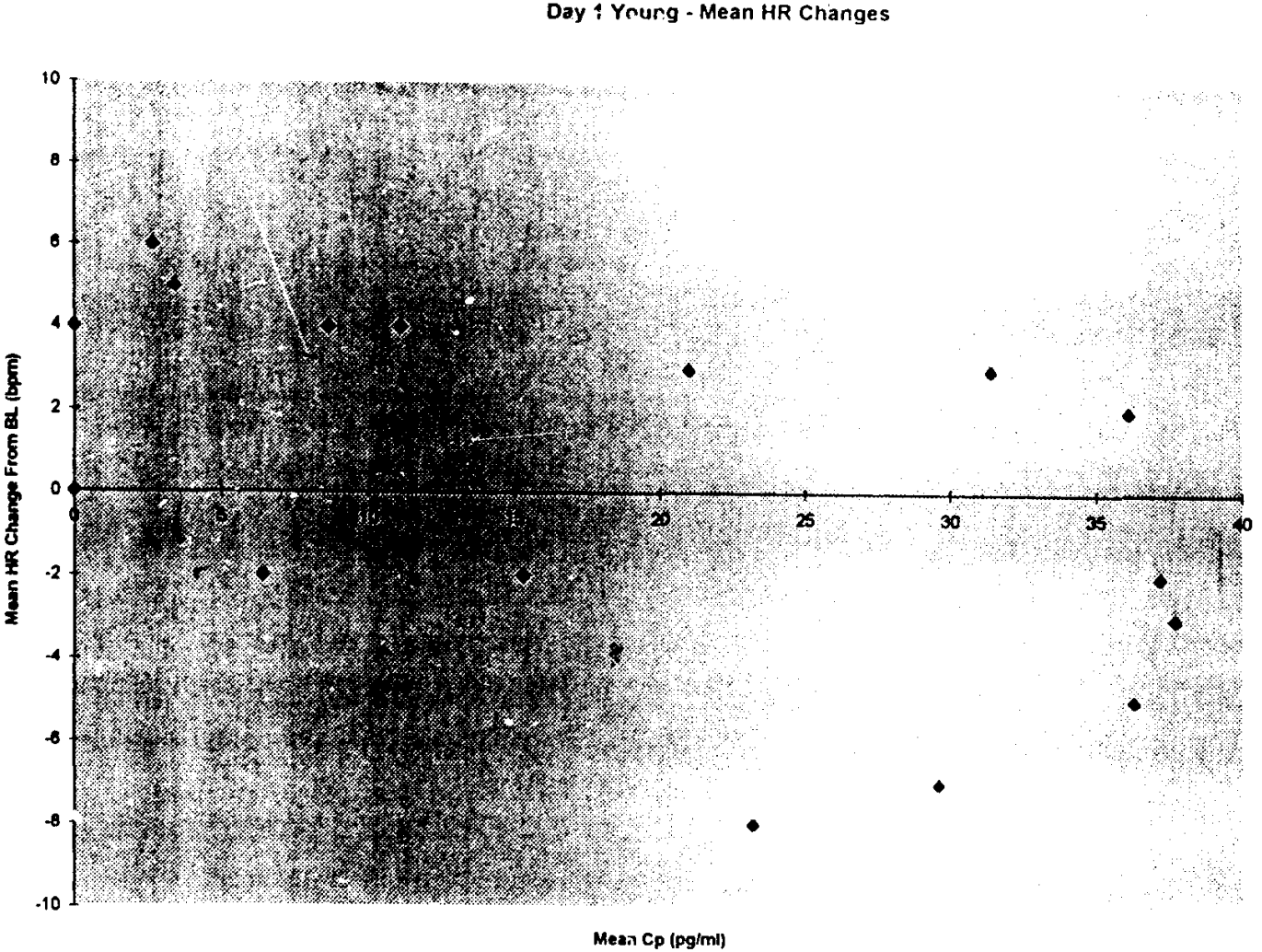


Figure 14

Day 10 Young - Mean HR Changes

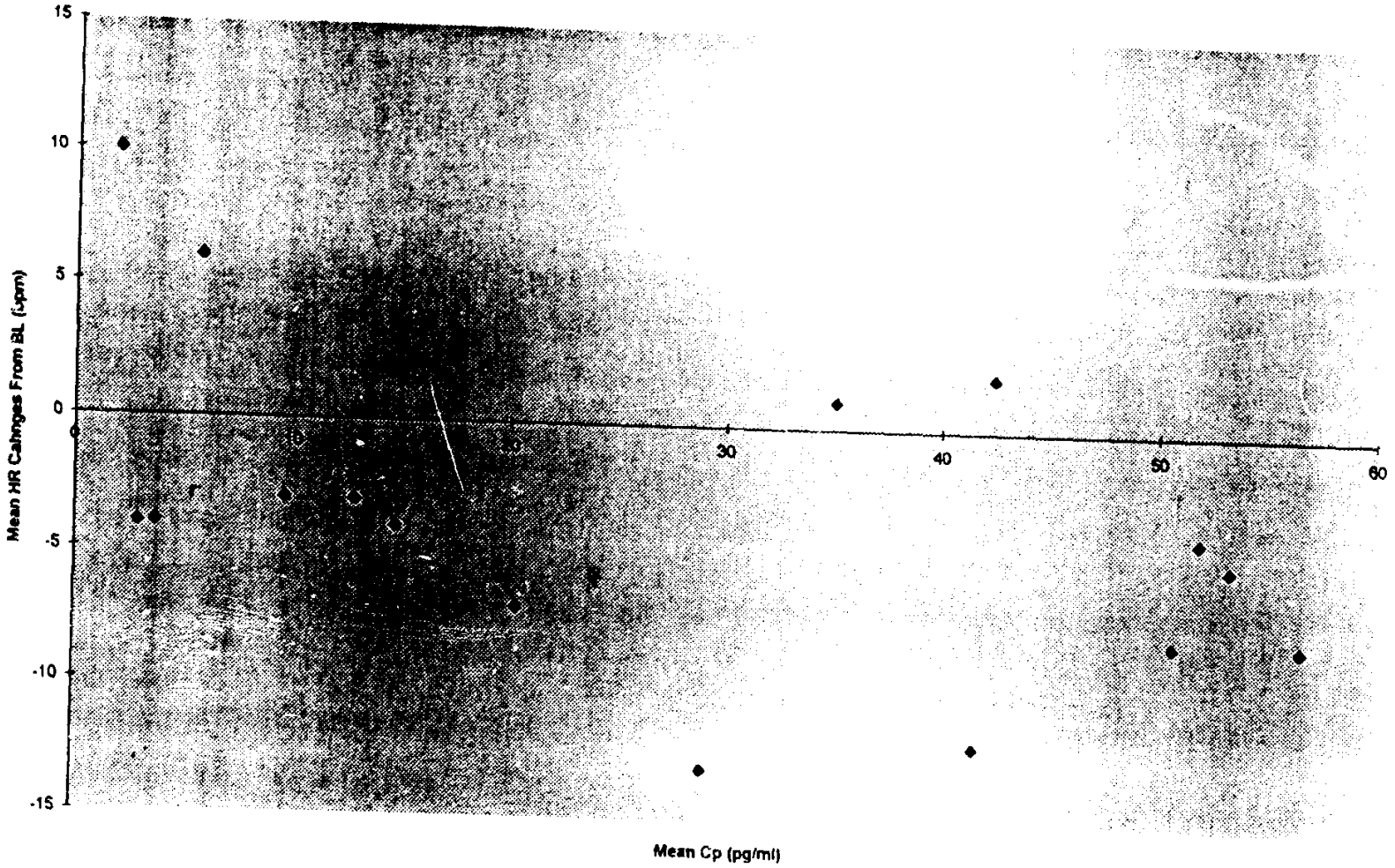


Figure 15

Day 1 Elderly - Mean HR Changes

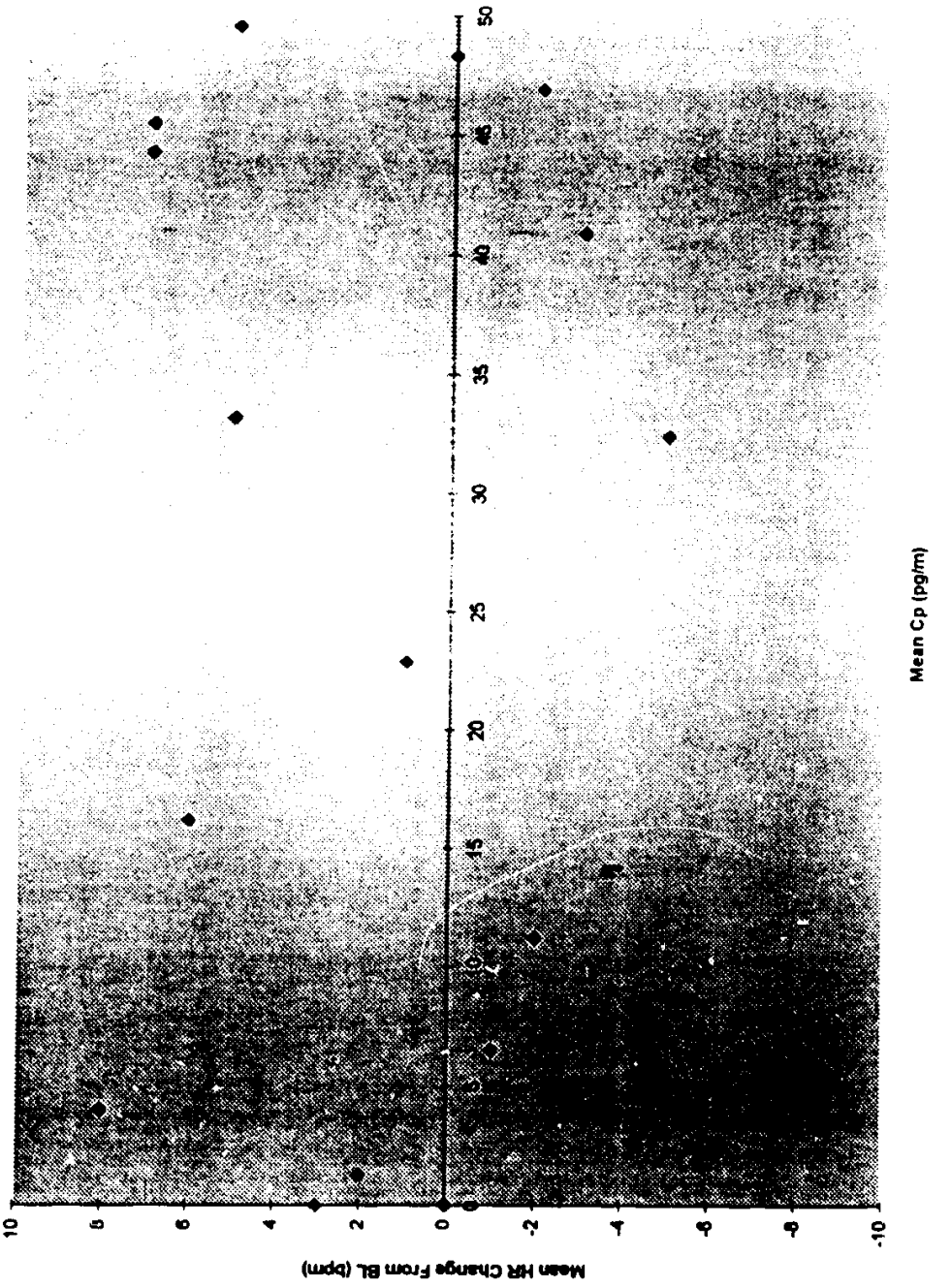


Figure 16

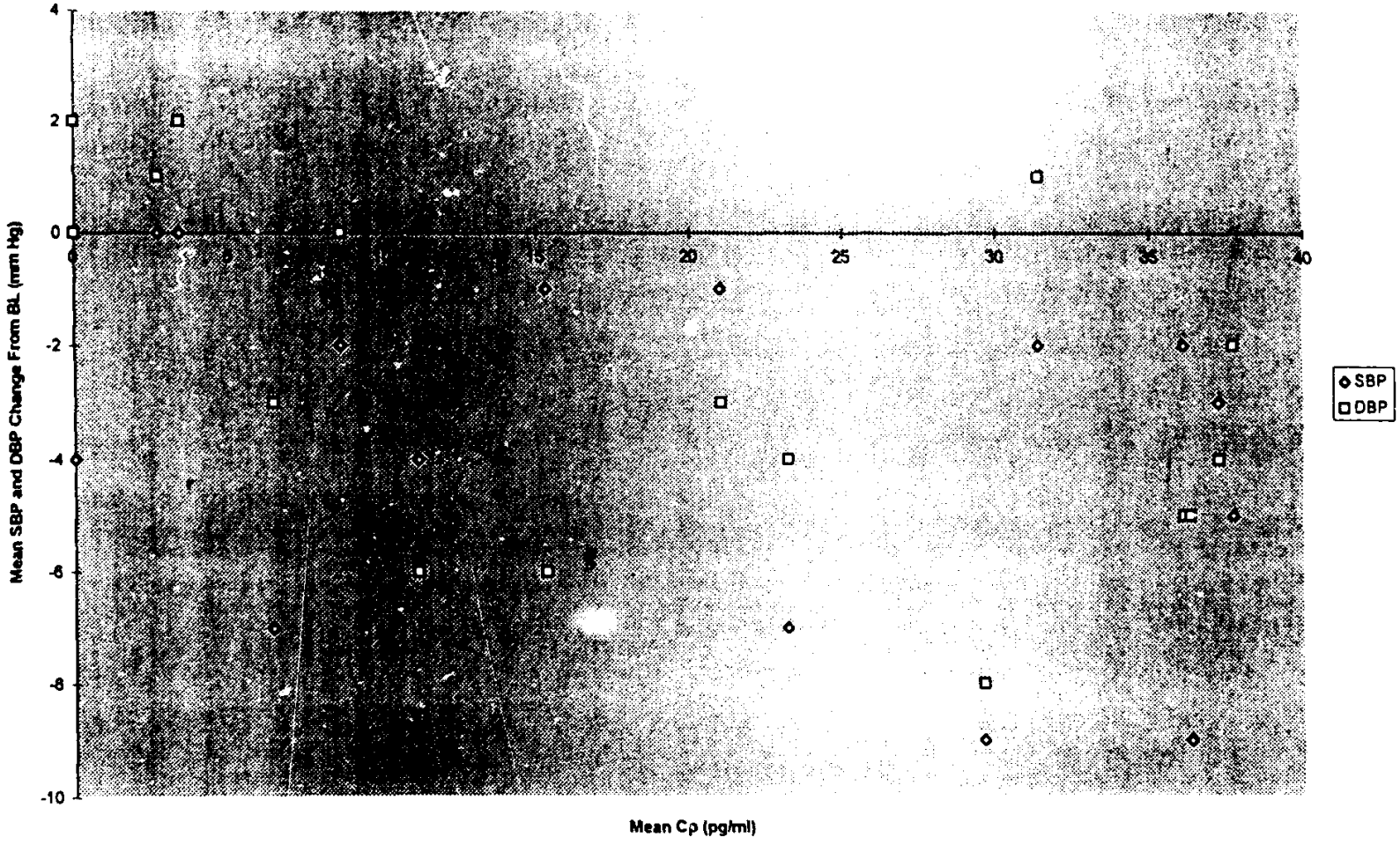


Figure 17

Day 10 Young - Mean SBP and DBP Changes
SBP
DBP
Mean SBP and DBP Changes From BL (mm Hg)
Mean Cp (pg/ml)
60
50
40
30
20
10
0
6
4
2
0
-2
-4
-6
-8
-10
-12
-14

