C. Important Milestones in Product Development

Major points addressed to the sponsor by the Agency throughout development with regard to the evaluation of efficacy for the combination product were as follows:

EOP2 meeting (3/8/99):

- To prove efficacy for the combination product, the agency expects the combination to be superior to the individual drugs at each time point measured during the clinical trial.

Medical Officers Review IND 58,460 amendment 3:

- To gain approval of BID dosing for the combination product, the agency would expect the combination to perform better at each IOP time point than the individual drugs.

Pre-NDA Meeting (5/30/01):

- In order to demonstrate the superiority of the fixed combination over the individual drugs, the agency expects the combination to lower IOP by a clinically significant amount.

- To evaluate the efficacy of the combination product, the agency will apply the criteria set forth in 21 CFR §300.50. The agency expects to see replication of study results in a minimum of two separate independent phase 3 controlled trials. The phase 3 trials should demonstrate superiority of the fixed combination over each individual components by a clinically significant amount. Differences of 2 mmHg are commonly seen in clinical trials without a change in therapy.

D. Foreign Marketing

Brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution has not been marketed in any country. However, the active ingredient brimonidine tartrate is marketed by Allergan as ALPHAGAN® 0.2% in several foreign countries. The other active ingredient, timolol maleate, is marketed for ophthalmic use by Merck (as Timoptic®, Timoptic-XE®, and in Cosopt®), Falcon Pharms, Akorn, Bausch and Lomb, Fougera, and Novex. Allergan markets timolol through its generic subsidiary Pacific Pharma .

II. **Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews** - See Chemistry, Pharmacology and Statistical Reviews

Table 1 - Quantitative Composition of Brimonidine Tartrate 0.2%/Timolol 0.5% Ophthalmic Solution

Ingredient	Concentration (% w/v)	Concentration (mg/mL)	Amount (g) for a
Brimonidine Tartrate	0.20	2.0	
Timolol Maleate	0.68[a]	6.8	
Benzalkonium Chloride	0.005	0.05	
Dibasic Sodium Phosphate			
Monobasic Sodium Phosphate			
Hydrochloric Acid, 1N			
Sodium Hydroxide, 1N			
Purified Water			

2 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 5

IV. Description of Clinical Data Sources

Table 3 – Clinical Data Sources

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	Sex/Race	#Pts enrolled/completed
190342-012T Phase 3 Safety and Efficacy	Multicenter, randomized, double masked, parallel, active control	3 months (plus 9-month masked extension)	Open angle glaucoma and ocular hypertension	brimonidine tartrate 0.2%/ timolol 0.5% brimonidine tartrate 0.2% timolol 0.5%	1gtt BID [a] 1 gtt TID 1 gtt BID [a]	248M/325F 427 white 99 black 40 hispanic 6 asian 1 other	573/497
190342-013T Phase 3 Safety and Efficacy	Multicenter, randomized, double masked, parallel, active control	3 months (plus 9-month masked extension)	Open angle glaucoma and ocular hypertension	brimonidine tartrate 0.2%/ timolol 0.5% brimonidine tartrate 0.2% timolol 0.5%	1gtt BID [a] 1 gtt TID 1 gtt BID [a]	270M/316F 452 white 88 black 38 hispanic 5 asian 3 other	586/502

[a] active drug administered in the morning and evening with masked vehicle administered in the afternoon

V. Clinical Review Methods

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.

VI. Integrated Review of Efficacy

Study 1 - Protocol 1910342-012T:

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

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

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

The following were requirements for entry into the study:

1) Male or female, 18 years of age or older.
2) Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity equivalent to a Snellen score of 20/100 or better in each eye.
3) Patient had ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma or pigmentary glaucoma and required bilateral administration of treatment.
4) Informed consent had been obtained.
5) Ability to follow study instructions and likely to complete all required visits.
6) Baseline (day 0, hour 0), patient had been appropriately washed out of his/her anti-glaucoma medication.
7) Baseline (day 0, hour 0), IOP $\geq$ 22 mm Hg and $\leq$ 34 mm Hg in each eye and asymmetry of IOP not greater than 5 mm Hg.
8) A negative urine pregnancy test result for women of childbearing potential within 2 days prior to baseline.

Exclusion Criteria

The following were criteria for exclusion from participating in the study:

1) Uncontrolled systemic disease
2) Severe cardiovascular disease unless the disease was controlled and clearance had been obtained from the patient's primary care physician and/or cardiologist.
3) Females who were pregnant, nursing, or planning a pregnancy or females of childbearing potential who were not using a highly effective means of contraception.
4) Abnormally low or high blood pressure or pulse rate as determined by the investigator.
5) Contraindication to beta-adrenoceptor antagonist therapy such as chronic obstructive pulmonary disease, bronchial asthma, sinus bradycardia, second and third degree atrioventricular block, overt cardiac failure and cardiogenic shock or uncontrolled congestive heart failure.
6) Contraindication to brimonidine therapy such as concurrent use of monoamine oxidase (MAO) inhibitor therapy and antidepressants which affect noradrenergic transmission (eg, tricyclic antidepressants and mianserin).
7) Contraindication to pupil dilation.
8) Known allergy or sensitivity to any of the study medication ingredients.
9) Anticipated alteration of existing chronic therapy with agents which could have a substantial effect on IOP including, but not necessarily limited to systemic adrenergic agents including beta-adrenergic blocking agents (eg, propanolol, metoprolol, nadolol, timolol, atenolol) or introduction of such therapy.

10) Anticipated wearing of contact lenses during the study.
11) Any other active ocular disease (eg, uveitis, ocular infections, or severe dry eye). However, patients with chronic mild blepharitis, cataract, age-related macular degeneration, or background diabetic retinopathy could be enrolled at the discretion of the investigator.
12) Corneal abnormalities that would preclude accurate readings with an applanation tonometer.
13) Required chronic use of other ocular medications during the study (intermittent use of artificial tear product was allowed).
14) Refractive laser surgery, intraocular filtering surgery or any other ocular surgery within the past 3 months.
15) Visual field loss which, in the opinion of the investigator, was functionally significant or evidence of progressive visual field loss within the last year.
16) Participation in an investigational drug or device research study within 30 days prior to baseline or concurrent participation in any other drug or device research study.
17) Patient had a condition or was in a situation which, in the investigator's opinion, might have put the patient at a significant risk, might have confounded study results, or might have interfered significantly with patient's participation in the study.

Study Medications

Combination (Allergan formulation number [redacted], lot numbers 11604, 11670) contained brimonidine tartrate 0.2%, timolol maleate 0.68% (equivalent to timolol 0.5%), sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, benzalkonium chloride 0.005%, hydrochloric acid and/or sodium hydroxide to adjust pH, and purified water (Manufactured by Allergan, Inc).

Brimonidine (ALPHAGAN ®, Allergan formulation number 7831X, lot numbers 11601A, 11601B, 11829A, 11829D) contained brimonidine tartrate 0.2%, benzalkonium chloride 0.005%, polyvinyl alcohol, sodium chloride, sodium citrate, citric acid, hydrochloric acid and/or sodium hydroxide to adjust pH, and purified water (Manufactured by Allergan, Inc).

Timolol (Allergan formulation number 8770X, lot numbers 11603, 11633B) contained timolol 0.5% (6.8 mg timolol maleate), sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, benzalkonium chloride 0.01%, hydrochloric acid and/or sodium hydroxide to adjust pH, and purified water (Manufactured by Allergan, Inc).

Vehicle of the Combination ophthalmic solution (Allergan formulation number [redacted] lot numbers 11605, 11669) contained sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, benzalkonium chloride 0.005%, hydrochloric acid and/or sodium hydroxide to adjust pH, and purified water (Manufactured by Allergan, Inc).

Study Masking

Each identically masked bottle of test medication was labeled with a patient number. The patients were provided with 2 different sized study medication bottles to be used each day (dispensed at each visit, as necessary). The larger sized bottle (15 mL) contained the medication to be used in the morning and evening. Each bottle had active medication. The smaller sized bottle (10 mL) contained the medication to be used in the afternoon, which was Brimonidine for the patients in the Brimonidine group and vehicle for the patients in the Combination and Timolol groups. This was the case for all patients in each of the 3 treatment groups in order to ensure masking. When necessary for the safety and proper treatment of the patient, the investigator had the ability to unmask the patient's treatment assignment to determine which study medication had been assigned and institute appropriate follow-up care. When possible, Allergan was to be notified prior to unmasking study medication. The trial is a 3-month study with masked treatment extended to 1 year. Although unmasking was necessary to perform a full analysis of the 3-month data, special efforts were made to avoid biasing the conduct of the final 9 months of the study.

