CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-764

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21-764/N-000
Drug Name:	Brimonidine Tartrate Ophthalmic Solution 0.15%
Indication(s):	Reduction of intraocular pressure
Applicant:	Alcon Research, Ltd.
	6201 South Freeway, Fort Worth, Texas 76134-2099
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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

In this submission the sponsor included a report of a Phase 3 study to evaluate the efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% in terms of reduction in intraocular pressure. The primary objective was to establish equivalency in the safety and efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% to those of ALPHAGAN P administered three times daily in patients with open-angle glaucoma or ocular hypertension.

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. Following the protocol, in order to demonstrate equivalence, the confidence limits at all post treatment observation time points had to be within ± 1.5 mmHg. In addition the majority of confidence limits had to be within ± 1.0 mmHg.

Results showed that overall all calculated 95% CIs were within ± 1.5 and most of them were within ± 1.0. In some subgroups e.g. age ≥65 years, Black race, Hazel or Green iris color and with certain diagnosis process the 95% CI of mean intraocular pressure were out side ±1.5 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.

From the results of the submitted study, and based on above mentioned criteria this reviewer concludes that Brimonidine Tartrate Ophthalmic Solution, 0.15% showed equivalent effect to ALPHAGAN P.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this submission the sponsor included a report of a Phase 3 study. There were two arms of this study namely; Brimonidine Tartrate Ophthalmic Solution, 0.15% and ALPHAGAN P administered three times daily in patients with open-angle glaucoma or ocular hypertension. The primary efficacy end point was mean reduction in intraoculat pressure.

1.3 STATISTICAL ISSUES AND FINDINGS

The study did not have a placebo arm. In the absence of a placebo arm it is difficult to evaluate the validity of the study. The sponsor mentioned that in long-term studies of patients with glaucoma, a disease that can cause irreversible loss of vision, the use of a placebo group was unethical. In such a situation alternatively we can compare the results with the historical data. The sponsor did not provide such data. In stead the sponsor provided results from two other ALPHAGAN P studies and claimed that the present study showed similar results as the historical ALPHAGAN P study.

2 INTRODUCTION

2.1 OVERVIEW

In this NDA the sponsor submitted data to support their claim that the use Brimonidine Tartrate Ophthalmic Solution, 0.15% is safe and efficacious for the treatment of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

The Brimonidine Tartrate Ophthalmic Solution, 0.15% clinical development plan was reviewed with the FDA at an End-of-Phase II meeting on January 29, 2003 to confirm the appropriateness of the clinical study designs, selection of comparative agents and total number of patients to be included in the overall plan. Pursuant to discussions with the FDA, the Phase III clinical plan consisted of a single multicenter, safety and efficacy study (C-02-49). The study was designed as an equivalence trial to compare Brimonidine Tartrate Ophthalmic Solution, 0.15% (dosed three-times-daily) with ALPHAGAN P (dosed three-times-daily).

2.2 DATA SOURCES

The submission was in hard copies. Submitted data was stored in folder `\\Cdsesub1\n21764\N_000\2004-06-28\C0249\` in the FDA's Electronic Document Room (EDR). The data quality of the submission was within acceptable limit.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY # C-02-49

Title: "A Three-Month, Randomized, Double-Masked, Parallel Group, Primary Therapy Study with a Planned Nine Month Extension of the Safety and IOP-Lowering Efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% Compared to ALPHAGAN P, 0.15% in Patients with Open Angle Glaucoma or Ocular Hypertension."

3.1.1.1 Design and Objectives

This was a prospective, randomized, multi-center (66 sites), double masked, parallel group, active controlled trial. Following the successful entry criteria the patients were assigned to one of the two treatment groups namely, Brimonidine Tartrate Ophthalmic Solution, 0.15% and ALPHAGAN P. Both of the solutions were applied three times daily (TID). The treatment assignment was performed following a pre-designed randomization procedure.

The study was prospectively designed to provide primary efficacy results based on data through the 3-month with visits at Week 1 (Baseline), Week 2, Week 6, and Month 3 at 8 AM, 10 AM, and 5 PM. The study was also prospectively designed to extend beyond the 3-month visit, with additional follow-up primarily for safety evaluation at Months 6, 9, and 12.