Figure 18

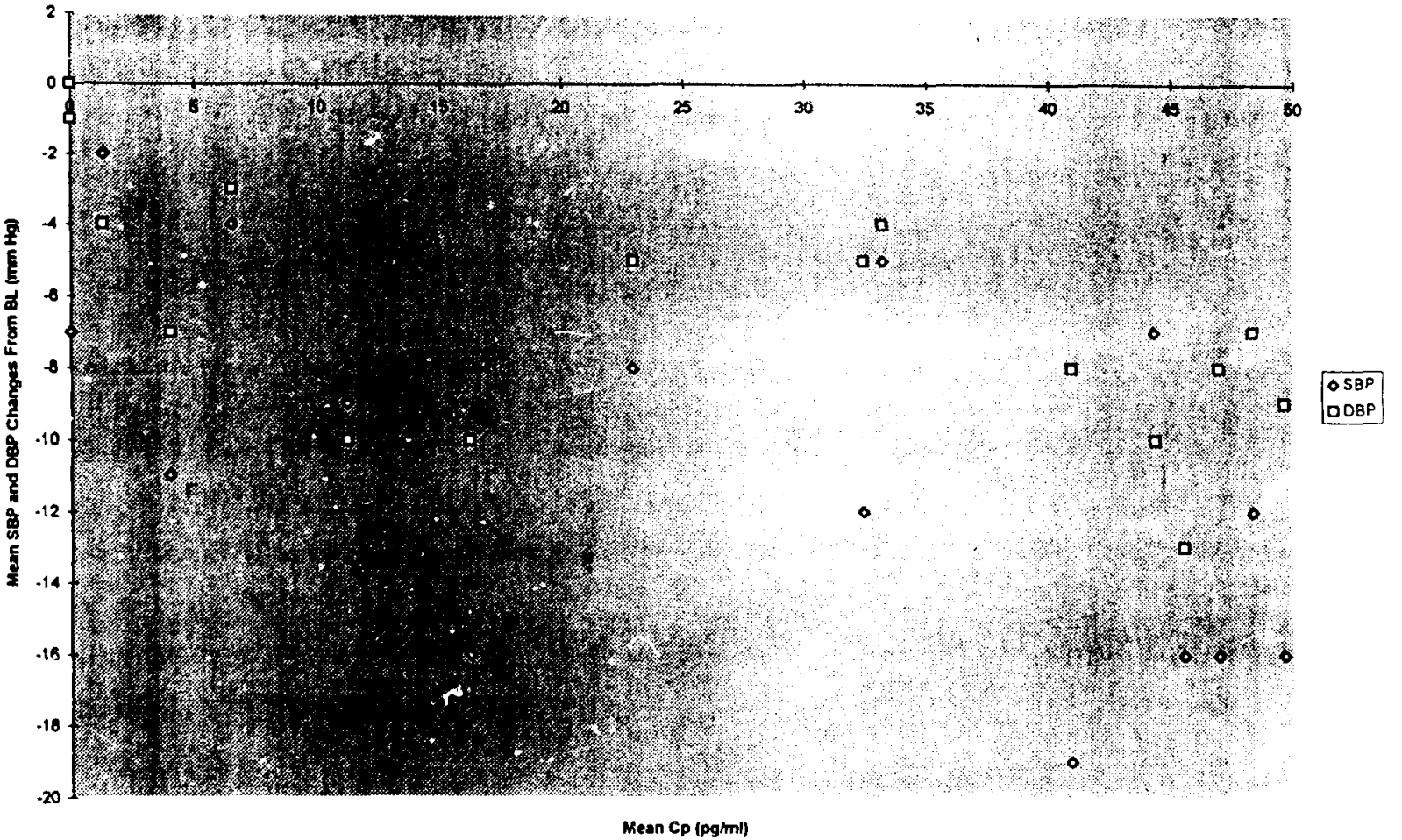


Figure 19

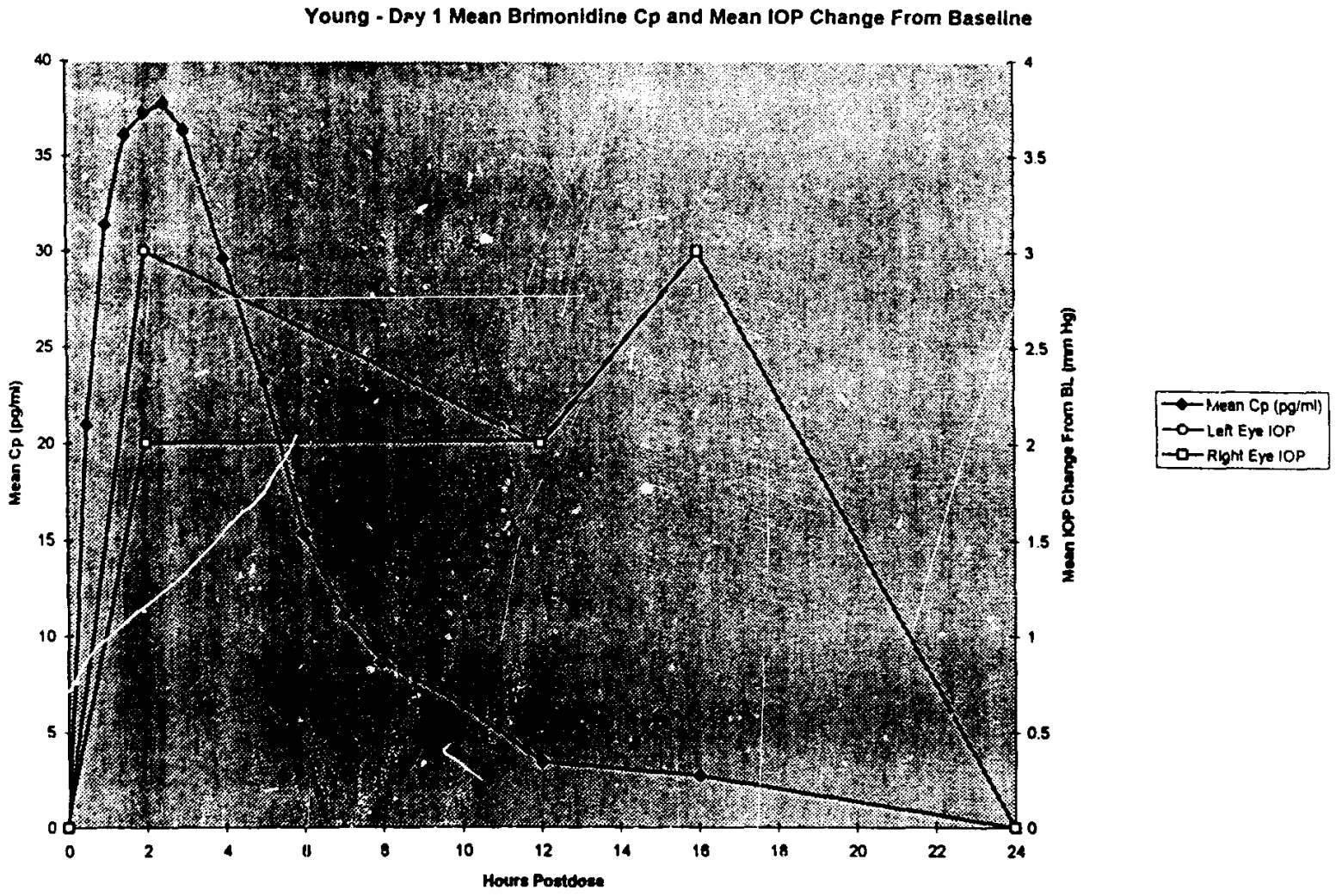


Figure 20

Young - Day 10 Mean Brimonidine Cp and Mean IOP Change From Baseline

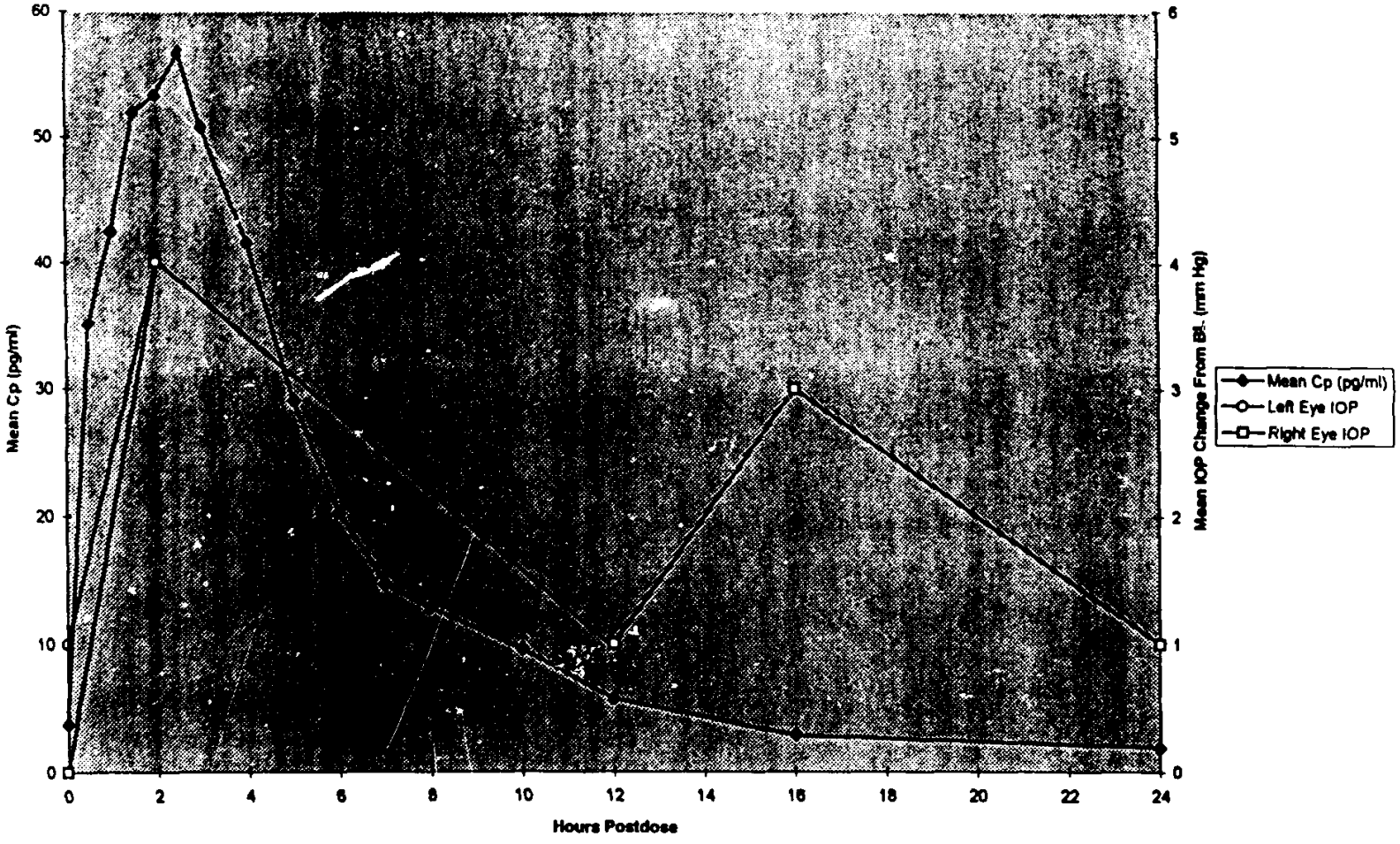
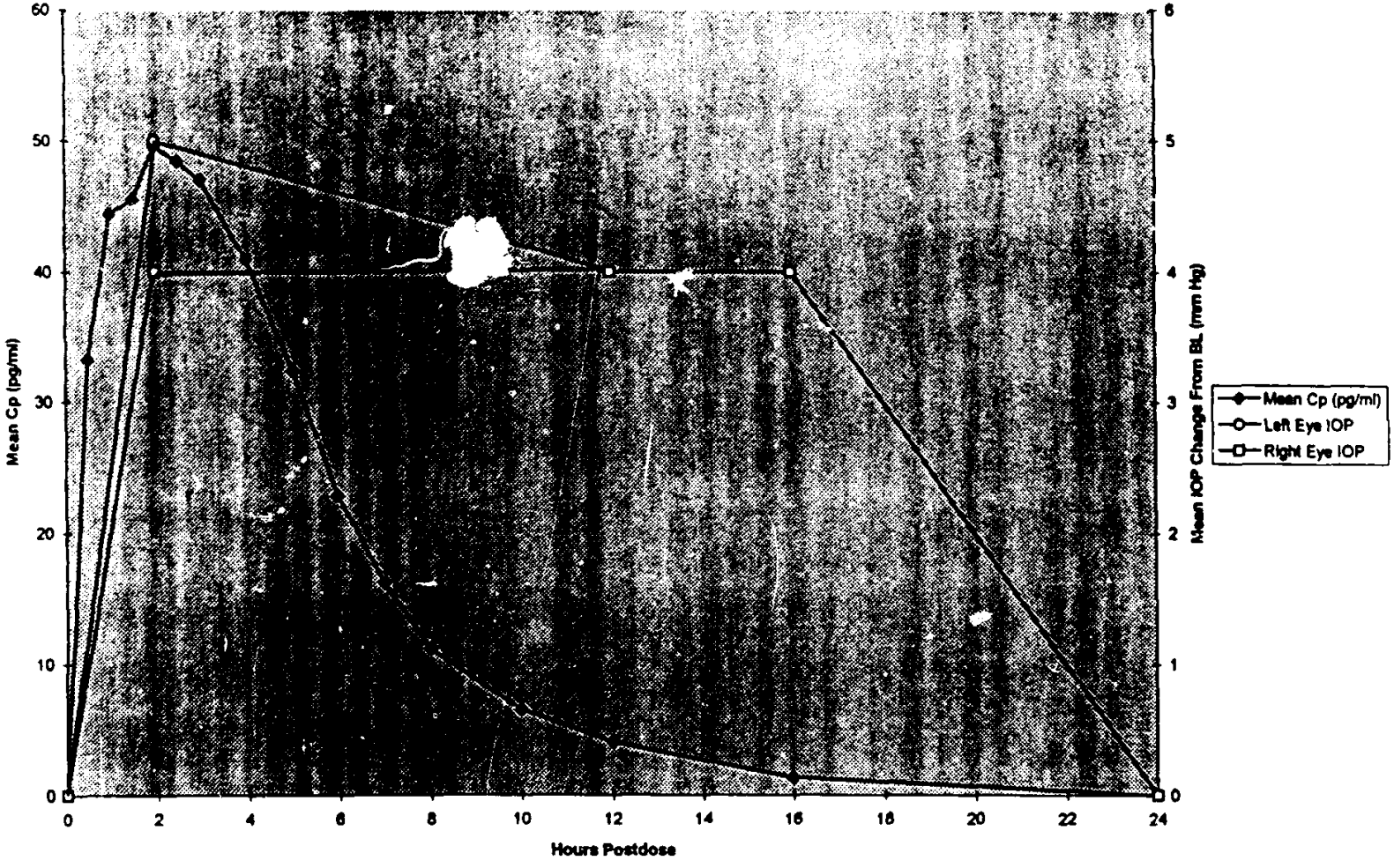


Figure 21

Elderly - Day 1 Mean Brimonidine Cp and Mean IOP Change From Baseline



4. Protocol No. A342-119-7831: "A Comparison of the Safety and Efficacy (and Pharmacokinetics) of Twice Daily vs. Three Times Daily Administration of Brimonidine 0.2% in Subjects with Open Angle Glaucoma or Ocular Hypertension"
(Report No. PK-1993-074)

Volume: 84

Pages: 84-001 to 84-391

Investigators & Location:

Study Dates: January 10, 1992 - September 9, 1992

OBJECTIVES:
(i) To evaluate the safety and efficacy of 0.2% brimonidine tartrate following twice daily (bid) or three times daily (tid) ocular instillation into both eyes of patients with open angle glaucoma or ocular hypertension.
(ii) To compare the plasma brimonidine concentrations at selected timepoints between the bid and tid dosing groups.

FORMULATION:
Brimonidine Tartrate (AGN 190342-LF) 0.2% Ophthalmic Solution - Formulation No. 7831X; Lot No. 09685; Batch Size

Vehicle - Formulation No. 7833X

STUDY POPULATION:
96 male or female patients aged 26 to 73 years with either newly diagnosed or established primary open angle glaucoma or ocular hypertension in each eye. Patients with previous diagnosis of either condition were receiving no more than 2 anti-glaucoma drugs. Inclusion criteria also included a post-washout intraocular pressure (IOP) of ≥23 mm Hg in each eye and visual acuity of 20/100 or better. No female patients who were either pregnant, nursing, or of child-bearing potential were allowed to enter into the study.

METHODS:
The study was a randomized, double blind, parallel group design in which patients

Dose Time	BID Group	TID Group	Sampling Time (hours postdose)
7-9am	0.2%	0.2%	~7 am (0 hr)
2-3pm	Vehicle	0.2%	~2 pm (7 hr)
10pm-12am	0.2%	0.2%	~6 pm (11 hr)

Plasma samples for the determination of brimonidine concentrations were obtained from 47 of the 96 patients, 24 patients in the bid group and 23 in the tid group, at the following times: before the study (Day 0), at week 3 before the am dose (0 hr), at week 6 before the am dose (0 hr), and at 7 and 11 hrs postdose, at week 8 before the am dose (0 hr), and at week 12 before the am dose (0 hr), and at 7 and 11 hrs postdose.

The primary efficacy measurement was reduction in IOP, and secondary measures were cup-to-disc ratio and visual field data. Safety measurements included reported adverse events, ocular and systemic discomfort, biomicroscopy variables, ophthalmoscopy, visual acuity, Schirmer tear test, heart rate, and blood pressure.

ASSAY:

DATA ANALYSIS:
Individual plasma brimonidine concentrations were determined and summary statistics computed for each group (i.e., mean, SD, SEM, and CV). No other pharmacokinetic parameters were determined. Trough concentrations were defined as those occurring prior to the first morning dose. A t-test was performed to test for significant differences in brimonidine plasma concentrations between male and female patients and measures of efficacy between the bid and tid dosing groups were tested with ANOVA ($p < 0.05$ in both cases).

RESULTS:
The plasma concentration data are provided in **Appendix 2** (Tables I through X). The mean trough (0 hr), and the 7, and 11 hour postdose levels are illustrated in Figures 1 through 3 for both groups. The mean trough concentrations are summarized in the following table and are plotted in Figure 1:

TROUGH BRIMONIDINE PLASMA CONCENTRATIONS (pg/ml)

Week	BID GROUP Mean ± SD (Range)	TID GROUP Mean ± SD (Range)
3	13.8 ± 14.3 (4.47-25.0) CV 104% N = 22	13.3 ± 7.48 (4.07-34.8) CV 56% N = 23
6	12.7 ± 9.23 (0.00-39.9) CV 73% N = 21	10.6 ± 9.63 (0.00-40.5) CV 91% N = 20
8	11.1 ± 13.5 (0.00-64.8) CV 121% N = 22	15.7 ± 15.3 (0.00-48.6) CV 98% N = 21
12	16.1 ± 14.6 (0.00-59.4) CV 90% N = 22	13.5 ± 9.92 (0.00-34.4) CV 73% N = 20

The mean trough concentrations were comparable between the groups and it appeared that steady-state plasma levels were attained at week 3. Mean trough concentrations for the bid and tid groups ranged between ~11 and ~16 pg/ml. The variability in trough concentrations between patients was high for both groups. The reductions from

baseline in IOP at the time of the morning trough determinations were not significantly different between the bid and tid groups.

The mean concentration data at 7 hrs postdose (i.e., at ~2 pm, just prior to the second dose) on weeks 6 and 12 are summarized in the following table and plotted in Figure 2:

BRIMONIDINE PLASMA CONCENTRATIONS AT 7 HOURS POSTDOSE (pg/ml)

Week	BID GROUP Mean ± SD (Range)	TID GROUP Mean ± SD (Range)
6	17.1 ± 13.5 (4.11-45.8) CV 79% N = 22	15.1 ± 9.28 (3.76-43.8) CV 61% N = 21
12	14.8 ± 7.96 (4.11-24.8) CV 54% N = 21	16.6 ± 12.0 (3.58-47.2) CV 73% N = 21

The plasma brimonidine concentrations were similar between the two groups and between weeks 6 and 12 within the groups. Although the between patient variability in these concentrations was lower than that for the trough levels, it still remained high.

The mean concentration data at 11 hrs postdose (i.e., at ~6 pm, ~4 hrs after the second dose) on weeks 6 and 12 are summarized in the following table and plotted in Figure 3:

BRIMONIDINE PLASMA CONCENTRATIONS AT 11 HOURS POSTDOSE (pg/ml)

Week	BID GROUP Mean ± SD (Range)	TID GROUP Mean ± SD (Range)
6	4.56 ± 3.34 (0.00-12.7) CV 73% N = 22	41.8 ± 20.0 (19.6-81.9) CV 48% N = 21
12	4.37 ± 2.31 (0.00-8.79) CV 53% N = 22	42.8 ± 21.5 (14.6-108) CV 50% N = 21

Mean brimonidine concentrations were ~9-10-fold higher for the tid group on weeks 6 and 12. The between patient variability in plasma levels was lower for the tid group

(i.e., ~50%) as compared to the bid group (i.e., ~50-70%). Statistically significant differences were detected in the mean decreases in IOP between the groups at 9 and 11 hrs postdose in favor of the tid group.

No gender analyses were reported with respect to the plasma concentration or IOP data.

REVIEWERS CONCLUSIONS:
Steady-state trough (i.e., predose) plasma brimonidine plasma concentrations appeared to be attained by 3 weeks of multiple bid or tid dosing. Mean trough plasma levels were similar between the two dosing groups at weeks 3, 6, 8, and 12 and ranged between ~11 and ~16 pg/ml.

The mean 7-hour postdose levels at weeks 6 and 12 were also similar between and within the groups and ranged between ~15 and ~17 pg/ml. However, mean concentrations at 11 hours postdose (i.e., 4 hours after the second dose) at weeks 6 and 12 were ~9-fold higher for the tid group (~40 pg/ml) compared to the bid (~4.5 pg/ml) group.

The between patient variability in plasma concentrations for both groups was high (i.e., ~50-120%) across all time intervals.

The reductions in IOP from baseline values for the two groups were not significantly different at the morning trough at weeks 3, 6, 8, and 12, but were significantly different at 9 and 11 hours after morning dosing at weeks 6 and 12.

