CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-398

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	21-398
Submission Date(s):	03MAY2007
Brand Name	Combigan™
Generic Name	Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Allergan
Relevant IND(s)	IND 58,460
Submission Type; Code	505(b)(2) resubmission of NDA ; N000 (AZ)
Formulation; Strength(s)	Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution
Indication	Reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.

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1. EXECUTIVE SUMMARY

Combigan™ ophthalmic solution is a combination product containing brimonidine 0.2%/timolol 0.5% proposed for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP. Brimonidine tartrate is a selective alpha-2 adrenergic agonist. Timolol is a non-selective beta-adrenergic receptor blocking agent. The individual components of the combination product are approved and marketed in the US as brimonidine, 0.2% (ALPHAGAN®) and timolol, 0.5% (TIMOPTIC®) and are used individually for the treatment of glaucoma. The treatment regimen for Combigan™ is one drop to the effected eye(s) twice daily. As monotherapy, brimonidine, 0.2% is administered three times daily and timolol, 0.5% is administered twice daily.

The Applicant submitted the original 505(b)(2) NDA 21-398 for Combigan™ (brimonidine 0.2%/timolol 0.5%) ophthalmic solution on 17SEP2001. An approvable letter was issued on 05JUN2002 based on the determination that the submitted studies failed to demonstrate the benefits of the proposed combination outweigh the risks. In the clinical studies, the contribution of each component in combination was

smaller than expected, and the magnitude of the observed effect was not sufficient to outweigh the risks. A complete response to the approvable letter was received on 13SEP2004, and a second approvable letter was issued on 14MAR2005, based on the same review findings. A complete response was submitted on 29JUN2006, and a third approvable letter was issued on 20DEC2006, based on the same review findings. The current submission dated 03MAY2007 is a complete response to the FDA's 20DEC2006 approvable action.

In support of the original NDA, the Applicant submitted pharmacokinetic data from three studies that evaluated the systemic bioavailability of brimonidine and timolol from Combigan™ following multiple dose administration. These included a Phase 1 crossover study evaluating the safety and pharmacokinetics of 0.2% brimonidine tartrate/0.5% timolol as the combination product compared with Alphagan® (0.2% brimonidine tartrate) and Timoptic® (0.5% timolol maleate) monotherapy following twice daily administration in normal, healthy, adult subjects for seven days; and two multicenter, randomized, double-masked, parallel studies evaluating the safety and efficacy of 0.2% brimonidine tartrate/0.5% timolol as the combination product administered twice daily compared with 0.5% timolol twice daily or Alphagan® three times daily for three months (plus a 9-month, masked extension) in patients with glaucoma or ocular hypertension, in which sparse PK sampling was performed. A complete review of these studies is presented in the original Office of Clinical Pharmacology and Biopharmaceutics review for NDA 21-398 dated 05FEB2002. Based on the original review, the Applicant has adequately evaluated the systemic exposure of brimonidine and timolol from the combination product brimonidine 0.2% /timolol 0.5% ophthalmic solution in healthy subjects as well as in patients under clinical use conditions.

Subsequent to the original approvable action, labeling recommendations made in the original Office of Clinical Pharmacology and Biopharmaceutics review for NDA 21-398 were not implemented. In response to a request from the FDA, the Applicant submitted the proposed labeling to the NDA formatted as outlined in the physician labeling rule (PLR; Federal Register Vol. 71, No. 15, January 24, 2006). This review focuses on a review of the proposed label in PLR format based on the findings from the original Office of Clinical Pharmacology and Biopharmaceutics review for NDA 21-398 dated 05FEB2002.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the original NDA submission is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

2. QUESTION BASED REVIEW

The clinical pharmacology and biopharmaceutics information for Combigan™ has been reviewed previously for the original 505(b)(2) NDA 21-398; no additional clinical pharmacology data were submitted in this resubmission. Refer to the original Office of Clinical Pharmacology and Biopharmaceutics review for NDA 21-398 dated 12NOV2002 for the question-based review.

3. LABELING RECOMMENDATIONS

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/s/

Kimberly Bergman
9/28/2007 01:56:07 PM
BIOPHARMACEUTICS

Charles Bonapace
9/28/2007 02:57:28 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Brimonidine Tartrate/Timolol Combination
PRODUCT (Brand Name):	COMBIGAN
DOSAGE FORM:	Ophthalmic solution
DOSAGE STRENGTHS:	Brimonidine Tartrate 0.2%, Timolol 0.5%
NDA:	21-398
NDA TYPE:	4S
SUBMISSION DATE:	9/17/01
SPONSOR:	Allergen Inc.
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Dennis Bashaw, Pharm.D.
OCPB DIVISON:	DPE III, HFD 880
ORM DIVISION:	ODE V, HFD 550

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RECOMMENDATION

The sponsor has evaluated the systemic exposure of brimonidine and timolol from the combination product brimonidine 0.2% /timolol 0.5% ophthalmic solution adequately in healthy subjects as well as in patients under clinical use conditions in three studies. NDA 21-398 is acceptable from the Office of Clinical Pharmacology and Biopharmaceutics standpoint. The labeling comments on page should be conveyed to the sponsor.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D._____

EXECUTIVE SUMMARY

The combination product Brimonidine 0.2%/Timolol 0.5% (will be referred to as Combination Product in this review) is indicated for the treatment of elevated intraocular pressure in patients with glaucoma or ocular hypertension, [redacted] Both brimonidine, 0.2% (ALPHAGAN®) and timolol, 0.5% (TIMOPTIC®) are used individually for the treatment of glaucoma. The treatment regimen for the Combination product is one drop to the effected eye(s) twice daily. As monotherapy brimonidine, 0.2% is administered three times daily and timolol, 0.5% is administered twice daily.

NDA 21-398 (Brimonidine 0.2%/Timolol 0.5%) has three pharmacokinetic studies that evaluate the systemic bioavailability of brimonidine and timolol from the Combination product. Study 016T was a pharmacokinetic study in 16 healthy volunteers, where the to-be-marketed combination product and the individual monotherapies were administered for 7 Days. Study 012T and 013T were two therapeutic drug monitoring studies conducted for a duration of 3 months, in which the systemic exposure of brimonidine and timolol were monitored in patients with glaucoma at the end of Week 2 and Month 3.

Results from Study 016T showed that the C_{max} and AUC_{0-12} of brimonidine in plasma was lower from the Combination product as compared to Brimonidine Monotherapy. This may be due to comparing drug concentrations between BID regimen (used for Combination product) and TID regimen (used for Brimonidine Montherapy). In comparison the C_{max} of timolol was 20% lower, but the AUC of timolol was similar from the Combination product as compared to the Timolol Monotherapy treatment arm. The t_{max} was increased from 1.40 hours to 2.42 hours in the Combination treatment arm, suggesting the absorption of timolol is slowed down in the Combination product. This may be related to a difference in benzalkonium chloride concentration in the Timoptic solution (0.01%) as compared to the Combination solution (0.005%). Benzalkonium chloride is known to increase the systemic exposure of ocular drug products.

Blood samples were taken in two Phase 3 clinical trials (Study 012T and 013T) in patients with glaucoma or ocular hypertension. Enrolled patients were randomized to receive one drop (approximately 35 μL) of the Combination product, Brimonidine Monotherapy or Timolol Monotherapy to each eye and pharmacokinetic samples were taken at approximately one hour after dosing at baseline, at the end of Week 2 and Month 3. Ocular dosing was twice daily for the Combination product, thrice daily for Brimonidine Monotherapy and twice daily for Timolol Montherapy. There was no increase in plasma brimonidine or timolol concentrations over time after Week 2. Brimonidine and timolol plasma concentrations from the Combination group were 30 to 40% lower than their respective monotherapy treatment values. These results were similar to that observed in the pharmacokinetic study (Study 016T). This suggests that the combination product is likely to be safer as compared to the monotherapy. The somnolence side effect observed with the ALPHAGAN® treatment would be less of an issue with the combination product. The safety database for this NDA reviewed by the Medical Officer (Dr. Jennifer Harris) suggested the same.