Patients of any race, two years of age or older and of either sex, diagnosed with open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension. For

each qualifying eye, the patients must have the mean IOP from 22 to 36 mmHg at 8 AM in both Eligibility 1 and 2 Visits.

The primary objective of the study was to compare the safety and efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% (0.001% polyquaternium-1 as preservative) to those of ALPHAGAN P (brimonidine tartrate ophthalmic solution), 0.15% administered three-times daily in patients with open-angle glaucoma or ocular hypertension.

3.1.1.2 Primary Efficacy Endpoint

The primary efficacy parameter was the mean IOP in the patient's worse eye measured at the 8 AM, 10 AM and 5 PM time points on Month 3. A mean IOP was calculated for each eye using the average of two consecutive measurements. If the two measurements for the same eye differed by more than 4 mmHg, a third measurement was taken and the two IOP measurements closest to each other were used.

If only one of a patient's eyes was dosed, the dosed eye was selected for analysis. If both of a patient's eyes were dosed, the worse eye was considered in the analysis, which was defined as:

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

3.1.1.3 Secondary Efficacy endpoint

Secondary efficacy measures was percentage of patients whose IOP reached a target level, e.g. the percentage of patients with IOP <18 mmHg.

3.1.1.4 Patient Analyzed

Intent-to-Treat Population: The intent-to-treat (ITT) population included all randomized patients who received study medication and had at least one on-therapy study visit.

Safety Population: All patients who received at least 1 administration of study medication comprised the safety population.

Per-Protocol Population: All patients who received study medication had at least one on-therapy study visit and satisfied protocol criteria were included in the per protocol population.

3.1.1.5 Disposition of Patients, Demography

Disposition and demographic characteristics of ITT patients is given in Table 1 and 2, respectively in the appendix. A total of eight hundred and forty two patients were randomized to one of two treatment groups. All 842 patients received study medication and all were included in the safety analysis. Of the 842 randomized patients, 18 discontinued the study prior to collection of any on-therapy study visit data; therefore, 824 patients were included in the ITT analysis. Fifty-eight patients

were excluded from the per protocol analysis: the 18 patients with no on-therapy study visit data, and 40 patients due to protocol violations. The violations included use of steroids (n=23), non-qualifying IOP (n=9), non-compliance (n=5), use of contraindicated anti-hypertensive medications (n=2), and missing baseline IOP data (n=1).

The mean age was 62.9 years ranging from 24 to 91 years. The frequency and percentages of patients by race were 581 (70.5%) Caucasian, 154 (18.7%) Black, 80 (9.7%) Hispanic, 4 (0.5%) Asian, and 5 (0.6%) Others. Irish colors were brown (443 patients, 53.8%), hazel (115 patients 14.0%), blue (228 patients, 27.7%), green (29 patients, 3.5%), and gray (9 patients, 1.1%). Four hundred ninety five patients (60.1%) were diagnosed with open-angle glaucoma, 313 (38.0%) with ocular hypertension, 10 (1.2%) with pigmentary glaucoma, and 6 (0.7%) with pseudoexfoliative glaucoma. There were no significant differences among the treatment groups in demographic or baseline characteristics.

Baseline IOP is displayed in Table 3 in the appendix. No significance difference was observed between treatment groups.

3.1.1.6 Sponsor's Analysis of Primary Efficacy Data

In the protocol, for the primary efficacy endpoint (difference in IOP between Brimonidine Tartrate and ALPHAGAN P arms), the sponsor proposed an analysis using a repeated measure analysis of variance. However, in the report the sponsor included results from test of equivalence and 95% two-sided confidence intervals for the treatment group difference based on analysis of variance at each individual visit and time point. The primary inference for the test of equivalence was based upon the per-protocol data set. In order to demonstrate equivalence, all of the confidence limits must have been within ± 1.5 mmHg; the margin of clinical relevance as was used for sample size justification. In addition the majority of confidence limits must have been within ± 1.0 mmHg. Since at all confidence limits the 95% CI had to be within ± 1.5 mmHg (union-intersection) no adjustment for multiple testing was necessary. Descriptive statistics were calculated for IOP, change from baseline IOP, and percent change from baseline IOP.

For the ITT data analysis, the last IOP observation was carried forward for missing visit. For the missing IOP at a visit time, the most recently measured IOP for that time of the day was used to impute the value. If a patient discontinued from the study, the last IOP measurement for each time of the day was carried forward to replace the IOP measurements for the missing value at the same time of the day.

