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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # :	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

TABLE OF CONTENTS

LIST OF TABLES

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

\\Cdsesub1\nonectd\N21398\N_000\2007-05-02

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 ≥ 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 ≥ 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 ≥ 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 ≥ 1 unit at any visit.

Salivary Flow Assessment: The amount of saliva collected at Baseline and Day 10 was categorized as low (≤ 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

Primary Statistical Reviewer: Christopher Khedouri

Date: 10/03/2007

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

cc:
HFD-520/Project Manager/ Alison Rodgers
HFD-520/Medical Officer/ William Boyd, M.D.
HFD-520/Deputy Division Dir/ Katherine Laessig, M.D.
HFD-520/Acting Division Dir/ Wiley Chambers, M.D.
HFD-725/Primary Statistical Reviewer/ Christopher Khedouri, Ph.D.
HFD-725/Statistical Team Leader/Thamban Valappil, Ph.D.
HFD-725/Biometrics Deputy Division Dir/Daphne Lin, Ph.D.
HFD-725/Biometrics Division Dir/ Mohammad Huque, Ph.D.
HFD-700/Office of Biostatistics/ Lillian Patrician, MS, MBA
HFD-700/Office of Biostatistics Deputy Dir/Edward Nevius, Ph.D.

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

/s/

Christopher Khedouri
10/3/2007 02:05:45 PM
BIOMETRICS

Thamban Valappil
10/3/2007 03:04:46 PM
BIOMETRICS