CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-770

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:	21-770
Drug Name:	Brimonidine Purite Ophthalmic Solution 0.1%
Indication(s):	Reduction of intraocular pressure
Applicant:	Allergan Inc.
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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 Purite Ophthalmic Solution, 0.1% in terms of reduction in intraocular pressure. The primary objective was to establish equivalency in safety and efficacy of Brimonidine Purite Ophthalmic Solution, 0.1% to those of ALPHAGAN 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 Purite and ALPHAGAN arms at all evaluation time points. Following the protocol, in order to demonstrate equivalence, the confidence limits at all follow-up time points had to be within ± 1.5 mmHg. In addition the majority of confidence limits had to be within ± 1.0 mmHg.

Results show that overall the calculated 95% CIs at all follow-up time points were within ± 1.5 and most of them were within ± 1.0. In some subgroups e.g. age ≥65 years, Black race, and baseline IOP>25mmHg, the 95% CI on difference of mean intraocular pressure were out side ±1.5 at some or all follow-up time points. Most of these subgroups had small samples and therefore the 95% CI interval tended to be wide, and hence 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 Purite Ophthalmic Solution, 0.1% showed equivalent effect to ALPHAGAN.

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 Purite Ophthalmic Solution, 0.1% and ALPHAGAN (Brimonidine Tartrate Ophthalmic Solution, 0.2%) administered three times daily in patients with glaucoma or ocular hypertension. The primary efficacy end point was mean reduction in intraocular 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 the choice of an active control rather than placebo (vehicle) was appropriate because of the 12-month duration of study treatment. The sponsor further mentioned that in the present study the selection of patients, study endpoints, dose and duration of treatment, and concomitant therapy were in general similar to studies that established the safety and efficacy of ALPHAGAN and ALPHAGAN P.

2 INTRODUCTION

2.1 OVERVIEW

In this NDA the sponsor submitted a report of a study to support their claim that the use Brimonidine Purite Ophthalmic Solution, 0.1% is safe and efficacious for the treatment of intraocular pressure in patients with glaucoma or ocular hypertension.

The sponsor originally submitted this clinical development protocol of Brimonidine Purite Ophthalmic Solution, 0.1% to the FDA on March 6, 2003. In some subsequent communication the FDA suggested some revision of this protocol 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 (#190342-021). The study was designed as an equivalence trial to compare Brimonidine Purite Ophthalmic Solution, 0.1% with ALPHAGAN (Brimonidine Tartrate Ophthalmic Solution, 0.2%). Both dosed three-times-daily.

2.2 DATA SOURCES

The submission was electronic. Submitted data was stored in folder \\Cdsesub1\n21770\N_000\ 2004-05-27\crt\datasets 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 #** 190342-021

Title: "A Multi-Center, Double-Masked, Randomized, Parallel, Three Month Study (Plus 9-Month, Masked Extension) of the Safety and Efficacy of 0.1% Brimonidine Purite™ Ophthalmic Solution Dosed Three-Times Daily Compared with 0.2% Brimonidine Tartrate Ophthalmic Solution Dosed Three-Times Daily in Patients with Glaucoma or Ocular Hypertension."

3.1.1.1 Design and Objectives

This was a prospective, randomized, multi-center (27 sites), double masked, parallel group, active controlled study. Following the successful entry criteria the patients were assigned to one of the two treatment groups namely, Brimonidine Purite Ophthalmic Solution, 0.1% and ALPHAGAN. 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.

Qualified patients with chronic glaucoma or ocular hypertension were stratified into 2 groups namely; intraocular pressure ≤ 25 mm Hg or intraocular pressure > 25 mm Hg based on the Day 0/Hour 0 average intraocular pressure between two eyes. Within each stratum, patients were randomly assigned Brimonidine Purite® 0.1% or ALPHAGAN in an even allocation (1:1).

Patients were male or female of at least 18 years of age with ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy/iridectomy, pseudoexfoliative glaucoma or pigmentary glaucoma in both eyes. For each eye, the patients must have the mean IOP from 22 to 34 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 Purite Ophthalmic Solution, 0.1% to those of ALPHAGAN 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 intraocular pressure (IOP). All patients were treated bilaterally, and the average IOP from both eyes was used in the analyses. The primary efficacy parameter was measured at the 8 AM, 10 AM and 5 PM time points over 3 months. The IOP was measured using the Goldmann applanation tonometer. A 2-person IOP reading method was used at all visits, where one person adjusted the dial in a masked fashion and a second person read and recorded the value. The right eye was measured first. At least 2, and if necessary 3, consecutive measurements were taken to determine the IOP. If the first 2 measurements differed by ≤ 2 mm Hg, a third measurement was not required. If the 2 measurements differed by > 2 mm Hg, a third measurement was to be made.

3.1.1.3 Secondary Efficacy endpoint

IOP Analysis in the Per Protocol Population

The primary analysis of IOP at all follow-up time points was repeated for the per protocol population. An exception was that the interaction effect was not examined.

Analysis of IOP Adjusted for Central Corneal Thickness

In evaluating IOP, the observed measurements were also adjusted for differences among patients in pre-study central corneal thickness based on Ehlers' approach (Ehlers et al, 1975). Linear relationships of corneal thickness (T) with the difference (ΔIOP) between intraocular hypdrostatic pressures at 10 and 30 mm Hg and the corresponding IOP from the applanation tonometer readings were reported as follows:

$\Delta IOP_{10} = a + b\ T$ where $a = 30.97$ and $b = -60.26$
$\Delta IOP_{30} = c + d\ T$ where $c = 40.04$ and $d = -76.38$

These 2 linear equations were generalized for any observed IOP value (IOPy) as

$$\Delta IOPy = \{a + [(c-a)/(30-10)]\ [IOPy-10]\} + \{b + [(d-b)/(30-10)]\ [IOPy-10]\}\ T$$

The adjusted IOP value was then calculated for any observed IOP value (IOPy) as adjusted IOPy = IOPy + ΔIOPy.