Reviewer's comment: For the analysis of difference in IOP, the division's preference is to analyze the data separately at each visit and demonstrate equivalence using the criteria stated in the previous paragraph i.e. all confidence limits be within ± 1.5 mmHg and the majority of confidence limits be within ± 1.0 mmHg.

3.1.1.7 Sample size calculation

The sample size of 750 patients was calculate to ensure that at least 650 evaluable patients (325 per treatment group) were followed for three months, at least 600 patients (300 per treatment group) were followed for six months. With 325 patients per group, there was at least 99% coverage probability that a 95% two-sided CI would fall within ± 1.5 mmHg and at least 90% coverage probability that a 95% two-sided CI would fall within ± 1.0 mmHg. The sample size estimate was based upon a standard deviation for IOP of 3.5 mmHg and a 5% chance of a Type I error.

3.1.1.8 Sponsor's Results and Conclusions

Sponsor's analysis results are presented in Table 4 and displayed in Figure 1 in the appendix. The sponsor's result demonstrated that in per-protocol population Brimonidine Tartrate Ophthalmic Solution 0.15% and ALPHAGAN P produce equivalent IOP lowering efficacy, specifically all of the 95% two-sided confidence limits were within ± 1.5 mmHg and most were within ± 1.0 mmHg. Moreover, the largest value for either the upper or lower 95% confidence limit was 1.2 mmHg. The per-protocol results were confirmed in the intent-to-treat analysis, in which all 95% confidence limits were also within ± 1.5 mmHg. Results of ITT population is given in Table 5 and displayed in Figure 2 in the appendix.

Results of sponsor's analysis of secondary efficacy endpoints in paired eye population

Patients were considered to have a clinically relevant response to treatment if their IOP decreased to less than 18 mmHg. When evaluated at each visit, up to 59% of patients in the Brimonidine Tartrate ophthalmic solution, 0.15% group and up to 62% of patients in the ALPHAGAN P group had IOP of less than 18 mmHg. Results for per-protocol and ITT population are given in Tables 10 and 11, respectively.

3.1.1.9 Reviewer's Findings and Conclusions

The sponsor described in the statistical analysis section that they analyzed the data using the LOCF method for missing value, however, their analysis results showed different sample sizes at different time points. Therefore, in sponsor's analysis LOCF might not have been applied appropriately. This reviewer reanalyzed the LOCF data using the methodology described by the sponsor in the study report. Results of this reviewer's analysis of per-protocol and ITT population are given in Tables 6 and 7, respectively. This reviewer's results differed slightly from those of the sponsor's, however the general conclusion remains the same i.e. in per-protocol population all of the 95% two-sided confidence limits were within ± 1.5 mmHg and most were within ± 1.0 mmHg. Similar results were also found from the ITT population.

There were 187 (about 22%) discontinued patients during the study period. In their analysis, the sponsor used the last observation carried forward (LOCF) method to impute the missing values. To verify the sensitivity of the missing values, in addition to the method of LOCF, this reviewer also analyzed the data using the baseline value carried forward (BOCF). Results of this analysis in per-protocol and ITT population are given in Tables 8 and 9, respectively. Results of this analysis lead to similar conclusion as was drawn from LOCF analysis.

Following the original statistical analysis plan, this reviewer also performed an analysis using the repeated measure analysis using treatment, evaluation timepoint, and center as factors. Results did not show any statistically significant difference between the two treatment groups. Same analysis was also repeated using additional factor for treatment-by-center interaction. The results did not show statistically significant treatment-by- center interaction ($p=0.18$). The treatment-by-center interaction was also tested separately for each visit. The results also did not show any statistically significant treatment-by-center interaction at any visit ($p>0.21$).

Comparing results from Tables 6, 7, 8 and 9 and following the equivalency criteria described in the protocol this reviewer concludes that Brimonidine Tartrate Ophthalmic Solution, 0.15% showed equivalent effect to ALPHAGAN-P 0.15% in lowering the intra ocular pressure.

3.2 EVALUATION OF SAFETY

3.2.1 SPONSOR'S ANALYSIS OF SAFETY DATA

The sponsor's analysis showed that generally, the adverse events reported were non-serious, mild to moderate and often resolved without treatment. Adverse events were similar between treatment groups, not age-dependent. The most frequent adverse events were those associated with allergic conjunctivitis – ocular hyperemia, conjunctivitis, allergic reaction, ocular follicles, and ocular pruritus. No treatment-related serious adverse events were reported. There was one death reported. The occurrence rates of most frequent adverse events are given in Table 12 in the appendix.

