Reference 45

MRL Clinical Study Report, Multicenter Study: A Randomized, Double-Masked, Parallel Study Comparing the 0.5% Timolol/2.0% MK–0507 Combination Ophthalmic Solution to the Concomitant Adminstration of 0.5% Timolol Ophthalmic Solution and 2.0% MK–0507 Ophthalmic Solution (Protocol 043).

CLINICAL STUDY REPORT

MK-0507A

A RANDOMIZED, DOUBLE-MASKED, PARALLEL STUDY COMPARING THE 0.5% TIMOLOL/2.0% MK-0507 COMBINATION OPHTHALMIC SOLUTION TO THE CONCOMITANT ADMINISTRATION OF 0.5% TIMOLOL OPHTHALMIC SOLUTION AND 2% MK-0507 OPHTHALMIC SOLUTION

(PROTOCOL NO. 043)

I. SYNOPSIS

II. COMPREHENSIVE STUDY SUMMARY

III. APPENDICES

CLINICAL STUDY REPORT

A Randomized, Double-Masked, Parallel Study Comparing the 0.5% Timolol/2.0% MK–0507 Combination Ophthalmic Solution to the Concomitant Administration of 0.5% Timolol Ophthalmic Solution and 2% MK–0507 Ophthalmic Solution

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MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

MK-0507A, Timolol/
MK-0507 Combination
Ophthalmic Solution

PROTOCOL TITLE/NO.: A Randomized, Double-Masked, Parallel Study Comparing the 0.5% Timolol/2.0% MK-0507 Combination Ophthalmic Solution to the Concomitant Administration of 0.5% Timolol Ophthalmic Solution and 2% MK-0507 Ophthalmic Solution #043

INVESTIGATOR(S)/STUDY CENTERS: Multicenter study, 19 investigators in the U.S.

PUBLICATIONS: Adamsons I, Anderson K, Strohmaier K, Clineschmidt CM. Three-month results of a clinical trial comparing 0.5% timolol/2.0% MK-507 combination to concomitant use of 0.5% timolol and 2.0% MK-507. Invest Ophthalmol Vis Sci 1995;36(4):S735. Clineschmidt CM, Strahlman ER, Anderson K and the Timolol/MK-507 Combination Study Group. Comparison of a fixed combination of dorzolamide and timolol (b.i.d.) to concomitant administration of dorzolamide (t.i.d.) plus timolol (b.i.d.) in patients with open-angle glaucoma for three months. Invest Ophthalmol Vis Sci 1995;36(4):5736. Strohmaier K, Snyder E, and Adamsons I. Long-term safety and efficacy of COSOPT, a fixed combination of dorzolamide and timolol. Invest Ophthalmol Vis Sci 1996;37(3):S1102.

PRIMARY THERAPY PERIOD: 4/93 through 2/95; study completed; in-house CRF cutoff 4/17/95

CLINICAL PHASE: III

DURATION OF TREATMENT: Three months of double-masked therapy followed by 9 months of open-label therapy.

OBJECTIVES: (1) To compare the IOP-lowering effect of the 0.5% timolol/2.0% MK-0507 combination administered b.i.d. to that of the concomitant administration of 0.5% timolol b.i.d. plus 2.0% MK-0507 t.i.d. for up to 3 months. (2) To compare the safety profile of the 0.5% timolol/2.0% MK-0507 combination to that of its components administered concomitantly in their usual monotherapy dose regimens over a 3-month period. (3) To evaluate the tolerability and the IOP-lowering effect of 0.5% timolol/2.0% MK-0507 after 1 year of treatment.

STUDY DESIGN: Parallel, randomized, double-masked, active-controlled, multicenter study followed by an open-label extension.

PATIENT ACCOUNTING:

	Total	Combination	Concomitant
ENTERED: Total	242	121	121
Male (Age Range)	121 (22-84)	50 (22-79)	71 (30-84)
Female (Age Range)	121 (25-82)	71 (29-81)	50 (25-82)
Three-Month Double-Masked Phase			
COMPLETED:	220	107	113
DISCONTINUED: Total	22	14	8
Clinical Adverse Experience	10	7	3
Laboratory Adverse Experience	0	0	0
Therapy Ineffective	8	5	3
Other	4	2	2

PATIENT ACCOUNTING (CONT.):

Nine-Month Open-Label Phase

	Total	Combination	Concomitant
Patients at Start of Phase*	220	107	113
COMPLETED:	203	99	104
DISCONTINUED: Total	17	8	9
Clinical Adverse Experience	9	6	3
Laboratory Adverse Experience	0	0	0
Therapy Ineffective	3	2	1
Other	5	0	5

*Number of patients entering the open-label phase based on their treatment group in the double-masked phase. All patients received the 0.5% timolol/2.0% MK-0507 combination during the open-label phase.

DOSAGE/FORMULATION NOS.:

The drug regimens used in this study were as follows: 0.5% timolol/2.0% MK-0507 b.i.d. (0507AESS001A002), 0.5% timolol b.i.d. (0950ESS004C060, 0950ESS004C069, and 0927W), 2.0% MK-0507 t.i.d. (0507ESS001A005 and 0507ESS001A006), and placebo t.i.d. (P0507ESS001P005 and P0507ESS001P003).

DIAGNOSIS/INCLUSION CRITERIA: Males or postmenopausal or sterilized females between 21 and 85 years of age with open-angle glaucoma or ocular hypertension in both eyes. After 2 weeks on 0.5% timolol b.i.d., baseline IOP was required to be ≥22 mm Hg in at least one eye (the same eye) immediately before the morning dose (Hour 0) and 2 hours later (Hour 2).

EVALUATION CRITERIA: Intraocular pressure (IOP) was measured at Hours 0, 2 and 8 on Day 1 (baseline) and on Days 15, 30, 60, and 90 (double-masked phase); IOP was measured at Hours 0 and 2 on Days 180, 270, and 365 (open-label phase). The primary efficacy parameter was the mean change in IOP from the time-matched baseline value in the worse eye. Safety was evaluated by monitoring patients for clinical and laboratory adverse experiences, ocular signs and symptoms, and changes in visual acuity, visual field, cup/disc ratio, and physical examination.

