# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-398**

# 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

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|---|---|
| **NDA # :** | 21,398 |
| **Drug Name:** | 0.2% Brimonidine Tartrate / 0.5% Timolol Fixed Combination Ophthalmic Solution |
| **Indication(s):** | Reduction of intraocular pressure in patients with glaucoma or ocular hypertension |
| **Applicant:** | Allergan Inc. |
| **Stamp Date:** | May 2, 2007 |
| **PDUFA Goal Date:** | November 2, 2007 |
| **Reviewer Completion Date:** | October 3, 2007 |
| **Biometrics Division:** | Division of Biometrics IV |
| **Medical Division:** | Division of Anti-Infective and Ophthalmology Drug Products |
| **Documents Reviewed:** | \\Cdsesub1\nonectd\N21398\N_000\2007-05-02 |
| **Statistical Reviewer:** | Christopher Khedouri, Ph.D. |
| **Concurring Reviewer:** | Thamban Valappil, Ph.D. |
| **Clinical Reviewer(s):** | William Boyd, M.D. |
| **Project Manager:** | Alison Rodgers |

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# 1. EXECUTIVE SUMMARY

## 1.1 Introduction

The current submission includes Study 190342-024T aimed to demonstrate improvement in the safety profile in glaucoma and ocular hypertension patients 40 years and older with Combination therapy (Alphagan (0.2% Brimonidine Tartrate and 0.5% Timolol) BID versus Concurrent therapy (Alphagan TID and 0.5% timolol BID). Results from an earlier study 190342-023T provided some preliminary evidence that Combination has an improved safety profile in subjects over the age of 40 years. An FDA approvable letter issued on December 20, 2006, recommended a confirmatory study be performed for which both the dry mouth and sleepiness endpoints would be expected to show significance with a magnitude at least that observed for subjects $\geq$ 40 years old in the previous 023T study. The objective of this review is to evaluate the evidence provided in the 024T study of an improved safety profile for patients treated with Combination therapy. This review does not attempt to assess whether the potential gains in safety with Combination therapy are substantial enough to outweigh the potential losses in efficacy. Refer to Medical Review of Dr. William Boyd for more information on this issue.

## 1.2 Conclusions and Recommendations

Overall results from the safety Study 024T provided some evidence towards an improvement in safety with Combination therapy versus Concurrent therapy. Study 024T met its primary endpoint by showing improvements (decreases) in the proportions of "sleepiness responders" among patients with glaucoma or ocular hypertension. Primary analysis findings, however, were not entirely robust. Secondary results of the three pre-specified secondary outcomes (tested sequentially) showed a significant improvement in the proportion of "Dry Mouth Responders" (p=.01), a marginal improvement in "Sleepiness Responders under 65 years of age" (p=.04) and no significant improvement in "Inappropriate Sleepiness Responders," (p=.24). Additionally, significant improvement observed for "Dry Mouth Responders" varied according to the patient's age, sex and race. Significant improvements in "Dry Mouth Responders" were not observed in the '$\geq$ 65', 'male' and 'black' sub-groups (Table 3).

In study 024T, interpretations of overall study findings may be limited due to lack of objective measures and lack of efficacy assessments. In addition, study duration was limited to only 10 days and safety benefits were only confirmed in a specific study population (e.g. patients 40 years of age and older with glaucoma or ocular hypertension) with no previous evidence to suggest similar improvements in other populations. The potential safety benefits over each of the timolol or brimonidine components are also not addressed in Study 024T.

There are also concerns regarding the potential loss of efficacy with Combination therapy versus Concurrent therapy. It should be noted that the previous studies failed to provide an adequate demonstration of non-inferiority for Combination therapy. To illustrate, evidence from Study 019T indicated potential inferiority of Combination therapy to Concurrent therapy with a loss of IOP lowering ability of 1.01 mm Hg (95% CI: 0.33, 1.69) at the 8 hour time point, post-baseline

(Day 28). Also, previous studies 012T and 013T failed to indicate any substantial gain in efficacy with respect to the IOP lowering ability.

Assessing the added safety benefit from Combination versus Concurrent therapy (Study 024T) given the loss of efficacy (Study 019T) is also limited due to various differences in the design, endpoints and populations of Studies 019T and 024T. Study 024T considered primarily an older study population (ages 40 years and older) in which the primary safety endpoint related to sleepiness was measured only up to Day 10 while non-inferiority Study 019T considered a younger study population (ages 18 years and older) where efficacy (IOP lowering) was measured on Day 28.

Overall, based on the collective evidence of efficacy and safety from the current and previous submissions, there are concerns regarding the loss of efficacy with Combination therapy versus Concurrent therapy. In addition, there is no data to support any substantial gain in safety beyond day 10, especially a gain which would outweigh the loss in the overall efficacy.

## 1.3 Brief Overview of the Study

Study 190342-024T was a Phase III, multi-center, randomized, parallel, double-blind trial. Patients were randomized 1:1 to either Combination or Concurrent therapy. The objective was to compare the safety of Combination with Concurrent therapy following ocular administration for 10 days in subjects with glaucoma or ocular hypertension. There were 604 treated subjects in the intent-to-treat (ITT) population for safety analysis with 304 subjects randomized to Combination therapy and 300 subjects to Concurrent therapy. There were 507 subjects included in the modified intent-to-treat (mITT) population.

The primary safety assessment variable was the current severity of sleepiness (using the 7-point Stanford Sleepiness Scale (SSS) questionnaire with 1 being the "most alert" and 7 being the "most tired") for subjects in the ITT population. Secondary assessment variables included current severity of dry mouth (using a 5-point scale questionnaire with 1 being "note experiencing the symptom at all" and 5 being "intolerable").

## 1.4 Statistical Issues and Findings

Based on the review of study 024T, the following comments should be noted:

- There is not substantial evidence of an improved safety profile in patients under 40 years of age due to a low percentage of subjects in this age group (only 3.5% of ITT population).

- The time period of 10 days used to assess improvements in this study may be too short to provide any meaningful safety information.

- Although Study 024T demonstrates marginal improvement in safety profile of the Combination therapy compared to Concurrent therapy, these results may not be clinically

meaningful to offset potential losses in efficacy with respect to IOP-lowering ability to Concurrent therapy.

- The Sponsor notes several statistically significant findings for endpoints which were not pre-specified as primary or secondary. Note that the study did not control for the overall type I error rate in testing some of these secondary endpoints to show statistical significance.

- More extensive sensitivity analyses should have been used to further improve the robustness of the overall data. Covariate analyses for various baseline factors as well as analyses using different assumptions for missing data would provide additional meaningful information.

# 2. INTRODUCTION

## 2.1 Overview

Elevated intraocular pressure (IOP) is a major risk factor in the progression of glaucomatous optic neuropathy with a lowering in IOP associated with reduced incidence and delayed progression glaucomatous optic neuropathy and visual field defects. Treatment regimens for a subject frequently begin with a prescription of a beta-blocker with a second drug added to regimen if the beta-blocker is ineffective. Since a non-selective beta-blocker, 0.5% timolol ophthalmic solution, and ALPHAGAN® (0.2% brimonidine ophthalmic solution), a selective and potent alpha-2 adrenoceptor agonist, have different sites of action and different mechanisms by which they lower IOP, there may be an additive IOP-lowering effect within the 2 medications are used conjunctively. Currently, the 2 marketed medications are often prescribed and used together, but this requires that the subject must have 2 separate bottles of medications. Use of 2 separate bottles requires subjects to dose 5 drops per eye per day with a 5-minute wait in-between dosing of the 2 bottles. Allergan has combined these 2 ocular hypotensive medications into a single formulation (Combination) to provide the benefit of adjunctive therapy with a more convenient dosing regimen (i.e. 1 drop in each eye BID). According to Allergan, use of Combination therapy versus Concurrent may improve patient compliance as well as the patient safety profile.

## 2.2 Previous Submissions

NDA 21-398, COMBIGAN™ was originally submitted on September 17, 2001 with an approvable letter issued on June 5, 2002. This letter indicated that the original NDA failed to adequately show that each component contributed to the claimed effect of the combination product as required by CFR 300.50. Allergan addressed these issues in a September 13, 2004 response which included the Phase III Studies Studies 190342-012T, 190342-013T and 190342-019T. However, this response was not adequate. Neither study 190342-012T nor 190342-013T demonstrated a clinically significant contribution of the Timolol 0.5% or Brimonidine Tartrate 0.2% components. Study 190342-019T also failed to show non-inferiority of Combination therapy (Alphagan (0.2% Brimonidine Tartrate) and 0.5% Timolol) BID to Concurrent therapy (Alphagan TID and 0.5% timolol BID). In addition, Combination therapy being inferior, it has also failed to demonstrate superiority to Alphagan therapy. Consequently, Allergan received another letter from FDA on March 14, 2005 which indicated that the submitted studies failed to demonstrate that the benefits of Combination therapy outweigh the risks (e.g. loss of IOP-lowering ability of approximately 1 mm Hg). This letter also indicated that an alternative dosing regimen such as Combination could provide a useful product if it could demonstrate a better safety profile than Concurrent therapy.

In response to the March 14, 2005 approvable letter, Allergan had provided the June 29, 2006 submission attempting to demonstrate a benefit risk ratio that conclusively favored COMBIGAN™ with effective IOP lowering in addition to less exposure to brimonidine and better safety and tolerability in comparison to the individual drugs used separately or concurrently. However, this application was not recommended for approval as the submitted

studies, incuding Phase III Study 190342-023T, failed to demonstrate that the risks of COMBIGAN™ outweighed the benefits. An FDA approvable letter was issued on December 20, 2006.

### 2.3 Previous Phase III Studies

Two Phase 3 studies (Study 190342-012T and Study 190342-013T) each compared Combination BID with 0.5% timolol BID or Alphagan TID. The studies failed to show that Combination administered for 12 months was superior to timolol and brimonidine in lowering elevated IOP for all time points considered. Further details of these studies are addressed in the April 2001 statistical review by Dr. Suktae Choi. Another Phase 3 study (Study 190342-019T) with 2:2:1 randomization compared Combination therapy BID versus Concurrent therapy versus Alphagan TID in patients with glaucoma or ocular hypertension over a 4 week duration. The Combination treatment failed to show non-inferiority or superiority to the Concurrent treatment. In Study 190342-019T, demonstration of non-inferiority required that the upper limit of the 95% CI for the difference was within a 1.0 mm Hg margin at two or all three time points (hours 0, 2 and 8) and within a 1.5 mm Hg margin at all three time points at Day 28. This study failed to demonstrate non-inferiority since the Hour 8 timepoint in which the difference in mean unadjusted IOP was 1.01 with 95% CI of (0.33, 1.69). Therefore, the Combination's IOP-lowering ability is likely to be inferior to that of brimonidine and timolol given concomitantly by approximately 1 mmHg. Superiority over Alphagan also could not be demonstrated at the Hour 8 time point, the difference in mean unadjusted IOP was -0.22 (-1.05, 0.61). Further details of study 190342-019T are addressed in the January 2005 statistical review by Dr. Karen Qi.

### 2.4 Data Sources

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## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy Assessments

No efficacy claims are made in Study 190342-024T.

### 3.2 Evaluation of Safety Assessments

#### 3.2.1 Study Design and Endpoints

Study 190342-024T was a Phase III, multi-center, randomized, parallel, double-blind trial. Patients were randomized 1:1 to either Combination or Concurrent therapy. The objective was to compare the safety of Combination with Concurrent therapy following ocular administration for 10 days in days in glaucoma and ocular hypertension patients. The dosage regimen is shown below:

**Table 1: Dosing Regimen of Combination and Concurrent Treatments**

| | Combination | | Concurrent | |
|---|---|---|---|---|
| **Timepoint** | **TID Bottle** | **BID Bottle** | **TID Bottle** | **BID Bottle** |
| Hour 0 | Vehicle | Brimonidine/Timolol | ALPHAGAN® | timolol |
| Hour 6 | Vehicle | NA | ALPHAGAN® | NA |
| Hour 12[a] | Vehicle | Brimonidine/Timolol | ALPHAGAN® | timolol |

Note: At Hour 0 and Hour 12, medication from the TID bottle was instilled first followed by the BID bottle after at least 5 minutes. Site staff administered study medication on study visit days (Days 1, 9, and 10).
a Hour 12 dose was not given on Day 10

To establish the safety of the Combination product, comparisons were made to ALPHAGAN® and timolol used concurrently, at the concentrations used in the Combination. ALPHAGAN® and timolol, the individual components of the Combination, are each marketed for the reduction of elevated IOP in patients with open-angle glaucoma or OHT.

The clinical hypothesis of this study was that the safety of Combination was better than that of the Concurrent. This study included safety assessments of sleepiness and dry mouth. The study consisted of 5 scheduled visits: Screening (Day –50 to Day -3), Baseline (Day –1), Day 1, Day 9, and Day 10.

The single primary endpoint for the study was the proportion of "Sleepiness Responders" in the ITT population. A Sleepiness Responder was defined as a patient with an SSS score of at least 4 (somewhat foggy, let down) at any post-baseline assessment who also demonstrated at least a 2-unit increase from the baseline score.

Three secondary endpoints were evaluated based on the ITT population:

1. The proportion of "Dry Mouth Responders": a Dry Mouth Responder was defined as a patient with a current severity of dry mouth score of at least 3 (moderate) at any post-baseline assessment who also demonstrated at least a 1-unit increase from the baseline score.

2. The proportion of "Sleepiness Responders" among patients < 65 years of age.

3. The proportion of "Inappropriate Sleepiness Responders: an Inappropriate Sleepiness Responder was defined as a patient who had a score of at least 3 (sometimes) at any post-baseline assessment who also demonstrated at least a 1-unit increase from the baseline score for the question of "Have you felt sleepy at times you feel you shouldn't?".

### 3.2.2 Subject Disposition and Demographic Characteristics

A total of 604 patients were randomized into the study and included in the ITT population, 304 patients were randomized to Combination and 300 patients to Concurrent therapy. All patients randomized were treated and included in the safety population; thus, the ITT and safety populations were identical. Five hundred seventy-seven (577) patients were included in the mITT population (ie, subset of safety population who were ≥ 40 years who had a baseline and at least 1 post-baseline evaluation for the primary endpoint based on the SSS). Of the 577 mITT patients, 290 were in the Combination group and 287 were in the Concurrent group. In the ITT population, 97.7% (590/604) of the patients completed the study and only 2.3% (14/604) discontinued prematurely: 1.6% (5/304) in the Combination group and 3.0% (9/300) in the Concurrent group.

### 3.2.3 Statistical Methodologies

**Statistical Tests**

The general association statistic of the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator was used to compare the treatment groups. The magnitude of treatment effects was assessed by the relative risk (RR), calculated as the ratio of the proportion of responders in the Concurrent-treated patients to the proportion in the Combination-treated patients. The 2-sided asymptotic 95% confidence interval (CI) for the RR was provided. In addition, a supplementary 2-sided 95% CI for the treatment difference in proportions was constructed using the normal approximation to the binomial distribution. The Breslow-Day test was used to assess treatment-by-investigator interaction. If a statistically significant interaction was observed, efforts were to be made to determine whether and how the interaction affected the treatment comparisons.

**Multiple Comparisons/Multiplicity**

A sequential test (gate-keeping) procedure was used for the analyses of the 3 secondary endpoints to control the overall type I error rate at 5% with the Dry Mouth Responder analysis tested first at the significance level of 0.05 followed by the analysis of Sleepiness Responders among patients < 65 years of age and then the analysis of Inappropriate Sleepiness Responder.

**Missing Data**

With the exception of responder analyses in the ITT population, all analyses were based on observed data only. For the responder analyses in the ITT population, missing data were imputed. For a given endpoint, the baseline observation was carried forward for those patients who were missing all post-baseline assessments and the patient was classified as a non-responder. A patient missing the baseline assessment was determined to be a responder/non-responder based only on the follow-up criteria (ie, a patient was deemed a responder if at least one post-baseline SSS score ≥ 4; at least 1 post-baseline Dry Mouth score ≥ 3, or at least 1 post-baseline Inappropriate Sleepiness score ≥ 3, etc).

### 3.2.4 Results and Conclusions

**Findings from Primary Safety Assessments**

The primary endpoint was the proportion of current severity of Sleepiness Responders (over the course of the study). The treatment groups had statistically comparable baseline scores on the SSS, $p = 0.642$. A significantly lower proportion of current severity of sleepiness responders was observed in the Combination group, 9.2% (28/304) vs. 19.3% (58/300), $p < 0.001$. The relative risk (RR) was 2.10, (95% CI: 1.38 to 3.20), indicating a significantly higher risk for sleepiness with Concurrent versus Combination.

**Findings from Secondary Safety Assessments**

The first secondary endpoint was the "proportion of current severity of Dry Mouth Responders" (over the course of the study). The treatment groups had statistically comparable baseline dry mouth scores, $p = 0.738$. A significantly lower proportion of current severity of dry mouth responders was observed in the Combination group 14.8% (45/304) versus 24.0%, $p = 0.005$. The RR (95% CI) was 1.62 (1.16 to 2.27).

The second secondary endpoint was the proportion of "current severity of Sleepiness Responders among patients < 65 years of age." The treatment groups < 65 years had statistically comparable baseline scores on the SSS, $p = 0.460$. A significantly lower proportion of current severity of sleepiness responders among patients < 65 years of age was observed in the Combination group, 11.6% (17/147) versus 20.6% (29/141), $p = 0.037$. The RR (95% CI) was 1.78 (1.02 to 3.09).

The third secondary endpoint was the proportion of "Inappropriate Sleepiness Responders". The treatment groups had statistically comparable baseline scores, $p = 0.476$. The proportion of Inappropriate Sleepiness Responders was 25.3% (77/304) in the Combination group and 29.7% (89/300) in the Concurrent group, $p = 0.239$. The RR (95% CI) was 1.17 (0.90 to 1.52). This difference was not statistically significant.

Note that a sequential test (gate-keeping) procedure was used for the analyses of the 3 secondary endpoints in the ITT population to control the overall type I error rate at 5%.

**Additional Analyses of Primary Safety Assessment**

The proportion of ITT patients with an increase from baseline current severity of sleepiness of $\geq 2$ units was lower with Combination than with Concurrent at Day 10 ($p = 0.035$, RR = 1.57) and Overall ($p = 0.022$, RR = 1.42). A composite analysis found the difference in proportions of patients who were neither Sleepiness nor Dry Mouth Responders favored Combination, (79.9% [243/304]) over Concurrent (64.3% [193/300]), $p < 0.001$, indicating less sleepiness and dry mouth occurring in patients treated with Combination. The RR (95% CI) was 0.80 (0.73 to 0.89).

## Other Analyses

Dry Mouth Responders: The proportion of patients with an increase from baseline current severity of dry mouth of $\geq 1$ unit confirmed the Dry Mouth Responder analysis. The proportion was lower with Combination than with Concurrent at each visit and Overall ($p \leq 0.010$, RR range 1.46 to 1.96).

Sleepiness Responders Aged < 65 Years: The proportion of patients < 65 years with an increase from baseline current severity of sleepiness of $\geq 2$ units confirmed the analysis of the secondary endpoint, Sleepiness Responders in patients < 65. The proportion lower with Combination than with Concurrent Overall ($p = 0.043$, RR = 1.56).

Inappropriate Sleepiness: There were no statistically significant differences between the 2 treatment groups in the proportion of patients with an increase from baseline inappropriate sleepiness of $\geq 1$ unit at any visit.

Salivary Flow Assessment: The amount of saliva collected at Baseline and Day 10 was categorized as low ($\leq 0.16$ grams/minute), reduced (> 0.16 to 0.30 grams/minute) and normal (> 0.30 grams/minute). The proportion of ITT patients who decreased from baseline by at least one category (normal to reduced or low, or reduced to low) was significantly less with Combination (12.6%) than with Concurrent treatment (30.1%), $p < 0.001$

Other Analyses of Sleepiness and Dry mouth: Other analyses of sleepiness and dry mouth were consistent with those of the primary and secondary responder endpoints. In particular, the subjective complaints of dry mouth were corroborated by the objective measurement of salivary flow: the proportion of patients with decreased salivary flow of at least 1 category from baseline was lower with Combination (12.6%) than with Concurrent (30.1%), $p < 0.001$.