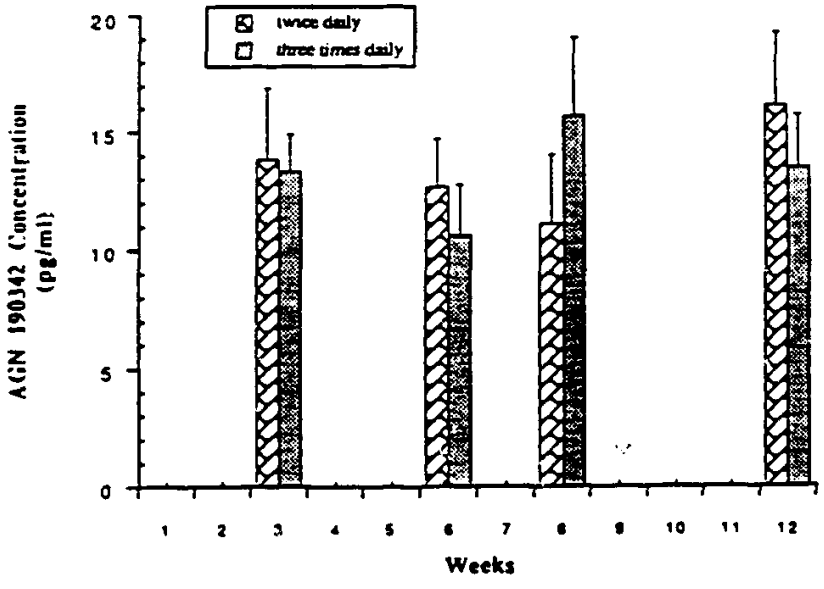


Figure 1

AGN 190342 concentraion in human plasma at 7 - 9 am (just before morning dose) in patients given twice-daily or three times daily ophthalmic dosing of 0.2% brimonidine tartrate (mean ± sem, N = 20-23)

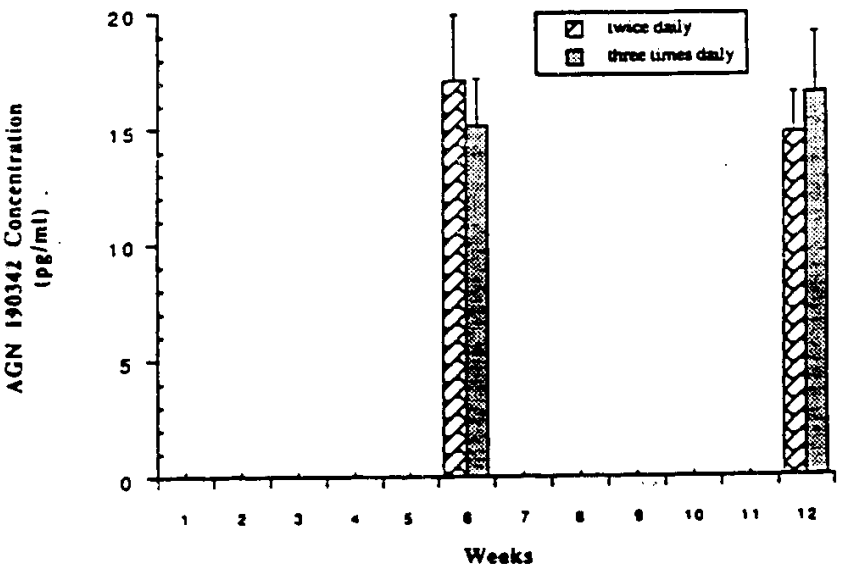


Figure 2

AGN 190342 concentration in human plasma at 2-3 pm (~7 hours from the morning dose) in patients given twice-daily or three times daily ophthalmic dosing of 0.2% brimonidine tartrate (mean ± sem, N = 21-22)

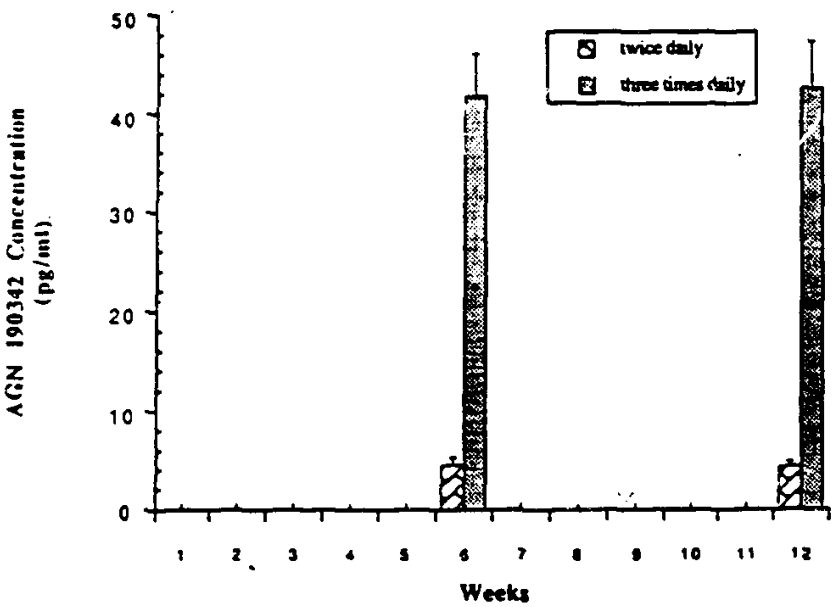


Figure 3

AGN 190342 concentration in human plasma at ~6 pm in patients given twice-daily (~11 hours from the morning dose) or three times daily (~4 hours from the second dose) ophthalmic dosing of 0.2% brimonidine tartrate solution (mean ± sem, N = 21-22)

5. Protocol No. PK-1991-RSCH-015-AGN 190342: "Plasma Protein Binding of ^{14}C-AGN 190342 by Equilibrium Dialysis for Mouse, Rat, Dog, Monkey, and Man" (Report: PK-1991-041)

Volume: 86

Pages: 86-101 to 86-112

Investigators & Location:

Study Dates: May, 1991 - August, 1991

OBJECTIVE:
To evaluate the *in vitro* binding of brimonidine tartrate (AGN 190342-LF) to the plasma proteins of mice, rats, monkeys, dogs, and humans using equilibrium dialysis.

DRUG SUBSTANCE:
Brimonidine tartrate (AGN 190342-LF) - Pharmaceutical Sciences Operations of Allergan, Lot #90119-367H

^{14}C-AGN 190342-LF - , Lot #100H9239, Specific Activity 120 μCi/mg, Radiochemical Purity 98%

METHODS:
Drug-free pooled plasma from mice, rats, dogs, monkeys, and humans was spiked with ^{14}C-AGN 190342 to yield initial (i.e., predialysis) concentrations of 0.333, 3.33, 33.3, and 333 ng/ml. Equal volumes (0.4ml) of spiked plasma and isotonic sodium/potassium phosphate buffer, pH 7.4, were placed into the dialysis cells separated by a dialysis membrane (MW cutoff 12,000 Daltons) and dialyzed at 37°C. Times to dialysis equilibrium were determined to be 4 hours for all species, except for mouse plasma, which was dialyzed for 5 hours. Radioactivity in plasma and buffer compartments was determined by liquid scintillation counting and the respective free, unbound fractions in plasma were determined, i.e., fu = (DPM Post-Dialysis Buffer)/(DPM Post-Dialysis Plasma). The post-dialysis volumes of the plasma and buffer compartments were measured to evaluate volume shifts during dialysis.

proteins can be ranked from highest to lowest as follows: monkey (66.3% unbound, 33.7% bound), dog (70.5% unbound, 29.5% bound), human (78.8% unbound, 21.2% bound), rat (80.5% unbound, 19.5% bound), and mouse (82.6% unbound, 17.4% bound). The sponsor reported no appreciable volume shifts between the plasma and buffer compartments.

REVIEWERS CONCLUSIONS:

The *in vitro* binding of brimonidine to plasma proteins of mice, rats, dogs, monkeys, and humans was low (i.e., <35%) for all species tested. In particular, the binding of the drug to human plasma proteins was ~21%.

Brimonidine plasma protein binding was linear (i.e., concentration independent) over the concentration range from ~0.2-200 ng/ml for all species.

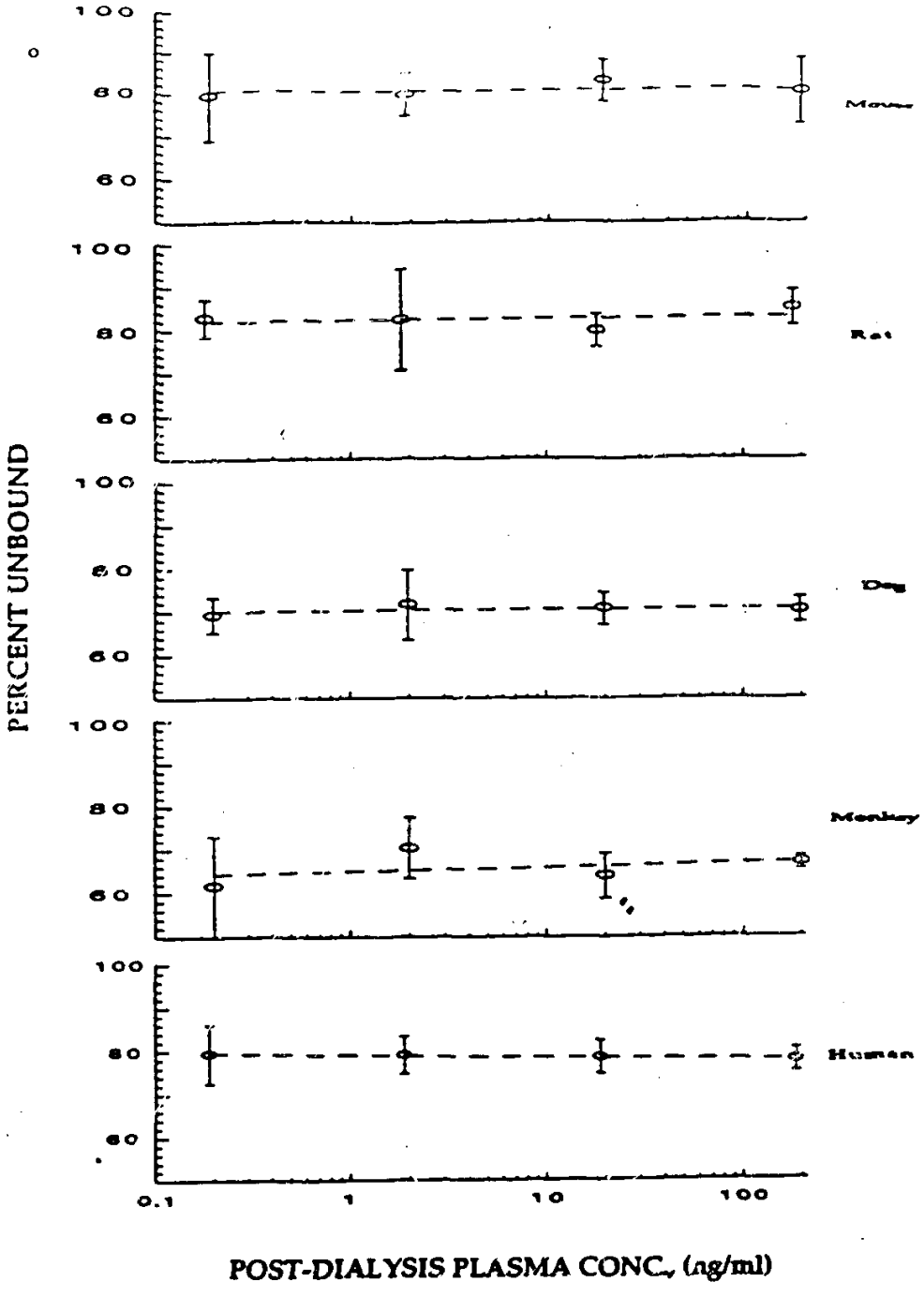


Figure 3. The effect of drug concentration on the percent binding of ^{14}C-AGN 190342 to plasma protein in mouse, rat, dog, monkey and human. Each data point presents 8 replicates at the post-dialysis plasma concentration. Symbols are mean values with error bars representing S.D. The broken-lines are computer generated linear regression slopes.

Table I. Summary for the free fraction values (%) of ^{14}C-AGN 190342 in the plasma of mouse, rat, dog, monkey and human.

SPECIES	PERCENT UNBOUND[a]
Mouse	80.5 ± 7.2
Rat	82.6 ± 7.0
Dog	70.5 ± 5.0
Monkey	66.3 ± 6.4
Human	78.8 ± 5.0

a Values are the mean of 32 replicates ± S.D.

6. Protocol No. PK-94-P009: "*In Vivo* Plasma Protein Binding of AGN 190342 in Mice, Rats, Rabbits, Dogs, Monkeys, and Humans"
(Report: PK-94-092)

Volume: 90

Pages: 90-246 to 90-259

Investigators & Location:

Study Dates: April 18, 1994 - May 31, 1994

OBJECTIVE:
To evaluate the *in vivo* binding of brimonidine tartrate (AGN 190342-LF) to plasma proteins of mice, rats, rabbits, monkeys, dogs, and humans following either systemic or ocular administration using equilibrium dialysis.

DRUG SUBSTANCE:
Brimonidine tartrate (AGN 190342-LF) - Pharmaceutical Sciences Operations of Allergan, Lot #90533

METHODS:
Plasma samples for equilibrium dialysis were obtained from *in vivo* animal studies in mice, rats, rabbits, dogs, and monkeys following oral administration of brimonidine tartrate. Human plasma samples for dialysis were obtained from clinical study A342-120-8042 between 0 and 4 hours following ocular instillation of 0.5% brimonidine tartrate into each eye of healthy volunteers. Equal volumes (0.4ml) of plasma and isotonic sodium/potassium phosphate buffer, pH 7.4, were placed into the dialysis cells separated by a dialysis membrane (MW cutoff 12,000 Daltons) and dialyzed for 5 hours at 37°C. The concentration of brimonidine was determined in the post-dialysis plasma and buffer compartments of the cells by the previously validated GC-MS method (Oneida Research Services, **Validation Report PK-1991-048**). The performance of the assay for this study was provided in the ORS **Analytical/Performance Report PK-94-069**). The respective free, unbound fractions in plasma were determined as:
fu = (Brimonidine Conc in Buffer)/(Brimonidine Conc in Post-Dialysis Plasma). The post-dialysis volumes of the plasma and buffer compartments were measured to evaluate volume shifts during dialysis.

RESULTS:
The percent unbound along with the pre- and post-dialysis plasma brimonidine concentrations are provided in Table VI for the human subjects. In Table VII, the binding data are summarized for all species. Similar to the *in vitro* binding results, the *in vivo* binding of drug to human plasma proteins was low over a post-dialysis plasma

concentration range from 53.2 to 119 pg/ml, i.e., 70.8% unbound, 29.2% bound. The mean *in vivo* free fractions (expressed as percent unbound) were lower for mice and dogs, and slightly greater for monkeys when compared to those obtained *in vitro*. The *in vivo* and *in vitro* free fractions were comparable for the rat.

REVIEWERS CONCLUSIONS:
The *in vivo* binding of drug to human plasma proteins was low over a post-dialysis plasma concentration range from 53.2 to 119 pg/ml, i.e., 70.8% unbound, 29.2% bound.

Table VI

Unbound fraction of AGN 190342 in human plasma collected between 0 and 4 hours after human subjects received a single eyedrop of 0.5% AGN 190342-LF solution in each eye

Subject ID	Concentration (ng/ml)			Percent Unbound
	Pre-dialysis Plasma	Post-dialysis Plasma	Post-dialysis Buffer	
104-2				
114-1				
114-3				
119-3				
120-2				
120-3				
117-2				

Table VII

Summary of AGN 190342 protein binding in mouse, rat, rabbit, dog, monkey and human plasma collected after ocular or systemic administration of AGN 190342-LF

Species	Range of Plasma AGN 190342 Concentrations (ng/ml)	Percent Unbound (Mean)	SD	CV (%)	SEM	N
Mouse	9.42 - 12.9	63.8[a]	NA[b]	NA	NA	2
Rat	4.56 - 366	80.6	15.5	19.2	5.48	8
Rabbit	1.74 - 9.16	78.0	9.1	11.7	4.55	4
Dog	1.58 - 1.90	53.5	10.9	20.3	6.27	3
Monkey	1.11 - 4.00	78.9	4.1	5.16	1.44	8
Human	0.0903 - 0.121	70.8	9.5	13.4	3.59	7

[a] Mean of 2 pooled plasma samples
[b] Not applicable, N = 2

7. Protocol No. PK-1992-RSCH-023-AGN 190342-LF: "Distribution of ^{14}C-AGN 190342 Between Blood and Plasma Determined *In Vitro* From Blood of Mouse, Rat, Monkey, and Human"
(Report: PK-1992-063)

Volume: 86

Pages: 86-113 to 86-123

Investigators & Location:

Study Dates: July 6, 1992 - August 5, 1992

OBJECTIVE:
To determine the *in vitro* blood to plasma binding ratio of brimonidine base (AGN 190342) from the blood of mice, rats, monkeys, and humans by adding radiolabeled brimonidine tartrate (^{14}C-AGN 190342-LF) to drug-free blood samples.

DRUG SUBSTANCE:
Brimonidine tartrate (AGN 190342-LF) - Pharmaceutical Sciences Operations of Allergan, Lot #90355; 1 mg brimonidine tartrate = 0.66 mg brimonidine base

^{14}C-AGN 190342-LF - Sigma Chemical Co., Lot #100H9239, Specific Activity 122 μCi/mg, Radiochemical Purity 98%

METHODS:
Aliquots (2-4ml) of freshly collected drug-free blood from mice, rats, monkeys, and a 78kg healthy volunteer were pre-incubated at 37°C for ~5 min, then spiked with ^{14}C-AGN 190342-LF, and re-incubated for 30 min. Three blood concentrations (low, medium, and high), expressed in terms of ^{14}C-AGN 190342, were prepared for each species. For human blood, these concentrations were 7.07, 70.7, and 707 ng base/ml. Following equilibration at 30 min, three aliquots (0.2 ml) of blood sample were combusted, and radioactivity was counted by liquid scintillation methods. Plasma was prepared from the remaining volume of the blood sample and the radioactivity in an equal volume (0.2 ml) of plasma was also determined by liquid scintillation counting. Replicate determinations of blood and plasma radioactivity were made for each of the three concentrations. The blood to plasma (B/P) AGN 190342 (brimonidine base) ratios were computed at each concentration as the ratio of mean blood concentration (dpm/ml)/mean plasma concentration (dpm/ml).

RESULTS:
Table I provides the B/P ratio data for all species studied. The mean B/P ratios in the human subject were 1.31 at 7.07 ng base/ml, 1.14 at 70.7 ng base/ml, and 1.12 at 707

ng base/ml.

REVIEWERS CONCLUSIONS:
The blood to plasma ratio data indicated comparable distribution of brimonidine between blood and plasma in human blood at concentrations of 70.7 and 707 ng base/ml. However, slightly greater distribution into blood compared to plasma (~30%) was observed at low blood concentration of 7.07 ng base/ml.

Table I

Concentration of ^{14}C-AGN 190342 in mouse, rat, monkey and human blood and plasma *in vitro*

Species	Initial Blood Concentration (ng/ml)	Replicates	Blood dpm/ml (Mean ± SD)	Plasma dpm/ml (Mean ± SD)	Blood/Plasma Ratio (Mean ± SD)
Mouse	10.6	N = 2	3440	2470	1.39
	106	N = 2	40330	28780	1.40
	1060	N = 2	443460	335368	1.32
Rat	7.07	N = 3	1690 ± 160	1540 ± 110	1.10 ± 0.11
	70.7	N = 3	18760 ± 1560	15860 ± 660	1.18 ± 0.13
	707	N = 3	206840 ± 8430	180190 ± 1820	1.15 ± 0.04
Monkey	5.30	N = 2	920	1300	0.71
	53	N = 2	14690	15480	0.95
	530	N = 2	174370	179550	0.97
Human	7.07	N = 3	1650 ± 30	1260 ± 40	1.31 ± 0.01
	70.7	N = 3	18170 ± 530	15880 ± 410	1.14 ± 0.04
	707	N = 3	205071 ± 2830	182500 ± 1500	1.12 ± 0.01

Allergan Notebook R-1992-2681 pp 22, 23, 24, 31, 32, 33

8. Protocol No. PK-1990-RSCH-013-AGN 190342: "*In Vitro* Metabolism of AGN 190342 in Rat, Dog, Monkey, and Human Liver Homogenates"
(Report: PK-1991-021)

Volume: 86

Pages: 86-151 to 86-183

Investigators & Location:

Study Dates: February 1, 1991 - April 5, 1991

OBJECTIVE:
To evaluate the *in vitro* hepatic metabolism of brimonidine (AGN 190342) in rat, dog, monkey, and human liver homogenates.

DRUG SUBSTANCE:
Brimonidine tartrate (AGN 190342-LF) - Pharmaceutical Sciences Operations of Allergan, Lot #90119; 1 mg brimonidine tartrate = 0.66 mg brimonidine base

^{14}C-AGN 190342-LF - Sigma Chemical Co., Lot #100H9239, Specific Activity 122 μCi/mg (~53.8 mCi/mmol), Radiochemical Purity 98%

METHODS:
Liver tissue from male Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, and human liver transplants were obtained and stored at -70°C until used. Liver microsomal fractions (i.e., 10,000 g supernatant fractions) were prepared for each species by standard methods in pH 7.4 phosphate bufferred saline (PBS) and subsequently stored at -20°C until ready for use. Drug solutions containing labeled and unlabeled brimonidine were prepared in PBS at concentrations ranging from 0.913-364 μg base equivalents/ml. A solution of the enzyme cofactor, NADPH, was also prepared in PBS and stored at -20°C until ready for use.

The liver homogenates were incubated with NADPH (final concentration 5.26 mM) and the various concentrations of drug at 37°C for 4-5 hours. An aliquot (70 μl) of the incubation sample was taken every hour and prepared for injection onto an HPLC system equipped with a radiometric detector to monitor the disappearance of ^{14}C-AGN 190342 and the formation of metabolites. The radioactive peak areas (PA) of ^{14}C-AGN 190342 and metabolites were used to calculate the percent (%) formation of each metabolite as: (PA of metabolite)/(total PA of ^{14}C-AGN 190342 and all metabolites)*100. Metabolites were referenced using Roman numerals corresponding to their respective HPLC retention times as follows:

Metabolite* or Drug	Retention Time(min)
MI	2.4
MIIc	5.2
MIIIa	7.7
MIIIb	9.0
MIV	11.9
MV	13.9
MVI	17.0
AGN 190342	18.3
MVII	21.3

The metabolic parameters, Km and Vmax, were determined by fitting the Michaelis-Menten model (i.,e., Metabolic Rate = (Vmax*C)/ (Km + C) to the metabolic rate constant vs. drug concentration data.

*The identification of the metabolites by LC-MS analysis and the proposed metabolic pathways are presented in the study summary that follows this one.