3.2.2 REVIEWER'S ANALYSIS OF SAFETY DATA

This reviewer did not perform any analysis on the safety data. This reviewer refers to the clinical review for safety analysis.

4 FINDINGS IN SPACIAL/SUBGROUP POPULATIONS

4.1.1 SPONSOR'S ANALYSIS OF SUB-GROUP POPULATION

The sponsor performed subgroup analysis by age (<65, ≥65 years), gender (M, F), race (Black, Caucasian, others), iris color (Brown, others), and diagnosis (Ocular hypertension, Open angle glaucoma, others). Sponsor's analysis did not show statistically significant interaction between treatment and any of the subgroup criteria. All interaction p-values were greater than 0.09.

4.1.2 REVIEWER'S ANALYSIS OF SUB-GROUP ANALYSIS

This reviewer's performed subgroup analysis in per-protocol population by age (<65, ≥65 years), gender (M, F), race (Black, Caucasian, others), iris color (Brown, others), and diagnosis. This reviewer's analysis showed that the 95% CI on difference of mean IOP in subgroup "age ≥65 years" at Week 2 time 8 hours was out side ±1.5. The sample sizes in this subgroup were 195 for ALPHAGAN P and 183 for Brimonidine Tartrate. The 95% CI on difference of mean IOP in subgroup of "Blacks" was outside ±1.5 in almost all visits. The sample sizes in this subgroup were 74 for ALPHAGAN P and 73 for Brimonidine Tartrate. Similar results were true for "Other races" subgroup. The sample sizes in this subgroup were 45 for ALPHAGAN P and 41 for Brimonidine Tartrate. The 95% CI on difference of mean IOP in subgroup of iris color "Hazel" was outside ±1.5 in all visits. The sample sizes in this subgroup were 59 for ALPHAGAN P and 51 for Brimonidine Tartrate. Similar results were true for iris color "Green" subgroup. The sample sizes in this subgroup were 19 for ALPHAGAN P and 19 for Brimonidine Tartrate. The 95% CI of mean IOP in subgroup of diagnosis code of "Open-Angle glaucoma" were outside ±1.5 at Week 2 time 8 hours and Week 12 time 8 hours. The sample sizes in this subgroup were 246 for ALPHAGAN P and 231 for Brimonidine Tartrate. Most of the 95% CI of mean IOP in subgroup by other diagnosis code were out side ±1.5 in all visits. The sample sizes in these subgroups were ≤5 in any of the two treatment groups.

Reviewer's comment: This reviewer understands that in the above-mentioned subgroups the sample sizes were small to very small, and hence the 95% CI interval tended to be wide. Therefore, the result may be due to small sample size and should interpreted along with clinical relevance.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In this submission the sponsor included a report of a Phase 3 study, namely Study #C-02-49 to evaluate the safety and efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% in terms of reduction in intraocular pressure (IOP). The primary objective was to establish equivalency in the safety and efficacy of Brimonidine Tartrate Ophthalmic Solution, 0.15% to those of ALPHAGAN P administered three-times daily in patients with open-angle glaucoma or ocular hypertension.

The primary inference for the test of equivalence was based on the per-protocol data set. In order to demonstrate equivalence, the 95% confidence limits on mean difference in IOP between Brimonidine Tartrate and ALPHAGAN P arms at all observation time points had to be within ± 1.5 mmHg, the margin of clinical relevance as was used for sample size justification. In addition the majority of the confidence limits must had to be within ± 1.0 mmHg.

5.2 CONCLUSIONS AND RECOMMENDATIONS

From the results of the submitted study, and based on the equivalence criteria proposed in the protocol this reviewer concludes that Brimonidine Tartrate Ophthalmic Solution, 0.15% showed equivalent effect to ALPHAGAN P.

