3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Per the CMC reviewed for this amendment:

In this amendment, the applicant provided a CMC section which includes the following information:

- Supporting documentation for a new configuration container closure system, [redacted] bottle to be used for this product
- Stability report including 36 months data on site validation batches (continue to support the proposed 24 month expiration dating period) and revised specification
- [redacted] validation report – referred to the microbiological review of this NDA

Sufficient information was provided on the revised container closure system. Issues regarding the identity and source of the newly observed impurity [redacted] were solved during the review process. [redacted]. A revised analytical procedure for impurities in the drug product was provided. The acceptance criterion of [redacted] established based on the Pharm/Tox qualification study. There are no remaining issues.

From the quality assurance perspective, this NDA is recommended for approval.

3.2 Animal Pharmacology/Toxicology

Per the Pharm/Tox review for this amendment:

Both timolol and bromonidine are approved drugs. These two drugs have been used separately or concomitantly in clinical practice for a long period of time and are considered safe, effective and well-tolerated. Nonclinical data with the combination product indicated that the ocular and systemic absorption of brimonidine and timolol in rabbits is comparable between the combination drug and the single drug formulations. No additional toxicologically significant effects were observed in animal studies, and no toxicological interaction between timolol and brimonidine tartrate was noted. In toxicity studies with the combination product containing exaggerated concentrations of impurities, neither ocular irritation nor pathological findings were noted, suggesting that the impurities do not pose a human safety concern. In summary, nonclinical data support the safety of the combination drug product.

Recommendations:
This application is approvable from a nonclinical perspective with some modifications of labeling as revised in the Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of clinical data utilized in this review include all the submitted trials conducted by the applicant as found in the following List of Clinical Studies in Section 4.2 of this review.

4.2 List of Clinical Studies

1. Study Number: 190342-023T

A Multi-Center, Randomized, Double-Masked, Parallel-Group Study to Evaluate the Safety of BID (Twice-Daily) Administration of 0.2% Brimonidine Tartrate/ 0.5% Timolol Fixed Combination Ophthalmic Solution Compared with ALPHAGAN (0.2% Brimonidine Tartrate) TID (Three Times Daily) and 0.5% Timolol BID Given Concurrently in Healthy, Adult Subjects for Ten Days

2. Study Number: 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 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

3. Study Number: 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 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

4.3 Review Strategy

The June 29, 2006, submission was submitted electronically. All subsequent amendments were submitted electronically. All study reports were reviewed. The three clinical study reports submitted formed the basis for the review of safety for the proposed indication.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

4.4 Data Quality and Integrity

There is no evidence that these studies were not conducted in accordance with acceptable clinical ethical standards.

4.5 Compliance with Good Clinical Practices

All studies were conducted in accordance with accepted clinical and ethical standards.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators for 190342-023T. The forms for -012T and -013T have previously been submitted to the NDA.

5 CLINICAL PHARMACOLOGY

Not applicable to this amendment. There are no remaining issues. See previous clinical pharmacology reviews for this NDA.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication sought in this new drug application is:

> Combigan (brimonidine tartrate/ timolol ophthalmic solution) 0.2%/0.5% is indicated for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.

6.1.1 Methods

All submitted clinical study reports, clinical protocols, summary documents, and cited references were reviewed. All submitted studies were reviewed separately and subsequently assessed in aggregate.

The application was submitted in electronic format including proposed draft labeling and Case Report Forms for discontinued subjects for each submitted trial.

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

6.1.2 General Discussion of Endpoints

See previous clinical reviews for this New Drug Application.

The data contained in the original NDA, in an amendment dated September 13, 2004, and in this amendment dated June 29, 2006, did not adequately show that each component made a contribution to the claimed effect of the combination product.

6.1.3 Study Design

Reviewer's Comments:

The 12 month clinical study reports for 190342-012T and 190342-013T are submitted here; the 3 month study reports for these protocols were included in the original NDA submission.

Both of these trials are described in detail in the original NDA review. See Section 6.1.6 of this review for 12 month IOP data from these trials.

Study Number: 190342-023T

Study Initiation Date: 26 November 2005
Study Completion Date: 23 February 2006

A Multi-Center, Randomized, Double-Masked, Parallel-Group Study to Evaluate the Safety of BID (Twice-Daily) Administration of 0.2% Brimonidine Tartrate/ 0.5% Timolol Fixed Combination Ophthalmic Solution Compared with ALPHAGAN® (0.2% Brimonidine Tartrate) TID (Three Times Daily) and 0.5% Timolol BID Given Concurrently in Healthy, Adult Subjects for Ten Days

Principal Investigator Name (Number), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Louis B Cantor, MD (2117) Indiana University 702 Rotary Circle, Room 145 Indianapolis, Indiana 46202	[redacted]	32	90901-90932
Richard M Evans, MD (2975) Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, Texas 78240	[redacted]	30	90401-90430
Donald L McCormack, MD (1942) Boulder Medical Center, PC 2750 Broadway Boulder, Colorado 80304	[redacted]	58	90701-90758

Thomas Mundorf, MD (1485) Mundorf Eye Center 1718 East 4thStreet, Suite 703 Charlotte, North Carolina 28204	none	13	90801-90813
Kenneth Sall, MD (2707) Sall Eye Research Medical Center 11423 187thStreet, Suite 200 Artesia, California 90701	none	120	90201-90321
Howard I Schenker, MD (2429) Rochester Ophthalmological Group, PC 2100 South Clinton Avenue Rochester, New York 14618	[redacted]	59	90601-90659
Thomas R Walters, MD (1634) Texan Eye Care, PA 1020 West 34thStreet Austin, Texas 78705	[redacted]	38	90501-90538
David Wirta, MD (3276) David Wirta, MD, Inc Eye Research Foundation 1501 Superior Avenue, Suite 303 92663	none	173	90001-90175

This study was a multicenter, randomized, double-masked, parallel-group safety study consisting of 5 scheduled visits: Screening (Day -21 to Day -3), Baseline (Day -1), Day 1, Day 9, and Day 10. Healthy, adult subjects were eligible to enter the study. A total of 452 subjects were enrolled and assigned in a 1:1 allocation to 1 of 2 masked treatment groups:

- Combination: 0.2% brimonidine tartrate/0.5% timolol combination ophthalmic solution administered BID, in the morning and evening, or

- Concurrent: ALPHAGAN® ophthalmic solution (0.2% brimonidine tartrate) administered TID (morning, afternoon, and evening) and timolol ophthalmic solution (0.5% timolol) administered BID (morning and evening).

For subjects in the Combination group, the Combination was administered BID (morning and evening) with vehicle of brimonidine administered TID (morning, afternoon, and evening) to maintain proper masking.

Subjects began study medication dosing in the morning (Hour 0) of Day 1. Morning dosing occurred at Hour 0 (between 07:00 and 09:00), afternoon dosing occurred at Hour 6 (6 hours after the Hour 0 dose), and evening dosing occurred at Hour 12 (12 hours after the Hour 0 dose). On Days 1, 9 and 10, subjects remained at the site for the entire length of the visit and dosing was performed by the site personnel.

No efficacy measurements were performed for this study. This study directly compared the safety of Combination and Concurrent by specifically assessing sleepiness, dry mouth, and dizziness. Safety assessments 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); dry mouth (using a 5-point scale questionnaire with 1 being "not experiencing the symptom at all" and 5 being "intolerable"); and dizziness (using a 5-point scale questionnaire with 1 being "not experiencing the symptom at all" and 5 being "intolerable")
- an assessment of the amount of saliva based on the weight of an unstimulated saliva collection
- the frequency of dry mouth, sleepiness, and dizziness since the subject's last visit as assessed by a retrospective 5-point scale questionnaire with 1 being "never" and 5 being "always."

The following data was collected as safety assessment with Day 10 being the primary timepoint for this study:

- current severity of dry mouth using 5-point scale questionnaire (1 = not experiencing the symptom at all, 2 = mild, 3 = moderate, 4 = severe, and 5 = intolerable)
- current severity of sleepiness using 7-point scale questionnaire (Stanford Sleepiness Scale (SSS)) with 1 being 'most alert' through 7 being 'most tired' (a score of "X", asleep, will be reassigned as "7" in the data analysis).

For each variable analyzed, the null hypothesis is that there is no difference between the Combination and Concurrent treatment groups in the raw score of the safety parameters of interest with the alternative hypothesis being that the difference does exist between the 2 treatment groups. The raw score from the safety data stated above will be analyzed at each scheduled visit using 2-way analysis of variance (ANOVA) with fixed effects of treatment and investigator. Hochberg's procedure will be used to adjust for the analyses of the 2 primary endpoints to control the overall type I error rate at 5%. Both hypothesis will be considered statistically significant at the 0.05 level if the greater p-value of the 2 analyses is less than or equal to 0.05. Otherwise, if the smaller p-value of the 2 analyses is less than or equal to 0.025, then the associated analysis will be considered statistically significant at the 0.05 level. In addition, a 2-sided 95% confidence interval for the treatment difference will be constructed.

Reviewer's Comment's:

The protocol specified a safety and ITT population. The analysis plan added a mITT population to be used for the analysis of the safety assessments prior to database lock. The mITT population consisted of subjects with baseline and at least 1 post-baseline assessment of the primary endpoint.

Of the ITT and safety subjects, only 1 subject from each treatment group was excluded from the mITT population. Subject 1942-90728 in the Combination group did not have any post-baseline

data. Subject 1942-90722 in the Concurrent group did not have a baseline current severity of sleepiness assessment. Thus, a total 450 subjects were included in the mITT population: 223 in the Combination group and 227 in the Concurrent group.

Although the study report states that the single primary endpoint for this study was the proportion of current severity of sleepiness responders and the single secondary endpoint for this study was the proportion of current severity of dry mouth responders, the statistical analysis plan provided for two primary efficacy variables as described in the preceding section. It is not clear why the study report makes this unnecessary distinction regarding primary and secondary endpoints since the change was made prior to database lock.

In addition to the safety assessments of sleepiness, dry mouth, and dizziness, standard safety measures performed during the study included adverse events (AEs), blood pressure (BP), and pulse rate (PR).

Inclusion Criteria:

1) Male or Female, at least 18 years of age and legal age of consent
2) Written informed consent and authorization have been obtained prior to any study-related procedures
3) Patient has ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy / iridectomy, pseudoexfoliative glaucoma, or pigmentary glaucoma in both eyes
4) A best-corrected visual acuity score equivalent to a Snellen acuity of 20/100 or better in each eye, using a logarithmic visual acuity chart for testing at 10 feet
5) Patient has a stable IOP and can be washed out of their IOP-lowering medications (if applicable)
6) Baseline: Patient has been appropriately washed out of all IOP-lowering medications
7) Patient requires bilateral IOP-lowering treatment
8) Acceptable fasting blood analysis (hematology, blood chemistry) and urinalysis results (acceptable blood and urinalysis results will be those within the reference range as defined by the laboratory or results "out-of-range" but still acceptable to the investigator and consistent with the study inclusion / exclusion criteria)
9) Negative screen for drugs of abuse, nicotine, and alcohol as well as negative checks for presence of HIV, hepatitis B surface antigen, and hepatitis C antibody
10) A negative urine pregnancy test for female patients of childbearing potential at the baseline visit. A female is considered to be of childbearing potential unless she is post-menopausal or without a uterus and/or both ovaries
11) Ability to follow study instructions and likely to complete all required visits

Exclusion Criteria:

1) Any uncontrolled systemic disease
2) Patients with any abnormality of the lids, ocular surface, or lachrymal duct system that could affect absorption

3) Active ocular disease (e.g., uveitis, ocular infections, chronic blepharitis, or severe dry eye), that in the opinion of the investigator would interfere with the interpretation of the study data. Myopia, strabismus, and cataracts are allowed provided other criteria are met
4) History of excessive consumption of alcohol, or alcohol-dependency within the last 2 years. Use of alcohol within 3 days prior to baseline, or anticipated use during the study
5) History of illicit drug abuse (e.g., phencyclidine, benzodiazepines, cannabinoids, amphetamines, barbiturates, cocaine, and opiates)
6) History of excessive consumption of xanthine-containing products, or caffeine-dependency, or anticipated excessive use during the course of the study
7) Required use of ocular medications (post baseline visit) other than the study medication (occasional use of artificial tears is allowed)
8) Treatment with any alpha-agonists, alpha-antagonists, or cold medications within 2 weeks prior to baseline or during the study
9) Patients who anticipate using tobacco products during the study
10) Patients who anticipate drinking more than 24 ounces of caffeinated drinks per day during the study
11) Females who are pregnant, nursing, or planning a pregnancy or who are of childbearing potential and not using a reliable method of contraception
12) Contraindication to beta-adrenoreceptor antagonist therapy. Contraindications include, but are not limited to, chronic obstructive pulmonary disease, bronchial asthma, sinus bradycardia, second and third degree atrioventricular block, uncontrolled congestive heart failure, history of severe myocardial infarction, or clinically relevant low or high heart (pulse) rate or blood pressure
13) Patients with cardiovascular disease should not be enrolled unless his/her disease is controlled and clearance has been obtained from the treating primary care physician or cardiologist
14) Contraindication to brimonidine therapy such as concurrent use of monoamine oxidase (MAO) inhibitor therapy
15) Concurrent use or anticipated treatment with adrenergic augmenting psychotropic drugs (i.e., tricyclic antidepressants such as desipramine or amitriptyline)
16) Patient has a sleep disorder or patient cannot or is unwilling to sleep approximately 8 hours / night for the week before and during the study
17) Anticipated wearing of contact lenses during the study (use of soft lenses should be discontinued at least two days prior to baseline, and use of rigid gas permeable (RGP) or hard contact lenses should be discontinued at least one week prior to baseline)
18) Current enrollment in an investigational drug or device study or participation in such a study within 30 days prior to the baseline visit
19) Patient has a condition or is in a situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study

Reviewer's Comments:

The inclusion/exclusion criteria for 190342-023T were similar to those of 190342-012T, 190342-013T, and 190342-019T.

Schedule of Visits and Measurements

Visits and Timepoints	Consent/ Hx[a] / PE	Lab Draw[b]	Eye Exam[c]	Preg Test[d]	BP/ PR	SME[e]/ AE	Question -naires[f]	Saliva Assess[g]	Dosing
Screening Day -21 to -3									
Anytime	X	X	X		X	X			
Baseline Day -1									
15:00-17:00				X	X	X	X	X	
Day 1	Randomization Prior to Hour 0								
Hour 0					X	X			X
Hour 6									X
Hour 8							X		
Hour 12									X
Day 9									
Hour 0					X	X			X
Hour 6									X
Hour 8							X		
Hour 12									X
Day 10									
Hour 0					X	X			X
Hour 6									X
Hour 8							X	X	
Early Exit									
Anytime					X	X	X	X	

Abbreviations: Hx = History, Lab = Laboratory, Preg = Pregnancy, BP = Blood Pressure, PR = Pulse Rate, AE = Adverse Event, SME = Serious Medical Event, Assess = Assessment, PE = Physical Exam

a Consent included study Informed Consent and Authorization. Medical and Social histories were taken.

b Laboratory draw included fasting blood draw, urinalysis, and urine drug screen. Fasting should not have begun until after consent was signed. Samples should have been collected and reviewed prior to randomization.

c Eye exam included visual acuity, biomicroscopy, and IOP.

d Pregnancy tests were given to females of child-bearing potential.

e SMEs were assessed between the time informed consent was signed and randomization into the study.

f Symptom questionnaires included sleepiness, dry mouth, and dizziness assessments.

g Subjects should have had no food or drink for at least 1 hour prior to assessment.

Source: Table 9.5-2

Demographics – MITT Population

		Combination (N=223)	Concurrent (N=227)	Total (N=450)	P-value[a]
Age (Years)	N	223	227	450	0.392
	Mean	31.0	30.1	30.6	
	SD	11.35	10.90	11.12	
	Median	27.0	27.0	27.0	
	Min	18	18	18	
	Max	61	62	62	
	<45	182 (81.6%)	194 (85.5%)	376 (83.6%)	
	45-65	41 (18.4%)	33 (14.5%)	74 (16.4%)	
	>65	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Sex	N	223	227	450	0.406
	Male	82 (36.8%)	75 (33.0%)	157 (34.9%)	
	Female	141 (63.2%)	152 (67.0%)	293 (65.1%)	
Race	N	223	227	450	0.949
	Black	23 (10.3%)	23 (10.1%)	46 (10.2%)	
	Non-Black	200 (89.7%)	204 (89.9%)	404 (89.8%)	
	Caucasian	114 (51.1%)	110 (48.5%)	224 (49.8%)	
	Asian	11 (4.9%)	3 (1.3%)	14 (3.1%)	
	Hispanic	68 (30.5%)	87 (38.3%)	155 (34.4%)	
	Other[b]	8 (3.6%)	4 (1.8%)	12 (2.7%)	

[a] P-values for age, height and weight are from a 1-way analysis of variance model.
P-values for sex and race (black vs. non-black) are from the Pearson's chi-square test, unless noted otherwsie.
[b] 'Other' race includes: Black/Carribean (counted as Black and not included in the Non-Black category total), Cuban, Middle-Eastern, Native American, Pacific Islander, Phillipino and Samoan.

Source: Table 14.1-2.1

Reviewer's Comments:

Although the inclusion/exclusion criteria for 190342-023T were similar to those of 190342-012T, 190342-013T, and 190342-019T, the demographics above reveal that 84% of subjects were less than 45 years of age. This is not consistent with the demographics of 190342-012T, 190342-013T, and 190342-019T.

In the first Special Protocol Assessment for 190342-023T, the following comment was sent to Allergan:

> "Healthy, adult subjects" are not the population studied in 190342-012T, 190342-013T, and 190342-019T. They are not the population which Allergan asserts experienced fewer ocular adverse events as well as fewer neurological adverse events than patients receiving brimonidine TID either alone or concurrently.
>
> Recommend the inclusion/exclusion criteria represent the population studied in 190342-012T, 190342-013T, and 190342-019T.

6.1.4 Efficacy Findings

No efficacy measurements were performed during study 190342-023T.

Reviewer's Comments:

Only baseline intraocular pressure was measured in 190342-023T.

6.1.5 Clinical Microbiology

Not applicable to this application.

6.1.6 Efficacy Conclusions

No efficacy measurements were performed during study 190342-023T.