## Treatment-related Adverse Events

Treatment-related adverse events (AEs) did not differ greatly between Combination and Concurrent treatments. However, larger numbers of patients in the Combination group reported an AE of eye irritation 17/224 (7.6%) vs. 6/228 (2.6%) (p=.016). Dry mouth was also numerically lower in the Combination arm 5/224 (2.2%) versus 12/228 (5.3%) (p=.09). AEs of headaches, somnolence and fatigue were slightly lower with Combination therapy.

## Conclusions

Overall results from Study 190342-024T provided evidence towards an improvement in safety with Combination therapy versus Concurrent therapy based on improvements in the proportions of "sleepiness responders" and "dry mouth responders" among patients with glaucoma or ocular hypertension. However, results were not entirely robust according to secondary analyses and sub-group analyses by age, gender and race.

# 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Sleepiness Responders by Age, Sex and Race

**Table 2: Proportion of Sleepiness Responders by Demographic Subgroup (ITT population)**

| Subgroup | Combination N = 304 | Concurrent N = 300 | RR[a] | P-Value[b] |
|---|---|---|---|---|
| < 65 years | 11.6% (17/147) | 20.6% (29/141) | 1.78 | 0.037 |
| ≥ 65 years | 7.0% (11/157) | 18.2% (29/159) | 2.60 | 0.003 |
| male | 6.7% (8/120) | 14.8% (18/122) | 2.21 | 0.042 |
| female | 10.9% (20/184) | 22.5% (40/178) | 2.07 | 0.003 |
| black | 5.3% (3/57) | 20.0% (11/55) | 3.80 | 0.018 |
| non-black | 10.1% (25/247) | 19.2% (47/245) | 1.90 | 0.004 |

Source: Sponsor Tables 14.3-4.1, 14.6-7.2 to 14.6-7.6
a Relative risk (RR) is the proportion of responders in the Concurrent group divided by the proportion of responders in the Combination group
b P-value from Pearson's chi-square test or Fisher's exact text

Statistical Reviewer Comments: *The proportion of Sleepiness Responders was significantly lower with Combination versus Concurrent in each demographic subgroup at the α=.05 level. Results were most significant in the 'female', 'non-black', and '≥ 65 years' subgroups. Note that statistical inferences for these comparisons are limited since the overall type I error rate was not adequately controlled.*

## 4.2 Dry Mouth Responders by Age, Sex and Race

**Table 3: Proportion of Dry Mouth Responders by Demographic Subgroup (ITT Population)**

| Subgroup | Combination N = 304 | Concurrent N = 300 | RR[a] | P-Value[b] |
|---|---|---|---|---|
| < 65 years | 12.9% (19/147) | 24.8% (35/141) | 1.92 | 0.010 |
| ≥ 65 years | 16.6% (26/157) | 23.3% (37/159) | 1.41 | 0.136 |
| male | 12.5% (15/120) | 14.8% (18/122) | 1.18 | 0.609 |
| female | 16.3% (30/184) | 30.3% (54/178) | 1.86 | 0.002 |

| | | | | |
|---|---|---|---|---|
| black | 8.8% (5/57) | 20.0% (11/55) | 2.28 | 0.090 |
| non-black | 16.2% (40/247) | 24.9% (61/245) | 1.54 | 0.017 |

Source: Sponsor Tables 14.6-8.1 to 14.6-8.6
a Relative risk (RR) is the proportion of responders in the Concurrent group divided by the proportion of responders in the Combination group
b P-value from Pearson's chi-square test or Fisher's exact text

**Statistical Reviewer Comments:** *The proportions of current severity of Dry Mouth Responders were numerically lower in the '≥ 65 years', 'male' and 'black' patient sub-groups. However, these comparisons were not found to be significant at the α=.05 level. Differences in proportions in the 'female', 'non-black' and '< 65 years' subgroups were significant at the α=.05 level. Note that statistical inferences for these comparisons are limited since the overall type I error rate was not adequately controlled.*

# 5. SUMMARY AND CONCLUSIONS

Overall results from the safety Study 024T provided some evidence towards an improvement in safety with Combination therapy versus Concurrent therapy. Study 024T met its primary endpoint by showing improvements (decreases) in the proportions of "sleepiness responders" among patients with glaucoma or ocular hypertension. Primary analysis findings, however, were not entirely robust. Secondary results of the three pre-specified secondary outcomes (tested sequentially) showed a significant improvement in the proportion of "Dry Mouth Responders" (p=.01), a marginal improvement in "Sleepiness Responders under 65 years of age" (p=.04) and no significant improvement in "Inappropriate Sleepiness Responders," (p=.24). Additionally, significant improvement observed for "Dry Mouth Responders" varied according to the patient's age, sex and race. Significant improvements in "Dry Mouth Responders" were not observed in the '≥ 65', 'male' and 'black' sub-groups (Table 3).

In study 024T, interpretations of overall study findings may be limited due to lack of objective measures and lack of efficacy assessments. In addition, study duration was limited to only 10 days and safety benefits were only confirmed in a specific study population (e.g. patients 40 years of age and older with glaucoma or ocular hypertension) with no previous evidence to suggest similar improvements in other populations. The potential safety benefits over each of the timolol or brimonidine components are also not addressed in Study 024T.

There are also concerns regarding the potential loss of efficacy with Combination therapy versus Concurrent therapy. It should be noted that the previous studies failed to provide an adequate demonstration of non-inferiority for Combination therapy. To illustrate, evidence from Study 019T indicated potential inferiority of Combination therapy to Concurrent therapy with a loss of IOP lowering ability of 1.01 mm Hg (95% CI: 0.33, 1.69) at the 8 hour time point, post-baseline (Day 28). Also, previous studies 012T and 013T failed to indicate any substantial gain in efficacy with respect to the IOP lowering ability.

Assessing the safety benefit from Combination versus Concurrent therapy (Study 024T) given the potential loss of efficacy (Study 019T) is also limited due to various differences in the design, endpoints and populations of Studies 019T and 024T. Study 024T considered primarily an older study population (ages 40 years and older) in which the primary safety endpoint related to sleepiness was measured only up to Day 10 while non-inferiority Study 019T considered a younger study population (ages 18 years and older) where efficacy (IOP lowering) was measured on Day 28.

Overall, based on the collective evidence of efficacy and safety from all submissions, there are concerns regarding the potential loss of efficacy with Combination therapy versus Concurrent therapy. In addition, there is no data to support any substantial gain in safety beyond day 10, especially a gain which would outweigh the loss in the overall efficacy.

# SIGNATURES/DISTRIBUTION LIST

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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

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# 1. EXECUTIVE SUMMARY

## 1.1 Introduction

NDA 21-398, COMBIGAN™ was originally submitted on September 17, 2001 with an approvable letter issued on June 5, 2002. This letter indicated that the original NDA failed to adequately show that each component contributed to the claimed effect of the combination product as required by 21 CFR 300.50. Allergan addressed these issues in a September 13, 2004 response which included Phase III Studies 190342-012T, 190342-013T and 190342-019T. However, this response was not adequate. Neither study 190342-012T nor 190342-013T demonstrated a clinically significant contribution of the Timolol 0.5% or Brimonidine Tartrate 0.2% components. Study 190342-019T also failed to show the non-inferiority of Combination therapy (Alphagan (0.2% Brimonidine Tartrate) and 0.5% Timolol BID) to Concurrent therapy (Alphagan TID and 0.5% timolol BID). Study 190342-019T also found Combination therapy to be inferior to Concurrent therapy and not superior to Alphagan therapy. Consequently, Allergan received another approvable letter from FDA on March 14, 2005 which indicated that the submitted studies failed to demonstrate that the benefits of Combination therapy outweigh the risks (e.g. loss of IOP-lowering ability of approximately 1 mm Hg).

In response to the March 14, 2005 approvable letter, Allergan has provided the current submission of June 29, 2006. Allergan contends that data in the current submission demonstrates the benefit risk ratio which conclusively favors COMBIGAN™ with effective IOP lowering in addition to less exposure to brimonidine and better safety and tolerability when compared to the individual drugs used separately or concurrently. Allergan's submission includes one new Clinical Study Report for NDA Protocol 190342-023T and two Clinical Study Reports for Protocols 190342-012T and 190342-013T over a 12 month period. Study reports for these protocols in the original NDA considered a 3 month period.

The primary focus of this review is Study 190342-023T. Since no efficacy claims are made in this study, the review considers the primary safety assessments and whether they would support an improved safety profile in patients on Combination therapy versus Concurrent therapy. Note that this review does not attempt to assess the overall risk benefit ratio of Combination therapy versus Concurrent therapy. These issues are addressed in the clinical review by the Medical Officer Dr. William Boyd.

## 1.2 Conclusions and Recommendations

Overall results from Study 190342-023T failed to show robust evidence towards an improvement in safety based on the proportions of dry mouth responders and sleepiness responders in healthy, adult subjects. The study failed to provide adequate evidence of an improved safety profile for the proportion of "sleepiness responders," a co-primary endpoint considered to be clinically most relevant. Statistical and clinical significance in this endpoint is considered as essential in demonstrating an improved safety profile of Combination therapy versus Concurrent therapy. Although statistical significance was found in the less clinically relevant co-primary endpoint,

proportion of "dry mouth responders", this finding by itself did not provide adequate evidence of an improved safety profile. Based on the discussions with the Medical officer, results of Study 190342-023T failed to address the deficiencies raised in the review of the original NDA. Therefore, Combination therapy is not recommended for approval.

### 1.3 Brief Overview of the Study

Study 190342-23T was a Phase III, multi-center, randomized, parallel, double-blind trial for 4 weeks. Patients were randomized 1:1 to either Combination or Concurrent therapy. The objective was to compare the safety of Combination with Concurrent therapy following ocular administration for 10 days in healthy, adult subjects. 452 subjects were enrolled in the ITT and safety populations with 450 subjects included in the modified intent-to-treat (mITT) population. Of these 450 subjects, 223 were in the Combination group and 227 were in the Concurrent group. Co-primary safety assessment variables included the current severity of sleepiness (using the 7-point Stanford Sleepiness Scale (SSS) questionnaire with 1 being the "most alert" and 7 being the "most tired") and current severity of dry mouth (using a 5-point scale questionnaire with 1 being "note experiencing the symptom at all" and 5 being "intolerable").

### 1.4 Statistical Issues and Findings

Combination therapy failed to provide substantial evidence of an improved safety profile over Concurrent therapy (Alphagan TID and 0.5% Timolol BID given concurrently) in healthy, adult subjects for ten days.

It is should be noted that the Sponsor's previous study protocols had defined two co-primary endpoints: proportion of "dry mouth responders" and proportion of "sleepiness responders." The Sponsor had proposed changing the definition of the endpoints so that "sleepiness responders" would be defined as the sole primary endpoint and "dry mouth responders" as the sole secondary endpoint. This designation is reflected in the Study Report of this submission. However, in the June 2006 teleconference, the Agency recommended that two co-primary endpoints should be defined as measuring severity of sleepiness and severity of dry mouth and that significance in both would provide a more convincing argument for an improved safety profile. Note that substantial evidence of an improved safety profile could not have been provided with either designation of the endpoints. This review considers proportion of "dry mouth responders" and proportion of "sleepiness responders" as co-primary endpoints with significance needed in both to provide adequate evidence of an improved safety profile, although evidence for efficacy was not adequate in the previous studies.

# 2. INTRODUCTION

## 2.1 Overview

Elevated intraocular pressure (IOP) is a major risk factor in the progression of glaucomatous optic neuropathy with a lowering in IOP associated with reduced incidence and delayed progression glaucomatous optic neuropathy and visual field defects. Treatment regimens for a subject frequently begin with a prescription of a beta-blocker with a second drug added to regimen if the beta-blocker is ineffective. A non-selective beta-blocker, 0.5% timolol ophthalmic solution, and ALPHAGAN® (0.2% brimonidine ophthalmic solution), a selective and potent alpha-2 adrenoceptor agonist, have both been shown to be effective therapies with a beta-blocker when they are used adjunctively. Because timolol and brimonidine have different sites of action and different mechanisms by which they lower IOP, there may be an additive IOP-lowering effect within the 2 medications are used conjunctively. Currently, the 2 marketed medications are often prescribed and used together, but this requires that the subject must have 2 separate bottles of medications. Use of 2 separate bottles requires subjects to dose 5 drops per eye per day with a 5-minute wait in-between dosing of the 2 bottles. Allergan has combined these 2 ocular hypotensive medications into a single formulation (Combination) to provide the benefit of adjunctive therapy with a more convenient dosing regimen (i.e. 1 drop in each eye BID). According to Allergan, use of Combination therapy versus Concurrent may improve patient compliance as well as the patient safety profile.

## 2.2 Previous Phase III Studies

Two Phase 3 studies (Study 190342-012T and Study 190342-013T) each compared Combination BID with 0.5% timolol BID or Alphagan TID. The studies failed to show that Combination administered for 12 months was superior to timolol and brimonidine in lowering elevated IOP for all time points considered. Another Phase 3 study (Study 190342-019T) with 2:2:1 randomization compared Combination therapy BID versus Concurrent therapy versus Alphagan TID in patients with glaucoma or ocular hypertension over a 4 week duration. The Combination treatment failed to show non-inferiority or superiority to the Concurrent treatment. In Study 190342-019T, demonstration of non-inferiority required that the upper limit of the 95% CI for the difference was within a 1.0 mm Hg margin at two or all three time points (hours 0, 2 and 8) at Day 28 and 1.5 mm Hg at all three time points at Day 28. This study failed to demonstrate non-inferiority due to the Hour 8 timepoint in which the difference in mean unadjusted IOP was 1.01 with 95% CI of (0.33, 1.69). Therefore, the Combination's IOP-lowering ability is likely to be inferior to that of brimonidine and timolol given concomitantly by approximately 1 mm Hg. Superiority over Alphagan also could not be demonstrated due to the Hour 8 time point, the difference in mean unadjusted IOP was -0.22 (-1.05, 0.61). Further details of study 190342-019T are addressed in the January 2005 statistical review by Dr. Karen Qi.

## 2.3 Data Sources

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# 3. STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy Assessments

No efficacy data was provided in Study 190342-023T.

## 3.2 Evaluation of Safety Assessments

### *3.2.1 Study Design and Endpoints*

Study 190342-23T was a Phase III, multi-center, randomized, parallel, double-blind trial for 4 weeks. Patients were randomized 1:1 to either Combination or Concurrent therapy. The objective was to compare the safety of Combination with Concurrent therapy following ocular administration for 10 days in healthy, adult subjects.

The study consisted of 5 scheduled visits: Screening (Day –21 to Day -3), Baseline (Day –1), Day 1, Day 9, and Day 10. The screening visit occurred at anytime during the day and within Day –21 to Day –3 prior to the baseline visit.

The primary safety endpoints for this study were the proportion of "Sleepiness Responders" and the proportion of "Dry Mouth Responders" in the modified intent-to-treat (mITT) population. A "Sleepiness Responder" was a subject who at any time over the course of the study (i.e. on Day 1, Day 9, Day 10) had a current severity of sleepiness score of at least 4 (Somewhat foggy, let down) on a 7-point scale as well as at least a 2-unit increase from the baseline score. A "Dry Mouth Responder" was a subject who at any time over the course of the study (i.e. on Day 1, Day 9, Day 10) had a current severity of dry mouth score of at least 3 (moderate) on a 5-point scale as well as at least a 1-unit increase from the baseline score.

Other safety assessments included: "Retrospective Question on Inappropriate Sleepiness", "Retrospective Questionnaire on Dry Mouth", "Salivary Flow Assessment", "Other analyses of Current Severity of Sleepiness", "Other Analyses of Current Severity of Dry Mouth" and "Analyses of Dizziness".

Additional sensitivity analyses considered the primary endpoints in the ITT population and safety population. A sensitivity analysis of the proportion of sleepiness responders was performed using restricted set of the mITT population. Subjects included would have a baseline score < 6 units and either reported SSS scores at every post-baseline visit or have met the criteria for a Sleepiness Responder at a post-baseline visit. Another sensitivity analysis was conducted for subjects with no major protocol violations.

### *3.2.2 Subject Disposition and Demographic Characteristics*

Three analysis populations were defined: the safety population consisting of all randomized and treated subjects, the modified intent-to-treat (mITT) population consisting of subjects with baseline and at least 1 post-baseline assessment of the primary endpoint, and the ITT population

consisting of all randomized subjects. 452 subjects were enrolled in the ITT and safety populations with 450 subjects included in the modified intent-to-treat (mITT) population. Of these 450 subjects, 223 were in the Combination group and 227 were in the Concurrent group. The mean age was approximately 30.6 years. There were more females included in the mITT population (65.1%). Approximately 49.8% of subjects were Caucasian, 10.2% Black, 34.4% Hispanic. There were no large differences in the treatment groups with respect to sex or gender classification.

### 3.2.3 Statistical Methodologies

*Statistical Tests*

The general association statistic of the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator was used for the treatment group comparisons. In addition a 2-sided 95% CI interval for the treatment difference in proportions was constructed. The Breslow-Day test was used to assess treatment-by-investigator interaction.

*Multiple Comparisons/Multiplicity*

The primary safety endpoints for this study were the proportion of "Sleepiness Responders" and the proportion of "Dry Mouth Responders" in the mITT population. Hochberg's procedure was applied to adjust for the two prospectively defined endpoints to control the overall type I error rate at 5%.

*Missing Data*

For subjects who did not have any post-baseline assessment, the baseline observation was carried forward. For subjects missing the baseline assessment, determination of responder status was based solely on the follow-up criteria.

### *3.2.4 Results and Conclusions*

*Findings from Primary Safety Assessments*

The proportion of "sleepiness responders" co-primary endpoint was 24.2% (54/223) with Combination versus 30.0% (68/227) with Concurrent therapy. The p-value for the difference in proportions was .179 which was above the .05 significance level required for the largest p-value under the Hochberg procedure for multiple testing. The proportion of "dry mouth responders" co-primary endpoint was 20.3% (45/222) for Combination therapy versus 30.0% (68/227). The p-value for the difference in proportions was .016 which was below the .05/2 = .025 significance level required under the Hochberg procedure when the larger of the two p-values (i.e. .179) is not significant. Therefore, primary study results showed significance in only one of the two co-primary endpoints. Note that the "sleepiness responders" endpoint is clinically the most relevant of the two endpoints. While "sleepiness responder" proportions were numerically lower (i.e. more favorable), results did not show significance. While the "dry mouth responders" endpoint

was also numerically lower and shown to be significant, significance in this endpoint alone did not provide adequate evidence of an improved safety profile.

*Findings from Other Safety Assessments*

Statistical inferences cannot be me made from findings of other safety assessments due to lack of study power for these comparisons as well as a lack of control of multiple testing. However results showed numerically lower responder rates for Combination to the single retrospective question on inappropriate sleepiness in comparison to Concurrent (38.7% vs. 50.0%). The proportion of subjects with decreased salivary flow of at least 1 category from baseline was also numerically lower with Combination than with Concurrent (10.0% vs. 34.1%). Other analyses of sleepiness and dry mouth also tended to show more favorable results with Combination therapy versus Concurrent. Analyses of dizziness, however, showed treatments to be similar.

*Treatment-related Adverse Events*

Treatment-related adverse events (AEs) did not differ greatly between Combination and Concurrent treatments. However, larger numbers of patients in the Combination group reported an AE of eye irritation 17/224 (7.6%) vs. 6/228 (2.6%) (p=.016). Dry mouth was also numerically lower in the Combination arm 5/224 (2.2%) versus 12/228 (5.3%) (p=.09). Treatment-related AEs of dry eye, eye pruritus, fatigue, headache and somnolence were similar between therapies.

*Conclusions*

Adequate evidence of an improved safety profile with Combination therapy versus Concurrent therapy could not be provided due to the lack of significance of proportion "sleepiness responders" a co-primary endpoint considered to be clinically most relevant as well as essential in demonstrating an improved safety profile of Combination therapy versus Concurrent therapy. Use of Combination therapy also raises concerns of adverse events related to eye irritation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

***Proportions of Sleepiness and Dry Mouth Responders by Sex and Race***

There were no notable treatment differences in sleepiness responders by sex and race. All treatment differences for the male, female, black and non-black subgroups were generally similar and non-significant. The proportion of dry mouth responders was generally similar between the Combination arm and Concurrent arms for the male and black subgroups. There were substantial differences in proportions for the female and non-black subgroups, 22.9% (32/140) vs. 34.9% (53/152) and 21.0% (42/200) vs. 31.9% (65/204) respectively. Due to the demographic characteristics of this study, male and black subgroups were relatively small, approximately 35% and 10% of the total sample size, so that analyses in these subgroups were less reliable.

