

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-764**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**



NEED TO BE COMMUNICATED TO THE SPONSOR

HAVE BEEN COMMUNICATED TO THE SPONSOR

**COMMENTS/SPECIAL INSTRUCTIONS/REVIEW FORMAT:**

*Reviewer's Note: This review is not written in QBR format, because many QBR questions are not relevant due to the nature of this application. To emphasize the important findings relevant to Clinical Pharmacology and Biopharmaceutics, a consult form format is used.*

**Recommendation**

From a Clinical Pharmacology and Biopharmaceutics perspective, the Human Pharmacokinetics and Bioavailability Section of this submission(s) for Brimonidine Tartrate Ophthalmic Solution, 0.15% is acceptable. The results from the PK study (C-03-01) suggest that topical ocular dosing with Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN<sup>®</sup> P (the approved brimonidine tartrate ophthalmic solution, 0.15% by Allergan) results in comparable systemic exposure. The ratios and associated one-sided 90% CIs for both treatment groups are within 80% to 125% for C<sub>max</sub>, AUC<sub>0-8</sub>, and AUC<sub>0-inf</sub>.

Recommendations for consideration for the final labeling are included in the Labeling section (Page 8).

**Background**

Brimonidine Tartrate Ophthalmic Solution, 0.15% is intended for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Brimonidine tartrate is a selective alpha-2-adrenergic agonist. Fluorophotometric studies suggest that brimonidine tartrate has a dual mechanism of action through reduction of aqueous humor production and enhancement of uveoscleral outflow. The active component of Brimonidine Tartrate Ophthalmic Solution, 0.15%, brimonidine tartrate, is an approved therapeutic agent for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The clinical safety and efficacy of brimonidine tartrate has been established in NDA 20-613 (ALPHAGAN<sup>®</sup> (brimonidine tartrate ophthalmic solution), 0.2%) and NDA 21-262 (ALPHAGAN<sup>®</sup> P), both of which were developed by Allergan, Inc.

This is a 505 (b)(2) application. The subject of this application has the same active ingredient at the same concentration as the reference product, Alphagan<sup>®</sup> P (NDA 21-262), but differs in the preservative (POLYQUAD vs. PURITE) and some other inactive ingredients used in the formulation (Table 1). The formulation of Alphagan<sup>®</sup> P was deduced from formulation analysis of the commercial product, indicated as "De-Formulation Results" in the following Table (Table 1).

**Table 1. Comparison of Alcon Inc.'s Brimonidine Tartrate Ophthalmic Solution, 0.15% and De-Formulation Results of Allergan's Alphagan P.**

<b>Ingredients</b>	<b>Brimonidine Tartrate Ophthalmic Solution, 0.15% %w/v</b>	<b>Alphagan P De-Formulation Results Average % w/v</b>
Brimonidine Tartrate	0.15	0.15
POLYQUAD	0.001	- <sup>a</sup>

PURITE
Povidone
Sodium Carboxymethylcellulose
Boric Acid
Sodium Borate
Calcium Chloride
Magnesium Chloride
Potassium Chloride
Mannitol
Sodium Chloride
Sodium Hydroxide and/or Hydrochloric Acid
Purified Water

<sup>a</sup> - = Absent from formula

<sup>b</sup> Calculations based on the assumption of similar degrees of hydration

<sup>c</sup> Average pH measured in ALPHAGAN P samples was 7.23

NDA 21-764 contains two studies (Table 2). Study C-02-49 is a bioequivalence (BE) study with clinical endpoints and Study C-03-01 is a BE study with systemic PK endpoints.

**Table 2. Clinical Studies**

Study	Title	Primary Objectives
Study C-02-49	A Three-Month, Randomized, Double-Masked, Parallel Group, Primary Therapy Study, with a planned Nine Month Extension, of the Safety and IOP-lowering Efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% Compared to ALPHAGAN P, 0.15% in Patients with POAG or Ocular Hypertension.	To compare the safety and efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% to that of ALPHAGAN P, 0.15%.
Study C-03-01	A Randomized, Double-Masked, Single-dose Pharmacokinetic Crossover Study of Brimonidine Tartrate Ophthalmic Solution, 0.15% and Alphagan P, 0.15% in healthy subjects.	To assess the extent of systemic exposure to Brimonidine following a single topical dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% or Alphagan P, 0.15% in healthy subjects.

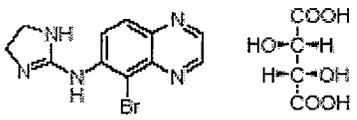
The sponsor requested a waiver of evidence of *in vivo* bioavailability or bioequivalence per 21CFR320.22(b)(1). However, we could not grant a waiver because although the new product is an ophthalmic solution containing the same active ingredient at the same concentration as the approved product, Alphagan<sup>®</sup> P, it contains different inactive ingredients.

Study C-03-01 (that used the to-be-marketed-formulation) could be used to fulfill the *in vivo* BA/BE requirements under 21CFR320.

**Drug Substance and Drug Product**

Drug Substance:

Brimonidine Tartrate

<b>Empirical Formula</b>	$C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$
<b>Molecular Weight</b>	442.23
<b>Chemical Names</b>	- 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
<b>Appearance</b>	White to off-white, pale yellow to yellow powder or crystals
<b>Solubility</b>	freely soluble in water at the selected pH range of 3.0 to 4.0 without pH adjustment.
<b>Structure</b>	

Drug Product:

The formulation used in clinical trials (FID: 104110) (Table 3) is the same as the one intended for marketing.