STATISTICAL PLANNING AND ANALYSIS: Efficacy: Ocular hypotensive effect was assessed using absolute change in intraocular pressure from the time-matched baseline values (morning trough, morning peak, or afternoon peak) using the patient's worse eye. The two treatment groups were compared to determine whether they are equivalent in their ability to reduce IOP. Treatment equivalence was defined as a 95.0% or greater confidence (probability) that the treatment-group difference in mean IOP change from baseline is within the interval -1.5 mm Hg to 1.5 mm Hg. A sample size of 120 patients per treatment group will provide a 0.79 probability of concluding that the absolute difference between mean change in IOP for the treatment groups is <1.5 mm Hg when there is truly no difference. This calculation assumes a standard deviation of 4.0 mm Hg. The primary determination of treatment equivalence was based on an average of the observed Month 2 and Month 3 data at afternoon peak (8 hours after the morning dose).

STATISTICAL PLANNING AND ANALYSIS (CONT.)

Safety: All patients who received study medication were included in the evaluation of clinical adverse experiences and laboratory adverse experiences. Ocular signs and symptoms, visual acuity, visual field defects, cup-to-disc ratio, blood pressure and pulse, and laboratory safety measurements were also evaluated. Treatment-group comparisons with regard to incidence of adverse experiences, ocular signs and symptoms, and visual field defects were made using Fisher's exact test (two-tailed).

All p-values were rounded to three decimal places, and statistical significance was declared if the rounded p-value was less than or equal to 0.050.

RESULTS:

Efficacy

During the double-masked phase, the mean change in IOP from baseline ranged from -3.1 mm Hg to -5.0 mm Hg for the combination group and from -3.9 mm Hg to -5.2 mm Hg for the concomitant therapy group. There is 97.1% confidence that the difference between treatment-group means at Hour 8 is within -1.5 mm Hg and 1.5 mm Hg. The point estimate for the treatment difference is -0.73 mm Hg, indicating that the IOP reduction was greater on average in the concomitant therapy group than in the combination group at Hour 8. IOP estimates and confidence levels for the difference between treatments at Hours 0, 2, and 8 are shown below.

IOP Estimates and Confidence Levels for Difference Between Treatments (mm Hg) --
Mean Change in IOP from Baseline Averaged over Month 2 and Month 3 Visit†

Exam	Sample Size Combination	Sample Size Concomitant	Difference Between Treatments	Standard Error of Difference	95% Conf. Int. for Diff. Between Means	Confidence Diff. Lies Between -1.5 and 1.5
Hour 0	112	116	-0.67 mm Hg	0.37	(-1.41, 0.06)	0.986*
Hour 2	112	115	-0.05 mm Hg	0.39	(-0.81, 0.71)	>0.999*
Hour 8	110	114	-0.73 mm Hg	0.41	(-1.53, 0.07)	0.971*

* = The confidence is 0.950 or more that the difference between treatment means lies between -1.5 and 1.5 mm Hg.

† All-Patients-Treated Analysis (Observed Cases) -- Worse Eye.
The difference between treatments (Concomitant-Combination) is a weighted average of the mean difference within each clinic based on the number of patients entered at each clinic.

Combination = 0.5% timolol/2.0% MK-0507 fixed combination b.i.d.
Concomitant = 0.5% timolol b.i.d. plus 2.0% MK-0507 t.i.d.

Among the 105 patients who received the combination in both phases of the study, the mean change in IOP from baseline (Day 1) during the open-label phase ranged from -3.8 to -3.5 mm Hg at Hour 0 and from -5.4 to -5.0 mm Hg at Hour 2; these changes were similar in magnitude to the mean change from baseline observed at Month 3 in this group (-3.8 mm Hg at Hour 0; -5.1 mm Hg at Hour 2). In addition, when patients who switched from the concomitant group to the combination are compared with those who continued on the combination, the confidence is >98% that the treatment groups are equivalent at Hour 0 and Hour 2 at Months 6, 9 and 12.

Safety

A clinical adverse experience summary is shown below. Of the 242 patients in the double-masked phase, 73 (30%) had a clinical adverse experience. Three patients (all in the combination group) had serious clinical adverse experiences, none of which was considered

RESULTS (CONT.):

drug related. One patient died of pneumonia that was considered definitely not drug related. Of the 220 patients in the open-label phase, 101 (46%) had a clinical adverse experience. Twenty-six of these patients had serious clinical adverse experiences; 2 patients died as the result of their adverse experiences. One patient died of colon and liver cancer that was considered probably not drug related. The other patient died from complications secondary to subarachnoid hemorrhage that was considered probably not drug related. One serious adverse experience (urolithiasis) was considered drug related (possibly); this patient recovered without treatment and completed the study with no further problems.

Clinical Adverse Experience Summary

	Combination		Concomitant	
Number (%) of Patients	No.	(%)	No.	(%)
Double-Masked Phase				
Patients evaluated	121		121	
With any adverse experience	41	(34)	32	(26)
Drug-related adverse experience†	12	(10)	12	(10)
Serious adverse experience	3	(2)	0	(0)
Patients who died	1	(1)	0	(0)
Discontinued due to adverse experience	7	(6)	3	(2)
Open-Label Phase				
Patients evaluated	220			
With any adverse experience	101	(46)		
Drug-related adverse experience†	14	(6)		
Serious adverse experience	26	(12)		
Patients who died	2	(1)		
Discontinued due to adverse experience	9	(4)		

Combination group is 0.5% timolol/2.0% MK-0507 fixed combination (b.i.d.)
Concomitant group is 0.5% timolol (b.i.d.) plus 2.0% MK-0507 (t.i.d.)
†Drug-related implies possibly, probably, or definitely caused by the test drug.