190342-012T

Mean Intraocular Pressure (mm Hg) at Each Scheduled Visit (Intent-to-Treat with Last Observation Carried Forward)

Timepoint		Combination N = 192	Brimonidine N = 186	Timolol N = 195
Baseline	hour 0	24.5	24.7	25.1[a]
	hour 2	22.8	23.2	23.5[a]
	hour 7	21.6	22.0	22.6[a]
	hour 9	21.4	21.9	22.5[a]
Week 2	hour 0	17.9	20.9[b]	19.2[c]
	hour 2	15.9	18.1[b]	18.5[c]
	hour 7	16.6	18.9[b]	18.4[c]
	hour 9	16.7	17.1	18.2[c]
Week 6	hour 0	18.0	21.2[b]	19.1[c]
	hour 2	15.7	18.2[b]	17.9[c]
	hour 7	16.6	19.4[b]	18.2[c]
	hour 9	16.8	17.1	18.0[c]
Month 3	hour 0	17.7	21.2[b]	19.3[c]
	hour 2	15.5	17.9[b]	18.1[c]
	hour 7	16.6	19.4[b]	18.3[c]
	hour 9	17.0	17.2	18.4[c]
Month 6	hour 0	18.3	21.4[b]	19.8[c]
	hour 2	15.9	18.4[b]	18.7[c]
	hour 7	17.0	19.7[b]	18.6[c]
	hour 9	17.0	17.5	18.6[c]
Month 9	hour 0	18.7	21.4[b]	19.8[c]
	hour 2	16.0	18.4[b]	18.5[c]
Month 12	hour 0	18.5	21.3[b]	19.9[c]
	hour 2	15.9	18.2[b]	18.7[c]
	hour 7	17.0	19.9[b]	18.8[c]
	hour 9	17.3	17.5	18.9[c]

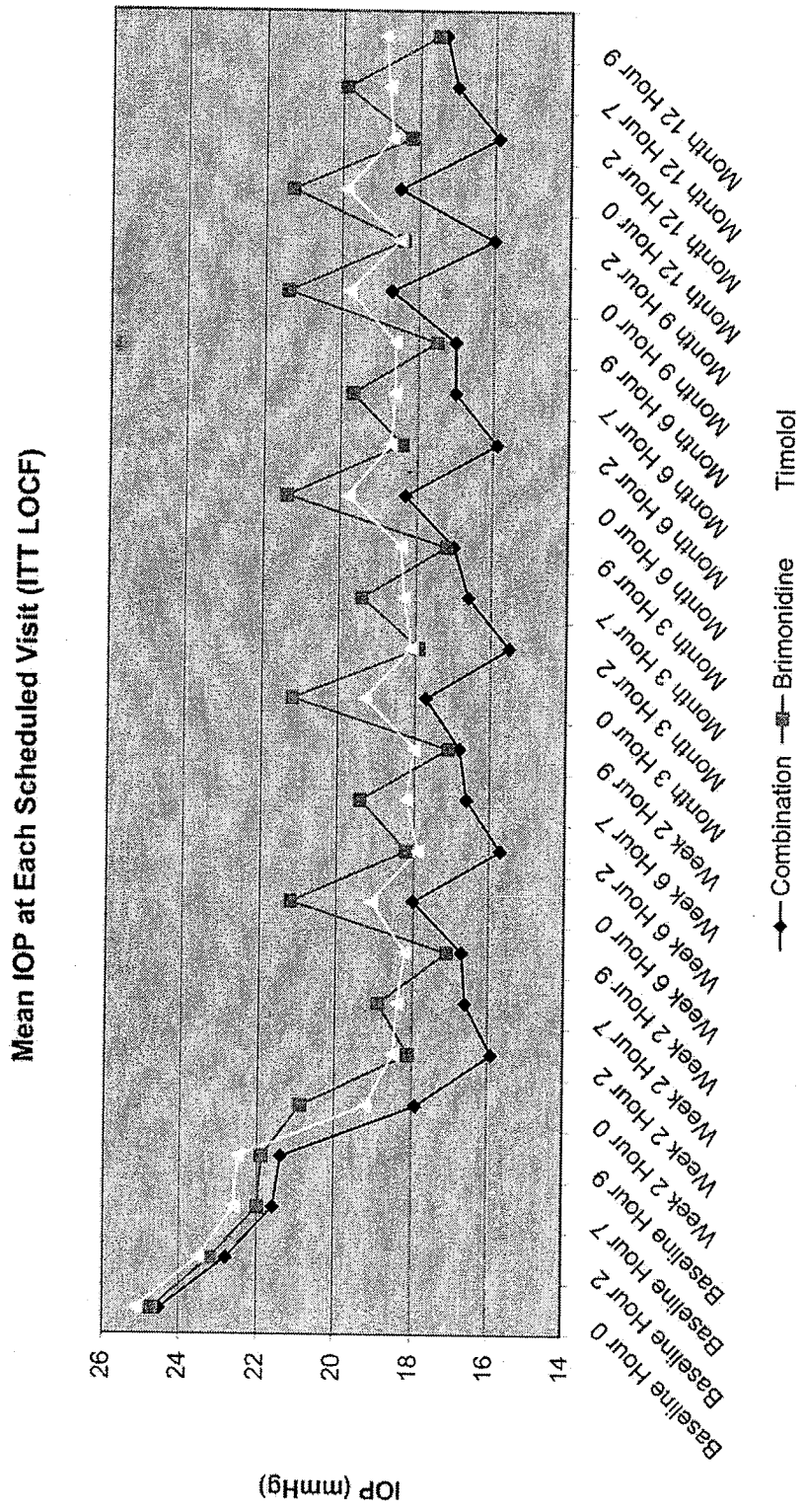
Source: Section 14.2, Tables 9.1 to 9.7
N = number of randomized patients; actual sample size may differ due to incomplete baseline visits.

a Combination mean IOP at baseline statistically significantly lower than Timolol ($p \leq 0.046$).

b Combination mean IOP statistically significantly lower than Brimonidine ($p < 0.001$). P-values calculated from pairwise contrasts from a single two-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

c Combination mean IOP statistically significantly lower than Timolol ($p \leq 0.026$). Same model as for Combination versus Brimonidine (b), with the addition of baseline IOP as covariate.

Source: Table 11.4.1.2


Mean IOP at Each Scheduled Visit (ITT LOCF)
IOP (mmHg)
26
24
22
20
18
16
14
Baseline Hour 0
Baseline Hour 2
Baseline Hour 7
Baseline Hour 9
Week 2 Hour 0
Week 2 Hour 2
Week 2 Hour 7
Week 2 Hour 9
Week 6 Hour 0
Week 6 Hour 2
Week 6 Hour 7
Week 6 Hour 9
Month 3 Hour 0
Month 3 Hour 2
Month 3 Hour 7
Month 3 Hour 9
Month 6 Hour 0
Month 6 Hour 2
Month 6 Hour 7
Month 6 Hour 9
Month 9 Hour 0
Month 9 Hour 2
Month 12 Hour 0
Month 12 Hour 2
Month 12 Hour 7
Month 12 Hour 9
Combination
Brimonidine
Timolol

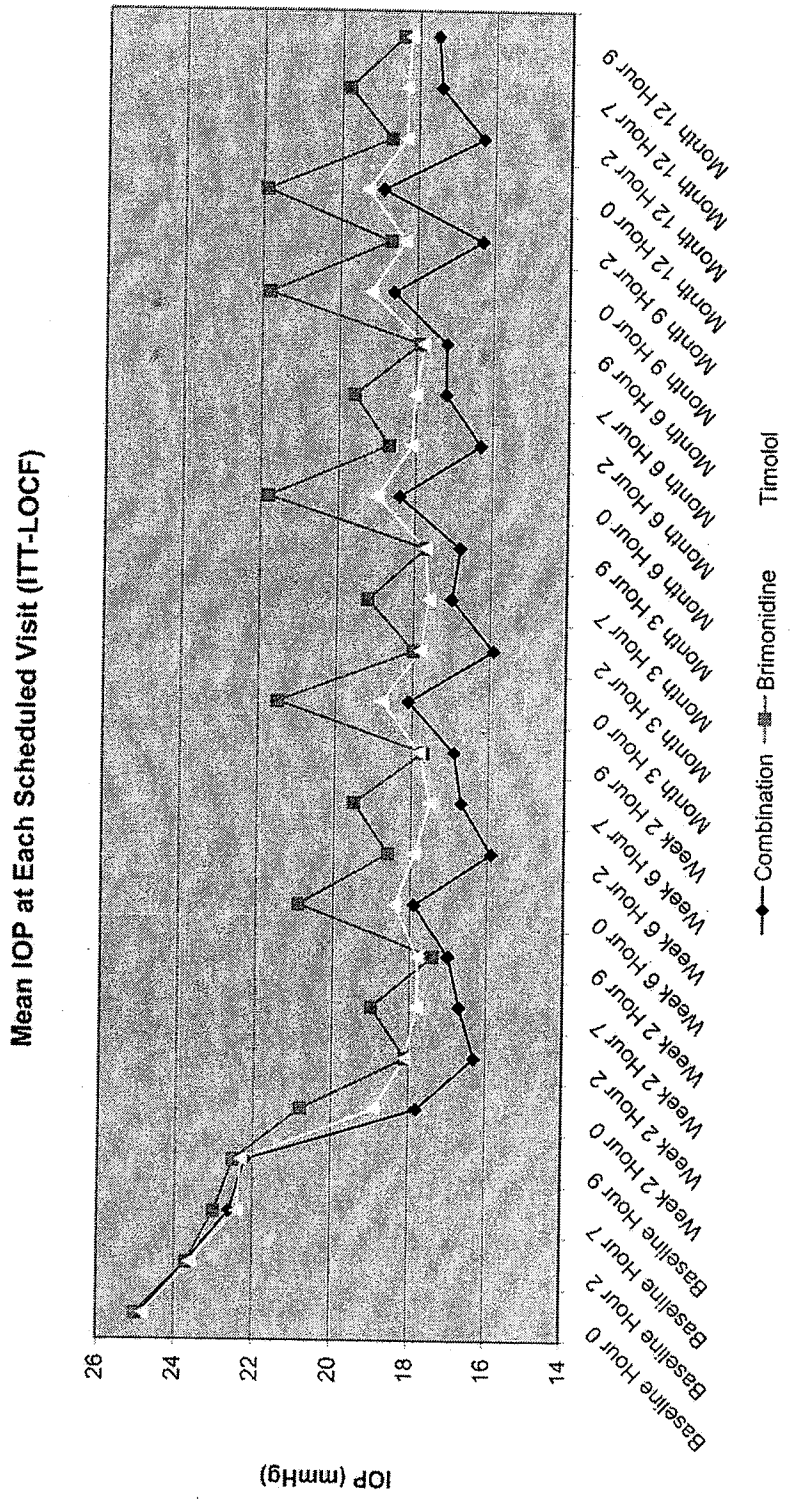
Mean Intraocular Pressure (mm Hg) at Each Scheduled Visit (Intent-to-Treat with Last Observation Carried Forward)

Timepoint		Combination N = 193	Brimonidine N = 196	Timolol N = 197
Baseline	hour 0	24.9	25.0	24.8
	hour 2	23.7	23.7	23.6
	hour 7	22.6	23.0	22.4
	hour 9	22.2	22.5	22.3
Week 2	hour 0	17.8	20.8[a]	18.9[b]
	hour 2	16.3	18.1[a]	18.1[b]
	hour 7	16.7	19.0[a]	17.8[b]
	hour 9	17.0	17.4	17.8[b]
Week 6	hour 0	17.9	20.9[a]	18.4
	hour 2	15.9	18.6[a]	17.9[b]
	hour 7	16.7	19.5[a]	17.5[b]
	hour 9	16.9	17.7[a]	17.8[b]
Month 3	hour 0	18.1	21.5[a]	18.8[b]
	hour 2	15.9	18.0[a]	17.8[b]
	hour 7	17.0	19.2[a]	17.6[b]
	hour 9	16.8	17.7[a]	17.7[b]
Month 6	hour 0	18.4	21.8[a]	19.0
	hour 2	16.3	18.7[a]	18.1[b]
	hour 7	17.2	19.6[a]	18.0[b]
	hour 9	17.2	17.9[a]	17.8[b]
Month 9	hour 0	18.6	21.8[a]	19.2
	hour 2	16.3	18.7[a]	18.3[b]
Month 12	hour 0	18.9	21.9[a]	19.3
	hour 2	16.3	18.7[a]	18.3[b]
	hour 7	17.4	19.8[a]	18.3[b]
	hour 9	17.5	18.4[a]	18.2[b]

Source: Section 14.2, Tables 9.1 to 9.7
N = number of randomized patients; actual sample size may differ due to incomplete baseline visits.

a Combination mean IOP statistically significantly lower than Brimonidine ($p \leq 0.030$). P-values calculated from pairwise contrasts from a single 2-way ANOVA model at each hour of diurnal measurement with fixed effects for treatment group and investigator.

b Combination mean IOP statistically significantly lower than Timolol ($p \leq 0.049$). Same model as for Combination versus Brimonidine (a).


Mean IOP at Each Scheduled Visit (ITT-LOCF)
IOP (mmHg)
26
24
22
20
18
16
14
Combination
Brimonidine
Timolol
Baseline Hour 0
Baseline Hour 2
Baseline Hour 7
Baseline Hour 9
Week 2 Hour 0
Week 2 Hour 2
Week 2 Hour 7
Week 2 Hour 9
Week 6 Hour 0
Week 6 Hour 2
Week 6 Hour 7
Week 6 Hour 9
Month 3 Hour 0
Month 3 Hour 2
Month 3 Hour 7
Month 3 Hour 9
Month 6 Hour 0
Month 6 Hour 2
Month 6 Hour 7
Month 6 Hour 9
Month 9 Hour 0
Month 9 Hour 2
Month 12 Hour 0
Month 12 Hour 2
Month 12 Hour 7
Month 12 Hour 9

Reviewer's Comments:

Neither study 190342-012T nor 190342-013T demonstrates a clinically significant contribution of timolol 0.5% or brimonidine tartrate 0.2% to the combination product. There is no new information to alter the conclusion from the original NDA review:

e) There are statistically significant differences in IOP at baseline between the combination and timolol in study 190342-012T.

f) Neither study 190342-012T nor 190342-013T demonstrates a clinically significant contribution of brimonidine tartrate 0.2% to the combination product.

g) There is a reproducible loss of IOP lowering ability of the combination versus brimonidine tartrate 0.2% seen in both phase 3 studies at hour 9 during each diurnal measurement.

h) Neither study 190342-012T nor 190342-013T demonstrates a clinically significant contribution of timolol 0.5% to the combination product.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths, other SAEs, or other significant AEs were reported during study 190342-023T.

7.1.2 Other Serious Adverse Events

No deaths, other SAEs, or other significant AEs were reported during study 190342-023T.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Discontinued Subjects

Investigator Subject	Age/Sex/Race	Date of Exit	Treatment Group	Date of First Dose	Reason for Discontinuation	Discontinuing AE
1634-90513	27/M/C	24JAN06	COMBINATION	24JAN2006	Adverse Event	WHEEZING
1634-90520	24/F/C	13FEB06	COMBINATION	04FEB2006	Other: SUBJECT LOST STUDY MED AND WAS NOT ABLE TO COMPLETE DAY 9.	
1942-90728	31/F/C	17JAN06	COMBINATION	17JAN2006	Adverse Event Adverse Event Adverse Event Adverse Event Adverse Event Adverse Event	CONFUSION DIZZINESS DRY EYES OU HEADACHE RUNNY NOSE SNEEZING
2117-90920	24/F/C	08FEB06	COMBINATION	04FEB2006	Adverse Event Adverse Event	OU SORE WORSENING CONJUNCTIVAL ERYTHEMA OU
2117-90927	18/F/C	13FEB06	COMBINATION	04FEB2006	Adverse Event	FATIGUE
2429-90658	34/F/B	23FEB06	COMBINATION	14FEB2006	Adverse Event	MIGRAINE
2707-90214	26/M/C	21DEC05	COMBINATION	20DEC2005	Protocol Violation	
2707-90317	22/F/C	25JAN06	COMBINATION	17JAN2006	Personal Reasons	
3276-90015	58/F/C	04DEC05	COMBINATION	26NOV2005	Adverse Event	VERTIGO
2707-90206	61/M/B/	15DEC05	CONCURRENT	07DEC2005	Other: WITHDREW CONSENT BY TELEPHONE 15 DEC 05	
3276-90108	19/F/C	08JAN06	CONCURRENT	30DEC2005	Adverse Event	INFLUENZA

Source: Table 16.2.1-1

Reviewer's Comments:

There was no statistically significant between-group difference in AEs leading to study discontinuation.

7.1.5 Common Adverse Events

Number (%) of Subjects with Adverse Events Regardless of Causality Reported by Greater than or Equal to 2% of Subjects in Either Treatment Group (Safety Population)

SYSTEM ORGAN CLASS Preferred Term[a]	Combination N = 224	Concurrent N = 228	P-Value[b]
EYE DISORDERS			
eye irritation	17 (7.6%)	6 (2.6%)	0.016
dry eye	8 (3.6%)	7 (3.1%)	0.766
eye pruritus	6 (2.7%)	4 (1.8%)	0.541[c]
GASTROINTESTINAL DISORDERS			
dry mouth	6 (2.7%)	13 (5.7%)	0.109
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
fatigue	11 (4.9%)	17 (7.5%)	0.262
NERVOUS SYSTEM DISORDERS			
headache	21 (9.4%)	16 (7.0%)	0.361
somnolence	10 (4.5%)	13 (5.7%)	0.549

Source: Tables 14.3-9.1

a system organ class and preferred terms from the MedDRA nomenclature
b unless otherwise specified, p-value based on Pearson's chi-square test
c between-group p-value based on Fisher's exact test

Source: Table 12.2-1

Reviewer's Comments:

The incidence of adverse events, regardless of causality, was 34.4% (77/224) of subjects in the Combination group and 36.8% (84/228) in the Concurrent group. The most frequently reported events (≥ 5%) were headache and eye irritation in the Combination group and headache, fatigue, somnolence, and dry mouth in the Concurrent group. The majority of adverse events were mild to moderate in severity.

There were no statistically significant differences between the 2 treatment groups for any of the individual adverse events except for eye irritation. Eye irritation was reported by 7.6% (17/224) of the subjects in the Combination group compared to 2.6% (6/228) in the Concurrent group (p = 0.016).