**Table 3. Composition of Brimonidine Tartrate Ophthalmic Solution, 0.15% (FID<sup>a</sup> 104110).**

<b>Component</b>	<b>% w/v</b>	<b>Function</b>	<b>Compendial Status</b>
Brimonidine Tartrate	0.15	Active Ingredient	Non-compendial
POLYQUAD (Polyquatarnium-1)	0.001 <sup>b</sup>	Preservative	Non-compendial
Povidone			USP
Boric Acid			NF
Sodium Borate			NF
Calcium Chloride			USP
Magnesium Chloride			USP
Potassium Chloride			USP
Mannitol			USP
Sodium Chloride			USP
Sodium Hydroxide and/or Hydrochloric Acid			NF
Purified Water			USP

<sup>a</sup>FID = Formulation Identification Number

<sup>b</sup>A \_\_\_\_\_

### Summary of Clinical Pharmacology and Biopharmaceutics Findings

The PK study, C-03-01, was conducted in healthy subjects. PK in patients was not determined. The disease state, open-angle glaucoma or ocular hypertension, is not expected to affect the absorption of the drug through the cornea and access to the general circulation. Therefore, PK study for brimonidine in healthy subjects is acceptable.

#### Study C-03-01

In this submission, the Sponsor conducted a single-center, double-masked, single-dose, 2-treatment period crossover pharmacokinetic study in healthy subjects to assess the extent of systemic exposure to brimonidine following a single topical dose (one drop to each eye in the morning) of Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN<sup>®</sup> P (brimonidine tartrate ophthalmic solution) 0.15%. There was a 7-day washout period between the two treatment periods. The pharmacokinetic parameters of brimonidine tartrate in 14 healthy subjects are shown in Table 4.

**Table 4. Mean Plasma Brimonidine Tartrate Pharmacokinetic Parameters (SD) Following a Single Topical Dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN<sup>®</sup> P (brimonidine tartrate ophthalmic solution) 0.15% in 14 Healthy Subjects**

Treatment	Plasma Brimonidine Tartrate Pharmacokinetic Parameters			
	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (hr)	AUC <sub>0-8</sub> (pg·hr/mL)	AUC <sub>0-inf</sub> (pg·hr/mL)
Brimonidine Tartrate Ophthalmic Solution, 0.15%	72.8 (18.9)	1.71 (0.70)	330 (82.2)	375 (89.3)
ALPHAGAN <sup>®</sup> P	74.3 (25.6)	1.65 (0.41)	329 (117)	372 (131)

The ratios and associated one-sided 90% CIs of brimonidine for both treatment groups are within 80% to 125% for C<sub>max</sub>, AUC<sub>0-8</sub>, and AUC<sub>0-inf</sub> (Table 5).

**Table 5. Geometric Means, Ratios, and One-Sided 90% Confidence Intervals for Brimonidine Pharmacokinetic Parameters (Reviewer's Analysis).**

		C <sub>max</sub> (pg/mL)	AUC <sub>0-8</sub> (pg·h/mL)	AUC <sub>0-inf</sub> (pg·h/mL)
Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test)	Geometric Mean	70.9	322	366
ALPHAGAN P (Reference)	Geometric Mean	69.7	307	345
Ratio (T/R) <sup>a</sup>		1.02	1.05	1.06
Upper 90% CL for Ratio <sup>b</sup>		1.18	1.20	1.22
Lower 90% CL for Ratio <sup>b</sup>		0.88	0.92	0.92

<sup>a</sup> Ratio (T/R) is defined as the ratio of the geometric means for Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test) relative to ALPHAGAN P (Reference).

<sup>b</sup> The upper and lower limits are based on two one-sided 90% confidence intervals.

The effect of gender on the pharmacokinetics of brimonidine following either oral or topical administration has

not been reported in the literature. In this study, females appeared to have higher mean  $C_{max}$  and AUC than male subjects. The differences between males and females in exposure were reduced when normalized to body weight.

When comparing exposure between test and reference treatments based on gender, mean  $C_{max}$  and AUC in male subjects appeared to be higher after the brimonidine tartrate treatment (test) than the Alphagan P treatment (reference) (Table 6). In contrast, mean  $C_{max}$  and AUC in female subjects appeared to be lower after the brimonidine tartrate treatment (test) than the Alphagan P treatment (reference) (Table 7). When the 90% CI (Test/Reference) analysis was performed based on gender, the 90% CI for male subjects were outside 80-125% for both  $C_{max}$  and AUC but included 100% (Table 6). These results suggest that the two products are equivalent (i.e. the 90% CI contains "100%") but that the underlying data are highly variable. This is borne out by the fact that the dataset included only 4 male subjects, thus the ability of the test to estimate the variability between the means (which is reflected in the wideness of the CI) was limited. For female subjects, the one-sided 90% CIs for both treatment groups in female subjects were within 80% to 125% for  $AUC_{0-8}$  and  $AUC_{0-inf}$ , but not for  $C_{max}$  (Table 7).