RESULTS:

In Figure 1, the radiochromatograms show the formation of brimonidine metabolites for each species. The metabolic pattern in the human microsomal fractions was qualitatively similar to that of monkey and rat, but different to that of the dog. The metabolite formation data are presented in Tables I through IV for each species. The formation of all metabolites was ~63% for rat (at 4 hours incubation), ~75% for monkey (at 5 hours incubation), and ~89% for human (at 5 hours incubation). After 4 hours incubation, only ~18% metabolite formation was observed for dog microsomes.

The formation of a total of 6 metabolites were detected in human liver homogenates. Metabolite V was formed to the greatest extent in human microsomes (34%), followed by MIIIa (20%), MI (15%), and MIV (14%). These metabolites have been tentatively identified as oxidation products of either the quinoxaline or imidazolidine rings of brimonidine. Approximately 10% of parent brimonidine remained after 5 hours of incubation for human microsomes.

As with human microsomes, MIIc formation was not detected in monkey homogenates at 5 hours incubation. However, while ~3-4% of MVII was formed by monkey liver, no formation was detected for human liver. The percentages of MIIIa (17%), IIIb (5%), IV (14%), and V (26%) formed in monkey homogenates were, in general, comparable to those for human. Approximately 25% of parent brimonidine remained at 5 hours of incubation for monkey microsomes. In contrast to human liver, rat homogenates formed MIIc and MVII, but not MIIIb. Metabolite V was formed to the greatest extent (20%), followed by MIV (13%), and MI (10%) Approximately 35% of parent brimonidine remained after 4 hours of incubation for rat microsomes. For dog liver, formation of MIIIb and MV were not detectable, and the extent of formation was <10% for the remaining metabolites. Approximately 80% of parent brimonidine remained after 4 hours of incubation for dog microsomes.

The computer-fitted Km and Vmax estimates are provided in Table V and the relationships between metabolic rate and brimonidine concentration are plotted in Figure 2 for each species. The estimates of Km were lowest for rat and human microsomes, at 21.5 and 26.5 μg/ml, respectively, and highest for dog liver (248 μg/ml). As shown by the curves in Figure 7, at low drug concentrations (i.e., <25 μg/ml), the metabolic rate appeared to be the greatest for human microsomes. The sponsor noted that at concentrations ~18 μg/ml or less, human microsomes showed the highest metabolic activity, followed by monkey, rat, and dog; no data was provided.

REVIEWERS CONCLUSIONS:
The *in vitro* hepatic metabolism of brimonidine was extensive in rat, dog, monkey, and human microsomal fractions, with up to 8 potential metabolites formed. The formation of 6 of the 8 metabolites were able to be detected from human homogenates, with most of these appearing to be oxidation products of the quinaxoline moiety of brimonidine (see study summary below). This would suggest metabolism by CYP450.

The metabolic activity appeared to be the highest for human and rat microsomes, followed by monkey, and then dog liver.

Figure 1 Formation of AGN 190342 metabolites in rat, dog, monkey, and human liver homogenates at a 4-hour incubation. (Initial drug concentration ~9.1 µg/ml, D denotes AGN 190342)

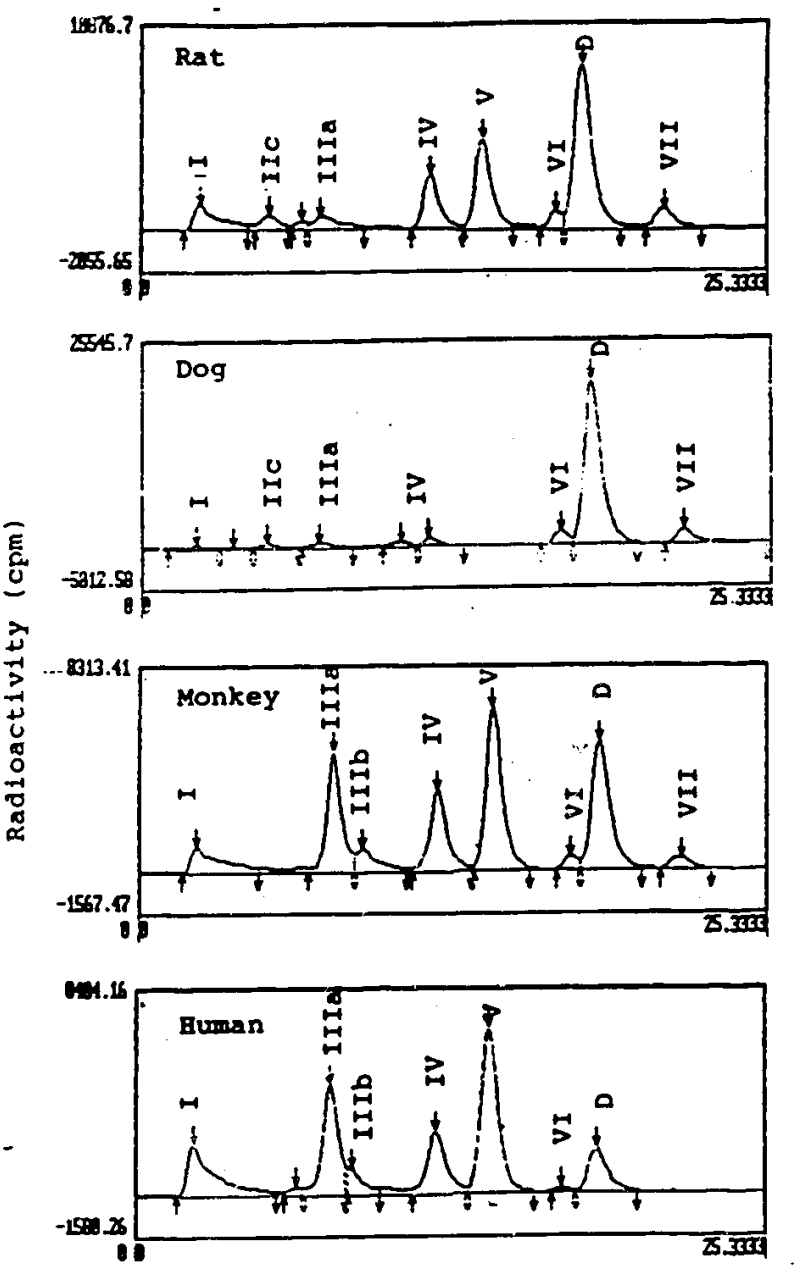


Table I. Percent (%) formation of AGN 190342 metabolites in rat liver homogenate[a]

Metabolite	Approximate Retention Time (min)	Incubation Time (Hour) 0	1	2	3	4
I	2.4	ND[b]	1.96 (0.36)	4.87 (0.03)	8.50 (1.45)	10.7 (3.2)
IIc	5.2	ND	0.520 (0.144)	3.28 (1.25)	3.64 (0.54)	4.27 (0.75)
IIIa	7.7	ND	0.724 (0.187)	2.80 (0.30)	2.31 (0.70)	6.56 (1.99)
IIIb	9.0	ND	ND	ND	ND	ND
IV	11.9	ND	6.51 (1.15)	10.1 (1.0)	12.3 (0.6)	12.7 (1.0)
V	13.9	ND	16.4 (2.2)	19.6 (2.1)	20.7 (1.6)	20.1 (0.9)
VI	17.0	ND	ND	1.43 (0.37)	2.47 (0.50)	3.13 (0.21)
AGN 190342	18.3	100	71.9 (4.1)	51.8 (6.3)	40.6 (6.0)	35.2 (8.7)
VII	21.3	ND	2.00 (0.08)	5.46 (0.38)	5.79 (0.26)	5.48 (0.07)

Total 6[illegible]%

[a] Mean (SD), N=2-3; Initial drug concentration = ~9.1 µg/ml.
[b] ND: Not detectable.

Table II. Percent (%) formation of AGN 190342 metabolites in dog liver homogenate[a]

Metabolite	Approximate Retention Time (min)	Incubation Time (Hour) 0	1	2	3	4
I	2.4	ND[b]	ND	0.734 (0.110)	1.03 (0.02)	0.923 (0.151)
IIc	5.2	ND	ND	1.31 (0.04)	1.97 (0.57)	1.42 (0.07)
IIIa	7.7	ND	ND	1.33 (0.09)	1.56 (0.15)	1.61 (0.19)
IIIb	9.0	ND	ND	ND	ND	ND
IV	11.9	ND	0.933 (0.057)	1.49 (0.16)	1.94 (0.11)	2.24 (0.21)
V	13.9	ND	ND	ND	ND	ND
VI	17.0	ND	0.857 (0.333)	2.35 (0.03)	2.93 (0.14)	3.12 (0.03)
AGN 190342	18.3	100	88.5 (3.4)	81.7 (0.6)	80.3 (0.2)	80.3 (0.4)
VII	21.3	ND	7.26 (0.29)	9.02 (0.19)	8.93 (0.42)	8.53 (0.03)

Total 18%

[a] Mean (SD), N=2-3; Initial drug concentration = ~9.1 µg/ml.

[b] ND: Not detectable.

Table III. Percent (%) formation of AGN 190342 metabolites in monkey liver homogenate[a]

Metabolite	Approximate Retention Time (min)	0	Incubation Time (Hour) 0.5	1	2	3	4	5
I	2.4	ND[b]	3.50 (0.86)	3.79 (1.06)	5.76 (1.81)	6.79 (0.64)	8.62 (0.78)	7.83 (0.78)
IIc	5.2	ND	ND	ND	ND	ND	ND	ND
IIIa	7.7	ND	1.41 (0.24)	3.37 (0.82)	6.85 (0.69)	11.9 (1.5)	14.6 (0.4)	17.0 (0.7)
IIIb	9.0	ND	ND	0.82 (0.19)	1.45 (0.09)	3.36 (0.29)	3.76 (1.01)	4.83 (0.81)
IV	11.9	ND	5.63 (0.82)	8.89 (0.83)	11.7 (1.3)	12.9 (0.7)	13.3 (0.7)	13.7 (0.4)
V	13.9	ND	9.07 (0.95)	13.6 (1.3)	20.0 (1.8)	21.9 (1.5)	24.7 (2.0)	26.4 (1.2)
VI	17.0	ND	ND	ND	0.923 (0.183)	1.44 (0.08)	1.91 (0.20)	1.96 (0.1)
AGN 190342	18.3	100	77.3 (0.6)	66.0 (1.0)	47.6 (1.1)	37.1 (0.9)	29.7 (0.9)	25.5 (0.8)
VII	21.3	ND	2.94 (0.34)	4.03 (0.44)	4.70 (0.87)	4.13 (0.60)	3.38 (0.49)	2.87 (0.51)

Total 75%

[a] Mean (SD), N=3; Initial drug concentration = ~9.1 µg/ml.

[b] ND: Not detectable.

Table IV. Percent (%) formation of AGN 190342 metabolites in human liver homogenate[a]

Metabolite	Approximate Retention Time (min)	Incubation Time (Hour) 0	0.5	1	2	3	4	5
I	2.4	ND	5.64 (2.52)	8.41 (0.48)	10.8 (0.4)	12.4 (1.5)	12.6 (0.5)	15.2 (0.1)
IIc	5.2	ND	ND	ND	ND	ND	ND	ND
IIIa	7.7	ND	3.18 (0.41)	5.10 (0.42)	11.2 (0.2)	15.4 (0.8)	19.0 (1.3)	20.5 (1.5)
IIIb	9.0	ND	ND	2.40 (0.14)	3.95 (0.13)	4.63 (0.12)	4.50 (1.02)	4.62 (0.75)
IV	11.9	ND	8.46 (0.66)	12.7 (0.3)	15.1 (0.6)	14.5 (0.6)	14.5 (0.3)	13.8 (0.3)
V	13.9	ND	22.7 (0.7)	31.9 (0.7)	38.2 (0.3)	37.1 (1.5)	35.9 (0.8)	33.7 (0.2)
VI	17.0	ND	ND	ND	ND	1.06 (0.18)	0.848 (0.108)	0.963 (0.070)
AGN 190342	18.3	99.7 (0.2)	60.0 (1.5)	39.2 (0.9)	20.8 (0.8)	14.5 (1.1)	11.6 (0.6)	9.88 (0.56)
VII	21.3	ND	ND	ND	ND	ND	ND	ND

Total 91%

[a] Mean (SD), N=3; Initial drug concentration = ~9.1 µg/ml.

[b] ND: Not detectable.

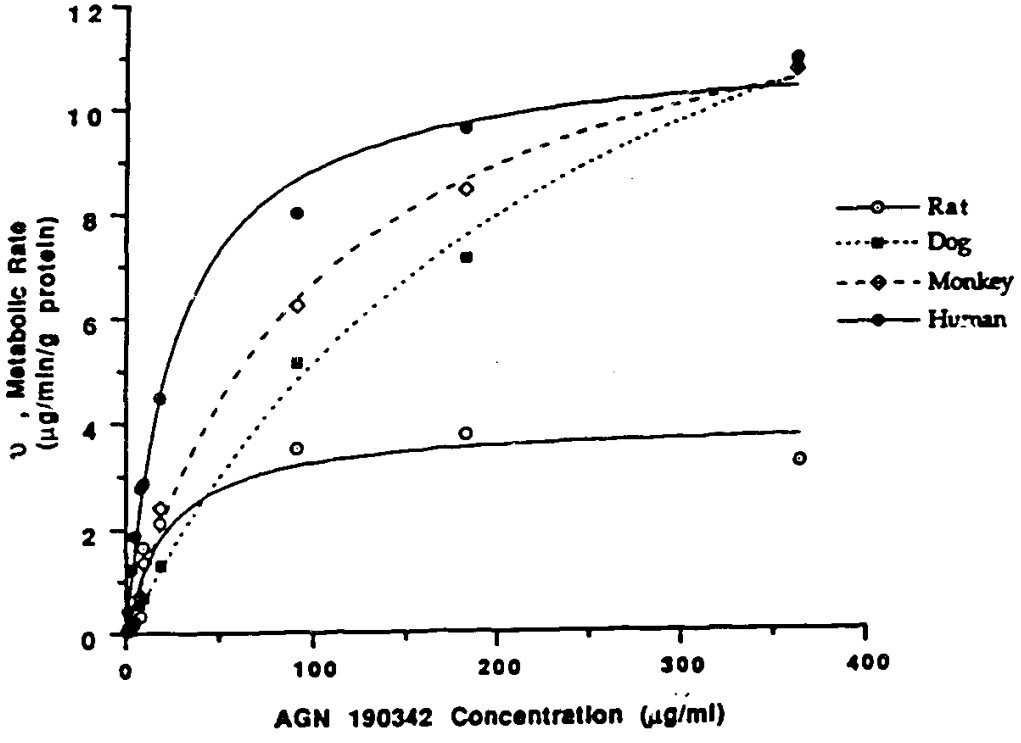
Table V. Computer-fitted Michaelis-Menten parameters (Vmax and Km) of AGN 190342 in rat, dog, monkey, and human liver homogenates[a]

Species	Km (μg/ml)	Vmax (μg/min/g protein)	r^2
Rat	21.5 (7.5)	3.94 (0.38)	0.967[b]
Dog	248 (32)	17.8 (1.2)	0.998
Monkey	104 (10)	13.6 (0.5)	0.998
Human	26.5 (2.9)	11.2 (0.3)	0.996

[a] Estimated value ± SEM

[b] r^2: correlation coefficient of fitting

Figure 2 The relationship between metabolic rate and drug concentration when AGN 190342 was incubated in rat, dog, monkey, or human liver homogenates. Computer-fitted lines are shown.



9. Report: PK-95-021: "Identification of *In Vitro* and *In Vivo* Metabolites of AGN 190342 Using Liquid Chromotography/Mass Spectrometry (MS) and MS/MS Analysis"

Volume: 86

Pages: 86-208 to 86-253

Investigators & Location:

Study Dates: April, 1994 - February, 1995

OBJECTIVE:
To profile and identify the metabolites of brimonidine *in vitro* using human liver and rat lung slices and *in vivo* following oral administration in rats.

DRUG SUBSTANCE:
Brimonidine tartrate (AGN 190342-LF) - Pharmaceutical Sciences Operations of Allergan, Lot #90355; 1 mg brimonidine tartrate = 0.66 mg brimonidine base

^{14}C-AGN 190342-LF - Lot #100H9239, Specific Activity 122 μCi/mg (~53.8 mCi/mmol), Radiochemical Purity 98%

METHODS:
Human liver was obtained from an outside source and liver slices were prepared and stored according to standard practice. Fresh rat lung slices were prepared from a female Sprague-Dawley rat. The human liver and rat lung slices were incubated with ^{14}C-AGN 190342-LF in buffer (pH 7.4) at 37°C over periods of 3, 6, or 24 hours. Following incubation, the slices were homogenized, deproteinized, and subsequently prepared for injection onto an LC/MS/MS system. For the *in vivo* study, urine samples were collected from Sprague-Dawley rats from 0-24 hrs following single oral doses of 10 mg/kg brimonidine tartrate and urine aliquots prepared for injection onto the same HPLC system. Reference standards of metabolites were synthesized by Allergan Chemical Sciences and the retention times of brimonidine or metabolite standards were used as identification markers during HPLC analysis. For metabolites without any synthesized reference standards, the structural identity was based on the mass spectral fragmentation pattern. Metabolites were identified with Roman numerals in order of increasing retention time (see previous study summary).

RESULTS:
The discussion of the results from this study will focus on those obtained from human liver slice studies since metabolism by rat lung slices was found to be limited (i.e., 4 metabolites detected accounting for <5% total radioactivity). In Figure 1, the radiochromatograms show eleven metabolites detected in human liver slices after 3

hours of incubation and [illegible] provides the characterization of the metabolites. Two additional metabolites [illegible], were detected in human liver slices but not in human liver microsomes. Th[illegible]d pathways of metabolism are shown in Figure 2. Brimonidine metabolism occurred *in vivo* and *in vitro* by two major routes: (1) alpha-carbon oxidation of the quinaxoline moiety to form MIIIa, MIV, and/or MV, which may undergo subsequent glucuronide conjugation, and (2) oxidative cleavage of the imidazoline ring to form MVI (guanidine metabolite).

REVIEWERS CONCLUSIONS:
Eleven metabolites of brimonidine were detected using *in vitro* human liver slices and at least 14 metabolites detected in rat urine following single oral administration.

The two major pathways of metabolism appeared to be (1) alpha-carbon oxidation of the quinaxoline moiety, which may be mediated by liver aldehyde oxidase, and (2) oxidative cleavage of the imidazoline ring, which may be mediated by CYP450.

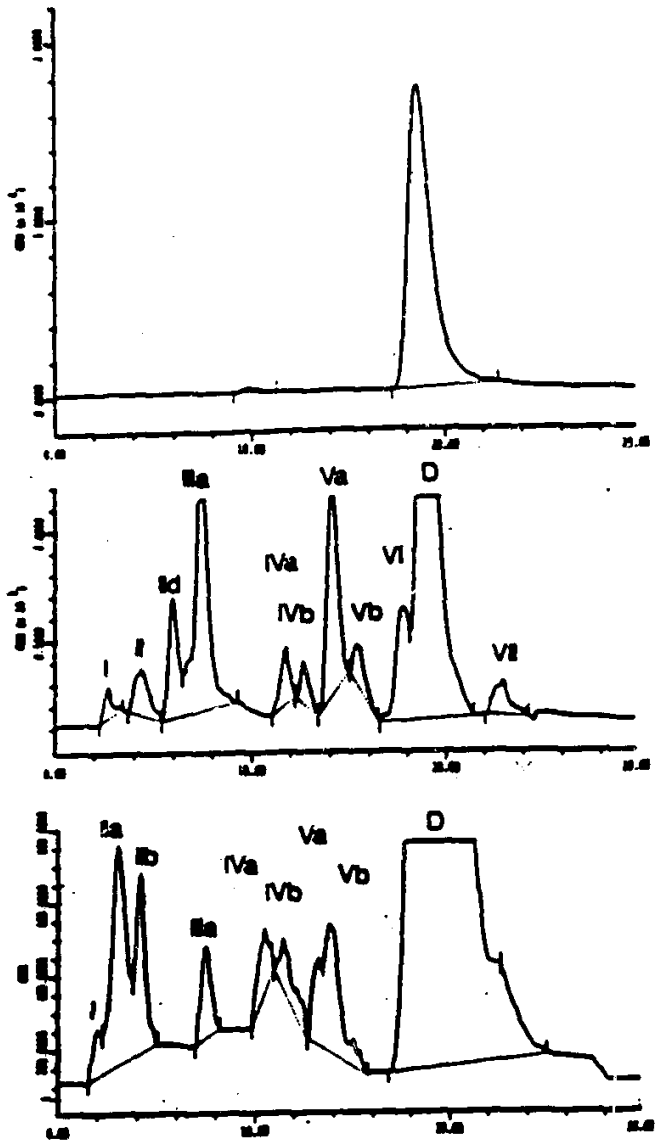


Figure 1. Radiochromatograms obtained for control sample (top) containing only ^{14}C-AGN 190342-LF or D, for liver slice homogenate (middle) and liver slice buffer medium (bottom) following a 3-hour incubation of ^{14}C-AGN 190342-LF in liver slice or control.