7.1.5.6 Additional analyses and explorations

Current Severity of Sleepiness
Proportion of Sleepiness Responders
[MITT]

Combination	Concurrent	P-value[A]
N = 223	N = 227	Difference[B]
54/223 (24.2%)	68/227 (30.0%)	95% CI[C]
		0.179
		-5.7%
		(-13.9%, 2.5%)

[A] P-value is from the general association statistic of the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.
[B] Difference of the proportions calculated as Combination group minus the Concurrent group.
[C] 2-sided 95% confidence interval of the difference in proportions calculated using the normal approximation to the binomial distribution.

Severity Score: 1 = feeling active, vital, alert or wide awake, 2 = functioning at high levels, but not at peak; able to concentrate, 3 = awake, but relaxed; responsive but not fully alert, 4 = somewhat foggy, let down, 5 = foggy; losing interest in remaining awake; slowed down, 6 = sleepy, woozy, fighting sleep; prefer to lie down, 7 = no longer fighting sleep, sleep onset soon; having dream-like thoughts; asleep.

Source: Table 14.3-2.1

Reviewer's Comments:

A Sleepiness Responder is a subject who on Day 1, Day 9, or Day 10 has a SSS severity score of at least 4 as well as at least a 2-unit increase from the baseline score.

The proportion of current severity of sleepiness responders was 24.2% (54/223) with Combination, numerically lower than 30.0% (68/227) with Concurrent, p = 0.179.

It would have greatly boosted Allergan's claim that the safety profile of the proposed combination product is significantly better than that of the individual agents taken as currently permitted in their approved labeling had the proportion of sleepiness responders been demonstrated as statistically and clinically significant. Inappropriate sleepiness is associated with decreased reaction time and impaired cognitive performance.

Current Severity of Dry Mouth
Proportion of Dry Mouth Responders
[MITT]

Combination	Concurrent	P-value[A] Difference[B] 95% CI[C]
N = 223	N = 227	0.016
45/222 (20.3%)	68/227 (30.0%)	-9.7%
		(-17.7%, -1.7%)

[A] P-value is from the general association statistic of the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.
[B] Difference of the proportions calculated as Combination group minus the Concurrent group.
[C] 2-sided 95% confidence interval of the difference in proportions calculated using the normal approximation to the binomial distribution.

Severity Score: 1 = not experiencing the symptom at all, 2 = mild, 3 = moderate, 4 = severe, 5 = intolerable.
Subjects missing baseline data or all post-baseline data are not included.

Source: Table 14.3-3.1

Reviewer's Comments:

A Dry Mouth Responder is a subject who on Day 1, Day 9, or Day 10 has a Current Severity of Dry Mouth score of at least 3 as well as at least a 1-unit increase from the baseline score.

The proportion of current severity of dry mouth responders was 20.3% (45/222) with Combination, statistically significantly less than 30.0% (68/227) with Concurrent, p = 0.016.

The adverse events in study -023T associated with dry mouth and oral conditions included: dry mouth, dry lips, thirst, gingival pain, oral pain, and pharyngolaryngeal pain.

Saliva Assessment (grams/minute)
Shift of Category from Baseline to Day 10
(Modified Intent-to-Treat Population)

Day 10 Category	Combination (N=223) Baseline Category			Concurrent (N=227) Baseline Category			P-value[a] Difference[b] (95% CI) [c]
	Normal	Reduced	Low	Normal	Reduced	Low	
Normal	135 (61.4%)	15 (6.8%)	0 (0.0%)	115 (50.9%)	6 (2.7%)	0 (0.0%)	<0.001 -21.4% (-28.7%,-14.2%)
Reduced	14 (6.4%)	35 (15.9%)	5 (2.3%)	36 (15.9%)	20 (8.8%)	2 (0.9%)	
Low	3 (1.4%)	5 (2.3%)	8 (3.6%)	12 (5.3%)	23 (10.2%)	12 (5.3%)	

Note: The amount of saliva collected at Baseline and Day 10 is categorized as low (<= 0.16 grams/min), reduced (>0.16 - 0.30 grams/min), or normal (>0.30 grams/min).
Subjects missing Baseline data or Day 10 data are not included in the counts or percents.
[a] P-value compares the proportion of subjects who decrease from baseline by at least one category (normal to reduced or low, reduced to low) and is from the general association statistic of the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.
[b] Difference of the proportions calculated as Combination group minus the Concurrent group.
[c] 2-sided 95% confidence interval of the difference in proportions calculated using the normal approximation to the binomial distribution.

Source: Table 14.3-4.1

Reviewer's Comments:

Allergan asserts the benefit with regard to dry mouth is confirmed by a between group difference in favor of the Combination for the objective measure of dry mouth, salivary flow. Salivary flow was not one of the two primary endpoints specified in this trial. The p-value shown above is uncorrected.

The proportion of subjects with decreased salivary flow of at least 1 category from baseline was statistically significantly lower with Combination (10.0%) than with Concurrent (31.4%), p < 0.001. The reduced and low categories used in this study are associated with a 33% and 85% risk of tooth demineralization over the next 2 months compared with no progression for the normal category.[1]

Although Study 190342-023T demonstrates that the safety profile of the proposed combination product is numerically superior than that of the individual agents taken as currently permitted in their approved labeling in the incidence of oral dryness adverse events, this particular difference in adverse events is not sufficient to offset the combination's inferior IOP-lowering ability (approximately 1-2 mmHg) compared to that of brimonidine and timolol given concomitantly.

1 Bardow A, Nyvad B, Nauntofte B. Relationships between medication intake, complaints of dry mouth, salivary flow rate and composition, and the rate of tooth demineralization in situ. Arch Oral Biol 2001;46:413-423.

7.1.7 Laboratory Findings

Clinical laboratory data were collected at Screening only. According to the protocol, no post-baseline laboratory data were collected.

7.1.8 Vital Signs

There were no statistically significant within or between-group differences in the change from baseline for systolic blood pressure, diastolic blood pressure, or mean pulse rate at any follow-up visit.

7.1.9 Electrocardiograms (ECGs)

No electrocardiograms were obtained in this clinical trial.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted was of sufficient quality and quantity to allow an adequate evaluation of safety of the drug product.

7.2.9 Additional Submissions, Including Safety Update

There were no additional submissions containing clinical data. There was no safety update submitted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Although Study 190342-023T demonstrates that the safety profile of the proposed combination product is numerically superior to the individual agents taken as currently permitted in their approved labeling in the incidence of oral dryness adverse events, this difference in adverse events is not sufficient to offset the combination's inferior IOP-lowering ability (approximately 1-2 mmHg) compared to that of brimonidine and timolol given concomitantly.

It would have greatly boosted Allergan's claim that the safety profile of the proposed combination product is significantly better than that of the individual agents taken as currently permitted in their approved labeling had the proportion of sleepiness responders been demonstrated as statistically and clinically significant. Inappropriate sleepiness is associated with decreased reaction time and impaired cognitive performance.

Although the inclusion/exclusion criteria for 190342-023T were similar to those of 190342-012T, 190342-013T, and 190342-019T, the demographics of -023T reveal that 84% of subjects were less than 45 years of age. This is not consistent with the demographics of 190342-012T, 190342-013T, and 190342-019T; the study population found in -023T is not the population

which Allergan asserts experienced fewer ocular adverse events as well as fewer neurological adverse events than patients receiving brimonidine TID either alone or concurrently in their previous trials.

In addition, ten days may be inadequate to distinguish a significant difference between the adverse event profiles for the two treatment groups.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There is no recommendation for changing the dosing regimen for the combination product. See section 1.3.2 for dosing considerations.

8.2 Drug-Drug Interactions

Drug-drug interactions were not evaluated in this submission. There are theoretical reactions per the individual labels for brimonidine and timolol:

- Antihypertensives/Cardiac glycosides
- Beta-adrenergic blocking agents
- Calcium antagonists
- Catecholamine-depleting drugs
- CNS Depressants
- CYP2D6 inhibitors
- Tricyclic Antidepressants.

8.3 Special Populations

An evaluation of this use of this product in special populations was conducted in the original NDA review. There were no significant differences seen in the IOP lowering ability of the combination product in any of the subgroups analyzed. There were no gender, age or race effects on safety or efficacy with the use of the combination product.

8.4 Pediatrics

As noted in the original NDA review, a clinical study report, AGN 190342-015 submitted by the sponsor evaluating Alphagan 0.2% dosed adjunctively with beta blockers in pediatric patients has been reviewed by the agency. Alphagan 0.2% used adjunctively with beta-blockers is safe

and effective in patients 7 years of age and older, and can be used with caution in patients between 3 and 7.

9 OVERALL ASSESSMENT

9.1 Conclusions

Although Study 190342-023T demonstrates that the safety profile of the proposed combination product is numerically superior to the individual agents taken as currently permitted in their approved labeling in the incidence of oral dryness adverse events, this difference in adverse events is not sufficient to offset the combination's inferior IOP-lowering ability (approximately 1-2 mmHg) compared to that of brimonidine and timolol given concomitantly.

9.2 Recommendation on Regulatory Action

NDA 21-398 for Combigan (brimonidine tartrate/timolol ophthalmic solution) 0.2% /0.5% is not recommended for approval.

9.3 Recommendation on Postmarketing Actions

Not applicable. This application is not recommended for approval.

9.4 Labeling Review

The labeling review for this combination product will be completed once the efficacy of this product has been demonstrated and the application recommended for approval.

9.5 Comments to Applicant

The submitted studies fail to demonstrate that the benefits of the proposed combination outweigh the risks. In the clinical studies, the contribution of each component was smaller than expected and the magnitude of the observed effect was not sufficient to outweigh the risks of the components' contribution. Before the application may be approved, it will be necessary for you to address this deficiency.

An alternative dosing regimen could provide a useful product if it could be demonstrated that the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling; the combination's IOP-lowering ability is inferior (approximately 1 mmHg) to that of brimonidine and timolol given concomitantly.

Study 190342-23T submitted in this amendment was designed to address this deficiency. Although Study 190342-023T demonstrates that the safety profile of the proposed combination product is numerically superior to the individual agents taken as currently permitted in their approved labeling in the incidence of oral dryness adverse events, this difference in adverse

events is not sufficient to offset the combination's inferior IOP-lowering ability (approximately 1-2 mmHg) compared to that of brimonidine and timolol given concomitantly.

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

/s/

William Boyd
12/13/2006 08:58:02 AM
MEDICAL OFFICER

Wiley Chambers
12/13/2006 09:33:23 AM
MEDICAL OFFICER

Deputy Division Director's Review of NDA 21-398

Original New Drug Application

Submission Date:	September 13, 2004
Review Completed:	March 10, 2005
Deputy Division Director:	Wiley A. Chambers, MD
Established Name:	**Combigan** (brimonidine tartrate/timolol maleate ophthalmic solution)
Applicant:	Allergan Inc.
Pharmacologic Category:	Alpha-2 agonist/ Beta blocker
Proposed Indication:	Reduction of intraocular pressure
Dosage Form:	Ophthalmic solution
Route of Administration:	Topical ocular
NDA Drug Classification:	4S

Table of Contents

I. Recommendations

A. Recommendation on Approvability

NDA 21-398 is not recommended for approval for lowering intraocular pressure in patients with [redacted] glaucoma or ocular hypertension because the benefits contributed by each component do not outweigh the potential risks that each additional component adds to the combination.

B. Recommendation on Postmarketing Studies and/or Risk Management Steps

No postmarketing studies are recommended. No risk management steps are recommended.

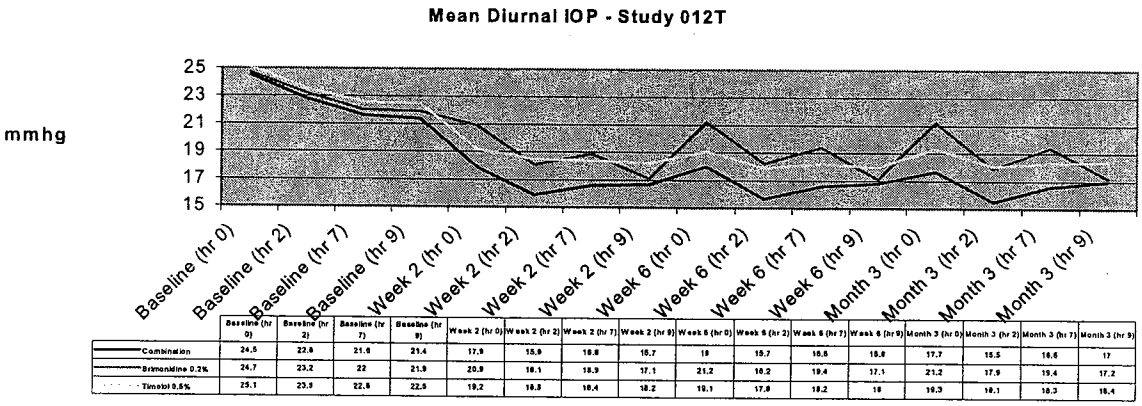
II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

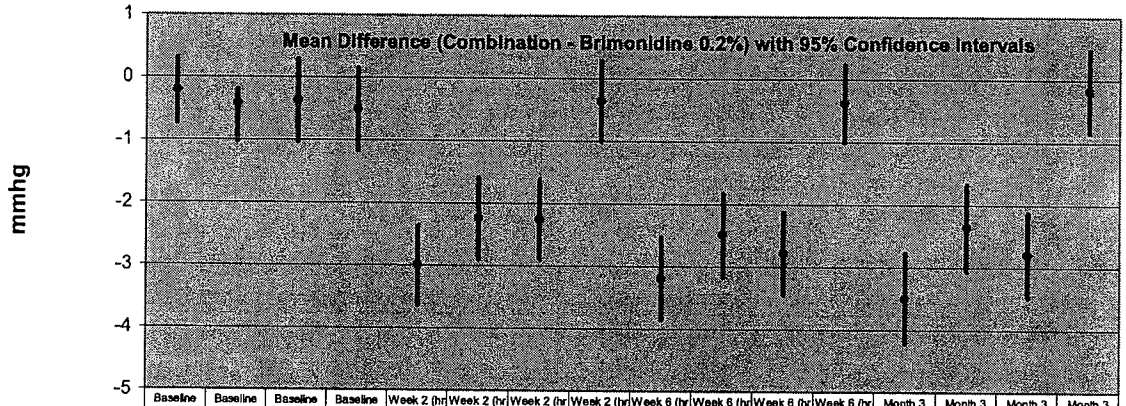
Ocular hypertension is defined as high intraocular pressure (IOP) and may lead to optic nerve head abnormalities and visual field defects. Currently there is no proven direct treatment for optic neuropathy regardless of the initiating cause. Therapy is focused on lowering the intraocular pressure. Presently, five classes of drugs are used to reduce IOP: adrenergic beta-receptor antagonists; cholinergic agonists; adrenergic agonists, carbonic anhydrase inhibitors; and prostaglandin/prostaglandin analogs.

The new drug product proposed in this application is a combination of two of the classes of approved products (alpha 2 agonists and beta blockers).

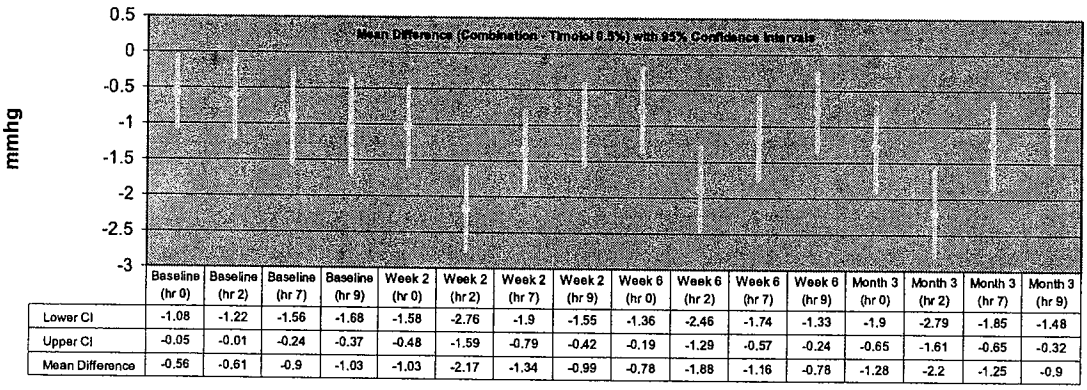
B. Efficacy



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Combination	24.5	22.8	21.8	21.4	17.9	15.9	16.8	16.7	18	19.7	16.6	16.8	17.7	15.5	16.6	17
Brimonidine 0.2%	24.7	23.2	22	21.9	20.8	18.1	18.9	17.1	21.2	18.2	19.4	17.1	21.2	17.9	19.4	17.2
Timolol 0.5%	25.1	23.9	22.6	22.5	19.2	18.3	18.4	18.2	19.1	17.8	18.2	18	18.9	18.1	18.3	18.4

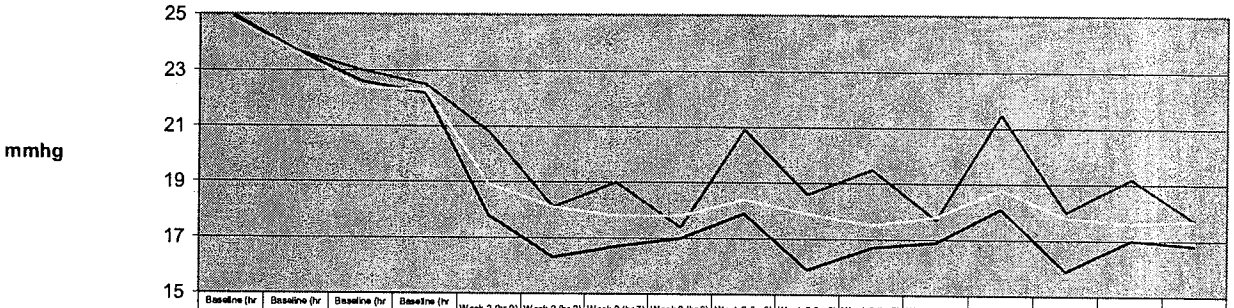


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.73	-1.03	-1.04	-1.17	-3.63	-2.9	-2.89	-1	-3.85	-3.15	-3.43	-1	-4.22	-3.05	-3.47	-0.84
Upper CI	0.31	-0.19	0.29	0.15	-2.36	-1.58	-1.62	0.28	-2.53	-1.82	-2.13	0.24	-2.77	-1.67	-2.12	0.48
Mean Difference	-0.21	-0.42	-0.38	-0.51	-2.99	-2.24	-2.26	-0.36	-3.19	-2.48	-2.78	-0.38	-3.5	-2.36	-2.8	-0.18