**Table 6. Geometric Means, Ratios, and One-Sided 90% Confidence Intervals for Brimonidine Pharmacokinetic Parameters-Male Subjects (N=4) (Reviewer's Analysis).**

		$C_{max}$ (pg/mL)	$AUC_{0-8}$ (pg*h/mL)	$AUC_{0-inf}$ (pg*h/mL)
Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test)	Geometric Mean	63.5	275	311
ALPHAGAN P (Reference)	Geometric Mean	47.2	202	227
Ratio (T/R) <sup>a</sup>		1.35	1.36	1.37
Upper 90% CL for Ratio <sup>b</sup>		0.96	0.96	0.85
Lower 90% CL for Ratio <sup>b</sup>		1.89	1.93	2.20

<sup>a</sup> Ratio (T/R) is defined as the ratio of the geometric means for Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test) relative to ALPHAGAN P (Reference).

<sup>b</sup> The upper and lower limits are based on two one-sided 90% confidence intervals.

**Table 7. Geometric Means, Ratios, and One-Sided 90% Confidence Intervals for Brimonidine Pharmacokinetic Parameters-Female Subjects (N=10) (Reviewer's Analysis).**

		$C_{max}$ (pg/mL)	$AUC_{0-8}$ (pg*h/mL)	$AUC_{0-inf}$ (pg*h/mL)
Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test)	Geometric Mean	74.1	343	391
ALPHAGAN P (Reference)	Geometric Mean	81.5	362	408
Ratio (T/R) <sup>a</sup>		0.91	0.95	0.96
Upper 90% CL for Ratio <sup>b</sup>		1.05	1.06	1.07
Lower 90% CL for Ratio <sup>b</sup>		0.79	0.84	0.86

<sup>a</sup> Ratio (T/R) is defined as the ratio of the geometric means for Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test) relative to ALPHAGAN P (Reference).

<sup>b</sup> The upper and lower limits are based on two one-sided 90% confidence intervals.

**Summary of Clinical Findings** (Please refer to Drs Rhea Lloyd (Medical) and Atiar Rahman (Statistics)'s reviews for details.)

In Study C-02-49, evaluations of intraocular pressure were done at 8 AM, 10 AM, and 5 PM in Week 1 (Baseline), Week 2, Week 6, and Month 3. The primary inference was based on the 95% CIs on differences in mean intraocular pressure between Brimonidine Tartrate and ALPHAGAN P arms at all evaluation time points. The equivalence was defined as the confidence limits at all post treatment observation time points had to be within  $\pm 1.5$  mmHg. In addition the majority of confidence limits had to be within  $\pm 1.0$  mmHg. Results showed that overall all calculated 95% CIs were within  $\pm 1.5$  mmHg and most of them were within  $\pm 1.0$  mmHg. In some subgroups e.g. age  $\geq 65$  years, Black race, Hazel or Green iris color and with certain diagnosis process the 95% CI of mean intraocular pressure were out side  $\pm 1.5$  mmHg at some or all visits. Most of these subgroups had small samples and hence the 95% CI interval tended to be wide, and conclusions are difficult to draw for subgroups. It was concluded that Brimonidine Tartrate Ophthalmic Solution, 0.15% showed equivalent effect to ALPHAGAN P.

**Analytical Methods for Study C-03-01**

Plasma concentrations of brimonidine were determined using a \_\_\_\_\_ ) method at \_\_\_\_\_. Analyte concentrations were calculated using \_\_\_\_\_ based on peak response ratios. The working range of the procedure was \_\_\_\_\_ pg/mL. The limit of quantitation for this assay was \_\_\_\_\_ pg/mL.

The details of analytical method and its validation were included in the validation report (TSLR03-039).

Assay Method and Sample preparation	
Analytical Site	
Internal Standard	
Matrix	Human plasma
Compound	Brimonidine
Mass to charge ratio (m/z)	691.0 $\rightarrow$ 450.0
Standard curve range	
QC levels	_____ and _____ pg/mL
Sensitivity (LOQ)	_____ pg/mL
Accuracy (% Theoretical)	_____ %
Intra-day	
Inter-day	_____ %



Tartrate Ophthalmic Solution, 0.15%, no dose adjustment is necessary when treating patients with hepatic or renal impairment.

**SIGNATURE OF REVIEWER:** Lei Zhang

Date \_\_\_\_\_

**SIGNATURE OF TEAM LEADER:** E. Dennis Bashaw

Date \_\_\_\_\_

**CC.:** HFD # [880]; **TL:** [Dennis Bashaw]; **DD:** [John Lazor];  
**DDDD** [Arzu Selen]

**Project Manager:** Raphael Rodriguez Date  
\_\_\_\_\_

**Appendix 1. Individual Study Review (Study C-03-01) (P. 10)**

**Appendix 2. OCPB Filing and Review Memo (P. 18)**

Appears This Way  
On Original

## Appendix 1. Individual Study Review (Study C-03-01)

*Study C-03-01: A Double-Masked, Single-Dose, Pharmacokinetic Crossover Study of Brimonidine Tartrate Ophthalmic Solution, 0.15% and ALPHAGAN<sup>®</sup> P (brimonidine tartrate ophthalmic solution) 0.15% in Healthy Subjects (Module 5, Vol. 1.1)*

---

**Study Period:** March 7, 2003 to March 27, 2003  
**Sample Analysis Period:** April 9, 2003 to April 14, 2003  
**Principle Investigators:** Lawrence A. Galitz, M.D.  
**Study Center:** SFBC International, Inc., 11190 Biscayne Boulevard, Miami, FL 33181 and 1460 N.E. 123rd Street

---

### PK Analytical Labs:

### Objectives:

To assess the extent of systemic exposure to brimonidine following a single topical dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN<sup>®</sup> P (brimonidine tartrate ophthalmic solution) 0.15% in healthy subjects.