Laboratory adverse experiences occurred in 10 (4%) of the 236 patients evaluated during the double-masked phase: 5 (4%) in the combination group and 5 (4%) in the concomitant group. Three patients in the combination group had drug-related laboratory adverse experiences: increased leukocyte count, decreased RBC count, and decreased serum bicarbonate in 1 patient each. During the open-label phase, laboratory adverse experiences occurred in 11 (5%) of the 211 patients evaluated and were considered drug related in two: crystalluria and oxaluria in 1 patient each. None of the laboratory adverse experiences in either phase was considered serious or caused the patient to discontinue the study.

CONCLUSIONS: In the treatment of elevated IOP in patients with glaucoma or ocular hypertension: (1) The IOP-lowering effect of the 0.5% timolol/2.0% MK-0507 fixed combination administered b.i.d. is equivalent to that of the concomitant administration of 0.5% timolol b.i.d. and 2.0% MK-0507 t.i.d. for up to 3 months. (2) The IOP-lowering effect of 0.5% timolol/2.0% MK-0507 is maintained for up to 1 year. (3) The fixed combination of 0.5% timolol/2.0% MK-0507 is generally well tolerated compared to concomitant administration of 0.5% timolol given b.i.d. and 2.0% MK-0507 given t.i.d. (4) The 0.5% timolol/2.0% MK-0507 fixed combination is generally well tolerated for up to 1 year.

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II. COMPREHENSIVE STUDY SUMMARY

A. BACKGROUND

Timolol ophthalmic solution, which contains the β-blocker timolol maleate, is the most commonly prescribed ocular hypotensive agent for the treatment of glaucoma. However, since glaucoma is a chronic progressive disease, the majority of patients eventually require additional medication for control of intraocular pressure (IOP). Many second-line agents (pilocarpine, epinephrine, and oral carbonic anhydrase inhibitors) have side effects that limit their use in many patients. MK-0507 (dorzolamide), Merck's topical carbonic anhydrase inhibitor, offers potential advantages over these agents.

As part of the MK-0507 Phase II program, a 1-week, placebo-controlled, pilot additivity study was undertaken in 31 patients [2.1.1][1]. This study assessed the degree of additional IOP lowering activity of 2.0% MK-0507 given b.i.d. (twice daily) to patients whose late-morning IOP measurements were ≥22 mm Hg while receiving 0.5% timolol b.i.d. The results indicated a clinically significant additive effect ranging from a 13% to 21% reduction in IOP.

To confirm these results, a large-scale Phase III trial was initiated to investigate the IOP-lowering activity of MK-0507 b.i.d. when added to 0.5% timolol b.i.d. This was a 2-week, randomized, double-masked study comparing MK-0507 to pilocarpine and to placebo, followed by a 6-month extension comparing MK-0507 to pilocarpine [2.1.2]. During the placebo-controlled phase of the study, the IOP-lowering effect of 2.0% MK-0507 b.i.d. was comparable to that of 2.0% pilocarpine q.i.d. (four times daily) and was significantly greater than that of placebo when added to 0.5% timolol. During the extension phase of this study, the IOP-lowering effect of 2.0% MK-0507 b.i.d. was maintained for 6 months and was again comparable to that of 2.0% pilocarpine q.i.d. when added to 0.5% timolol.

Formulated as a combination product, MK-0507 plus timolol would provide a more convenient dosing regimen for patients whose IOP is not controlled by timolol alone. In these patients, b.i.d. administration of the timolol/MK-0507 combination would replace the use of two separate products.

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[1] Refer to F. List of Appendices. Within a bracket, the first number refers to an Appendix Category, the second number refers to an Appendix within that Category, and the third number (optional) refers to a document within the Appendix, e.g., [1.1.3] = Appendix Category 1, Appendix 1, Document No. 3.

A. BACKGROUND (CONT.)

The first human study of the timolol/MK-0507 combination was a 2-week, double-masked, ocular tolerability study in 15 normal volunteers [2.1.3]. Ten subjects received the 0.5% timolol/2.0% MK-0507 combination and the remaining 5 received placebo. Stinging, burning and tearing were the side effects reported most frequently among patients receiving the timolol/MK-0507 combination. Hyperemia and corneal staining were the most frequent signs noted. The only significant difference between the treatment groups was a greater frequency of stinging on Day 1 among subjects receiving the timolol/MK-0507 combination. Thus, the timolol/MK-0507 combination was generally well tolerated as compared to placebo.

This study was designed to assess whether the timolol/MK-0507 combination is as efficacious in lowering IOP as the concomitant administration of both of its component drugs. Therefore, 2.0% MK-0507 was administered t.i.d. (three times daily) when given concomitantly with 0.5% timolol b.i.d. in order to compare the timolol/MK-0507 combination to its components given according to their respective monotherapy dosage regimens. This concomitant regimen reflects the approved dosage for adjunctive use of dorzolamide in the U.S.; however, in other countries, dorzolamide may be administered b.i.d. when used as adjunctive therapy with an ophthalmic beta-blocker.

B. SUMMARY OF PROTOCOL AND STUDY PROCEDURES

1. Protection of Human Subjects

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

For copies of the Ethical Review Committee Approval letters, see [3.6].

2. Investigators

Nineteen investigators participated in this study at 19 sites in the United States [3.5]. For the curricula vitae of the primary investigators, see [3.7].

3. Hypotheses and Objectives

a. Hypotheses

1) The 0.5% timolol/2.0% MK-0507 combination, administered b.i.d., will have an IOP-lowering effect equivalent (within 1.5 mm Hg) to that of the concomitant administration of its components (i.e., 0.5% timolol administered b.i.d. plus 2.0% MK-0507 administered t.i.d.) for up to 3 months.

2) The 0.5% timolol/2.0% MK-0507 combination will have a safety profile comparable to that of its components administered concomitantly over a 3-month period.