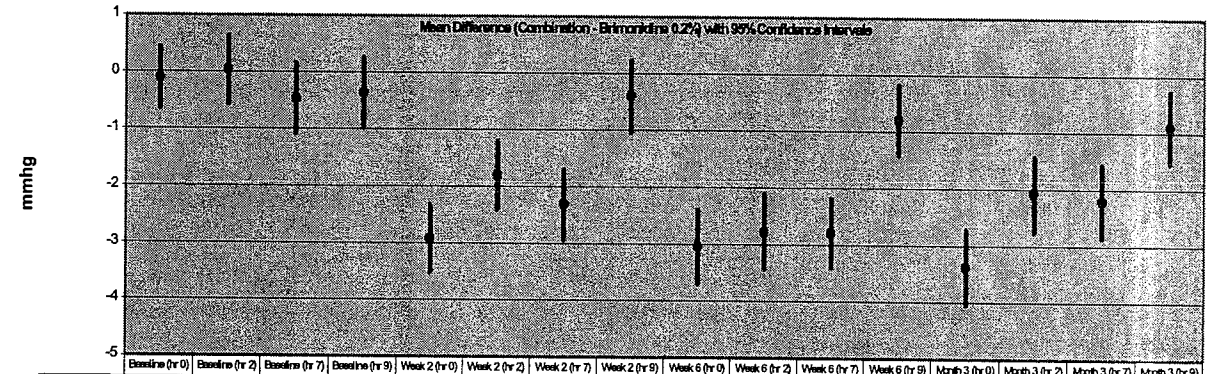


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-1.08	-1.22	-1.56	-1.68	-1.58	-2.76	-1.9	-1.55	-1.36	-2.46	-1.74	-1.33	-1.9	-2.79	-1.85	-1.48
Upper CI	-0.05	-0.01	-0.24	-0.37	-0.48	-1.59	-0.79	-0.42	-0.19	-1.29	-0.57	-0.24	-0.65	-1.61	-0.65	-0.32
Mean Difference	-0.56	-0.61	-0.9	-1.03	-1.03	-2.17	-1.34	-0.99	-0.78	-1.88	-1.16	-0.78	-1.28	-2.2	-1.25	-0.9

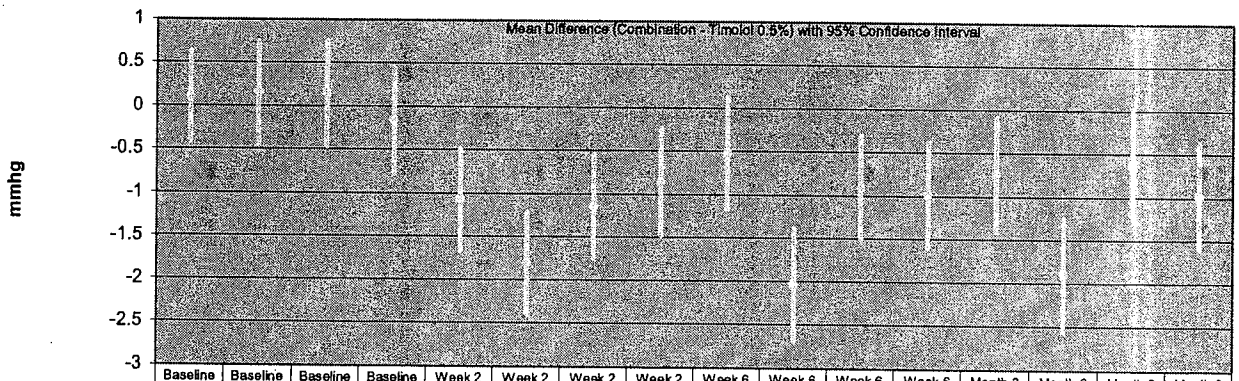
Mean Diurnal IOP - Study 013T



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Combination	24.9	23.7	22.6	22.2	17.8	16.3	16.7	17	17.9	15.9	16.7	16.9	18.1	15.9	17	16.8
Brimonidine 0.2%	25	23.7	23	22.5	20.8	18.1	19	17.4	20.9	18.6	19.5	17.7	21.5	18	19.2	17.7
Timolol 0.5%	24.8	23.6	22.4	22.3	18.9	18.1	17.8	17.8	18.4	17.9	17.5	17.8	18.8	17.8	17.6	17.7



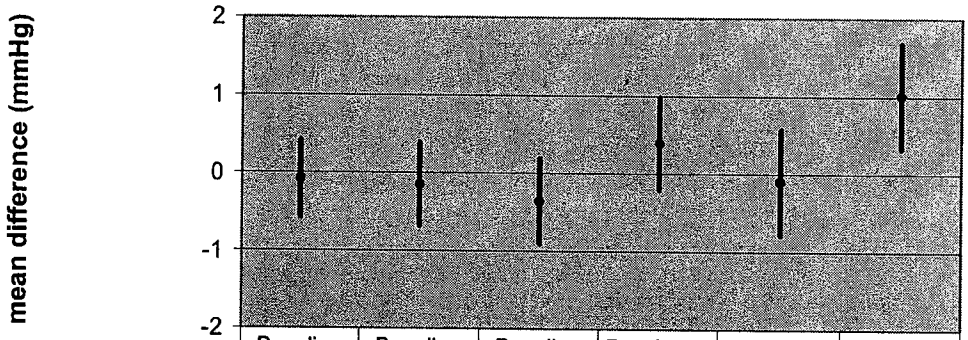
	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.64	-0.56	-1.07	-0.98	-3.51	-2.4	-2.92	-1.03	-3.68	-3.42	-3.39	-1.41	-4.04	-2.74	-2.84	-1.53
Upper CI	0.42	0.62	0.14	0.25	-2.34	-1.21	-1.71	0.22	-2.4	-2.11	-2.19	-0.19	-2.72	-1.42	-1.58	-0.28
Mean Difference	-0.11	0.03	-0.47	-0.36	-2.92	-1.81	-2.31	-0.4	-3.04	-2.77	-2.79	-0.8	-3.38	-2.08	-2.21	-0.9



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 2 (hr 7)	Week 2 (hr 9)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.42	-0.44	-0.47	-0.77	-1.66	-2.41	-1.75	-1.48	-1.17	-2.69	-1.51	-1.6	-1.41	-2.56	-1.26	-1.61
Upper CI	0.63	0.74	0.75	0.45	-0.49	-1.22	-0.54	-0.24	0.11	-1.39	-0.31	-0.38	-0.09	-1.24	0	-0.37
Mean Difference	0.1	0.15	0.14	-0.16	-1.08	-1.81	-1.15	-0.86	-0.53	-2.04	-0.91	-0.99	-0.75	-1.9	-0.63	-0.99

Study 190342-019T

Mean Difference in IOP (combination-concurrent) with 95% Confidence Intervals



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 8)	Day 28 (hr 0)	Day 28 (hr 2)	Day 28 (hr 8)
Lower CI	-0.57	-0.68	-0.91	-0.21	-0.78	0.33
Upper CI	0.42	0.39	0.19	0.99	0.58	1.69
• Mean Difference	-0.08	-0.15	-0.36	0.39	-0.1	1.01

vol 6, section 14.2, tables 14.2-1.1 and 14.2-1.2

IOP < 18 mmHg at All Time points - ITT Population

	Combination N=176	Concurrent N=169	Alphagan N=87	Combination vs. Concurrent	Combination vs. Alphagan	Concurrent vs. Alphagan
				p-values [a]		
Yes	63 (35%)	73 (43.2%)	13 (14.9%)	0.16	<0.001	<0.001

Vol 6, section 14.2, table 14.2-5

Comments: *The addition of brimonidine to timolol results in a minimal amount of additional IOP reduction (approximately 1 mmHg). The addition of timolol to brimonidine results in a minimal amount of additional IOP reduction (approximately 3 mmHg). The combination is slightly inferior to brimonidine and timolol being given concomitantly (approximately 1 mmHg). A slightly lower percentage of patients receiving the combination had all of their IOP measurements below 18 mmHg at all timepoints (35% versus 43%).*

C. Safety

Number of patients (%)	190342-012T and -013T Pooled 3-Month Data			190342-012T and -013T Pooled 12-Month Data			190342-019T			190342-506T			190342-507T	
	Comb	Brim	Timolol	Comb	Brim	Timolol	Comb	Concur	Brim	Comb	Brim	Timolol	Comb	Concur
	N = 385	N = 382	N = 392	N = 385	N = 382	N = 392	N = 174	N = 167	N = 85	N = 196	N = 202	N = 191	N = 188	N = 183
Body as a whole														
Infection	18 (4.7)	14 (3.7)	15 (3.8)	39 (10.1)	35 (9.2)	36 (9.2)	1 (0.6)	4 (2.4)	1 (1.2)	4 (2.0)	0c	0c	1 (0.5)	4 (2.2)
Asthenia	9 (2.3)	13 (3.4)	2 (0.5)[b]	11 (2.9)	17 (4.5)	3 (0.8)[b]	6 (3.4)	3 (1.8)	3 (3.5)	1 (0.5)	0	0	4 (2.1)	3 (1.6)
Accidental injury	3 (0.8)	3 (0.8)	3 (0.8)	11 (2.9)	5 (1.3)	10 (2.6)	0	0	0	0	0	0	0	0
Headache	8 (2.1)	11 (2.9)	5 (1.3)	9 (2.3)	16 (4.2)	9 (2.3)	5 (2.9)	6 (3.6)	2 (2.4)	3 (1.5)	2 (1.0)	0	12 (6.4)	14 (7.7)
Allergic reaction	2 (0.5)	6 (1.6)	3 (0.8)	7 (1.8)	12 (3.1)	5 (1.3)	0	1 (0.6)	0	0	1 (0.5)	0	0	0
Back pain	3 (0.8)	5 (1.3)	3 (0.8)	6 (1.6)	14 (3.7)	9 (2.3)	0	0	0	0	1 (0.5)	3 (1.6)	0	0
Flu syndrome	1 (0.3)	0	1 (0.3)	6 (1.6)	3 (0.8)	4 (1.0)	2 (1.1)	0	1 (1.2)	6 (3.1)	2 (1.0)	1 (0.5)	2 (1.1)	0
Cardiovascular														
Hypertension	10 (2.6)	7 (1.8)	5 (1.3)	25 (6.5)	13 (3.4)[a]	17 (4.3)	0	1 (0.6)	0	4 (2.0)	1 (0.5)	2 (1.0)	6 (3.2)	2 (1.1)
Digestive														
LFTs abnormal	4 (1.0)	2 (0.5)	3 (0.8)	10 (2.6)	3 (0.8)	8 (2.0)	0	0	0	2 (1.0)	0	1 (0.5)	1 (0.5)	0
Oral dryness	7 (1.8)	36 (9.4)[a]	2 (0.5)	8 (2.1)	36 (9.4)[a]	2 (0.5)	4 (2.3)	9 (5.4)	3 (3.5)	1 (0.5)	4 (2.0)	0	4 (2.1)	2 (1.1)
Nausea	3 (0.8)	2 (0.5)	1 (0.3)	8 (2.1)	4 (1.0)	2 (0.5)	1 (0.6)	1 (0.6)	1 (1.2)	0	0	0	1 (0.5)	0
Dyspepsia	2 (0.5)	3 (0.8)	5 (1.3)	6 (1.6)	5 (1.3)	10 (2.6)	0	0	0	1 (0.5)	0	1 (0.5)	0	0
Metabolic and Nutritional Disorders														
Hypercholesterolemia	1 (0.3)	1 (0.3)	1 (0.3)	14 (3.6)	4 (1.0)[a]	7 (1.8)	0	0	0	0	0	0	0	0
Diabetes mellitus	2 (0.5)	1 (0.3)	1 (0.3)	8 (2.1)	5 (1.3)	3 (0.8)	0	0	0	0	0	0	0	0
Peripheral edema	5 (1.3)	1 (0.3)	3 (0.8)	8 (2.1)	1 (0.3)[a]	4 (1.0)	1 (0.6)	1 (0.6)	0	0	0	0	1 (0.5)	1(0.5)
Musculoskeletal														
Arthritis	1 (0.3)	2 (0.5)	1 (0.3)	9 (2.3)	7 (1.8)	6 (1.5)	0	0	0	0	1 (0.5)	0	0	0
Depression	5 (1.3)	2 (0.5)	0[b]	9 (2.3)	5 (1.3)	1 (0.3)[b]	0	2 (1.2)	0	0	0	0	0	1 (0.5)
Somnolence	6 (1.6)	14 (3.7)	2 (0.5)	6 (1.6)	15 (3.9)[b]	2 (0.5)	0	2 (1.2)	2 (2.4)	4 (2.0)	4 (2.0)	1 (0.5)	4 (2.1)	3 (1.6)
Dizziness	5 (1.3)	6 (1.6)	6 (1.5)	5 (1.3)	6 (1.6)	7 (1.8)	0	1 (0.6)	2 (2.4)	1 (0.5)	3 (1.5)	3 (1.6)	1 (0.5)	1 (0.5)
Respiratory														
Bronchitis	3 (0.8)	3 (0.8)	1 (0.3)	9 (2.3)	7 (1.8)	3 (0.8)	0	2 (1.2)	0	1 (0.5)	1 (0.5)	0	1 (0.5)	2 (1.1)
Skin														
Rash	0	0	5 (1.3)	3 (0.8)	1 (0.3)	9 (2.3)	0	1 (0.6)	0	1 (0.5)	0	0	0	0
Special Senses														
Conjunctival hyperemia	32 (8.3)	39 (10.2)	21 (5.4)	66 (17.1)	90 (23.6)[a]	31 (7.9)[b]	2 (1.1)	1 (0.6)	0	9 (4.6)	9 (4.5)	4 (2.1)	7 (3.7)	7 (3.8)
Burning sensation in eye	38 (9.9)	21 (5.5)[a]	45 (11.5)	43 (11.2)	30 (7.9)	53 (13.5)	16 (9.2)	10 (6.0)	3 (3.5)	4 (2.0)	4 (2.0)	3 (1.6)	2 (1.1)	5 (2.7)
Stinging sensation in eye	21 (5.5)	7 (1.8)[a]	26 (6.6)	25 (6.5)	11 (2.9)[a]	27 (6.9)	9 (5.2)	6 (3.6)	0	0	0	0	0	0
Eye pruritus	9 (2.3)	25 (6.5)[a]	9 (2.3)	22 (5.7)	47 (12.3)[a]	15 (3.8)	1 (0.6)	0	1 (1.2)	2 (1.0)	7 (3.5)	3 (1.6)	9 (4.8)	5 (2.7)
Allergic conjunctivitis	4 (1.0)	17 (4.5)[a]	0	20 (5.2)	37 (9.7)[a]	2 (0.5)[b]	0	2 (1.2)	0	4 (2.0)	8 (4.0)[c]	0[c]	3 (1.6)	2 (1.1)
Conjunctival folliculosis	5 (1.3)	16 (4.2)[a]	2 (0.5)	19 (4.9)	35 (9.2)[a]	7 (1.8)[b]	0	0	0	3 (1.5)	6 (3.0)	1 (0.5)	2 (1.1)	0
Visual disturbance	16 (4.2)	16 (4.2)	7 (1.8)	18 (4.7)	18 (4.7)	16 (4.1)	6 (3.4)	6 (3.6)	0	3 (1.5)	3 (1.5)	3 (1.6)	4 (2.1)	7 (3.8)
Blepharitis	8 (2.1)	7 (1.8)	3 (0.8)	16 (4.2)	16 (4.2)	5 (1.3)[b]	0	0	0	3 (1.5)	1 (0.5)	0	0	0
Erythema eyelid	7 (1.8)	5 (1.3)	2 (0.5)	16 (4.2)	13 (3.4)	4 (1.0)[b]	1 (0.6)	0	0	1 (0.5)	2 (1.0)	0	1 (0.5)	0
Epiphora	7 (1.8)	10 (2.6)	5 (1.3)	14 (3.6)	20 (5.2)	7 (1.8)	1 (0.6)	0	0	4 (2.0)	0	2 (1.0)	4 (2.1)	3 (1.6)
Corneal erosion	9 (2.3)	6 (1.6)	5 (1.3)	14 (3.6)	7 (1.8)	13 (3.3)	1 (0.6)	0	0	1 (0.5)	0	2 (1.0)	0	0
Superficial punctate keratitis	6 (1.6)	5 (1.3)	3 (0.8)	14 (3.6)	5 (1.3)[a]	7 (1.8)	2 (1.1)	0	0	0	3 (1.5)	1 (0.5)	0	0
Eye dryness	7 (1.8)	9 (2.4)	2 (0.5)	12 (3.1)	14 (3.7)	5 (1.3)	0	2 (1.2)	0	2 (1.0)	2 (1.0)	0	1 (0.5)	0
Eye discharge	6 (1.6)	2 (0.5)	0[b]	12 (3.1)	9 (2.4)	4 (1.0)[b]	0	0	0	1 (0.5)	0	0	0	0
Eyelid edema	5 (1.3)	4 (1.0)	2 (0.5)	11 (2.9)	7 (1.8)	5 (1.3)	1 (0.6)	0	0	1 (0.5)	2 (1.0)	0	1 (0.5)	0
Foreign body sensation	7 (1.8)	14 (3.7)	7 (1.8)	8 (2.1)	19 (5.0)[a]	7 (1.8)	3 (1.7)	4 (2.4)	1 (1.2)	2 (1.0)	0	0	0	3 (1.6)
Eye pain	4 (1.0)	7 (1.8)	7 (1.8)	8 (2.1)	12 (3.1)	11 (2.8)	2 (1.1)	3 (1.8)	2 (2.4)	3 (1.5)	2 (1.0)	0	11 (5.9)	11 (6.0)
Irritation eye	1 (0.3)	2 (0.5)	3 (0.8)	8 (2.1)	3 (0.8)	5 (1.3)	0	2 (1.2)	0	0	1 (0.5)	2 (1.0)	2 (1.1)	0
Visual field defect	3 (0.8)	4 (1.0)	2 (0.5)	5 (1.3)	11 (2.9)	7 (1.8)	0	0	0	4 (2.0)	0[c]	0[c]	1 (0.5)	0
Cataract	2 (0.5)	1 (0.3)	1 (0.3)	4 (1.0)	10 (2.6)	7 (1.8)	0	0	1 (1.2)	0	0	2 (1.0)	1 (0.5)	0
Visual acuity worsened	2 (0.5)	2 (0.5)	3 (0.8)	4 (1.0)	5 (1.3)	10 (2.6)	4 (2.3)	2 (1.2)	0	2 (1.0)	1 (0.5)	0	1 (0.5)	2 (1.1)
Conjunctival edema	0	1 (0.3)	3 (0.8)	2 (0.5)	8 (2.1)	4 (1.0)	0	0	0	0	0	0	0	0
Follicular conjunctivitis	0	3 (0.8)	0	1 (0.3)	10 (2.6)[a]	0	0	0	0	2 (1.0)	0	0	0	0
Conjunctivitis	1 (0.3)	3 (0.8)	1 (0.3)	2 (0.5)	5 (1.3)	4 (1.0)	0	1 (0.6)	0	0	4 (2.0)[c]	0	0	2 (1.1)
Urogenital														
Urinary infection	4 (1.0)	4 (1.0)	1 (0.3)	10 (2.6)	9 (2.4)	5 (1.3)	0	0	0	1 (0.5)	2 (1.0)	0	0	0

Vol. 4, section 2.7.4, table 2.7.4.2-3
Comb = brimonidine tartrate 0.2%/timolol 0.5%; Timolol = timolol 0.5%; Brim = brimonidine tartrate 0.2%; Concur = concurrent brimonidine tartrate 0.2%/timolol 0.5%
[a] $p < 0.05$ for Combination vs. Brimonidine
[b] $p < 0.05$ for Combination vs. Timolol
[c] $p < 0.05$ for proportions among treatment groups

Reviewer's Comments: *There is significant variability in the reported adverse events between the different studies. The combination is associated with all of the risks attributed to either of the individual ingredients. Timolol appears to slightly mask ~~of~~ some of the events attributed to brimonidine, but the potential masking of these events does not eliminate them and does not outweigh the decrease in IOP reduction seen in the afternoon. The systemic risks of timolol and brimonidine outweigh their potential benefit in the combination and for the equivalent risks seen with the concomitant; the efficacy is slightly decreased with the combination.*

D. Dosing, Regimen, and Administration
In the clinical studies evaluating safety, efficacy and bioequivalence, one drop of brimonidine tartrate ophthalmic solution was administered three times daily to the affected eye.