**Study Design:** This study was a single-center, double-masked, single-dose, 2-treatment period crossover pharmacokinetic study in healthy subjects. The extent of systemic exposure to brimonidine following a single topical drop (in the morning) in each eye of either Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN<sup>®</sup> P was determined. There was a 7-day washout period between the two treatment periods. Subjects were randomized to the sequence of medication dosed. Based on the concentration of brimonidine (0.15%) and a 41.8  $\mu$ L drop volume, a single bilateral topical ocular dose of Brimonidine Tartrate Ophthalmic Solution, 0.15%, yielded 125.4  $\mu$ g of brimonidine. Based on a 49.6  $\mu$ L drop volume, a single bilateral topical ocular dose of ALPHAGAN P yielded 148.8  $\mu$ g of brimonidine. (*Reviewer's Note: The drop sizes were not recorded in the study, therefore, PK parameters were not adjusted based on doses. The variability in PK parameters among patients may partially reflect different drop volumes received.*)

**Subjects:** A total of 15 healthy subjects were enrolled. 14 subjects (4 males and 10 females) completed the study (Table 1.1). Subject 205 discontinued the study prior to the second treatment period, and therefore had no data available in treatment Period 2 for treatment comparison analyses. Thus, the 14 subjects who completed the study were used in the analyses for within-patient comparisons between the two treatment groups. Among the 14 subjects, one was Black, 5 were Caucasians, and 8 were Hispanic.

**Table 1.1. Baseline Demographic Characteristics (Subjects who completed the study).**

	Mean	Std	Min	Max
Age (y)	34.1	8.0	18	41
Weight (lb.)	151.5	2.5	111	198
Height (in.)	64.2	25.3	61	70

**Identity of Investigational Product:**

		Lot Numbers	Formulation Identification Numbers
Test Product	Brimonidine Tartrate Ophthalmic Solution, 0.15%	02-500445-1	104110
Reference Product	ALPHAGAN <sup>®</sup> P (brimonidine tartrate ophthalmic solution) 0.15%	02-500448-1	104368

**Sample Collection:**

After instillation of each study medication (on Day 1 and Day 9), blood samples were collected at the following post-dose time points for analysis of the pharmacokinetic plasma profile of brimonidine: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours.

**Sample Analysis:** Plasma concentrations of brimonidine were determined using a \_\_\_\_\_ method at \_\_\_\_\_ A \_\_\_\_\_

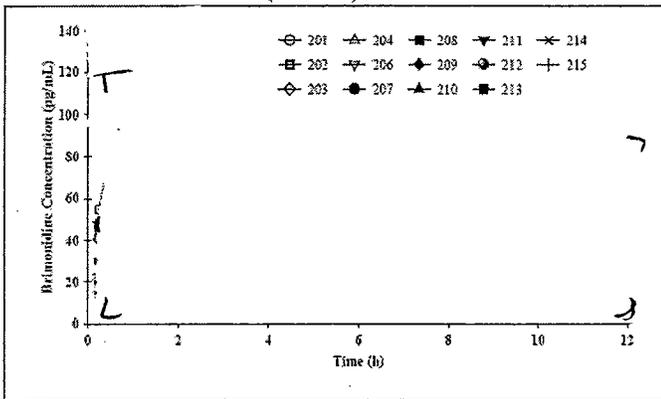
of brimonidine was used as the internal standard. The working range of the procedure was \_\_\_\_\_ pg/mL. The limit of quantitation for this assay was \_\_\_\_\_ pg/mL. The details of analytical method and its validation were included in the validation report \_\_\_\_\_ 13-039).

**Pharmacokinetic and Statistical Analysis:** Plasma concentration of brimonidine at each of the post-dose time points was determined for evaluation of  $C_{max}$ ,  $T_{max}$ ,  $t_{1/2}$ ,  $AUC_{0-12}$ , and  $AUC_{0-inf}$ .

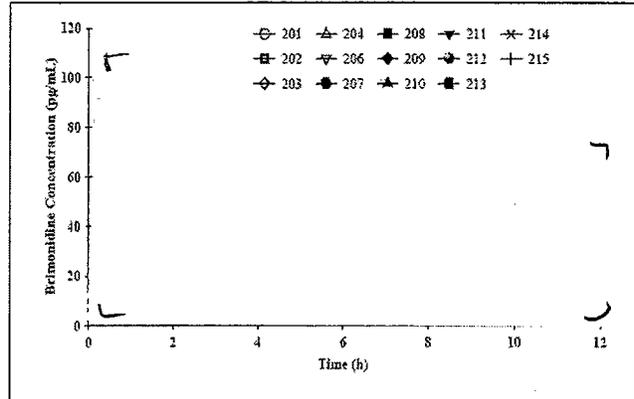
Geometric means, ratios of the geometric means, and two one-sided 90% confidence intervals on the ratios of the geometric means were presented for the  $C_{max}$ ,  $AUC_{0-12}$ , and  $AUC_{0-inf}$  parameters for the test and reference treatments (Alphagan P). (*Reviewer's Note: Because the Sponsor is proposing an every 8 hour dosing interval, we performed a new calculation of the AUC based on a 0-8hr observation period. 90% confidence interval was calculated on the ratio of geometric means.*)