Efficacy Variable

Intraocular Pressure

IOP was measured using the [redacted] applanation tonometer. Both eyes were tested, with the right eye preceding the left eye. Two consecutive measurements were made for each eye to determine IOP. If the first 2 measurements differed by more than 2 mm Hg, a third measurement was required. Entry IOP was defined as the mean (if 2 measurements taken) or median (if 3 measurements taken) value.

Diurnal IOP measurements were to be performed at hour 0 (ideally between 7:00 AM and 8:30 AM), and at 2, 7 and 9 hours after hour 0 on day 0 (baseline), weeks 2 and 6, and months 3, 6, and 12. At the month 9 visit, IOP was to be measured at hours 0 and 2. Whenever possible, the hour 0 measurement was to be performed at approximately the same time throughout the study.

Pharmacoeconomic Evaluation by Investigator

Investigators were to make pharmacoeconomic evaluations at the month 3 and month 12 (or exit) visits. Investigators were asked if they would choose to continue the patient on the current regimen assuming that the study medication was commercially available and the investigator had prescribed it to the patient outside of a clinical trial. Investigators were advised to consider relevant factors including patient Quality of Life (QOL), IOP reduction, AEs, etc.

Patient Comfort/Satisfaction

Prior to entering the study, patients were to be asked about the level of comfort and satisfaction they had with their previous eye drops. At each follow-up visit, the patients'

level of comfort and satisfaction with the study treatment was assessed by asking them the following questions, "Overall, how would you rate the overall comfort of your eye drops?"and "Overall, how satisfied have you been with your eye drops?".

Safety Variable

Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence in a patient administered a pharmaceutical product and that did not necessarily have a causal relationship with this treatment. The occurrence of AEs was monitored throughout the study. At each post-baseline visit AE's were elicited from the patient. All reported AEs were documented on the appropriate CRF, along with information which included the onset date, resolution date (if applicable), duration, severity, whether or not the event was serious, relationship to study drug, whether treatment was required, and outcome of the event. The severity of an AE was classified as mild, moderate, severe, or non-applicable using the definitions described in the protocol. The relationship of an AE to study drug was classified as unrelated, possible, probable, or definitely related using the definitions outlined in the protocol.

A serious adverse event (SAE) included any AE occurring at any dose that resulted in any of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not have resulted in death, been life-threatening, or required hospitalization could have been considered SAEs when, based upon appropriate judgment, they may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition.

All AEs that were drug-related and unexpected (ie, not listed as treatment-related in the Clinical Investigator's Brochure [CIB]) were reported to the governing IRB at least annually.

Biomicroscopy

Slit lamp biomicroscopy without pupil dilation was to be performed at the prestudy, baseline, and each follow-up visit. The examinations included evaluation of the condition of the lids, lid margins, conjunctiva, anterior chamber, cornea, lens, and vitreous. Observations were recorded using a 5-point scale (0 = none, 0.5 = trace 1 = mild, 2 = moderate, and 3 = severe).

Visual Acuity

Best-corrected visual acuity (VA) was to be measured for each eye using an ETDRS chart at the prestudy, baseline, and each follow-up visit.

Visual Field
Visual field examination (without pupil dilation) was to be performed at the prestudy and baseline visits, and at months 3, 6 and 12 using Humphrey automated perimetry. Either full-threshold 24-2 or Swedish Interactive Thresholding Algorithm (SITA) programs could be used. All tests for each patient were to be done using the same equipment.

Ophthalmoscopy and Cup/disc Ratio
The vitreous and optic nerve head were to be evaluated through a dilated pupil at the prestudy visit and after the hour 9 IOP measurements at months 3, 6 and 12. Cup/disc ratio was graded using the Allergan Armaly chart, and recorded in units from 0.0 to 0.9. Fundus pathology observations were recorded using a 5-point scale (0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe).

Heart Rate
Heart rate was to be measured at the prestudy, baseline, and each follow-up visit with patients in a resting state (seated) for at least 5 minutes

Blood Pressure
Systolic and diastolic blood pressure were to be measured at the prestudy, baseline, and each follow-up visit by a sphygmomanometer with patients in a resting state (seated upright) for at least 5 minutes, and recorded in mm Hg using the same arm each time.

Clinical Laboratory Data
Fasting blood and urine samples were to be obtained at the prestudy visit and at months 3 and 12.

Corneal Pachymetry
At either the prestudy or baseline (day 0) visits, central corneal thickness of each eye was to be measured using an ultrasonic pachymeter.

Pregnancy
Urine pregnancy tests were to be performed for females of childbearing potential at baseline (day 0), month 3 and month 12 or at the exit visit.

Study Design and Schedule of Assessments

Table 4 – Examination Schedule – Study 012T

Visit	Hour	History/Consent /Pachymetry[a]	Pregnancy Test	LAB[b]	HR /BP	IOP	VA/ BIO	VF	OPH[d]/ C/D ratio	PK Samples Blood Draw[f]	Patient Comfort/ General Inquiry	Patient Satisfaction	PE/ RU[j]
Prestudy	0	X		X	X	X	X	X[c]	X		X	X	
Washout Period (4-28 Days)[g]													
Baseline (Day 0)	0 2 7 9		X		X X	X X X X	X	X		X			
First dose instilled the evening of day 0 between 1900 and 2100. Medication was instilled at each visit following the hour 0 and hour 7 examinations													
Week 2	0 2 7 9				X X	X X X X	X			collect only at hour 1	X	X	
Week 6	0 2 7 9				X X	X X X X	X				X	X	
Month 3	0 2 7 9		X	X	X X	X X X X	X	X	X	collect only at hour 1	X	X	X (PE only)
Month 6[h]	0 2 7 9				X X	X X X X	X	X	X		X	X	
Month 9[h]	0 2				X X	X X	X				X	X	
Month 12 or Exit[h,i]	0 2 7 9		X	X	X X	X X X X	X	X	X	collect only at hour 1	X	X	X

Examination Schedule (con't)

Note: LAB = Hematology, chemistry and urinalysis; HR = Heart Rate; BP = Blood Pressure (systolic/ diastolic); IOP = Intraocular Pressure; VA=Visual Acuity; BIO = Biomicroscopy; VF = Visual Field Examination; OPH = Ophthalmoscopy; C/ D = Cup/ Disc Ratio; PK = Pharmacokinetics; PE = Pharmacoeconomics; RU = Research Utilization

a Pachymetry was performed at either the prestudy or baseline visit.

b Blood and urine samples collected under fasting conditions.

c If VF > 6 mos or not at all prior to baseline, prestudy and baseline VF exams were performed.
If VF≤ 6 mos prior to baseline, then only a baseline VF was necessary.

d Ophthalmoscopy was performed after hour 9 IOP measurement.

e Blood samples for PK analysis were collected in a patient subset at selected sites.

f For those patients discontinuing from the study early and returning for office visits during their planned 12 month study period, the investigator will complete a questionnaire to identify the resources used during this period.

g For patients who were not going into washout, a minimum 2- day wait between prestudy and baseline visits was necessary.

h Visits at 6, 9 and 12 months from baseline will occur during the masked extension period of the study.

i Patients last dosing will occur in the afternoon of the month 12 visit. If the patient discontinued from the study prior to month 12 visit, all of the month 12 measurements were performed at the exit visit.

Patients who were chronically treated with ocular hypotensive medications were required to undergo appropriate washout periods prior to study entry to eliminate any residual effects of other active ocular hypotensive medications. Patients who did not require a washout of ocular hypotensive medications were to have a waiting period of at least 2 days after the prestudy visit to ensure that all potential effects from pupil dilating agents were gone. The washout period was a minimum of 4 to 28 days depending on the medication, according to the following schedule.