III. Reviews from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

Reviews have been completed from Chemistry/Manufacturing, Non-clinical Pharmacology/Toxicology, Microbiology (sterility assurance), Clinical Pharmacology, and the Division of Drug Marketing, Advertising and Communications (DDMAC). There are no outstanding or unresolved issues from any of the reviews.

IV. Labeling

Labeling recommendations are deferred until the application is otherwise approvable from a clinical prospective.

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

/s/

Wiley Chambers
3/10/05 02:12:16 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-398
Submission Number	N-000
Submission Code	AZ
Letter Date	September 13, 2004
Stamp Date	September 15, 2004
PDUFA Goal Date	March 14, 2005
Reviewer Name	Jennifer Harris, MD
Review Completion Date	January 19, 2005
Established Name	brimonidine tartrate-timolol maleate ophthalmic solution 0.2%/0.5%
(Proposed) Trade Name	Combigan
Therapeutic Class	alpha-agonist/beta-blocker
Applicant	Allergan, Inc.
Priority Designation	S
Formulation	ophthalmic solution
Dosing Regimen	One drop B.I.D.
Indication	treatment of elevated intraocular pressure in patients with ocular hypertension or [redacted] glaucoma
Intended Population	patients with ocular hypertension or [redacted] glaucoma

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The results of the study submitted in this amendment do not address the deficiencies raised in the review of the original NDA. As per 21 CFR §300.50, when two or more drugs are combined, each component must demonstrate 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. The data contained in the original NDA did not adequately show that each component made a contribution to the claimed effect of the combination product. Study 190342-19T submitted in this amendment was designed to address this deficiency by showing equivalency between the combination product and each of the individual components dosed concurrently, thus demonstrating that each component makes a contribution to the claimed effect as required. Study 190342-019T fails to demonstrate that the efficacy of the combination product is equivalent to the efficacy attained when each of the individual components are dosed concurrently.

There were no increased risks associated with the use of the combination product. There were no new safety concerns raised with the use of the combination product as compared to its individual components. The adverse event profile of the combination product was similar to concurrent therapy in study 190342-019T. This study was of short duration (28 days); however, based on the totality of the data available from the phase 3 trials conducted with the combination product, it would be expected that the combination would have a similar safety profile compared to when its individual ingredients are used together for an extended period.

Overall, the risks associated with the use of the combination product as compared to concurrent therapy is equivalent; however, the effectiveness of the combination for the treatment of increased intraocular pressure (IOP) is inferior. Therefore, the combination is not recommended for approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

N/A – the drug product is not recommended for approval.

1.2.2 Required Phase 4 Commitments

N/A – the drug product is not recommended for approval.

1.2.3 Other Phase 4 Requests

N/A – the drug product is not recommended for approval.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The original NDA review for brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution concluded that sufficient evidence had not been presented to demonstrate that there was a contribution of each of the individual components to the overall affect of the drug as required by 21CFR§300.50. This amendment has been submitted in response to the approvable action taken and contains the results of one clinical trial, 190342-019T. This trial was designed to demonstrate that brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution is equivalent to using each of the individual ingredients concomitantly and thus demonstrating that there is a benefit to the combination because in addition to the equivalent safety and efficacy, there was increased compliance due to a less cumbersome dosing schedule (i.e. no dosing in the middle of the day).

Tradename:	*Brimonidine Tartrate 0.2%/Timolol 0.5% (Ophthalmic Solution)*
Sponsor:	*Allergan* *2525 DuPont Drive* *P.O.Box 19534* *Irvine, California 92623*
Pharmacologic Category:	*α-agonist/β-blocker*
Proposed Indication:	*Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension*
Intended Population:	*Patients with ocular hypertension or* [redacted] *glaucoma*
Dosage Form and Route of Administration:	*Ophthalmic solution for topical ocular administration*

Number of Pivotal Efficacy/Safety Trials:	*1*
Number of patients enrolled	*426*
Number of patients in safety database:	*426*

1.3.2 Efficacy

This review contains the efficacy results from one trial 190342-019T. This was a controlled trial designed to demonstrate that brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution was equivalent to using each of the individual ingredients concomitantly.

The primary efficacy assessment in this study was IOP measured at Hours 0, 2, and 8 at Baseline and at Day 28. These time points were chosen to evaluate diurnal variations in IOP at baseline and the maintenance of sustained IOP reductions throughout the day at the Day 28 follow-up visit.

To demonstrate equivalency of the combination product to each of the components given concurrently, the division requires that the 95% confidence interval for the mean difference in IOP be within 1mmHg for the majority of time points or within 1.5 mmHg for all time points measured.

The study design and endpoints chosen for this clinical trial were a result of the review of the original NDA and were delineated in the approvable letter dated 6/5/02.

This study has failed to demonstrate that the efficacy of the combination product is equivalent to the efficacy attained when each of the individual components are dosed concurrently. The combination product consistently losses efficacy approximately 8 hours after dosing in this trial and in the trials submitted for review in the original NDA. This could possibly be due to the non-adherence to the approved dosing schedule for each of the individual components when used alone. Specifically, brimonidine tartrate 0.2% is only given b.i.d when used in the combination product as opposed to the approved dose of t.i.d.

1.3.3 Safety

The development program for this combination product has adequately met ICH guidelines for the extent and duration of exposure needed to assess safety. The design of the trials as well as the number and types of patients studied are adequate to assess the overall safety for this product. Overall, the studies for the combination product provide a safety database of 2618 patients with glaucoma or ocular hypertension and 18 health subjects. The study submitted in this NDA amendment contains a database of 432 patients with 176 exposed to the combination product.

There were no increased risks associated with the use of the combination product. There were no new safety concerns raised with the use of the combination product as compared to its individual components. The adverse event profile of the combination product was similar to concurrent therapy in study 190342-019T. This study was of short duration (28 days); however, based on the totality of the data available from the phase 3 trials conducted with the combination product, it would be expected that the combination would have a similar safety profile compared to when its individual ingredients are used together for an extended period.

1.3.4 Dosing Regimen and Administration

There is no recommendation for changing the dosing regimen for the combination product. See section 1.3.2 for dosing considerations.

1.3.5 Drug-Drug Interactions

N/A – there were no drug-drug interactions evaluated for this drug product

1.3.6 Special Populations

An evaluation of this use of this product in special populations was conducted in the original NDA review. There were no significant differences seen in the IOP lowering ability of the combination product in any of the subgroups analyzed. There were no gender, age or race effects on safety or efficacy with the use of the combination product.

2 INTEGRATED REVIEW OF EFFICACY

2.1 Indication

The proposed indication for brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution is for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension (OHT).

2.1.1 Methods

This review contains the efficacy results from one trial 190342-019T. This was a controlled trial desinged to demonstrate that brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution was equivalent to using each of the individual ingredients concomitantly. The original NDA submitted for the product contained the results of two safety and efficacy trials 190342-012T and 190342-013T. The original review concluded that sufficient evidence had not been presented to demonstrate that there was a contribution of each of the individual ingredients to the overall affect of the drug as required by 21CFR§300.50. The sponsor has submitted the results of this new study in this amendment to satisfy this regulatory requirement by demonstrating that the benefits of the combination are equivalent to the benefits of timolol administered in the morning and evening and brimonidine administered three times daily, approximately 8 hours apart as currently labeled.

2.1.2 General Discussion of Endpoints

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

The clinical hypothesis was that the efficacy of Combination was not inferior to that of concurrent treatment with the individual components of the Combination as measured by mean IOP.

The primary efficacy assessment in this study was IOP measured at Hours 0, 2, and 8 at Baseline and at Day 28. These time points were chosen to evaluate diurnal variations in IOP at baseline and the maintenance of sustained IOP reductions throughout the day at the Day 28 follow-up visit.

To demonstrate equivalency of the combination product to each of the components given concurrently, the division requires that the 95% confidence interval for the mean difference in

IOP be within 1mmHg for the majority of time points or within 1.5 mmHg for all timpanist measured.

The study design and endpoints chosen for this clinical trial were a result of the review of the original NDA and were delineated in the approvable letter dated 6/5/02. The trial and endpoints were design to demonstrate the contribution of each of the individual components to the overall efficacy of the fixed combination as required by regulation.

2.1.3 Study Design

This clinical trial was a multicenter, double-masked, 3-arm, parallel-group study with a 4-week study period consisting of 3 scheduled visits: Prestudy, Day 0 (Baseline), and Day 28. Patients with OHT, chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy/iridectomy, pseudoexfoliative glaucoma, or pigmentary glaucoma, and who required bilateral administration of treatment were eligible to enter the study. A total of 432 patients were enrolled and assigned in a 2:2:1 allocation, respectively, to 1 of 3 masked treatment groups:

- 0.2% brimonidine tartrate/0.5% timolol combination ophthalmic solution (Combination) administered BID, in the morning and evening, or
- ALPHAGAN® ophthalmic solution (0.2% brimonidine tartrate) and timolol ophthalmic solution (0.5% timolol) (Concurrent) administered TID (morning, afternoon, and evening) and BID (morning and evening), respectively, or
- ALPHAGAN® ophthalmic solution (0.2% brimonidine tartrate) administered TID, in the morning, afternoon, and evening.

For patients in the Combination group, the Combination was administered BID (morning and evening) with the vehicle administered TID (morning, afternoon, and evening) to maintain proper masking. For patients in the Concurrent group, ALPHAGAN® was administered TID (morning, afternoon, and evening) and timolol was administered BID in the morning and evening. For patients in the ALPHAGAN® group, treatment was administered TID (morning, afternoon, and evening) and vehicle was administered BID (morning and evening) to maintain proper masking.

Patients began study medication dosing in the evening of the Day 0 (Baseline) visit.

Dosing Time[a]	Combination		Concurrent		ALPHAGAN®	
	Vehicle	Combination	ALPHAGAN®	Timolol	ALPHAGAN®	Vehicle
08:00	X	X	X	X	X	X
14:00	X		X		X	
20:00	X	X	X	X	X	X

[a] At 08:00 and 20:00, the 15 mL, 3 times daily (TID) bottle was to be dosed first, followed by the 10 mL, twice daily (BID) bottle, with a minimum interval of 5 minutes between dosings.

Inclusion/Exclusion Criteria

Inclusion Criteria

- Male or female, 18 years of age and of legal age of consent
- Patient with OHT, chronic open-angle glaucoma, or chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative glaucoma or pigmentary glaucoma in both eyes and is treatment naïve, i.e., never been treated with IOP-lowering medications to the best knowledge of the patient and investigator
- Patient to be treated bilaterally for this study
- Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity equivalent to a Snellen score of 20/100 or better in each eye at the prestudy visit
- Written informed consent and written authorization for use or release of health and research study information have been obtained prior to any study procedures
- Patient able and willing to follow study instructions and likely to complete all required visits
- Baseline (Day 0, Hour 0) IOP > 21 mm Hg and < 32 mm Hg in each eye, with IOP asymmetry between the eyes < 5 mm Hg
- A negative urine pregnancy test result at Baseline (Day 0, Hour 0) for women of childbearing potential

Exclusion Criteria

- Uncontrolled systemic disease (e.g., hypertension, diabetes)
- Females who were pregnant, nursing, or planning a pregnancy or females of childbearing potential who were not using a highly effective means of contraception.
- Known allergy or hypersensitivity to any of the study medication or its components
- Corneal abnormalities that precluded accurate IOP readings with an applanation tonometer

- Recent (within previous 2 months) or anticipated alteration of existing chronic therapy or introduction of therapy with agents that may have had a substantial effect on IOP, including, but not necessarily limited to, systemic adrenergic agents, including α-adrenergic blocking agents (eg, propranolol, metoprolol, nadolol, oral timolol, and atenolol)

- Intermittent use of oral, injectable, or topical ophthalmic steroids within 21 days prior to the prestudy visit or anticipated use during the study

- Any active ocular disease other than glaucoma (eg, uveitis, ocular infections, or severe dry eye). However, patients with cataracts age-related macular degeneration, or background diabetic retinopathy may have been enrolled at the discretion of the investigator.

- Required chronic use of other ocular medications during the study. Occasional use of artificial tear products or topical antihistamines was allowed.

- Functionally significant visual field loss or evidence of progressive visual field loss within the past year, as determined by the investigator

- Refractive surgery, laser trabeculoplasty, or other laser surgery within the past 3 months, or other intraocular surgery (eg, uncomplicated cataract surgery) within the past 6 months, or filtering surgery within the past 12 months of study participation or any history of corneal grafts

- Contraindication to pupil dilation

- Contraindication to alpha-adrenoceptor antagonist therapy such as chronic obstructive pulmonary disease, bronchial asthma, sinus bradycardia, second and third degree atrioventricular block, uncontrolled congestive heart failure, history of severe myocardial infarction, or clinically relevant low or high heart (pulse) rate or blood pressure

- Patients with cardiovascular disease unless the disease was controlled and clearance had been obtained from the patient's primary care physician and/or cardiologist

- Contraindication to brimonidine therapy such as concurrent use of monoamine oxidase (MAO) inhibitor therapy

- Concurrent use or anticipated treatment with adrenergic augmenting psychotropic drugs (ie, tricyclic antidepressants such as desipramine or amitriptyline)

- Anticipated wearing of contact lenses during the study (use of soft lenses should have been discontinued for at least 2 days prior to Day 0, and use of rigid gas permeable [RGP] or hard contact lenses should have been discontinued at least 1 week prior to Day 0)

- Current enrollment or participation in an investigational drug or device clinical trial within 30 days prior to Day 0

- Patient had a condition or situation that, in the investigator's opinion, may have put the patient at significant risk, confounded the study results, or interfered significantly with the patient's participation in the study.

Schedule of Assessments

Visit Day	Time	AE Query	Heart Rate and Blood Pressure[b]	Visual Acuity[b]	Biomicro-scopy[b]	IOP	Visual Field	Kerato-metry	Pregnancy Test[c]	Pachy-metry	Ophthalmo-scopy[d]
Prestudy[e]				X	X	X					X
There was a minimum of 2 days and a maximum of 4 weeks between the Prestudy and Day 0 (Baseline) visits.											
Day 0 Baseline	T_0		X	X	X	X	X[f]	X[g]	X	X[h]	
	T_0+2h					X					
	T_0+8h					X					
	Patients with IOP ≥21 mm Hg and ≥32 mm Hg in each eye at Day 0, Hour 0 were randomized and began dosing in the evening of the Baseline visit (between 1900 and 2100 hours)										
Day 28 or exit	T_0	X	X	X	X	X					
	T_0+2h					X					
	The last dose of medication was administered in the afternoon on Day 28 at T_0 + 6h (1400 hours)										
	T_0+8h					X					X

NOTE: AE = adverse event, IOP = intraocular pressure

a. T_0 occurred between 0700 - 0900 hours at Days 0 and 28 (prior to morning dosing on Day 28). All patients had their visits at approximately the same time of day during the study. On Day 0, the T_0+2h and T_0+8h examinations occurred at 2 hours and 8 hours after the Hour 0 IOP measurement, respectively. At the Day 28 visit, the T_0+2h and T_0+8h examinations occurred 2 hours and 8 hours after the Hour 0 morning dosing, respectively,

b. At Day 0 and Day 28 (or exit), visual acuity, heart rate, blood pressure, and biomicroscopy were performed prior to IOP measurements at Hour 0.

c. Pregnancy tests performed on female study patients of child-bearing potential

d. Ophthalmoscopy (and the instillation of mydriatics) were performed after the IOP measurement and visual field examination (if visual field was completed at the Prestudy visit).

e. Included written informed consent and authorization, and completed medical and ophthalmic histories. Medical and ophthalmic histories were updated at the Day 0 (Baseline) visit.

f. Visual field examination was performed at either the Prestudy or Day 0 (Baseline) visit or within 6 months prior to Day 0. Only 1 visual field examination was required. Visual field examinations should have been performed using a Humphrey automated perimetry test machine

g. Keratometry was performed prior to the IOP and corneal pachymetry measurements at the Prestudy or Day 0 (Baseline) visit.