## 5. SUMMARY AND CONCLUSIONS

Overall results from Study 190342-023T failed to show robust evidence towards an improvement in safety based on the proportions of dry mouth responders and sleepiness responders in healthy, adult subjects. The study failed to provide adequate evidence of an improved safety profile for the proportion of "sleepiness responders," a co-primary endpoint considered to be clinically most relevant. Statistical and clinical significance in this endpoint is considered as essential in demonstrating an improved safety profile of Combination therapy versus Concurrent therapy. Although statistical significance was found in the less clinically relevant co-primary endpoint, proportion of "dry mouth responders", this finding by itself did not provide adequate evidence of an improved safety profile. Based on the discussions with the Medical officer, results of Study 190342-023T failed to address the deficiencies raised in the review of the original NDA. Therefore, Combination therapy is not recommended for approval.

## SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Christopher Khedouri, Ph.D.

Date: 11/29/2006

Concurring Reviewer: Thamban Valappil, Ph.D., Team Leader

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HFD-520/Clinical TL/Dr. Boyd
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Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 21-398

**Drug Name:** Brimonidine Tartrate 0.2% / Timolol 0.5% ophthalmic solution

**Indication(s):** Reduction of intraocular pressure in patients with glaucoma or ocular hypertension

**Applicant:** Allergan

**Date(s):** January 3, 2005

**Review Priority:** Standard

**Biometrics Division:** DBIII

**Statistical Reviewer:** Karen Qi

**Concurring Reviewers:** Stan Lin

**Medical Division:** 550

**Clinical Team:** Jennifer Harris, Wiley Chambers

**Project Manager:** Mike Puglisi

**Keywords:** non-inferiority, superiority, ANOVA

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

The brimonidine tartrate 0.2% / timolol 0.5% combination ophthalmic solution BID failed to demonstrate non-inferiority or superiority to concurrent brimonidine tartrate 0.2% TID and timolol 0.5% BID in lowering elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension (OHT). This is because the upper limit of 95% confidence interval (CI) for the difference in mean value of IOP between the two treatment groups at one follow-up time point, Hour 8 on Day 28, was not within the non-inferiority margin defined in the protocol; actually at Hour 8, the combination treatment group had a statistically significantly higher mean IOP than the concurrent treatment group.

## 1.2 Brief Overview of Clinical Studies

In order to assess the efficacy and safety of brimonidine tartrate 0.2% / timolol 0.5% combination ophthalmic solution BID for treatment of elevated IOP in patients with glaucoma or OHT, Allergan submitted a series of clinical studies including 2 pivotal phase 3 trials, 190342-12T and 190342-013T, since September 17, 2001 under NDA 21-398, and got an approvable action letter from FDA on June 5, 2002. On September 13, 2004, Allergan made another submission including a phase 3 trial, 190342-019T, and a summary of clinical safety report including the 12-month data for Studies 190342-12T and 190342-13T, as well as data from 190342-019T. This review will focus on the phase 3 trial, 190342-19T.

Study 190342-19T was a multicenter, double-masked, randomized, parallel, and 4-week trial. The study consisted of 3 treatment groups: 1) brimonidine 0.2% / timolol 0.5% combination ophthalmic solution BID (henceforth referred to as Combination), 2) concurrent Alphagan® (0.2% brimonidine tartrate) TID and timolol 0.5% BID (henceforth referred to as Concurrent) ophthalmic solutions, and 3) Alphagan® ophthalmic solution TID (henceforth referred to as Alphagan). The objective was to evaluate the efficacy and safety of Combination BID compared with Concurrent for 4 weeks in treatment of adult patients with glaucoma or OHT. The Alphagan group was used for validation of study outcomes.

There were 3 scheduled visits: prestudy, baseline (Day 0) and Day 28. The study medication was instilled bilaterally. IOP for both eyes was measured once at the prestudy visit, while diurnal IOP measurements were made at Hours 0, 2 and 8 at baseline (Day 0) and Day 28. The Hour 0 study examinations at baseline and Day 28 were scheduled between 07:00 and 09:00. A total number of 432 patients from 32 sites in United States were randomized in a 2:2:1 allocation to Combination (n=176), Concurrent (n=169), or Alphagan (n=87) groups, stratified by the average IOP from both eyes at Hour 0 at Day 0 across two groups: 1) IOP $\leq$ 25 mm Hg or 2) IOP > 25 mm Hg. The efficacy variables included IOP measurements unadjusted for corneal thickness (henceforth referred to as unadjusted IOP), and IOP adjusted for corneal thickness based on Ehler's approach (henceforth referred as adjusted IOP).

## 1.3 Statistical Issues and Findings

The Combination treatment apparently did not show non-inferiority or superiority to the Concurrent treatment. No statistical issues were found.

# 2. INTRODUCTION

## 2.1 Overview

Timolol 0.5% BID and Brimonidine 0.2% TID have been shown to be effective adjunctive therapies with beta-blocker for lowering IOP when they are used adjunctively. However, using them separately requires patients to dose five drops per day, which may reduce dosing compliance. A more convenient dosing regimen may improve dosing compliance. Allergan has been conducting trials to evaluate the efficacy and safety of Timolol 0.5% / Brimonidine 0.2% combination ophthalmic solution using two doses daily. The studies including 2 pivotal phase 3 trials, 190342-12T and 190342-013T, were submitted to FDA under NDA 21-398. On June 5, 2002, Allergan got a FDA approvable action letter. The present submission is a supplement to NDA 21-398 and includes a phase 3 study, 190342-019T and a summary of clinical safety report including the 12-month data for Studies190342-12T and 190342-013T, as well as data from 190342-019T. This review will focus on the phase 3 study, 190342-19T which was entitled "A multi-center, double-masked, randomized, parallel, and 4-week study of the safety and efficacy of 0.2% Brimonidine Tartrate / 0.5% Timolol combination ophthalmic solution BID compared with concurrent, Alphagan® TID and Timolol BID (0.2% Brimonidine Tartrate and 0.5% Timolol) ophthalmic solutions and Alphagan® (0.2% Brimonidine Tartrate) ophthalmic solution TID in treatment-naïve patients with glaucoma or ocular hypertension". In the study, a total of number of 432 patients from 32 sites in United States was randomized into 3 treatment groups: 176 in Combination, 169 in Concurrent, and 87 in Alphagan.

## 2.2 Data Sources

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# 3. STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy

*Study Design*

Study 190342-19T was a multicenter, double-masked, randomized, parallel, and 4-week trial. The objective was to evaluate the efficacy and safety of Combination BID compared with Concurrent for 4 weeks in treatment of adult patients with glaucoma or OHT. The Alphagan was used for validation of study outcomes.

The study consisted of 3 scheduled visits: prestudy, baseline (Day 0) and Day 28. IOP for both eyes was measured once at the prestudy visit and at Hours 0, 2 and 8 at baseline (Day 0) and Day 28. The Hour 0 study examinations at Days 0 and 28 were scheduled between 07:00 and 09:00. Patients were randomized to Combination (n=176), Concurrent (n=169), or Alphagan (n=87) groups in a 2:2:1 ratio, stratified by the average IOP from both eyes at Hour 0 at Day 0 (IOP $\leq$ 25 mm Hg or IOP > 25 mm Hg).

*Efficacy Assessments*

IOP was the key efficacy parameter and was measured twice at each time point for each eye. If the two measurements differ by 2 mm Hg or less, a third measurement was not required. If the two measurements differed by more than 2 mm Hg, a third measurement was made. A single value of IOP was derived for each eye by calculating the average IOP if 2 measurements were taken and the median IOP if 3 were

taken. For each patient, the IOP averaged between both eyes at the same time point was used for analysis. If an IOP measurement was available for only one eye at a time point, mean IOP was represented by the IOP from that eye particular time point.

*Analysis Sets*

There were two analysis populations. The intent-to-treat (ITT) population consisted of all randomized patients, and was used for the analysis of all efficacy analyses and summaries of baseline characteristics. The per protocol (PP) population included patients who had no major protocol violations, received study medication, and had at least one follow-up visit.

*Missing Data*

Missing values of IOP was imputed using the last observation carried forward (LOCF) for the analysis based on ITT population only. Data from a patient's last observation visit was carried forward in the analysis to the same hour of the subsequent visit.

*Patient Disposition, Demographic and Baseline Characteristics*

Among the 432 patients enrolled in the study, 176 were randomized to Combination group, 169 in Concurrent group, and 87 in Alphagan group. In the ITT population, 93.3% (403/432) of patients completed the study. Overall, 6.7% (29/432) of patients discontinued the study prior to Day 28: 6.3% (11/176) of patients in Combination group, 6.5% (11/169) of patients in the Concurrent group, and 8.0% (7/87) of patients in the ALPHAGAN group. The most frequently reported reason for discontinuation of the study was adverse events (3.9%, 17/432). A total of 4.0% (7/176) of patients in the Combination group, 4.1% (7/169) of patients in the Concurrent group, and 3.4% (3/87) of patients in the Alphagan group discontinued due to adverse events. Other reasons for discontinuation were administrative reasons (1.6%, 7/432), protocol violation (0.7%, 3/432), and other reasons (0.5%, 2/432). The PP population included 406 patients, with 167 in Combination, 160 in Concurrent, and 79 in Alphagan. Detailed information on patient disposition is shown in Table 1 below.

**Table 1. Patient Disposition**

| Exit Status | Combination | Concurrent | Alphagan | Total |
|---|---|---|---|---|
| ITT population | | | | |
| Enrolled | 176 | 169 | 87 | 432 |
| Completed | 165 (93.8%) | 158 (93.5%) | 80 (92.0%) | 403 (93.3%) |
| Discontinued | 11 ( 6.3%) | 11 ( 6.5%) | 7 ( 8.0%) | 29 ( 6.7%) |
| Lack of Efficacy | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Adverse Events | 7 ( 4.0%) | 7 ( 4.1%) | 3 ( 3.4%) | 17 ( 3.9%) |
| Ocular | 2 ( 1.1%) | 3 ( 1.8%) | 1 ( 1.1%) | 6 ( 1.4%) |
| Non-ocular | 6 ( 3.4%) | 4 ( 2.4%) | 2 ( 2.3%) | 12 ( 2.8%) |
| Pregnancy | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Administrative Reason | 2 ( 1.1%) | 2 ( 1.2%) | 3 ( 3.4%) | 7 ( 1.6%) |
| Lost to Follow Up | 2 ( 1.1%) | 2 ( 1.2%) | 2 ( 2.3%) | 6 ( 1.4%) |
| Personal Reasons | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 1.1%) | 1 ( 0.2%) |
| Protocol Violation | 1 ( 0.6%) | 2 ( 1.2%) | 0 ( 0.0%) | 3 ( 0.7%) |
| Other | 1 ( 0.6%) | 0 ( 0.0%) | 1 ( 1.1%) | 2 ( 0.5%) |
| PP population | | | | |
| Enrolled | 167 | 160 | 79 | 406 |
| Completed | 158 (94.6%) | 152 (95.0%) | 76 (96.2%) | 386 (95.1%) |
| Discontinued | 9 ( 5.4%) | 8 ( 5.0%) | 3 ( 3.8%) | 20 ( 4.9%) |
| Lack of Efficacy | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Adverse Events | 7 ( 4.2%) | 6 ( 3.8%) | 3 ( 3.8%) | 16 ( 3.9%) |
| Ocular | 2 ( 1.2%) | 3 ( 1.9%) | 1 ( 1.3%) | 6 ( 1.5%) |
| Non-ocular | 6 ( 3.6%) | 3 ( 1.9%) | 2 ( 2.5%) | 11 ( 2.7%) |
| Pregnancy | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Administrative Reason | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Lost to Follow Up | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Personal Reasons | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Protocol Violation | 1 ( 0.6%) | 2 ( 1.3%) | 0 ( 0.0%) | 3 (0.7%) |
| Other | 1 ( 0.6%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.6%) |

Of all 432 patients in ITT population, the mean age was 57.5 years (range 20 to 89 years). There were more females (60.9%, 263/432) than males (39.1%, 169/432). The entry diagnosis was glaucoma for 27.1% (117/432) of patients, OHT for 67.6% (292/432) of patients, and glaucoma in one eye and OHT in the other eye for 5.3% (23/432) of patients. At baseline, the mean values for central corneal thickness, visual field deviation and ocular anterior radius were 564.3 μm (range 397 to 698 μm), -2.657 dB (range -27.43 to 7.45 dB) and 7.722 mm (range 7.08 to 8.54 mm), respectively. There were no statistically significant difference among the 3 treatment groups for any of these demographic and baseline characteristics. The detailed information on the demographic and baseline characteristics is displayed in Table 2 below. Since demographic and baseline characteristics for PP population were similar to those for ITT population, the results for PP population will not be reported.

**Table 2. Demographics (ITT population)**

| | Combination (N=176) | Concurrent (N=169) | Alphagan (N=87) | Total (N=432) | P-value[a] |
|---|---|---|---|---|---|
| Age (yrs) | | | | | 0.208 |
| Mean | 57.2 | 58.6 | 55.9 | 57.5 | |
| SD | 12.63 | 10.97 | 12.99 | 12.10 | |
| Median | 56.5 | 59.0 | 56.0 | 57.0 | |
| Min | 20 | 22 | 21 | 20 | |
| Max | 89 | 85 | 85 | 89 | |
| < 45 | 22 (12.5%) | 16 ( 9.5%) | 14 (16.1%) | 52 (12.0%) | |
| 45 – 65 | 102 (58.0%) | 99 (58.6%) | 55 (63.2%) | 256 (59.3%) | |
| > 65 | 52 (29.5%) | 54 (32.0%) | 18 (20.7%) | 124 (28.7%) | |
| Sex | | | | | 0.485 |
| Male | 74 (42.0%) | 65 (38.5%) | 30 (34.5%) | 169 (39.1%) | |
| Female | 102 (58.0%) | 104 (61.5%) | 57 (65.5%) | 263 (60.9%) | |
| Race | | | | | 0.639 |
| Non-Black | 144 (81.8%) | 142 (84.0%) | 69 (79.3%) | 355 (82.2%) | |
| Asian | 3 ( 1.7%) | 1 ( 0.6%) | 0 ( 0.0%) | 4 ( 0.9%) | |
| Caucasian | 115 (65.3%) | 119 (70.4%) | 57 (65.5%) | 291 (67.4%) | |
| Hispanic | 25 (14.2%) | 22 (13.0%) | 10 (11.5%) | 57 (13.2%) | |
| Other | 1 ( 0.6%) | 0 ( 0.0%) | 2 ( 2.3%) | 3 ( 0.7%) | |
| Black | 32 (18.2%) | 27 (16.0%) | 18 (20.7%) | 77 (17.8%) | |
| Weight (kg) | | | | | 0.441 |
| Mean | 84.93 | 83.82 | 87.56 | 85.03 | |
| SD | 22.704 | 18.887 | 26.616 | 22.171 | |
| Median | 81.15 | 81.60 | 81.20 | 81.20 | |
| Min | 39.5 | 48.5 | 51.3 | 39.5 | |
| Max | 170.1 | 149.7 | 176.9 | 176.9 | |
| Height (cm) | | | | | 0.629 |
| Mean | 168.2 | 167.6 | 167.0 | 167.7 | |
| SD | 9.58 | 9.68 | 9.81 | 9.65 | |
| Median | 168.0 | 165.0 | 165.0 | 168.0 | |
| Min | 147 | 147 | 147 | 147 | |
| Max | 188 | 193 | 191 | 193 | |
| Iris Color | | | | | 0.421 |
| Light | 76 (43.2%) | 84 (49.7%) | 43 (49.4%) | 203 (47.0%) | |
| Blue | 37 (21.0%) | 37 (21.9%) | 22 (25.3%) | 96 (22.2%) | |
| Green | 8 ( 4.5%) | 11 ( 6.5%) | 6 ( 6.9%) | 25 ( 5.8%) | |
| Hazel | 28 (15.9%) | 36 (21.3%) | 14 (16.1%) | 78 (18.1%) | |
| Other | 3 ( 1.7%) | 0 ( 0.0%) | 1 ( 1.1%) | 4 ( 0.9%) | |
| Dark | 100 (56.8%) | 85 (50.3%) | 44 (50.6%) | 229 (53.0%) | |
| Brown | 100 (56.8%) | 85 (50.3%) | 44 (50.6%) | 229 (53.0%) | |
| Dark Brown | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | |

[a] P-values for continuous variables were from 1-way ANOVA, and P-values for categorical variables were from Pearson's Chi-Square test.

(to be continued)

**Table 2. Demographics (ITT population)**

| | Combination (N=176) | Concurrent (N=169) | Alphagan (N=87) | Total (N=432) | P-value[a] |
|---|---|---|---|---|---|
| Mean Deviation of Visual Field (dB)[b] | | | | | 0.213 |
| Mean | -2.362 | -3.031 | -2.529 | -2.657 | |
| SD | 3.0058 | 4.3873 | 2.9805 | 3.6107 | |
| Median | -1.675 | -1.750 | -1.730 | -1.720 | |
| Min | -14.00 | -27.43 | -14.81 | -27.43 | |
| Max | 2.06 | 7.45 | 2.07 | 7.45 | |
| Corneal Thickness (microns)[c] | | | | | 0.659 |
| Mean | 562.3 | 565.5 | 566.2 | 564.3 | |
| SD | 36.37 | 40.53 | 40.44 | 38.82 | |
| Median | 559.5 | 566.0 | 565.0 | 563.5 | |
| Min | 454 | 397 | 475 | 397 | |
| Max | 698 | 682 | 660 | 698 | |
| < 555 | 71 (40.3%) | 72 (42.6%) | 32 (36.8%) | 175 (40.5%) | |
| >= 555 - < 600 | 83 (47.2%) | 64 (37.9%) | 37 (42.5%) | 184 (42.6%) | |
| >= 600 | 22 (12.5%) | 33 (19.5%) | 18 (20.7%) | 73 (16.9%) | |
| Ocular Anterior Radium (mm)[c] | | | | | 0.201 |
| Mean | 7.730 | 7.737 | 7.676 | 7.722 | |
| SD | 0.2611 | 0.2782 | 0.2505 | 0.2662 | |
| Median | 7.730 | 7.730 | 7.670 | 7.725 | |
| Min | 7.08 | 7.09 | 7.09 | 7.08 | |
| Max | 8.54 | 8.37 | 8.52 | 8.54 | |
| Ophthalmic Diagnosis | | | | | 0.796 |
| Glaucoma | 50 (28.4%) | 42 (24.9%) | 25 (28.7%) | 117 (27.1%) | |
| OHT | 119 (67.6%) | 116 (68.6%) | 57 (65.5%) | 292 (67.6%) | |
| Glaucoma / OHT | 7 ( 4.0%) | 11 ( 6.5%) | 5 ( 5.7%) | 23 ( 5.3%) | |

[a] P-values for continuous variables were from 1-way ANOVA, and P-values for categorical variables were from Pearson's Chi-Square test.
[b] Worse value between both eyes was used.
[c] Averaged value from both eyes were used.

*Efficacy Endpoints and Statistical Methodologies*

The primary analysis was the comparison of unadjusted IOP between Combination and Concurrent in ITT population. A combined test of non-inferiority test using a confidence interval approach and statistical superiority test was performed. That is,

- Non-inferiority test

  Both the non-inferiority margins $\delta = 1.0$ mm Hg and $\delta = 1.5$ mm Hg were tested. The null hypothesis was that the mean unadjusted IOP for the Combination group was at least $\delta$ mm Hg greater than that of Concurrent group. The alternative hypothesis was that the mean of the unadjusted IOP for the Combination group was not $\delta$ mm Hg or more higher than that of the Concurrent group. A two-sided 95% CI based on 2-way ANOVA including factors for treatment and investigator was conducted for the difference in mean of the unadjusted IOP between the 2 groups at each time point at Day 28 to test the hypothesis. If the upper limit of the 95% CI for the difference was within a 1.0 mm Hg Margin at two or all three time points at Day 28 and 1.5 mm Hg

at all three time points at Day 28, then the Combination treatment would be declared non-inferior to the Concurrent treatment.