The primary analysis of IOP at all follow-up time points was repeated for IOP adjusted for pre-study central corneal thickness.

Other efficacy analyses were of IOP change from baseline and adjusted IOP change from baseline. Both analyses were based on the ITT population. IOP change from baseline was defined as the follow-up IOP minus baseline IOP, calculated on the corresponding diurnal time points. For a given patient, the IOP change from baseline was calculated separately for each eye. The average of the changes from both eyes was used as the IOP change for the patient. The change in adjusted IOP was calculated similarly.

3.1.1.4 Patient Analyzed

Intent-to-Treat Population: The intent-to-treat (ITT) population included all randomized patients.

Safety Population: The safety population included all patients who received at least 1 administration of study medication.

Per-Protocol Population: The per-protocol (PP) population included all patients with no major protocol violation.

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 433 patients were enrolled in the study, with 215 patients randomized to Brimonidine Purite 0.1% and 218 patients to ALPHAGAN. In the ITT and safety populations, 81.1% (351/433) of patients completed month 3: 85.1% (183/215) in the Brimonidine Purite 0.1% group and 77.1% (168/218) in the ALPHAGAN group. In general, patient disposition in the per-protocol population was similar to that in the ITT and safety populations. Discontinued patients comprised 14.9% (32/215) of the Brimonidine Purite 0.1% group and 22.9% (50/218) of the ALPHAGAN group by the month 3 visit. A greater percentage of patients in the ALPHAGAN group discontinued for lack of efficacy and due to adverse events compared with the Brimonidine Purite 0.1% group. Most patients in each treatment group completed week 6: 94.0% (202/215) in the Brimonidine Purite 0.1% group and 89.4% (195/218) in the ALPHAGAN group.

The 2 treatment groups were comparable at baseline. In general, demographics in the per protocol population were similar to those in the ITT and safety populations. In the ITT population, the overall mean age was 62.4 years and ranged from 19 to 93 years. The population was 43.2% (187/433) males and 56.8% (246/433) females. The population was primarily Caucasian, 78.8% (341/433) with 11.3% (49/433) black. The most common iris colors were brown for 42.3% (183/433) and blue for 34.2% (148/433) of patients. Mean central corneal thickness was 565.6 microns and ranged from 448 to 661 microns. The ophthalmic diagnosis at study entry was chronic open-angle glaucoma for 64.4% (279/433) of patients, ocular hypertension for 33.5% (145/433), and mixed diagnosis (1 eye with glaucoma and the fellow eye with ocular hypertension) for 2.1% (9/433) of patients. No washout of pre-study glaucoma mediations was required for 31.6% (137/433) of patients. Washout was required for 68.4% (296/433) of patients, including 19.9% (86/433) for alpha-agonists, 19.4% (84/433) for prostaglandins, and 13.9% (60/433) for beta-blocking agents.
The most frequently reported conditions on medical history were musculoskeletal findings for 63.0% (273/433) of patients, post-menopausal for 61.0% (150/246) of females, gynecologic conditions for 60.0% (149/246) of females, and systemic hypertension for 54.3% (235/433) of patients. The most frequently reported conditions on ophthalmic history were cataract for 72.3% (313/433) of patients,

lid conditions for 46.4% (201/433), vitreal disease for 29.3% (127/433), and corneal disease for 27.7% (120/433) of patients.

Overall, 99.1% (429/433) of patients were taking one or more drugs prior to study start. The most frequently reported medications used prior to study start were ophthalmologicals for 65.1% (282/433) of patients, antiglaucoma preparations and miotics for 47.3% (205/433), other antiglaucoma preparations (i.e., latanoprost) for 30.5% (132/433), platelet aggregation inhibitors excluding heparin for 28.9% (125/433), and beta-blocking agents for 28.4% (123/433).

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

Sponsor's Methods for the primary efficacy analyses were described in the protocol. Secondary efficacy and safety analyses were outlined briefly in the protocol and detailed later in the analysis plan. The statistical analysis plan for the study was finalized prior to the 3-month database lock and unmasking. The following changes were made to the analyses listed in the study protocol based on the 20 October 2003 pre-NDA meeting with the FDA:

- The primary efficacy variable was changed from IOP adjusted for central corneal thickness to unadjusted IOP; adjusted IOP was changed to a secondary efficacy variable.
- For the FDA, equivalence was used to analyze the primary variable rather than the combined strategy of non-inferiority and superiority tests as was originally proposed.

In addition, the following change in analysis method was made:

- Ordinal categorical variables were analyzed using the Wilcoxon rank-sum test rather than the Cochran-Mantel-Haenszel (CMH) method stratified by site with modified ridit scores.

All data analyses were performed based on the observed data. The only exception was the analysis of mean IOP in the ITT population, in which missing values were imputed using the method of last observation carried forward (LOCF). If no follow-up visit data were collected, the baseline IOP was carried forward. For the analysis of IOP, the average from both eyes was used. In the case where data existed for only one eye, the collected data served as the IOP for that patient at that time point. With the exception of IOP, if day 0 data were missing and pre-study data existed, the pre-study data were used as baseline. For IOP, pre-study data were not used for missing IOP data at day 0. For patients who did not have central corneal thickness measured at the pre-study visit, the observed IOP was used in the analysis of adjusted IOP. Note that only 1 patient was missing the baseline corneal thickness.

The primary analysis was of IOP during the initial 3-month study period in the ITT population using a 2-way analysis of variance (ANOVA) model with fixed effects of treatment and investigator. Last observation carried forward (LOCF) was used to impute missing values. The equivalence of efficacy was tested at each time point. For equivalence tests, a confidence interval (CI) approach was used. A 2-sided CI was constructed based on the 2-way ANOVA model for the estimated difference in mean IOP (Brimonidine Purite 0.1% group minus ALPHAGAN group).