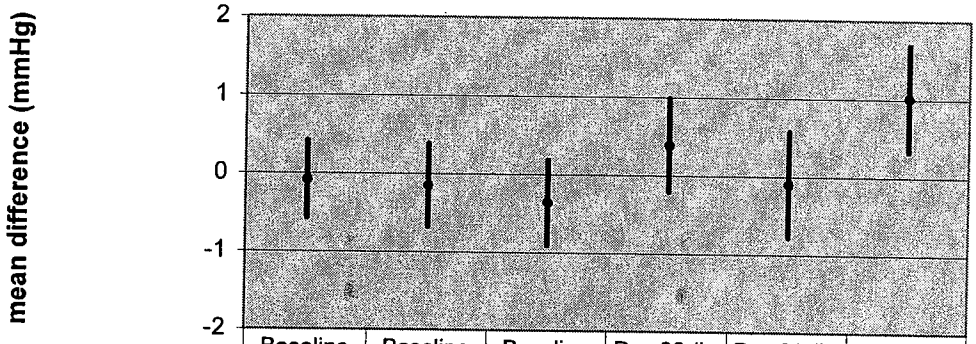
h. Ultrasound corneal pachymetry was performed at either the Prestudy or Day 0 (Baseline) visit after the IOP measurement and visual field examination

Clinical Sites

Investigator Number	Name	Location	Number of Patients
[redacted]			
3761	Jason Bacharach, MD	Petaluma, CA	29
[redacted]			
4084	Luca Bigatti, MD	Rochester, NY	13
[redacted]			
3809	William Davitt, MD	El Paso, TX	36
2450	Harvey, Dubiner, MD	Morrow, GA	15
[redacted]			
3212	Michael Tepedino, MD	High Point, NC	19
[redacted]			
3276	David Wirta, MD	Newport Beach, CA	18
[redacted]			

2.1.4 Efficacy Findings

Mean Difference in IOP (combination-concurrent) with 95% Confidence Intervals

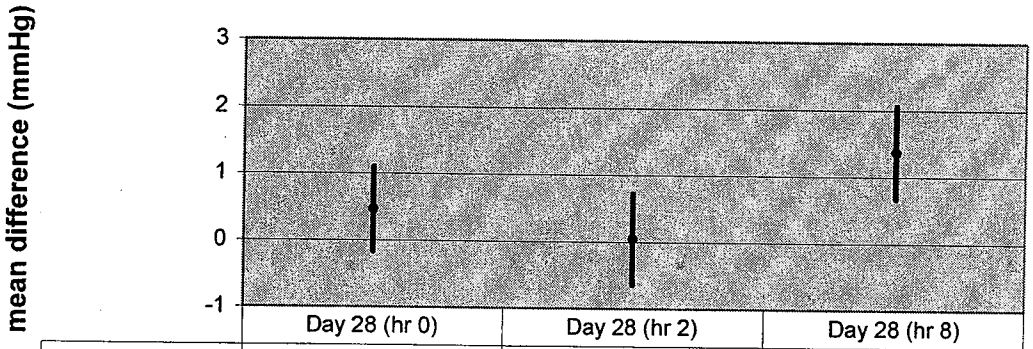


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 8)	Day 28 (hr 0)	Day 28 (hr 2)	Day 28 (hr 8)
Lower CI	-0.57	-0.68	-0.91	-0.21	-0.78	0.33
Upper CI	0.42	0.39	0.19	0.99	0.58	1.69
• Mean Difference	-0.08	-0.15	-0.36	0.39	-0.1	1.01

vol 6, section 14.2, tables 14.2-1.1 and 14.2-1.2

The combination product fails to demonstrate equivalency to the individual components given concurrently at the 8 hr time point. This is consistent with the results of the review of the studies in the original NDA which consistently showed the loss of efficacy approximately 8 hrs after dosing. This is likely due to the fact that t.i.d dosing of brimonidine which is required for effective IOP lowering is not present in the combination dosing schedule.

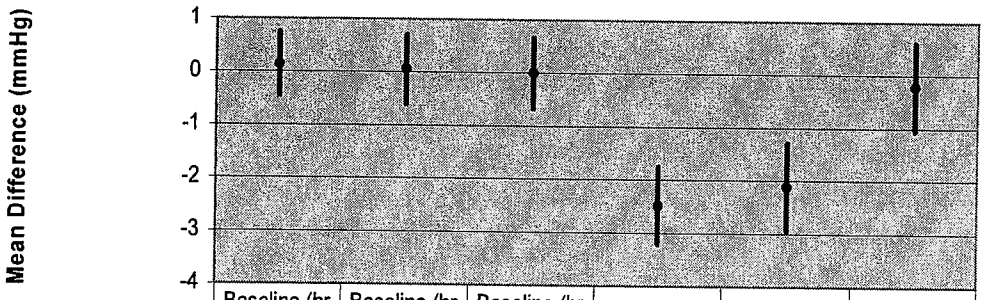
Mean Change from Baseline (combination-concurrent) with 95% Confidence Intervals



	Day 28 (hr 0)	Day 28 (hr 2)	Day 28 (hr 8)
Lower CI	-0.17	-0.64	0.67
Upper CI	1.1	0.73	2.06
• Mean Difference	0.47	0.05	1.37

The loss of efficacy at the 8 hr time point is also seen when the data is analyzed based on the mean change from baseline.

Mean Difference in IOP (Combination-Alphagan) with 95% Confidence Intervals

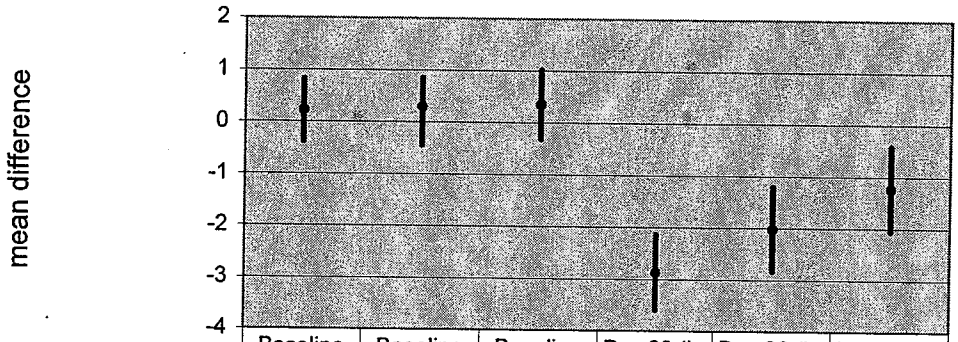


	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 8)	Day 28 (hr 0)	Day 28 (hr 2)	Day 28 (hr 8)
Lower CI	-0.45	-0.6	-0.67	-3.21	-2.94	-1.05
Upper CI	0.75	0.71	0.66	-1.75	-1.29	0.61
• Mean Difference	0.15	0.06	0	-2.48	-2.11	-0.22

vol 6, section 14.2, tables 14.2-1.1 and 14.2-1.2

The results demonstrate a contribution of timolol to the combination product of approximately 2 mmHg for 2/3 time points measured. The contribution of timolol appears to be loss by the 8 hr time point (i.e. is no statistical difference between the combination product and brimonidine)

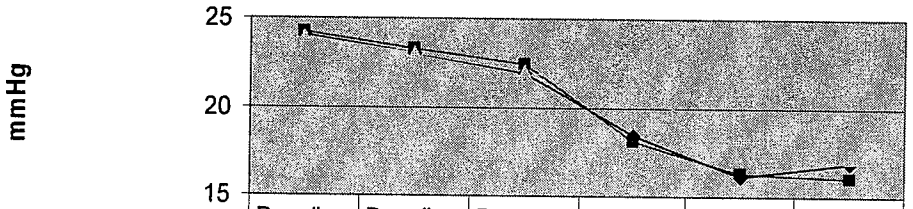
Mean Difference (Concurrent-Alphagan) with 95% Confidence Intervals



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 8)	Day 28 (hr 0)	Day 28 (hr 2)	Day 28 (hr 8)
Lower CI	-0.38	-0.45	-0.32	-3.6	-2.84	-2.06
Upper CI	0.83	0.86	1.02	-2.13	-1.19	-0.4
• Mean Difference	0.23	0.29	0.35	-2.87	-2.02	-1.23

vol 6, section 14.2, tables 14.2-1.1 and 14.2-1.2

Mean Diurnal IOP



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 8)	Day 28 (hr 0)	Day 28 (hr 2)	Day 28 (hr 8)
Combination	24.1	23	21.9	18.4	16.1	16.9
Concurrent	24.2	23.3	22.4	18.1	16.3	16
Alphagan	24	23	22	20.9	18.3	17.2

vol 6, section 14.2, tables 14.2-1.1 and 14.2-1.2

IOP < 18 mmHg at All Time points - ITT Population

	Combination N=176	Concurrent N=169	Alphagan N=87	Combination vs. Concurrent	Combination vs. Alphagan	Concurrent vs. Alphagan
				p-values [a]		
Yes	63 (35%)	73 (43.2%)	13 (14.9%)	0.16	<0.001	<0.001

Vol 6, section 14.2, table 14.2-5

Subgroup Analyses

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.

2.1.5 Clinical Microbiology

N/A – There is no proposed antimicrobial indication for this product.

2.1.6 Efficacy Conclusions

Brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution has failed to demonstrate equivalence to each of the individual components given concomitantly. The combination product appears to loose its efficacy approximately 8 hours after dosing. This is likely due to the fact that one of the components (brimonidine tartrate 0.2%) is not given at the labeled efficacious dose (i.e., t.i.d.) when used in the combination product (i.e. b.i.d.).

3 INTEGRATED REVIEW OF SAFETY

3.1 Methods and Findings

This review addresses the safety data from study 190342-019T. A full review of the safety of the combination product was conducted in the first review cycle. For the purpose of labeling for this drug product, the pooled 12-month data from study 190342-012T and 190342-013T along with the currently labeled adverse events and postmarketing data from each of the individual components will be used to determine the adverse events associated with the use of Combigan. The current study under review, 190342-019T, is not sufficient to determine the adverse event profile due to the short duration.

The following studies have been included in the safety review for brimonidine tartrate 0.2%/timolol 0.5% combination ophthalmic solution where appropriate:

190342-012T (US) – full review of the safety profile is contained in the original medical officer's review

190342-013T (US) – full review of the safety profile is contained in the original medical officer's review

190342-019T (US) – included in this review
190342-506T (Europe) – see section 3.1.5.4
190342-507T (Europe) – see section 3.1.5.4

3.1.1 Deaths

There were no deaths during this study.

3.1.2 Other Serious Adverse Events

Serious adverse events were reported for 0.6% (1/167) of patients in the Concurrent group and 1.2% (1/85) of patients in the Alphagan group. There were no serious AE's reported for patients in the Combination group.

Serious Adverse Events – Study 190342-019T

Patient	Age/Sex	Treatment	Adverse Event	Outcome	Exit Status
3761-5231	77/M	Concurrent	Congestive heart failure	Hospitalized	Discontinued
2450-1074	56/F	Alphagan	Fractured femur 2° to fall	Hospitalized	Completed

3.1.3 Dropouts and Other Significant Adverse Events

3.1.3.1 Overall profile of dropouts

Patient Disposition – Study 190342-019T

	Combination	Concurrent	Alphagan
Enrolled	176	169	87
Completed	165 (93.8%)	158 (93.5%)	80 (92%)
Discontinued	11 (6.3%)	11 (6.5%)	7 (8.0%)
Lack of Efficacy	0	0	0
Adverse Events	7 (4.0%)	7 (4.1%)	3 (3.4%)
Ocular	2 (1.1%)	3 (1.8%)	1 (1.1%)
Non-ocular	6 (3.4%)	4 (2.4%)	2 (2.3%)
Administrative Reason	2 (1.1%)	2 (1.2%)	3 (3.4%)
Lost to Follow-Up	2 (1.1%)	2 (1.2%)	2 (2.3%)
Personal Reasons	0	0	1 (1.1%)
Protocol violation	1 (0.6%)	2 (1.2%)	0
Other	1 (0.6%)	0	1 (1.1%)

Vol 6, section 14.1, table 14.1-1

3.1.3.2 Adverse events associated with dropouts

Discontinued Patients Secondary to Adverse Events - Study 190342-019T

Patient	Treatment	Treatment Exposure (days)	Reason
0595-1405	Combination	4	Sinusitis
2450-1078	Combination	5	Burning sensation in eye
3636-5050	Combination	2	Gastroenteritis
3761-1011	Combination	4	Asthenia
4082-1348	Combination	11	Hypotension
4084-5106	Combination	1	Eye pain, visual disturbance
4091-1103	Combination	15	Asthenia
2876-1244	Concurrent	7	Ataxia, palpitation
2986-1431	Concurrent	4	Hypotension
3212-1418	Concurrent	8	Headache
3761-1020	Concurrent	1	Eye pain
3761-5007	Concurrent	7	Allergic conjunctivitis, visual acuity worsened
3906-1281	Concurrent	4	Burning sensation in eye
4084-5109	Concurrent	6	Irritant, contact dermatitis
0124-1114	Alphagan	12	Dizziness
3719-1156	Alphagan	10	Asthenia
4084-1208	Alphagan	29	Corneal abrasion, eye pain, eye pruritus

Vol 7, section 16.2.1, listing 16.2.1

3.1.3.3 Other significant adverse events

N/A - all significant adverse events have been listed in sections 3.1.1 and 3.1.2.

3.1.4 Other Search Strategies

N/A – no addition search strategies have been conducted. The review of the deaths, serious adverse events and adverse events associated with dropouts in this trial and the two phase 3 trials reviewed in the original submission for this product give an adequate profile of the significant adverse events associated with this drug product.

3.1.5 Common Adverse Events

3.1.5.1 Eliciting adverse events data in the development program

A query for adverse events was conducted at a single time point in this study due to the short duration. At day 28 (study exit), patients were asked general, non-directed questions to elicit adverse events. Directed questioning and examinations were performed as appropriate.

3.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms used in this study were consistent with the actual adverse events experienced.

3.1.5.3 Incidence of common adverse events

See section 3.1.5.4.

3.1.5.4 Common adverse event tables

Adverse Events Reported by > 2% of Patients in any Treatment Group – Phase 3 Studies 012T, 013T, 019T, 506T and 507T

Number of patients (%)	190342-012T and -013T Pooled 3-Month Data			190342-012T and -013T Pooled 12-Month Data			190342-019T			190342-506T			190342-507T	
	Comb	Brim	Timolol	Comb	Brim	Timolol	Comb	Concur	Brim	Comb	Brim	Timolol	Comb	Concur
	N = 385	N = 382	N = 392	N = 385	N = 382	N = 392	N = 174	N = 167	N = 85	N = 196	N = 202	N = 191	N = 188	N = 183
Body as a whole														
Infection	18 (4.7)	14 (3.7)	15 (3.8)	39 (10.1)	35 (9.2)	36 (9.2)	1 (0.6)	4 (2.4)	1 (1.2)	4 (2.0)	0c	0c	1 (0.5)	4 (2.2)
Asthenia	9 (2.3)	13 (3.4)	2 (0.5)[b]	11 (2.9)	17 (4.5)	3 (0.8)[b]	6 (3.4)	3 (1.8)	3 (3.5)	1 (0.5)	0	0	4 (2.1)	3 (1.6)
Accidental injury	3 (0.8)	3 (0.8)	3 (0.8)	11 (2.9)	5 (1.3)	10 (2.6)	0	0	0	0	0	0	0	0
Headache	8 (2.1)	11 (2.9)	5 (1.3)	9 (2.3)	16 (4.2)	9 (2.3)	5 (2.9)	6 (3.6)	2 (2.4)	3 (1.5)	2 (1.0)	0	12 (6.4)	14 (7.7)
Allergic reaction	2 (0.5)	6 (1.6)	3 (0.8)	7 (1.8)	12 (3.1)	5 (1.3)	0	1 (0.6)	0	0	1 (0.5)	0	0	0
Back pain	3 (0.8)	5 (1.3)	3 (0.8)	6 (1.6)	14 (3.7)	9 (2.3)	0	0	0	0	1 (0.5)	3 (1.6)	0	0
Flu syndrome	1 (0.3)	0	1 (0.3)	6 (1.6)	3 (0.8)	4 (1.0)	2 (1.1)	0	1 (1.2)	6 (3.1)	2 (1.0)	1 (0.5)	2 (1.1)	0
Cardiovascular														
Hypertension	10 (2.6)	7 (1.8)	5 (1.3)	25 (6.5)	13 (3.4)[a]	17 (4.3)	0	1 (0.6)	0	4 (2.0)	1 (0.5)	2 (1.0)	6 (3.2)	2 (1.1)
Digestive														
LFTs abnormal	4 (1.0)	2 (0.5)	3 (0.8)	10 (2.6)	3 (0.8)	8 (2.0)	0	0	0	2 (1.0)	0	1 (0.5)	1 (0.5)	0
Oral dryness	7 (1.8)	36 (9.4)[a]	2 (0.5)	8 (2.1)	36 (9.4)[a]	2 (0.5)	4 (2.3)	9 (5.4)	3 (3.5)	1 (0.5)	4 (2.0)	0	4 (2.1)	2 (1.1)
Nausea	3 (0.8)	2 (0.5)	1 (0.3)	8 (2.1)	4 (1.0)	2 (0.5)	1 (0.6)	1 (0.6)	1 (1.2)	0	0	0	1 (0.5)	0
Dyspepsia	2 (0.5)	3 (0.8)	5 (1.3)	6 (1.6)	5 (1.3)	10 (2.6)	0	0	0	1 (0.5)	0	1 (0.5)	0	0
Metabolic and Nutritional Disorders														
Hypercholesterolemia	1 (0.3)	1 (0.3)	1 (0.3)	14 (3.6)	4 (1.0)[a]	7 (1.8)	0	0	0	0	0	0	0	0
Diabetes mellitus	2 (0.5)	1 (0.3)	1 (0.3)	8 (2.1)	5 (1.3)	3 (0.8)	0	0	0	0	0	0	0	0
Peripheral edema	5 (1.3)	1 (0.3)	3 (0.8)	8 (2.1)	1 (0.3)[a]	4 (1.0)	1 (0.6)	1 (0.6)	0	0	0	0	1 (0.5)	1(0.5)
Musculoskeletal														
Arthritis	1 (0.3)	2 (0.5)	1 (0.3)	9 (2.3)	7 (1.8)	6 (1.5)	0	0	0	0	1 (0.5)	0	0	0
Depression	5 (1.3)	2 (0.5)	0[b]	9 (2.3)	5 (1.3)	1 (0.3)[b]	0	2 (1.2)	0	0	0	0	0	1 (0.5)
Somnolence	6 (1.6)	14 (3.7)	2 (0.5)	6 (1.6)	15 (3.9)[b]	2 (0.5)	0	2 (1.2)	2 (2.4)	4 (2.0)	4 (2.0)	1 (0.5)	4 (2.1)	3 (1.6)
Dizziness	5 (1.3)	6 (1.6)	6 (1.5)	5 (1.3)	6 (1.6)	7 (1.8)	0	1 (0.6)	2 (2.4)	1 (0.5)	3 (1.5)	3 (1.6)	1 (0.5)	1 (0.5)
Respiratory														