Table 5 - Washout Schedule

Medication Class	Examples	Minimum Washout Period
Parasympathomimetics	carbachol, pilocarpine hydrochloride	4 days
Carbonic Anhydrase Inhibitors (systemic or topical)	acetazolamide, dorzolamide hydrochloride	4 days
Sympathomimetics	dipivefrin hydrochloride, epinephrine	2 weeks
Topical alpha-agonists	apraclonidine hydrochloride, brimonidine tartrate	2 weeks
Topical beta-blockers	timolol maleate, levobunolol hydrochloride betaxolol hydrochloride metipranolol	4 weeks
Topical prostaglandins	latanoprost	4 weeks
Combination product	dorzolamide hydrochloride/ timolol maleate	4 weeks

Reviewer's Comments: *The washout period for all drugs was in accordance with agency recommendations.*

Subject Disposition and Demographics

Table - 6 Subject Disposition – Study 012T

Treatment	Number of Patients Randomized (N=573)	Number of Patients Discontinued (N=76)
Combination	192	16
Brimonidine tartrate 0.2%	186	37
Timolol 0.5%	195	23

Table 7 – Discontinued Patients and Reason – Study 012T

Patient	Treatment	Reason
0169-1269	Combination	dyspnea
1584-1389	Combination	relocated
1634-1285	Combination	lost to follow-up
2232-1357	Combination	personal reasons
2366-1055	Combination	improper entry (atenolol use)
2366-1344	Combination	sinusitis
2707-1066	Combination	headache, nervousness, somnolence
2707-1068	Combination	lack of efficacy
2821-1027	Combination	unable to comply w/ study visits
2851-1187	Combination	asthenia
2952-1152	Combination	Personal reasons
2966-1021	Combination	eye pruritus
2984-1599	Combination	lost to follow-up
3179-1367	Combination	vasodilatation, oral dryness, nausea, dizziness, eyelid edema, eyelid erythema, abnormal vision
3225-1507	Combination	relocated
3276-1632	Combination	oral dryness
1584-1380	Brimonidine	dermatitis, conjunctival folliculosis, eye pruritus
1634-1286	Brimonidine	blepharitis
1634-1424	Brimonidine	improper entry (amitriptyline use)
1634-1584	Brimonidine	lack of efficacy
1634-1588	Brimonidine	lack of efficacy
1634-1662	Brimonidine	improper entry (Asthma history)
1634-1663	Brimonidine	eyelid edema, eyelid erythema, eye pruritus, eye discharge
2078-1254	Brimonidine	somnolence, depression, conjunctival folliculosis
2232-1183	Brimonidine	Follicular conjunctivitis
2232-1360	Brimonidine	Eyelid edema, epiphora, burning, sensation in eye
2232-1362	Brimonidine	Asthenia, decreased libido, vitreous detachment
2366-1339	Brimonidine	Headache, somnolence, dizziness
2450-1166	Brimonidine	Lack of efficacy
2450-1170	Brimonidine	Somnolence
2450-1460	Brimonidine	Improper entry (IOP asymmetry)
2707-1046	Brimonidine	Lack of efficacy
2707-1062	Brimonidine	Burning sensation in eye
2707-1330	Brimonidine	Asthenia
2821-1026	Brimonidine	Allergic conjunctivitis
2821-1036	Brimonidine	Relocated

Patient	Treatment	Reason
2851-1190	Brimonidine	Bradycardia
2851-1199	Brimonidine	Eyelid pruritus
2952-1159	Brimonidine	Lack of efficacy
2965-1402	Brimonidine	Lack of efficacy
2965-1645	Brimonidine	Lack of efficacy
2966-1015	Brimonidine	Eyelid edema, conjunctival hyperemia, eye dryness, eye pruritus
2973-1601	Brimonidine	Asthenia, dizziness
2974-1490	Brimonidine	Allergic conjunctivitis
2981-1320	Brimonidine	Allergic conjunctivitis
2981-1322	Brimonidine	Allergic conjunctivitis
2984-1146	Brimonidine	Allergic conjunctivitis
3179-1371	Brimonidine	Asthenia, headache, oral dryness, dizziness, confusion, visual disturbance
3276-1473	Brimonidine	Dizziness
3276-1483	Brimonidine	Improper entry (triavil use)
3276-1637	Brimonidine	Oral dryness
3294-1128	Brimonidine	Lack of efficacy
3329-1281	Brimonidine	Bradycardia
1485-1215	Timolol	Lack of efficacy
1584-1384	Timolol	Improper entry (disipramine use)
2027-1297	Timolol	Dyspnea
2078-1251	Timolol	Tachycardia, eyelid erythema
2232-1349	Timolol	Stinging sensation, visual disturbance
2232-1365	Timolol	Pneumonia
2366-1059	Timolol	Relocated
2366-1060	Timolol	Lost to follow-up
2450-1461	Timolol	Headache, photophobia
2707-1042	Timolol	Lack of efficacy
2707-1067	Timolol	Dizziness, burning sensation, eye pain
2707-1073	Timolol	Improper entry (asthma history)
2821-1437	Timolol	Lack of efficacy
2851-1194	Timolol	Improper entry (hx of restrictive ventilatory defect)
2851-1195	Timolol	Personal reasons
2974-1126	Timolol	Personal reasons
2974-1493	Timolol	Lack of efficacy
2981-1314	Timolol	Improper entry
2984-1144	Timolol	Personal reasons
2984-1594	Timolol	Conjunctival hyperemia, conjunctival folliculosis
3225-1088	Timolol	Improper entry (COPD)
3225-1508	Timolol	Pamelor use
3276-1642	Timolol	bronchitis

Demographics

Table 8 - Demographics (Intent-to-Treat) – Study 012T

		Combination (N=192)	Brimonidine (N=186)	Timolol (N=195)	P value
Age	Mean	62.8	63.8	61.9	0.266
	Std	11.43	11.78	11.91	
	Min	33	32	34	
	Max	84	89	89	
Age group					
< 45		14 (7.3%)	14 (7.5%)	20 (10.3%)	
45 - 65		87 (45.3%)	79 (42.5%)	91 (46.7%)	
> 65		91 (47.4%)	93 (50%)	84 (43.1%)	
Sex					0.246
Male		84 (43.8%)	72 (38.7%)	92 (47.2%)	
Female		108 (56.3%)	114 (61.3%)	103 (52.8%)	
Race					0.962
Caucasian		141 (73.4%)	141 (75.8%)	145 (74.4%)	
Black		34 (17.7%)	31 (16.7%)	34 (17.4%)	
Asian		3 (1.6%)	2 (1.1%)	1 (0.5%)	
Hispanic		13 (6.8%)	12 (6.5%)	15 (7.7%)	
Other		1 (0.5%)	0	0	
Iris Color					0.302
Blue		59 (30.7%)	62 (33.3%)	54 (27.7%)	
Brown		89 (46.4%)	83 (44.6%)	100 (51.3%)	
Green		6 (3.1%)	13 (7%)	5 (2.6%)	
Hazel		31 (16.1%)	24 (12.9%)	27 (13.8%)	
Black		1 (0.5%)	0	2 (1%)	
Other		6 (3.1%)	4 (2.2%)	7 (3.6%)	
Light		102 (53.1%)	103 (55.4%)	93 (47.7%)	
Dark		90 (46.9%)	83 (44.6%)	102 (52.3%)	

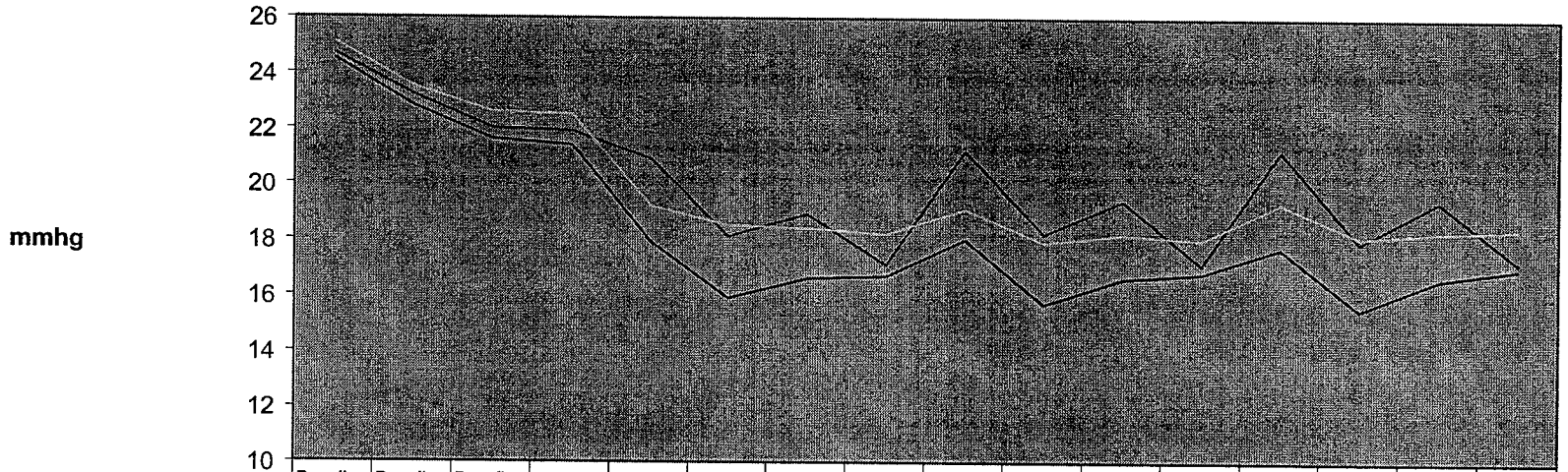
Reviewers Comments:

There were no statistical significant differences in demographics between the treatment groups.