If the limits of the 95% CI were within ± 1.0 mm Hg at the majority of follow-up time points, and within ± 1.5 mm Hg at all follow-up time points, the Brimonidine Purite 0.1% treatment was to be declared equivalent to the ALPHAGAN treatment.

Also following the original analysis plan, if the upper limits of the 95% CI were less than +1.0 mm Hg at the majority of follow-up time points, and less than +1.5 mm Hg at all follow-up time points, the Brimonidine Purite 0.1% treatment was to be declared non-inferior to the ALPHAGAN treatment. Superiority was tested at each follow-up time point; the treatment group difference was considered statistically significant if the p-value was ≤ 0.05.

Potential treatment-by-investigator interaction was examined using a separate ANOVA model with fixed effects of treatment, investigator, and their interaction. Only investigators who enrolled at least 3 patients per treatment group were included. The interaction effect was considered statistically significant if the p-value was ≤ 0.05.

Reviewer's comment: The sponsor's choice of interaction test level of 0.05 is too stringent. There is no hard and fast rule for the choice of test level to test such interaction; however the division's general policy is to use a test level of at least 0.10.

3.1.1.7 Sample size calculation

The sample size estimate was based on a non-inferiority test of the difference between Brimonidine Purite 0.1% versus ALPHAGAN with respect to IOP. The calculation assumed a standard deviation of 3.9 mm Hg, power of 90%, and a non-inferiority margin of 1.5 mm Hg on a per visit/hour basis. A total of 384 patients were needed to complete at least 288 patients at 3 months, based on an anticipated dropout rate of 25%. Actual enrollment was 433 patients. A number of patients were in the washout period when the required sample size was reached and they were allowed to enroll in the study.

3.1.1.8 Sponsor's Results and Conclusions

Primary Endpoint:

At baseline in the ITT population, mean IOP was 24.7, 23.3, and 22.6 mm Hg at hours 0, 2, and 8 respectively, in the Brimonidine Purite 0.1% group and 24.7, 23.2, and 22.1 mm Hg respectively, in the ALPHAGAN group. There were no statistically significant differences between the 2 treatment groups at baseline.

During follow-up for the primary endpoint IOP, there were no statistically significant differences between the 2 treatment groups at any follow-up time point. The upper limit of the 95% CI was less than +1.0 mm Hg for all follow-up time points, and the lower limit was greater than -1.0 mm Hg for all but one (hour 2 month 3) follow-up time points. All CIs at all follow-up time points were within ±1.5 mm Hg. Thus both equivalence and non-inferiority of Brimonidine Purite 0.1% to ALPHAGAN were demonstrated. The Sponsor's analysis results are given in Table 4 in the appendix.

Secondary efficacy:

Intraocular Pressure Adjusted for Central Corneal Thickness

At baseline in the ITT population, mean IOP adjusted for central corneal thickness was 21.3, 20.0, and 19.2 mm Hg at hours 0, 2, and 8 respectively, in the Brimonidine Purite 0.1% group and 21.8, 20.3, and 19.2 mm Hg respectively, in the ALPHAGAN group. There were no statistically significant differences between the 2 treatment groups at baseline.

During follow-up, all lower confidence limits of the 95% lower confidence limits were below –1.0, with four were found to be below –1.5. Therefore, due to the above definition the two treatments were not equivalent. However, the mean adjusted IOP with Brimonidine Purite 0.1% was found to be non-inferior to ALPHAGAN in the ITT population. Brimonidine Purite 0.1% was also found to be superior to ALPHAGAN at hour 0 of week 2 and hours 2 and 8 of month 3 ($p \leq 0.047$). The sponsor's analysis results are given in Table 5 in the appendix.

Change from Baseline Intraocular Pressure

Mean change from baseline IOP ranged from -3.3 to -5.4 mm Hg at hours 0, 2, and 8 with Brimonidine Purite 0.1% and from -3.0 to -5.2 mm Hg with ALPHAGAN. Within each treatment group, the mean decreases from baseline IOP were statistically significant at each follow-up time point ($p < 0.001$). Brimonidine Purite 0.1% was superior to ALPHAGAN at hour 8 of month 3 ($p = 0.024$). There were no other statistically significant differences between the 2 treatment groups during follow-up.

Change from Baseline Intraocular Pressure Adjusted for Central Corneal Thickness

Mean change from baseline adjusted IOP ranged from -3.2 to -5.4 mm Hg at hours 0, 2, and 8 with Brimonidine Purite 0.1% and from -3.0 to -5.3 mm Hg with ALPHAGAN. Within each treatment group, the mean decreases from baseline IOP adjusted for central corneal thickness were statistically significant at each follow-up time point ($p < 0.001$). Brimonidine Purite 0.1% was superior to ALPHAGAN at hour 8 of month 3 ($p = 0.032$). There were no other statistically significant differences between the 2 treatment groups during follow-up.

Analysis of per-protocol population

At baseline in the per protocol population, mean IOP at hours 0, 2 and 8 were 24.7, 23.3, and 22.6 mm Hg respectively, in the Brimonidine Purite® 0.1% group and 24.7, 23.3, and 22.1 mm Hg respectively, in the ALPHAGAN group. There were no statistically significant differences between the 2 treatment groups at baseline. During follow-up, the mean IOP of the Brimonidine Purite 0.1% group was found to be equivalent, and also non-inferior to that of the ALPHAGAN group. The results of the sponsor's analysis are given in Table 6 in the appendix. There were no statistically significant differences between the 2 treatment groups at any of the follow-up time points.

The upper limit of the 95% CI was less than +1.0 mm Hg for the majority (7/9) of follow-up time points, and the lower limit was greater than -1.0 mm Hg for all (9/9) follow-up time points. All CIs were within ±1.5 mm Hg. Thus both equivalence and non-inferiority of Brimonidine Purite 0.1% to ALPHAGAN were demonstrated.