Number of patients (%)	190342-012T and -013T Pooled 3-Month Data			190342-012T and -013T Pooled 12-Month Data			190342-019T			190342-506T			190342-507T	
	Comb	Brim	Timolol	Comb	Brim	Timolol	Comb	Concur	Brim	Comb	Brim	Timolol	Comb	Concur
	N = 385	N = 382	N = 392	N = 385	N = 382	N = 392	N = 174	N = 167	N = 85	N = 196	N = 202	N = 191	N = 188	N = 183
Bronchitis	3 (0.8)	3 (0.8)	1 (0.3)	9 (2.3)	7 (1.8)	3 (0.8)	0	2 (1.2)	0	1 (0.5)	1 (0.5)	0	1 (0.5)	2 (1.1)
Skin														
Rash	0	0	5 (1.3)	3 (0.8)	1 (0.3)	9 (2.3)	0	1 (0.6)	0	1 (0.5)	0	0	0	0
Special Senses														
Conjunctival hyperemia	32 (8.3)	39 (10.2)	21 (5.4)	66 (17.1)	90 (23.6)[a]	31 (7.9)[b]	2 (1.1)	1 (0.6)	0	9 (4.6)	9 (4.5)	4 (2.1)	7 (3.7)	7 (3.8)
Burning sensation in eye	38 (9.9)	21 (5.5)[a]	45 (11.5)	43 (11.2)	30 (7.9)	53 (13.5)	16 (9.2)	10 (6.0)	3 (3.5)	4 (2.0)	4 (2.0)	3 (1.6)	2 (1.1)	5 (2.7)
Stinging sensation in eye	21 (5.5)	7 (1.8)[a]	26 (6.6)	25 (6.5)	11 (2.9)[a]	27 (6.9)	9 (5.2)	6 (3.6)	0	0	0	0	0	0
Eye pruritus	9 (2.3)	25 (6.5)[a]	9 (2.3)	22 (5.7)	47 (12.3)[a]	15 (3.8)	1 (0.6)	0	1 (1.2)	2 (1.0)	7 (3.5)	3 (1.6)	9 (4.8)	5 (2.7)
Allergic conjunctivitis	4 (1.0)	17 (4.5)[a]	0	20 (5.2)	37 (9.7)[a]	2 (0.5)[b]	0	2 (1.2)	0	4 (2.0)	8 (4.0)[c]	0[c]	3 (1.6)	2 (1.1)
Conjunctival folliculosis	5 (1.3)	16 (4.2)[a]	2 (0.5)	19 (4.9)	35 (9.2)[a]	7 (1.8)[b]	0	0	0	3 (1.5)	6 (3.0)	1 (0.5)	2 (1.1)	0
Visual disturbance	16 (4.2)	16 (4.2)	7 (1.8)	18 (4.7)	18 (4.7)	16 (4.1)	6 (3.4)	6 (3.6)	0	3 (1.5)	3 (1.5)	3 (1.6)	4 (2.1)	7 (3.8)
Blepharitis	8 (2.1)	7 (1.8)	3 (0.8)	16 (4.2)	16 (4.2)	5 (1.3)[b]	0	0	0	3 (1.5)	1 (0.5)	0	0	0
Erythema eyelid	7 (1.8)	5 (1.3)	2 (0.5)	16 (4.2)	13 (3.4)	4 (1.0)[b]	1 (0.6)	0	0	1 (0.5)	2 (1.0)	0	1 (0.5)	0
Epiphora	7 (1.8)	10 (2.6)	5 (1.3)	14 (3.6)	20 (5.2)	7 (1.8)	1 (0.6)	0	0	4 (2.0)	0	2 (1.0)	4 (2.1)	3 (1.6)
Corneal erosion	9 (2.3)	6 (1.6)	5 (1.3)	14 (3.6)	7 (1.8)	13 (3.3)	1 (0.6)	0	0	1 (0.5)	0	2 (1.0)	0	0
Superficial punctate keratitis	6 (1.6)	5 (1.3)	3 (0.8)	14 (3.6)	5 (1.3)[a]	7 (1.8)	2 (1.1)	0	0	0	3 (1.5)	1 (0.5)	0	0
Eye dryness	7 (1.8)	9 (2.4)	2 (0.5)	12 (3.1)	14 (3.7)	5 (1.3)	0	2 (1.2)	0	2 (1.0)	2 (1.0)	0	1 (0.5)	0
Eye discharge	6 (1.6)	2 (0.5)	0[b]	12 (3.1)	9 (2.4)	4 (1.0)[b]	0	0	0	1 (0.5)	0	0	0	0
Eyelid edema	5 (1.3)	4 (1.0)	2 (0.5)	11 (2.9)	7 (1.8)	5 (1.3)	1 (0.6)	0	0	1 (0.5)	2 (1.0)	0	1 (0.5)	0
Foreign body sensation	7 (1.8)	14 (3.7)	7 (1.8)	8 (2.1)	19 (5.0)[a]	7 (1.8)	3 (1.7)	4 (2.4)	1 (1.2)	2 (1.0)	0	0	0	3 (1.6)
Eye pain	4 (1.0)	7 (1.8)	7 (1.8)	8 (2.1)	12 (3.1)	11 (2.8)	2 (1.1)	3 (1.8)	2 (2.4)	3 (1.5)	2 (1.0)	0	11 (5.9)	11 (6.0)
Irritation eye	1 (0.3)	2 (0.5)	3 (0.8)	8 (2.1)	3 (0.8)	5 (1.3)	0	2 (1.2)	0	0	1 (0.5)	2 (1.0)	2 (1.1)	0
Visual field defect	3 (0.8)	4 (1.0)	2 (0.5)	5 (1.3)	11 (2.9)	7 (1.8)	0	0	0	4 (2.0)	0[c]	0[c]	1 (0.5)	0
Cataract	2 (0.5)	1 (0.3)	1 (0.3)	4 (1.0)	10 (2.6)	7 (1.8)	0	0	1 (1.2)	0	0	2 (1.0)	1 (0.5)	0
Visual acuity	2 (0.5)	2 (0.5)	3 (0.8)	4 (1.0)	5 (1.3)	10 (2.6)	4 (2.3)	2 (1.2)	0	2 (1.0)	1 (0.5)	0	1 (0.5)	2 (1.1)

Number of patients (%)	**190342-012T and -013T Pooled 3-Month Data**			**190342-012T and -013T Pooled 12-Month Data**			**190342-019T**			**190342-506T**			**190342-507T**	
	Comb	**Brim**	**Timolol**	**Comb**	**Brim**	**Timolol**	**Comb**	**Concur**	**Brim**	**Comb**	**Brim**	**Timolol**	**Comb**	**Concur**
	N = 385	**N = 382**	**N = 392**	**N = 385**	**N = 382**	**N = 392**	**N = 174**	**N = 167**	**N = 85**	**N = 196**	**N = 202**	**N = 191**	**N = 188**	**N = 183**
worsened														
Conjunctival	0	1 (0.3)	3 (0.8)	2 (0.5)	8 (2.1)	4 (1.0)	0	0	0	0	0	0	0	0
edema														
Follicular conjunctivitis	0	3 (0.8)	0	1 (0.3)	10 (2.6)[a]	0	0	0	0	2 (1.0)	0	0	0	0
Conjunctivitis	1 (0.3)	3 (0.8)	1 (0.3)	2 (0.5)	5 (1.3)	4 (1.0)	0	1 (0.6)	0	0	4 (2.0)[c]	0	0	2 (1.1)
Urogenital														
Urinary infection	4 (1.0)	4 (1.0)	1 (0.3)	10 (2.6)	9 (2.4)	5 (1.3)	0	0	0	1 (0.5)	2 (1.0)	0	0	0

Vol. 4, section 2.7.4, table 2.7.4.2-3
Comb = brimonidine tartrate 0.2%/timolol 0.5%; Timolol = timolol 0.5%; Brim = brimonidine tartrate 0.2%; Concur = concurrent brimonidine tartrate 0.2%/timolol 0.5%
[a] $p < 0.05$ for Combination vs. Brimonidine
[b] $p < 0.05$ for Combination vs. Timolol
[c] $p < 0.05$ for proportions among treatment groups

3.1.5.5 Identifying common and drug-related adverse events

This study did not contain a placebo control arm, therefore events that are solely related to the drug product cannot be analyzed. The adverse events experienced in this trial for the combination product are consistent with known adverse events associated with the individual components. There dose not appear to be any new or increased risk of adverse events associated with the combination product over its individual components.

3.1.5.6 Additional analyses and explorations

N/A – no further analyses are warranted. See section 3.1.5.5

3.1.6 Less Common Adverse Events

N/A – The size of the database submitted in the NDA amendment is not large enough to adequately evaluate rare adverse events.

3.1.7 Laboratory Findings

N/A – Laboratory data were not collected in this study.

3.1.8 Vital Signs

3.1.8.1 Overview of vital signs testing in the development program

Pulse rate and blood pressures (systolic and diastolic) were measured while patients were at rest (seated) for at least 5 minutes. Each were measured at Day 0, Hour 0 (baseline) and Day 28, Hour 0.

3.1.8.2 Selection of studies and analyses for overall drug-control comparisons

N/A – This amendment contains one (1) controlled trial. No specific selection of studies was required.

3.1.8.3 Standard analyses and explorations of vital signs data

There were no statistical or clinically meaningful changes seen in systolic or diastolic blood pressure for any of the treatment groups during this study. There were statistically significant changes in pulse rate seen in the combination and concurrent therapy groups. These changes were not clinically meaningful and are expected due to the beta-blocking effect of the timolol component.

Hear Rate (beat/min) – Study 190342-019T

		Combination (N=174)	Concurrent (N=167)	Alphagan (N=85)	p-value [a]
Baseline	N	174	166	84	0.92
	Mean	72.5	72.7	72.2	
	SD	8.8	10	10.2	
Day 28	N	171	164	81	0.003
	Mean	-3.1	-2.2	0.7	
	SD	7.5	9	8.6	
	p-value [b]	<0.001	0.002	0.46	

[a] a 1-way analysis of variance model is used to test the equality of treatment means
[b] a paired t-test is used to test for within-group change from baseline

3.1.8.4 Additional analyses and explorations

N/A – no additional analyses are required due to the size of the database.

3.1.9 Electrocardiograms (ECGs)

N/A – ECGs were not preformed during this study.

3.1.10 Immunogenicity

N/A – immunogenicity testing has not been conducted for this drug product.

3.1.11 Human Carcinogenicity

N/A – no human carcinogenicity studies have been conducted for this drug product. Neither of the individual components had positive carcinogenic effects during preclinical testing (see the NDA review for each individual drug's).

3.1.12 Special Safety Studies

N/A – there have been no special safety concerns identified for this product.

3.1.13 Withdrawal Phenomena and/or Abuse Potential

N/A – there have been no withdrawal phenomena or abuse potential associated with this combination product or the individual components.

3.1.14 Human Reproduction and Pregnancy Data

N/A – trials in pregnant women have not been conducted for the combination product or for the individual components.

3.1.15 Assessment of Effect on Growth

N/A – growth effects have not been have not been conducted for the combination product or for the individual components.

3.1.16 Overdose Experience

N/A – there have been no overdose experiences identified with this drug product or the individual components.

3.1.17 Postmarketing Experience

N/A – This is a new combination product. There is no post marketing experience with this product. Each of the individual components are currently marketed. The adverse event identified in this review for the combination product is consistent with the labeled events of each of the individual components.

3.2 Adequacy of Patient Exposure and Safety Assessments

3.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The clinical data source for this amendment review is study 190342-019T. There were 432 patients enrolled and 403 patients who completed the four week study. Patients in this study were dosed B.I.D with the combination product. Due to the short duration and limited exposure to the drug, the safety information from this trial was not used as the primary source to evaluate the safety for this product.

The primary sources of safety data for the use of the combination product are the phase 3 studies 190342-012T and190342-013T. In these studies the combination product was administered B.I.D. for 12 months. In the pooled 12-month data for these studies, 385 patients received the Combination, 382 patients received Brimonidine, and 392 patients received Timolol. The review of these studies was completed during the first review cycle.

3.2.1.1 Study type and design/patient enumeration

Overall, the studies for the combination product provide a safety data base of 2,618 patients with glaucoma or ocular hypertension and 18 healthy subjects. A total of 968 patients received the combination, 694 patients received brimonidine tartrate 0.2%, 606 patients received timolol 0.5%, 350 patients received concurrent brimonidine tartrate 0.2% and timolol 0.5%, and 18

normal subjects participated in a 3-way crossover study of the combination and individual components.

Patients were exposed to the study medications for the longest duration in the US phase 3 studies 012T and 013T (12 months of exposure in each study). In the pooled 12-month data from these studies, 292 patients received Combination treatment for > 316 to < 406 days.

Phase 1 Study
The pharmacokinetic study 016T enrolled 18 healthy subjects: 15 subjects received the Combination, 16 subjects received Brimonidine, and 17 subjects received Timolol. Overall, 15 subjects completed each of the 7-day treatments in the 3-period crossover design.

Phase 2 Study
The phase 2 study 011T enrolled 73 patients: 25 patients received the Combination, 25 patients received Brimonidine, and 23 patients received Timolol. Overall, 72 patients completed the 7-day study.

Phase 3 Studies
Studies 012T and 013T (pooled 12-month data):
In the pooled 12-month data for studies 012T and 013T, 385 patients received the Combination, 382 patients received Brimonidine, and 392 patients received Timolol The majority of patients in each group were exposed to the study drugs for 316 to 406 days.

See section 3.2.1.3 for overall exposure in Study 190342-019T

3.2.1.2 Demographics

Demographics – Study 190342-019T – Intent-to-Treat Population

	Combination (N=176)	**Concurrent (N=169)**	**Alphagan (N=87)**	**P-value**
Age (years)				0.21
Mean	57.2	58.6	55.9	
Min	20	22	21	
Max	89	85	85	
Sex				0.5
Male	74 (42%)	65 (38.5%)	30 (34.5%)	
Female	102 (58%)	104 (61.5%)	57 (65.5%)	
Race				0.64
Asian	3 (1.7%)	1 (0.6%)	0	
Black	32 (18.2%)	27 (16%)	18 (20.7%)	
Caucasian	115 (65.3%)	119 (70.4%)	57 (65.5%)	
Hispanic	25 (14.2%)	22 (13%)	10 (11.5%)	
Iris Color				0.42
Light	76 (43.2%)	84 (49.7%)	43 (49.4%)	
Dark	100 (56.8%)	85 (50.3%)	44 (50.6%)	
Corneal Thickness				0.66

Mean	562.3	565.5	566.2	
Min	454	397	475	
Max	698	682	660	
Ocular Diagnosis				0.8
Glaucoma	50 (28.4%)	42 (24.9%)	25 (28.7%)	
Ocular Hypertension	119 (67.6%)	116 (68.6%)	57 (65.5%)	
Glaucoma/OHT	7 (4%)	11 (6.5%)	5 (5.7%)	

3.2.1.3 Extent of exposure (dose/duration)

Duration of Treatment Exposure – Study 190342-019T

Duration (days) [a]	**Combination (N=174)**	**Concurrent (N=167)**	**Alphagan (N=85)**	**p-value [b]**
Mean	28.4	28.5	29.3	0.448
SD	6.18	5.48	4.12	
Median	29	29	29	
Min	1	1	10	
Max	50	42	40	

Vol. 6, section14.3, table 14.3-1-2.
[a] treatment duration is defined as the number of days between the date of first dose and the date of last treatment plus 1 day.
[b] a 1-way analysis of variance is performed to evaluate differences among treatment groups.

3.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The complete safety profile for this combination product has been derived from studies conducted under IND 58,460. Additionally, the safety profile for the individual components have been review in their respective NDA's and throughout the postmarketing period. There are no other secondary sources of data.

3.2.2.1 Other studies

N/A -The safety data from the phase 3 studies conducted on this drug product are contained in the original NDA review and in this amendment. Other safety data available are from short term phase 1 or phase 2 trials. These data were not used as a primary source for safety due to the short duration and limited exposure to the drug.

3.2.2.2 Postmarketing experience

N/A – this is a new combination product. Post marketing data is not available. See section 3.1.17.

3.2.2.3 Literature

N/A – there was no independent literature review necessary for the evaluation of this drug product.

3.2.3 Adequacy of Overall Clinical Experience

The development program for this combination product has adequately met ICH guidelines for the extent and duration of exposure needed to assess safety. The design of the trials as well as the number and types of patients studied are adequate to assess the overall safety for this product.

3.2.4 Adequacy of Special Animal and/or In Vitro Testing

An evaluation of the preclinical program for this product was conducted during the original review cycle. The preclinical program was found to be adequate and this product was recommended for approval from a preclinical perspective.

3.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial. In addition, the evaluation of blood pressure and pulse measurements were adequate to address the systemic affects associated with topical use of beta-blockers.

3.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

N/A – evaluation of metabolic, clearance and interaction workup was not required for this topical ophthalmic drug product.

3.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Specific adverse events that are associated with the use of the topical use of each of the components contained in this combination product are well known and delineated in the current labeling for these products. Adequate safety information has been collected for the combination product during development to determine that events associated with combination are consistent with those events expected based on what is known about the individual components. There are no further safety studies recommended for the combination product.

3.2.8 Assessment of Quality and Completeness of Data

The overall safety database provided in the original NDA submission and this amendment are adequate to evaluate the safety profile for the combination product. During the development

program, approximately 600 patients were exposed to the combination product with another 167 patients who were exposed to each of the individual ingredients concomitantly. Adequate monitoring for potential adverse events was done in these clinical trials including biomicroscopy, visual acuity testing, heart rate and blood pressure monitoring, adverse events querying, etc.