Efficacy Analysis – Protocol 190342-012T (intent-to-treat population)

♦Efficacy Variables

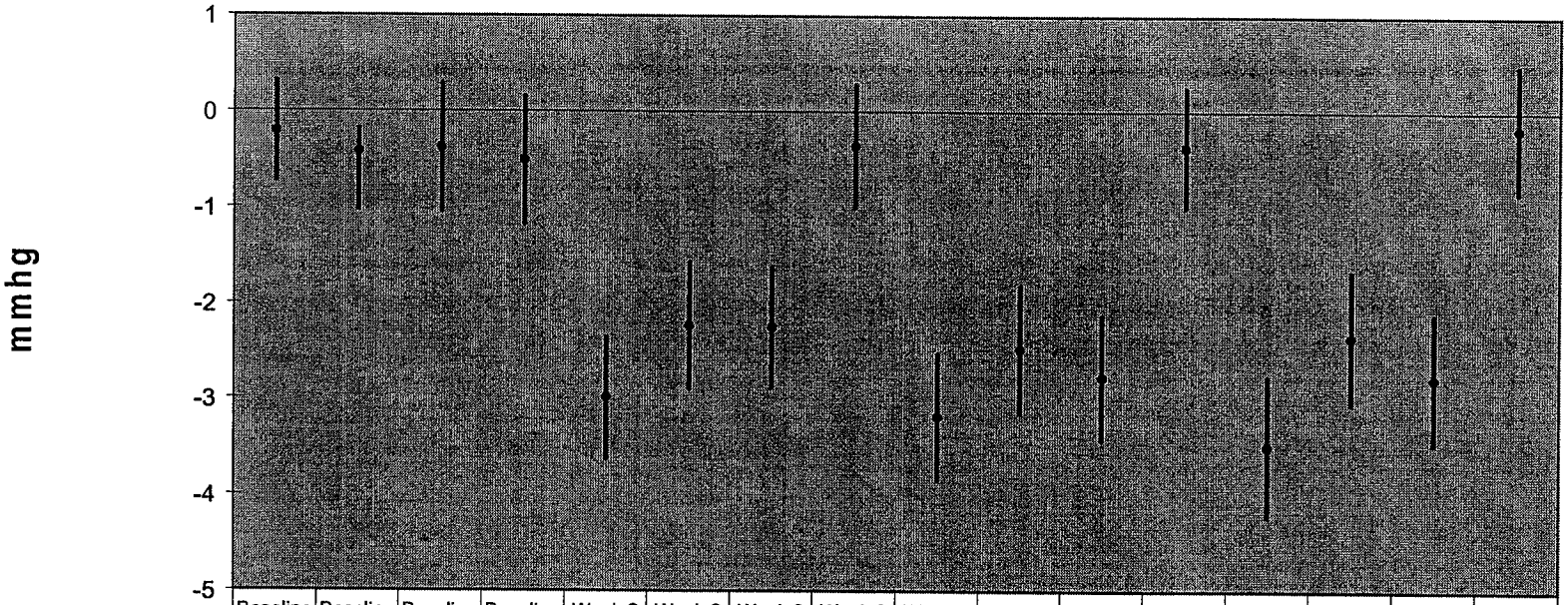
Mean Diurnal IOP - Study 012T



	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	21.6	21.4	17.9	15.9	16.6	16.7	18	15.7	16.6	16.8	17.7	15.5	16.6	17
Brimonidine 0.2%	24.7	23.2	22	21.9	20.9	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	23.5	22.6	22.5	19.2	18.5	18.4	18.2	19.1	17.9	18.2	18	19.3	18.1	18.3	18.4

Revewers Comments: *On average, the combination product lowers IOP by 6.9 mmhg (30%) at peak effect and 4.8mmhg (21%) at trough effect.*

Mean Difference (Combination - Brimonidine 0.2%) with 95% Confidence Intervals Study 012T



	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

Reviewer's Comments: *There is no statistically significant difference between the combination and brimonidine at hr 9 for week 2, week 6 and month 3. The study demonstrates a contribution from timolol 0.5% of only 2-3 mmHg at 9 of the 12 timepoints measured.*

Mean Difference (Combination - Timolol 0.5%) with 95% Confidence Intervals Study 012T

	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

Reviewer's comments: *There are significant between group differences favoring the combination at baseline. The study demonstrates a contribution from Alphagan 0.2 % of only 1-2 mmHg throughout the study.*

Adverse Events

During the initial 3 months of the study, 56.3% (108/192) of patients in the Combination group, 66.7% (124/186) of patients in the Brimonidine group, and 53.8% (105/195) of patients in the Timolol group experienced 1 or more adverse events. The overall incidence of adverse events was lower with the Combination than with Brimonidine.

Serious adverse events were reported for 0.5% (1/192) of patients in the Combination group, 3.8% (7/186) of patients in the Brimonidine group, and 3.6% (7/195) of patients in the Timolol group. There were no deaths during the initial 3 months.

Only 1 serious adverse event was ocular. An 88-year-old female was taking Brimonidine for approximately 7 weeks when she was diagnosed with worsening macular degeneration in both eyes. The patient's prestudy ophthalmic history had included macular degeneration. No treatment was performed for this condition.

Table 9– Number (%) of Patients with Adverse Events Reported by > 2% of Patients in Any Treatment Group – Study 012T

BODY SYSTEM Preferred Term	Combination N = 192	Brimonidine N = 186	Timolol N = 195
BODY AS A WHOLE			
infection	7 (3.6%)	8 (4.3%)	7 (3.6%)
headache	6 (3.1%)	8 (4.3%)	3 (1.5%)
asthenia	6 (3.1%)	7 (3.8%)	1 (0.5%)
back pain	2 (1.0%)	4 (2.2%)	1 (0.5%)
CARDIOVASCULAR			
hypertension	5 (2.6%)	5 (2.7%)	2 (1.0%)
DIGESTIVE			
oral dryness	3 (1.6%)	17 (9.1%)	1 (0.5%)
dyspepsia	2 (1.0%)	3 (1.6%)	4 (2.1%)
NERVOUS			
somnolence	4 (2.1%)	7 (3.8%)	2 (1.0%)
dizziness	4 (2.1%)	4 (2.2%)	3 (1.5%)
insomnia	1 (0.5%)	2 (1.1%)	4 (2.1%)
RESPIRATORY			
rhinitis	4 (2.1%)	2 (1.1%)	4 (2.1%)
dyspnea	1 (0.5%)	0 (0.0%)	4 (2.1%)
SPECIAL SENSES (OCULAR)			
conjunctival hyperemia	16 (8.3%)	16 (8.6%)	10 (5.1%)
burning sensation in eye	15 (7.8%)	10 (5.4%)	20 (10.3%)
visual disturbance	10 (5.2%)	5 (2.7%)	4 (2.1%)
stinging sensation eye	8 (4.2%)	3 (1.6%)	15 (7.7%)
eye pruritus	6 (3.1%)	12 (6.5%)	6 (3.1%)

BODY SYSTEM Preferred Term	Combination N = 192	Brimonidine N = 186	Timolol N = 195
corneal erosion	5 (2.6%)	4 (2.2%)	4 (2.1%)
foreign body sensation	5 (2.6%)	4 (2.2%)	2 (1.0%)
erythema eyelid	5 (2.5%)	3 (1.6%)	1 (0.5%)
blepharitis	4 (2.1%)	4 (2.2%)	2 (1.0%)
conjunctival folliculosis	3 (1.6%)	7 (3.8%)	1 (0.5%)
superficial punctate keratitis	3 (1.6%)	4 (2.2%)	0 (0.0%)
eye dryness	2 (1.0%)	5 (2.7%)	1 (0.5%)
eye pain	2 (1.0%)	3 (1.6%)	5 (2.6%)
allergic conjunctivitis	1 (0.5%)	10 (5.4%)	0 (0.0%)