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6 APPENDIX

Table 1
Disposition

	Number of Subjects		
	Brimonidine 0.15% N (%)	ALPHAGAN P N (%)	Total N (%)
Randomized	417 (49.5)	425 (50.5)	842
Included in safety evaluations	417 (100.0)	425 (100.0)	842 (100.0)
Included in intent-to-treat efficacy analysis	408 (97.8)	416 (97.9)	824 (97.9)
Included in per protocol efficacy analysis	387 (92.8)	397 (93.4)	784 (93.1)
Discontinued prematurely	95 (22.8)	92 (21.6)	187 (21.9)
-Inadequate control of IOP	15 (3.6)	19 (4.4)	34 (4.0)
-Adverse event	65 (15.6)	57 (13.4)	122 (14.5)
-Patient decision	7 (1.7)	3 (0.7)	10 (1.2)
- Lost to follow-up	1 (0.2)	3 (0.7)	4 (0.5)
- Non-compliance	2 (0.5)	2 (0.5)	4 (0.5)
- Other	5 (1.2)	8 (1.9)	13 (1.5)

Source: Table 10.1.-1 and 10.1.-2 of Sponsor's Analysis

Table 2
Demographic Statistics by Treatment Group
Intent-to-Treat Patients

	Total		Brimonidine 0.15%		ALPHAGAN P		
	N	%	N	%	N	%	p-value[a]
Total	824	100.0	408	49.5	416	50.5	
Age							
<65 years [b]	428	51.9	214	52.5	214	51.4	0.7720
≥65 years	396	48.1	194	47.5	202	48.6	
Age (≥ 65 years)							
≥65- <75 years	262	66.2	131	67.5	131	64.9	0.5726
≥75- <85 years	120	30.3	58	29.9	62	30.7	
≥85- <95 years	14	3.5	5	2.6	9	4.5	
≥95 years	0	0.0	0	0.0	0	0.0	
Sex							
Male	387	47.0	190	46.6	197	47.4	0.8209
Female	437	53.0	218	53.4	219	52.6	
Race							
Caucasian	581	70.5	289	70.8	292	70.2	0.9231
Black	154	18.7	76	18.6	78	18.8	
Asian	4	0.5	1	0.2	3	0.7	
Hispanic	80	9.7	40	9.8	40	9.6	
Other	5	0.6	2	0.5	3	0.7	
Iris Color							
Brown	443	53.8	216	52.9	227	54.6	0.8771
Hazel	115	14.0	54	13.2	61	14.7	
Green	29	3.5	15	3.7	14	3.4	
Blue	228	27.7	119	29.2	109	26.2	
Grey	9	1.1	4	1.0	5	1.2	
Diagnosis							
Ocular Hypertension	313	38.0	158	38.7	155	37.3	0.4034
Open-Angle Glaucoma	495	60.1	240	58.8	255	61.3	
Pigmentary Glaucoma	10	1.2	5	1.2	5	1.2	
Pseudoexfoliation Glaucoma	6	0.7	5	1.2	1	0.2	

[a] p-value from chi-square or Fisher's exact test.
[b] Although the study protocol allowed patients age 2 years and older, the minimum age for an enrolled patient was 24 years.
Source: Table 11.2.-2 of Sponsor's Analysis

Table 3 Baseline IOP Comparison
Intent-to-Treat Data

		8AM	10AM	5PM
Brimonidine Tartrate 0.15%	**Mean (mmHg)**	25.4	24.3	23.2
	Std	2.9	3.2	3.4
	N	408	408	408
	Min	16	16	11
	Max	36	36	35
ALPHAGAN P	**Mean (mmHg)**	25.7	24.3	23.5
	Std	3.0	3.3	3.3
	N	416	416	416
	Min	18	17	14
	Max	36	36	35

Source: Table 11.2.-3 of Sponsor's Analysis

Table 4
Mean IOP Comparison of Brimonidine Tartrate Ophthalmic Solution 0.15% and ALPHAGAN P
(Per-Protocol Population)

Treatment	Baseline			Week 2			Week 6			Month 3		
	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM
Brimonidine 0.15%												
N	387	387	387	383	382	368	374	371	365	348	347	343
Mean (mmHg)	25.4	24.3	23.2	20.7	17.8	17.1	20.9	17.8	17.3	20.7	17.8	16.9
ALPHAGAN P												
N	397	397	397	393	393	385	373	373	364	346	345	337
Mean (mmHg)	25.7	24.4	23.5	21.3	18.3	17.3	21.1	18.0	17.2	21.3	17.9	16.9
Difference	-0.3	-0.1	-0.3	-0.6	-0.5	-0.1	-0.2	-0.2	0.1	-0.6	-0.1	0.0
P-value	0.227	0.769	0.248	0.037	0.093	0.622	0.434	0.581	0.658	0.024	0.673	0.902
Upper 95% CI	0.2	0.4	0.2	0.0	0.1	0.4	0.3	0.4	0.7	-0.1	0.4	0.6
Lower 95% CI	-0.7	-0.5	-0.7	-1.1	-1.0	-0.7	-0.8	-0.7	-0.4	-1.2	-0.7	-0.5