**Pharmacokinetic Results:**

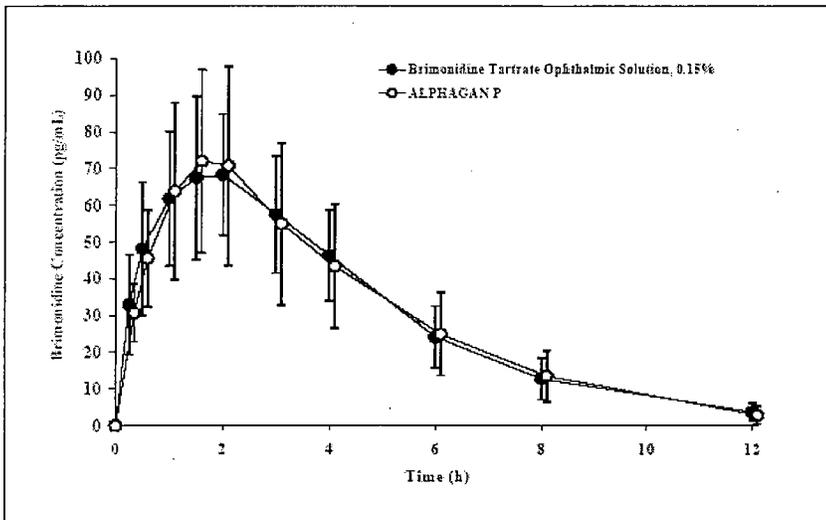
Data from 14 subjects were included in PK and statistical analysis. Figures 1.1 a and b show individual plasma concentration time profile (linear) of brimonidine after a single bilateral topical ocular dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% (a) or ALPHAGAN P (b) from the 14 subjects who completed the study. Mean data were shown in Figures 1.2.



**Figure 1.1a. Individual Brimonidine Plasma Concentrations in Healthy Subjects After A Single Bilateral Topical Ocular Dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% (Linear Plot).**



**Figure 1.1b. Individual Brimonidine Plasma Concentrations in Healthy Subjects After A Single Bilateral Topical Ocular Dose of ALPHAGAN P (Linear Plot).**



**Figure 1.2. Mean ( $\pm$  Std) Brimonidine Plasma Concentrations in Healthy Subjects After A Single Bilateral Topical Ocular Dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN P (Sample times are staggered for presentation purposes. Linear Plot.)**

Individual and mean  $C_{max}$ ,  $AUC_{0-8}$ ,  $AUC_{0-inf}$  values for brimonidine were listed in Appendix, Tables A1 and A2. The mean  $T_{max}$  values were  $1.71 \pm 0.70$  hours (range 0.50 to 3.00 hours) and  $1.65 \pm 0.41$  hours (range 0.53 to 2.00 hours) for the Brimonidine Tartrate Ophthalmic Solution, 0.15% and the ALPHAGAN P treatment groups, respectively. Mean terminal half-lives were around 2 hr for both treatment groups.

The geometric means of  $C_{max}$  and AUC ( $AUC_{0-8}$  and  $AUC_{0-inf}$ ) values for brimonidine, the ratios of these geometric means, and the one-sided 90% confidence intervals (CI) for single doses of Brimonidine Tartrate

Ophthalmic Solution, 0.15% (Test), and ALPHAGAN P (Reference) are provided in Table 1.2. (*Reviewer's Note: The Sponsor did not analyze data for AUC<sub>0-8</sub> in the initial study report. They were asked to do so during the review process. In their Jan 20, 2005 submission, AUC<sub>0-8</sub> data were provided. CI data from the Sponsor for C<sub>max</sub>, AUC<sub>0-8</sub>, and AUC<sub>0-inf</sub> were slightly different from what we obtained, possibly because the Sponsor calculated two one-sided 90% confidence limits as two-sided 80% confidence intervals in their SAS program.*)

Both our and Sponsor's analysis concluded that the ratios and associated one-sided 90% CIs of brimonidine for both treatment groups are within 80% to 125% for C<sub>max</sub>, AUC<sub>0-8</sub>, and AUC<sub>0-inf</sub> (Table 1.2).