Plasma brimonidine and timolol concentrations in males were 30 to 47% lower than in females. Similar trends were observed both in the pharmacokinetic study as well as during therapeutic drug monitoring. Body weight was not a significant covariate in the stepwise regression analysis. There was no effect of age on the plasma concentrations of brimonidine and timolol. The correlation of plasma drug concentrations to that at the active site in the eye and in turn its effect on the pharmacodynamic effect of lowering intraocular pressure is unknown. The clinical efficacy and safety trials did not indicate any gender differences in either efficacy or safety from the combination product (as per discussion with the Medical Officer, Dr. Jennifer Harris). Hence, the difference in the plasma concentrations of brimonidine and timolol in males and females do not suggest any clinical significance.

SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

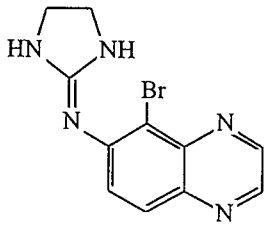
(A) DRUG/DRUG PRODUCT INFORMATION

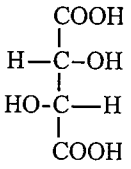
Dosage Form: Brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution

Indication: For reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension [redacted]

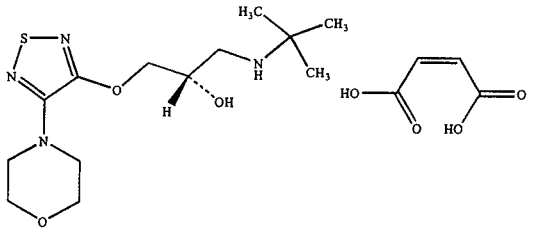
Pharmacologic Class: Selective alpha-2 adrenergic agonist (brimonidine tartrate) with a non-selective beta-adrenergic receptor blocking agent (timolol maleate)

Chemical Name: 5-bromo-6-(2-imidazolidinylideneamino)quinoxaline L-tartrate





(-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1:1)



Dosage and administration: One drop to the affected eye(s) twice daily.

Foreign marketing history: The combination product has not been marketed in any country. However, the individual products are marketed in US.

Formulation:

Ingredient	Concentration (%w/v)
Brimonidine Tartrate	0.2
Timolol Maleate	0.68
Benzalkonium chloride	0.005
Dibasic sodium phosphate	[redacted]
Monobasic sodium phosphate	[redacted]
Hydrochloric acid,	[redacted]
Sodium Hydroxide,	[redacted]

(B) CLINICAL PHARMACOLOGY

Is Brimonidine and Timolol systemically absorbed upon topical ocular administration of the Combination product? How does the systemic exposure of these active ingredients from the Combination product differ from the Monotherapy with Brimonidine and Timolol?

Brimonidine and timolol are systemically absorbed upon topical application. The systemic exposure of brimonidine and timolol was evaluated in 16 healthy volunteers in a pharmacokinetic study of 7 days duration and in patients with glaucoma in therapeutic drug monitoring clinical efficacy and safety trials of 3 month duration. Plasma samples were taken from 173 and 120 patients, respectively, from the two studies at one hour post dosing at the end of Week 2 and Month 3.

Healthy Voluneers:

Brimonidine:
Mean (SD) peak brimonidine plasma concentration from the combination product after 7 days of dosing was 0.03 (0.01) ng/mL. Peak concentrations occurred within 1-4 hours of ocular dosing and declined with systemic half-life of approximately 3 hours. The mean AUC_{0-12} (SD) in the Combination product was 0.13 (0.06) ng.hr/mL and for the Monotherapy was 0.14 (0.11) ng.hr/mL. Brimonidine concentrations in the Combination therapy was lower than the Monotherapy treatment arm, probably due to the BID and TID treatment regimens, respectively. These differences were not statistically significant.

Timolol:
Mean (SD) peak timolol plasma concentration from the combination product after 7 days of dosing was 0.4 (0.2) ng/mL. Peak concentrations occurred within 1-3 hours of ocular dosing and declined with systemic half-life of approximately 7 hours. These concentrations were 20% lower (0.5 ng/mL) to that observed with Timolol Monotherapy in a crossover study in healthy volunteers. However, these concentrations are similar to that reported in the TIMOPTIC® label, where the reported mean plasma concentration following the morning dose of timolol is 0.46

ng/mL and following the afternoon dose is 0.35 ng/mL (Ref: PDR 2001). The mean AUC_{0-12} (SD) in the Combination product was 2.92 (1.68) ng.hr/mL and for the Monotherapy was 2.91 (1.23) ng.hr/mL.

The lower concentrations of timolol in the combination therapy may be related to a difference in benzalkonium chloride concentration in the Timoptic solution (0.01%) as compared to the Combination solution (0.005%). Benzalkonium chloride is known to increase systemic exposure when administered topically to the eye (Ref: Ashton et.a. Pharm. Res. (8), 1166-1174, 1991).

Patients:
In pateints, blood samples were taken at one hour post dose at the end of Week 2 and Month 3.

Brimonidine:
The mean plasma concentrations of brimonidine were similar at week 2 and Month 3, ranging between 0.06-0.08 ng/mL, but was higher than that observed in healthy volunteers after 7 days of treatment (i.e. 0.03 ng/mL). There could be multifactorial reasons for this difference, such as, sampling time, duration of treatment, patient population, number of subjects studied etc. In patients also, the brimonidine plasma concentrations were lower in the Combination therapy group as compared to the Monotherapy group.

Timolol:
The mean plasma concentrations of timolol were similar at week 2 and Month 3, ranging between 0.7-1.2 ng/mL, but was higher than that observed in healthy volunteers after 7 days of treatment (i.e. 0.4 ng/mL). In patients too, the timolol plasma concentrations were lower in the Combination therapy group as compared to the Monotherapy group.

Since, the brimonidine and timolol plasma concentrations are lower in the Combination product, as compared to the respective monotherpies, the Combination product should be safer, which was also shown in the safety database reviewed by the Medical Officer.

(C) INTRINSIC FACTORS

What intrinsic factors influence exposure of brimonidine and timolol and what is the impact of any differences of exposure on pharmacodynamics?

Plasma brimonidine and timolol concentrations in males were 30 to 47% lower than in females in all studies. Body weight was not significant covariate in the stepwise regression analysis. There was no effect of age on the plasma concentrations of brimonidine and timolol. The correlation of plasma drug concentrations to that that at the active site in the eye and in turn its effect on the pharmacodynamic effect of lowering intraocular pressure is unknown. Hence, the impact of this difference on the efficacy in the males cannot be explained. Discussions with the Medical Officer, Dr. Jennifer Harris indicated that there was no gender effect on the efficacy or safety of the product. The effect of race on plasma concentrations was not evaluated.

(D) ANALYTICAL VALIDATION

Are the analytical methods adequately validated for assessing plasma concentrations of brimonidine and timolol?

The analytical methods are adequately validated and acceptable.