Reviewer's Comments: *The adverse event profile of the combination product is similar to brimonidine and timolol.*

Table 10 - Serious Adverse Events – Study 012T

Patient Number	Treatment	Adverse Event	Discontinued from Study
1634-1583	Combination	L5 Radiculopathy	No
2232-1354	Brimonidine	Urosepsis, acute pyelonephritis	No
2707-1041	Brimonidine	Pneumonia	No
2965-1649	Brimonidine	Breast cancer	No
2974-1125	Brimonidine	Excessive Vaginal Bleeding	No
2981-1656	Brimonidine	Atypical chest pain, increased hypertension	No
3276-1479	Brimonidine	Choledocholithiasis, cholecystitis	No
3276-1526	Brimonidine	Worsening macular degeneration, toe ulceration/osteomyelitis, peripheral vascular disease	no
2027-1297	Timolol	Sick sinus syndrome, bradycardia	No
2232-1365	Timolol	Legionnaires disease	No
2707-1327	Timolol	Atherosclerosis, corotid artery disease	No
2952-1536	Timolol	Coronary artery disease, heart block	No
2981-1314	Timolol	Shortness of breath, chest pain, angina	No
2981-1447	Timolol	Unstable angina, reflux disease, conductive disease	No
3329-1274	Timolol	osteoarthritis	No

Visual Acuity

Table 11 - Visual Acuity Change from Baseline – Study 012

Visual Acuity Change (lines)	Combination (N=192)	Brimonidine (N=186)	Timolol (N=195)
≥ 2	4 (2.1%)	1 (0.5%)	1 (0.5%)
≥1 to <2	8 (4.2%)	2 (1.1%)	11 (5.7%)
>0 to <1	12 (6.3%)	7 (3.8%)	7 (3.6%)
0	68 (36%)	80 (43.2%)	98 (50.5%)
> -1 to <0	31 (16.4%)	34 (18.4%)	19 (9.8%)
>-2 to ≤-1	55 (29.1%)	51 (27.6%)	44 (22.7%)
≤-2	11 (5.8%)	10 (5.4%)	14 (7.2%)

Reviewer's Comments:

There are no statistically significant differences between the treatment groups for change in visual acuity. Over 90% of patients in each treatment group show no clinically significant change (defined as > 2 line change) in vision.

Table 12– Cup-Disc Ratio Change from Baseline at Month 3 – Study 012

Cup-Disc Ratio Change from Baseline	Combination (N=192)	Brimonidine (N=186)	Timolol (N=195)
≥0. 2	2 (1.1%)	1 (0.6%)	1 (0.5%)
≥0.1 to <0.2	3 (1.6%)	4 (2.3%)	6 (3.2%)
>0 to <0.1	14 (7.6%)	19 (10.7%)	16 (8.6%)
0	157 (85.3%)	144 (81.4%)	156 (83.9%)
> -0.1 to <0	4 (2.2%)	5 (2.8%)	4 (2.2%)
>-0.2 to ≤-0.1	4 (2.2%)	4 (2.3%)	2 (1.1%)
≤-0.2	0	0	1 (0.5%)

Reviewer's Comments:

There are no clinically significant differences between the treatment groups for change in cup-disc ratio throughout the study.

Table 13 - Visual Field Change from Baseline at Month 3 – Study 012T

Visual Field Change from Baseline	Combination (N=192)	Brimonidine (N=186)	Timolol (N=195)	Combination vs. Brimonidine P-value	Combination vs. Timolol P-value
				0.185	0.251
Patients with HVF	88	90	87		
≤-5dB	1 (1.1%)	3 (3.3%)	4 (4.6%)		
> -5dB to ≤5dB	86 (97.7%)	87 (96.7%)	82 (94.3%)		
>5dB	1 (1.1%)	0 (0.0%)	1 (1.1%)		

Reviewers Comment:
There are no statistically significant differences between the treatment groups for change in visual field.

Table 14 - Mean Pulse (beats/min) Change from Baseline at Each Scheduled Visit – Study 012T

Timepoint		Combination N=192	Brimonidine N=186	Timolol N=195	Combination vs. Brimonidine P-value	Combination vs. Timolol P-value
Baseline	hour 0	70.6	70.9	71.7		
	hour 2	71.4	71.5	71.3		
Week 2	hour 0	-3.1	0.4	-2.8	<0.001	0.731
	hour 2	-4.8	-1.1	-3.7	<0.001	0.265
Week 6	hour 0	-2.0	0	-1.0	0.006	0.939
	hour 2	-4.4	-0.5	-3.1	<0.001	0.165
Month 3	hour 0	-4.0	0	-3.0	0.007	0.657
	hour 2	-3.6	-0.6	-2.9	0.004	0.454

Reviewer's Comments:

There are statistically significant changes in pulse rate between the combination and brimonidine at each time point throughout the study. These changes do not reach clinical significance. There are no statistically significant differences between the combination and timolol throughout the study. Bradycardia was reported as an adverse event for 2 combination patients, 2 brimonidine patients and 1 timolol patient.

Blood Pressure

Reviewer's Comments:
There were no clinically significant changes in blood pressure between any of the treatment groups at any point throughout the study. Hypotension was reported as an adverse event for 1 combination patient and 2 timolol patients.

Hematology, Blood Chemistry, and Urinalysis

Reviewer's Comments:

There does not appear to be any clinically significant differences between treatment groups in the mean change from baseline to month 3 in any of the hematology, chemistry and urinalysis parameters measured.

Study 2 - Protocol 1910342-013T:

Title: Same as Protocol 190342-012T

Objective: Same as Protocol 190342-012T

Study Design: Same as Protocol 190342-012T

Test Drug Schedule: Same as Protocol 190342-012T

Clinical Sites – Study 013T

Principal Investigator (Center Number)	**Number of Subjects Enrolled**
John Brennan, MD (3219)	29
David Brodstein, MD (3283)	19
Robert Caine, MD (3376)	14
Neil Choplin, MD (1486)	22
Richard Evans, MD (2975)	35
David Gendelman, MD (3293)	8
Donald Kellum, MD (2963)	21
Wallace Landholm, MD (3523)	36
Robert Noecker, MD (2942)	24
Scott Pastor, MD (2889)	19
Aron Rose, MD (3295)	3
Michael Rotberg, MD (2037)	33
Michael Savitt, MD (3343)	13
Howard Schenker, MD (2429)	34
Elizabeth Sharpe, MD (1995)	30
John Sheppard, MD (2091)	29
Mark Sherwood, MD (2118)	33
Robert Shields, MD (1724)	21
Steven Simmons, MD (1655)	12
Alfred Solish, MD (0202)	20
Richard Sturm, MD (1587)	22
Sidney Weiss, MD (0565)	15
Jeffrey Whitsett, MD (3185)	27
Robert Williams, MD (2710)	34
Brandon Wool, MD (2835)	24

Investigator [redacted] was disqualified due to non-compliance with the investigator agreement. The primary analyses included data from this center. The analyses of IOP excluding data from this center indicated no significant impact of this site's data on the overall results of the study.

Reviewer's Comments:

The agency prefers patients to be randomized with at least ten patients per arm per center in multicenter trials so that interaction between centers can be evaluated.