- Superiority test

  The null hypothesis was that there was no difference in unadjusted IOP between the Combination and Concurrent groups, and the alternative hypothesis was that there was a difference. The hypothesis was tested using a 2-way ANOVA including factors for treatment and investigator at the significance level of 0.05.

In addition, pairwise comparisons of IOP at baseline among the 3 treatment groups were made using contrasts from the ANOVA. If baseline IOP was significantly different between any two groups, then the primary endpoint was analyzed using ANCOVA with fixed effects for treatment and investigator, and baseline IOP as a covariate. Also, the treatment-by-investigator interaction was examined using ANOVA for the investigators who had enrolled at least 3 patients per treatment arm.

The following secondary efficacy analyses were conducted using the same methods as those for the primary analysis unless otherwise specified:

- Comparisons of unadjusted IOP between Combination and Alphagan or between Concurrent and Alphagan in ITT population
- Comparison of unadjusted IOP between Combination and Concurrent in PP population without imputation of missing IOP
- Pairwise comparison of change from baseline in unadjusted IOP at all 3 time points on Day 28 among 3 treatment groups in ITT population
- Comparison of the incidence of patients achieving target unadjusted IOP < 18 mm Hg at all 3 time points on Day 28 among 3 treatment groups in ITT population, using Cochran-Mantel-Haenszel (CMH) test with modified ridit scores, adjusting for investigator
- Analyses for adjusted IOP was performed using the same methods as those for unadjusted IOP for the following endpoints:
  - Adjusted IOP values on baseline and Day 28
  - Change from baseline in adjusted IOP on Day 28
  - Incidence rate of patients achieving target adjusted IOP < 18 mm Hg at all follow-up time points

*Results and Conclusions*

Primary Analysis

- Comparison of unadjusted IOP between Combination and Concurrent in ITT population with LOCF

At baseline, the mean values of unadjusted IOP among the 3 time points in the ITT population ranged from 21.9 to 24.1 mm Hg in the Combination group, 22.4 to 24.2 mm Hg in the Concurrent group, and 22.0 to 24.0 mm Hg in the Alphagan group. There was no statistically significant difference in mean value of unadjusted IOP between any 2 of the 3 treatment groups at any baseline time point. Thus ANCOVA with baseline IOP as a covariate was not performed.

At Day 28, the mean values of unadjusted IOP ranged from 16.1 to 18.4 mm Hg in Combination group, and 16.0 to 18.1 mm Hg in Concurrent group. The upper limit of the 95% CI for the difference in mean of unadjusted IOP between Combination and Current (Combination – Concurrent) was 0.99 mm Hg at Hour 0, 0.58 mm Hg at Hour 2, and 1.69 mm Hg at Hour 8. Obviously, the upper limit of the 2-sided 95% CI at Hour 8 was not within the 1.5 mm Hg non-inferiority margin. Thus, the Combination treatment cannot be declared non-inferiority to the Concurrent treatment. Moreover, the mean of unadjusted IOP in the Combination group was not significantly different from that in the Concurrent group at all time points except Hour 8, when the Combination group had a significantly higher mean IOP than the Concurrent group (16.9 vs 16.0 mm Hg, p=0.004). The results are displayed in Table 3 below. There was no significant interaction between treatment and investigational site at any time point at either baseline or Day 28.

Secondary Analyses

- Comparisons of unadjusted IOP between Combination and Alphagan or between Concurrent and Alphagan in ITT population with LOCF

  The mean values of unadjusted IOP at Day 28 were significantly lower in each of the Combination and Concurrent groups compared with the Alphagan group at Hours 0 and 2 ($p<0.0001$). The Concurrent group also had significantly lower mean IOP than Alphagan group at Hour 8 (p=0.004). The results are displayed in Table 3 below.

- Comparison of unadjusted IOP between Combination and Concurrent in PP population without imputation of missing IOP

  At baseline and Day 28, the mean values of unadjusted IOP for PP population in the 3 treatment groups were very similar to those for ITT population. Hence they are not reported here.

  At Day 28, the upper limit of the 95% CI for the between-group difference in mean unadjusted IOP (Combination – Concurrent) was 1.09 mm Hg at Hour 0, 0.54 mm Hg at Hour 2, and 1.70 mm Hg at Hour 8. Therefore, the difference in mean unadjusted IOP between the Combination and Concurrent groups was within the 1 mm Hg non-inferiority margin only at 1 time point; and within the 1.5 mm Hg non-inferiority only at 2 time points. This again indicates that the Combination group cannot be declared non-inferiority to Concurrent group.

  The mean unadjusted IOP values at Day 28 were significantly lower in each of Combination and Concurrent groups compared with Alphagan at Hours 0 and 2 ($p<0.001$). The Concurrent group also had significantly lower mean unadjusted IOP than Alphagan group at Hour 8 (p=0.002). Since the results were very similar to those for ITT population, they are not tabulated in detail here.

**Table 3. Mean of Unadjusted IOP (mm Hg) at Each Scheduled Time Point (ITT Population with LOCF)**

| Time Point | | Combination (N=176) | Concurrent (N=169) | Alphagan (N=87) | Combination vs Concurrent P-value Difference (95% CI)[a] | Combination vs Alphagan P-value Difference (95% CI)[a] | Concurrent vs Alphagan P-value Difference (95% CI)[a] |
|---|---|---|---|---|---|---|---|
| Baseline | | | | | | | |
| | Hour 0 | | | | 0.754 | 0.629 | 0.461 |
| | Mean | 24.1 | 24.2 | 24.0 | -0.08 | 0.15 | 0.23 |
| | SD | 2.20 | 2.64 | 2.21 | (-0.57, 0.42) | (-0.45, 0.75) | (-0.38, 0.83) |
| | Median | 23.5 | 23.5 | 23.5 | | | |
| | Min | 21.0 | 21.0 | 21.0 | | | |
| | Max | 30.8 | 32.5 | 31.5 | | | |
| | Hour 2 | | | | 0.596 | 0.866 | 0.547 |
| | Mean | 23.0 | 23.3 | 23.0 | -0.15 | 0.06 | 0.20 |
| | SD | 2.48 | 2.78 | 2.87 | (-0.68, 0.39) | (-0.60, 0.71) | (-0.45, 0.86) |
| | Median | 22.8 | 23.0 | 23.0 | | | |
| | Min | 16.5 | 15.0 | 14.0 | | | |
| | Max | 30.5 | 31.5 | 32.3 | | | |
| | Hour 8 | | | | 0.201 | 0.989 | 0.302 |
| | Mean | 21.9 | 22.4 | 22.0 | -0.36 | -0.00 | 0.35 |
| | SD | 2.58 | 3.05 | 2.69 | (-0.91, 0.19) | (-0.67, 0.66) | (-0.32, 1.02) |
| | Median | 21.9 | 22.0 | 22.0 | | | |
| | Min | 14.0 | 12.5 | 16.3 | | | |
| | Max | 28.3 | 31.8 | 29.0 | | | |
| Day 28 | | | | | | | |
| | Hour 0 | | | | 0.206 | <0.001[b] | <0.001[c] |
| | Mean | 18.4 | 18.1 | 20.9 | 0.39 | -2.48 | -2.87 |
| | SD | 2.95 | 3.07 | 3.37 | (-0.21, 0.99) | (-3.21, -1.75) | (-3.60, -2.13) |
| | Median | 18.3 | 18.0 | 20.5 | | | |
| | Min | 11.3 | 9.0 | 14.5 | | | |
| | Max | 27.3 | 31.5 | 29.0 | | | |
| | Hour 2 | | | | 0.777 | <0.001[b] | <0.001[c] |
| | Mean | 16.1 | 16.3 | 18.3 | -0.10 | -2.11 | -2.02 |
| | SD | 3.45 | 3.13 | 3.25 | (-0.78, 0.58) | (-2.94, -1.29) | (-2.84, -1.19) |
| | Median | 15.6 | 16.0 | 18.0 | | | |
| | Min | 8.0 | 9.8 | 12.0 | | | |
| | Max | 29.5 | 27.5 | 28.0 | | | |
| | Hour 8 | | | | 0.004[d] | 0.604 | 0.004[c] |
| | Mean | 16.9 | 16.0 | 17.2 | 1.01 | -0.22 | -1.23 |
| | SD | 3.50 | 3.10 | 3.24 | (0.33, 1.69) | (-1.05, 0.61) | (-2.06, -0.40) |
| | Median | 16.6 | 16.0 | 17.0 | | | |
| | Min | 8.8 | 9.3 | 11.0 | | | |
| | Max | 28.3 | 27.3 | 26.0 | | | |

[a] P-values and 95% CI were based on pairwise contrasts from a 2-way ANOVA at each time point with factors for treatment and investigator.

[b] Combination mean of unadjusted IOP statistically significantly lower than Alphagan at Hours 0 and 2 on Day 28 ($p<0.001$).

[c] Concurrent mean of unadjusted IOP statistically significantly lower than Alphagan at all time points on Day 28 ($p<0.001$ for Hours 0 and 2, and $p=0.004$ at Hour 8).

[d] Concurrent mean of unadjusted IOP statistically significantly lower than Combination at Hour 8 on Day 28 ($p=0.004$).

- Comparison of change from baseline in unadjusted IOP at all time points on Day 28 among 3 treatment groups in ITT population with LOCF

  The mean of the changes from baseline in unadjusted IOP at Day 28 ranged from -5.0 to -7.0 mm Hg in the Combination group, and -6.1 to -7.0 mm Hg in the Concurrent group, and -3.1 to -4.9 mm Hg in the Alphagan group. The mean decrease from baseline in IOP were statistically significant within each treatment group at each time point at Day 28 ($p<0.001$).

  At Day 28, there was no statistically significant difference in mean decrease from baseline in IOP between the Combination and Concurrent groups at all time points except Hour 8, when Concurrent group had a greater decrease from baseline IOP than Combination group (-6.4 vs. -5.0 mm Hg, $p<0.001$). The upper limit of the 95% CI for the between-group difference in mean change from baseline IOP (Combination – Concurrent) was 1.10 mm Hg at Hour 0, 0.73 mm Hg at Hour 2, and 2.06 mm Hg at Hour8. On the other hand, each of Combination and Concurrent groups had statistically significantly greater mean decreases from baseline in unadjusted IOP values than those in Alphagan group at Hours 0 and 2 ($P<0.001$), and the Concurrent group also had significantly greater decrease than Alphagan at Hour 8. The detailed results are shown in Table 4 below.

**Table 4. Mean Change from Baseline in Unadjusted IOP (mm Hg) at Each Scheduled Time Point at Day 28 (ITT Population with LOCF)**

| Time Point | | Combination (N=176) | Concurrent (N=169) | Alphagan (N=87) | Combination vs Concurrent P-value Difference (95% CI)[a] | Combination vs Alphagan P-value Difference (95% CI)[a] | Concurrent vs Alphagan P-value Difference (95% CI)[a] |
|---|---|---|---|---|---|---|---|
| Day 28 | | | | | 0.148 | <0.001[c] | <0.001[d] |
| | Hour 0 | | | | 0.47 | -2.63 | -3.10 |
| | Mean | -5.7 | -6.1 | -3.1 | (-0.17, 1.10) | (-3.40, -1.86) | (-3.87, -2.32) |
| | SD | 3.08 | 3.16 | 2.72 | | | |
| | Median | -5.8 | -6.0 | -3.3 | | | |
| | Min | -14.3 | -17.0 | -10.0 | | | |
| | Max | 3.3 | 1.5 | 2.5 | | | |
| | P-value[b] | <0.001 | <0.001 | <0.001 | | | |
| | Hour 2 | | | | 0.892 | <0.001[c] | <0.001[d] |
| | Mean | -7.0 | -7.0 | -4.8 | 0.05 | -2.18 | -2.23 |
| | SD | 3.23 | 3.31 | 3.24 | (-0.64, 0.73) | (-3.01, -1.34) | (-3.06, -1.39) |
| | Median | -7.0 | -7.0 | -5.0 | | | |
| | Min | -15.8 | -15.0 | -13.3 | | | |
| | Max | 0.5 | 1.8 | 6.3 | | | |
| | P-value[b] | <0.001 | <0.001 | <0.001 | | | |
| | Hour 8 | | | | <0.001[e] | 0.619 | <0.001[d] |
| | Mean | -5.0 | -6.4 | -4.9 | 1.37 | -0.21 | -1.58 |
| | SD | 3.19 | 3.53 | 3.46 | (0.67, 2.06) | (-1.06, 0.63) | (-2.43, -0.73) |
| | Median | -5.3 | -6.5 | -5.0 | | | |
| | Min | -15.8 | -16.3 | -14.5 | | | |
| | Max | 3.5 | 3.5 | 2.0 | | | |
| | P-value[b] | <0.001 | <0.001 | <0.001 | | | |

[a] P-values and 95% CI were based on pairwise contrasts from a 2-way ANOVA at each time point with factors for treatment and investigator.
[b] P-values for within-group changes from baseline were from paired t-tests.
[c] Combination mean change from baseline unadjusted IOP statistically significantly greater than Alphagan at Hours 0 and 2 on Day 28 ($p<0.001$).
[d] Concurrent mean change from baseline unadjusted IOP statistically significantly greater than Alphagan at all time points on Day 28 ($p<0.001$).
[e] Concurrent mean change from baseline unadjusted IOP statistically significantly greater than Combination at Hour 8 on Day 28 ($p<0.001$).

- Comparison of the incidence of patients achieving target unadjusted IOP < 18 mm Hg at all follow-up time points among 3 treatment groups in ITT population with LOCF

  There was no statistically significant difference between the Combination (35.8%, 63/176) and Concurrent (43.2%, 73/169) groups in the number of patients who achieved target unadjusted IOP < 18 mm Hg at all follow-up time points. However, each of Combination and Concurrent groups had significantly higher percentage of patients achieving target unadjusted IOP < 18 mm Hg than Alphagan group (14.9%, 13/87, p<0.001). The detailed results are shown in Table 5 below.

**Table 5. Number of Patients Achieving Unadjusted IOP < 18 mm Hg at All Follow-Up Time Points (ITT population with LOCF)**

| Day 28 | Combination (N=176) | Concurrent (N=169) | Alphagan (N=87) |
|---|---|---|---|
| Yes | 63 (35.8%) | 73 (43.2%) | 13 (14.9%)[a] |
| No | 113 (64.2%) | 96 (56.8%) | 74 (85.1%) |

[a] Number (percent) of patients achieving target pressure statistically significantly greater with each of Combination and Concurrent than with Alphagan (p<0.001) based on Pearson's chi-square test.

- Comparison of adjusted IOP among 3 treatment groups in ITT population with LOCF

  At baseline, mean values of adjusted IOP for the ITT population ranged from 19.0 to 21.2 mm Hg in Combination group, 19.2 to 21.1 mm Hg in Concurrent group, and 18.8 to 20.8 mm Hg in Alphagan group. There was no statistically significantly different in mean value of adjusted IOP between any treatment groups at any baseline time point.

  At Day 28, mean value of adjusted IOP ranged from 13.2 to 15.5 mm Hg in the Combination group, 12.9 to 15.0 mm Hg in the Concurrent group, and 14.0 to 17.8 mm Hg in Alphagan group. The upper limit of the 95% CI for the between-group difference in mean adjusted IOP (Combination – Concurrent) was 1.32 mm Hg at Hour 0, 0.90 mm Hg at Hour 2, and 2.00 mm Hg at Hour 8. Thus, the difference in mean adjusted IOP between Combination and Concurrent groups was within the 1 mm Hg non-inferiority margin only at 1 time point (Hour 2); and within the 1.5 mm Hg margin of non-inferiority at only 2 time points (Hours 0 and 2). Moreover, there was no significant difference in mean value of adjusted IOP between the Combination and Concurrent groups at all time points except Hour 8, when the Concurrent group had a lower mean adjusted IOP than the Combination group (12.9 vs. 14.0 mm Hg, p=0.003). Meanwhile, at Day 28, mean adjusted IOP value was significantly lower in each of Combination and Concurrent groups compared with Alphagan group at Hours 0 and 2 (p<0.001). Other comparative results were very similar to those for unadjusted IOP. Thus, they are not tabulated here.

- Comparison of change from baseline in adjusted IOP at Hours 0, 2 and 8 on Day 28 among 3 treatment groups in ITT population with LOCF

  The results of the comparison of change from baseline in adjusted IOP at all time point on Day 28 among the treatment groups were almost identical to those for unadjusted IOP in terms of numerical and statistical advantage. So they are not reported here.

- Comparison of the incidence of patients achieving target adjusted IOP < 18 mm Hg at all follow-up time points among 3 treatment groups in ITT population with LOCF

The percentage of patients achieving targeted adjusted IOP < 18 mm Hg in the Combination group (71.6%, 126/176) was not significantly different from that in the Concurrent (76.9%, 130/169) group. However, each of the Combination and Concurrent groups had significantly higher percentage of patients achieving target unadjusted IOP < 18 mm Hg than the Alphagan group (54.0%, 47/87, p<0.005). The detailed results are displayed in Table 6 below.

**Table 6. Number of Patients Achieving Adjusted IOP < 18 mm Hg at All Follow-Up Time Points (ITT population with LOCF)**

| Day 28 | Combination (N=176) | Concurrent (N=169) | Alphagan (N=87) |
|---|---|---|---|
| Yes | 126 (71.6%) | 130 (76.9%) | 47 (54.0%)[a] |
| No | 50 (28.4%) | 39 (23.1%) | 40 (46.0%) |

[a] Number (percent) of patients achieving target pressure statistically significantly greater with each of Combination and Concurrent than with Alphagan (p<0.001) based on Pearson's chi-square test.

Supplemental Analysis

- Comparison of mean diurnal IOP among the 3 treatment groups

A supplemental analysis was performed to summarize the mean diurnal IOP averaged over all 3 time points at baseline and Day 28 (hereafter referred to as mean diurnal IOP). Baseline mean diurnal IOP was 17.1, 16.8 and 18.8 mm Hg in the Combination, Concurrent and Alphagan groups, respectively, with no significant difference between any of the treatment groups. At Day 28, there was no significant difference in mean diurnal IOP between the Combination and Concurrent groups (17.1 vs 16.8 mm Hg), and each of the Combination and Concurrent groups had a significantly lower mean diurnal IOP than the Alphagan group (18.8 mm Hg, p<0.001). Detailed results are shown in Table 7.

**Table 7. Mean Diurnal IOP (ITT Population with LOCF)**

| Time Point | Combination (N=176) | Concurrent (N=169) | Alphagan (N=87) | Combination vs Concurrent P-value Difference (95% CI)[a] | Combination vs Alphagan P-value Difference (95% CI)[a] | Concurrent vs Alphagan P-value Difference (95% CI)[a] |
|---|---|---|---|---|---|---|
| Baseline | 23.0 | 23.3 | 23.0 | 0.404<br>-0.19<br>(-0.65, 0.26) | 0.814<br>0.07<br>(-0.49, 0.62) | 0.359<br>0.26<br>(-0.30, 0.82) |
| Day 28 | 17.1 | 16.8 | 18.8 | 0.139<br>0.43<br>(-0.14, 1.01) | <0.001[b]<br>-1.60<br>(-2.30, -0.90) | <0.001[b]<br>-2.04<br>(-2.74, -1.33) |

[a] P-values and 95% CI were based on pairwise contrasts from a 2-way ANOVA at each time point with factors for treatment and investigator.

[b] Both Combination mean IOP and Concurrent mean IOP statistically significantly lower than Alphagan (p<0.001).

*Reviewer's Comments*

The data was re-analyzed by reviewer according to the statistical analysis plan. The results for efficacy analyses match with those submitted by sponsor.

In ITT population with LOCF, the results from the primary analysis indicated that the upper limit of 95% for the difference in mean values of unadjusted IOP between the Combination and Concurrent groups

(Combination-Concurrent) was within the 1.5 mm Hg non-inferiority margin at only 2 time points (0.99 mm Hg at Hour 2, and 0.58 mm Hg at Hour 2). This did not meet one of the two criteria for declaring non-inferiority of the Combination to Concurrent which was defined in the protocol and required that the upper limit of the 95% CI for the difference in means of unadjusted IOP between the two groups should be less than 1.5 mm Hg for all 3 time points at Day 28. Thus, the Combination treatment failed to demonstrate non-inferiority to the Concurrent treatment. Furthermore, the means of unadjusted IOP were not statistically significantly different between these two groups at all follow-up time points except at Hour 8, when the Combination group even had a significantly higher mean IOP than Concurrent group. The analyses based on PP population gave similar results. The study failed to demonstrate non-inferiority or superiority of the Combination treatment to the Concurrent treatment.