Brimonidine in human plasma

Methodology:	GC/MS
Calibration range:	5-250 pg/mL
Lower limit of detection:	5 pg/mL
Inter-day precision:	% CV: 4.15-7.77%
Inter-day accuracy:	101-118% of the theoretical concentration
Intra-day precision:	%CV 2.29-4.94%
Intra-day accuracy:	99.5-119% of the theoretical concentration
Stability:	
Bench top	25 hours at room temperature
Freezer storage	At -80°C for 12 months
Freeze-thaw	3 cycles at -80°C
Extract storage:	32.5 hours at 15°C, 70.5 hours at 4°C
Specificity:	No specific interaction

Timolol in human plasma

Methodology:	LC/MS/MS
Calibration range:	5-1000 pg/mL
Lower limit of detection:	5 pg/mL
Inter-day precision:	% CV: 2.3-4.95%
Inter-day accuracy:	107-112% of the theoretical concentration
Intra-day precision:	%CV 1.60-4.63%
Intra-day accuracy:	104-110% of the theoretical concentration
Stability:	
Bench top	2.5 hours at room temperature
Freezer storage	48 days at -80°C and 20 days at -20°C (ongoing)
Freeze-thaw	3 cycles at -80°C
Extract storage:	59 hours at room temperature and 65 hours at 4°C
Specificity:	No specific interaction
Percent recovery:	78.5%

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APPENDICES

APPENDIX A

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APPENDIX B

INDIVIDUAL STUDY REPORTS

Study 190342-016T:

A Single-Center, Randomized, Double-Masked, Crossover Study To Evaluate the Safety and Pharmacokinetic Profile of Twice-Daily Administration of 0.2% Brimonidine Tartrate/0.5% Timolol Fixed-Combination Ophthalmic Solution Compared with ALPHAGAN ® (0.2% Brimonidine Tartrate) and Timoptic ® (0.5% Timolol Maleate) Monotherapy Twice Daily, in Normal, Healthy, Adult Subjects for Seven Days

The study design is given in the following Table.

Study Design	Randomized, double-masked, 3-period crossover design
Study Population	N=18 healthy subjects, 13 Caucasian, 5 Black 9M and 9F, Ages 18-55, weight 120-208 lbs
Treatment Group	A = Brimonidine 0.2%/timolol 0.5% combination product (Lot 11604) B = Bimonidine 0.2% (ALPHAGAN®) (Lot 11601) C= Timolol 0.5% (Timoptic®) (Lot 11774)
Dosage and Administration	35 µL (1 drop) to each eye BID for 7 days, morning and evening 12 hours apart, each dosing period separated by 7 days washout period. Total duration of study 35 days.
Sampling: Blood	For Brimonidine and Timolol: Day 7, 21 and 35: pre dose, 15, 30, 45 mins and 1, 1.5, 2, 3, 4, 8, 12, 18, and 24 hours post dose.
Urine	None
Analysis	Bimonidine by GC/MS Timolol by LC/MS/MS, validation acceptable, details in the overall summary section of the review Lower Limits of Quantitation Plasma / Urine Brimonidine 5 pg/mL NA Timolol 5 pg/mL NA

Observations:

Brimonidine:

The plasma PK parameters of brimonidine from the Combination and Brimonidine treatments are summarized in the following Table:

Table: Pharmacokinetic Parameters of Brimonidine in the Combination and Brimonidine Treatments

Treatment	Statistic	Tmax (h)	Cmax (pg/mL)	AUC0-12 (pg.h/mL)	t1/2 (h)
Brimonidine	N	16	16	16	15[b]
	Mean	1.30	34.7	141	2.22
	SD	0.59	22.6	106	0.62
Combination	N	15[a]	15[a]	15[a]	14[a,c]
	Mean	1.28	32.7	128	2.43
	SD	0.46	15.0	61	0.51

[a] Subject 1003 dropped out after sampling in Period 1.

[b] $t_{1/2}$ could not be computed reliably in subject 1019 due to poor regression coefficients.

[c] $t_{1/2}$ could not be computed reliably in subject 1004 due to poor regression coefficients.
N= Number of subjects SD= Standard Deviation

- The C_{max} and AUC_{0-12} values of brimonidine following Combination treatment were not statistically significantly different from those following Brimonidine monotherapy treatment, p= 0.329 for C_{max} and p=0.327 for AUC_{0-12}, respectively. Although, the mean plasma concentrations of brimonidine were lower in the Combination therapy at almost all time points.
- The inter-individual variability was very high.

Timolol:
The plasma PK parameters of timolol from the Combination and Timolol treatments are summarized in the following Table.

Table: Pharmacokinetic Parameters of Timolol Following Combination and Timolol Treatments

Treatment	Statistic	Tmax (h)	Cmax (pg/mL)	AUC0-12 (pg.h/mL)	t1/2 (h)
Timolol	N	14[a]	14[a]	14[a]	14[a]
	Mean	1.40	507	2909	7.94
	SD	0.66	269	1231	3.38
Combination	N	15	15	15	14[b]
	Mean	2.42	406	2919	7.32
	SD	1.17	216	1679	1.42

[a] Subject 1024 missed 4 doses of Timolol from Day 32 to Day 34 and was not included in the statistical analysis.
[b] $t_{1/2}$ could not be computed reliably in subject 1019 due to poor regression coefficient.

- The C_{max} of timolol was approximately 20% lower following Combination treatment than following Timolol monotherapy treatment, but the difference was not statistically significantly different (p=0.088).
- The AUC_{0-12} values of timolol following Combination treatment was not statistically significantly different than following Timolol monotherapy treatment, p=0.662.

Figure: Mean (SD) plasma concentration time profile of Brimonidine after twice daily administration of Bimonidine alone (A) and Combination (C)

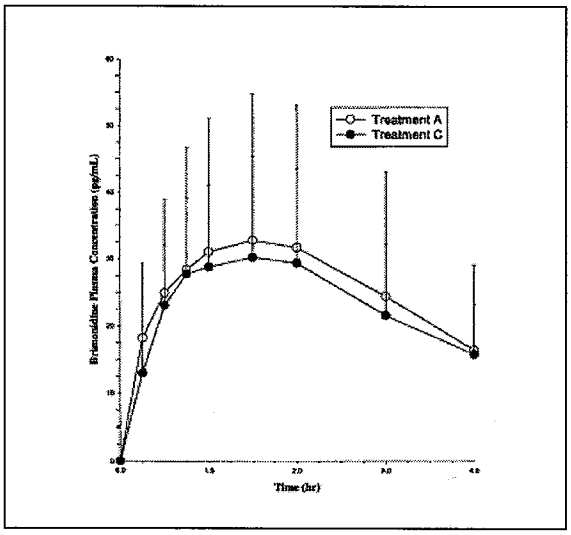
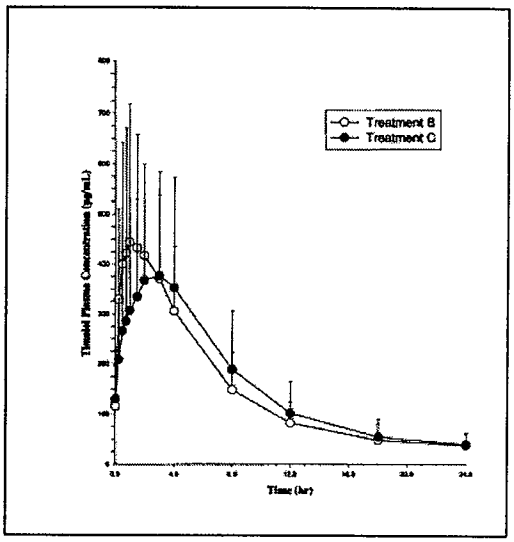
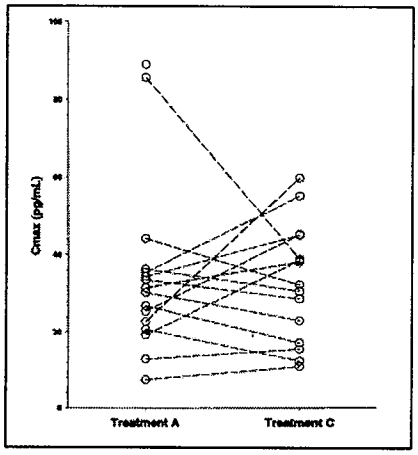


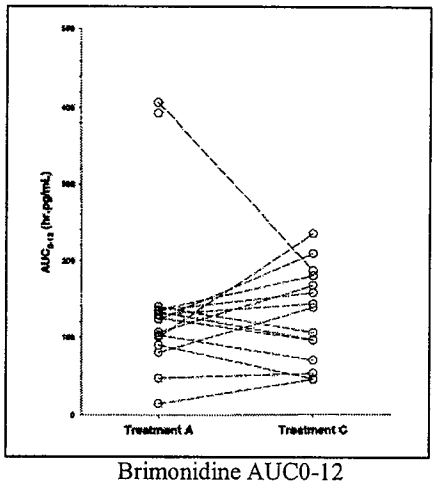
Figure: Mean (SD) plasma concentration time profile of Timolol after twice daily administration of Timololalone (B) and Combination (C)