Subject Disposition and Demographics

Table 15 - Subject Disposition – Study 013T

Treatment	Number of Patients Randomized (N=586)	Number of Patients Discontinued (N=84)
Combination	193	20
Brimonidine tartrate 0.2%	196	47
Timolol 0.5%	197	17

Table 16 – Discontinued Patients and Reason – Study 013T

Patient	Treatment	Reason
0057-1220	Combination	Sponsor terminated study
0057-1222	Combination	Sponsor terminated study
0057-1224	Combination	Sponsor terminated study
0202-1173	Combination	Depression
0202-1174	Combination	Conjunctival hyperemia, eye discharge, eye edema
0565-1256	Combination	Allergic conjunctivitis
0565-1262	Combination	Lack of efficacy
1486-1499	Combination	Eyelid edema, allergic conjunctivitis
1486-1506	Combination	Lack of efficacy
1724-1093	Combination	Lack of efficacy
1995-1129	Combination	Lack of efficacy
2037-1053	Combination	Improper entry – tricyclic medication
2037-1055	Combination	Lack of efficacy
2118-1312	Combination	Asthenia, chest pain, paresthesia

Patient	Treatment	Reason
2710-1245	Combination	Bronchospasm
2710-1393	Combination	Lack of efficacy
2835-1549	Combination	Allergic conjunctivitis
3185-1048	Combination	Improper entry – hx of asthma, on steroids
3185-1072	Combination	Personal reasons – family illness
3376-1545	Combination	Concomitant therapy - inhalers
0057-1217	Brimonidine	Eye pruritus
0057-1219	Brimonidine	Conjunctival hyperemia
0057-1225	Brimonidine	Sponsor terminated study
0565-1254	Brimonidine	Allergic conjunctivitis
1486-1513	Brimonidine	Lack of efficacy
1486-1518	Brimonidine	Death – pt s/p triple CABG
1486-1519	Brimonidine	Lack of efficacy
1587-1626	Brimonidine	Lack of efficacy
1724-1095	Brimonidine	Asthenia
1724-1350	Brimonidine	Personal reasons – unable to make appointments
1724-1697	Brimonidine	Allergic contact dermatitis
1995-1125	Brimonidine	Epiphora, conjunctival hyperemia, eye pruritus
1995-1127	Brimonidine	Foreign body sensation
1995-1136	Brimonidine	Lack of efficacy
1995-1397	Brimonidine	Epiphora, eyelid erythema, conjunctival hyperemia
1995-1399	Brimonidine	Lack of efficacy
2037-1059	Brimonidine	Epiphora, conjunctival folliculosis, eye pruritus, burning
2037-1342	Brimonidine	Follicular conjunctivitis
2037-1476	Brimonidine	Conjunctival folliculosis/hyperemia
2037-1483	Brimonidine	hypotension
2091-1149	Brimonidine	Peripheral edema
2429-1381	Brimonidine	Lack of efficacy
2710-1197	Brimonidine	Allergic contact dermatitis, follicular conjunctivitis
2710-1247	Brimonidine	Allergic contact dermatitis
2710-1390	Brimonidine	Lack of efficacy
2710-1392	Brimonidine	Lack of efficacy
2889-1109	Brimonidine	Improper entry – did not meet criteria for baseline visit
2942-1429	Brimonidine	Worsened visual acuity
2942-1436	Brimonidine	Conjunctival hyperemia, eye pruritus, foreign body sensation
2942-1443	Brimonidine	Conjunctival hyperemia, visual disturbance, superficial punctate keratitis
2942-1444	Brimonidine	Dyspnea
2942-1601	Brimonidine	Abdominal pain
2963-1463	Brimonidine	Somnolence
2963-1470	Brimonidine	Lost to follow-up
2975-1166	Brimonidine	Conjunctival hyperemia/folliculosis, eye edema
2975-1368	Brimonidine	Allergic conjunctivitis

Patient	Treatment	Reason
3219-1008	Brimonidine	Improper entry – previous laser iridotomy
3219-1359	Brimonidine	Non-compliance: unwilling to come for study visits
3343-1586	Brimonidine	Rhinitis, epiphora conjunctival hyperemia, eye pain/pruritus
3376-1535	Brimonidine	Improper entry – hx of asthma
3376-1543	Brimonidine	Improper entry – IOP to low at entry
3523-1653	Brimonidine	Allergic conjunctivitis
3523-1659	Brimonidine	Lack of efficacy
3523-1661	Brimonidine	Allergic conjunctivitis
3523-1678	Brimonidine	Allergic conjunctivitis
3523-1752	Brimonidine	Allergic conjunctivitis
3523-1755	Brimonidine	Lack of efficacy
0057-1218	Timolol	Personal reasons
0057-1221	Timolol	Sponsor terminated study
0057-1223	Timolol	Lost to follow-up
1587-1620	Timolol	Eye burning, visual disturbance
1995-1128	Timolol	Emphysema
2118-1269	Timolol	Personal reasons
2118-1310	Timolol	Tachycardia, nausea, sweating
2429-1036	Timolol	Splenomegaly
2429-1298	Timolol	Personal reasons – unable to make diurnal appointments
2429-1490	Timolol	Erythema, hyperemia, burning, foreign body sensation
2835-1556	Timolol	Personal reasons – unable to come to daytime visits
3185-1062	Timolol	Personal reasons – withdrew consent
3185-1069	Timolol	Lost to follow-up
3219-1283	Timolol	Lack of efficacy
3293-1016	Timolol	Lack of efficacy
3293-1020	Timolol	Improper entry
3295-1205	Timolol	Herpes zoster

Demographics

Table 17 - Demographics (Intent-to-Treat) – Study 013T

		Combination (N=193)	Brimonidine (N=196)	Timolol (N=197)	P-value
Age	Mean	61.2	63.8	62.2	0.125
	Std	13.16	11.81	12.62	
	Min	23	28	26	
	Max	86	86	87	
Age group					
< 45		26 (13.5%)	18 (9.2%)	19 (9.6%)	
45 - 65		91 (47.2%)	75 (38.3%)	90 (45.7%)	
> 65		76 (39.4%)	103 (52.6%)	88 (44.7%)	
Sex					0.123
Male		97 (50.3%)	79 (40.3%)	94 (47.7%)	
Female		96 (49.7%)	117 (59.7%)	103 (52.3%)	
Race					0.069
Caucasian		149 (77.2%)	163 (83.2%)	140 (71.1%)	
Black		25 (13%)	24 (12.2%)	39 (19.8%)	
Asian		1 (0.5%)	0	4 (2%)	
Hispanic		17 (8.8%)	8 (4.1%)	13 (6.6%)	
Other		1 (0.5%)	1 (0.5%)	1 (0.5%)	
Iris Color					0.161
Blue		67 (34.7%)	60 (30.6%)	62 (31.5%)	
Brown		81 (42%)	88 (44.9%)	102 (51.8%)	
Green		13 (6.7%)	9 (4.6%)	7 (3.6%)	
Hazel		27 (14%)	33 (16.8%)	21 (10.7%)	
Black		1 (0.5%)	0	0	
Other		4 (2.1%)	6 (3.1%)	5 (2.5%)	
Light		111 (57.5%)	108 (55.1%)	95 (48.2%)	
Dark		82 (42.5%)	88 (44.9%)	102 (51.8%)	

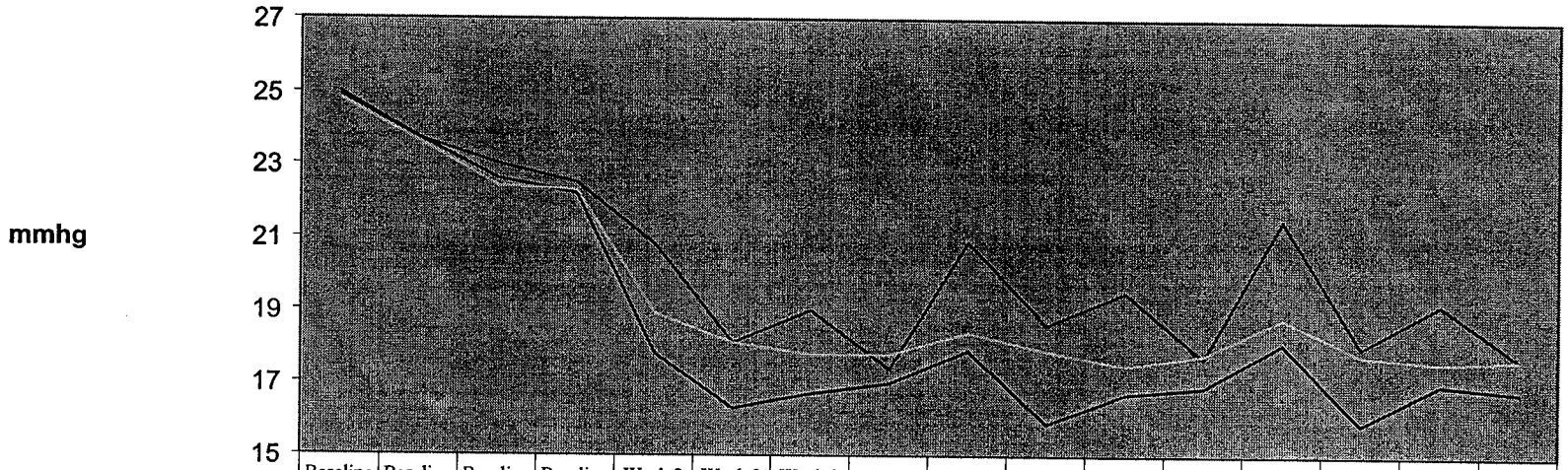
Reviewers Comments:

There were no statistical significant differences in demographics between the treatment groups.