### 3.2 Evaluation of Safety

Please refer to Dr. Harris's review report.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

The interaction between treatment group and subgroup of gender, race or age at each time point was investigated. No statistically significant interaction between treatment and gender, race or age was found. However, within each gender, the mean of unadjusted IOP was significantly different among the 3 groups at the 3 post baseline time points. Pairwise comparisons indicated that these significant differences were the results of the significant differences between each of the Combination and Concurrent groups and the Alphagan group at all follow-up points except for female patients at Hour 8 on Day 28, when the significant difference came from the significant difference between the Combination and Concurrent groups.

### 4.2 Other Special/Subgroup Populations

The treatment by iris color interaction was not significant at all time points except at Hour 0 on Day 28. Within each iris color (dark or light), the mean of unadjusted IOP was significantly different among the 3 groups at the 3 follow-up time points.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

One of the two criteria for declaring non-inferiority of the Combination to Concurrent, defined in the protocol, was that the upper limit of the 95% CI for the difference in means of unadjusted IOP between the two groups (Combination – Concurrent) in ITT population should be less than 1.5 mm Hg for all 3 post baseline time points. However, the 95% CI for the difference at Hour 8 on Day 28 was (0.33, 1.69), which appeared not to meet the criteria. The analysis results for PP population supported the finding. Therefore, the study failed to demonstrate non-inferiority of Combination to Concurrent.

### 5.2 Conclusions and Recommendations

The upper limit of the 95% CI for the difference in means of unadjusted IOP between the Combination and Concurrent groups at Hour 8 on Day 28 was not within the non-inferiority margin defined in the

protocol, and no significant difference in mean of unadjusted IOP between the two treatment groups at any post baseline time point except at Hour 8, when the Combination group actually had a significantly higher mean IOP than the Concurrent group. The secondary analyses supported the findings. Thus, the Combination treatment cannot be declared non-inferior or superior to the Concurrent treatment.

## SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer:Karen Qi, Ph. D.
Date: 01/19/05

Concurring Reviewer(s): Stan Lin, Ph. D.

Statistical Team Leader:Stan Lin, Ph. D.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
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# Statistical Review and Evaluation

## CLINICAL STUDIES

| | |
|---|---|
| NDA: | 21398 |
| Name of drug: | Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution |
| Applicant: | Allergan, Inc. |
| Indication: | For reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension |
| Documents reviewed: | Statistical reports from |
| | \\Cdsesub1\n21398\N_000\2001-09-17\clinstat |
| | Data from |
| | \\Cdsesub1\n21398\N_000\2001-09-17\Crt |
| Project manager: | Michael Puglisi |
| Clinical reviewer: | Jennifer Harris, M.D. |
| Dates: | Received 9/18/2001 |
| Statistical reviewer: | Suktae Choi, Ph.D. |
| Statistics team leader: | Stan Lin, Ph.D. |
| Biometrics division director: | Mo Huque, Ph.D. |

Keywords: NDA review, clinical studies, analysis of variance

# 1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

This NDA failed to show that Brimonidine Tartrate 0.2%/Timolol 0.5 % Ophthalmic Solution has an adequate efficacy in lowering the elevated IOP of patients with glaucoma or ocular hypertension compare with 0.5% Timolol and ALPHAGAN®. In this submission, Brimonidine Tartrate 0.2%/Timolol 0.5 % Ophthalmic Solution, is a combination formulation of two active drugs Brimonidine and Timolol. Therefore, adequate efficacy compare to each active drug is necessary for approval.

## 1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Sponsor submitted four studies in this NDA, one PK study (190342-016t), one Phase II study (190342-011t), and two Phase III studies (190342-012t, 190342-013t). This review focused only on two Phase III studies.

### 1.2.1 STUDY 190342-012T

This study was a multicenter (27 sites in U.S.), double-masked, randomized study (into 3 groups, Combined, Brimonidine, and Timolol treated group), with 3-month duration (plus 9-month for safety). Among 573 enrolled (Combination =192, Brimonidine =186, Timolol =195), 497 of them completed. The objectives were to compare the safety and efficacy of Combination vs. Brimonidine and Combination vs. Timolol. Efficacy variable was IOP, measured at hours 0, 2, 7, and 9 on each visit day (Baseline, Week 2, Week 6, Month 3, Month 9, and Month 12). Both analysis results of IOP measurement, and IOP change from baseline were reported in submission. Protocol-specified statistical analysis of efficacy was a two-step of pairwise comparisons (Combination vs. each active drug) of IOP change from baseline with common variance estimation using 2-way ANOVA with factors of treatment group and investigator.

First issue of this study is an over power due to over estimation of sample size. Based on 573 enrolled patients, the power of the analyses is greater than 99.99% with mean difference of 2 mm Hg between treatment groups. Therefore, even if p-values from statistical analyses are less than 0.05, additional evidences will be necessary (e.g. adequate mean difference between treatment groups) to conclude for adequate treatment difference of efficacy. Sponsor concluded the combination formulation treated group shows superior to two other active drugs treated groups in efficacy based on their analysis results as shown in Table 3 of appendix.

For comparison between Combination and Brimonidine at hour 9, merely small amount of differences were detected (less than 0.5 mm Hg) and statistical comparisons show no significant differences for every post baseline visits (Week 2, Week 6, Month 3). For comparison of IOP measurements change from baseline at hour 9, similar results were found.

For comparison between Combination and Timolol, baseline comparisons show significant differences for all four times of IOP measurements. Because of this result, sponsor changed their statistical model by adding baseline scores as covariate in the analyses of IOP change from baseline. In this case, analysis of IOP measurement and analysis of IOP change from baseline become equivalent; they provide same p-values of treatment group comparison. On the other hand, analysis of IOP change from baseline without covariate of baseline scores must not be ignored because change from baseline is also one of the method of adjust baseline scores, and moreover, it was a protocol-specified model. However, sponsor did not submit these analysis results. Based on this reviewer's analysis using this protocol-specified model, results were very surprising; five time points failed to show significant differences out of 12 timepoints (4 measurements for 3 visits), and LS mean differences were also consistently smaller than sponsor's modified model (adding baseline scores as covariate). Table 11 and Figure 9 of appendix compares the two models; sponsor's modified model, and protocol-specified model. As shown in the figure, protocol specified model shows smaller differences consistently than modified model. Overall, analysis results are not consistent in two baseline adjustment models. This implies that the comparisons of these two treated groups are very sensitive to the imbalanced baseline scores. Therefore, in comparison of IOP measurements between Combination and Timolol treated groups, sponsor's analysis results were not robust, so that failed to show enough evidence of efficacy contribution of combination formulation.

As discussed above, since the sample size was over estimated, it is also important to verify that the difference between two treatment groups are big enough to show adequate efficacy contribution even if they are significantly different from statistical analyses. As shown in Table 3, Table 11 and Figure 9 of appendix, mean differences between Combination and active drugs are less than 2 mm Hg for many of hours/visits. Based on discussions with medical reviewer, we agreed that this study failed to show enough evidence of efficacy of combination formulation.

### 1.2.2 STUDY 190342-013T

The objectives and design of this study coincide with study 190342-012t. Among 586 enrolled (Combination=193, Brimonidine=196, Timolol=197), 502 of them completed. Similar to study 190342-012T, the sample size is overestimated in this study, too. Table 7 of appendix shows the mean values and mean differences between treatment groups for each visit/hour. The table shows that for comparison between Combination and Brimonidine at hour 9, differences between treatment groups were less than 1 mm Hg and statistical comparison shows no significant difference for all the post-baseline visits. For comparison between Combination and Timolol, most of post baseline measurements show that the difference of treatment groups are significantly less than 2 mm Hg. Overall, this study does not support efficacy contribution of this combination formulation.

### 1.3 PRINCIPAL FINDINGS

1. Sample size was over estimated. So, we need more evidence of adequate efficacy difference between treatment groups (e.g., adequate mean differences) other than hypothesis test.
2. Majors of the differences of mean IOP between treatment groups at post-baseline visits are less than 2 mm Hg. Among those, most of them are significantly less than 2 mm Hg.
3. In study 190342-012t, a significant difference was detected at baseline comparison of mean IOP between Combined and Timolol treated groups. In addition, different statistical models including baseline scores provide very different analysis results. This implies that the analysis is too sensitive to the baseline scores. Therefore, the sponsor's statistical analysis results are not reliable.
4. For the measurements at 9 hours of each post-baseline visit, differences between Combination treated group and Brimonidine treated group are less than 1 mm Hg for both studies, which are remarkably smaller than the differences in other times.

## 2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

### 2.1 INTRODUCTION AND BACKGROUND

Sponsor submitted this NDA for Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution to show safety and efficacy in lowering the elevated IOP of patients with glaucoma or ocular hypertension when applied topically to the eye twice daily. It is a new combination formulation of brimonidine tartrate, which is the active drug substance of ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% (NDA 20-613), and Timolol Maleate Ophthalmic Solution USP, 0.5% (ANDA 74-747). The combination formulation should show adequate difference of efficacy from each active drugs based on CFR § 300.50 stated as follow:

> Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

### 2.2 DATA ANALYZED AND SOURCES

Sponsor submitted four studies in this NDA, one PK study (190342-016t), one Phase II study (190342-011t), and two Phase III studies (190342-012t, 190342-013t). This review focused only on two Phase III studies. Sponsor submitted both hard and electronic copy, and submission was filed on November 17, 2001. Reviewed sources and data are listed as following table.

**Summary of sources and data reviewed**

| Source | Type | Description |
|---|---|---|
| **General** | | |
| Vol. 1 | Hard Copy | Meeting Minutes, Summary of Efficacy, etc. |
| **Study 190342-012t:** A Multicenter, Double-Masked, Randomized, Parallel Study of the Safety and Efficacy of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution Twice-Daily compare with 0.5% Timolol Twice-Daily or ALPHAGAN® Three-Times-Daily for Three Months (Plus 9-Month, Masked Extension) in Patients with Glaucoma or Ocular Hypertension. | | |
| Vol. 59 – 67 | Hard Copy | Final Report for the study |
| \\Cdsesub1\n21398\N_000\2001-09-17\clinstat\glaucoma\190342-012t.pdf | PDF File | Final Report for the study |
| \\Cdsesub1\n21398\N_000\2001-09-17\Crt\190342-012tanalysis\iop.xpt | SAS Transport File | Efficacy Data used in Reviewer's Analyses |
| **Study 190342-013t:** A Multicenter, Double-Masked, Randomized, Parallel Study of the Safety and Efficacy of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution Twice-Daily compare with 0.5% Timolol Twice-Daily or ALPHAGAN® Three-Times-Daily for Three Months (Plus 9-Month, Masked Extension) in Patients with Glaucoma or Ocular Hypertension. | | |
| Vol. 58 – 78 | Hard Copy | Final Report for the study |
| \\Cdsesub1\n21398\N_000\2001-09-17\clinstat\glaucoma\190342-013t.pdf | PDF File | Final Report for the study |
| \\Cdsesub1\n21398\N_000\2001-09-17\Crt\190342-013analysis\iop.xpt | SAS Transport File | Efficacy Data used in Reviewer's Analyses |

## 2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

Clinical designs of two Phase III studies, 190342-012t and 190342-013t, were coincide. The studies were double-masked, randomized, parallel, 3 arms (Combined, Brimonidine, Timolol), with duration of 3 month (plus 9-month extension). Visits were at baseline, week 2, week 6, and month 3. For each visit, IOP was measured in mm Hg, at hour 0 (between 7:00 AM and 8:30 AM), and at 2, 7 and 9 hours after hour 0.

### 2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Sponsor concluded the efficacy evidence of this study as follow:

> The efficacy results of the phase 3 studies demonstrated that the Combination treatment administered BID for 3 months effectively lowered elevated IOP in patients with glaucoma or ocular hypertension at all post-dose timepoints. The diurnal IOP results show that Combination administered BID was clinically and statistically more effective in lowering IOP than Timolol BID and Brimonidine TID, administered as monotherapies. Overall, the Combination treatment produced consistent IOP control throughout the day, with lower mean IOPs than with either Brimonidine or Timolol treatment, and showed less diurnal variation compared to treatment with Brimonidine.

The sponsor's conclusion is based on their statistical analysis results shown in Table 2 of appendix

2.3.2 STATISTICAL METHODOLOGIES

Following is quoted from summarized statistical method for both Phase III studies in sponsor's submission.

> All data were summarized with descriptive statistics, frequency tables, and/or data listings. Safety analyses included all patients who received at least 1 dose of study medication. Analyses were performed for the primary efficacy variable IOP using the intent-to-treat (ITT) population with last observation carried forward (LOCF), and the per protocol population with observed cases.
>
> Ordinal categorical variables were analyzed by the Wilcoxon rank-sum tests. Nominal categorical variables were analyzed using Fisher's exact or Pearson's chi-square tests. Within-group changes from baseline for categorical variables were analyzed using the Wilcoxon signed-rank test. Continuous variables (eg, IOP) were analyzed using analysis of variance (ANOVA). Within-group changes from baseline for continuous variables were analyzed using paired t-tests.
>
> A 2-way ANOVA model with factors for treatment and investigator was used for the analysis of IOP. Comparisons were made between the Combination and each of the 2 monotherapies in a pairwise fashion using contrasts from the ANOVA model, with the same error term. A separate ANOVA model was employed at each hour/visit measurement of IOP. Each of the 2 null hypotheses (Combination versus Timolol and Combination versus Brimonidine) was tested at the 0.05 significance level. Point estimates of the mean treatment differences, as well as 2-sided 95% confidence intervals (CI) of the difference, were provided at each timepoint.

Sponsor's primary efficacy analysis model specified in the protocol was 2-way ANOVA with dependent variable of IOP measurement change from baseline and factors of treatment group and investigator. In the NDA submission, analysis results of IOP measurement (not change from baseline) with same factors were also included with protocol specified analysis results. However, for comparison between Combination and Timolol in study 190342-012T, baseline score was added as a covariate to adjust imbalanced IOP measurements at baseline, so that it became an ANCOVA. The analyses, we can consider as baseline adjustment, are as follow;

A. IOP change from baseline = Treatment Group + Investigator
B. IOP = Treatment Group + Investigator + IOP Baseline Score
C. IOP change from baseline = Treatment Group + Investigator + IOP Baseline Score

Sponsor's submission includes only the analysis results of model B and C. In fact, these two models are identical. On the other hand, model A is protocol specified, and also a baseline-adjusting model. This reviewer believes this model can not be ignored because it can be used to check the robustness of the sponsor's analysis to the imbalanced baseline.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

*2.3.3.1 Study 190342-012t*

Following synopsis is quoted from sponsor's submission

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

**Study Center(s):**
27 sites in the United States

**Objectives:**
To compare the safety and efficacy of twice-daily dosed brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution combination (henceforth referred to as Combination) with that of twice-daily dosed timolol ophthalmic solution 0.5% (henceforth referred to as Timolol) and three-times-daily dosed ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% (henceforth referred to as Brimonidine) administered for three months (plus 9-month masked extension) in patients with glaucoma or ocular hypertension.

**Methodology:**
Structure: multicenter, double-masked, randomized, parallel-group, active control
Randomization: patients were randomized to one of the 3 masked treatment groups (Combination, Brimonidine or Timolol) based on an even allocation at each site
Visit Schedule: prestudy, baseline (day 0), week 2, week 6, month 3, month 6, month 9, and month 12

**Determination of Sample Size**
A sample size of 150 completed patients per treatment group was required for appropriate assessment of safety. The power calculation was based on change from baseline IOP. With 150 completed patients per treatment group, an estimated common standard deviation of 3.2 mm Hg, and using a 2-sample t-test with 2-sided alternatives and a significance level of 0.05, the power was 98% to detect a 1.5 mm Hg difference between groups. The power to simultaneously reject the null hypothesis in both primary comparisons was, therefore, approximately 96%.

**Number of Patients (Planned and Analyzed):**
560 planned to enroll; 573 enrolled (Combination = 192, Brimonidine = 186, Timolol = 195); 497 completed. Mean (range) age: 62.8 (32 to 89) years; 43.3% (248/573) males, 56.7% (325/573) females.

Comments: Sample size was calculated based on mean difference between treatment groups of 1.5 mm Hg IOP measurement, which is small. Expected power of 96% is also exceptionally big. Moreover, the number of patients enrolled in the study was extended for 20% of expected drop out subjects, but it was not necessary because LOCF method was used for dropout subjects in analyses of ITT population. In fact, the power will be greater than 99.99% with the sample size of 573 and mean difference of 2 mm Hg. Therefore,

even if the P-values from statistical analyses are less than 0.05, additional evidences will be necessary (e.g. adequate mean difference between treatment groups) to conclude into adequate treatment difference of efficacy.

**Dose and Mode of Administration:**
Brimonidine tartrate 0.2%/timolol 0.5% combination ophthalmic solution, one drop (~35 μL) instilled in each eye BID in the morning and evening; and vehicle of the Combination ophthalmic solution, one drop (~35 μL) instilled in each eye once daily (QD) in the afternoon (for masking purposes). Active control ALPHAGAN (brimonidine tartrate ophthalmic solution) 0.2%; one drop (~35 μL) instilled in each eye TID in the morning, afternoon, and evening. Active control timolol ophthalmic solution 0.5%; one drop (~35 μL) instilled in each eye BID in the morning and evening; and vehicle of the Combination ophthalmic solution, one drop (~35 μL) instilled in each eye once daily (QD) in the afternoon (for masking purposes).

**Duration of Treatment:**
3 months (with a 9-month masked extension)

**Criteria for Evaluation:**
Efficacy:
IOP (hours 0, 2, 7, and 9), patient satisfaction questionnaire, patient comfort of study medication questionnaire, pharmacoeconomic evaluation by investigator.
Safety:
Adverse events (AE), biomicroscopy, visual acuity (VA), visual field, ophthalmoscopy, cup/disc ratio, heart rate, blood pressure, hematology, serum chemistry, urinalysis and pregnancy test.
Other:
Quantitation of plasma brimonidine and timolol concentrations (at selected sites), resource utilization (to be reported upon completion of the 1 year study).

**Conclusions for efficacy evaluation:**
The Combination treatment (brimonidine tartrate 0.2%/timolol 0.5%) administered BID for 3 months was superior to Timolol (timolol 0.5%) BID and Brimonidine (brimonidine tartrate 0.2%) TID in lowering the elevated IOP of patients with glaucoma or ocular hypertension.

Sponsor's conclusion of efficacy evaluation is based on their statistical analysis results as shown in Table 3 and Figure 1 of appendix (analysis of IOP measurements), and Table 4 and Figure 2 of appendix (analysis of IOP change from baseline) of appendix. For a few subjects, they have missing at baseline for some hours. In that case, this subject was excluded from efficacy analysis of the missing hour for each visit. Therefore, the numbers of subjects analyzed are slightly different for each hour. Agency does not agree with any exclusion from the efficacy analysis as long as the patient was randomized and took study medication. In this study, these numbers are small and balanced, no further examination was performed.

For comparison between Combination and Timolol, problem begins from imbalanced baseline IOP scores. As discussed in Statistical Methodologies section above, sponsor's analyses include baseline scores as covariate, and this reviewer analyzed efficacy data with protocol specified model. The results of these two methods were different. Figure 9

of appendix shows 95% Confidence Intervals of difference of LS mean of IOP change from baseline between Combination and Timolol treated groups from two different models (B and C in section 2.3.2). As shown in the figure, the results of protocol specified model show less efficacy consistently over the time (solid bars are higher than dotted bars in pairwise), and 5 of them show not significantly different from Timolol treated group (5 solid bars cover 0). In fact, it is impossible to find the true model using data, but we can check the sensitivity of a model using other similar models. In this case, we can conclude that the sponsor's model is too sensitive to baseline score adjustment method. Consequently, the sponsor's analysis results are not reliable.

For comparison between Combination and Brimonidine at hour 9, merely small amount of differences were detected (less than 0.5 mm Hg) and statistical comparisons show no significant differences for every post baseline visits (Week 2, Week 6, Month 3).