3) The tolerability and IOP-lowering effect of 0.5% timolol/2.0% MK-0507 will be maintained through 1 year of treatment.

b. Objectives

1) To compare the IOP-lowering effect of the 0.5% timolol/2.0% MK-0507 combination administered b.i.d. to that of the concomitant administration of 0.5% timolol b.i.d. plus 2.0% MK-0507 t.i.d. for up to 3 months.

2) To compare the safety profile of the 0.5% timolol/2.0% MK-0507 combination to that of its components administered concomitantly in their usual monotherapy dose regimens over a 3-month period.

3) To evaluate the tolerability and the IOP-lowering effect of 0.5% timolol/2.0% MK-0507 after 1 year of treatment.

4. Patient Selection

a. Inclusion Criteria

This study was conducted in male or female (postmenopausal or sterilized) patients 21 to 85 years of age with open-angle glaucoma or ocular hypertension in both eyes. Patients also had a baseline IOP of ≥22 mm Hg in at least one eye (the same eye) at Hours 0 and 2 on Day 1 after receiving 0.5% timolol b.i.d. alone for 2 weeks.

b. Exclusion Criteria

Ocular

1) Best corrected distance Snellen visual acuity worse than 20/80 in both eyes.

4. **Patient Selection (Cont.)**

2) Contact lens use within 3 weeks of study start or during the study.

3) History or evidence of clinically significant dry eye syndrome.

4) History or evidence of intraocular surgery, significant ocular trauma, or intraocular laser treatment. However, patients may have had laser trabeculoplasty more than 3 months prior to entry into the study.

5) History or evidence of acute or recent ocular infection, imbedded corneal foreign body, and/or ocular inflammation within 2 months of study start; or of herpes simplex keratitis or corneal ulcer within 1 year.

6) Significant ocular symptoms or signs such as photophobia, flashes or streaks of light, metamorphopsia, diplopia or transient loss of vision.

7) Narrow anterior chamber angles judged to be potentially occludable if pupillary dilatation were to occur.

8) History or evidence of acute or chronic angle closure.

9) Pupil dilation not sufficient for adequate evaluation of the retina.

Pharmacologic

1) Concomitant systemic or dermatologic medication known to affect intraocular pressure, e.g., clonidine, carbonic anhydrase inhibitors, corticosteroids, scopolamine, etc. However, calcium channel blockers and angiotensin converting enzyme inhibitors were not prohibited. Oral ß-blocking agents were allowed if their administration remained constant during the study.

2) History of or current use of illicit drugs or chronic alcohol abuse.

3) Participation in any study involving administration of an investigational drug within 4 weeks of study start.

General/Systemic

1) History of hypersensitivity to any components of timolol or to a carbonic anhydrase inhibitor; severe or serious hypersensitivity to sulfonamides.

2) Any contraindication to the use of timolol ophthalmic solution.

4. **Patient Selection** (Cont.)

3) History or evidence of bronchial asthma or of clinically significant chronic obstructive pulmonary disease.

4) History or evidence of sinus bradycardia (50 bpm or less); second or third degree atrioventricular block; uncompensated heart failure; overt cardiac failure or cardiogenic shock. Athletes did not have to be excluded because of a low pulse rate.

5. **Study Design**

This was a 3-month, parallel, randomized, double-masked, active-controlled, multicenter study followed by a 9-month open-label extension. All patients in the study were required to have either open-angle glaucoma or ocular hypertension in both eyes. Any topical ocular treatment other than study drug and any systemic or dermatologic treatment known to significantly affect IOP was not permitted during this study.

a. Prestudy Evaluation

Between Study Days -21 to -14, all patients had a complete ophthalmologic examination, a physical examination, and a laboratory evaluation (hematology, blood chemistry, and urinalysis). During the 2 weeks prior to Study Day 1, all patients received 0.5% timolol b.i.d. alone at 0830 hours and bedtime. On Day -7, patients returned to the clinic for an IOP check and symptom evaluation at 0830 (prior to the morning dose of timolol) and 1030 hours.

b. Study Procedures

On Study Day 1, patients reported to the clinic prior to administration of the morning dose of timolol. After an ocular examination, a baseline IOP measurement was obtained. One drop of timolol was then instilled into each eye at 0830 hours. Ocular examinations and IOP measurements were repeated at 1030 and 1630 hours.

5. **Study Design** (Cont.)

Patients were entered into the study if their IOP was ≥22 mm Hg in at least one eye at both 0830 and 1030 hours; if only one eye met the IOP criterion, it was required to be the same eye at both time points. Patients were assigned to one of the following treatment groups according to a randomized allocation schedule [3.8]:

1) 0.5% timolol/2.0% MK-0507 b.i.d. plus placebo t.i.d.

2) 0.5% timolol b.i.d. plus 2.0% MK-0507 t.i.d.

Since iris color may alter the effect of the antiglaucoma medications used in this study, patients were stratified by iris color in order to ensure approximately equal distributions of light irides (blue, green and hazel) and dark irides (brown and black) among the treatment groups. The specific allocation number assigned to each patient was based on the patient's iris color as follows: a patient with light irides was assigned the lowest number available, and a patient with dark irides was assigned the highest number available.

Patients were instructed to administer the b.i.d. test drug at 0830 hours and bedtime and to administer the t.i.d. test drug at 0840 hours, 1430 hours, and bedtime (10 minutes after the b.i.d. test drug). Dosing began at bedtime on Study Day 1.

Patients returned to the clinic four times during the masked portion of the study, on Days 15, 30, 60, and 90. Both test drugs were administered at the clinic on these days; the b.i.d. drug was administered at 0830 hours, and the t.i.d. drug was administered at 0840 and 1430 hours. Examinations were performed at 0830, 1030, and 1630 hours and included visual acuity (at 0830 only), symptomatology, external and anterior segment examination, and measurement of IOP.