Efficacy Analysis – Protocol 190342-013T (intent-to-treat population)

♦Efficacy Variables

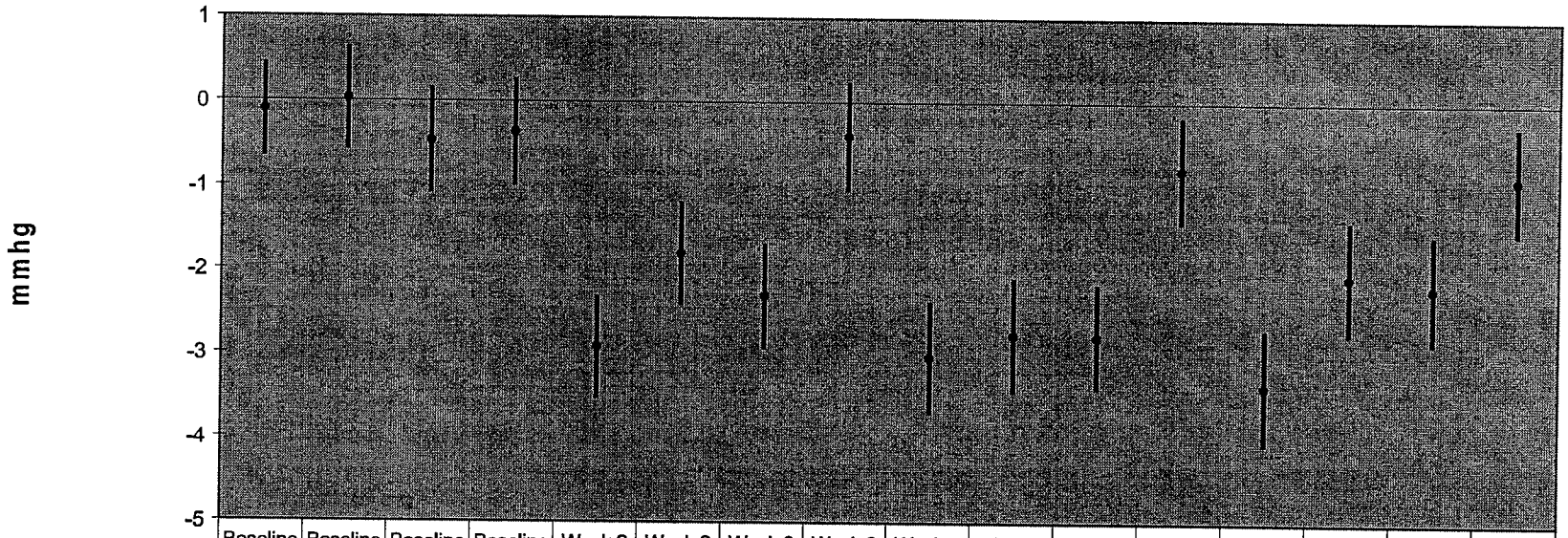
Mean Diurnal IOP - Study 013T



	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

Reviewer's comments:. *On average, the combination product lowers IOP by 7.7 mmhg (32%) at peak effect and 5.8 mmhg (25%) at trough effect.*

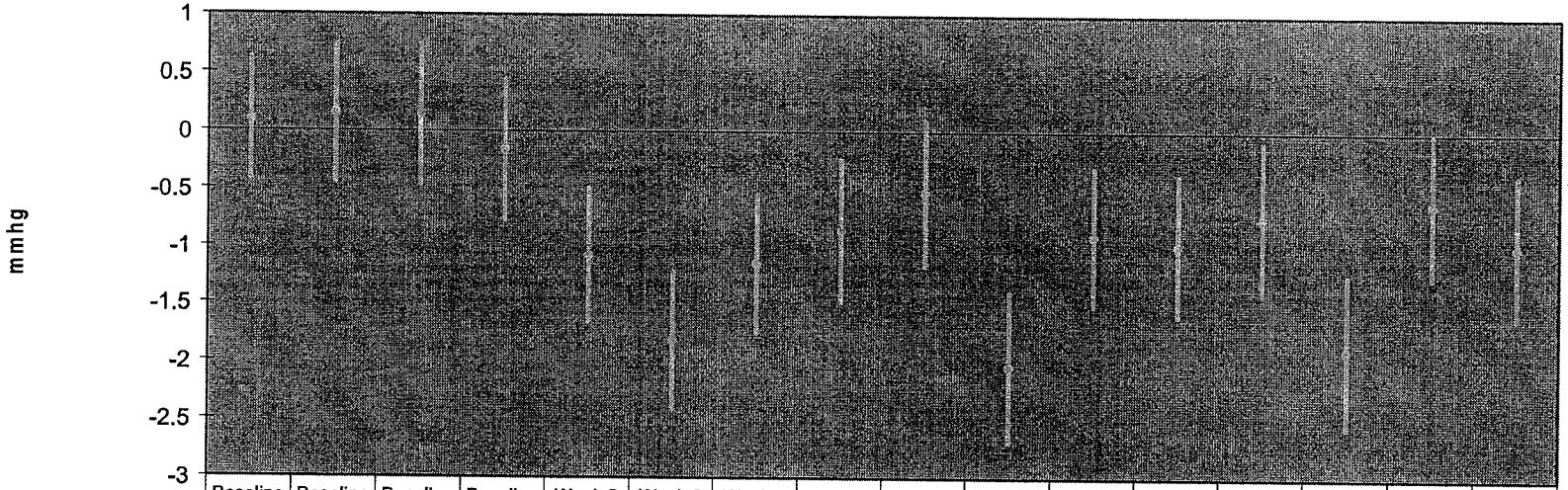
Mean Difference (Combination - Brimonidine 0.2%) with 95% Confidence Intervals Study 0.13T



	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

Reviewer's Comments: *The difference between the combination and brimonidine is not statistically significant at week 2, hour 9. The study demonstrates a contribution from timolol 0.5% of only 1-3 mmHg for the majority of timepoints measured.*

Mean Difference (Combination - Timolol 0.5%) with 95% Confidence Interval
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)
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

Reviewer's comments: *The study demonstrates a contribution from Alphagan 0.2 % of only 0.5-2 mmHg throughout the study.*

Adverse Events

Table 18 – Number (%) of Patients with Adverse Events Reported by > 2% of Patients in Any Treatment Group – Study 013T

BODY SYSTEM Preferred Term	Combination N = 193	Brimonidine N = 196	Timolol N = 197
BODY AS A WHOLE			
infection	11 (5.7%)	6 (3.1%)	8 (4.1%)
asthenia	3 (1.6%)	6 (3.1%)	1 (0.5%)
CARDIOVASCULAR			
hypertension	5 (2.6%)	2 (1.0%)	3 (1.5%)
DIGESTIVE			
oral dryness	2 (2.1%)	19 (9.7%)[a]	1 (0.5%)
NERVOUS			
depression	4 (2.1%)	1 (0.5%)	0
somnolence	2 (1.0%)	7 (3.6%)	0
SPECIAL SENSES (OCULAR)			
burning sensation in eye	23 (11.9%)	11 (5.6%)[b]	25 (12.7%)
conjunctival hyperemia	16 (8.3%)	23 (11.7%)	11 (5.6%)
stinging sensation eye	13 (6.7%)	4 (2.0%)b	11 (5.6%)
visual disturbance	6 (3.1%)	11 (5.6%)	3 (1.5%)
epiphora	5 (2.6%)	8 (4.1%)	3 (1.5%)
eye dryness	5 (2.6%)	4 (2.0%)	1 (0.5%)
eye discharge	5 (2.6%)	1 (0.5%)	0[b]
blepharitis	4 (2.1%)	3 (1.5%)	1 (0.5%)
corneal erosion	4 (2.1%)	2 (1.0%)	1 (0.5%)
eye pruritus	3 (1.6%)	13 (6.6%)[a]	3 (1.5%)
allergic conjunctivitis	3 (1.6%)	7 (3.6%)	0
foreign body sensation	2 (1.0%)	10 (5.1%)[a]	5 (2.5%)
conjunctival folliculosis	2 (1.0%)	9 (4.6%)[a]	1 (0.5%)
eye pain	2 (1.0%)	4 (2.0%)	2 (1.0%)

a incidence with combination lower than with monotherapy
b incidence with combination higher than with monotherapy

Reviewer's comments:
There is no increase risk of adverse events associated with the combination product over its individual ingredients.