3.1.1.9 Reviewer's Findings and Conclusions

In order to verify sponsor's analysis results this reviewer reanalyzed the ITT 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 7 and 8, 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 at all follow-up time points were within ± 1.5 mmHg and most were within ± 1.0 mmHg. Similar results were also found from the ITT population. The results are also shown graphically in Figures 1 and 2 for per-protocol and ITT population, respectively.

There were 82 (about 19%) 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 9 and 10, respectively. Results of this analysis lead to similar conclusion as was drawn from LOCF analysis.

For further exploratory analysis this reviewer also performed an analysis using the repeated measure analysis using treatment, center, and observation time points as factors. Results did not show any statistically significant difference between the two treatment groups. Same analysis was also repeated using additional factor of the treatment-by-center interaction. Results did not show statistically significant treatment-by- center interaction. A second exploratory analysis was performed using the generalized linear model at each visit. Results showed no center by treatment interaction at any visit.

Frequencies and percentages who achieved IOP< 18 mmHg in per-protocol and ITT populations are given in Tables 11 and 12 in the appendix.

Comparing results from Tables 7, 8, 9, and 10 and following the equivalency criteria described in the protocol this reviewer concludes that Brimonidine Purite Ophthalmic Solution, 0.1% showed equivalent effect to ALPHAGAN in lowering the intraocular pressure.
The two treatment groups did not show any statistically significant difference in percentage of patients who achieved IOP< 18 mmHg.

3.2 EVALUATION OF SAFETY

3.2.1 SPONSOR'S ANALYSIS OF SAFETY DATA

All 433 patients enrolled in the study received at least 1 dose of study medication and were included in the safety analyses. The mean duration of treatment exposure was 87.8 days in the Brimonidine Purite 0.1% group and 84.1 days in the ALPHAGAN group. Most patients were exposed from 57 to 138 days.

Adverse events were reported for 50.2% (108/215) of patients in the Brimonidine Purite 0.1% group and 57.3% (125/218) in the ALPHAGAN group. The most frequently reported events (≥ 5% in either treatment group) were allergic conjunctivitis, conjunctival hyperemia, eye pruritus, and oral dryness. Statistically significant differences between the 2 treatment groups were noted for 3 individual adverse events namely, the incidences of oral dryness, asthenia and incidence of eye pain.

Oral dryness and asthenia were significantly lower in Brimonidine Purite 0.1% group than with ALPHAGAN group ($p \leq 0.020$), while the incidence of eye pain was significantly higher in Brimonidine Purite 0.1% group than in ALPHAGAN group ($p = 0.014$).

Treatment-related adverse events were reported for 26.0% of patients in the Brimonidine Purite 0.1% group and 38.5% in the ALPHAGAN group ($p = 0.005$). The most frequently reported ($\geq 5\%$ in either treatment group) treatment-related adverse events were allergic conjunctivitis, conjunctival hyperemia, and oral dryness. Statistically significant differences between the 2 treatment groups were noted for one individual treatment-related adverse event: the incidence of oral dryness which was significantly lower with Brimonidine Purite 0.1% than with ALPHAGAN ($p = 0.019$).

Adverse events led to premature discontinuation of the study prior to or at the month 3 visit were 8.8% in the Brimonidine Purite 0.1% group and 15.1% (33/218) in the ALPHAGAN group ($p = 0.044$). The most frequently reported event leading to discontinuation was allergic conjunctivitis.

Serious adverse events were reported for 5 patients in the Brimonidine Purite 0.1% group which were angina pectoris, coronary artery disorder, chest pain, cholecystitis, and bone fracture – cause unknown. Serious adverse events were reported for 4 patients in the ALPHAGAN group which were atrial fibrillation, cerebral ischemia with hypertension, cerebrovascular accident, and intestinal perforation. None of the events were considered treatment-related. No deaths occurred during the study.

Adverse events reported by greater than or equal to 2% of patients in either treatment group during the initial 3 months of the study are summarized in Table 13 in the appendix. Statistically significant differences between 2 treatment groups were noted for 3 individual adverse events namely, the incidences of oral dryness and asthenia which were significantly lower with Brimonidine Purite 0.1% than with ALPHAGAN ($p \leq 0.020$), and the incidence of eye pain which was significantly higher with Brimonidine Purite 0.1% than with ALPHAGAN ($p = 0.014$).

The majority of adverse events were mild to moderate in severity. The incidence of treatment related adverse events was 26.0% in the Brimonidine Purite 0.1% group and 38.5% in the ALPHAGAN group ($p = 0.005$). The most frequently reported ($\geq 5\%$ in either treatment group) treatment-related adverse events were allergic conjunctivitis, conjunctival hyperemia, and oral dryness.

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 did not perform any demographic subgroup analysis.

4.1.2 REVIEWER'S ANALYSIS OF SUB-GROUP ANALYSIS

This reviewer's performed subgroup analysis by age (<65, ≥65 years), gender (M, F), race (Black, Caucasian, others), iris color (Dark, Light), diagnosis and Day 0/Hour 0 IOP (≤25 mmHg, >25 mmHg) . This reviewer's analysis showed that in some groups, the 95% CI on difference of mean IOP at some follow-up time points were out side ±1.5. The following table shows such subgroups in the per-protocol population along with their corresponding 95% confidence intervals and sample sizes. The ITT population also showed similar results.