As discussed above, since the sample size was over estimated, it is also important to verify that the difference between two treatment groups are big enough to show adequate efficacy contribution even if they are significantly different from statistical analyses. As shown in Table 3, Table 11 and Figure 9 of appendix, mean differences between Combination and active drugs are less than 2 mm Hg for many of hours/visits. Based on discussions with medical reviewer, we agreed that this study failed to show enough evidence of efficacy of combination formulation.

Analysis results for PP (per protocol) populations are summarized in Table 5 and 6, and Figure 3 and 4. As shown, results are similar to the results for ITT.

*2.3.3.2 Study 190342-013t*

This study has a same clinical design with study 190342-012t except followings:

> **Study Center(s):**
> 26 sites in the United States
>
> **Number of Patients (Planned and Analyzed):**
> A total of 586 patients were enrolled in the study, with 193 patients randomized to Combination, 196 patients randomized to Brimonidine and 197 patients randomized to Timolol groups. In the ITT population, 96.2% (564/586) of patients completed 2 weeks of treatment, 92.3% (541/586) of patients completed 6 weeks, and 85.7% (502/586) completed 3 months.

Comments: The sample size is also overestimated in this study. Same argument of previous study can be applied.

Sponsor's conclusion of this study is also exactly same as previous study;

> **Conclusions for efficacy evaluation:**
> The Combination treatment (brimonidine tartrate 0.2%/timolol 0.5%) administered BID for 3 months was superior to Timolol (timolol 0.5%) BID and Brimonidine

(brimonidine tartrate 0.2%) TID in lowering the elevated IOP of patients with glaucoma or ocular hypertension.

Sponsor's conclusion of efficacy evaluation is based on their statistical analysis results as shown in Table 7 and Figure 5 (analysis of IOP measurements), and Table 8 and Figure 6 (analysis of IOP change from baseline) of appendix. For comparison between Combination and Brimonidine at hour 9, differences between treatment groups were less than 1 mm Hg and statistical comparison shows no significant difference for all the post-baseline visits. For comparison between Combination and Timolol, most of post baseline measurements show that the difference of treatment groups are significantly less than 2 mm Hg.

Analysis results for PP (per protocol) populations are summarized in Table 9 and 10, and Figure 7 and 8. As shown, results for PP are similar to the results for ITT.

2.3.4 STATISTICAL REVIEWER'S FINDINGS

1. Sample size was over estimated. So, we need more evidence of adequate efficacy difference between treatment groups (e.g., adequate mean differences) other than the hypothesis test.

   - Sample size was calculated based on mean difference between treatment groups of 1.5 mm Hg IOP measurement, while agency considers 2 mm Hg as a minimum difference required for clinically meaningful efficacy. Expected power of 96% is also exceptionally big. Moreover, the number of patients enrolled in the study was extended for 20% of expected drop out subjects, but it was not proper because LOCF method was applied for dropout subjects in analyses of ITT population. In fact, the power will be greater than 99.99% with the sample size of 573 and mean difference of 2 mm Hg. Therefore, even if the P-values from statistical analyses are less than 0.05, additional evidences will be necessary (e.g. adequate mean difference between treatment groups) to conclude into adequate treatment difference of efficacy.

2. Majors of the differences of mean IOP between treatment groups at post-baseline visits are less than 2 mm Hg. Among those, most of them are significantly less than 2 mm Hg.

   - See Tables 3 ~ 11 and Figures 1 ~ 9 of appendix.

3. In study 190342-012t, a significant difference was detected at baseline comparison of mean IOP between Combined and Timolol treated groups. In addition, different statistical models including baseline scores provide very different analysis results. In other words, the analysis is too sensitive to the baseline scores. Therefore, the sponsor's statistical analysis results are not reliable.

   - The analysis models to adjust baseline we can consider are as follow;

     A. IOP change from baseline = Treatment Group + Investigator
     B. IOP = Treatment Group + Investigator + IOP Baseline Score
     C. IOP change from baseline = Treatment Group + Investigator + IOP Baseline Score

Sponsor's submission includes only the analysis results of model B and C. In fact, these two models are identical. On the other hand, model A is protocol specified, and also a baseline-adjusting model. This reviewer believes this model can not be ignored because it can be used to check the sensitivity of the sponsor's analysis to the imbalanced baseline. Therefore this reviewer analyzed efficacy data using this model, and the results are reported later in this report.

### 2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Analysis of interaction between treatment group and subgroup were calculated for gender, race, age, and body weight for each visit/hour. For gender subgroup, a few timepoints showed interactions (slightly less than 0.05) in study 190342-12t, but none of them changed statistical comparison results of treatment groups when adjusted for gender. For other subgroups, no significant results were detected.

### 2.5 STATISTICAL AND TECHNICAL ISSUES

1. Overestimation of sample size
   For both Phase III studies, sample size was overestimated. Both study planned 560 subjects; 573 (study 190342-12t) and 586 (study 190342-13t) subjects were enrolled and included in ITT population. Sponsor insists that 450 patients are required for safety evaluation, which provides 96% power already, then added 20% for expected dropout subjects. However, sponsor used LOCF method for dropout patients. Therefore we do not loose any subjects due to dropout in efficacy calculation. Figure 10 is a power graph using 573 subjects and standard deviation of 3.2. As shown in the graph, power reaches 100% before mean difference becomes 1.5. Also, if the true mean difference between treatment groups is 1 mm Hg, the probability to show the significant difference is over 80%. Therefore, if the expected contribution of combination drug is 2 mm Hg, significant difference result may not be enough. In this NDA, majors of mean differences between treatment groups over timepoints were less than 2 mm Hg, and among those, most of them are significantly smaller than 2 mm Hg.

2. Imbalanced baseline; model selection, checking robustness of the model.
   In study 190342-012t, imbalanced baseline IOP scores were detected from a comparison of Combination and Timolol treated drug. There are three models we can consider.

   A. IOP change from baseline = Treatment Group + Investigator
   B. IOP = Treatment Group + Investigator + IOP Baseline Score
   C. IOP change from baseline = Treatment Group + Investigator + IOP Baseline Score

   Model A is protocol specified, but sponsor submitted model B and C only, which were not planned in the protocol. In fact, these two models are identical. Analysis results of model B (or C) show significant difference between treatment groups for all timepoints. However, analysis results from model A showed not significance in

many timepoints. As shown in Figure 9 of appendix, model A shows less efficacy consistently over the timepoints. In fact, we can not tell that model which model is closer to the truth. However, we can conclude that the sponsor's analysis results are not reliable because the results are sensitive to model selection.

### 2.6 CONCLUSIONS AND RECOMMENDATIONS

Two Phase III studies (190342-012t, 190342-013t) were submitted for efficacy of Brimonidine Tartrate 0.2%/Timolol 0.5 % Ophthalmic Solution, a combination formulation of two active drugs Brimonidine and Timolol. These two studies were identically designed with IOP measurements as primary efficacy endpoints; 4 measurements per visit, 4 visits during 3-month duration. According to CRF § 300.50, combination formulation should show an adequate difference from each active drug.

For both studies, significant differences between treatment groups were found in many timepoints (visit/hour). However, the sample size was overestimated. Therefore, each statistical analysis result proves that the efficacy between two treatment groups is unequal, but not sufficiently different. However, mean difference between combination formulation and each active drug are not sufficient for both studies.

For comparison between combination formulation and Timolol treated groups in study 190342-012t, imbalanced baseline scores were detected. Sponsor modified the model by adding baseline scores as a covariate, but it didn't show the consistent results from model using mean difference from baseline without baseline score covariate, which is protocol specified. Therefore, sponsor's analysis results are not reliable.

In conclusion, both studies failed to show a sufficient efficacy of Brimonidine Tartrate 0.2%/Timolol 0.5 % Ophthalmic Solution in lowering the elevated IOP of patients with glaucoma or ocular hypertension.

## 2.7 APPENDIX

### 2.7.1 TABLES AND FIGURES

**Table 1 Demographics**

| Category | | Study 190342-012T | | | Study 190342-013T | | |
|---|---|---|---|---|---|---|---|
| | | Combination (N = 192) | Brimonidine (N = 186) | Timolol (N = 195) | Combination (N = 193) | Brimonidine (N = 196) | Timolol (N = 197) |
| Age | Mean | 62.8 | 63.8 | 61.9 | 61.2 | 63.8 | 62.2 |
| | SD | 11.43 | 11.78 | 11.91 | 13.16 | 11.81 | 12.62 |
| Sex | Male | 84 (43.8%) | 72 (38.7%) | 92 (47.2%) | 97 (50.3%) | 79 (40.3%) | 94 (47.7%) |
| | Female | 108 (56.3%) | 114 (61.3%) | 103 (52.8%) | 96 (49.7%) | 117 (59.7%) | 103 (52.3%) |
| Race | White | 141 (73.4%) | 141 (75.8%) | 145 (74.4%) | 149 (77.2%) | 163 (83.2%) | 140 (71.1%) |
| | Black | 34 (17.7%) | 31 (16.7%) | 34 (17.4%) | 25 (13.0%) | 24 (12.2%) | 39 (19.8%) |
| | Asian | 3 (1.6%) | 2 (1.1%) | 1 (0.5%) | 1 (0.5%) | 0 (0.0%) | 4 (2.0%) |
| | Hispanic | 13 (6.8%) | 12 (6.5%) | 15 (7.7%) | 17 (8.8%) | 8 (4.1%) | 13 (6.6%) |
| | Other | 1 (0.5%) | 0 (0%) | 0 (0%) | 1 (0.5%) | 1 (0.5%) | 1 (0.5%) |
| Height (cm) | Mean | 167.4 | 166.9 | 167.6 | 169.7 | 167.2 | 168.2 |
| | SD | 10.85 | 10.84 | 10.6 | 10.49 | 9.27 | 10.85 |
| Weight (kg) | Mean | 80.6 | 82.2 | 83.2 | 83.8 | 80.1 | 81.7 |
| | SD | 17.6 | 20.08 | 18.6 | 18.0 | 18.3 | 19.4 |

**Table 2 Mean IOP (mmHg) in Individual Phase 3 Studies (ITT with LOCF)**

| Timepoint visit | Study 190342-012T | | | Study 190342-013T | | |
|---|---|---|---|---|---|---|
| | Combination (N = 192) | Brimonidine (N = 186) | Timolol (N = 195) | Combination (N = 193) | Brimonidine (N = 196) | Timolol (N = 197) |
| Baseline | | | | | | |
| hour 0 | 24.5 | 24.7 | 25.1 [a] | 24.9 | 25.0 | 24.8 |
| hour 2 | 22.8 | 23.2 | 23.5 [a] | 23.7 | 23.7 | 23.6 |
| hour 7 | 21.6 | 22.0 | 22.6 [a] | 22.6 | 23.0 | 22.4 |
| hour 9 | 21.4 | 21.9 | 22.5 [a] | 22.2 | 22.5 | 22.3 |
| Week 2 | | | | | | |
| hour 0 | 17.9 | 20.9 [b] | 19.2 [c] | 17.8 | 20.8 [b] | 18.9 [c] |
| hour 2 | 15.9 | 18.1 [b] | 18.5 [c] | 16.3 | 18.1 [b] | 18.1 [c] |
| hour 7 | 16.6 | 18.9 [b] | 18.4 [c] | 16.7 | 19.0 [b] | 17.8 [c] |
| hour 9 | 16.7 | 17.1 | 18.2 [c] | 17.0 | 17.4 | 17.8 [c] |
| Week 6 | | | | | | |
| hour 0 | 18.0 | 21.2 [b] | 19.1 [c] | 17.9 | 20.9 [b] | 18.4 |
| hour 2 | 15.7 | 18.2 [b] | 17.9 [c] | 15.9 | 18.6 [b] | 17.9 [c] |
| hour 7 | 16.6 | 19.4 [b] | 18.2 [c] | 16.7 | 19.5 [b] | 17.5 [c] |
| hour 9 | 16.8 | 17.1 | 18.0 [c] | 16.9 | 17.7 [b] | 17.8 [c] |
| Month 3 | | | | | | |
| hour 0 | 17.7 | 21.2 [b] | 19.3 [c] | 18.1 | 21.5 [b] | 18.8 [c] |
| hour 2 | 15.5 | 17.9 [b] | 18.1 [c] | 15.9 | 18.0 [b] | 17.8 [c] |
| hour 7 | 16.6 | 19.4 [b] | 18.3 [c] | 17.0 | 19.2 [b] | 17.6 [c] |
| hour 9 | 17.0 | 17.2 | 18.4 [c] | 16.8 | 17.7 [b] | 17.7 [c] |

a Combination mean IOP at baseline statistically significantly lower than Timolol ($p < 0.05$).
b Combination mean IOP statistically significantly lower than Brimonidine ($p < 0.05$).
c Combination mean IOP statistically significantly lower than Timolol ($p < 0.05$).

**Table 3 Mean IOP (mm Hg) and statistical comparison results between treatment groups at Each Scheduled Visit; ITT, LOCF, 190342-012T**

| Timepoint | | Combination (N = 192) | | Brimonidine (N = 186) | | Timolol (N = 195) | | Combination vs. Brimonidine | Combination vs. Timolol |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | N | Mean | N | Mean | LS Mean Diff (95% CI) | LS Mean Diff (95% CI) |
| Baseline | hour 0 | 192 | 24.5 | 186 | 24.7 | 195 | 25.1 | -0.21 (-0.73, 0.31) [a] | -0.56 (-1.08, -0.05) [a] |
| | hour 2 | 190 | 22.8 | 186 | 23.2 | 194 | 23.5 | -0.42 (-1.03, 0.19) [a] | -0.61 (-1.22, -0.01) [a] |
| | hour 7 | 191 | 21.6 | 185 | 22.0 | 195 | 22.6 | -0.38 (-1.04, 0.29) [a] | -0.90 (-1.56, -0.24) [a] |
| | hour 9 | 190 | 21.4 | 186 | 21.9 | 193 | 22.5 | -0.51 (-1.17, 0.15) [a] | -1.03 (-1.68, -0.37) [a] |
| Week 2 | hour 0 | 192 | 17.9 | 186 | 20.9 | 195 | 19.2 | -2.99 (-3.63, -2.36) [a] | -1.03 (-1.58, -0.48) [b] |
| | hour 2 | 190 | 15.9 | 186 | 18.1 | 194 | 18.5 | -2.24 (-2.90, -1.58) [a] | -2.17 (-2.76, -1.59) [b] |
| | hour 7 | 191 | 16.6 | 185 | 18.9 | 195 | 18.4 | -2.26 (-2.89, -1.62) [a] | -1.34 (-1.90, -0.79) [b] |
| | hour 9 | 190 | 16.7 | 186 | 17.1 | 193 | 18.2 | -0.36 (-1.00, 0.28) [a] | -0.99 (-1.55, -0.42) [b] |
| Week 6 | hour 0 | 192 | 18.0 | 186 | 21.2 | 195 | 19.1 | -3.19 (-3.85, -2.53) [a] | -0.78 (-1.36, -0.19) [b] |
| | hour 2 | 190 | 15.7 | 186 | 18.2 | 194 | 17.9 | -2.48 (-3.15, -1.82) [a] | -1.88 (-2.46, -1.29) [b] |
| | hour 7 | 191 | 16.6 | 185 | 19.4 | 195 | 18.2 | -2.78 (-3.43, -2.13) [a] | -1.16 (-1.74, -0.57) [b] |
| | hour 9 | 190 | 16.8 | 186 | 17.1 | 193 | 18.0 | -0.38 (-1.00, 0.24) [a] | -0.78 (-1.33, -0.24) [b] |
| Month 3 | hour 0 | 192 | 17.7 | 186 | 21.2 | 195 | 19.3 | -3.50 (-4.22, -2.77) [a] | -1.28 (-1.90, -0.65) [b] |
| | hour 2 | 190 | 15.5 | 186 | 17.9 | 194 | 18.1 | -2.36 (-3.05, -1.67) [a] | -2.20 (-2.20, -1.61) [b] |
| | hour 7 | 191 | 16.6 | 185 | 19.4 | 195 | 18.3 | -2.80 (-3.47, -1.67) [a] | -1.25 (-1.85, -0.65) [b] |
| | hour 9 | 190 | 17.0 | 186 | 17.2 | 193 | 18.4 | -0.18 (-0.84, 0.48) [a] | -0.90 (-1.48, -0.32) [b] |

Note: The difference between treatment groups is calculated by taking the Least Square mean from the first treatment group and subtracting the Least Square mean from the second.

[a] 95% confidence intervals are from pairwise contrasts from a single two-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

[b] Same model as [a] with the addition of baseline IOP as a covariate.

Source: Table 9.1, 9.2, 9.3, and 9.4 of 14.0 Tables, Figures, and Graphs of study 190342-012T. Vol 57.

**Table 4 Mean IOP (mm Hg) change from baseline and statistical comparison results between treatment groups at Each Scheduled Visit; ITT, LOCF, 190342-012T**

| Timepoint | | Combination (N = 192) | | Brimonidine (N = 186) | | Timolol (N = 195) | | Combination vs. Brimonidine | Combination vs. Timolol |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | N | Mean | N | Mean | LS Mean Diff (95% CI) | LS Mean Diff (95% CI) |
| Week 2 | hour 0 | 192 | 17.9 | 186 | 20.9 | 195 | 19.2 | -2.99 (-3.63, -2.36) [a] | -1.03 (-1.58, -0.48) [b] |
| | hour 2 | 190 | 15.9 | 186 | 18.1 | 194 | 18.5 | -2.24 (-2.90, -1.58) [a] | -2.17 (-2.76, -1.59) [b] |
| | hour 7 | 191 | 16.6 | 185 | 18.9 | 195 | 18.4 | -2.26 (-2.89, -1.62) [a] | -1.34 (-1.90, -0.79) [b] |
| | hour 9 | 190 | 16.7 | 186 | 17.1 | 193 | 18.2 | -0.36 (-1.00, 0.28) [a] | -0.99 (-1.55, -0.42) [b] |
| Week 6 | hour 0 | 192 | 18.0 | 186 | 21.2 | 195 | 19.1 | -3.19 (-3.85, -2.53) [a] | -0.78 (-1.36, -0.19) [b] |
| | hour 2 | 190 | 15.7 | 186 | 18.2 | 194 | 17.9 | -2.48 (-3.15, -1.82) [a] | -1.88 (-2.46, -1.29) [b] |
| | hour 7 | 191 | 16.6 | 185 | 19.4 | 195 | 18.2 | -2.78 (-3.43, -2.13) [a] | -1.16 (-1.74, -0.57) [b] |
| | hour 9 | 190 | 16.8 | 186 | 17.1 | 193 | 18.0 | -0.38 (-1.00, 0.24) [a] | -0.78 (-1.33, -0.24) [b] |
| Month 3 | hour 0 | 192 | 17.7 | 186 | 21.2 | 195 | 19.3 | -3.50 (-4.22, -2.77) [a] | -1.28 (-1.90, -0.65) [b] |
| | hour 2 | 190 | 15.5 | 186 | 17.9 | 194 | 18.1 | -2.36 (-3.05, -1.67) [a] | -2.20 (-2.20, -1.61) [b] |
| | hour 7 | 191 | 16.6 | 185 | 19.4 | 195 | 18.3 | -2.80 (-3.47, -1.67) [a] | -1.25 (-1.85, -0.65) [b] |
| | hour 9 | 190 | 17.0 | 186 | 17.2 | 193 | 18.4 | -0.18 (-0.84, 0.48) [a] | -0.90 (-1.48, -0.32) [b] |

Note: The difference between treatment groups is calculated by taking the Least Square mean from the first treatment group and subtracting the Least Square mean from the second.

[a] 95% confidence intervals are from pairwise contrasts from a single two-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

[b] Same model as [a] with the addition of baseline IOP as a covariate.

Source: Table 8.1, 8.2, 8.3, and 9.1 of 14.0 Tables, Figures, and Graphs of study 190342-012T. Vol 57.