**Table 1.2. Geometric Means, Ratios, and One-Sided 90% Confidence Intervals for Brimonidine Pharmacokinetic Parameters (Reviewer's Analysis).**

		C <sub>max</sub> (pg/mL)	AUC <sub>0-8</sub> (pg*h/mL)	AUC <sub>0-inf</sub> (pg*h/mL)
Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test)	Geometric Mean	70.9	322	366
ALPHAGAN P (Reference)	Geometric Mean	69.7	307	345
Ratio (T/R) <sup>a</sup>		1.02	1.05	1.06
Upper 90% CL for Ratio <sup>b</sup>		1.18	1.20	1.22
Lower 90% CL for Ratio <sup>b</sup>		0.88	0.92	0.92

**Results from the Sponsor:**

		C <sub>max</sub> (pg/mL)	AUC <sub>0-8</sub> (pg*h/mL)	AUC <sub>0-inf</sub> (pg*h/mL)
Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test)	Geometric Mean	70.9	322	366
ALPHAGAN P (Reference)	Geometric Mean	69.7	307	346
Ratio (T/R) <sup>a</sup>		1.02	1.05	1.06
Upper 90% CL for Ratio <sup>b</sup>		1.19	1.24	1.25
Lower 90% CL for Ratio <sup>b</sup>		0.869	0.888	0.894

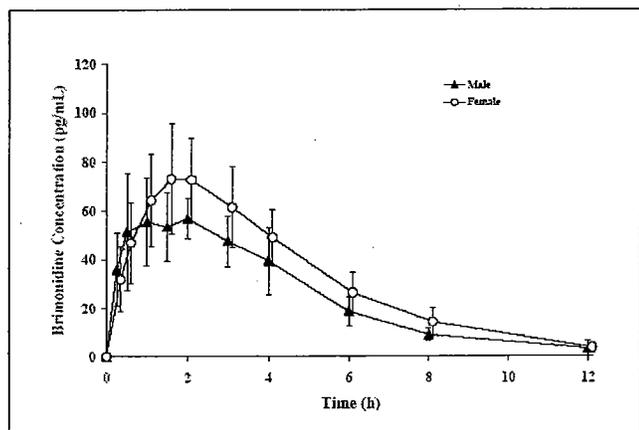
<sup>a</sup> Ratio (T/R) is defined as the ratio of the geometric means for Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test) relative to ALPHAGAN P (Reference).

<sup>b</sup> The upper and lower limits are based on two one-sided 90% confidence intervals.

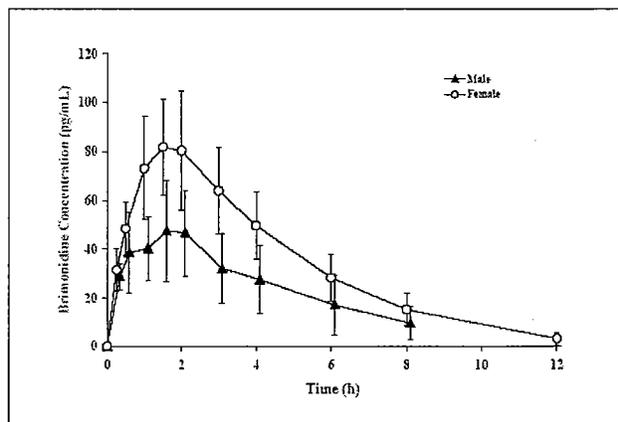
**Gender Effect:**

Although the study was not designed to assess gender differences and there were only 4 male subjects vs. 10 female subjects, the Sponsor conducted additional analyses to examine treatment differences by gender.

The mean plasma brimonidine concentration-time profiles for the 4 male and 10 female subjects following a single bilateral topical ocular dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% and ALPHAGAN P are presented in Figures 1.3a and 1.3b. Mean plasma brimonidine concentrations were higher in females than in males. The mean difference was larger for the ALPHAGAN P treatment group. When normalized to 70 kg body weight (plasma concentration \* body weight in kg/70 kg), these differences in plasma concentration were reduced (data not shown).



**Figure 1.3a. Mean ( $\pm$  Std) Brimonidine Plasma Concentrations in Healthy Male (N=4) and Female (N=10) Subjects After A Single Bilateral Topical Ocular Dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% (Sample times are staggered for presentation purposes.)**



**Figure 1.3b. Mean ( $\pm$  Std) Brimonidine Plasma Concentrations in Healthy Male (N=4) and Female (N=10) Subjects After A Single Bilateral Topical Ocular Dose of ALPHAGAN P (Sample times are staggered for presentation purposes.)**

When comparing exposure between test and reference treatments based on gender, mean  $C_{max}$  and AUC in male subjects appeared to be higher after the brimonidine tartrate treatment (test) than the Alphagan P treatment (reference) (Table 1.3). Subject 203 (male) had the biggest difference between the Brimonidine Tartrate Ophthalmic Solution, 0.15% and ALPHAGAN P treatment groups (Appendix, Tables A1 and A2) which may be due to loss of part of the dose. Lower exposure from Subject 203 in the Alphagan P treatment arm may contribute partly to the difference observed. When data from Subject 203 was excluded, the mean  $C_{max}$  and AUC in male subjects were still higher after the brimonidine tartrate treatment than the Alphagan P treatment, but the differences were smaller (Table 1.3).

**Table 1.3. Mean  $\pm$  Std Brimonidine Pharmacokinetic Parameters in Male Healthy Subjects After A Single Bilateral Topical Ocular Dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN P (N=4).**

Pharmacokinetic Parameters	Brimonidine Tartrate Ophthalmic Solution, 0.15% (N=4)	ALPHAGAN P (N=4)	Brimonidine Tartrate Ophthalmic Solution, 0.15% (N=3), exclude Subject 203	ALPHAGAN P (N=3), exclude Subject 203
$C_{max}$ (pg/mL)	64 $\pm$ 8.9	50 $\pm$ 20	67 $\pm$ 8.5	57 $\pm$ 18
AUC <sub>0-8</sub> (pg*h/mL)	278 $\pm$ 50.6	218 $\pm$ 91.4	295 $\pm$ 46.6	252 $\pm$ 73
AUC <sub>0-inf</sub> (pg*h/mL)	313 $\pm$ 46.1	248 $\pm$ 113	324 $\pm$ 49.8	292 $\pm$ 89

In contrast, mean  $C_{max}$  and AUC in female subjects appeared to be lower after the brimonidine tartrate treatment (test) than the Alphagan P treatment (reference) (Table 1.4).