Table 19 - Serious Adverse Events – Study 013T

Patient Number	Treatment	Adverse Event	Discontinued from Study
0202-1173	Combination	Depression	Yes
3523-1664	Combination	Prostate carcinoma	No
1486-1518	Brimonidine	Death/right heart failure	Yes
1655-1335	Brimonidine	Abdominal pain	No
2710-1390	Brimonidine	Accidental injury (left knee)	No
2942-1604	Brimonidine	Coronary artery disease	No
0202-1169	Timolol	Kidney calculus	No
1995-1128	Timolol	Emphysema	Yes
2118-1310	Timolol	Nausea/sweating/tachycardia	Yes
2429-1036	Timolol	splenomegaly	Yes

Visual Acuity

Table 20 - Visual Acuity Change from Baseline – Study 013T

Visual Acuity Change (lines)	Combination (N=193)	Brimonidine (N=196)	Timolol (N=197)
≥ 2	2 (1.0%)	0	1 (0.5%)
≥1 to <2	12 (6.2%)	10 (5.1%)	8 (4.1%)
>0 to <1	10 (5.2%)	7 (3.6%)	10 (5.1%)
0	97 (50.3%)	99 (50.8%)	95 (48.2%)
> -1 to <0	25 (13.0%)	19 (9.7%)	21 (10.7%)
>-2 to ≤-1	39 (20.2%)	41 (21.0%)	47 (23.9%)
≤-2	8 (4.1%)	19 (9.7%)	15 (7.6%)

Reviewer's Comments:

There are no statistically significant differences between the treatment groups for change in visual acuity. Over 90% of patients in each treatment group show no clinically significant change (defined as > 2 line change) in vision.

Table 21– Cup-Disc Ratio Change from Baseline at Month 3 – Study 013T

Cup-Disc Ratio Change from Baseline	Combination (N=193)	Brimonidine (N=196)	Timolol (N=187)
≥0. 2	1 (0.5%)	1 (0.5%)	2 (1.1%)
≥0.1 to <0.2	0	0	1 (0.5%)
>0 to <0.1	5 (2.6%)	7 (3.8%)	8 (4.3%)
0	178 (94.2%)	170 (91.4%)	169 (90.4%)
> -0.1 to <0	0	1 (0.5%)	2 (1.1%)
>-0.2 to ≤-0.1	4 (2.1%)	6 (3.2%)	3 (1.6%)
≤-0.2	1 (0.5%)	1 (0.5%)	2 (1.1%)

Reviewer's Comments:

There are no clinically significant differences between the treatment groups for change in cup-disc ratio throughout the study.

Table 22 - Visual Field Change from Baseline at Month 3 – Study 013T

Visual Field Change from Baseline	Combination (N=193)	Brimonidine (N=196)	Timolol (N=197)	Combination vs. Brimonidine P-value	Combination vs. Timolol P-value
				0.159	0.659
≤-5dB	1 (1.5%)	0	3 (4.3%)		
> -5dB to ≤5dB	67 (98.5%)	72 (98.6%)	66 (94.3%)		
>5dB	0	1 (1.4%)	1 (1.4%)		

Reviewers comment:
There are no statistically significant differences between the treatment groups for change in visual field.

Table 23- Mean Pulse (beats/min) Change from Baseline at Each Scheduled Visit – Study 013T

Timepoint		Combination N = 193	Brimonidine N = 196	Timolol N = 197	Combination vs. Brimonidine P-value	Combination vs. Timolol P-value
Baseline	hour 0	71.8	71.9	71.6		
	hour 2	71.5	70.2	70.6		
Week 2	hour 0	-2.2	-1.7	-2.0	0.601	0.759
	hour 2	-2.4	0	-2.4	0.007	0.975
Week 6	hour 0	-3.2	-1.2	-2.8	0.036	0.703
	hour 2	-3.7	-0.1	-3	<0.001	0.454
Month 3	hour 0	-2.6	-1.8	-3.2	0.437	0.543
	hour 2	-2.1	1.0	-2.9	0.002	0.410

Reviewer's Comments:

There are no clinically significant differences in mean pulse rate between the three treatment groups at any time point. Bradycardia was reported as an adverse event for 1 patient on combination treatment. The event was ongoing at three months.

Blood Pressure

Reviewer's Comments:
There were no clinically significant changes in blood pressure between any of the treatment groups at any point throughout the study. Hypotension was reported as an adverse event for 1 patient on brimonidine therapy and was discontinued from the study.

Hematology, Blood Chemistry, and Urinalysis

Reviewer's Comments:

There does not appear to be any clinically significant differences between treatment groups in the mean change from baseline to month 3 in any of the hematology, chemistry and urinalysis parameters measured.

VII. Integrated Review of Safety

Table 24 – Number (%) of Patients with Adverse Events Reported by > 2% of Patients in Any Treatment Group in the Pooled Phase 3 Studies 012T and 013T

BODY SYSTEM Preferred Term	Combination N = 385	Brimonidine N = 382	Timolol N = 392
BODY AS A WHOLE			
infection	18 (4.7%)	14 (3.7%)	15 (3.8%)
asthenia	9 (2.3%)	13 (3.4%)	2 (0.5%)[b]
headache	8 (2.1%)	11 (2.9%)	5 (1.3%)
CARDIOVASCULAR			
hypertension	10 (2.6%)	7 (1.8%)	5 (1.3%)
DIGESTIVE			
oral dryness	7 (1.8%)	36 (9.4%)[a]	2 (0.5%)
NERVOUS			
somnolence	6 (1.6%)	14 (3.7%)	2 (0.5%)
SPECIAL SENSES (OCULAR)			
burning sensation in eye	38 (9.9%)	21 (5.5%)[b]	45 (11.5%)
conjunctival hyperemia	32 (8.3%)	39 (10.2%)	21 (5.4%)
stinging sensation eye	21 (5.5%)	7 (1.8%)[b]	26 (6.6%)
visual disturbance	16 (4.2%)	16 (4.2%)	7 (1.8%)
eye pruritus	9 (2.3%)	25 (6.5%)[a]	9 (2.3%)
corneal erosion	9 (2.3%)	6 (1.6%)	5 (1.3%)
blepharitis	8 (2.1%)	7 (1.8%)	3 (0.8%)
foreign body sensation	7 (1.8%)	14 (3.7%)	7 (1.8%)
epiphora	7 (1.8%)	10 (2.6%)	5 (1.3%)
eye dryness	7 (1.8%)	9 (2.4%)	2 (0.5%)
conjunctival folliculosis	5 (1.3%)	16 (4.2%)[a]	2 (0.5%)
allergic conjunctivitis	4 (1.0%)	17 (4.5%)a	0

a incidence with the Combination was lower than with monotherapy
b incidence with the Combination was higher than with monotherapy

Reviewers Comments:

There are no new safety concerns related to the combination product as compared to its individual components. It would be expected that the combination would have a similar safety profile compared to when its individual ingredients are used together.

VIII. Dosing, Regiment, and Administration Issues

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 which 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.

IX. Use in 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 can be used with caution in patients between 3 and 7.

X. Conclusions and Recommendations

A. Conclusions

1) *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. Major concerns raised in the submitted phase three trials are related to the failure to adequately show that each component makes a contribution to the claimed affect:*

Brimonidine contribution issues:

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

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

c) *The difference in the mean IOP lowering effect of the combination versus timolol 0.5% is not statistically significant in 2/12 timepoints in study 013T.*

d) *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.*

Timolol contribution issue:

a) *The difference in the mean IOP lowering effect of the combination versus brimonidine tartrate 0.2% is not statistically significant in 3/12 timepoints in study 012T and 1/12 timepoints in study 013T.*

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

2) *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.*

B. Recommendation:

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

Jennifer D. Harris, M.D.
Medical Officer, Ophthalmology

cc:
Original NDA 21-398
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/Chem/Tso
HFD-550/PM/Puglisi
HFD-550/Pharm/ZChen
HFD-550/Stat/Lin
HFD-550/PK/Bashaw
HFD-340/Carreras
HFD-550/SMO/Chambers
HFD-550/Div Dir/Simon

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 01:28:24 PM
MEDICAL OFFICER

Wiley Chambers
3/21/02 11:54:46 AM
MEDICAL OFFICER