Title: Subgroups in Which the 95% Confidence Interval is outside ±1.5 in Per-Protocol Population

PP Population					95% Confidence Interval	
Sub-Group	Visit	Hour	Sample Size Brimo	ALPHA	Lower	Upper
Female	Week 0	8	118	116	-1.69	-0.11
Male	Week 2	0	87	92	-0.44	1.64
	Week 6	0	87	92	-072	1.54
	Month 3	2	87	92	-0.34	1.74
Age≥65	Week 0	8	117	109	-1.81	0.30
	Week 2	8	117	109	-1.56	0.59
	Month 3	2	117	109	-0.38	1.63
Iris Color Dark	Week 6	2	82	93	-1.75	0.24
	Month 3	0	82	93	-0.36	1.87
Iris Color Light	Week 0	8	123	115	-1.62	0.26
	Month 3	2	123	115	-0.25	1.54
Black	All visit Except:: Week 0 Week 6	All hours Hour 0 Hours 2, 8	25	24	All values < -1.5	All values >1.5
Day 0/Hour 0 IOP > 25	Week 0	8	66	65	-1.91	0.63
	Week 2	0	66	65	-0.66	1.77
	Week 2	8	66	65	-1.82	0.74
	Week 6	0	66	65	-0.52	2.03
	Week 6	2	66	65	-1.72	0.83
	Month 3	0	66	65	-0.40	2.46
	Month 3	2	66	65	-0.59	1.98
	Month 3	8	66	65	-0.81	1.59

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 the small sample size and should be interpreted carefully along with the 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 #190342-021 to evaluate the safety and efficacy of Brimonidine Purite Ophthalmic Solution, 0.1% in terms of reduction in intraocular pressure (IOP). The primary objective was to establish equivalency in the safety and efficacy of Brimonidine Purite Ophthalmic Solution, 0.1% to those of ALPHAGAN 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. Following the protocol, in order to demonstrate equivalence, the 95% confidence limits on mean difference in IOP between Brimonidine Purite and ALPHAGAN arms at all follow-up 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 had to be within ± 1.0 mmHg.

Results showed that in per-protocol population at all follow-up time points the 95% two-sided confidence limits were within ± 1.5 mmHg and most were within ± 1.0 mmHg. Similar results were also found in the ITT population. This reviewer's analysis showed that in some subgroups the 95% CI on difference of mean IOP at some follow-up time points were out side ±1.5. However, the sample sizes in these subgroups were small, and hence the 95% CI interval tended to be wide. Therefore, the result may be due to the small sample size.

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 Purite Ophthalmic Solution 0.1% showed equivalent effect to ALPHAGAN.

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Mathematical Statistician

Concur: Stan Lin, Ph.D.
Team Leader

cc:
Archival NDA 21-770
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HFD-550/Mr. Puglisi
HFD-725/ Chron
HFD-725/ Dr. Huque
HFD-725/ Dr. Lin
HFD-725/ Dr. Rahman
HFD-700/Dr. Anello

6 APPENDIX

Table 1
Disposition

	Brim P 0.1% (N=215)	Alphagan (N=218)	Total (N=433)
All Randomized Population	215	218	433
Completed Month 3	183 (85.1%)	168 (77.1%)	351 (81.1%)
Discontinued	32 (14.9%)	50 (22.9%)	82 (18.9%)
Lack of Efficacy	10 (4.7%)	13 (6.0%)	23 (5.3%)
Adverse Event	19 (8.8%)	33 (15.1%)	52 (12.0%)
Ocular	19 (8.8%)	26 (11.9%)	45 (10.4%)
Non-Ocular	0 (0.0%)	9 (4.1%)	9 (2.1%)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Personal Reasons	2 (0.9%)	3 (1.4%)	5 (1.2%)
Protocol Violations	1 (0.5%)	0 (0.0%)	1 (0.2%)
Other	0 (0.0%)	1 (0.5%)	1 (0.2%)
Per Protocol Population	205	208	413
Safety Population	215	218	433

Source: Table 14.1-1 of Sponsor's Analysis

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

		Brim P 0.1% (N=215)	Alphagan (N=218)	Total (N=433)	P-value
Age (years)	N	215	218	433	0.113
	Mean	61.5	63.3	62.4	
	SD	11.84	11.66	11.77	
	Median	62.0	64.0	63.0	
	Min	19	23	19	
	Max	91	93	93	
	<45	15 (7.0%)	16 (7.3%)	31 (7.2%)	
	45-65	117 (54.4%)	106 (48.6%)	223 (51.5%)	
	>65	83 (38.6%)	96 (44.0%)	179 (41.3%)	
Sex	N	215	218	433	0.719
	Male	91 (42.3%)	96 (44.0%)	187 (43.2%)	
	Female	124 (57.7%)	122 (56.0%)	246 (56.8%)	
Race	N	215	218	433	0.839
	Black	25 (11.6%)	24 (11.0%)	49 (11.3%)	
	Non-Black	190 (88.4%)	194 (89.0%)	384 (88.7%)	
	Caucasian	173 (80.5%)	168 (77.1%)	341 (78.8%)	
	Asian	1 (0.5%)	1 (0.5%)	2 (0.5%)	
	Hispanic	13 (6.0%)	22 (10.1%)	35 (8.1%)	
	Other[b]	3 (1.4%)	3 (1.4%)	6 (1.4%)	
Iris Color	N	215	218	433	0.182
	Dark	84 (39.1%)	99 (45.4%)	183 (42.3%)	
	Brown	84 (39.1%)	99 (45.4%)	183 (42.3%)	
	Light	131 (60.9%)	119 (54.6%)	250 (57.7%)	
	Blue	78 (36.3%)	70 (32.1%)	148 (34.2%)	
	Green	10 (4.7%)	11 (5.0%)	21 (4.8%)	
	Hazel	38 (17.7%)	34 (15.6%)	72 (16.6%)	
	Other[c]	5 (2.3%)	4 (1.8%)	9 (2.1%)	