On Day 90, patients also underwent a physical examination, laboratory tests, dilated ophthalmoscopy, and a visual field examination. The masked OCUMETERs were then collected and supplies for the open-label phase were distributed. All patients received 0.5% timolol/2.0% MK-0507 b.i.d. during the open-label phase.

Patients returned to the clinic three times during the open-label phase, on Days 180, 270, and 365. Test drug was administered at the clinic at 0830 hours on these days, and ocular examinations were performed at 0830 and 1030 hours.

5. **Study Design (Cont.)**

   c. **Posttreatment Evaluations**

      Within 5 days of completing or discontinuing the study, each patient had a physical examination, dilated ophthalmoscopy, and a visual field examination. Laboratory tests (hematology, blood chemistry, and urinalysis) were performed on the day the patient completed or discontinued the study. The final ocular examination (visual acuity, symptomatology, external and anterior segment examination, and measurement of IOP) was also performed on the day the patient completed or discontinued the study.

   All data for this study were collected on case report forms [3.4] and were received at MRL by April 17, 1995. For study audit information, see [3.1]. For further details of the study procedures, see [3.2].

6. **Clinical Observations and Laboratory Measurements**

   Table 1 outlines the schedule of clinical and laboratory evaluations performed for this study.

6. Clinical Observations and Laboratory Measurements (Cont.)

Table 1

Observation Schedule

	Prestudy Screening	Day -7 Hours Postdose			Study Days 1, 15, 30, 60, and 90 Hours Following Drop				Study Days 180, 270, and 365 Hours Following Drop			Day 90 and
	Days -21 to -14	0*	0**	2	0*	0**	2	8	0*	0**	2	Poststudy†
General Ocular and Medical History	X											
Physical Examination	X											X
Laboratory Tests††	X											X
Symptomatology	X	X	X	X	X	X	X	X	X	X	X	
External and Anterior Segment Exam	X				X		X	X	X		X	
Visual Acuity	X				X				X			
IOP Measurement	X	X		X	X		X	X	X		X	
Lens and Ophthalmoscopy	X											X
Visual Field	X											X

* Immediately predose.

** Immediately postdose.

† Poststudy is within 5 days of completing study and following the final IOP measurement.

†† Laboratory tests consisted of hematology (RBC count, mean corpuscular volume, hemoglobin, hematocrit, WBC count [total and differential], and platelet count), blood chemistry (alkaline phosphatase, ALT, AST, blood urea nitrogen, creatinine, glucose, total protein, albumin, sodium, potassium, chloride, and bicarbonate), and urinalysis (pH, protein, glucose, and blood).

Data Source: [3.2]

7. Evaluation Criteria

a. Efficacy

Intraocular pressure (IOP) was measured prior to the morning dose (Hour 0), 2 hours after the morning dose (Hour 2), and 8 hours after the morning dose (Hour 8) on Day 1 (baseline) and on Days 15, 30, 60, and 90 (double-masked phase); IOP was measured at Hours 0 and 2 on Days 180, 270, and 365 (open-label phase). The primary efficacy parameter was the mean change in IOP from the time-matched baseline value in the worse eye.

b. Safety

Patients were monitored for unexpected signs and symptoms throughout the study, and those judged as having clinical adverse experiences were graded as:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort enough to cause interference with usual activity)
- Severe (incapacitating with inability to work or do usual activity)

Clinical adverse experiences were also evaluated by the investigator for seriousness, relationship to test drug, action taken, and outcome. Ocular signs and symptoms were also reported and were graded as mild, moderate, or severe. The nonocular symptom of unusual taste was also reported and was classified as sweet, sour, or bitter.

Patients were also monitored for changes in visual acuity, visual field, cup-to-disc ratio, physical examination, and laboratory tests (hematology, blood chemistry, and urinalysis). Any changes in visual field or physical examination that were considered clinically significant were also reported as adverse experiences. Laboratory values were compared to the respective normal range [4.23], and those designated by the investigator as laboratory adverse experiences were evaluated for seriousness, relationship to test drug, and outcome.

8. Statistical Planning and Analysis

a. Statistical Planning

1) Study Questions

The statistical analysis of the 3-month double-masked portion of this study addressed the following questions concerning the efficacy and safety of the 0.5% timolol/2.0% MK-0507 fixed combination:

- How does the IOP-lowering effect of 0.5% timolol/2.0% MK-0507 given b.i.d. compare to that of concomitant administration of 0.5% timolol given b.i.d. and 2.0% MK-0507 given t.i.d.?

- How does the safety profile of 0.5% timolol/2.0% MK-0507 given b.i.d. compare to that of its components administered concomitantly?

The statistical analysis of the 9-month open-label phase of this study addressed the following questions concerning the efficacy and safety of the 0.5% timolol/2.0% MK-0507 fixed combination:

- Is the IOP-lowering effect of 0.5% timolol/2.0% MK-0507 maintained through 1 year of treatment?

- Do patients who receive concomitant administration of timolol 0.5% b.i.d. and 2.0% MK-0507 t.i.d. for 3 months and are then switched to the fixed combination (0.5% timolol/2.0% MK-0507) b.i.d. for 9 months have IOP control comparable to patients who receive the fixed combination b.i.d. for 12 months?

- Is 0.5% timolol/2.0% MK-0507 well tolerated at 1 year of treatment?

The second study question for the open-label phase (regarding the comparison of IOP control between patients who are switched from concomitant therapy to the fixed combination for 9 months and patients who receive the fixed combination for 12 months) was not explicitly included in the protocol. Since it is a pertinent question, it has been included here.

In this section and in sections that follow, combination group refers to patients who received 0.5% timolol/2.0% MK-0507 fixed combination b.i.d. and concomitant group refers to patients who received 0.5% timolol b.i.d. concomitant with 2.0% MK-0507 t.i.d.