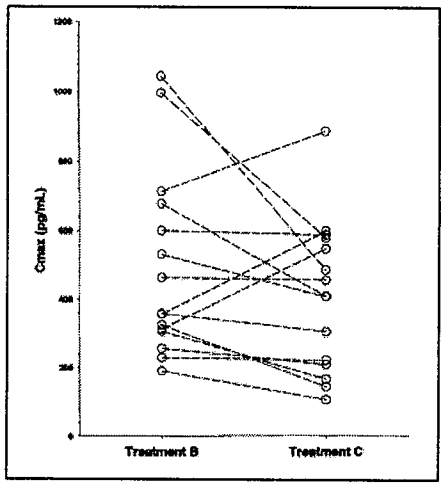
Comparison of individual C_{max} and AUC in the alone treatment arm for brimonidine (A) and timolol (B) vs. the combination treatment arm is shown in the following figures.



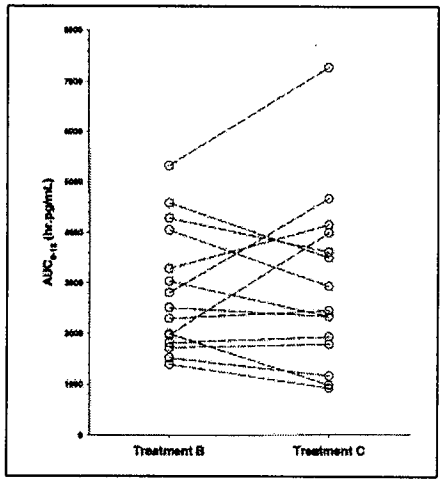
Brimonidine Cmax



Brimonidine AUC0-12



Timolol Cmax



Timolol AUC0-12

As can be seen in the figures there was no specific trend (increase or decrease) in the individual subjects brimonidine or timolol AUC and C_{max} from the Combination therapy as compared to the Monotherapy.

Gender Differences in Pharmacokinetics:

The summary of PK parameters for different treatments by gender is shown in the following Table.

Table: Summary of Pharmacokinetic Parameters of Brimonidine and Timolol by Gender After Multiple-Dose Ocular Administration of Timolol, Brimonidine, or Combination

			Female			Male		
Compound	Treatment	Statistic	Cmax (pg/mL)	AUC0-12 (pg.h/mL)	t1/2 (h)	Cmax (pg/mL)	AUC0-12 (pg.h/mL)	t1/2 (h)
Brimonidine	Brimonidine	N	9	9	8	7	7	7
		Mean	35.1	142	2.23	34.1	140	2.21
		SD	20.7	101	0.80	26.5	121	0.40
		%CV	58.8	71.1	35.8	77.6	86.5	18.3
	Combination	N	9	9	9	6	6	5
		Mean	36.5	144	2.42	26.8	104	2.45
		SD	15.7	62	0.58	13.1	54	0.44
		%CV	42.9	43.2	23.9	48.7	51.7	17.9
Timolol	Timolol	N	8	8	8	6	6	6
		Mean	668	3620	8.17	292	1950	7.64
		SD	249	1120	4.31	69	523	1.95
		%CV	37.3	30.9	52.7	23.6	26.7	25.5
	Combination	N	9	9	8	6	6	6
		Mean	461	3200	7.29	323	2510	7.37
		SD	218	1810	1.48	204	1520	1.47
		%CV	47.2	56.7	20.4	63.1	60.5	19.9

- No apparent gender differences were observed for the brimonidine PK parameters following either Brimonidine Monotherapy. Following Combination treatment the brimonidine AUC and Cmax were 28% lower in males.
- For timolol, there was a trend toward lower C_{max} and AUC_{0-12} values in male subjects, which was especially apparent following Timolol monotherapy treatment (56%↓).

Safety:

No serious adverse events were noted during the study. There were no noticeable differences in adverse events among treatment groups. Most common side effects were headache, nasal irritation and rhinitis.

Conclusions:

- The C_{max} and AUC_{0-12} of brimonidine in plasma was lower from the Combination product as compared to Brimonidine Monotherapy. This is probably due to comparing drug concentrations between BID regimen (used for Combination product) and TID regimen (used for Brimonidine Montherapy).
- The C_{max} of timolol was 20% lower, but the AUC was similar from the Combination product as compared to the Timolol Monotherapy treatment arm. The t_{max} was increased from 1.40 hours to 2.42 hours in the Combination treatment arm, suggesting the absorption of timolol is slowed down in the Combination product. This may be related to a difference in benzalkonium chloride concentration in the Timoptic solution (0.01%) as compared to the Combination solution (0.005%). Benzalkonium chloride has been reported to have affected systemic drug exposure of timolol in the rabbit when administered topically to the eyes.
- Plasma concentrations of brimonidine and timolol were lower in males as compared to females.

Study 190342-012T-01:

A Multicenter, Double-Masked, Randomized, Parallel Study of The Safety and Efficacy of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution Twice-Daily Compared with 0.5% Timolol Twice-Daily or ALPHAGAN®Three-Times-Daily for Three Months (Plus 9-Month, Masked Extension) in Patients with Glaucoma or Ocular Hypertension

Objectives:

- Examine plasma concentrations of brimonidine and/or timolol on Day 0, Week 2 and Month 3 in patients with glaucoma or ocular hypertension
- Evaluate the population pharmacokinetics of brimonidine and timolol

Treatments: one drop to each eye

- Brimonidine tartrate 0.2%/timolol 0.5% combination ophthalmic solution BID (referred to as Combination) for three months (plus 9-month, masked extension)
- Timolol 0.5% BID monotherapy (referred to as Timolol) for three months (plus 9-month, masked extension)
- Brimonidine tartrate 0.2% TID monotherapy (referred to as Brimonidine) for three months (plus 9-month, masked extension)

Study Population:

Pharmacokinetic analyses were performed on samples collected from 173 patients:

- 59 patients in the Combination group
  - 29 females and 30 males
  - 2 Asian, 9 Black, 41 Caucasian, 7 Hispanic
  - Ages 34-83 years
  - Weight 47-159 Kg
- 59 patients in the Brimonidine group
  - 34 females and 25 males
  - 1 Asian, 6 Black, 43 Caucasian, 9 Hispanic
  - Ages 31-88 years
  - Weight 50-129 Kg
- 55 patients in the Timolol group
  - 28 females and 27 males
  - 1 Asian, 8 Black, 38 Caucasian, 1 Hispanic
  - Ages 35-89 years
  - Weight 45-131 Kg

Blood Samples:

Blood samples were collected from six to eight selected sites for the measurement of plasma brimonidine and timolol concentrations at Hour 0 (after the IOP measurement and

prior to dosing) for Baseline (Day 0), at Hour-One post-dose for Week 2, and for Month 3.

Pharmacokinetic and statistical analysis:

- One sample t-test within each group: For comparing plasma brimonidine and timolol concentrations between Week 2 and Month 3.
- Two-Sample t-test: For comparison of drug concentrations between Combination and their respective monotherapy treatment groups.
- Correlation of individual concentrations for evaluating gender differences.
- Correlation of individual concentrations with age and body weight, explored by linear regression analysis at p-value of 0.05. Brimonidine and timolol concentrations on Week 2 and Month 3 were treated as response (dependent) variables, while age and body weight, were treated as independent variables.
- Further analyses were performed to identify whether the concentrations were affected by gender and/or body weight due to potential correlation between the two independent variables. Stepwise regression analysis with body weight and gender as variables was performed for brimonidine as well as timolol concentrations for both the Combination and Monotherapy treatment groups at a p-value of 0.15.