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

		Brim P 0.1% (N=215)	Alphagan (N=218)	Total (N=433)	P-value[a]
Central Corneal Thickness (microns) [d]	N	215	217	432	0.083
	Mean	568.7	562.5	565.6	
	SD	35.25	39.27	37.41	
	Median	571.5	559.0	564.0	
	Min	448	466	448	
	Max	656	661	661	
	N	215	217	432	
	<555	69 (32.1%)	97 (44.7%)	166 (38.4%)	
	>=555 to <600	108 (50.2%)	82 (37.8%)	190 (44.0%)	
	>=600	38 (17.7%)	38 (17.5%)	76 (17.6%)	
Weight (kg)	N	215	218	433	0.356
	Mean	83.9	85.7	84.8	
	SD	19.41	21.35	20.41	
	Median	81.6	83.1	82.6	
	Min	45	45	45	
	Max	147	204	204	
Height (cm)	N	215	218	433	0.994
	Mean	167.5	167.5	167.5	
	SD	9.97	10.61	10.28	
	Median	168.0	168.0	168.0	
	Min	142	140	140	
	Max	201	193	201	

Source: Table 14.1-3.1 of Sponsor's Analysis

Table 3
Baseline IOP Comparison
Intent-to-Treat Data

		Brim P 0.1% (N=215)	Alphagan (N=218)	Difference	95% CI	P-value
Hour 0	N	215	218	-0.02	(-0.47, 0.44)	0.945
	Mean	24.7	24.7			
	SD	2.49	2.39			
	Median	24.0	24.0			
	Min	22	22			
	Max	34	33			
Hour 2	N	215	218	0.11	(-0.44, 0.66)	0.704
	Mean	23.3	23.2			
	SD	3.07	3.00			
	Median	23.0	22.8			
	Min	16	15			
	Max	43	33			
Hour 8	N	215	217	0.42	(-0.20, 1.04)	0.185
	Mean	22.6	22.1			
	SD	3.46	3.37			
	Median	22.0	22.0			
	Min	15	14			
	Max	43	33			

Source: Table 14.2-1.1 of Sponsor's Analysis

Table 4
Mean IOP Comparison of Brimonidine Purite Ophthalmic Solution 0.1% and ALPHAGAN
(Intent-to-Treat Population)

Visit Hour	Brimonidine Purite® 0.1% N = 215	ALPHAGAN N = 218	Estimated Difference	95% CI
Week 2				
Hour 0	20.7	21.0	-0.30	-0.90 to 0.30
Hour 2	18.0	18.0	-0.02	-0.58 to 0.54
Hour 8	17.4	17.2	0.17	-0.46 to 0.80
Week 6				
Hour 0	21.3	21.4	-0.12	-0.78 to 0.54
Hour 2	18.3	18.1	0.22	-0.40 to 0.84
Hour 8	17.4	17.2	0.19	-0.42 to 0.80
Month 3				
Hour 0	21.4	21.7	-0.30	-0.96 to 0.35
Hour 2	18.2	18.6	-0.40	-1.00 to 0.21
Hour 8	17.2	17.6	-0.33	-0.95 to 0.29

Note confidence intervals (CI) are based on the 2-way ANOVA model with fixed effects of treatment and investigator using the type III sum of squares. Estimated difference (Brimonidine Purite® 0.1% minus ALPHAGAN) is based on the least-squares means from the ANOVA model.

Source: Table 11.4.1.1 of Sponsor's Analysis

Table 5
Mean IOP Adjusted for Central Corneal Thickness Visit Hour Week 2
Comparison of Brimonidine Purite Ophthalmic Solution 0.1% and ALPHAGAN
(Intent-to-Treat Population)

Visit Hour	Brimonidine Purite® 0.1% N = 215	ALPHAGAN® N = 218	Estimated Difference	95% CI
Week 2				
Hour 0	17.3	18.1	-0.77	-1.53 to -0.02
Hour 2	14.6	15.1	-0.48	-1.17 to 0.21
Hour 8	14.0	14.3	-0.28	-1.02 to 0.46
Week 6				
Hour 0	17.9	18.5	-0.59	-1.40 to 0.22
Hour 2	15.0	15.2	-0.23	-1.00 to 0.53
Hour 8	14.1	14.3	-0.25	-1.02 to 0.51
Month 3				
Hour 0	18.0	18.8	-0.77	-1.58 to 0.03
Hour 2	14.9	15.7	-0.84	-1.58 to -0.10
Hour 8	13.9	14.7	-0.77	-1.53 to -0.01

Note confidence intervals (CI) are based on the 2-way ANOVA model with fixed effects of treatment and investigator using the type III sum of squares. Estimated difference (Brimonidine Purite® 0.1% minus ALPHAGAN) is based on the least-squares means from the ANOVA model.

Source: Table 11.4.1.2 of Sponsor's Analysis

Table 6
Mean IOP Comparison of Brimonidine Purite Ophthalmic Solution 0.1% and ALPHAGAN
(Per-Protocol Population)

Visit Hour	Brimonidine Purite® 0.1% N = 205	ALPHAGAN N = 208	Estimated Difference	95% CI
Week 2				
Hour 0	20.8	20.9	-0.15	-0.84 to 0.54
Hour 2	18.0	17.8	0.14	-0.45 to 0.73
Hour 8	17.1	16.8	0.37	-0.31 to 1.05
Week 6				
Hour 0	21.0	21.2	-0.09	-0.83 to 0.66
Hour 2	18.2	17.8	0.45	-0.21 to 1.10
Hour 8	17.1	16.9	0.29	-0.37 to 0.95
Month 3				
Hour 0	21.4	21.6	-0.14	-0.93 to 0.65
Hour 2	18.0	18.1	-0.09	-0.74 to 0.56
Hour 8	17.1	17.0	0.12	-0.60 to 0.84

Note confidence intervals (CI) are based on the 2-way ANOVA model with fixed effects of treatment and investigator using the type III sum of squares. Estimated difference (Brimonidine Purite® 0.1% minus ALPHAGAN) is based on the least-squares means from the ANOVA model.