3.2.9 Additional Submissions, Including Safety Update

N/A – there are no additional submissions associated with this amendment.

3.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The primary sources of safety data are from studies 190342-012T and190342-013T which contain 12 months of safety data of the combination product. This data was reviewed during the first review cycle. There were no new safety concerns raised with the use of the combination product as compared to its individual components. A more meaningful safety evaluation is to compare the combination product versus the use of the two individual components when used concomitantly. This was done in the trial submitted in this amendment; however, due to the short duration of the study and the limited exposure, no conclusions can be drawn from this comparison. Based on the totality of the data available from the phase 3 trials conducted with the combination product, it would be expected that the combination would have a similar safety profile compared to when its individual ingredients are used together.

3.4 General Methodology

3.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

N/A – this amendment contains the results of (1) controlled trial.

3.4.1.1 Pooled data vs. individual study data

N/A – see section 3.4.1.

3.4.1.2 Combining data

N/A – see section 3.4.1.

3.4.2 Explorations for Predictive Factors

N/A – there have been no predictive factors associated with the use of either of the components contained in this combination product. Further explorations were not conducted during this development program.

3.4.2.1 Explorations for dose dependency for adverse findings

N/A – see section 3.4.2

3.4.2.2 Explorations for time dependency for adverse findings

N/A – see section 3.4.2

3.4.2.3 Explorations for drug-demographic interactions

N/A – see section 3.4.2

3.4.2.4 Explorations for drug-disease interactions

N/A – see section 3.4.2

3.4.2.5 Explorations for drug-drug interactions

N/A – see section 3.4.2

3.4.3 Causality Determination

See section 3.1.5.5.

4 OVERALL ASSESSMENT

4.1 Conclusions

The results of the study submitted in this amendment do not resolve the deficiencies raised in the review of the original NDA. As per 21 CFR §300.50, when two or more drugs are combined, each component must demonstrate 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. The data contained in the original NDA failed to adequately show that each component made a contribution to the claimed effect of the combination product. Study 190342-19T submitted in this amendment was designed to address this deficiency by showing equivalency between the combination product and each of the individual components dosed concurrently, thus demonstrating that there is a benefit to the combination because in addition to equivalent safety and efficacy, there was increased compliance due to a less cumbersome dosing regimen (i.e., no dosing in the middle of the day).

Study 190342-019T failed to demonstrate that the efficacy of the combination product is equivalent to the efficacy attained when each of the individual components are dosed concurrently.

There were no increased risks associated with the use of the combination product. There were no new safety concerns raised with the use of the combination product as compared to its individual components. The adverse event profile of the combination product was similar to concurrent therapy in study 190342-019T. This study was of short duration (28 days); however, based on the totality of the data available from the phase 3 trials conducted with the combination product, it would be expected that the combination would have a similar safety profile compared to when its individual ingredients are used together for an extended period.

Overall, the risks associated with the use of the combination product as compared to concurrent therapy is equivalent, however, the effectiveness of the combination for the treatment of increased intraocular pressure (IOP) is inferior. Therefore, the combination is not recommended for approval.

4.2 Recommendation on Regulatory Action

Brimonidine tartrate 0.2%-timolol maleate 0.5% ophthalmic solution is not recommended for approval. All studies submitted to date have failed to demonstrate that each of the individual components make a contribution to the claimed effect as required in 21 §300.50. There are no further recommendations for the development of this combination product. The trials conducted to date have been of adequate design and duration to assess the potential use of this drug product.

4.3 Recommendation on Postmarketing Actions

N/A – the drug product is not recommended for approval.

4.3.1 Risk Management Activity

N/A – the drug product is not recommended for approval.

4.3.2 Required Phase 4 Commitments

N/A – the drug product is not recommended for approval.

4.3.3 Other Phase 4 Requests

N/A – the drug product is not recommended for approval.

4.4 Labeling Review

The labeling review for this combination product will be completed once the efficacy of this product has been demonstrated and is recommended for approval. A review from the Division of Medication Errors and Technical Support (DMETS) was conducted during the first review cycle of the original NDA. A second review will be required prior to approval.

4.5 Comments to Applicant

All studies submitted to date have not demonstrated that each of the individual components make a contribution to the claimed effect of the combination product as required in 21 §300.50.

Study 190342-019T has not demonstrated equivalency between the combination product and the individual components dosed concurrently.

The risks of combination and concurrent therapy are similar; however, the product is less effective when used as a combination drop; therefore, the risk/benefit ratio does not favor combining the two components.

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

/s/

Jennifer Harris
3/4/05 09:19:51 AM
MEDICAL OFFICER

Wiley Chambers
3/4/05 09:56:01 AM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-398
120-Day Safety Update

NDA 21-398 Medical Officer's Review	Submission: 1/16/02 Review Completed: 3/15/02

Proposed Tradename:	Combigan
Generic Name:	Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution
Sponsor:	Allergan 2525 Dupont Drive P.O. Box 19534 Irvine, California 92623-9534
Pharmacologic Category:	Alpha 2-agonist/β-blocker
Proposed Indication:	Lowering of elevated intraocular pressure (IOP) in patients with [redacted] glaucoma or ocular hypertension
Dosage Form and Route of Administration:	Ophthalmic suspension for topical ocular administration
Submitted:	Pooled 120-Day Safety Information for Protocols 190342-012T and 190342-013T

Table 1 – Incidence of Adverse Events Reported by ≥ 1% of Patients in the Combination Treatment Group for 12-month Pooled Data

BODY SYSTEM Preferred Term	Combination N = 385	Brimonidine N = 382	Timolol N = 392
BODY AS A WHOLE			
infection	34 (8.8%)	29 (7.6%)	26 (6.6%)
asthenia	11 (2.9%)	16 (4.2%)	3 (0.8%)
headache	8 (2.1%)	13 (3.4%)	7 (1.8%)
allergic reaction	6 (1.6%)	12 (3.1%)	5 (1.3%)
back pain	6 (1.6%)	12 (3.1%)	5 (1.3%)
accidental injury	5 (1.3%)	4 (1.0%)	8 (2.0%)
arm pain	4 (1.0%)	3 (0.8%)	3 (0.8%)
flu syndrome	4 (1.0%)	2 (0.5%)	4 (1.0%)
CARDIOVASCULAR			
hypertension	18 (4.7%)	11 (2.9%)	10 (2.6%)
bradycardia	5 (1.3%)	2 (0.5%)	1 (0.3%)
DIGESTIVE			
oral dryness	8 (2.1%)	36 (9.4%)	2 (0.5%)
nausea	8 (2.1%)	3 (0.8%)	1 (0.3%)
dyspepsia	5 (1.3%)	4 (1.0%)	6 (1.5%)
diarrhea	5 (1.3%)	4 (1.0%)	3 (0.8%)
liver function tests, abnormal	5 (1.3%)	2 (0.5%)	5 (1.3%)
periodontal abscess	4 (1.0%)	1 (0.3%)	3 (0.8%)
cholelithiasis	4 (1.0%)	1 (0.3%)	1 (0.3%)
rectal disorder	4 (1.0%)	1 (0.3%)	0
gastrointestinal disorder	4 (1.0%)	0	0
Metabolic and Nutritional Disorders			
hypercholesterolemia	7 (1.8%)	2 (0.5%)	4 (1.0%)
peripheral edema	7 (1.8%)	2 (0.5%)	4 (1.0%)
creatine phosphokinase, increased	5 (1.3%)	1 (0.3%)	2 (0.5%)
Musculoskeletal			
arthritis	8 (2.1%)	5 (1.3%)	4 (1.0%)
NERVOUS			
depression	7 (1.8%)	5 (1.3%)	1 (0.3%)
somnolence	6 (1.6%)	15 (3.9%)	2 (0.5%)
dizziness	5 (1.3%)	6 (1.6%)	7 (1.8%)
insomnia	4 (1.0%)	2 (0.5%)	4 (1.0%)
RESPIRATORY			
rhinitis	6 (1.6%)	6 (1.6%)	5 (1.3%)

BODY SYSTEM Preferred Term	Combination N = 385	Brimonidine N = 382	Timolol N = 392
bronchitis	6 (1.6%)	6 (1.6%)	3 (0.8%)
sinusitis	6 (1.6%)	2 (0.5%)	0
infection sinus	5 (1.3%)	2 (0.5%)	3 (0.8%)
dyspnea	4 (1.0%)	1 (0.3%)	7 (1.8%)
SPECIAL SENSES (OCULAR)			
conjunctival hyperemia	52 (13.5%)	66 (17.3%)	28 (7.1%)
burning sensation in eye	41 (10.6%)	24 (6.3%)	49 (12.5%)
stinging sensation eye	24 (6.2%)	9 (2.4%)	27 (6.9%)
eye pruritus	18 (4.7%)	37 (9.7%)	12 (3.1%)
visual disturbance	17 (4.4%)	19 (5.0%)	13 (3.3%)
allergic conjunctivitis	13 (3.4%)	31 (8.1%)	1 (0.3%)
epiphora	12 (3.1%)	17 (4.5%)	7 (1.8%)
blepharitis	12 (3.1%)	12 (3.1%)	3 (0.8%)
erythema eyelid	12 (3.1%)	11 (2.9%)	3 (0.8%)
conjunctival folliculosis	11 (2.9%)	27 (7.1%)	5 (1.3%)
eye discharge	11 (2.9%)	6 (1.6%)	4 (1.0%)
eye dryness	10 (2.6%)	10 (2.6%)	4 (1.0%)
corneal erosion	10 (2.6%)	6 (1.6%)	9 (2.3%)
superficial punctate keratitis	10 (2.6%)	5 (1.3%)	6 (1.5%)
foreign body sensation	8 (2.1%)	16 (4.2%)	7 (1.8%)
eyelid edema	8 (2.1%)	6 (1.6%)	3 (0.8%)
eye pain	7 (1.8%)	10 (2.6%)	10 (2.6%)
irritation eye	7 (1.8%)	3 (0.8%)	4 (1.0%)
visual field defect	4 (1.0%)	9 (2.4%)	4 (1.0%)
eye edema	4 (1.0%)	4 (1.0%)	1 (0.3%)
vitreous floaters	4 (1.0%)	3 (0.8%)	4 (1.0%)
retinal disorder	4 (1.0%)	1 (0.3%)	1 (0.3%)
papillary hypertrophy	4 (1.0%)	1 (0.3%)	0

The 120-day incidence rates for all adverse effects related to the combination drop show a slight increase over the rates reported in the 3-month studies. This is not unexpected due to the longer duration of exposure to the study drug.

The most frequently reported ocular events (>5%) in the Combination group were conjunctival hyperemia, burning sensation in the eye, and stinging sensation in the eye. Other ocular events reported for >3% of patients receiving the Combination were eye pruritus, visual disturbance, allergic conjunctivitis, epiphora , blepharitis, and eyelid erythema.

Serous adverse events were reported for 4.2% (16/385) of patients in the Combination group, 4.5% (17/382) of patients in the Brimonidine group, and 3.6% (14/392) of patients in the Timolol group.

A total of 4 deaths were reported during the studies. In addition to the death reported in the NDA submission, patient 3225-1085 (Brimonidine) died of natural causes, patient 2942-1437 (Combination) died of cardiac arrest and patient 2037-1481 (Timolol) died of respiratory arrest and atrial fibrillation.

Reviewer's Comments:
Information contained in this safety update is comparable to previous safety information reviewed for the original NDA. There has been no new safety information learned about the Combination that would change the original conclusions about its safety.

Reviewer's Conclusions
Original conclusions about the safety of the Combination drug remain unchanged. There are no new safety findings with the use of the Combination in lowering intraocular pressure in patients with [redacted] glaucoma or ocular hypertension versus the individual monotherapies.

Jennifer D. Harris, M.D.
Medical Officer

NDA 21-398
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-550/ Div Dir/Simon
HFD-880/Biopharm/Tandon
HFD-725/Biostats/Choi
HFD-550/Chem/Lu
HFD-550/PharmTox/Chen
HFD-550/PM/Puglisi
HFD-340/Carreras

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

/s/

Jennifer Harris
3/20/02 01:06:54 PM
MEDICAL OFFICER

Wiley Chambers
3/21/02 11:02:37 AM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-398

Tradename:	**Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution**
Sponsor:	**Allergan** **2525 Dupont Drive** **P.O.Box 19534** **Irvine, California 92623** Lewis Gryziewicz (714) 246-6088
Proposed Indication:	**Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension**
Date of Submission:	September 19, 2001
Date of Review:	January 14, 2002

Table of Contents

Executive Summary

I. Recommendations

The submitted studies in NDA 21-398 are not sufficient to establish efficacy for the use of brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution in lowering intraocular pressure in patients with [redacted] glaucoma or ocular hypertension.

It is recommended that the sponsor submit additional information to support the efficacy contribution of timolol 0.5% and brimonidine tartrate 0.2 % to the timolol 0.5%/brimonide tartrate 0.2% combination product in lowering intraocular pressure in patients with [redacted] glaucoma or ocular hypertension.

II. Summary of Clinical Findings

A. Overview of clinical program

The primary sources of efficacy and safety data for the use of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution were two phase 3 studies; 190342-012T and 190342-013T. The primary efficacy variable in both trials was intraocular pressure (IOP). The analysis was based on the assessment of mean IOP at each individual timepoint. IOP for this trial was measured at the following timepoints: baseline, week 2, week 6, and 3 months at hours 0, 2,7,9. It is the division's policy to determine efficacy for IOP lowering drugs based on the analyses of the difference in mean IOP between drug and placebo with 95% confidence intervals at each timepoint. A clinically significant amount of IOP lowering is expected to be at least a 25% reduction from baseline at the time of peak effect and at least 20% reduction from baseline at the time of trough effect.

The criteria necessary to demonstrate the efficacy of a combination product is defined in 21 CFR §300.50 which requires that when two or more drugs are combined, each component must demonstrate 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. The criteria used by the division to show the contribution of timolol and brimonidine in the combination product was to demonstrate superiority of the combination product over each individual component by a statistically and clinically significant amount. A 2mmHg change in IOP has been observed in clinical studies without treatment and the ability to accurately measure IOP with applanation tonometry in increments of less than 2mmHg is unreliable.

B. Efficacy

The submitted studies in NDA 21-398 are not sufficient to establish the efficacy of the combination product in lowering IOP in patients with glaucoma or ocular hypertension. This is based on the inability to show a clinically significant contribution of brimonidine tartrate to the combination product in the submitted phase 3 trials.

Neither study 190342-012T nor 190342-013T demonstrates a clinically significant contribution of timolol 0.5% or brimonidine tartrate 0.2% to the combination product. Additionally, there are statistically significant differences in IOP at baseline between the combination and timolol in study 190342-012T and the difference in the mean IOP lowering effect between the two components is not statistically significant in 2/12 timepoints in study 013T.

C. Safety

The submitted studies in NDA 21-398 demonstrate no new safety findings with the use of brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution in lowering intraocular pressure in patients with [redacted] glaucoma or ocular hypertension versus individual monotherapies.

D. Dosing

Timolol ophthalmic solution and Brimonidine tartrate ophthalmic solution are currently marketed individually as monotherapies for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Currently, brimonidine tartrate and timolol are often prescribed and used together. Brimonidine tartrate is marketed as 0.2% and Timolol is marketed as both 0.5% and 0.25% ophthalmic solutions. Because patients requiring adjunctive therapy are likely to have been previously treated with maximal doses of monotherapy, the concentration of timolol chosen for the combination was 0.5%.

In the United States, the recommended regimen for timolol is QD or BID, and for brimonidine tartrate, TID. BID dosing was selected by the sponsor for the Combination product based on anecdotal evidence that brimonidine may be effective BID when dosed with timolol. The agency has not reviewed any data that substantiates this hypothesis.

In evaluation of the two phase 3 studies, there is a reproducible loss of IOP lowering ability of the combination versus brimonidine tartrate 0.2% seen when the evening IOP (hour 9 measurement) is measured for each diurnal period throughout the study. The difference between the IOP lowering ability of the combination vs. brimonidine losses its statistical significance for 4 out of the 6 evening IOP measurements. While the reason for this is only speculative, it may be secondary to the missed evening dose of brimonidine in the combination group since it is only given BID.

E. Special Populations

Mean IOP measurements were examined in patient subgroups defined by age, sex and race. There were no significant differences seen in the IOP lowering ability of the combination product in any of the subgroups analyzed. There are no gender, age or race effects on safety or efficacy with the use of the combination product.

A clinical study report, AGN 190342-015 submitted by the sponsor evaluating Alphagan 0.2% dosed adjunctively with beta blockers in pediatric patients has been reviewed by the agency. Alphagan 0.2% used adjunctively with beta-blockers is safe and effective in patients 7 years of age and older, and may be used with caution between the ages of 3 and 7.

Clinical Review

I. Introduction and Background

A. Proposed Trade Name and Drug Class

Tradename:	Brimonidine Tartrate 0.2%/Timolol 0.5% (Ophthalmic Solution)
Sponsor:	Allergan 2525 Dupont Drive P.O.Box 19534 Irvine, California 92623
Pharmacologic Category:	α-agonist/β-blocker
Proposed Indication:	Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension
Dosage Form and Route of Administration:	Ophthalmic solution for topical ocular administration

B. Clinical Background

Elevated intraocular pressure (IOP) is a major risk factor in the progression of glaucomatous optic neuropathy. In clinical practice, the treatment regimen for a patient often begins with the prescription of a beta-blocker. If the beta-blocker does not lower the IOP sufficiently, a second drug is frequently added to the regimen. Ideally, the second drug is one that has a favorable therapeutic index and has additivity to the beta-blocker.

Timolol and brimonidine tartrate are currently marketed individually as monotherapies for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Timolol decreases aqueous humor production with little or no significant effect on episcleral venous pressure, outflow facility or uveoscleral outflow (Epstein et al, 1989). It is effective at lowering IOP, but a second concomitant treatment may be prescribed if adequate IOP control has not been achieved. Brimonidine tartrate is believed to reduce IOP through a dual mechanism of action: reduction of aqueous humor production and increase in nonpressure-dependent uveoscleral outflow (Toris, 1999). Because timolol and brimonidine tartrate have different sites of action and different mechanisms by which they lower IOP, it is reasonable to expect that there may be an added IOP-lowering effect when the two are used adjunctively (Traverso, 1998).