TABLE I. Characterization of human liver slice metabolites of ^{14}C-AGN 190342 by an ion-pair HPLC method.

Peak Name	Retention Time	Peak Identity
MIa	2.5	unidentified metabolit
MIIa	3.3	conjugated metabolite
MIIb	4.0	conjugated metabolite
synthesized standard	5.1	AGN 192597
MIIc	5.2	imidazoline-4', 5'-dione metabolite
synthesized standard	5.4	AGN 192614
synthesized standard	6.0	AGN 192119
MIId	5.9	imidazoline-4'-one metabolite
synthesized standard	7.5	AGN 191858
MIIIa	7.5	quinoxalin-2,3-dione metabolites
MIV a-b	12	hydroxyquinoxaline or quinoxalinone metabolites
MV a-b	14	hydroxyquinoxaline or quinoxalinone metabolites
synthesized standard	17	AGN 191383
MVI	17	guanidine metabolite
synthesized standard	23	AGN 192076
MVII	23	dehydro-AGN 190342 metabolite
parent drug (D)	19	AGN 190342

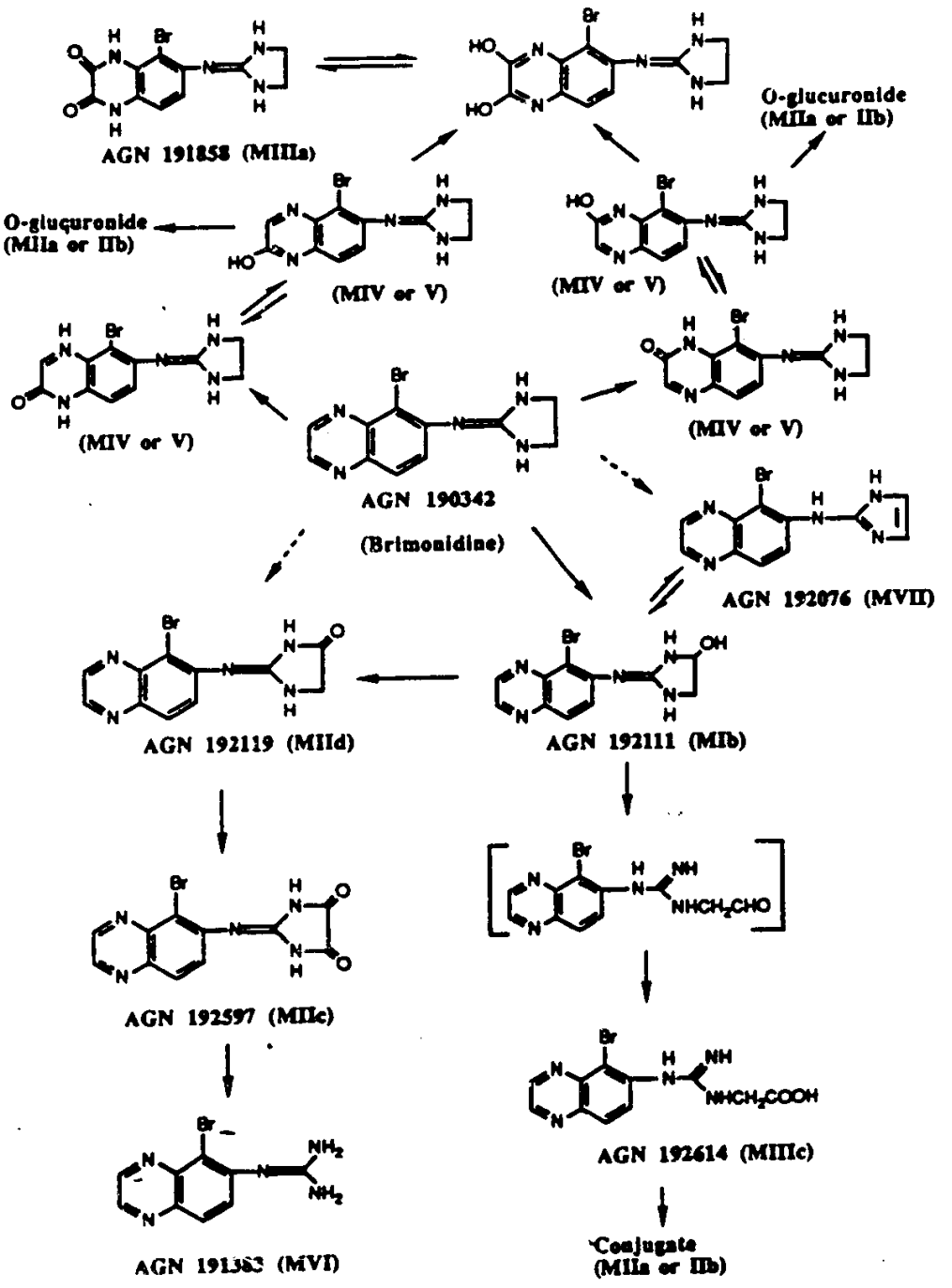


Figure 2 Proposed metabolic pathways of AGN 190342 (brimonidine)

APPENDIX 2:

PROPOSED LABELING

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Division of Dermatologic and Dental Drug Products, HFD-540

NDA 20-613 (Original Submission 09-11-1995)
Drug: ALPHAGAN™ (brimonidine tartrate ophthalmic solution) 0.2% Sterile

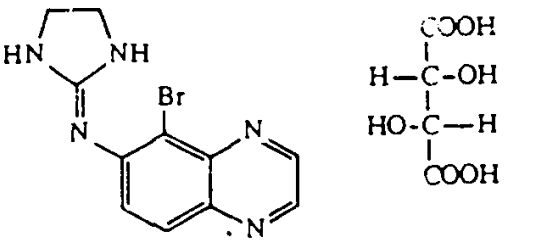
Sponsor: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534
Contact Person: Adelbert L. Stagg, Ph.D.
Director, Regulatory Affairs
714-246-6931

Number of Volumes: Thirtyfive (35)
Date CDER Received : 09-11-1995
Date Assigned: 09-18-1995
Date Review Started: 02-26-1996
Date Ist Draft Completed: 05-28-1996

Dosage and Route of Administration: Topical, Ophthalmic solution
Category: Alpha-2 adrenoreceptor agonist
Indication: For lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

Review Objective: To evaluate the preclinical safety data and the labeling draft of an already approved drug prior to its approval for long-term use.

Chemical Name: 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate
Proprietary Name: Brimonidine tartrate
Code Names: AGN 190342-LF
UK-14,304-18
Chemical Structure:



AGN 190342-LF
Brimonidine tartrate

Chemical Composition

Ingredient	Percent (w/v)	mg/mL	Composition for a 140 liter batch

Related Submissions

INDs:
NDA:

Background and Rationale

Animal Studies

In addition to a large number of supporting studies already reviewed under IND and NDA , the current submission has also included several new relevant studies.

NEW STUDIES

Unless specified, study was conducted by the sponsor. All studies reviewed here included duly signed GLP statements.

Vehicle: Same buffered vehicle was used in all studies (see composition).

PHARMACOLOGY

1. Pharmacology of Brimonidine Metabolites (BIO-94-059; November 1994).

Study Objective / Procedures

The major catabolic pathways of brimonidine in animals and humans involve α-C-oxidation to quinoxalinone and quinoxalin-2, 3-dione derivatives, and cleavage of the imidazoline ring to the aryl guanidine. In a radioligand binding assay, brimonidine and five of its metabolites were evaluated to determine the contributory potential of all compounds to the biological response expressed by the topically administered brimonidine. It is believed that the pharmacological target for brimonidine in the human eye is an α-2 adrenoceptor. Therefore, to determine the potential biological activity in humans, affinity of each compound was determined at subtypes of the α-adrenoceptors.

Receptor binding assays used membrane suspensions prepared from human cerebral cortex and homogenates of CHO-C10 and CHO-RNG cells; [^{3}H] rauwolscine and [^{3}H] prazosin were used as radioligands. The parameters determined included binding isotherms, equilibrium dissociation and affinity constants.

Results / Conclusions

Brimonidine and its metabolites exhibited low affinity for the α-1 adrenoceptors (>1,000 nM). Parent drug expressed high affinity for α-2A subtype (2.7 nM), and moderate affinity for the α-2B (52 nM) and α-2C (44 nM) subtypes. At the α-2A subtypes, only guanidine metabolite

(AGN 19183) exhibited moderate activity , it was about 15 times less potent than brimonidine, other metabolites were >100 times less potent. However, quantitatively AGN 19183 is a minor metabolite and therefore is less likely to contribute significantly to the overall biological response of topically administered brimonidine.

2. Effects of the α_2-Agonists, Brimonidine, Clonidine and p-Aminoclonidine on Arteriolar Caliber in Microvasculature Associated with Human Retinal Xenografts in the Hamster Cheek Pouch Preparation (BIO-95-074; January, 1995).

Study Objective / Procedures

To investigate the effects of α-agonists on human retinal microvasculature, brimonidine, clonidine, and p-aminoclonidine were examined in the microvasculature associated with human retinal tissue transplants in cheek pouch of adult Golden hamsters. Retinas excised from human eyes obtained from the eye bank 6-8 hours postmortem were transplanted in the cheek pouch. Test substances were administered by localized topical microsuffusion to the abluminal side of the arteriolar segment associated with the microvasculature of the retinal xenograft.

Results / Conclusions

Brimonidine did not affect the arteriolar caliber in the microvasculature at $1x10^{-9}$ to $1x10^{-5}$M concentration. Clonidine produced up to 35% concentration-dependent ($1x10^{-8}$ to $1x10^{-4}$M) decrease in arteriolar caliber, p-aminoclonidine caused 21% decrease at concentration as low as $1x10^{-11}$M. Brimonidine was 3-10 fold less potent at the α-1 receptor than the other two compounds. It was inferred that compounds more potent at α-1 receptors are more efficient at inducing vasoconstriction.

BIODISPOSITION

3. ^{14}C-AGN 190342-LF: Ocular Pharmacokinetics Studies After Multiple Ocular Doses to Cynomolgus Monkeys (P-94-074; August, 1994).

Facility:

Study Aim / Design / Procedures

This study investigated the ocular and systemic absorption of 0.5% ^{14}C-brimonidine tartrate solution (~8 uCi / 35 uL / eye) following twice daily (at 12-hour intervals) eye instillation for two weeks in both eyes of young male cynomolgus monkeys (3.5-4.8 kg). The ocular absorption was also investigated in the treated and untreated eyes after twice daily applications for two weeks into the right eye only. Two monkeys were sacrificed at the following time points after

the final dose instillation on day 14: 1 hour, 15, 60, and 90 days. Tear samples were collected from both eyes of all animals on days 1, 7, and 13 at 1 hour postdose in the evening, prior to morning dose and sacrifice. At the same time points, blood samples were also collected. Following sacrifice, eyes were removed and the ocular tissues were dissected.

The amount of total radioactivity was determined in the whole blood, plasma, tears, conjunctiva, and intraocular tissues. The concentrations of parent drug and metabolites were determined by HPLC in tear samples, conjunctiva, and extracts of aqueous humor, cornea, iris and ciliary body.

Results / Conclusions

The mean plasma Cmax was 3.25 ng/mL after the final dose. Reportedly, these concentrations were 20-55 times higher than observed in humans. The steady state level (2.7 ng/mL) was achieved by day 7. Traces of radioactivity (0.1 ng equivalent / mL) were still present in the plasma at 90 days postdose.

Drug penetrated rapidly through the cornea and was found in all intraocular tissues (iris, ciliary body, choroid / retina), indicating a high affinity of melanin for basic compounds. The maximum tissue concentrations (ug equivalent / g) ranked as follows: iris (610)>lower bulbar conjunctiva (56.2)>ciliary body (32.7)>choroid / retina (29.3)>upper bulbar conjunctiva (29.1)>upper sclera (20.1)>lower sclera (17.7)>cornea (9.8)>lens (0.7)>aqueous humor (0.3)>vitreous humor (0.1). Radioactivity was detected in the untreated eyes indicating a transfer via the systemic circulation to the contralateral eye. However, the amounts of radioactivity in the contralateral eyes were 1-3 fold lower than the dosed eyes.

The intact drug accounted for the major portion (68.9-97.7%) of the total radioactivity in all ocular tissues at all time points. Three metabolites were detected. The parent drug and radioactivity were eliminated in an apparent polyexponential fashion with mean terminal T½ of total radioactivity in iris and vitreous humor of 33.3 and 44.2 days, respectively.

4. In Vivo Plasma Protein Binding of AGN 190342 in Mice, Rats, Rabbits, Dogs, Monkeys, and Humans (P-94-092; November, 1994).

Study Objectives / Procedures

It is believed that only the the free drug present at the action site can produce the pharmacological effects. In this study, the binding characteristics of brimonidine to plasma proteins were investigated to understand its overall systemic biodisposition and pharmacodynamics. Plasma samples obtained from mice, rats, rabbits, dogs, monkeys (dietary / gavage: 2.5-10 mg / kg), and humans administered systemic or ocular doses were subjected to equilibrium dialysis against phosphate buffer pH 7.4 at 37 °C for 5 hours. The plasma concentrations of free and bound drug were determined by gas chromatography-mass

spectrometric methods.

Results / Conclusions

The mean unbound drug fractions in mouse, rat, rabbit, dog, monkey and human plasma were 63.8, 80.6, 78.0, 53.5, 78.9, and 70.8 percent, respectively. These determinations were made in an approximately 4000-fold range of concentrations. The fractions of free drug in the plasma appeared to be independent of plasma drug concentrations. It was inferred that a major portion of drug was not bound to plasma proteins.

5. ^{14}C-AGN 190342-LF: Placental Transfer and Milk Secretion Studies in the Rat After Single Oral Doses (PK95-017; February, 1995).

Facility

Study Objective / Procedures

The placental transfer and secretion of drug radioactivity into milk of pregnant CD rats were investigated following single oral doses of ^{14}C- brimonidine tartrate at a dose level of 0.25 mg / kg (= 0.165 mg base / kg). Three rats were sacrificed at time points ranging from 0.5 to 72 hours postdose to determine the tissue concentrations of radioactivity. One pregnant rat per time point was used for whole-body autoradioagraphy.

Results / Conclusions

Data indicated that radioactivity was absorbed rapidly by pregnant and lactating rats, and the maximum amounts in most tissues were recorded at 30 minutes postdose. However, the transfer of radioactivity across the placenta and into the circulation was limited. The amount of radioactivity in the fetal blood was 10-27 % of that in the maternal blood (28.3 ng equivalent/g) and fetal tissues contained less than 0.1% of the administered dose. The parent drug accounted for a major portion of the total radioactivity in fetal liver; the rest was distributed among the five metabolites. The milk : plasma ratios of radioactivity (mainly brimonidine and quinoxalinone metabolite) were 1.4, 12 and 0.98 at 0.5, 8, and 24 hour postdose, indicating that the concentration in milk was similar or higher than in the maternal plasma. At 24 hours postdose, the radioactivity in milk, maternal and fetal tissues / organs declined rapidly with a T½ of 3.6-6.0 hours for total drug derived chemical moieties in tissues and plasma.

The whole-body autoradiography data revealed the levels of radioactivity in the following decreasing order: GI-tract, liver, kidneys, and urinary bladder; lowest levels were found in the fetuses, CNS, and certain endocrine glands. Overall, it was inferred that the fetal exposure

to drug via the placental route was low.

6. Profiling of Brimonidine and Metabolites in Maternal and Fetal Tissues of Study No. ALG/32 Titled, "^{14}C-AGN 190342-LF: Placental Transfer and Milk Secretion Studies in the Rat After Single Oral Doses" (P-95-035; April 1995).

Study Objective / Procedures

The maternal and fetal tissues and breast milk samples saved from study number 5 (above) were analyzed for metabolites using liquid scintillation counting and HPLC with radioisotope detection. The tissue metabolite profiles because of high radioactivity concentrations were mostly obtained at the early sampling times (0.5 and 2.0 hours).

Results

Because of a very low level of radioactivity found in the ovary, none of the drug related moieties were detectable Similarly, only trace amounts of metabolites were found in the amniotic fluid. At both time points (0.5 and 2.0 hours), most of the radioactivity in the placenta, uterus and fetal liver was present in the intact drug.The amounts of parent drug as percent of total radioactivity were 86 at 0.5 hour and 50 at 2 hours. At 2 hours postdose in the uterus, the 50% of radioactivity was present in the parent drug. In the fetal liver, brimonidine almost accounted for 100% of the radioactivity. The concentration of radioactivity in the fetal blood was below the quantifiable limits of HPLC assay (49.8 pg / mL). The percent distribution of radioactive moieties (M= metabolite) in the maternal liver at 0.5 hour was as follows:

Brimonidine = 12
M I-II = 21
M IIIa = 32
M IIIb = 10
M IV = 7
M V = 18

Milk contained parent drug (47%) and traces of metabolites at 0.5 hour, however, at 2 and 8 hour postdose, metabolite V (a quinoxalinone derivative) became the major radioactive component. No radioactivity was detected in 24-hour milk samples.

CARCINOGENICITY STUDIES

7. AGN 190342-LF: Potential Tumorigenic Effects in Prolonged Dietary Administration to Mice (ALG 12/ 942061; February 1992 to November 1993).

Facility:

MATERIALS

Test Compound: Analysis of AGN 190342-LF (light yellow powder), batch number 90533-4401 used in both carcinogenicity studies indicated the following percent purity (w/v) data:

Test Animals: Seven weeks old male (20-32g) and female (20-28g) Crl:CD-1 (ICR) BR mice were purchased from On arrival animals were acclimatized for 3 weeks. Prior to study initiation, five mice of each sex were sacrificed and subjected to gross pathologic examination to check for lesions due to infection.

STUDY DESIGN

Dose Selection: The dose levels of 0.1, 0.5, and 2.5 mg (base) /kg / day were selected following two 13-week dietary dose range-finding (0.1-10 mg / kg / day) studies. At 2.5 mg / kg / day dose level, minor gastric and splenic changes possibly adaptive in nature, were observed.

Animal Assignment: Animals were assigned to five test groups, and each group contained 50 animals per sex.

Group	Dose (mg base /kg/day)
1. Control I	0.0
2. Control II	0.0
3. Low-dose	0.1
4. Mid-dose	0.5
5. High dose	2.5

In addition, 10 mice/sex/group were assigned to four satellite groups # 1, 3, 4, 5. These groups were used for toxicokinetic determinations and assessment of histopathological changes in the gastrointestinal tract. Five mice per sex from each satellite group were sacrificed after 26 weeks of treatment, and the rest of the satellite group animals were sacrificed after 52 weeks.

Diet Preparation and Administration

The individual test diets were prepared weekly by mixing and homogenizing the pre-mix concentrate of the test compound with the basal diet. The percent amount of active ingredient in the diets was determined in batches mixed at weeks 1, 13, 26, 39, 52, and 91. Brimonidine base forms 66.5% of the salt, therefore, the actual dosages administered were 0.15, 0.75, and 3.75 mg/kg/day for groups 3, 4 and 5, respectively. The concentrations of drug in the diets were changed whenever necessary to maintain the required nominal dose levels. Animals received diet and water *ad libitum*. Controls received basal diet. Animals in the main study were treated for 91 weeks, however, since terminal procedures took 9 days to complete, the treated animals continued to receive the test compound in their diet until the day of sacrifice.

OBSERVATIONS / DETERMINATIONS

Clinical Observations

Animals were examined daily for signs of toxicity, morbidity, mortality, and behavioral changes. The detailed palpations were conducted at regular intervals.

Body weight / Food consumption / Drug intake

Food consumption and body weight for each animal were recorded on weekly basis. Each week, the group mean achieved intake of test substance (mg/kg/day) was determined from the group mean body weight, food consumption and the dietary level of drug.

Ophthalmoscopy

All animals were subjected to ophthalmoscopic examinations prior to study initiation and during treatment weeks 26, 52, 78, and 90.