Observations:

Baseline (Day 0 data):

Brimonidine: Not quantifiable in any of the three treatment groups

Timolol: One plasma sample from the Combination treatment group had measurable timolol concentration (7.3 pg/mL from patient 1039) on Day 0 (baseline sample). Two plasma samples from the Brimonidine Monotherapy treatment group had measurable timolol concentration (41.9 pg/mL from patient 1163 on Month 3 and 5.15 pg/mL from patient 1464 on Month 3). The plasma timolol concentrations from patients 1039 and 1464 are attributed to the background noise as the blood levels were near the LLOQ (5 pg/mL), while that from patient 1163 could not be explained.

Week 2 and Month 3:

Brimonidine: One-hour post-dose plasma brimonidine concentrations (pg/mL) from the Combination and Brimonidine groups are summarized in the following Table:

	Combination BID		Brimonidine TID	
	Week 2	Month 3	Week 2	Month 3
N	56	53*	55	48*
Mean	60.1 pg/mL	64.4 pg/mL	80.7 pg/mL	73.6 pg/mL
SD	31.3	37.8	46.0	42.1

Mean and SD in pg/mL

*not all patients enrolled at Week 2 continued to Month 3

Plasma brimonidine concentrations at Month 3 were not significantly different from that at Week 2 for both the Combination (p-value = 0.114) and Brimonidine treatment groups (p-value = 0.240), suggesting concentrations remained steady from Week 2 to Month3.

Timolol: One-hour post-dose plasma timolol concentrations (ng/mL) from the Combination and Timolol groups are summarized in the following Table:

	Combination BID		Timolol BID	
	Week 2	Month 3	Week 2	Month 3
N	56	53*	52	47*
Mean	0.732 ng/mL	0.782 ng/mL	1.04 ng/mL	1.26 ng/mL
SD	0.427	0.544	0.70	1.01

Mean and SD in ng/mL
*not all patients enrolled at Week 2 continued to Month 3

Plasma timolol concentrations at Month 3 was not significantly different from that at Week 2 for both Combination (p-value = 0.09) and Timolol treatment groups (p-value = 0.071), suggesting concentrations remained steady from Week 2 to Month3.

Monotherapy versus Combination therapy comparisons:

Brimonidine:

Week 2: Brimonidine concentrations were 25% lower in the Combination treatment group than in the Brimonidine Monotherapy treatment group at Week 2 (p-value = 0.007).

Month 3: The difference was not statistically significantl at Month 3 (p-value = 0.255).

Timolol:

Week 2: Timolol concentrations were 30% lower in the Combination treatment group than in the Timolol Monotherapy treatment group at Week 2 (p-value = 0.007)

Month 3: Timolol concentrations were 38% lower in the Combination treatment group than in the Timolol Monotherapy treatment group at Month 3 (p-value = 0.005).

Gender Differences:

Brimonidine:

Table Mean brimonidine concentrations (pg/mL) separated by gender on Week 2 and Month 3 following Combination BID and Brimonidine TID treatment.

	Combination BID				Brimonidine TID			
	Week 2		Month 3		Week 2		Month 3	
	Male	Female	Male	Female	Male	Female	Male	Female
N	27	29	28	25	21	34	18	30
Mean (pg/mL)	46.2	72.9	50.3	80.3	52.3	98.3	65.0	78.7
SD	24.4	31.8	32.6	37.5	20.2	48.9	33.3	46.4

Plasma brimonidine levels were significantly lower in males than in females for both Combination and Monotherapy.

- Combination Therapy: 36% lower in males at Week 2 (p-value <0.001)
  37% lower in males at Month 3 (p-value =0.003)
- Monotherapy: 47% lower in males at Week 2 (p-value <0.001)
  Not significant on Month 3 (p-value = 0.024)

Timolol:

Table Mean timolol concentrations (ng/mL) separated by gender on Week 2 and Month 3 following Combination BID and Timolol BID treatment.

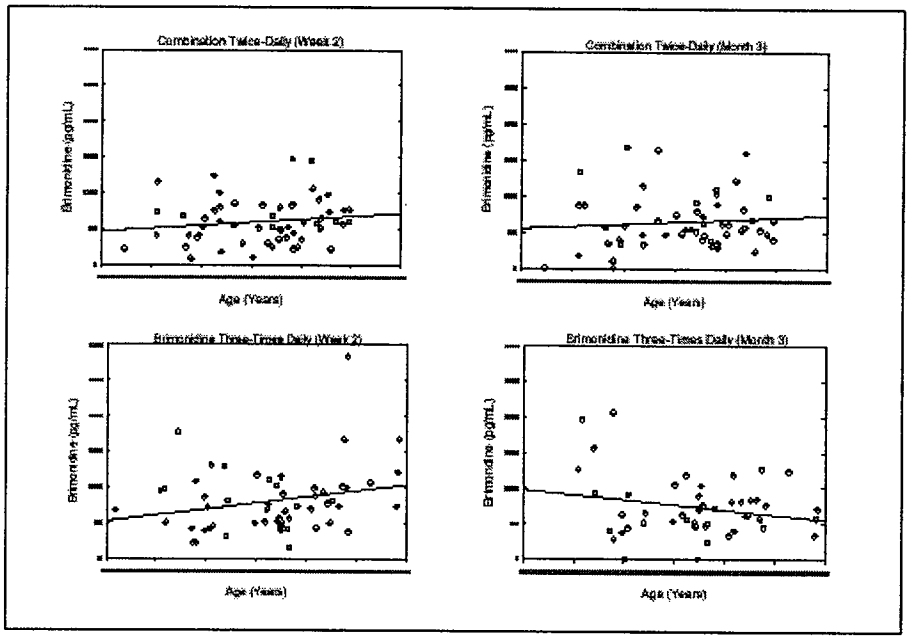
	Combination BID				Timolol BID			
	Week 2		Month 3		Week 2		Month 3	
	Male	Female	Male	Female	Male	Female	Male	Female
N	27	29	28	25	26	26	23	24
Mean (ng/mL)	0.594	0.86	0.56	1.03	0.923	1.17	1.25	1.28
SD	0.37	0.443	0.397	0.584	0.66	0.725	1.11	0.94

Plasma timolol levels were significantly lower in males than in females for Combination therapy group only.

- Combination Therapy: 31% lower in males at Week 2 (p-value = 0.018)
  46% lower in males at Month 3 (p-value = 0.002)
- Monotherapy: Not significant at Week 2 or Month 3.

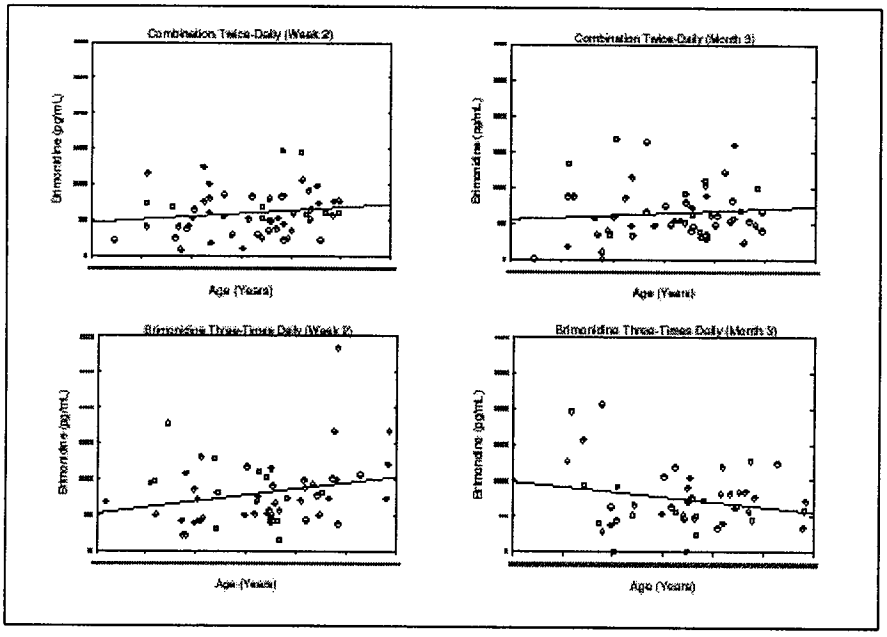
Effect of Age:

Brimonidine: The regression plots of plasma brimonidine concentrations for the Combination and Brimonidine treatment groups at 1 hour after the dose at Week 2 and Month 3 versus age are presented in the following Figures.