Source: Table 11.4.1.-1 of Sponsor's Analysis

Table 5
Mean IOP Comparison of Brimonidine Tartrate Ophthalmic Solution 0.15% and ALPHAGAN P
(Intent-to-Treat Population)

Treatment	Baseline			Week 2			Week 6			Month 3		
	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM
Brimonidine 0.15%												
N	408	408	408	407	406	405	408	407	406	408	407	406
Mean (mmHg)	25.4	24.3	23.2	20.7	17.8	17.2	20.8	17.8	17.4	20.8	17.8	16.9
ALPHAGAN P												
N	416	416	416	416	411	409	416	411	406	416	411	409
Mean (mmHg)	25.7	24.3	23.5	21.2	18.2	17.3	21.1	17.9	17.2	21.2	17.9	16.9
Difference	-0.3	0.0	-0.3	-0.6	-0.5	-0.1	-0.3	-0.2	0.2	-0.4	-0.1	0.0
P-value	0.170	0.849	0.255	0.040	0.104	0.841	0.352	0.565	0.476	0.158	0.703	0.887
Upper 95% CI	0.1	0.4	0.2	0.0	0.1	0.5	0.3	0.4	0.7	0.2	0.4	0.5
Lower 95% CI	-0.7	-0.5	-0.7	-1.1	-1.0	-0.6	-0.8	-0.7	-0.3	-0.9	-0.7	-0.6

Source: Table 11.4.1.-2 of Sponsor's Analysis

Table 6
Mean IOP Comparison
(Per-Protocol Population, using LOCF for missing values)
Reviewer's Table

Treatment	Baseline			Week 2			Week 6			Month 3		
	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM
Brimonidine 0.15%												
N	387	387	387	387	387	387	387	387	387	387	387	387
Mean (mmHg)	25.2	24.1	23.0	20.7	17.9	17.4	20.9	17.8	17.4	20.9	17.8	17.0
SD	3.1	3.5	3.7	3.9	3.5	3.7	4.2	4.1	3.8	4.5	3.9	3.7
ALPHAGAN P												
N	397	397	397	397	397	397	397	397	397	397	397	397
Mean (mmHg)	25.4	24.2	23.4	21.3	18.3	17.5	21.1	18.1	17.2	21.3	18.0	17.0
SD	3.1	3.5	3.7	4.1	3.8	3.9	4.2	4.0	3.4	4.5	4.3	3.9
Difference	0.3	0.1	0.4	0.6	0.5	0.1	0.2	0.3	-0.2	0.5	0.4	0.1
P-value	0.230	0.762	0.127	0.048	0.082	0.727	0.499	0.376	0.558	0.157	0.488	0.843
Upper 95% CI	0.7	0.6	0.9	1.1	1.0	0.6	0.8	0.8	0.373	1.1	0.8	0.6
Lower 95% CI	-0.2	-0.4	-0.1	0.0	-0.1	-0.4	-0.4	-0.3	-0.7	-0.2	-0.4	-0.5

Table 7
Mean IOP Comparison
(Intent-to-Treat Population, using LOCF for missing values)
Reviewer's Table