Source: Table 11.4.2.6 of Sponsor's Analysis

Table 7
Mean IOP Comparison
(Per-Protocol Population, using LOCF for missing values)
Reviewer's Table

Treatment	Baseline			Week 2			Week 6			Month 3		
	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8
Brimonidine 0.1%												
N	205	205	205	205	205	205	205	205	205	205	205	205
Mean (mmHg)	24.7	23.4	22.6	21.2	18.0	17.4	21.4	18.4	17.4	21.4	18.2	17.3
SD	2.5	3.1	3.5	3.2	3.3	3.4	3.2	3.4	3.4	3.4	3.2	3.2
ALPHAGAN P												
N	208	208	208	208	208	208	208	208	208	208	208	208
Mean (mmHg)	24.7	23.3	22.1	21.0	18.0	17.2	21.5	18.1	17.2	21.8	18.6	17.6
SD	2.4	3.1	3.4	3.5	3.0	3.6	4.0	3.5	3.5	4.0	3.6	3.6
Difference	0.00	-0.12	-0.48	0.30	0.04	-0.14	0.15	-0.24	-0.15	0.37	0.43	0.33
Upper 95% CI	0.48	0.48	0.19	0.95	0.65	0.54	0.85	0.43	0.52	1.09	1.09	0.99
Lower 95% CI	-0.48	-0.71	-1.15	-0.35	-0.58	-0.82	-0.56	-0.90	-0.82	-0.34	-0.23	-0.33

Table 8
Mean IOP Comparison
(Intent-to-Treat Population, using LOCF for missing values)
Reviewer's Table

Treatment	Baseline			Week 2			Week 6			Month 3		
	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8
Brimonidine 0.1%												
N	215	215	215	215	215	215	215	215	215	215	215	215
Mean (mmHg)	24.7	23.3	22.6	20.7	18.0	17.4	21.3	18.3	17.4	21.4	18.2	17.2
SD	2.5	3.1	3.5	3.2	3.3	3.3	3.0	3.4	3.4	3.3	3.2	3.1
ALPHAGAN P												
N	218	218	218	218	218	218	218	218	218	218	218	218
Mean (mmHg)	24.7	23.2	22.1	21.0	18.0	17.2	21.4	18.1	17.2	21.7	18.6	17.6
SD	2.4	3.0	3.4	3.5	3.0	3.6	4.0	3.4	3.5	3.9	3.5	3.6
Difference	0.00	-0.11	-0.45	0.32	0.03	-0.18	0.15	-0.19	-0.18	0.30	0.40	0.34
Upper 95% CI	0.47	0.47	0.20	0.95	0.62	0.48	0.83	0.45	0.47	0.99	1.04	0.98
Lower 95% CI	-0.46	-0.68	-1.09	-0.31	-0.60	-0.83	-0.54	-0.83	-0.83	-0.38	-0.23	-0.30

Table 9
Mean IOP Comparison
(Per-Protocol Population, using BOCF for missing values)
Reviewer's Table

Treatment	Baseline			Week 2			Week 6			Month 3		
	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8
Brimonidine 0.1%												
N	205	205	205	205	205	205	205	205	205	205	205	205
Mean (mmHg)	24.7	23.4	22.6	20.8	18.0	17.4	21.4	18.4	16.9	21.4	18.2	17.3
SD	2.5	3.1	3.5	3.2	3.3	3.4	3.2	3.4	3.4	3.4	3.2	3.2
ALPHAGAN												
N	208	208	207	208	208	208	208	208	208	208	208	208
Mean (mmHg)	24.7	23.3	22.1	21.1	18.0	17.2	21.5	18.1	17.2	21.8	18.6	17.6
SD	2.4	3.1	3.4	3.5	3.0	3.6	4.0	3.5	3.5	4.0	3.4	3.6
Difference	0.00	-0.12	-0.49	0.30	0.04	-0.14	0.14	-0.24	-0.15	0.37	0.43	0.33
Upper 95% CI	0.48	0.48	0.18	0.95	0.65	0.54	0.85	0.43	0.52	1.09	1.09	1.00
Lower 95% CI	-0.48	-0.71	-1.16	-0.35	-0.58	-0.82	-0.56	-0.90	-0.82	-0.34	-0.23	-0.33

Table 10
Mean IOP Comparison
(Intent-to-Treat Population, using BOCF for missing values)
Reviewer's Table

Treatment	Baseline			Week 2			Week 6			Month 3		
	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8	Hour 0	Hour 2	Hour 8
Brimonidine 0.1%												
N	215	215	215	215	215	215	215	215	215	215	215	215
Mean (mmHg)	24.7	23.3	22.6	20.7	18.0	17.4	21.3	18.3	17.4	21.4	18.2	17.2
SD	2.5	3.1	3.5	3.2	3.3	3.3	3.2	3.4	3.4	3.3	3.2	3.1
ALPHAGAN												
N	218	218	217	218	218	218	218	218	218	218	218	218
Mean (mmHg)	24.7	23.2	22.1	21.0	18.0	17.2	21.4	18.1	17.2	21.7	18.6	17.6
SD	2.4	3.0	3.4	3.5	3.0	3.6	4.0	3.4	3.5	3.9	3.5	3.6
Difference	0.00	-0.11	-0.46	0.32	0.03	-0.18	-0.15	-0.19	-0.18	0.30	0.40	0.34
Upper 95% CI	0.45	0.47	0.19	0.95	0.62	0.48	0.83	0.45	0.47	0.99	1.04	0.98
Lower 95% CI	-0.46	-0.68	-1.1	-0.31	-0.57	-0.83	-0.54	-0.83	-0.83	-0.38	-0.24	-0.30