8. **Statistical Planning and Analysis (Cont.)**

2) **Statistical Hypothesis and Power**

The null hypothesis is that the 0.5% timolol/2.0% MK-0507 combination, administered b.i.d., will have an IOP-lowering effect equivalent (within 1.5 mm Hg) to that of the concomitant administration of its components (i.e., 0.5% timolol administered b.i.d. plus 2.0% MK-0507 administered t.i.d.) for up to 3 months. The alternative hypothesis is that the treatment groups are not equivalent.

Ocular hypotensive effect was assessed using the change in intraocular pressure from the time-matched baseline measurements obtained on Day 1. The change from baseline was calculated using the patient's worse eye. If only one eye met the entry criterion, then that eye was defined as the worse eye. However, if both eyes met the criterion, then the worse eye was defined as follows:

- The eye with the higher intraocular pressure immediately prior to the administration of 0.5% timolol on Day 1. If both eyes were equal, then
- the eye with the higher intraocular pressure 2 hours following the administration of 0.5% timolol on Day 1. If both eyes were equal, then
- the eye with the higher intraocular pressure 8 hours following the administration of 0.5% timolol on Day 1. If both eyes were equal, then
- the right eye was selected.

For the few patients who did not meet the IOP entry criterion, the same decision rule was used to define the worse eye.

The principal determination of equivalency was based on the average change in IOP from baseline for the treatment groups over the Month 2 and Month 3 examinations at Hour 8.

The definition of treatment equivalence was stated in the protocol as follows: a 95% confidence interval for the difference between the means that is no wider than 3 mm Hg and contains zero as an interior point. However, a carefully conducted study that limits variation in the response may be severely penalized (for example, when the estimated difference is much less than 1.5 mm Hg but the confidence interval is narrow and does not include zero as an interior point). Therefore, the criterion for

8. **Statistical Planning and Analysis (Cont.)**

establishing equivalency was revised in the Data Analysis Plan (DAP) [3.3] as follows: the confidence must be 95% or better that the absolute difference between mean change in IOP for the treatment groups is less than 1.5 mm Hg. The DAP was written before the data base was unmasked to the patients' treatment assignments.

While the study was in progress, enrollment was increased from 80 to 120 patients per treatment group in anticipation of this change in the definition of treatment equivalence. A sample size of 120 patients per treatment group provides 79% probability of concluding that the absolute difference between mean change in IOP for the treatment groups is less than 1.5 mm Hg when there is truly no difference, assuming a standard deviation of 4.0 mm Hg.

b. Statistical Analysis

For a more rigorous description of the methods and procedures that are discussed below, see the Data Analysis Plan (DAP) [3.3].

1) Approaches to the Analysis

Four approaches to the efficacy analysis were specified in the protocol and are listed below.

1. All-Patients-Treated (Intention-to-Treat), Last Observation Carried Forward
2. All-Patients-Treated (Intention-to-Treat), Observed Cases
3. Per-Protocol, Last Observation Carried Forward
4. Per-Protocol, Observed Cases

These approaches differ with respect to the inclusion/exclusion of protocol violators and the handling of missing data. The DAP states that two of these approaches, the "All-Patients-Treated," Observed Cases approach and the "Per-Protocol," Last Observation Carried Forward approach, would not be used because they have provided little additional insight in evaluating efficacy in other MRL studies. Of the remaining approaches, the "All-Patients-Treated," Last Observation Carried Forward (APT-LOCF) approach is used for both the double-masked and open-label portions of the study while the "Per-Protocol," Observed Cases (PP-OC) approach is used for the double-masked portion of the study only.

8. **Statistical Planning and Analysis (Cont.)**

The APT-LOCF approach was identified in the protocol as the definitive analysis. While the DAP states that this approach is of primary interest, it also states that the primary determination of treatment equivalence will be based entirely on data at the Hour 8 time point with a simple averaging of the patients' Month 2 and Month 3 observed IOP change from baseline. The Month 2 and Month 3 data were averaged in order to utilize both visits at which the IOP-lowering effect has most likely been established; observed cases were used because averaging data that has been estimated from previous examinations could underestimate the variability of the data. In this report, analyses which use the average of observed values for Month 2 and Month 3 will be labeled as "All-Patients-Treated," Observed Cases (APT-OC). Thus, the APT-OC approach is used instead of the APT-LOCF approach for the principle assessment of treatment equivalence. The APT-OC approach is also used for selected supplementary information pertaining to (1) the validity of the assumptions for the principle equivalency analysis and (2) supplementary assessments of treatment equivalence using the average of the Month 2 and Month 3 change in IOP from baseline measurements for the secondary Hour 0 and Hour 2 time points. The APT-OC approach is not used for any other analyses.

All-Patients-Treated, Average Observed Cases - Months 2 and 3 (APT-OC)

This approach as it pertained to Hour 8, was used to address the primary hypothesis of the study. All patients randomized to study medication with efficacy data at Month 2 and/or Month 3 for Hour 8 were included. Missing data were not estimated. This approach was also used for supplementary analyses pertaining to the validity of the assumptions for the principal equivalency analysis and for the assessment of treatment equivalence using the average of Month 2 and Month 3 change in IOP from baseline measurements for the secondary Hour 0 and Hour 2 time points.

All-Patients-Treated, Last Observation Carried Forward (APT-LOCF)

In the APT-LOCF approach, all patients randomized to study medication with efficacy data for at least one visit after randomization were included. Missing data were estimated from previous time-matched observations occurring within the double-masked phase of the study. Patients with missing data at the first visit of the masked phase were not included until a visit with data was reached. This approach was used for descriptive summaries of the IOP data and for secondary assessments of treatment equivalence at individual visits.

8. **Statistical Planning and Analysis** (Cont.)

Per-Protocol, Observed Cases (PP-OC)

In the PP-OC approach, examinations associated with a serious violation of the protocol were excluded. Missing data points were not estimated. This approach was used for analysis of both primary and secondary endpoints of the double-masked phase only.