Laboratory Investigations

Hematologic (9 tests) and clinical chemistry (16 tests) determinations were made during weeks 90 and 91 on nonfasting blood samples drawn from 10 animals / sex / group. Blood samples to determine plasma drug concentrations were drawn from 4-5 satellite mice / sex / group in weeks 26 and 52, and from 6 main study mice / sex / group in week 91.

Sacrifice and Pathology

All mice that died during the study or were sacrificed on schedule were necropsied. All organs and body cavities were examined for gross abnormalities. The adrenals, brain, heart, kidneys,

liver, ovaries, spleen, testes (with epididymides), and uterus were removed and weighed. About 25 organs / tissues were subjected to histopathologic examinations.
These examinations involved the following:

Main Study: The specified tissues from all mice found dead during the study in both control groups and all the drug treated groups, and from all mice from control I and high dose groups sacrificed at study termination.

All abnormal tissues removed during gross pathologic examination.

The spleen, stomach, alimentary tract and uterus tissues of all mice sacrificed at study termination from the control II, low- and mid-dose groups.

Satellite Groups: The stomach and alimentary tract of all control, low-, mid- and high-dose mice died during the study or sacrificed in weeks 27 and 53.

REPORTED RESULTS

Test Compound and Dietary Analysis: The concentration of test compound in the diet ranged from 116 to 124% of the nominal values.

Clinical Observations and Mortality: No drug or dose related clinical signs of toxicity were observed. In males, the lowest mortality rate was recorded in the highest dose group (table). In females,

Mortality....Main Study (Weeks 1-91)

	MALES					FEMALES				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
% Mortality	40	48	34	36	28	42	42	30	40	42

the mortality rates at the mid- and high-dose levels were similar to the control groups. There were no dose or drug related effects on survival. In the satellite groups, all 4 unscheduled deaths (one male sacrificed moribund in week 13; 3 females, one died in week 26, one died week 52, one sacrificed moribund in week 34) occurred in the control groups.

Body weight / Food Consumption: The group mean gain in body weight (weeks 0-91) in the high dose groups was marginally lower than the controls, however, the differences were not statistically significant. No other intergroup differences in body weights were observed. A few changes in gain in body weight in the satellite groups were sporadically distributed, and

therefore, were not considered to be of any toxicologic significance. No significant intergroup differences in the food consumption were observed in the main study or satellite groups.

Efficiency of Food and Drug Intakes: The efficiency of food utilization determined during the first 13 weeks of treatment in the main and satellite groups was similar to controls. Similarly, achieved (group mean) intake of drug in different treatment groups was in good agreement with the nominal values.

Ophthalmoscopy: No drug related ocular lesions were observed.

Laboratory Investigations: Except for high plasma glucose (26%; $p<0.05$) level in the mid- and high dose- males and increased alkaline phosphatase activity (44%; $p<0.001$) in high-dose females, the values of all other hematologic and biochemical parameters were similar to controls.

Pharmacokinetics: Plasma drug concentrations were dose dependent, however, no accumulation of drug was observed over the study period (quantifiable limit= 49.8 pg / mL). Although the plasma drug concentrations were higher in females, the differences were not statistically significant. The average plasma drug concentrations in both sexes throughout the study were 0.180 ± 0.112, 0.828 ± 0.337, and 4.402 ± 1.679 ng / mL for the low-, mid- and high dose groups, respectively.

According to study authors, the plasma drug concentrations in low- dose mice were slightly higher than the mean Cmax of 0.0465 ng/mL in humans following a single 50 uL ocular dose of 0.2% brimonidine tartrate in both eyes. The plasma concentrations (Cmax) observed in the low-, mid-, and high dose mice of both sexes throughout the study were approximately 4, 18, and 95 times higher than that recorded in humans.

Gross Pathology and Organ Weights: No drug or dose-related macroscopic abnormalities were observed. A few sporadically distributed gross changes in all groups were considered spontaneous age associated lesions. Similarly, sporadic changes in the absolute organ weights of mice sacrificed after 26, 52, or 91 weeks of treatment were not associated with any corroborative histopathologic changes.

Histopathology: No drug related neoplastic changes were observed. A few statistically significant non-neoplastic lesions associated with drug treatment were observed in the intestine, stomach, and spleen (table). In the intestines, the hypertrophy of the *tunica muscularis* was mainly observed in the ileum and colon. A significant incidence of mucosal epithelial hyperplasia was observed in the ileum of high dose females. In the high- dose satellite groups, hypertrophy of the *tunica muscularis* was observed in 6/10 females. Reportedly, these intestinal lesions are known pharmacological actions of high doses of the test drug and other α-adrenergic compounds.

Moderate gastric and splenic changes were observed in the high-dose males and control II

females (table).

Summary of non-neoplastic histopathological changes in mice fed brimonidine tartrate

Organ / lesion	MALES 1	2	3	4	5	FEMALES 1	2	3	4	5
Number examined	50	50	50	50	50	50	50	50	50	50
INTESTINE										
Muscle hypertrophy:										
Ileum	0	0	0	0	2	0	0	2	0	13**
Colon	0	0	0	0	7**	1	1	0	2	19**
Epithelial hyperplasia in Ileum	0	0	0	0	0	0	0	0	0	10**
STOMACH										
Epithelial hyperplasia, non-glandular epithelium	0	1	1	2	6*	0	0	0	2	0
SPLEEN										
Extramedullary hemopoiesis										
Moderate	11	13	14	15	21*	8	17	13	11	13

* P<0.05 ** P<0.01

8. AGN 190342-LF: Potential Tumorigenic Effects in Prolonged Dietary Administration to Rats (ALG 13 / 942062; November 1991 to December 1993).

Facility:

MATERIALS

Test Compound: Same batch # and purity data as in mouse carcinogenicity study (# 7).

Test Animals: Six weeks old male (136-204g) and female (114-170g) Crl:CD-1 (SD) BR rats were obtained from · Prior to study initiation, animals were acclimatized for 11-12 days, and five rats / sex were sacrificed for gross pathologic examination to check for lesions due to infectious diseases.

STUDY DESIGN

Dose Selection: The dose levels of 0.05, 0.25, and 1.0 mg (base) / kg / day for this study were selected based on two dietary studies, a 13-week toxicity study, and a 6-day study to obtain plasma drug concentrations at lower dosages (0.025 and 0.5 mg/kg/day) than those used in the 13-week study (0.4, 1.0 and 2.5 mg / kg / day). At the 2.5 mg / kg / day and to a lesser extent at 1.0 mg / kg / day dose levels, microscopic changes in the intestines were observed; the high-dose was also associated with lower body weight gain and food intake.

Animal Assignment: Rats in the main study were assigned to five test groups, each group contained 60 rates per sex.

Group	Dose (mg base /kg/day)
1. Control I	0.00
2. Control II	0.00
3. Low-dose	0.05
4. Mid- dose	0.25
5. High-dose	1.00

In addition, 30 rats / sex / group were assigned to four satellite groups # 1, 3, 4, and 5. These groups treated for 52 weeks constituted a separate one year chronic toxicity study (ALG 13 / 93-1479). However, blood samples were drawn from these groups to supplement the toxicokinetic data in the main study.

Diet Preparation and Administration

The individual test diets were prepared weekly by mixing and homogenizing the pre-mix concentrate of the test compound with the basal diet. The percent amount of active ingredient in various diets was determined in batches prepared in weeks 1, 13, 26, 39, 52, 91, and 104. Brimonidine base forms 66.5% of the salt, therefore, the actual dosages of the test compound administered were 0.075, 0.375, and 1.5 mg/kg/day for groups 3, 4, and 5, respectively. The concentrations of the test substance in the diets were changed whenever necessary to maintain the required nominal dose levels. Rats received diet and water *ad libitum*. Controls received basal diet. Animals in the main study were treated for 104 weeks, however, since terminal procedures took 11 days to complete, the treated rats continued to receive the test compound in their diets until the day of sacrifice.

OBSERVATIONS / DETERMINATIONS

Clinical Observations / Body weight / Food consumption / Drug Intake

Same as in the mouse carcinogenicity study.

Ophthalmoscopy

All rats were subjected to ophthalmoscopic examinations prior to study initiation and during weeks 26, 52, 78, and 104.

Laboratory Investigations

Hematologic (9 tests) and clinical chemistry (16 tests) determinations were made on nonfasting blood samples drawn from 10 rats / sex / group in week 104. For determination of plasma drug concentration, blood samples were also drawn from 10 rats / sex of satellite groups in weeks 13 and 52.

Sacrifice and Pathology

All rats that died during the study or sacrificed on schedule were subjected to gross pathological examination. About 25 tissues / organs from all rats found dead or sacrificed at study termination in control I and high dose group were subjected to histopathologic examination. In addition, nine major organs from these animals were removed and weighed.

REPORTED RESULTS

Test Compound and Dietary Analysis: Same as in the mouse carcinogenicity study.

Clinical Observations and Mortality: The clinical signs such as tense posture, aggression, vocalization, and hyperactivity were observed in all groups including controls. These signs first noticed in week 19, however, were more intense and prevalent in the high dose males. The study authors considered these findings not related to drug treatment.

There were no drug or dose related effects on the mortality rate (table).

Mortality (Weeks 1-104)

	MALES					FEMALES				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
% Mortality	53	62	75	70	45	63	55	62	63	62

Food Consumption / Body Weight:

The group mean body weight gains (weeks 0-104) in the high- dose males (12%) and females

(8%) were lower than in the pooled controls, and the differences were statistically significant ($p<0.05$) for males. This decrease was mainly established during the first 18 weeks of treatment, where mean body weight gain was statistically lower for both sexes. During the first 18 weeks, both high- dose groups also indicated a slightly lower (7-8%) but statistically significant ($p<0.05$) mean food intake in comparison with the pooled controls.

Efficiency of Food and Drug Intakes: The efficiency of food utilization determined during the first 26 weeks of treatment in the drug groups was similar to controls. The achieved group mean intake of drug in three treatment groups was also in good agreement with the nominal values.

Ophthalmoscopy: No drug related ocular lesions were observed during the ophthalmoscopic examinations in weeks 26, 52, and 78. However, at the examinations conducted in 104 week, a high incidence of keratitis and neovascularization was observed in the high dose males (table).

Corneal Lesions (keratitis, neovascularization) in rats fed brimonidine tartrate for 104 weeks.

Groups:	MALES 1	2	3	4	5	FEMALES 1	2	3	4	5
Number examined	30	23	15	18	33	22	28	23	25	24
Corneal Lesions										
Lackluster	13	8	6	9	9	7	6	11	12	7
Keratitis	6	3	3	5	17	4	1	3	3	4
Neovascularization	3	1	2	5	13	-	1	3	3	4
% affected										
- lackluster	43	35	40	50	27	32	21	48	48	29
-keratitis	20	13	20	28	51	18	4	13	12	17
-neovascularization	10	4	13	28	39	0	4	0	4	13

Reportedly, these lesions were related to a secondary pharmacological action of high doses of brimonidine tartrate, whereby tear formation and blinking reflex were reduced.

Laboratory Investigations: There were no drug related changes in the hematologic parameters. However, some small but statistically significant ($p<0.05$) changes in a few biochemical parameters in blood were observed. These included reduced blood glucose and higher alkaline phosphatase levels in high- dose animals and mid-dose females, lower total protein in mid- and high dose males, and lower sodium, calcium, and cholesterol levels in high dose males. Because of a lack of any corroborative histopathologic evidence, these changes were not considered to be of any toxicological significance.

Pharmacokinetics: Plasma drug levels were dose dependent in both sexes, however, the levels at week 104 were approximately one to four times those observed at 13 and 52 weeks. It was inferred that the elevated plasma drug concentrations at week 104 were due to physiological and biochemical changes associated with aging. The average drug concentrations for both sexes throughout the study were 0.297±0.275, 0.64±0.296 and 3.609±1.215 ng / mL at the low-, mid- and high-dose levels, respectively.

Gross Pathology and Organ Weights: Mean absolute weights of liver and kidneys in mid- and high-dose males (12-14%) and females (9-12%) were significantly ($P<0.05$ to 0.01) reduced; in males significantly ($P<0.05$) reduced heart (6%) and spleen (12%) weights were also observed in the high dose group. However, no dose-related trend or any corroborative microscopic changes were observed in any of these organs.

Gross pathologic examination revealed a marked incidence of small, thickened and or/ misshapen cecum in the mid- and high-dose groups.

<u>Cecum</u>

Thickening: Males- controls, 0/60; mid-dose, 4/60; high-dose, 28/60
Females: controls, 0/60; mid-dose, 7/60; high-dose, 16/60

Small: Males- controls, 1/60, mid-dose, 11/60; high-dose, 19/60
Females: controls, 0/60; mid-dose, 12/60; high-dose, 25/60

Misshapen: Males- controls, 0/60; mid-dose, 8/60; high-dose, 27/60
Females- controls, 0/60; mid-dose, 5/60; high-dose, 19/60

When compared to controls, a higher incidence of thickening of the ileum and pale foci in the lungs were also observed in high-dose males and females. In addition, a reduction in adipose tissue was observed in a greater number of high-dose females and plantar swellings were observed in a significant number of high-dose males and females. Accordingly, minor gastric and pulmonary changes in high-dosage groups were probably adaptive in nature. The reduction in adipose tissue in high- dose females was probably related to the generally low body weights. However, the cause of plantar swellings remained unexplained.

Histopathology: No drug related alterations to the normally observed spontaneous distribution of tumors were observed. However, drug treatment did induce a number of non-neoplastic lesions (table). A high incidence of hypertrophy of the tunica muscularis was observed in various zones of intestine in mid- and high-dose rats of both sexes. Epithelial hyperplasia was more prominent in the ileum of high-dose groups as well as duodenum and jejunum of high-dose males. Reportedly, such changes characteristic of pharmacologic action of drug, were also observed in other studies where animals were sacrificed after 13 or 52 weeks of treatment. However, these reversible changes were observed in rodents but not in primates.

A significant ($P<0.01$) incidence of ulceration of the gastric non-glandular epithelium in high-

dose females was observed (controls, 9/120; low-dose, 5/60; mid-dose, 8/60; high-dose, 13/60). In the high-dose males, the incidence in fact was lower than in controls (controls, 18/120; high-dose, 2/60). The significance of this sex-specific effect remained unexplained.

Summary of non-neoplastic histopathologic changes in rats fed brimonidine tartrate for 104 weeks.

Organ / lesion	Groups..Males 1	2	3	4	5	Groups..Females 1	2	3	4	5
No. Examined	60	60	60	60	60	60	60	60	60	60
Intestines										
Hypertrophy of the tunica muscularis:										
Duodenum	1	0	1	3	12**	0	0	0	0	3*
Jejunum	0	0	0	2	14**	0	0	0	1	4*
Ileum	0	1	2	13**	51**	0	0	1	9**	42**
Cecum	0	1	2	18**	48**	1	0	2	15**	45**
Colon	0	2	1	6*	20**	1	0	1	8**	17**
Mucosal epithelial hyperplasia:										
Duodenum	0	0	0	1	7**	0	0	0	0	2
Jejunum	0	0	0	0	4*	0	0	0	1	2
Ileum	0	0	0	3	12**	0	0	0	1	12**
Eye										
Keratitis	8	7	7	5	17**	4	2	1	1	7
Lungs										
Focal alveolar macrophage aggregation	6	7	12	9	19**	2	3	2	2	11**
Paws										
Paw ulceration	29	34	32	41	50**	6	13	20*	18**	25**
Plasmacytosis (lumbar lymph node)	11	16	12	22	24*	4	5	6	3	4
Paw lesions as factors contributing to death	2	7	8	16*	12**	1	0	0	1	1

* P<0.05 ** P<0.01

In the eyes of high-dose males, a high incidence of unilateral minimal focal keratitis was observed. This lesion also seen during the ophthalmoscopic examination was linked to the secondary pharmacological action of the test drug.

A significant incidence of small focal aggregation of alveolar macrophages was observed in rats receiving 1.0 mg drug / kg / day. This change correlated well with the macroscopic observation of pale foci on the surface of lobes of the lungs.

An increased incidence of ulceration of the paws was observed in the high-dose animals and all drug treated females. It was associated with an increase in plasmacytosis in lumbar lymph nodes. This incidence was determined to be a factor responsible for several deaths in mid- and high-dose males.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDIES

9. An Oral Teratology Study in Rats with AGN 190342-LF (SLS.15; December 1993-January 1994).

Facility:

STUDY DESIGN AND PROCEDURES

Animals: Approximately 13 weeks old Sprague-Dawley Crl: CD^{R}BR VAF/Plus^{R}female rats (236-305g).

Mating: Females were cohabitated with the healthy adult males of the same strain. The gestation day 0 was confirmed by a sperm positive vaginal smear.

Dose Groups: After a dose-range finding oral teratology study (0.1, 0.4, 1.0, 2.5, 5.0) in the same strain, the following dose levels were selected for the main study: placebo (vehicle), 0.1, 1.0 and 2.5 mg brimonidine tartrate / kgbw / day. The doses are equivalent to 0.066. 0.660 and 1.650 mg / kg / day of the base, respectively. Thirty females were assigned to each dose group. Whenever possible, the first five rats were assigned to the toxicokinetic phase of the study.

Treatment: Mated females received a single daily dose via gavage from gestation day 6 through gestation day 15.

PARAMETERS EVALUATED

Clinical Observations: Daily

Body weights: Individual weights were determined on gestation days 0, 6 through 16 and 20. Body weight changes were calculated for gestation intervals: 0-6, 6-9, 9-12, 12-16, 16-20 and 6-16.

Food Consumption: Individual food consumption (g/animal/day and g/kg/day) was measured during gestation intervals mentioned under body weights.

Toxicokinetics: Blood samples for the determination of plasma drug concentrations by gas chromatography-mass spectrometry were drawn on gestation days 6, 13, and 15 prior to dosing and 2 hours postdose.

Necropsy: On gestation day 20, all females were sacrificed and subjected to necropsy examination. The uterus was examined for viable and nonviable fetuses and early and late resorptions. The number of corpora lutea on each ovary was also recorded.

Fetal Morphology: Fetuses were examined for external and internal (visceral) or skeletal abnormalities. Fetuses were weighed individually. The crown-rump length of each late resorption was measured. Approximately one-half of the fetuses from each litter were dissected for the visceral examination, rest were used for skeletal examination.

RESULTS

Maternal survival and Pregnancy status: No deaths occurred during the study. The group pregnancy rates were as follows: control and low-dose, 96%; mid- and high-dose, 92%.

Clinical Observations: The following signs of toxicity were observed in the mid- and high-dose females, primarily following dosing:

Mid-dose: A low incidence of reddish vaginal discharge and urine staining in the urogenital area.

High-dose: Reddish vaginal discharge and blue discoloration of vaginal opening; urine staining in the abdominal and urogenital areas; wobbly gait and decreased activity. Ocular signs included dilated pupils, dark material around the eyes, and partially closed eyelids.

These clinical signs were considered exaggerated pharmacologic effects of sedation.

Body weights: A small (5-7%) but statistically significant ($P<0.05$) dose-dependent decrease in body weight was observed at the mid- and high-dose levels. This change observed for the first time at day 7 persisted till gestation day 20.

Food Consumption: Food consumption was markedly (P<0.05) reduced in the mid- (15%) and high-dose (45%) females between gestation days 6 to 9. However, the terminal values for food consumption (days 6-16) were improved to -5 and -13%, respectively.

Cesarean Section Parameters and Fetal Morphology: Maternal necropsy examination did not reveal any drug related lesions. A small but statistically insignificant decrease in mean fetal body weight was observed at the high-dose level. No intergroup differences were observed for corpora lutea, implantation sites, viable fetuses, early and late resorptions, and fetal sex ratios. In addition, no drug-related malformations or developmental variations were observed.

Toxicokinetics: The mean plasma drug concentrations at 2 hours post-dose on gestation days 6 and 15 were dose dependent. The concentrations on day 6 were 0.705, 5.54 and 15.1 ng/mL at the low-, mid- and high- dose levels, respectively. The corresponding values on day 15 were 0.620, 5.81, and 19.5 ng/mL. On days 13 and 15, pre-dose plasma drug concentrations at the low- and mid-dose levels were below the limit of quantitation (49.8 pg/mL), and ranged from less than the quantifiable limit to less than 0.22 ng/mL at the high-dose level.