**Table 5 Mean IOP (mm Hg) and statistical comparison results between treatment groups at Each Scheduled Visit; PP, LOCF, 190342-012T**

| Timepoint | | Combination (N = 191) | | Brimonidine (N = 186) | | Timolol (N = 193) | | Combination vs. Brimonidine[a] | Combination vs. Timolol[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | N | Mean | N | Mean | LS Mean Diff (95% CI) | LS Mean Diff (95% CI) |
| Baseline | hour 0 | 191 | 24.5 | 186 | 24.7 | 193 | 25.1 | -0.23 (-0.75, 0.29) | -0.59 (-1.10, -0.07) |
| | hour 2 | 189 | 22.8 | 186 | 23.2 | 192 | 23.5 | -0.43 (-1.04, 0.18) | -0.63 (-1.23, -0.02) |
| | hour 7 | 191 | 21.6 | 185 | 22.0 | 193 | 22.6 | -0.38 (-1.04, 0.29) | -0.90 (-1.57, -0.24) |
| | hour 9 | 190 | 21.4 | 186 | 21.9 | 191 | 22.5 | -0.51 (-1.17, 0.15) | -1.03 (-1.69, -0.38) |
| Week 2 | hour 0 | 186 | 17.9 | 178 | 20.8 | 183 | 19.3 | -2.99 (-3.63, -2.35) | -1.02 (-1.58, -0.46) |
| | hour 2 | 184 | 15.8 | 175 | 17.9 | 183 | 18.3 | -2.08 (-2.74, -1.42) | -2.19 (-2.77, -1.62) |
| | hour 7 | 174 | 16.5 | 168 | 18.8 | 180 | 18.3 | -2.26 (-2.91, -1.61) | -1.40 (-1.96, -0.83) |
| | hour 9 | 173 | 16.5 | 168 | 16.7 | 183 | 18.0 | -0.13 (-0.77, 0.50) | -1.06 (-1.62, -0.50) |
| Week 6 | hour 0 | 177 | 18.0 | 166 | 21.0 | 174 | 19.0 | -3.06 (-3.75, -2.38) | -0.64 (-1.23, -0.04) |
| | hour 2 | 178 | 15.6 | 163 | 17.7 | 175 | 17.9 | -2.08 (-2.73, -1.42) | -1.79 (-2.36, -1.22) |
| | hour 7 | 176 | 16.6 | 161 | 19.2 | 171 | 18.1 | -2.61 (-3.29, -1.94) | -1.08 (-1.68, -0.47) |
| | hour 9 | 179 | 16.8 | 158 | 16.6 | 171 | 17.9 | 0.10 (-0.52, 0.72) | -0.71 (-1.25, -0.16) |
| Month 3 | hour 0 | 174 | 17.3 | 152 | 20.8 | 175 | 19.2 | -3.55 (-4.26, -2.84) | -1.49 (-2.09, -0.88) |
| | hour 2 | 172 | 15.3 | 152 | 17.2 | 175 | 17.9 | -1.91 (-2.59, -1.24) | -2.22 (-2.79, -1.64) |
| | hour 7 | 167 | 16.6 | 149 | 19.1 | 174 | 18.2 | -2.55 (-3.25, -1.85) | -1.14 (-1.73, -0.55) |
| | hour 9 | 171 | 17.0 | 147 | 16.6 | 174 | 18.3 | 0.26 (-0.43, 0.95) | -0.86 (-1.44, -0.27) |

Note: The difference between treatment groups is calculated by taking the Least Square mean from the first treatment group and subtracting the Least Square mean from the second.

[a] 95% confidence intervals are from pairwise contrasts from a single two-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

Source: Table 11.1, 11.2, 11.3, and 11.4 of 14.0 Tables, Figures, and Graphs of study 190342-012T. Vol 57.

**Table 6 Mean IOP (mm Hg) change from baseline and statistical comparison results between treatment groups at Each Scheduled Visit; PP, LOCF, 190342-012T**

| Timepoint | | Combination (N = 191) | | Brimonidine (N = 186) | | Timolol (N = 194) | | Combination vs. Brimonidine[a] | Combination vs. Timolol[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | N | Mean | N | Mean | LS Mean Diff (95% CI) | LS Mean Diff (95% CI) |
| Week 2 | hour 0 | 186 | -6.7 | 178 | -3.9 | 183 | -5.9 | -2.78 (-3.38, -2.18) | -1.03 (-1.59, -0.47) |
| | hour 2 | 184 | -7.1 | 175 | -5.3 | 183 | -5.2 | -1.72 (-2.38, -1.06) | -2.20 (-2.78, -1.62) |
| | hour 7 | 174 | -5.3 | 168 | -3.2 | 180 | -4.4 | -1.97 (-2.66, -1.28) | -1.41 (-1.98, -0.85) |
| | hour 9 | 173 | -4.9 | 168 | -5.2 | 183 | -4.5 | 0.31 (-0.39, 1.01) | -1.04 (-1.61, -0.48) |
| Week 6 | hour 0 | 177 | -6.6 | 166 | -3.6 | 174 | -6.2 | -2.97 (-3.61, -2.33) | -0.62 (-0.62, -0.02) |
| | hour 2 | 178 | -7.2 | 163 | -5.3 | 175 | -5.8 | -1.87 (-2.53, -1.21) | -1.78 (-2.36, -1.21) |
| | hour 7 | 176 | -5.1 | 161 | -2.5 | 171 | -4.7 | -2.63 (-3.37, -1.89) | -1.07 (-1.68, -0.47) |
| | hour 9 | 179 | -4.7 | 158 | -5.0 | 171 | -4.7 | 0.25 (-0.43, 0.92) | -0.72 (-1.26, -0.17) |
| Month 3 | hour 0 | 174 | -7.2 | 152 | -3.7 | 175 | -5.9 | -3.50 (-4.16, -2.85) | -1.51 (-2.11, -0.90) |
| | hour 2 | 172 | -7.5 | 152 | -5.7 | 175 | -5.6 | -1.77 (-2.44, -1.11) | -2.22 (-2.79, -1.64) |
| | hour 7 | 167 | -5.0 | 149 | -2.6 | 174 | -4.5 | -2.48 (-3.20, -1.76) | -1.15 (-1.74, -0.56) |
| | hour 9 | 171 | -4.5 | 147 | -5.0 | 174 | -4.2 | 0.47 (-0.23, 1.17) | -0.84 (-1.42, -0.26) |

Note: The difference between treatment groups is calculated by taking the Least Square mean from the first treatment group and subtracting the Least Square mean from the second.

[a] 95% confidence intervals are from pairwise contrasts from a single two-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

Source: Table 10.1, 10.2, 10.3, and 9.1 of 14.0 Tables, Figures, and Graphs of study 190342-012T. Vol 57.

**Table 7 Mean IOP (mm Hg) and statistical comparison results between treatment groups at Each Scheduled Visit; ITT, LOCF, 190342-013T**

| Timepoint | | Combination (N = 192) | | Brimonidine (N = 186) | | Timolol (N = 195) | | Combination vs. Brimonidine[a] | Combination vs. Timolol[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | N | Mean | N | Mean | LS Mean Diff (95% CI) [a] | LS Mean Diff (95% CI) [a] |
| Baseline | hour 0 | 193 | 24.9 | 196 | 25.0 | 197 | 24.8 | -0.11 (-0.64, 0.42) | 0.10 (-0.42, 0.63) |
| | hour 2 | 193 | 23.7 | 196 | 23.7 | 197 | 23.6 | 0.03 (-0.56, 0.62) | 0.15 (-0.44, 0.74) |
| | hour 7 | 193 | 22.6 | 195 | 23.0 | 197 | 22.4 | -0.47 (-1.07, 0.14) | 0.14 (-0.47, 0.75) |
| | hour 9 | 191 | 22.2 | 192 | 22.5 | 195 | 22.3 | -0.36 (-0.98, 0.25) | -0.16 (-0.77, 0.45) |
| Week 2 | hour 0 | 193 | 17.8 | 196 | 20.8 | 197 | 18.9 | -2.82 (-3.41, -2.22) | -1.18 (-1.77, -0.59) |
| | hour 2 | 193 | 16.3 | 196 | 18.1 | 197 | 18.1 | -1.84 (-2.46, -1.21) | -1.97 (-2.59, -1.34) |
| | hour 7 | 193 | 16.7 | 195 | 19.0 | 197 | 17.8 | -1.85 (-2.47, -1.23) | -1.29 (-1.91, -0.67) |
| | hour 9 | 191 | 17.0 | 192 | 17.4 | 195 | 17.8 | -0.03 (-0.69, 0.62) | -0.70 (-1.36, -0.05) |
| Week 6 | hour 0 | 193 | 17.9 | 196 | 20.9 | 197 | 18.4 | -2.93 (-3.54, -2.32) | -0.64 (-1.25, -0.03) |
| | hour 2 | 193 | 15.9 | 196 | 18.6 | 197 | 17.9 | -2.80 (-3.47, -2.12) | -2.19 (-2.87, -1.52) |
| | hour 7 | 193 | 16.7 | 195 | 19.5 | 197 | 17.5 | -2.32 (-2.95, -1.70) | -1.05 (-1.67, -0.42) |
| | hour 9 | 191 | 16.9 | 192 | 17.7 | 195 | 17.8 | -0.43 (-1.09, 0.24) | -0.82 (-1.48, -0.16) |
| Month 3 | hour 0 | 193 | 18.1 | 196 | 21.5 | 197 | 18.8 | -3.27 (-3.93, -2.61) | -0.85 (-1.51, -0.20) |
| | hour 2 | 193 | 15.9 | 196 | 18.0 | 197 | 17.8 | -2.12 (-2.78, -1.45) | -2.05 (-2.72, -1.38) |
| | hour 7 | 193 | 17.0 | 195 | 19.2 | 197 | 17.6 | -1.75 (-2.40, -1.09) | -0.77 (-1.42, -0.12) |
| | hour 9 | 191 | 16.8 | 192 | 17.7 | 195 | 17.7 | -0.55 (-1.21, 0.11) | -0.83 (-1.49, -0.17) |

Note: The difference between treatment groups is calculated by taking the Least Square mean from the first treatment group and subtracting the Least Square mean from the second.

a. 95% confidence intervals are from pairwise contrasts from a single two-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

Source: Table 9.1, 9.2, 9.3, and 9.4 of 14.0 Tables, Figures, and Graphs of study 190342-013T. Vol 68.

**Table 8 Mean IOP (mm Hg) change from baseline and statistical comparison results between treatment groups at Each Scheduled Visit; ITT, LOCF, 190342-013T**

| Timepoint | | Combination (N = 192) | | Brimonidine (N = 186) | | Timolol (N = 195) | | Combination vs. Brimonidine[a] | Combination vs. Timolol[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | N | Mean | N | Mean | LS Mean Diff (95% CI) | LS Mean Diff (95% CI) |
| Week 2 | hour 0 | 193 | -7.1 | 196 | -4.3 | 197 | -5.9 | -2.82 (-3.41, -2.22) | -1.18 (-1.77, -0.59) |
| | hour 2 | 193 | -7.4 | 196 | -5.6 | 197 | -5.5 | -1.84 (-2.46, -1.21) | -1.97 (-2.59, -1.34) |
| | hour 7 | 193 | -5.9 | 195 | -4.0 | 197 | -4.6 | -1.85 (-2.47, -1.23) | -1.29 (-1.91, -0.67) |
| | hour 9 | 191 | -5.2 | 192 | -5.1 | 195 | -4.5 | -0.03 (-0.69, 0.62) | -0.70 (-1.36, -0.05) |
| Week 6 | hour 0 | 193 | -7.1 | 196 | -4.1 | 197 | -6.4 | -2.93 (-3.54, -2.32) | -0.64 (-1.25, -0.03) |
| | hour 2 | 193 | -7.9 | 196 | -5.1 | 197 | -5.7 | -2.80 (-3.47, -2.12) | -2.19 (-2.87, -1.52) |
| | hour 7 | 193 | -5.9 | 195 | -3.5 | 197 | -4.8 | -2.32 (-2.95, -1.70) | -1.05 (-1.67, -0.42) |
| | hour 9 | 191 | -5.3 | 192 | -4.9 | 195 | -4.5 | -0.43 (-1.09, 0.24) | -0.82 (-1.48, -0.16) |
| Month 3 | hour 0 | 193 | -6.9 | 196 | -3.6 | 197 | -6.0 | -3.27 (-3.93, -2.61) | -0.85 (-1.51, -0.20) |
| | hour 2 | 193 | -7.8 | 196 | -5.7 | 197 | -5.8 | -2.12 (-2.78, -1.45) | -2.05 (-2.72, -1.38) |
| | hour 7 | 193 | -5.5 | 195 | -3.8 | 197 | -4.8 | -1.75 (-2.40, -1.09) | -0.77 (-1.42, -0.12) |
| | hour 9 | 191 | -5.4 | 192 | -4.8 | 195 | -4.6 | -0.55 (-1.21, 0.11) | -0.83 (-1.49, -0.17) |

Note: The difference between treatment groups is calculated by taking the Least Square mean from the first treatment group and subtracting the Least Square mean from the second.

[a] 95% confidence intervals are from pairwise contrasts from a single two-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

Source: Table 8.1, 8.2, 8.3, and 9.1 of 14.0 Tables, Figures, and Graphs of study 190342-013T. Vol 68.

**Table 9 Mean IOP (mm Hg) and statistical comparison results between treatment groups at Each Scheduled Visit; PP, LOCF, 190342-013T**

| Timepoint | | Combination (N = 191) | | Brimonidine (N = 194) | | Timolol (N = 196) | | Combination vs. Brimonidine[a] | Combination vs. Timolol[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | N | Mean | N | Mean | LS Mean Diff (95% CI) [a] | LS Mean Diff (95% CI) [a] |
| Baseline | hour 0 | 191 | 25.0 | 194 | 25.1 | 194 | 24.8 | -0.13 (-0.65, 0.39) | 0.14 (-0.38, 0.66) |
| | hour 2 | 191 | 23.8 | 194 | 23.8 | 194 | 23.6 | -0.02 (-0.60, 0.57) | 0.17 (-0.42, 0.76) |
| | hour 7 | 191 | 22.6 | 193 | 23.0 | 194 | 22.4 | -0.49 (-1.10, 0.12) | 0.15 (-0.46, 0.76) |
| | hour 9 | 189 | 22.2 | 191 | 22.5 | 192 | 22.3 | -0.39 (-1.01, 0.22) | -0.15 (-0.77, 0.46) |
| Week 2 | hour 0 | 186 | 17.8 | 180 | 20.7 | 188 | 18.8 | -2.81 (-3.38, -2.24) | -0.97 (-1.54, -0.41) |
| | hour 2 | 186 | 16.2 | 180 | 17.8 | 189 | 17.9 | -1.48 (-2.05, -0.91) | -1.70 (-2.26, -1.14) |
| | hour 7 | 185 | 16.6 | 177 | 18.8 | 187 | 17.6 | -2.16 (-2.75, -1.57) | -1.03 (-1.61, -0.44) |
| | hour 9 | 184 | 16.8 | 176 | 17.0 | 186 | 17.6 | -0.19 (-0.77, 0.40) | -0.77 (-1.35, -0.20) |
| Week 6 | hour 0 | 178 | 17.9 | 173 | 20.8 | 181 | 18.3 | -2.74 (-3.38, -2.09) | -0.27 (-0.91, 0.38) |
| | hour 2 | 178 | 15.7 | 174 | 18.5 | 182 | 17.7 | -2.64 (-3.29, -1.99) | -1.90 (-2.54, -1.26) |
| | hour 7 | 174 | 16.5 | 172 | 19.4 | 181 | 17.5 | -2.72 (-3.32, -2.11) | -0.87 (-1.47, -0.27) |
| | hour 9 | 176 | 16.8 | 169 | 17.3 | 181 | 17.7 | -0.41 (-1.03, 0.21) | -0.89 (-1.50, -0.28) |
| Month 3 | hour 0 | 174 | 18.0 | 162 | 21.1 | 175 | 18.6 | -3.01 (-3.67, -2.36) | -0.66 (-1.30, -0.01) |
| | hour 2 | 176 | 15.7 | 160 | 17.6 | 177 | 17.6 | -1.81 (-2.43, -1.19) | -1.87 (-2.47, -1.26) |
| | hour 7 | 172 | 16.8 | 157 | 19.1 | 176 | 17.5 | -2.19 (-2.84, -1.54) | -0.63 (-1.27, 0.00) |
| | hour 9 | 172 | 16.6 | 155 | 17.3 | 176 | 17.6 | -0.56 (-1.20, 0.08) | -0.97 (-1.59, -0.35) |

Note: The difference between treatment groups is calculated by taking the Least Square mean from the first treatment group and subtracting the Least Square mean from the second.

[a] 95% confidence intervals are from pairwise contrasts from a single two-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

Source: Table 11.1, 11.2, 11.3, and 11.4 of 14.0 Tables, Figures, and Graphs of study 190342-013T. Vol 68.

**Table 10 Mean IOP (mm Hg) change from baseline and statistical comparison results between treatment groups at Each Scheduled Visit; PP, LOCF, 190342-013T**

| Timepoint | | Combination (N = ) | | Brimonidine (N = ) | | Timolol (N = ) | | Combination vs. Brimonidine[a] | Combination vs. Timolol[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | N | Mean | N | Mean | LS Mean Diff (95% CI) | LS Mean Diff (95% CI) |
| Week 2 | hour 0 | 186 | -7.2 | 180 | -4.5 | 188 | -6.1 | -2.63 (-3.21, -2.05) | -1.05 (-1.63, 0.47) |
| | hour 2 | 186 | -7.6 | 180 | -6.0 | 189 | -5.6 | -1.54 (-2.17, -0.91) | -1.91 (-2.53, -1.29) |
| | hour 7 | 185 | -5.9 | 177 | -4.2 | 187 | -4.8 | -1.72 (-2.36, -1.09) | -1.13 (-1.76, -0.51) |
| | hour 9 | 184 | -5.3 | 176 | -5.5 | 186 | -4.7 | 0.29 (-0.38, 0.95) | -0.57 (-1.22, 0.09) |
| Week 6 | hour 0 | 178 | -7.1 | 173 | -4.4 | 181 | -6.6 | -2.58 (-3.20, -1.95) | -0.43 (-1.05, 0.18) |
| | hour 2 | 178 | -8.0 | 174 | -5.4 | 182 | -5.8 | -2.59 (-3.29, -1.90) | -2.16 (-2.85, -1.47) |
| | hour 7 | 174 | -5.9 | 172 | -3.6 | 181 | -4.9 | -2.26 (-2.91, -1.60) | -0.99 (-1.65, -0.34) |
| | hour 9 | 176 | -5.3 | 169 | -5.3 | 181 | -4.6 | 0.09 (-0.60, 0.78) | -0.69 (-1.36, -0.01) |
| Month 3 | hour 0 | 174 | -6.9 | 162 | -3.9 | 175 | -6.2 | -2.91 (-3.60, -2.22) | -0.70 (-1.38, -0.02) |
| | hour 2 | 176 | -8.0 | 160 | -6.2 | 177 | -5.9 | -1.80 (-2.48, -1.11) | -2.03 (-2.70, -1.36) |
| | hour 7 | 172 | -5.7 | 157 | -3.9 | 176 | -4.9 | -1.73 (-2.43, -1.03) | -0.71 (-1.39, -0.02) |
| | hour 9 | 172 | -5.5 | 155 | -5.2 | 176 | -4.7 | -0.17 (-0.85, 0.52) | -0.71 (-1.38, -0.05) |

Note: The difference between treatment groups is calculated by taking the Least Square mean from the first treatment group and subtracting the Least Square mean from the second.

[a] 95% confidence intervals are from pairwise contrasts from a single two-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

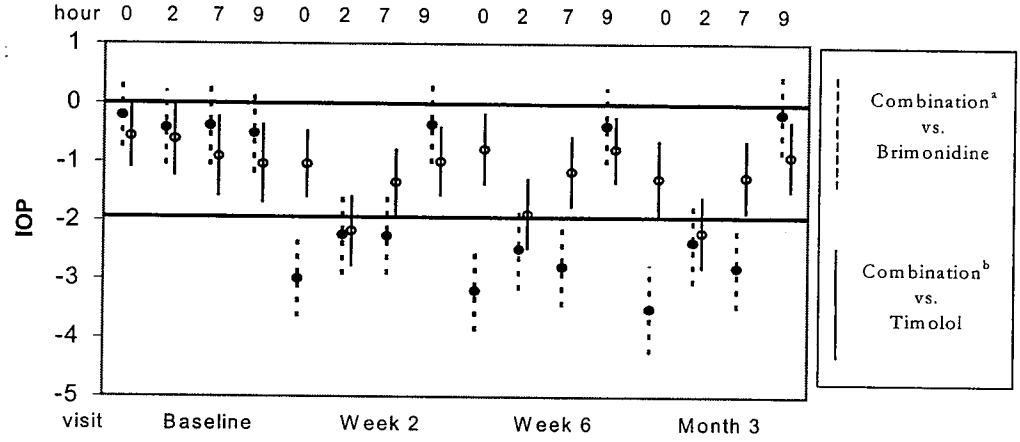
Source: Table 10.1, 10.2, 10.3, and 9.1 of 14.0 Tables, Figures, and Graphs of study 190342-013T. Vol 68.