2) **Analytical Methods**

Efficacy Comparisons - Double-Masked Phase

Treatment equivalence was assessed with the estimated confidence level (probability) that the means of the two treatments differed by ≤1.5 mm Hg at Hour 8 (1630 hours), based on an average of the Month 2 and Month 3 data. The Hour 8 time point occurred 2 hours after the afternoon dose when patients in the combination group received placebo and patients in the concomitant group received 2% MK-0507; thus, it is the time point most likely to detect differences between the treatment groups. Since there is a general concern that drug effects may wane with time, it was more important to demonstrate equivalence in the second half of the masked treatment phase than the first half. Thus, the primary determination of equivalence was based on a between-group comparison of the measured change in IOP from baseline at Hour 8 (1630 hours), averaged over the Month 2 and Month 3 visits. A 95% confidence interval for the estimated difference in treatment effect was also calculated for descriptive purposes only.

Confidence levels were also calculated for Hour 0 and Hour 2 data using the same averaging scheme. They were also calculated for data at each of the scheduled visits (Week 2, Months 1, 2, and 3) for all three time points (Hour 0, Hour 2, and Hour 8). However, these additional confidence level estimates (and associated 95% confidence intervals) were not the principal basis for demonstrating equivalence. Rather, they were calculated to address secondary questions related to treatment equivalence. All confidence estimates were rounded to three significant figures.

Clinics with larger numbers of patients and an even distribution of patients over the treatment groups were given greater weight than clinics with smaller numbers of patients and an uneven distribution of patients over the treatment groups.

8. Statistical Planning and Analysis (Cont.)

Efficacy Comparisons - Open-Label Phase

Maintenance of effect was assessed with 95% confidence intervals for the change in IOP from the time-matched baseline at Hour 0 and Hour 2 at Months 6, 9, and 12. This analysis was performed only for the group of patients who received the fixed combination during both phases of the study. The IOP-lowering effect in this group of patients was also compared between the last visit in the double-masked phase and each visit in the open-label phase.

Secondary comparisons were made for the change in IOP from the time-matched baseline between the patients who received the fixed combination during both phases and those who switched from the concomitant group during the double-masked phase to the combination during the open-label phase. These comparisons were made at Hour 0 and Hour 2 at Months 6, 9, and 12 and were assessed with the estimated confidence level (probability) that the difference between the means of each group was <1.5 mm Hg. In addition, a 95% confidence interval for each estimated difference was also calculated.

Safety Comparisons and Baseline Comparisons

All patients who received study medication were included in the evaluation of clinical adverse experiences, laboratory adverse experiences, ocular signs and symptoms, visual acuity, visual field defects, visual field global indices, cup-to-disc ratio, blood pressure and pulse rate, and laboratory safety measurements.

Fisher's exact test (two-tailed) was used to compare the treatment groups with regard to the following dichotomous variables:

- patient characteristics (race, sex)
- secondary diagnoses
- prior and concomitant therapies
- incidence of clinical and laboratory adverse experiences
- incidence of emergent or worsening ocular signs and symptoms
- incidence of visual angle doubling
- incidence of emergent or worsening visual field defects
- incidence of "clinically significant progression" of visual field defects from baseline

8. **Statistical Planning and Analysis (Cont.)**

Age at entry and baseline IOP were compared between the treatment groups using a two-way ANOVA model with investigator and treatment as main effects and no interaction. SAS® Type III Sums of Squares were used.

Summaries of continuous safety parameters were based on an "All-Patients-Treated," Last Observation Carried Forward approach. The same two-way ANOVA model used for baseline IOP was also used to compare treatment groups with respect to the mean change from baseline in pupil diameter, blood pressure, and pulse rate.

All p-values were rounded to three decimal places and statistical significance declared if the rounded p-value was less than or equal to 0.050. In the Results section, the word "significant" refers to statistical significance.

9. **Clinical Supplies**

All patients received open-label 0.5% timolol b.i.d. for at least 2 weeks prior to Study Day 1. Labels on these containers included the name of the product, the control number, and dosing instructions.

During the double-masked phase, each patient received one of two active treatments: (1) the 0.5% timolol/2.0% MK-0507 combination b.i.d. plus placebo t.i.d. or (2) 0.5% timolol b.i.d. plus 2.0% MK-0507 t.i.d. All masked OCUMETERs were labeled with the control number, the patient's allocation number, and dosing instructions. These labels included a disclosure panel that identified the contents of the OCUMETER beneath a mask. In the event of an emergency, the investigator could swab the mask with alcohol to reveal the treatment the patient was receiving. All labels, masked and unmasked, were returned to MRL at the end of the study.

During the open-label phase, all patients received the 0.5% timolol/2.0% MK-0507 combination b.i.d. Labels on these containers included the name of the product, the control number, and dosing instructions.

9. **Clinical Supplies (Cont.)**

Table 2 lists the formulation numbers and control numbers used in this study. All supplies were packaged in 5-mL OCUMETERs.

Table 2

Formulation and Control Numbers

Product Name	Formulation No.	Control No.
0.5% timolol/2.0% MK-0507	0507AESS001A002	C-Y649, C-Y828, WP-A134
0.5% timolol	0950ESS004C060	C-Y619
	0950ESS004C069	C-Y649, WP-A134, WP-A440
	0927W	WP-A108, WP-A339
2.0% MK-0507	0507ESS001A005	C-Y649, WP-A134
	0507ESS001A006	WP-A440
Placebo	P0507ESS001P005	C-Y649
	P0507ESS001P003	WP-A134

Data Source: Not Applicable

C. RESULTS

In this section and in sections that follow, combination group refers to patients who received 0.5% timolol/2.0% MK-0507 fixed combination b.i.d. and concomitant group refers to patients who received 0.5% timolol b.i.d. concomitant with 2.0% MK-0507 t.i.d.