10. An Oral Teratology Study in Rabbits with AGN 190342-LF (SLS 3202.17; February-March 1994).

Facility:

STUDY DESIGN AND PROCEDURES

Animals / Artificial Insemination: Approximately six-month old (3.0-4.1 kg) NZW female rabbits were artificially inseminated with semen from adult males of the same strain. The day of insemination was considered day 0 of gestation.

Dose Groups and Treatment: The dose levels of 0.25, 1.0 and 5.0 mg/kg/day (expressed as salt) for the current study were established following a dose-range finding oral teratology study in the same strain of female rabbits under the similar experimental conditions. The doses are equivalent to 0.165, 0.660, and 3.330 mg base / kg / day. The test solutions were administered by oral intubation once daily from gestation day 6 through gestation day 18. Controls received 2.0 mL vehicle / kg / day, equivalent to that received by the high-dose groups. Each group contained 23 females. The first three animals of each group were assigned to the toxicokinetics phase of the study.

PARAMETERS EVALUATED

Clinical Observations: Daily

Body weights: Individual weights were determined on gestation days 0, 6 through 19, 24 and 29. The changes in body weight were calculated for gestation intervals: 0-6, 6-9, 9-12, 12-15, 15-19, 19-24, 24-29, 6-19 and 19-29.

Food consumption: Food consumption for individual animals was determined daily during gestation; and consumption was calculated for the same gestation intervals mentioned under the body weights.

Blood collection: Blood samples from animals assigned to the toxicokinetics phase of the study were drawn on gestation days 6, 13, and 18.

Necropsy / Cesarean section: Females which aborted or were found dead during the study were immediately subjected to necropsy examination. All survivors were necropsied on gestation day 29. In all cases, uterus was removed and examined for viable and nonviable fetuses and early and late resorptions. The number of corpora lutea on each ovary was also recorded.

Fetal Morphology: Fetuses were weighed individually and examined for external and internal (visceral) or skeletal abnormalities. The crown-rump length of each late resorption was determined. Each fetus was dissected for visceral examination and sex determination.

RESULTS

Maternal survival and Pregnancy status: Two high-dose animals were found dead, one each on gestation days 11 and 12. Necropsy examination in both cases revealed perforated esophagus due to faulty intubation. Two high-dose females aborted, one each on gestation days 21 and 23. These abortions were considered to be related to the pharmacological effects of the drug. The group pregnancy rates were as follows: control, 70%; low-dose, 80%; mid-dose, 100%, and high-dose, 90%.

Clinical observations: Primarily following dosing, a few transient signs in the high-dose females included decreased activity, wobbly gait, constricted pupils, partially closed eyelids, slow breathing and limp body tone. Some of these sedation signs were also observed in a few mid- and low-dose females.

Body weight / Food consumption: A small but significant (~2%; $P<0.05$) decrease in body weight occurred only in the high-dose group during gestation days 6-9. However, during the same period in the same group, the decrease in food consumption was much more pronounced (35%; $P<0.001$).

Cesarean Section Parameters and Fetal Morphology

Maternal gross necropsy examination for survivors did not reveal any intergroup differences. All cesarean section parameters were comparable among the groups, and no drug related

malformations or developmental variations were observed.

Toxicokinetics: The mean plasma drug concentrations at 0.5 hour postdose on gestation days 6 and 18 were dose dependent. The plasma drug concentrations on day 6 were 0.247, 2.90, and 6.33 ng/mL at low-, mid- and high-dose levels, respectively. The corresponding values on day 18 were 0.242, 0.743, and 1.42 ng/mL. The pre-dose concentrations on gestation days 6, 13, and 18 were below the quantitation limit of 49.8 pg / mL.

LABELING

Pregnancy category B is appropriate. All statements made in the preclinical portion of the draft are supported by relevant studies conducted under the GLP guidelines.

TOXICOLOGIST'S DISCUSSION AND INTERPRETATION OF SAFETY DATA

Brimonidine was originally developed by in the early 1970's as a centrally acting anti-hypertensive agent. However, because of its poor clinical efficacy, drug was not developed any further for oral use. The current sponsor (Allergan, Inc.) has tested 0.5% ophthalmic solution of brimonidine tartrate for the treatment of post-operative elevated intraocular pressure (IOP) associated with argon laser trabculoplasty in patients with open-angle glaucoma (OAG) and / or ocular hypertension (OHT), and a 0.2% solution for lowering IOP in patients with chronic OAG or OHT. To investigate the pharmacologic and toxicologic effects of the drug, and to ascertain its safety, the compound was very extensively tested in multiple animal species (rat, mouse, rabbit, dog, monkey) at doses much higher than the proposed clinical dose of 0.002 mg / kg /day. Most of these studies were conducted with 0.5% ophthalmic solution.

The systemic pharmacologic drug actions included antihypertensive effects in conscious rat, rabbit and dog, and bradycardia generally accompanied by reductions in blood pressure. However, additional *in vivo* and *in vitro* investigations revealed that bradycardia was not due to direct cardiac action, because cardiac output or contractility were not impaired. Irrespective of the route (i.v., ocular, oral), subchronic and chronic treatment in all species induced pupillary constriction and sedation in a dose dependent fashion. However, the effect lasted only for a few hours after the drug administration.

In subchronic (4-14 weeks) and chronic studies (6, 12 months) conducted in several species at higher doses (upto 2.5 mg/kg/day), exaggerated pharmacological effects were observed. These included sedation, ataxia, hypoactivity, ptosis, decreased muscle tone, hypotension, and bradycardia. Rodents also exhibited abdominal, distension, intestinal intussusception, hypertrophy of the tunica muscularis, hyperplasia of goblet cells of the intestines and non-glandular epithelium of the stomach. In rat oral (0.05-1.0 mg base / kg / day) carcinogenicity study, no ocular lesions were observed during the ophthalmoscopic examinations in weeks 26, 52, and 78, however in week 104, high incidences of keratitis and neovascularization were observed in high-dose males. Reportedly, these lesions were related to a secondary

pharmacological action of high doses of brimonidine tartrate, whereby tear formation and blinking reflex were reduced.

Brimonidine was well absorbed ocularly through the corneal surface, however, it remained mostly unmetabolized in the eye. The pharmacokinetic profiles after systemic drug administration in mice, rats, dogs, and monkeys were characterized by rapid absorption, extensive body distribution, rapid clearance and low oral bioavailablity, indicating a significant first pass metabolism of drug. In the mouse oral carcinogenicity study (0.1-2.5 mg base/kg/day), no drug accumulation was observed over the study period.

Chronic ocular and systemic toxicity studies in rabbits indicated that the formulation (0.5%) produced no eye discomfort, irritation, corneal reaction, or morphologic abnormalities of lens and retina.

The reproductive and developmental toxicity studies did not reveal any adverse effects on fertility and general reproductive performance; no embryo lethality or teratogenic effects were observed. A substantial amount of the administered drug was found in the milk. However, the fetal exposure to drug via the placental route was low.

Oral carcinogenicity studies in mice (0.1, 0.5, and 2.5 mg base / kg / day) and rats (0.05, 0.25. and 1.0 mg base / kg / day) did not reveal any oncogenic potential for brimonidine tartrate.

The proposed daily use of 0.2% ophthalmic solution of brimonidine tartrate will be equivalent to 157 ug base per day for a 70 kg subject or about 0.002 mg / kg / day. The drug has been tested in multiple species up to a dose level of 1250 times higher (2.5 mg / kg / day) than the clinical dose without any remarkable local or systemic adverse effects. Long-term multidose pharmacokinetic studies did not indicate any tissue accumulation of drug. In addition, no extensive binding of brimonidine to plasma proteins was observed. Apparently, drug has exhibited a very good margin of safety.

REGULATORY CONCLUSION: I have no objection to the approval of this new drug application.

Kumar Mainigi 6/4/96

Kumar D. Mainigi, Ph.D., M.P.H., D.A.B.T.
Toxicologist

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-613 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 4/15/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9/7/95	9/13/95	9/20/95
AMENDMENT	10/12/95	10/13/95	10/24/95

NAME & ADDRESS OF APPLICANT: Allergan
2525 DuPont Drive
P. O. Box 19534
Irvine, CA 92713

DRUG PRODUCT NAME

Proprietary: **Alphagan**
Nonproprietary/USAN:
Brimonidine Tartrate
Code Names/#'s: AGN190342-LF
Chemical Type/: 1S
Therapeutic Class: Ocular
Anti-hypertension agent

ANDA Suitability Petition/DESI/Patent Status:

US Patent # 3,890,319 expired on 6/17/92
The applicant requests (8/13/95) a five year exclusivity per section 505(c)(3)(D) and 505(j)(4)(D) of Federal Food, Drug and Cosmetic Act.

PHARMACOLOGICAL CATEGORY/INDICATION:

Alpha-2-adrenoreceptor agonist/anti-hypertension agent

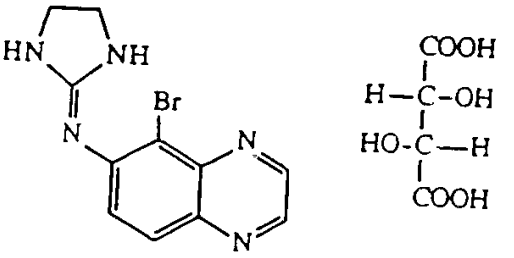
DOSAGE FORM:	Solution
STRENGTHS:	0.2%
ROUTE OF ADMINISTRATION:	Topical/ocular
DISPENSED:	__x__ **Rx** _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: 5-Bromo-6-(2-immidazolin-2-ylamino) quinoxalin L-Tartrate

CAS #: 59803-98-4
Molecular weight: 442.24
Molecular formula: $C_{15}H_{16}N_5O_6Br$
Code: AGN 190342-LF

Chemical Structure:



AGN 190342-LF
Brimonidine tartrate

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

NDA

Phone/fax: 10/2/95 and 2/12/96

CONSULTS:

Environmental Assessment for NDA 20-490, Alphagan (brimonidine tartrate) 0.5% Solution on file in FDA. Separate EA review report and FONSI will be issued for this NDA

REMARKS/COMMENTS:

The drug product is a 0.2% solution packaged in white opaque multiple-dose containers made of low density polyethylene. It is manufactured, packaged, and labeled by Allergan Inc. in Puerto Rico. At the time of this NDA submission, brimonidine tartrate is a new molecular entity. The bulk drug substance is manufactured ,

CONCLUSIONS & RECOMMENDATIONS:

The application is **not approvable** for the manufacturin and controls under section 505 of the Act. Specific items which are not approvable are identified under drug product specifications, stability, container/closure system, and environmental assessment. Other deficiencies are information request, they should not constitute the reasons for "not approvable"

Specific deficiencies listed below have been communicated to the sponsor by Fax on March 19, 1996.

DRUG SUBSTANCE:

2. What tests are performed at before shipping to Allergan America for release testings (information).

3. The analytical methods specified in drug substance specification on pg. 2-063 and pg. 3-197 should be consistent (the same version) with the methods provided in the method validation package (Appendix D) for validation by district laboratory (information).

4. Describe the stress conditions for the observation and isolation of degradants in technical reports PA-1992-022B provided in amendment dated 10/12/95 (information).

5. Provide updated stability data for lot 91226, 91227 & 91228 made with the proposed manufacturing process.

6. Provide the corresponding batch # of bulk drug substance used in the manufacturing of finished dosage validation batches lots 7021A, 7022A, and 7023A (information).

Drug product

7. Please explain the inconsistency of the related substance specifications on pg. 2-100, 2-143, pg. 2-145, 4-236, 5-245, and pg, 137 of amendment 10/12/95. Is the product specifications the same as stability specifications particularly with respect to impurities (**approvability**).

   If the product specifications on release and stability are different, please indicate so clearly. Revise and update the all specifications through out the NDA application. The regulatory methods (give reference page #) should be included in the specifications, and the methods should be consistent with the methods (versions) provided in Appendix E to be used in method validation.

8. In the container/closure extraction studies on pg. 5-

9. What is the label adhesive, with or without inks, used in the stability studies supporting the expiry on pg. 4-236
(information)?

For long term stability, the storage conditions should be 25°C +/- 2°C, and 40% RH.

Provide stability of the three validation batches of drug product (7021A, 7022A and 7023A). Include container/closure information, manufacturing dates, and lots size in the stability reporting (**Approvability**).

10. Provide the investigation report on label extraction study as soon as possible (**approvability**).

11. For primary container label and secondary container or box label, the storage temp. should be consistent with the package insert which is stored at "15 to 25°C".

12. Provide a list of samples including reference standards for method validation purpose.

13. For method validation, send two copies of vol. 1.7 to the attention of

Su Tso
FDA, HFD-550
9201 Corporate Blvd.
Rockville, MD

Su C. Tso, Ph.D.
Review Chemist

cc: Orig. NDA 20-613
HFD-550/Division File
HFD-550/Tso
HFD-550/Carreras
HFD-550/Mainigi
HFD-550/Vincent
HFD-550/Holmes
HFD-550/SUPERVISOR/Patel
HFD-830/Sheinin

HS 12/5
5-15-96

JUL 11 1996

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-613 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 6/14/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	4/25/96	4/16/96	5/10/96
AMENDMENT	5/8/96	5/9/96	5/20/96
AMENDMENT	5/16/96	5/17/96	5/24/96

NAME & ADDRESS OF APPLICANT: Allergan
2525 DuPont Drive
P. O. Box 19534
Irvine, CA 92713

DRUG PRODUCT NAME

Proprietary: **Alphagan**
Nonproprietary/USAN:
Brimonidine Tartrate
Code Names/#'s: AGN190342-LF
Chemical Type/: 1S
Therapeutic Class:
Ocular
Anti-hypertension agent

ANDA Suitability Petition/DESI/Patent Status:

US Patent # 3,890,319 expired on 6/17/92
The applicant requests (8/13/95) a five year exclusivity per section 505(c)(3)(D) and 505(j)(4)(D) of Federal Food, Drug and Cosmetic Act.

PHARMACOLOGICAL CATEGORY/INDICATION:

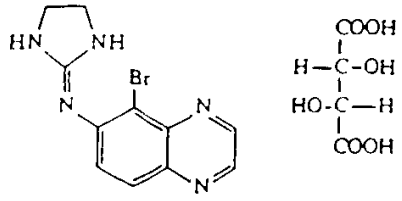
Alpha-2-adrenoreceptor agonist/anti-hypertension agent

DOSAGE FORM:	Solution
STRENGTHS:	0.2%
ROUTE OF ADMINISTRATION:	Topical/ocular
DISPENSED:	__x__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: 5-Bromo-6-(2-immidazolin-2-ylamino) quinoxalin L-Tartrate

Chemical Structure:



AGN 190342-LF
Brimonidine tartrate

RELATED DOCUMENTS (if applicable):

CMC review # 1, 4/15/96
EA review and FONSI, 5/3/96
FDA e-mail, 5/6, 5/7, and 5/24/96

REMARKS/COMMENTS:

Amendment dated 4/25/96 is the response to the deficiencies of CMC review #1 dated 4/15/96 which was faxed to the sponsor. In addition, the revised EA document is provided in this amendment which has been reviewed by this reviewer. Refer to EA review dated 5/3/96. Signed FONSI is attached with this report.

All facilities are in GMP compliance (review #1).

Method validation request sent on 5/24/96

The deficiencies of Chemistry review dated 4/15/96 were communicated to the sponsor by Fax on March 19, 1996. This report covers the review of the responses provided in amendments of April 25, 1996 & May 8, 1996. Amendment 5/16/96 is the final revised method validation package which was sent for method validation on 4/24/96.

Comments on the Chemist's review dated 4/25/96 from Dr. Patel was faxed to Dr. Stagg of Allergan on 5/24/96. Amendment dated 6/4/96 is the firm's responses to Dr. Patel's comments.

was sent for method validation on 4/24/96.

Comments on the Chemist's review dated 4/25/96 from Dr. Patel was faxed to Dr. Stagg of Allergan on 5/24/96. Amendment dated 6/4/96 is the firm's responses to Dr. Patel's comments.

CONCLUSIONS & RECOMMENDATIONS:

The application is **approvable** for the manufacturing and controls under section 505 of the Act. However the application lacks sufficient stability data to support the proposed container/closure system. Twelve month expiry can only be granted at this time (the physician's sample will have a shorter expiry due to high water loss). As additional stability data is received, the application will be reviewed for extension of expiry.

ALLERGAN SHOULD BE INFORMED THAT THE CONTAINER/CLOSURE EXTRACTABLES SHOULD NOT INCREASE BEYOND

IN ADDITION, ALLERGAN SHOULD BE NOTIFIED THE STABILITY CONDITIONS REQUIRED FOR POST APPROVAL STABILITY STUDY. THE STORAGE TEMPERATURE SHOULD BE CONSISTENT ON ALL LABEL, AND THE TEMPERATURE SHOULD BE SUPPORTED BY THE STABILITY DATA.

Su C. Tso, Ph.D.
Review Chemist

cc: Orig. NDA 20-613
HFD-550/Division File
HFD-550/Tso
HFD-550/Carreras
HFD-550/Mainigi
HFD-550/Vincent
HFD-550/Holmes
HFD-550/SUPERVISOR/Patel
HFD-830/Sheinin

Harmukh B. Patel
7-11-96

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-613 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 7/19/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	6/12/96	7/2/96	7/10/96
AMENDMENT	7/16/96		

NAME & ADDRESS OF APPLICANT: Allergan
2525 DuPont Drive
P. O. Box 19534
Irvine, CA 92713

DRUG PRODUCT NAME

Proprietary: **Alphagan**
Nonproprietary/USAN:
Brimonidine Tartrate
Code Names/#'s: AGN190342-LF
Chemical Type/: 1S
Therapeutic Class: Ocular
Anti-hypertension agent

ANDA Suitability Petition/DESI/Patent Status:

US Patent # 3,890,319 expired on 6/17/92
The applicant requests (8/13/95) a five year exclusivity per section 505(c)(3)(D) and 505(j)(4)(D) of Federal Food, Drug and Cosmetic Act.

PHARMACOLOGICAL CATEGORY/INDICATION:

Alpha-2-adrenoreceptor agonist/anti-hypertension agent

DOSAGE FORM:	Solution
STRENGTHS:	0.2%
ROUTE OF ADMINISTRATION:	Topical/ocular
DISPENSED:	__x__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: 5-Bromo-6-(2-immidazolin-2-ylamino) quinoxalin L-Tartrate
CAS #: 59803-98-4
Molecular weight: 442.24
Molecular formula: $C_{15}H_{16}N_5O_6Br$
Code: AGN 190342-LF
Chemical structure:

RELATED DOCUMENTS (if applicable):

CMC review # 1, 4/15/96
CMC review # 2, 6/14/96
FDA fax: 5/24/96

RECOMMENDATION:

Allergan has addressed all CMC deficiencies adequately.

RECOMMEND APPROVAL FOR EXPIRY OF 12 MONTH FOR THE 2.5 ML/6 ML CONTAINER AND 18 MONTHS FOR ALL OTHER CONTAINERS. ALLERGAN SHOULD BE NOTIFIED BY WRITING THAT FUTURE STABILITY CONDITIONS FOR OPHTHALMIC DRUG PRODUCTS and for extension of the expiration dating period for this drug product (ALPHAGAN) must be:
LONG TERM: 25°C/40%RH,
ACCELERATED: 40°C/20%RH

Su C. Tso, Ph.D.
Review Chemist

Kasmukh B. Patel
7-22-96

cc: Orig. NDA 20-613
HFD-550/Division File
HFD-550/Tso
HFD-550/Carreras
HFD-540/Mainigi
HFD-160/Vincent
HFD-550/Holmes
HFD-550/SUPERVISOR/Patel
HFD-830/Sheinin

Consult #441 (HFD-540)

ALPHAGAN LIQUIFILM

Brimonidine Tartrate
Ophthalmic Solution 0.5%

A review revealed no names which sounds like or looks like the proposed name.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Janice Keith Milli, Chair 5/30/95

COMPLETED

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Alphagan

(brimonidine tartrate Ophthalmic Solution) 0.2%

NDA 20-613

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFLAMMATORY, ANAGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-613

Alphagan

(Brimonidine Tartrate Ophthalmic Solution), 0.2%

The Food and Drug administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decision maker before decisions are make about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered all the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Alphagan ((brimonidine tartrate Ophthalmic Solution), 0.2%, Allergan Inc. has prepared an abbreviated environmental assessment according to 21 CFR 25.31a(b)(3) which evaluates the environmental impacts of the manufacture, use, and disposal of the drug product. Alphagan ((brimonidine tartrate Solution) is for the treatment of open angle glaucoma or ocular hypertension. It is to be used by the patients in home. Brimonidine tartrate drug substance is manufactured by
At where the drug substance is manufactured, waste water generated are pH adjusted and discharged to local Public treatment plant; scrubbers and condensers are in place, there is no permitted air control devices required by regulation; solid wastes are sent to offsite for disposal, recovered solvent are sent for recycling or used for fuels blending. The drug product Alphagan will be manufactured by Allergen America at Hormigueros, Puerto Rico. At this facility where the drug product will be manufactured, solid waste sent for offsite disposal by licensed transporter and aqueous waste generated is discharged (after pH adjustment) to local Public treatment plant. The manufacturing sites are properly licensed by the environmental authorities.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture minimize occupational exposures and environmental release.