Treatment	Baseline			Week 2			Week 6			Month 3		
	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM
Brimonidine 0.15%												
N	408	408	407	408	408	408	408	408	408	408	408	408
Mean (mmHg)	25.1	24.1	23.0	20.7	17.8	17.2	20.8	17.8	17.4	20.8	17.8	16.9
SD	3.2	3.5	3.4	4.0	3.6	3.54	4.2	4.06	3.9	4.5	3.9	3.7
ALPHAGAN P												
N	416	416	416	416	416	416	416	416	416	416	416	416
Mean (mmHg)	25.5	24.1	23.3	21.2	18.3	17.4	21.1	18.0	17.3	21.2	17.9	17.1
SD	3.2	3.5	3.7	4.1	3.8	3.9	4.27	4.1	3.9	4.6	4.3	4.0
Difference	0.3	0.1	0.4	0.6	0.5	-0.2	0.3	0.2	-0.1	0.4	0.1	0.1
P-value	0.131	0.835	0.159	0.047	0.063	0.557	0.383	0.478	0.735	0.216	0.609	0.578
Upper 95% CI	0.8	0.5	0.9	1.1	1.0	0.7	0.8	0.8	0.437	1.0	0.7	0.7
Lower 95% CI	-0.1	-0.4	-0.1	0.0	-0.0	-0.4	-0.3	-0.3	-0.6	-0.2	-0.4	-0.4

Table 8
Mean IOP Comparison
(Per-Protocol Population, using BOCF for missing values)
Reviewer's Table

Treatment	Baseline			Week 2			Week 6			Month 3		
	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM
Brimonidine 0.15%												
N	387	387	387	387	387	387	387	387	387	387	387	387
Mean (mmHg)	25.2	24.1	23.0	20.7	17.9	17.4	20.9	18.0	17.6	21.1	18.4	17.5
SD	3.1	3.5	3.7	3.9	3.5	3.7	4.2	4.3	4.0	4.6	4.3	4.2
ALPHAGAN P												
N	397	397	397	397	397	397	397	397	397	397	397	397
Mean (mmHg)	25.4	24.2	23.4	21.3	18.3	17.5	21.1	18.3	17.7	21.8	18.7	17.8
SD	3.1	3.5	3.7	4.1	3.8	3.9	4.2	4.3	4.0	4.6	4.7	4.4
Difference	0.3	0.1	0.4	0.6	0.5	0.1	0.4	0.3	0.1	0.7	0.3	0.3
P-value	0.230	0.762	0.127	0.048	0.081	0.721	0.247	0.292	0.785	0.038	0.310	0.407
Upper 95% CI	0.7	0.6	0.9	1.1	1.0	0.6	0.9	0.9	0.6	1.3	1.0	0.9
Lower 95% CI	-0.2	-0.4	-0.1	0.0	-0.1	-0.4	-0.3	-0.3	-0.5	0.0	-0.3	-0.4

Table 9
Mean IOP Comparison
(Intent-to-Treat Population, using BOCF for missing values)
Reviewer's Table

Treatment	Baseline			Week 2			Week 6			Month 3		
	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM
Brimonidine 0.15%												
N	408	408	408	408	408	408	408	408	408	408	408	408
Mean (mmHg)	25.1	24.1	23.0	20.7	17.8	17.3	20.8	17.8	17.4	20.8	17.8	16.9
SD	3.2	3.5	3.7	4.0	3.6	3.6	4.2	4.1	3.9	4.5	3.9	3.7
ALPHAGAN P												
N	416	416	416	416	416	416	416	416	416	416	416	416
Mean (mmHg)	25.5	24.1	23.3	21.2	18.3	17.4	21.1	18.0	17.3	21.2	18.0	17.1
SD	3.2	3.5	3.7	4.1	3.8	3.9	4.27	4.1	3.9	4.6	4.4	4.0
Difference	0.3	0.1	0.4	0.6	0.5	0.1	0.3	0.2	-0.1	0.4	0.2	0.1
P-value	0.131	0.835	0.151	0.048	0.057	0.583	0.383	0.450	0.708	0.216	0.577	0.603
Upper 95% CI	0.8	0.5	0.9	1.1	1.0	0.6	0.8	0.8	0.4	1.0	0.7	0.7
Lower 95% CI	-0.1	-0.4	-0.1	0.0	-0.0	-0.4	-0.3	-0.3	-0.6	-0.2	-0.4	-0.4

Table 10

Frequency and Percent of Patients Who Achieved IOP<18 mmHg (Per-Protocol Population)

Treatment	Week 2			Week 6			Month 3		
	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM
Brimonidine 0.15%									
Total	383	382	368	374	371	365	348	347	343
N with IOP<18mmHg	79	189	215	77	183	206	75	168	202
% with IOP<18mmHg	20.6	49.5	58.4	20.6	49.3	56.4	21.6	48.4	58.9
ALPHAGAN P									
Total	393	393	385	373	373	364	346	345	337
N with IOP<18mmHg	60	173	225	70	181	206	65	178	209
% with IOP<18mmHg	15.3	44.0	58.4	18.8	48.5	56.6	18.8	51.6	62.0
P-Value	0.052	0.128	0.996	0.531	0.827	0.966	0.364	0.403	0.405