The p-values for the t-test for slope for plasma brimonidine concentrations for Combination and Brimonidine treatment groups versus age were 0.218 and 0.674, respectively, indicating the absence of an age effect.

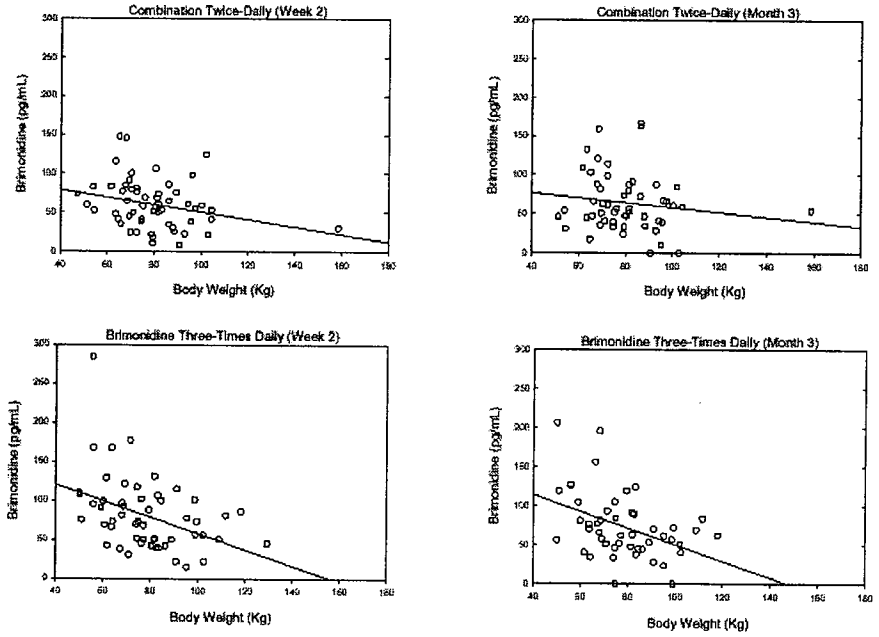
Timolol: The regression plots of plasma timolol concentrations for the Combination and Timolol treatment groups at 1 hour after the dose at Week 2 and Month 3 versus age are presented in the following Figures.



The p-values for the t-test for slope for plasma timolol concentrations for Combination and Timolol treatment groups versus age were 0.255 and 0.455, respectively, indicating the absence of an age effect.

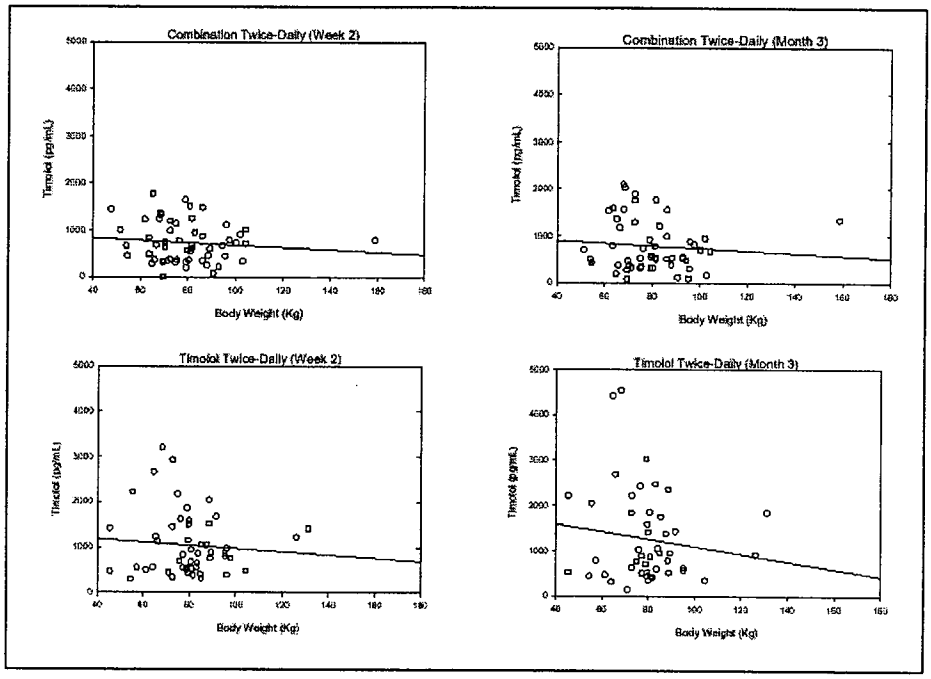
Effect of Body Weight:

Brimonidine: The regression plots of plasma brimonidine concentrations for the Combination and Brimonidine treatment groups at 1 hour after the dose at Week 2 and Month 3 versus body weight are presented in the following Figures.



The p-values for the t-test for slope for plasma brimonidine concentrations for Combination and Brimonidine treatment groups versus body weight were 0.041 and <0.001, respectively

Timolol: The regression plots of plasma timolol concentrations for the Combination and Timolol treatment groups at 1 hour after the dose at Week 2 and Month 3 versus body weight are presented in the following Figures.



The p-values for the t-test for slope for plasma timolol concentrations for Combination and Timolol treatment groups versus body weight were 0.345 and 0.271, respectively, indicating no body weight effect.

Since the body weight of female group was lower than that of the male group for each treatment, further analyses were performed to identify whether the concentrations were affected by gender and/or body weight due to potential correlation between the two independent variables. To do this, the plasma brimonidine/timolol concentrations were analyzed by stepwise regression analysis with body weight and gender as variables. The results of the stepwise regression for brimonidine concentration indicate that for Combination treatment only gender was significant while for Brimonidine Monotherapy treatment, both gender and body weight were significant. Analyses for the timolol concentrations indicate that, for the Combination treatment, only gender was significant, while for Timolol Monotherapy treatment, neither gender nor body weight were significant.

Conclusions:

- One-hour post-dose plasma brimonidine and timolol concentrations were steady and did not increase after Week 2.
- The brimonidine and timolol plasma concentrations for the Combination group were lower than their respective monotherapy treatment values. This may provide a more favorable safety profile for the Combination treatment.
- Plasma brimonidine and timolol concentrations in males were significantly lower than in females for the Combination and Brimonidine monotherapy treatments. The difference was not significant for Timolol monotherapy treatment.

Study 190342-013T-01:

A Multicenter, Double-Masked, Randomized, ParallelStudy of The Safety and Efficacy of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution Twice-Daily Compared with 0.5% Timolol Twice-Daily or ALPHAGAN®Three-Times-Daily for Three Months (Plus 9-Month, Masked Extension) in Patients with Glaucoma or Ocular Hypertension

The study design was exactly the same as Study 190342-012T-01, hence will not be repeated here, only the study population and results will be discussed.