Prepared by Su C. Tso, Ph.D.
Chemist, HFD-550

May 3, 1996
Date

Concurred by H. Patel, Ph.D.
Acting Team Leader, HFD-550

May 6, 1996
Date

Nancy B. Sager
Environmental Scientist, HFD-004

5/20/96
Date

Attachments: Environment Assessment review reports
Material Safety Data Sheet for ganciclovir
FOI copy of the Environmental Assessment

cc: Original: NDA 20-613
HFD-550/SCTso
HFD-550/Holmes
HFD-004/NSager
HFD-004/Docket File
HFD-019/FOI copy
FONSI file: NDA 20-613

The following Environmental Assessment is authorized for dissemination to the public under the Freedom of Information Act by Allergan, Inc.

ENVIRONMENTAL ASSESSMENT

PURSUANT TO 21 CFR 25.31

BRIMONIDINE 0.2% OPHTHALMIC SOLUTION
Revision 2

1. **DATE**: April 19, 1996

2. **NAME OF APPLICANT**

Allergan, Inc.

3. **ADDRESS:**

2525 Dupont Drive
Irvine, California 92715

4. **DESCRIPTION OF PROPOSED ACTION:**

A New Drug Application is being submitted to the Food and Drug Administration requesting approval of an ophthalmic solution whose active ingredient is brimonidine tartrate (hereinafter referred to as "the Product"), to be manufactured at Allergan America, Puerto Rico Road, 345 km. 1.5, P. O. Box 60 Hormigueros, Puerto Rico, 00660. Allergan America is a wholly owned subsidiary of Allergan, Inc. headquartered in Irvine, California. Allergan is proposing to manufacture, fill and package the Product and hereby submits this Environmental Assessment. This Environmental Assessment was prepared pursuant to 21 CFR 25.31. The active ingredient, brimonidine tartrate, is manufactured by:

The following alternate supplier is included in the NDA for manufacture of the intermediate, 6 aminoquinoxaline:

The Product is intended for use in humans and will be used by patients chronically. The Product will be used as a safe and effective chronic treatment of open angle glaucoma or ocular hypertension.

The environment adjacent to, and present at, the facility is industrial, commercial, residential and rural in nature. The environment adjacent to, and present at, the facility is light industrial, residential and rural in nature. The environment adjacent to, and present at, the Allergan America facility are light industrial, commercial, residential and rural in nature. The environment at Allergan's customers' locations is widespread and the nature will be diverse.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

The active ingredient brimonidine tartrate will be manufactured at the facility for Allergan, Inc. The chemical and physical data for the active ingredient brimonidine tartrate follows:

Formula

Molecular Formula

$C_{15}H_{16}N_5O_6Br$

Molecular Weight

442.24

Nomenclature

IUPAC Chemical Name

5-Bromo-6-(2-imidazolidinylideneamino)quinoxaline L-tartrate

Proprietary Name

Brimonidine tartrate

USAN Name

Brimonidine tartrate

Allergan Code Number (AGN #)

AGN 190342-LF

Chemical Abstract Services Number

59803-98-4

Other Names

5-Bromo-n-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine

5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline L-tartrate

5-Bromo-6-(imidazolin-2-ylamino)quinoxaline L-tartrate

UK 14304

Physical and Chemical Characteristics

Physical Description:

Off-white, pale yellow to pale pink powder

Melting Range

202°C to 210°C with decomposition

pK_a Value

7.78 ± 0.05

The Product will be packaged for market in 5 ml fill/10 ml container, 10 ml fill/10 ml container, and 15 ml fill/15 ml container as well as a physician sample size of 2.5 ml fill/6 ml container (manufactured at Allergan America) containing the active ingredient brimonidine tartrate at 0.2% w/v, with the following inactive ingredients:

Chemical Name	*Molecular Formula*	*Molecular Weight*	*CAS Number*

Aqueous solutions of brimonidine tartrate degrade slowly under extreme conditions of temperature and alkaline pH. The major degradation product was isolated and identified as 6-amino-5-bromoquinoxaline. The degradation product is also a synthetic precursor of brimonidine.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

a. Substances Expected to be Emitted

At the facility, a series of reactions will be undertaken in order to produce the final active substance, brimonidine tartrate, in accordance with FDA requirements. The active ingredient, brimonidine tartrate, will then be passed through a wire-mesh sieve to yield a fine powder of narrow particle size distribution. All sieving operations will be conducted in a glove box to minimize contact with employees. Then, the active ingredient will be tumbled in order to achieve homogeneity of the entire blend. The active ingredient will then be sent to Allergan America facility for inclusion in the formulation of the Product.

During the production of the brimonidine tartrate, the following substances are expected to be introduced into the environment either as waste water discharges, air emissions captured through condensers, hazardous waste (recycled or incinerated), or solid waste (recycled or disposed). Also, the quality control laboratories will generate laboratory waste chemicals.

As an alternate supplier, the facility would manufacture the intermediate 6-aminoquinoxaline using the same process as

At the Allergan America facility, the Product will be mixed in batch operations in accordance with FDA requirements. The products will then be filled into the appropriate unit dose containers, labeled appropriately and packaged for shipment to the customer.

During the production of solutions, the following substances are expected to be introduced into the environment: off-specification Product or cleaning residuals from Product manufacture. Also, the quality control laboratories will generate laboratory waste chemicals.

This Product is expected to be distributed evenly across the US as well as other countries. It is assumed that the customers will dispose of the containers after use in the local trash collection system which will either recycle the bottles or landfill them.

b. Controls Exercised

At the facility, although not expected, residual (very insignificant) amounts of the brimonidine tartrate process chemical reactants may enter the

environment at the sites of manufacture as the result of equipment and facilities cleaning. However, because of the high cost of pharmaceutical materials, as well as GMP provisions requiring strict accounting of their use, the manufacturing process is expected to result in minimal residual releases to the environment. Also, negligible emissions are expected due to the low production volume.

Any residuals in washwaters are neutralized and discharged to the Department of Public Services publicly owned treatment works (POTW). The U.S. Environmental Protection Agency Federal Categorical Pretreatment Standards for Pharmaceutical Manufacturing Point Source Category, Subpart C - Chemical Synthesis Products Subcategory, Pretreatment Standards for New Sources applies to this discharge. Chemicals including laboratory chemicals which cannot be recycled or reused are sent offsite for proper disposal. Hazardous wastes generated by are sent for fuels blending and incineration. There are no permitted air control devices required at the facility. The facility employs local scrubbers and condensers which are integral to the process equipment. Recovered solvents are sent for recycling or for fuels blending. Solid wastes are recycled where possible and disposed of where recycling is not possible.

At the facility, although not expected, residual (very insignificant) amounts of the manufacturing substances may enter the environment at the sites of production as the result of equipment and facilities cleaning. However, because of the high cost of pharmaceutical materials, as well as Good Manufacturing Practices (GMP) provisions requiring strict accounting of their use, the manufacturing process is expected to result in minimal residual releases to the environment. Solvents are captured using condensers. The solvents are either recycled or disposed via incineration. Filters are used to capture the active ingredient.

At the Allergan America facility, although not expected, residual (very insignificant) amounts of the manufacturing substances may enter the environment at the sites of production as the result of equipment and facilities cleaning. However, because of the high cost of pharmaceutical materials, as well as GMP provisions requiring strict accounting of their use, the manufacturing process is expected to result in minimal residual releases to the environment. Also, negligible emissions are expected due to the low production volume.

Any residuals (solutions or cleaning residues) in washwaters are pH adjusted and discharged to the Municipal Sewage treatment facility which is permitted by the Puerto Rican Environmental Quality Board and the U.S. Environmental Protection Agency. Chemicals which cannot be recycled or reused are sent offsite for proper disposal . Three diesel generators, one diesel pump for fire suppression water and two boilers operate under air pollution control permits.

Returned Goods (finished product) are not received at the Allergan America facility located at Puerto Rico Road, 345 km. 1.5, P. O. Box 60 Hormigueros, Puerto Rico, 00660. Returned Goods are sent by the customer to the Allergan facility located at 8301 Mars Drive, P.O. Box 2675, Waco, Texas, 76712. The Allergan facility located in Waco disposes of returned goods using Laidlaw Environmental Services, Inc. located at 500 Battleground Road, La Porte, Texas 77571. Returned goods are either incinerated or buried if they cannot be resold.

Allergan America disposes of rejected or off-specification batches, ingredients, and sub-components of a batch by incineration/fuels blending
f Puerto Rico, Inc. located
provides this service for Allergan America)
or burial at an industrial landfill .
provides this service for Allergan America).

c. Statement of Compliance with Emission Requirements

is in compliance with all applicable federal (OSHA, EPA), state and local environmental, health and safety regulations.

is in compliance with all applicable national, provincial and local environmental, health and safety regulations.

Allergan America is in compliance with all applicable federal (OSHA, EPA), state and local environmental, health and safety regulations except as noted in the next sentences. The Allergan America facility has received two notices of violation concerning noise emanating from the facility air conditioning and emergency power generation systems. Allergan, while denying it is in violation of any noise control limit regulation, is currently working with the Puerto Rican Environmental Quality Board to resolve these issues. Allergan has received notices of violation for wastewater discharge exceedances of permitted parameter limits. Allergan is currently working with PRASA, the regulatory agency for wastewater discharge permitting and enforcement in Puerto Rico, to resolve these issues.

It is assumed that the customers of the finished Product operate in compliance with applicable federal (OSHA, EPA), state and local environmental, health and safety regulations.

d. Effect On Compliance

Approval of this New Drug Application and the production of the active substance, brimonidine tartrate, will have no significant adverse effects on compliance with applicable environmental regulations.

e. Quantity Entering Environment

In the manufacture of the active substance, brimonidine tartrate, the quantity entering the environment from the manufacturing process is negligible.

In the manufacture of the Product, the quantity entering the environment from the manufacturing process is negligible. Since this is a topical ophthalmic product administered in drop-quantities by the patient, insignificant emissions to the air or discharges to wastewater will result from the patient's use of the drug product but will be minimal. There are also insignificant waste impacts anticipated from the patient's use.

7 - 11.

The Product is an ophthalmic pharmaceutical for topical administration. Items 7 - 11 therefore are not required. See 21 CFR Section 25.31(a)(3)(ii).

12. LIST OF PREPARER(S):

Michael Whaley, REA
Director
Environmental Health

PERSONS AND AGENCIES CONSULTED:

Su C. Tso, Ph.D., Chemist, Division of Topical Drug Products, CDER, FDA

13. CERTIFICATION

The undersigned official certifies that the information presented in this report is true, accurate, and complete to the best of the knowledge of Allergan, Inc.

Michael Whaley

ALLERGAN, INC.
Michael Whaley
Director
Environmental Health

Date: April 19, 1996

14. REFERENCES

21 CFR 25.31

15. APPENDICES

None.

ALLERGAN R&D
MATERIAL SAFETY DATA SHEET

NFPA Rating: Health: 2 Flammability: 0 Reactivity: 0 Special: 0

PRODUCT IDENTIFICATION

Compound Name:	**BRIMONIDINE TARTRATE (AGN 190342)**
Class of Compound:	Alpha-2 Adrenergic Agonist
Manufacturer's Name:	Allergan, Inc. Research & Development
Address:	2525 Dupont Drive Irvine, CA 92715
24-Hr. Phone Number	Allergan, Inc. 714-752-4335
Phone Number between 7 am-5 p.m. Pacific Time M-F	714-724-5940
Date Prepared:	February 14, 1996

HAZARDOUS INGREDIENTS

Brimonidine tartrate (CAS # 59803-98-4) is a member of a class of compounds which acts on the α_2-receptor of the adrenergic autonomic nervous system. Some of these compounds are used in the treatment of systemic hypertension. In the eye, α_2-adrenergic agonists lower IOP and are additive to β-adrenergic antagonist therapy. No Permissible or Recommended Exposure Level has been established for any of these compounds.

HAZARDS IDENTIFICATION AND FIRST AID

Emergency Overview: This is an experimental compound. The pharmacological and toxicological properties of this compound have not been fully investigated. Workers should handle this material in a fume hood. If a fume hood is unavailable, wear a NIOSH-approved respirator. Workers should also wear latex gloves, lab aprons and safety glasses when handling this compound.

Primary Routes of Entry into the Body:	Inhalation, skin and eye contact
Potential Health Effects	The full range of possible human health effects has not yet been determined for this compound. Other potential health effects listed in this MSDS are based on known effects caused by other alpha 2 adrenergic agonists Common side effects of members of this class of compounds include hypotension, dry mouth and drowsiness. Overexposure to clonidine may cause nausea, vomiting, anorexia, sexual dysfunction, hypotension, bradycardia, contact dermatitis, irritability, miosis and fatigue.
Emergency First Aid Procedures:	
Eye Contact:	Immediately flush eyes with water for 15 minutes. Obtain medical attention.
Skin Contact:	Immediately flush skin with water for 15 minutes Remove contaminated clothing and shoes. Wash contaminated clothing before reuse. Destroy or thoroughly clean contaminated shoes. Get medical attention if symptoms are present.
Inhalation:	Move to fresh air. If symptoms occur, obtain medical attention. Treat symptomatically.
Ingestion:	Consult a physician or poison control center immediately.

FIRE FIGHTING MEASURES

Flash Point °F (Method)	No data for this product
Fire-Extinguishing Materials:	Water fog, CO_2, foam or dry chemical

Specific Firefighting Procedures:	Use self-contained breathing apparatus in enclosed or confined spaces or as otherwise needed.
Unusual Fire and Explosion Hazards:	None known

SAFE HANDLING MEASURES

Steps to be Taken if Material is Spilled or Released:	Sweep up or take up with absorbent material Flush spill area with water.
Waste Disposal Methods:	Dispose of according to federal, state and/or local regulations.
Precautions to be Taken in Handling and Storage:	Keep away from oxidizing materials. Store in a cool, well-ventilated area.
Mutagenicity:	Ames tests do not indicate a genetic or carcinogenic risk.
Reproductive toxicity:	In rat and rabbit teratology studies, this compound showed no embryolethal or teratogenic activity.

EXPOSURE CONTROL

Engineering Controls:	This compound should be handled in a glove box, laboratory hood or other effective local exhaust ventilation.
Respiratory Protection:	This material does not have established exposure limits. If not using a fume hood when handling this compound, wear a NIOSH approved air-purifying respirator for dusts and mists when working with small quantities (milligrams). For larger quantities (pounds), wear a powered air-purifying respirator or a positive pressure air-supplied respirator.
Eye Protection:	Wear safety glasses with side shields (or goggles) and a face shield.

Protective Clothing:	Rubber (latex) gloves are recommended when handling this compound in dry or aqueous form. When using this compound dissolved in organic solvent, wear gloves that provide protection against that solvent. Wear lab coat or other protective clothing.
Hygienic Work Practices:	Wash hands thoroughly after handling. No eating, drinking or smoking in area.

PHYSICAL AND CHEMICAL PROPERTIES

Melting Point:	202-210° C
Specific Gravity:	No data for this product
Vapor Pressure (mm Hg at 20° C):	No data for this product
Appearance:	Pale yellow, non-hygroscopic, crystalline solid. Free base is fluorescent.

REACTIVITY DATA

Stability:	Stable
Materials to Avoid:	Store away from oxidizers and heat.
Hazardous Polymerization:	None known
Hazardous Decomposition Products:	None known

TOXICOLOGICAL INFORMATION

INGESTION: LD_{50} for the mouse was 50 mg/kg. The No observed adverse effect level was 25 mg/kg. LD_{50} for the rat was 100 mg/kg. The No observed adverse effect level was 10 mg/kg. Monkeys dosed orally with 2.5 mg/kg/day for one month survived without systemic effect except for the pharmacologic effect of sedation.
EYE: Monkeys dosed with 0.8% solution for one month exhibited no systemic effects.

INTRAVENOUS: The LD_{50} for the mouse was 50 mg/kg. The No observed adverse effect level was 10 mg/kg. LD_{50} for the rat was 100 mg/kg. The No observed adverse effect level was 25 mg/kg.

CHRONIC: Mice were fed doses up to 2.5 mg/kg/day for 21 months. There was no evidence of a treatment-related effect on body weight, food and water consumption, ophthalmology, hematology or clinical chemistry parameters. There was no evidence of oncogenicity.

Rats were fed doses up to 2.5 mg/kg/day for 2 years. There was no evidence to suggest an oncogenic effect.

REPRODUCTIVE: A fertility and general reproduction study in rats consisted of doses up to 0.66 mg/kg/day to the F_0 generation males for 70 days prior and during mating and to the F_0 females for 14 days prior to mating and during gestation and lactation. Drug related effects included reduced body weight gains in the F_0 males and reduced body weight gains in the F_1 pups in lactation in the high dose group. Following weaning, no remarkable drug-related effects were noted in the F_1 generation. No treatment-related effects occurred in the F_2 generation.

Teratology studies were conducted in rats with doses up to 2.5 mg/kg/day for days 6-15 post-coitum. Studies in rabbits were with doses up to 4.0 mg/kg/day from days 7 through 18 of pregnancy. Dose-dependent weight and growth loss was observed in both. There was no embryolethal or teratogenic activity in either study.

MUTAGENICITY: Ames tests using *Salmonella* tester strains did not indicate a genetic or carcinogenic risk. A chromosomal aberration assay in Chinese Hamster Ovary cells resulted in no significant increase in chromosomal aberrations at the concentrations analyzed.

The preceding information is based on available data and is believed to be correct. However, no warranty is expressed or to be implied regarding the accuracy of this information, the results to be obtained from the use thereof or the hazards connected with the use of the material. Since the information contained herein may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use. This information is furnished upon the condition that the persons receiving it shall make their own determinations of the effects, properties, and protections which pertain to their particular conditions.

JUN 13 1996

SYO
Chapman

REVIEW FOR DIVISION OF
ANALGESIC, ANTI-INFLAMMATORY, and OPHTHALMIC DRUG PRODUCTS
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGIST'S REVIEW NO. 1
June 12, 1996

MICROBIOLOGY REVIEWER: Carol K. Vincent, Microbiology Staff, HFD-805

A. 1. NDA No.: 20-613

PRODUCT NAME: ALPHAGAN (brimonidine tartrate ophthalmic solution) 0.2% Sterile

APPLICANT:	MANUFACTURING SITE:
Allergan 2525 Dupont Drive P O Box 19534 Irvine, CA 92713-9534	Allergan America State Road 346 Km 1.6 Barrio Hormicueros Hormicueros, Puerto Rico

2. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Solution, topical drops

3. METHOD(s) OF STERILIZATION: Aseptic fill

4. PHARMACOLOGICAL CATEGORY / PRINCIPAL INDICATION:

For lowering intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) and / or ocular hypertension (OHT).

5. DRUG PRIORITY CLASSIFICATION: 1 S

B.

1.	INITIAL APPLICATION DATE:	08-31-95
2.	APPLICATION FILED:	11-06-95
3.	RECEIVED FOR REVIEW:	10-04-95
4.	AMENDMENT:	02-28-96
5.	RECEIVED FOR REVIEW:	03-07-96
6.	AMENDMENT:	04-25-96
7.	RECEIVED FOR REVIEW:	05-20-96

C. CONCLUSION: We recommend NDA 20-613 for approval for microbiological quality and sterility assurance based on the sterilization process validation information and other information submitted on 08-31-95, 02-28-96, and 04-25-96.

cc:
Orig. NDA 20-613
HFD-540/Chambers/Tso/Chapman
HFD-160/Consult file/CKVincent (HFD-805)
Drafted by: CKVincent/12-04-95/05-20-96/
Revised by: CKVincent/06-10-96
R/D Init by: PHCooney/06-12-96

Carol K. Vincent (HFD-805) 6-12-96

D. Thissen for PH Cooney 6-12-96