**Table 1.4. Mean ± Std (range) Brimonidine Pharmacokinetic Parameters in Female Healthy Subjects After A Single Bilateral Topical Ocular Dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN P (N=10).**

Pharmacokinetic Parameters	Brimonidine Tartrate Ophthalmic Solution, 0.15% (N=4)	ALPHAGAN P (N=4)
C <sub>max</sub> (pg/mL)	76 ± 21	84 ± 21
AUC <sub>0-8</sub> (pg*h/mL)	351 ± 85	374 ± 96
AUC <sub>0-inf</sub> (pg*h/mL)	400 ± 92	421 ± 106

The geometric means of C<sub>max</sub> and AUC (AUC<sub>0-8</sub> and AUC<sub>0-inf</sub>) values, the ratios of these geometric means, and the one-sided 90% confidence intervals (CI) for single doses of Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test), and ALPHAGAN P (Reference) were reanalyzed based on gender. There were only 4 male subjects, and it was underpowered to determine bioequivalence between treatments in males. The data are listed in Table 1.5. 90% CI for C<sub>max</sub> and AUC (AUC<sub>0-8</sub> and AUC<sub>0-inf</sub>) were outside 80-125% but included 100%. For female subjects, 90% CI for AUC<sub>0-8</sub> and AUC<sub>0-inf</sub> were within 80-125% but C<sub>max</sub> was outside 80-125% range (Table 1.6).

**Table 1.5. Geometric Means, Ratios, and One-Sided 90% Confidence Intervals for Brimonidine Pharmacokinetic Parameters-Male Subjects (Reviewer's Analysis).**

		C <sub>max</sub> (pg/mL)	AUC <sub>0-8</sub> (pg*h/mL)	AUC <sub>0-inf</sub> (pg*h/mL)
Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test)	Geometric Mean	63.5	275	311
ALPHAGAN P (Reference)	Geometric Mean	47.2	202	227
Ratio (T/R) <sup>a</sup>		1.35	1.36	1.37
Upper 90% CL for Ratio <sup>b</sup>		0.96	0.96	0.85
Lower 90% CL for Ratio <sup>b</sup>		1.89	1.93	2.20

<sup>a</sup> Ratio (T/R) is defined as the ratio of the geometric means for Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test) relative to ALPHAGAN P (Reference).

<sup>b</sup> The upper and lower limits are based on two one-sided 90% confidence intervals.

Appears This Way  
On Original

**Table 1.6. Geometric Means, Ratios, and One-Sided 90% Confidence Intervals for Brimonidine Pharmacokinetic Parameters-Female Subjects (Reviewer's Analysis).**

		<b>C<sub>max</sub></b> <b>(pg/mL)</b>	<b>AUC<sub>0-8</sub></b> <b>(pg*h/mL)</b>	<b>AUC<sub>0-inf</sub></b> <b>(pg*h/mL)</b>
Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test)	Geometric Mean	74.1	343	391
ALPHAGAN P (Reference)	Geometric Mean	81.5	362	408
Ratio (T/R) <sup>a</sup>		0.91	0.95	0.96
Upper 90% CL for Ratio <sup>b</sup>		1.05	1.06	1.07
Lower 90% CL for Ratio <sup>b</sup>		0.79	0.84	0.86

<sup>a</sup>Ratio (T/R) is defined as the ratio of the geometric means for Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test) relative to ALPHAGAN P (Reference).

<sup>b</sup>The upper and lower limits are based on two one-sided 90% confidence intervals.

**Summary:** The results of the present study indicate that there are no apparent differences in the mean pharmacokinetic parameters between Brimonidine Tartrate Ophthalmic Solution, 0.15% and ALPHAGAN P. After topical ocular dosing of 0.15% brimonidine solutions, the peak plasma concentrations were reached within 0.5 to 3 hours of administration, with a mean half-life of approximately 2 hours, consistent with the pharmacokinetics reported in the ALPHAGAN P product insert. The results from this study suggest that topical ocular dosing with Brimonidine Tartrate Ophthalmic Solution, 0.15% or ALPHAGAN P results in comparable systemic exposure of brimonidine. The ratios and associated one-sided 90% CIs of brimonidine for both treatment groups are within 30% to 125% for C<sub>max</sub>, AUC<sub>0-8</sub>, and AUC<sub>0-inf</sub>.