**Table 11 Differences and pairwise statistical comparisons of LS Mean of IOP change from baseline (mm Hg) between Combination and Timolol Treated Groups at Each Scheduled Visit from Two Different Models; ITT, LOCF, 190342-012T**

| Timepoint | | LS Mean Difference [a] | | 95% Confidence Intervals | | P-Values | |
|---|---|---|---|---|---|---|---|
| | | Modified [b] | Protocol specified [c] | Modified [b] | Protocol specified [c] | Modified [b] | Protocol specified [c] |
| Week 2 | hour 0 | -1.03 | -0.80 | (-1.58, -0.48) | (-1.38, -0.21) | <0.001 | -0.008 |
| | hour 2 | -2.17 | -1.87 | (-2.76, -1.59) | (-2.53, -1.22) | <0.001 | <0.001 |
| | hour 7 | -1.34 | -0.86 | (-1.90, -0.79) | (-1.51, -0.20) | <0.001 | 0.011 |
| | hour 9 | -0.99 | -0.42 | (-1.55, -0.42) | (-1.09, 0.24) | <0.001 | 0.213 |
| Week 6 | hour 0 | -0.78 | -0.56 | (-1.36, -0.19) | (-1.18, 0.06) | <0.001 | 0.077 |
| | hour 2 | -1.88 | -1.59 | (-2.46, -1.29) | (-2.23, -0.95) | <0.001 | <0.001 |
| | hour 7 | -1.16 | -0.64 | (-1.74, -0.57) | (-1.33, 0.05) | <0.001 | 0.071 |
| | hour 9 | -0.78 | -0.23 | (-1.33, -0.24) | (-0.87, 0.41) | 0.005 | 0.481 |
| Month 3 | hour 0 | -1.28 | -1.09 | (-1.90, -0.65) | (-1.73, -0.44) | <0.001 | 0.001 |
| | hour 2 | -2.20 | -1.94 | (-2.79, -1.61) | (-2.58, -1.30) | <0.001 | <0.001 |
| | hour 7 | -1.25 | -0.77 | (-1.85, -0.65) | (-1.46, -0.08) | <0.001 | 0.029 |
| | hour 9 | -0.90 | -0.39 | (-1.48, -0.32) | (-1.05, 0.27) | 0.002 | 0.246 |

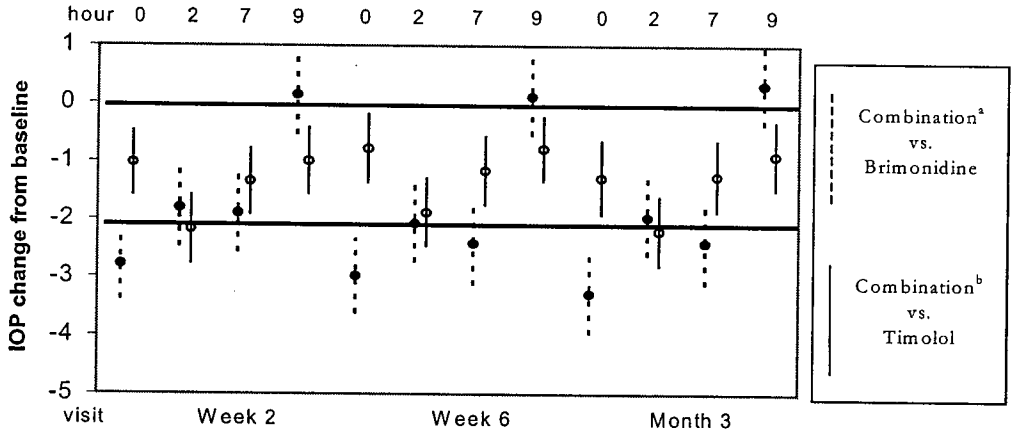
a. The difference between Combination and Timolol treated groups.
b. pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group, investigator and IOP measurement at baseline.
c. Model 2: pairwise contrasts from a single two-way ANOVA model at each hour of IOP measurement change from baseline with fixed effects for treatment group and investigator.

**Figure 1** 95% Confidence Intervals of Differences of LS Mean of IOP (mm Hg) at Each Scheduled Visit from; ITT, LOCF, 190342-012T



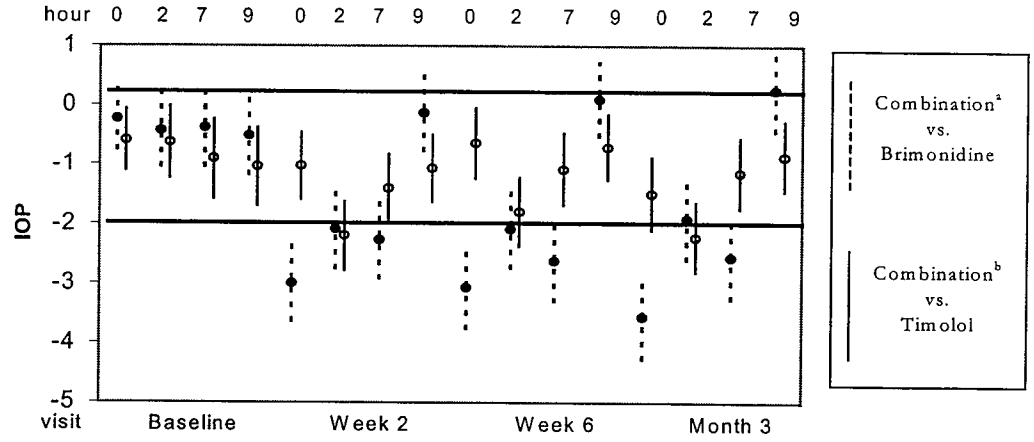

a. Pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group and investigator.
b. Pairwise contrasts from a single two-way ANOVA model at each hour of IOP measurement with fixed effects for treatment group, investigator and IOP measurement at baseline.
Source: Table 9.1, 9.2, 9.3, and 9.4 of 14.0 Tables, Figures, and Graphs of study 190342-012T. Vol 57.

**Figure 2** 95% Confidence Intervals of Differences of LS Mean of IOP change from baseline (mm Hg) at Each Scheduled Visit from; ITT, LOCF, 190342-012T



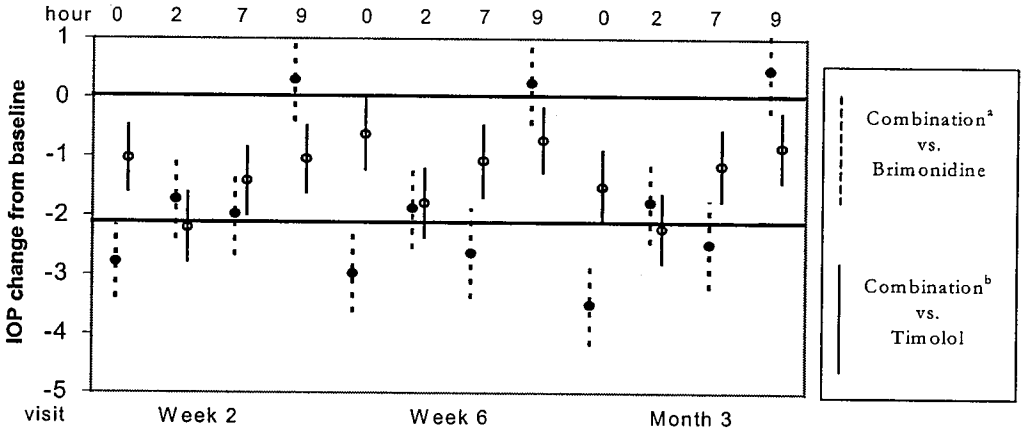

a. Pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group and investigator.
b. Pairwise contrasts from a single two-way ANOVA model at each hour of IOP measurement with fixed effects for treatment group, investigator and IOP measurement at baseline.
Source: Table 8.1, 8.2, 8.3, and 9.1 of 14.0 Tables, Figures, and Graphs of study 190342-012T. Vol 57.

**Figure 3** **95% Confidence Intervals of Differences of LS Mean of IOP (mm Hg) at Each Scheduled Visit from; PP, LOCF, 190342-012T**



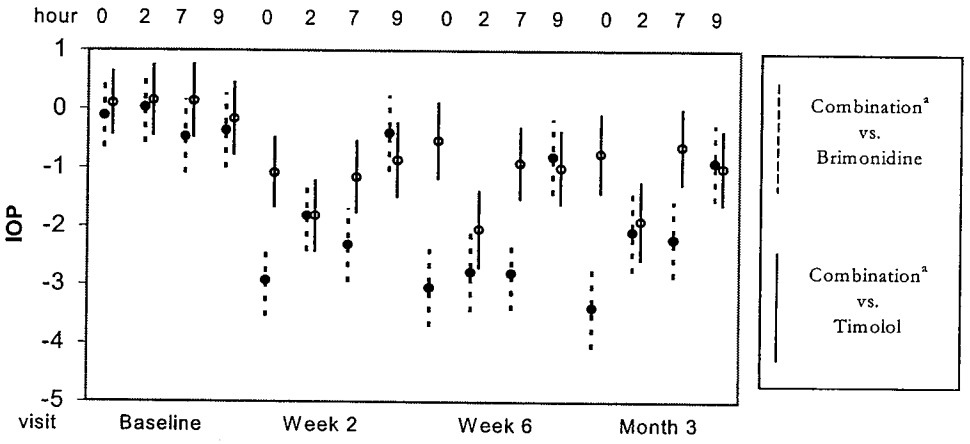

a. Pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group and investigator.
b. Pairwise contrasts from a single two-way ANOVA model at each hour of IOP measurement with fixed effects for treatment group, investigator and IOP measurement at baseline.
Source: Table 11.1, 11.2, 11.3, and 11.4 of 14.0 Tables, Figures, and Graphs of study 190342-012T. Vol 57.

**Figure 4** **95% Confidence Intervals of Differences of LS Mean of IOP change from baseline (mm Hg) at Each Scheduled Visit from; PP, LOCF, 190342-012T**




a. Pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group and investigator.
b. Pairwise contrasts from a single two-way ANOVA model at each hour of IOP measurement with fixed effects for treatment group, investigator and IOP measurement at baseline.
Source: Table 10.1, 10.2, 10.3, and 11.1 of 14.0 Tables, Figures, and Graphs of study 190342-012T. Vol 57.

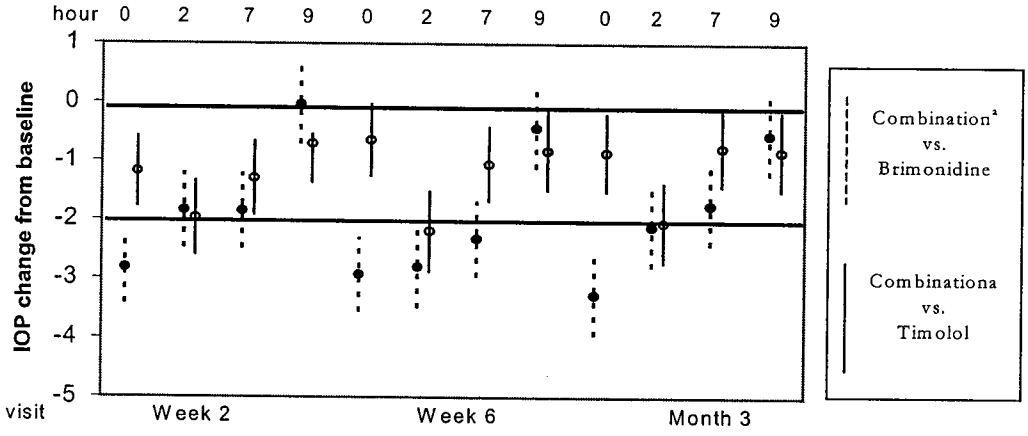
**Figure 5** **95% Confidence Intervals of Differences of LS Mean of IOP (mm Hg) at Each Scheduled Visit from; ITT, LOCF, 190342-013T**




a. Pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group and investigator.

Source: Table 9.1, 9.2, 9.3, and 9.4 of 14.0 Tables, Figures, and Graphs of study 190342-013T. Vol 68.

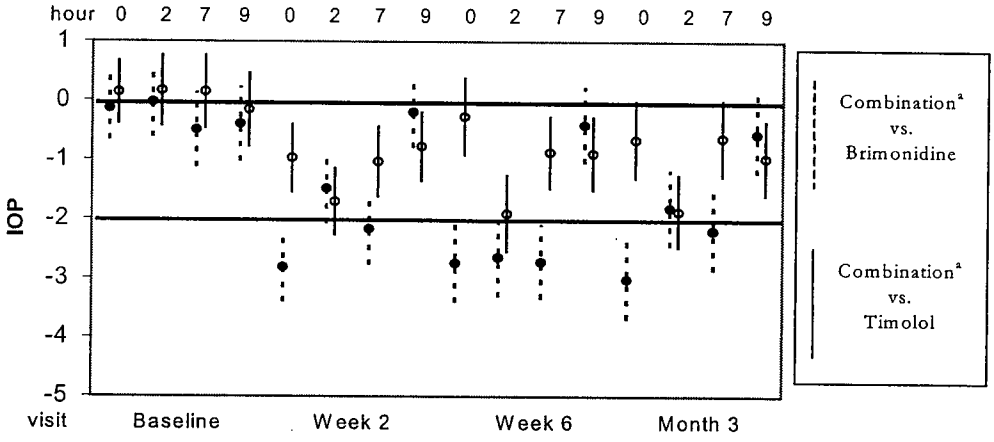
**Figure 6** **95% Confidence Intervals of Differences of LS Mean of IOP change from baseline (mm Hg) at Each Scheduled Visit from; ITT, LOCF, 190342-013T**




a. Pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group and investigator.

Source: Table 8.1, 8.2, 8.3, and 9.1 of 14.0 Tables, Figures, and Graphs of study 190342-013T. Vol 68.

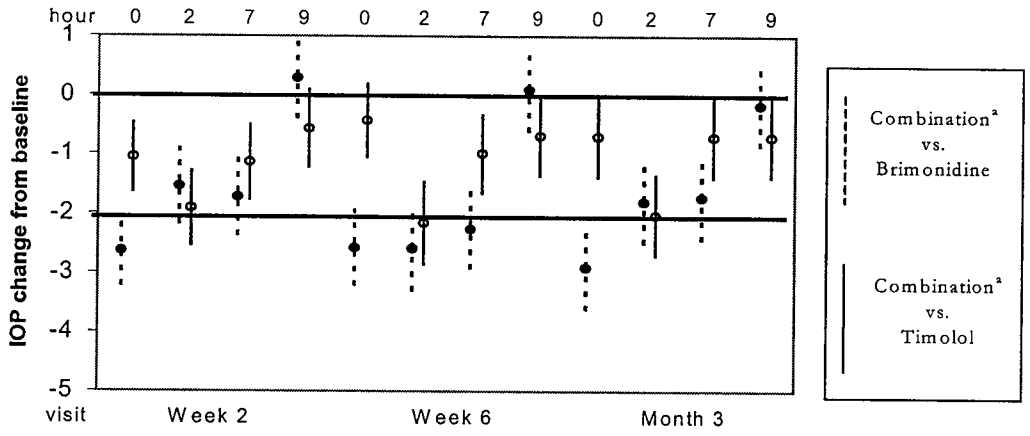
**Figure 7** 95% Confidence Intervals of Differences of LS Mean of IOP (mm Hg) at Each Scheduled Visit from; PP, LOCF, 190342-013T




a. Pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group and investigator.

Source: Table 11.1, 11.2, 11.3, and 11.4 of 14.0 Tables, Figures, and Graphs of study 190342-013T. Vol 68.

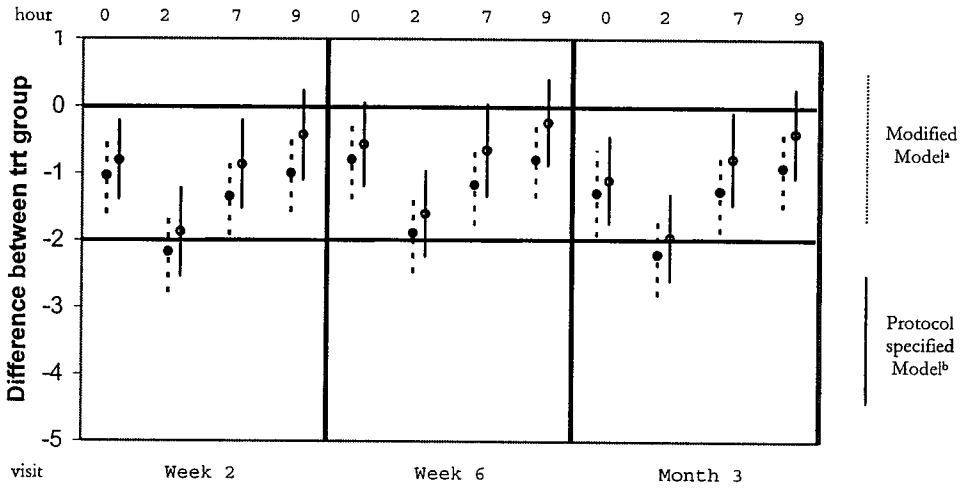
**Figure 8** 95% Confidence Intervals of Differences of LS Mean of IOP change from baseline (mm Hg) at Each Scheduled Visit from; PP, LOCF, 190342-013T




b. Pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group and investigator.

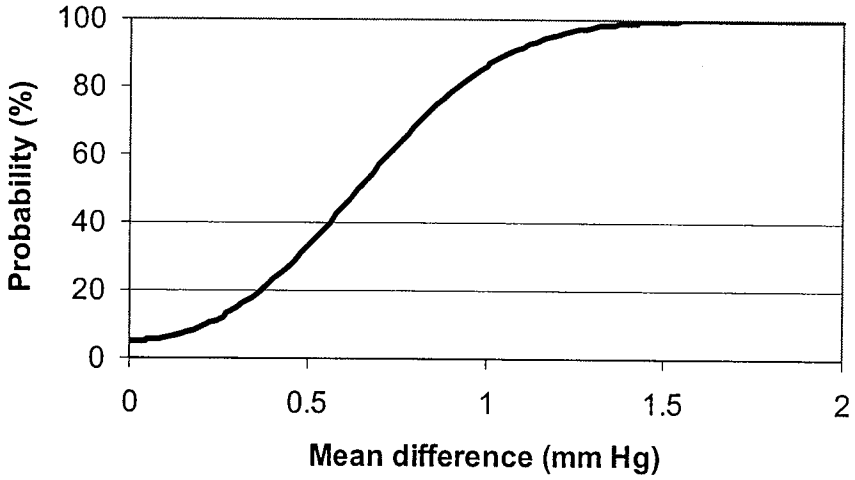
Source: Table 8.1, 8.2, 8.3, and 9.1 of 14.0 Tables, Figures, and Graphs of study 190342-013T. Vol 68.

Figure 9 **95% Confidence Intervals of Differences of LS Mean of IOP change from baseline (mm Hg) between Combination and Timolol Treated Groups at Each Scheduled Visit from Two Different Models; ITT, LOCF, 190342-012T**




a. Modified Model: Pairwise contrasts from a single ANCOVA model at each hour of IOP measurement with fixed effects for treatment group, investigator and IOP measurement at baseline.
b. Protocol Specified Model: Pairwise contrasts from a single two-way ANOVA model at each hour of IOP measurement change from baseline with fixed effects for treatment group and investigator.
Source: Table 8.1, 8.2, 8.3, and 9.1 of 14.0 Tables, Figures, and Graphs of study 190342-012T. Vol 57, and reviewer's analyses using data sponsor's submitted

Figure 10 **Power (probability to conclude significant difference between treatment group) graph.**




Based on standard deviation of 3.2 mm Hg, 2-sample t-test with 2-sided alternatives, significant level of 0.05, 2-step comparison adjusted.

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Suktae Choi
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UNKNOWN