Source: Table 11.4.1.-7 of Sponsor's Analysis

Table 11

Frequency and Percent of Patients Who Achieved IOP<18 mmHg (ITT Population)

Treatment	Week 2			Week 6			Month 3		
	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM
Brimonidine 0.15%									
Total	407	406	405	408	407	406	408	407	406
N with IOP<18mmHg	87	204	230	86	202	224	85	194	236
% with IOP<18mmHg	21.4	50.2	56.8	21.1	49.6	55.2	20.8	47.7	58.1
ALPHAGAN P									
Total	416	411	409	416	411	409	416	411	409
N with IOP<18mmHg	63	183	237	77	201	230	80	210	244
% with IOP<18mmHg	15.1	44.5	57.9	18.5	48.9	56.2	19.2	51.1	59.7
P-Value	0.021	0.102	0.739	0.355	0.835	0.790	0.566	0.327	0.657

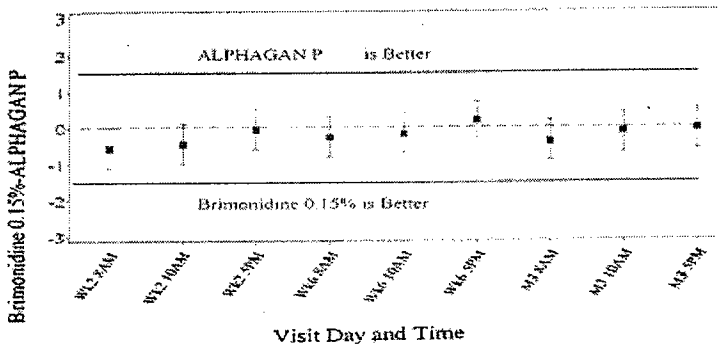
Source: Table 11.4.1.-8 of Sponsor's Analysis

Table 12
Most Frequent Ocular Adverse Events Related to Therapy Overall Safety Population

Adverse Event	Brimonidine 0.15% N=417		ALPHAGAN P N=425	
	n	%	n	%
Ocular Hyperemia	40	9.6	30	7.1
Conjunctivitis	30	7.2	28	6.6
-Allergic Conjunctivitis	26	6.2	27	6.4
-Viral Conjunctivitis	1	0.2	0	0
- Unspecified Conjunctivitis	3	0.7	1	0.2
Allergic Reaction	22	5.3	15	3.5
Conjunctival Follicles	19	4.6	13	3.1
Ocular Pruritus	13	3.1	11	2.6
Ocular Discomfort	6	1.4	9	2.1

Figure 1

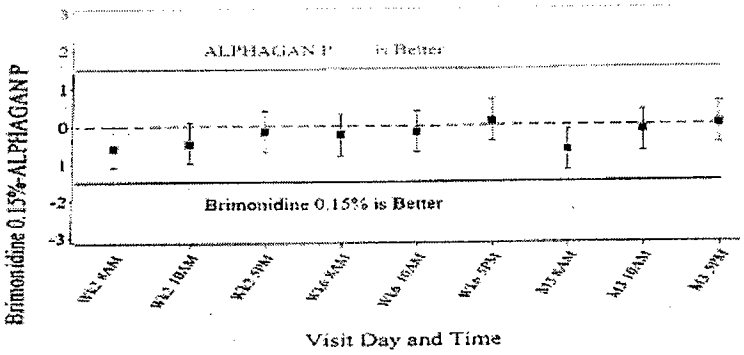
IOP Least Squares Means Differences Between Brimonidine Tartrate Ophthalmic Solution, 0.15% and ALPHAGAN P and 95% Confidence Intervals (Per Protocol Data)



Brimonidine 0.15% = Brimonidine Tartrate Ophthalmic Solution, 0.15%

Figure 2

IOP Least Squares Means Differences Between Brimonidine Tartrate Ophthalmic Solution, 0.15% and ALPHAGAN P and 95% Confidence Intervals (Intent-to-Treat Data)



Brimonidine 0.15% = Brimonidine Tartrate Ophthalmic Solution, 0.15%

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