The effect of gender on the pharmacokinetics of brimonidine following either oral or topical administration has not been reported in the literature. This study only enrolled 4 male subjects. Preliminary analyses on PK parameters based on gender suggest that female had higher mean C<sub>max</sub> and AUC than male subjects. The ratios of geometric means of C<sub>max</sub> and AUC (AUC<sub>0-8</sub> and AUC<sub>0-inf</sub>) values, and the one-sided 90% confidence intervals (CI) for single doses of Brimonidine Tartrate Ophthalmic Solution, 0.15% (Test), and ALPHAGAN P (Reference) based on gender indicate that male subjects showed higher brimonidine exposure (both C<sub>max</sub> and AUC) after the brimonidine tartrate treatment than the Alphagan P treatment. However, there were only 4 male subjects and it was underpowered to determine bioequivalence between treatments in males. The one-sided 90% CIs of brimonidine for female subjects were within 80% to 125% for AUC<sub>0-8</sub>, and AUC<sub>0-inf</sub>, but not for C<sub>max</sub> (79%, 105%).

#### Appendix for Study C-03-01

**Table A1. Individual and Mean Plasma Brimonidine Pharmacokinetic Parameters in Healthy Subjects After A Single Bilateral Topical Ocular Dose of Brimonidine Tartrate Ophthalmic Solution, 0.15% (Reviewer's Analysis)**

<b>Subject No.</b> <b>(Gender)</b>	<b>C<sub>max</sub></b> <b>(pg/mL)</b>	<b>T<sub>max</sub> (h)</b>	<b>AUC<sub>0-8</sub></b> <b>(pg*h/mL)</b>	<b>AUC<sub>0-inf</sub></b> <b>(pg*h/mL)</b>	<b>t<sub>1/2</sub> (h)</b>
201 (M)	T				T
202 (F)					
203 (M)	L				L

204 (M)					
206 (M)					
207 (F)					
208 (F)					
209 (F)					
210 (F)					
211 (F)					
212 (F)					
213 (F)					
214 (F)					
215 (F)					
Mean	72.8	1.71	330	375	2.1
Std	18.9	0.70	82.2	89.3	0.6

**Table A2. Individual and Mean Plasma Brimonidine Pharmacokinetic Parameters in Healthy Subjects After A Single Bilateral Topical Ocular Dose of ALPHAGAN P (Reviewer's Analysis)**

Subject No. (Gender)	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (h)	AUC 0-8 (pg*h/mL)	AUC 0-inf (pg*h/mL)	t <sub>1/2</sub> (h)
201 (M)					
202 (F)					
203 (M)					
204 (M)					
206 (M)					
207 (F)					
208 (F)					
209 (F)					
210 (F)					
211 (F)					
212 (F)					
213 (F)					
214 (F)					
215 (F)					
Mean	74.3	1.65	329	372	2.0
Std	25.6	0.41	117	131	0.3

Appears This Way  
On Original

**Appendix 2. OCPB Filing and Review Memo**

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

General Information About the Submission				
	Information		Information	
NDA Number	21-764	Brand Name	TBD	
OCPB Division (I, II, III)	DPE III (HFD-880)	Generic Name	Brimonidine Tartrate	
Medical Division	DAAODP (HFD-550)	Drug Class	Selective alpha-2-adrenergic agonist	
OCPB Reviewer	Lei Zhang, Ph.D.	Indication(s)		
OCPB Team Leader	Dennis Bashaw, Pharm.D.	Dosage Form	0.15% Ophthalmic Solution	
		Dosing Regimen	Every 8 hours (one drop per affected eye)	
Date of Submission	4/27/2004	Route of Administration	Topical ocular	
Estimated Due Date of OCPB Review	1/15/2005	Sponsor	Alcon	
PDUFA Due Date	2/28/2005	Priority Classification	New Dosage Form (3-S)	
Division Due Date			IND 64,330	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			The sponsor requested a waiver of evidence of in vivo bioavailability or bioequivalence per 21CFR320.22(b)(1).
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:	X	1	1	Study C-03-01 (PK of Alphagan P was also studied), to-be-marketed formulation was used in this study
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

NDA 21-764  
0.15% Brimonidine Tartrate  
Ophthalmic Solution  
Original NDA Review

<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>	X			
<b>Total Number of Studies</b>		1	1	
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?	X	<ul style="list-style-type: none"> <li>A waiver of evidence of <i>in vivo</i> bioavailability or bioequivalence could not be granted under 21CFR320.22(b)(1). Because not all conditions cited under 21CFR320.22(b)(1) are met by the new product. Namely, although the new product is an ophthalmic solution containing the same active ingredient at the same concentration as the approved product, Alphagan P, it contains different inactive ingredients.</li> <li>Study C-03-01 could be used to fulfill the <i>in vivo</i> BA/BE requirements under 21CFR320. The acceptability of the study results to support approval of this new product is a review issue.</li> <li>Please provide raw PK data from Study C-03-01 in SAS format.</li> </ul>		
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> <li>Can waiver be granted under 21CFR320.22(b)(1)?</li> <li>If not, what information is needed from Sponsor to fulfill the requirement under 21CFR320?</li> </ul>		
Other comments or information not included above		This is a 505 (b)(2) application. The reference product is Alphagan® P (NDA 21-262).		
Primary reviewer Signature and Date		Lei Zhang, 6/21/2004		
Secondary reviewer Signature and Date		Dennis Bashaw, 6/21/2004		

Appears This Way  
On Original

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

/s/  
-----

Lei Zhang  
2/7/05 10:37:25 AM  
BIOPHARMACEUTICS

Dennis Bashaw  
2/7/05 11:32:51 AM  
BIOPHARMACEUTICS

Appears This Way  
On Original