Table 11

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

Treatment	Visit 3			Visit 4			Visit 5		
	0 Hrs.	2 Hrs.	8 Hrs.	0 Hrs.	2 Hrs.	8 Hrs.	0 Hrs.	2 Hrs.	8 Hrs.
Brimonidine P 0.1%									
Total	205	205	205	205	205	205	205	205	205
N with IOP<18mmHg	39	100	124	25	107	119	21	101	117
% with IOP<18mmHg	19.0	48.8	60.5	12.2	52.2	58.0	10.2	49.3	57.1
ALPHAGAN									
Total	208	208	208	208	208	208	208	208	208
N with IOP<18mmHg	36	98	122	34	106	134	27	98	117
% with IOP<18mmHg	17.3	47.1	58.7	16.3	51.0	64.4	13.0	47.1	56.25
P-Values	0.702	0.768	0.764	0.261	0.844	0.191	0.444	0.694	0.921

Table 12

Frequency and Percent of Patients Who Achieved IOP<18 mmHg (ITT Population) Reviewer's table

Treatment	Week 2			Week 6			Month 3		
	8AM	10AM	5PM	8AM	10AM	5PM	8AM	10AM	5PM
Brimonidine 0.15%									
Total	215	215	215	215	215	215	215	215	215
N with IOP<18mmHg	43	105	129	28	114	124	23	106	124
% with IOP<18mmHg	20.0	48.8	60.0	13.0	53.0	57.7	10.7	49.3	57.7
ALPHAGAN P									
Total	218	218	218	218	218	218	218	218	218
N with IOP<18mmHg	37	103	131	36	109	139	27	102	122
% with IOP<18mmHg	17.0	47.2	60.1	16.5	50.0	63.8	12.4	46.8	56.0
P-Values	0.458	0.923	1.000	0.344	0.564	0.202	0.653	0.631	0.771

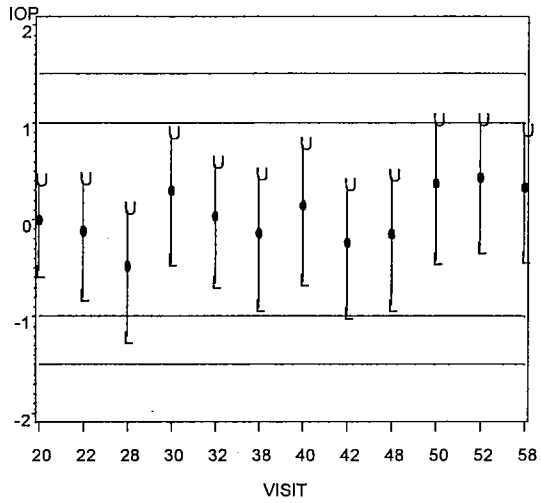
Table 13
Number (%) of Patients with Adverse Events Regardless of Causality Reported by Greater than or Equal to 2% of Patients in Either Group

BODY SYSTEM Preferred Term[a]	Brimonidine Purite® 0.1% N = 215	ALPHAGAN® N = 218	P-Value[b]
BODY AS A WHOLE			
infection	6 (2.8%)	1 (0.5%)	0.067[c]
asthenia	2 (0.9%)	10 (4.6%)	0.020
headache	2 (0.9%)	5 (2.3%)	0.449[c]
CARDIOVASCULAR			
hypertension	3 (1.4%)	8 (3.7%)	0.133
DIGESTIVE			
oral dryness	3 (1.4%)	13 (6.0%)	0.012
periodontal abscess	0 (0.0%)	5 (2.3%)	0.061[c]
NERVOUS			
somnolence	2 (0.9%)	5 (2.3%)	0.449[c]
SPECIAL SENSES			
allergic conjunctivitis	22 (10.2%)	23 (10.6%)	0.914
conjunctival hyperemia	16 (7.4%)	21 (9.6%)	0.415
eye pain	6 (2.8%)	0 (0.0%)	0.014[c]
eye pruritus	4 (1.9%)	11 (5.0%)	0.070
conjunctival folliculosis	4 (1.9%)	6 (2.8%)	0.751[c]
burning sensation in eye	2 (0.9%)	5 (2.3%)	0.449[c]

a body system and preferred terms from Allergan's modified COSTART dictionary
b between-group p-value based on Pearson's chi-square test unless otherwise noted
c between-group p-value based on Fisher's exact test
Source: Table 12.2.2 of Sponsor's Analysis

Figure 1

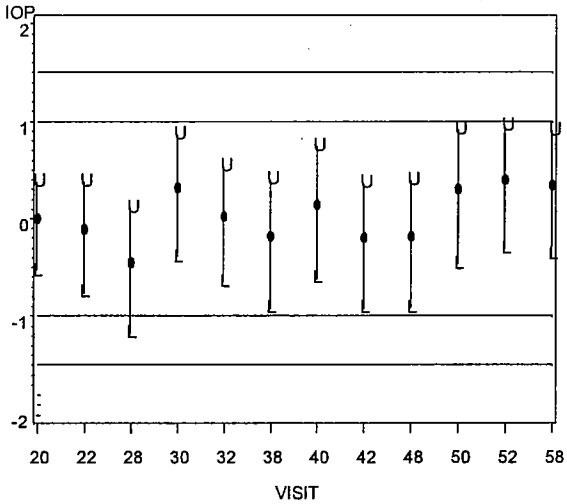
IOP Mean Differences Between Brimonidine Purite0.1% and ALPHAGAN
And the Confidence intervals
(Per-Protocol Population LOCF)



In X-Axis Visit ij indicates Visit i and Hour j
Visit2=Baseline, Visit3=Week2, Visit4=Week6, and Visit5=Month3

Figure 2

IOP Mean Differences Between Brimonidine Purite0.1% and ALPHAGAN
And the Confidence intervals
(ITT Population LOCF)



In X-Axis Visit ij indicates Visit i and Hour j
Visit2=Baseline, Visit3=Week2, Visit4=Week6, and Visit5=Month3

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/s/

Atiar Rahman
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Stan Lin
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