Study Population:

Pharmacokinetic analyses were performed on samples collected from 120 patients:

- 55 patients in the Combination group
  - 28 females and 27 males
  - 8 Black, 43 Caucasian, 4 Hispanic
  - Ages 31-85 years
  - Weight 49-125 Kg
- 49 patients in the Brimonidine group
  - 31 females and 18 males
  - 5 Black, 42 Caucasian, 1 Hispanic, 1 Other
  - Ages 40-84 years
  - Weight 51-109 Kg
- 54 patients in the Timolol group
  - 26 females and 28 males
  - 1 Asian, 15 Black, 35 Caucasian, 3 Hispanic
  - Ages 29-87 years
  - Weight 53-121 Kg

Observations:

Baseline (Day 0 data):

Brimonidine: Not quantifiable in any of the three treatment groups, except one sample in Timolol treatment group had a quantifiable level of brimonidine (132 pg/mL at Month 3). This finding could not be attributed to anything by the sponsor

Timolol: Two plasma samples from the Brimonidine Monotherapy treatment group had measurable timolol concentration (5.26 pg/mL from patient 1148 on Week 2 and 6.14 pg/mL from patient 1417 on Day 0). These values are very close to the LLOQ. Timolol concentrations from the brimonidine group cannot be possible, hence, they were attributed to background noise by the sponsor.

Week 2 and Month 3:

Brimonidine: One-hour post-dose plasma brimonidine concentrations (pg/mL) from the Combination and Brimonidine groups are summarized in the following Table:

	Combination BID		Brimonidine TID	
	Week 2	Month 3	Week 2	Month 3
N	54	48*	48	41*
Mean	49.7 pg/mL	52.8 pg/mL	81pg/mL	78.6 pg/mL
SD	36.1	46.7	63.8	48.9

Mean and SD in pg/mL
*not all patients enrolled at Week 2 continued to Month 3

The plasma brimonidine concentrations at one hour postdose at Month 3 were not significantly different from those at Week 2 in both the Combination (p-value = 0.5782) and Brimonidine Monotherapy (p-value = 0.6812) treatment groups, indicating that the concentrations remain steady from 2 weeks to 3 months of treatment.

Timolol: One-hour post-dose plasma timolol concentrations (ng/mL) from the Combination and Timolol groups are summarized in the following Table:

	Combination BID		Timolol BID	
	Week 2	Month 3	Week 2	Month 3
N	54	48*	50	50*
Mean	0.499 ng/mL	0.586 ng/mL	0.950 ng/mL	0.873 ng/mL
SD	0.327	0.580	0.709	0.516

Mean and SD in ng/mL
*not all patients enrolled at Week 2 continued to Month 3

Plasma timolol concentrations at Month 3 was not significantly different from that at Week 2 for both Combination (p-value = 0.2671) and Timolol treatment groups (p-value = 0.2854), indicating concentrations remain steady from 2 weeks to 3 months of treatment.

Monotherapy versus Combination therapy comparisons:

Brimonidine:

Week 2: Brimonidine concentrations were 39% lower in the Combination treatment group than in the Brimonidine Monotherapy treatment group at Week 2 (p-value = 0.004).

Month 3: Brimonidine concentrations were 33% lower in the Combination treatment group than in the Brimonidine Monotherapy treatment group at Month 3 (p-value = 0.0132).

Timolol:

Week 2: Timolol concentrations were 47% lower in the Combination treatment group than in the Timolol Monotherapy treatment group at Week 2 (p-value < 0.0001)

Month 3: Timolol concentrations were 33% lower in the Combination treatment group than in the Timolol Monotherapy treatment group at Month 3 (p-value = 0.0111).

Gender Differences:

Brimonidine:

Table Mean brimonidine concentrations (pg/mL) separated by gender on Week 2 and Month 3 following Combination BID and Brimonidine TID treatment.

	Combination BID (pg/mL)				Brimonidine TID (pg/mL)			
	Week 2		Month 3		Week 2		Month 3	
	Male	Female	Male	Female	Male	Female	Male	Female
N	27	27	22	26	18	30	15	26
Mean	50.0	49.3	40.6	63.2	59.4	93.9	57.6	90.8
SD	42.4	29.3	30.2	55.6	35.4	73.5	32.4	53.2

- Combination Therapy: Not significantly different at Week 2 and Month 3 .
- Monotherapy: 37% lower in males at Week 2 (p-value=0.0339)
  37% lower in males at Month 3 (p-value=0.0173)

Timolol:

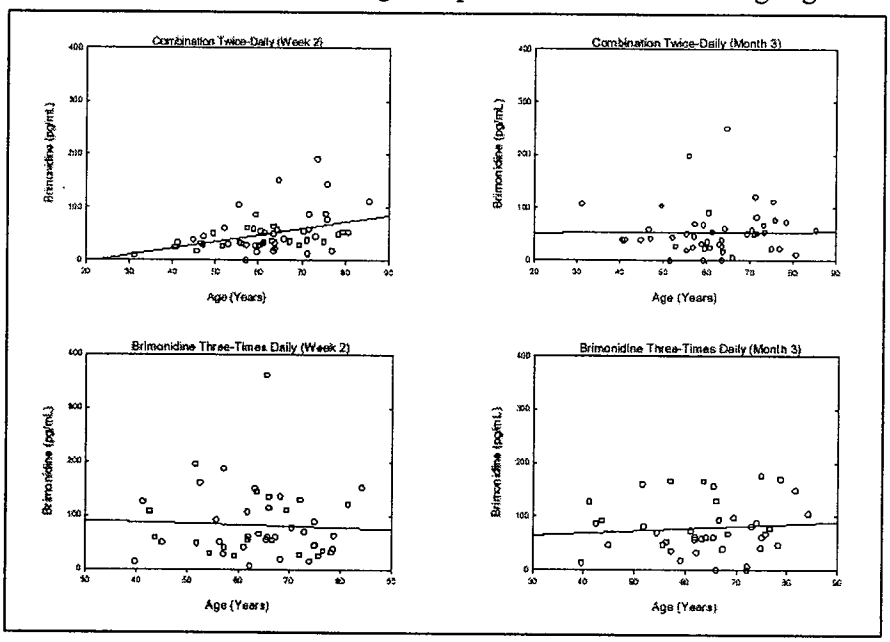
Table Mean timolol concentrations (ng/mL) separated by gender on Week 2 and Month 3 following Combination BID and Timolol BID treatment.

	Combination BID (ng/mL)				Timolol BID (ng/mL)			
	Week 2		Month 3		Week 2		Month 3	
	Male	Female	Male	Female	Male	Female	Male	Female
N	27	27	22	26	26	24	24	26
Mean	0.415	0.584	0.371	0.767	0.679	1.24	0.655	1.07
SD	0.284	0.350	0.232	0.715	0.442	0.829	0.367	0.556

- Combination Therapy: Not significantly different at Week 2
  52% lower in males at Month 3 (p-value = 0.0121)
- Monotherapy: 45% lower in males at Week 2 (p-value = 0.0055)
  39% lower in males at Month 3 (p-value = 0.0028)

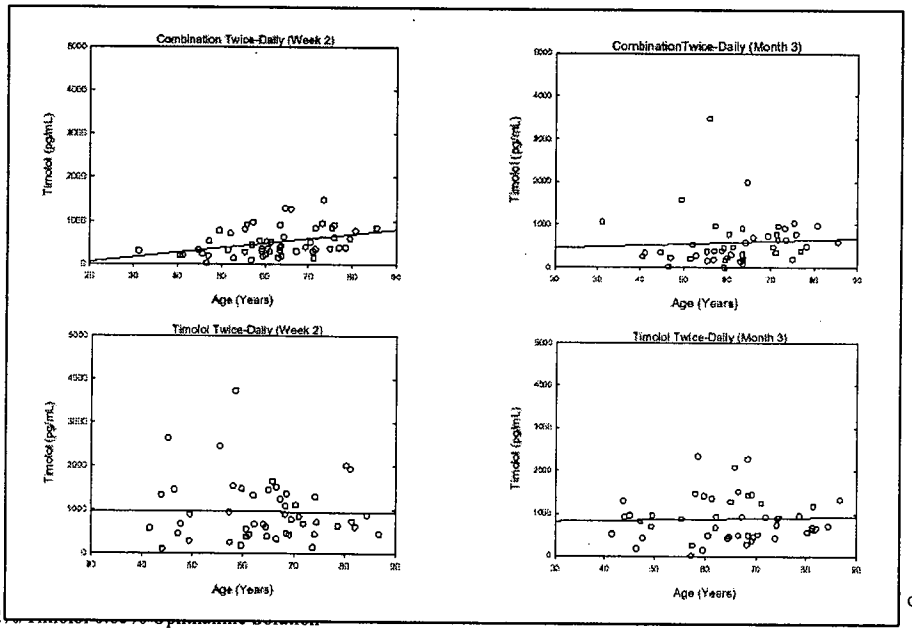
Effect of Age:

Brimonidine: The regression plots of plasma brimonidine concentrations for the Combination and Brimonidine treatment groups at 1 hour after the dose at Week 2 and Month 3 versus age are presented in the following Figures.



The p-values for the t-test for slope for plasma brimonidine concentrations for Combination and Brimonidine treatment groups versus age were 0.0554 and 0.9154, respectively, indicating the absence of an age effect.

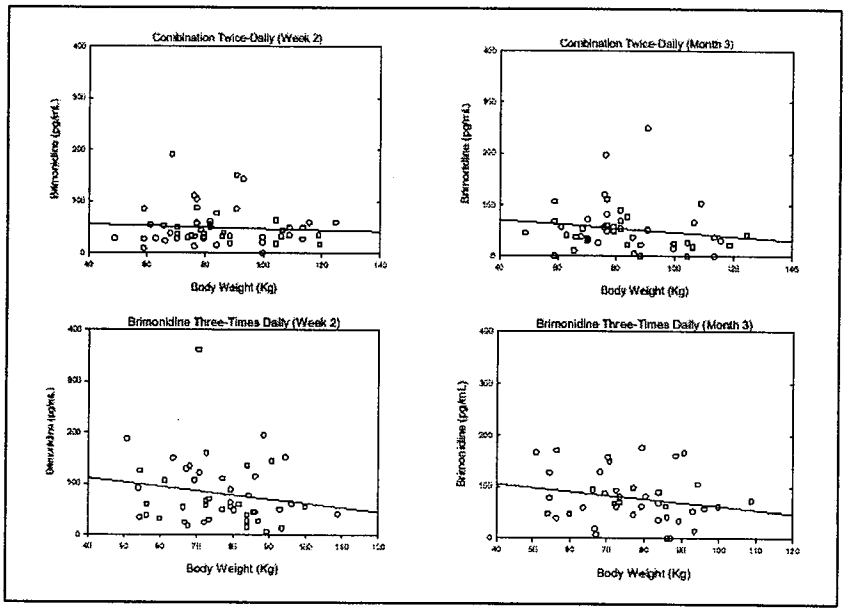
Timolol: The regression plots of plasma timolol concentrations for the Combination and Timolol treatment groups at 1 hour after the dose at Week 2 and Month 3 versus age are presented in the following Figures.



The p-values for the t-test for slope for plasma timolol concentrations for Combination and Timolol treatment groups versus age were 0.0793 and 0.9150, respectively, indicating the absence of an age effect.

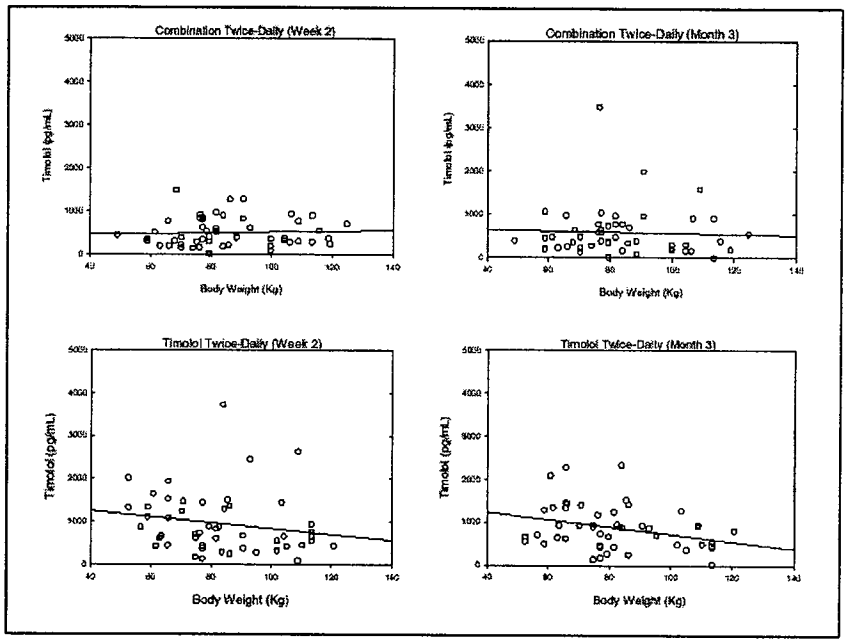
Effect of Body Weight:

Brimonidine: The regression plots of plasma brimonidine concentrations for the Combination and Brimonidine treatment groups at 1 hour after the dose at Week 2 and Month 3 versus body weight are presented in the following Figures.



The p-values for the t-test for slope for plasma brimonidine concentrations for Combination and Brimonidine treatment groups versus body weight were 0.2482 and 0.0848, respectively, indicating no body weight effect.

Timolol: The regression plots of plasma timolol concentrations for the Combination and Timolol treatment groups at 1 hour after the dose at Week 2 and Month 3 versus body weight are presented in the following Figures.



The p-values for the t-test for slope for plasma timolol concentrations for Combination and Timolol treatment groups versus body weight were 0.9794 and 0.0224, respectively, indicating body weight effect for the Timolol Monotherapy treatment group.

Since the body weight of female group was lower than that of the male group for each treatment, further analyses were performed to identify whether the concentrations were affected by gender and/or body weight due to potential correlation between the two independent variables. To do this, the plasma brimonidine/timolol concentrations were analyzed by stepwise regression analysis with body weight and gender as variables. The results of the stepwise regression for brimonidine concentration indicate that for Combination treatment neither gender nor body weight were significant, while for Brimonidine monotherapy treatment, only gender was significant. Analyses for the timolol concentrations indicate that for both Combination and Timolol Monotherapy treatment, only gender was significant

Conclusions:

- One-hour post-dose plasma brimonidine and timolol concentrations were steady and did not increase after Week 2.
- Brimonidine and timolol plasma concentrations for the Combination group were lower than their respective monotherapy treatment values.
- Plasma brimonidine and timolol concentrations in males were significantly lower than in females following Brimonidine and Timolol Monotherapy treatments. The difference was not significant for brimonidine concentrations following Combination treatment, but was significant for timolol following Combination treatment.

APPENDIX C

FILING AND REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-398	Brand Name	
OCPB Division (I, II, III)	III	Generic Name	Brimonidine tartrate 0.2%/Timolol 0.5%
Medical Division	HFD 550	Drug Class	Alpha agonist and Adrenergic receptor blocking agent
OCPB Reviewer	Veneeta Tandon	Indication(s)	Intra ocular pressure reduction
OCPB Team Leader	Dennis Bashaw	Dosage Form	Ophthalmic solution
		Dosing Regimen	1 drop b.i.d.
Date of Submission	17 Sep 01	Route of Administration	topical
Estimated Due Date of OCPB Review		Sponsor	Allergan
PDUFA Due Date	17 July 02	Priority Classification	
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
single dose:				
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:	X	2		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

Filability and QBR comments

	"X" if yes	*Comments*
Application filable ?	*Yes*	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Are the plasma concentrations of brimonidine and timolol combination product similar to the monotherapy product of brimonidine and timolol?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Veneeta Tandon, 10/10/01**	
Secondary reviewer Signature and Date	**Dennis Bashaw**	

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

/s/

Veneta Tandon
2/5/02 08:45:20 AM
BIOPHARMACEUTICS

Dennis, I have made changes on page 4, 8, 33 and 39 after the briefing, Thanks

Dennis Bashaw
2/5/02 11:53:22 AM
BIOPHARMACEUTICS