1. Patient Characteristics

Table 3 presents the number of patients entered into the study by investigator and treatment group. A total of 242 patients were entered into the study. During the double-masked phase, 121 patients received the 0.5% timolol/2.0% MK-0507 combination solution (b.i.d.) and an identical number received concomitant administration of 0.5% timolol solution (b.i.d.) with 2.0% MK-0507 solution (t.i.d.). A total of 19 investigators participated in the study. Investigator Spirn enrolled the least number of patients (N=2) while investigator DuBiner enrolled the greatest number (N=24). Only two investigators (Spirn and Cyrlin) enrolled fewer than 9 patients at their clinic.

1. **Patient Characteristics (Cont.)**

Table 3

Number of Patients Entered Into the Study
by Investigator and Treatment Group

Study Number	Investigator	Location	Combination	Concomitant	Total
1	Allen, Robert	Charlottesville, VA	10	9	19
2	Brown, Reay	Atlanta, GA	5	5	10
3	Cacioppo, Leonard	Brooksville, FL	7	5	12
4	Cyrlin, Marshall	Southfield, MI	2	4	6
5	DuBiner, Harvey	Morrow, GA	12	12	24
6	Greenberg, Marvin	Tamarac, FL	4	5	9
7	Hoff, Mark	Sarasota, FL	7	6	13
8	Karp, David	Louisville, KY	5	5	10
9	Laibovitz, Robert	Austin, TX	6	7	13
10	Lewis, Richard	Sacramento, CA	7	8	15
11	McMahon, Charles	Colorado Springs, CO	10	10	20
12	Ostrov, Charles	Minneapolis, MN	9	8	17
13	Samples, John	Portland, OR	8	7	15
14	Schuman, Joel	Boston, MA	4	5	9
15	Shrader, C. Eric	Wichita, KS	7	8	15
16	Spirn, Franklin	Clark, NJ	1	1	2
17	Vela-Thomas, Angela	Atlanta, GA	7	6	13
18	Wilensky, Jacob	Chicago, IL	4	5	9
19	Greenidge, Kevin	New York, NY	6	5	11
	Total		121	121	242

Data Source: [4.8]

Table 4 displays the number of patients entered into the study by age category and sex. The mean age of males and females was comparable within and across treatment groups (<3 years difference).

Table 5 summarizes baseline demographic characteristics by treatment group. A greater proportion of females were randomized to the combination group than to the concomitant group (59% versus 41%, respectively). Although this difference was statistically significant (p=0.010), no significant gender effect on IOP reduction was detected when baseline covariates were analyzed (See Table 3, [4.1]). The combination group had 4 patients who were not of white or black race; otherwise, the groups were comparable with respect to racial origin. Similar distributions were also observed with regard to iris color, age, and baseline IOP (worse eye) and no statistically significant differences were noted between the treatment groups.

1. Patient Characteristics (Cont.)

Table 4

Number of Patients Entered into the Study by Age Category and Sex

Age (Years)	Combination			Concomitant			Total		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
<35	1	2	3	1	2	3	2	4	6
35-44	5	6	11	4	10	14	9	16	25
45-54	10	5	15	5	11	16	15	16	31
55-64	22	14	36	11	15	26	33	29	62
65-74	26	19	45	22	20	42	48	39	87
75-110	7	4	11	7	13	20	14	17	31
Total	71	50	121	50	71	121	121	121	242
Mean	61.4	59.9	60.7	63.3	60.5	61.7	62.2	60.3	61.2
SD	10.4	13.1	11.6	11.7	13.8	13.0	11.0	13.5	12.3
Median	63.0	62.0	63.0	66.0	63.0	65.0	65.0	62.0	64.0
Range	29-81	22-79	22-81	25-82	30-84	25-84	25-82	22-84	22-84

Data Source: [4.8]

1. Patient Characteristics (Cont.)

Table 5

Baseline Demographic Characteristics
by Treatment Group

	Combination (N=121)	Concomitant (N=121)	Total (N=242)
	N (%)	N (%)	N (%)
Sex[a]			
Male	50 (41)	71 (59)	121 (50)
Female	71 (59)	50 (41)	121 (50)
Race			
White	88 (73)	92 (76)	180 (74)
Black	29 (24)	29 (24)	58 (24)
Hispanic	3 (2)	0 (0)	3 (1)
Chinese	1 (1)	0 (0)	1 (0)
Iris Color			
Dark Brown	30 (25)	24 (20)	54 (22)
Brown	29 (24)	33 (27)	62 (26)
Hazel	17 (14)	19 (16)	36 (15)
Green	3 (2)	5 (4)	8 (3)
Blue	42 (35)	40 (33)	82 (34)
Age (Years)			
N	121	121	242
Mean [SD]	60.7 [11.6]	61.7 [13.0]	61.2 [12.3]
Median	63	65	64
Range	22-81	25-84	22-84
Baseline IOP (mm Hg) - Worse Eye			
Hour 0			
N	121	121	242
Mean [SD]	26.1 [3.0]	26.1 [3.8]	26.1 [3.4]
Median	25	26	26
Range	22-34	20-48	20-48
Hour 2			
N	121	121	242
Mean [SD]	25.0 [3.3]	25.0 [3.7]	25.0 [3.5]
Median	24	24	24
Range	19-39	18-48	18-48
Hour 8			
N	119	120	239
Mean [SD]	23.7 [3.8]	23.3 [4.2]	23.5 [4.0]
Median	23.0	23.0	23.0
Range	15-36	14-47	14-47

[a] p=0.010, significantly more females in the combination group.

Data Source: [4.8] and [4.11]

1. **Patient Characteristics (Cont.)**

Table 6 presents the number (%) of patients with secondary diagnoses by body system and by specific secondary diagnosis. Only the specific diagnoses with an observed incidence ≥3% in either group are shown. A significantly greater proportion of patients in the combination group had a musculoskeletal disorder than in the concomitant group (29% vs. 16%; p=0.020). A significantly greater proportion of patients in the combination group had a respiratory system disorder than in the concomitant group (16% vs. 7%; p=0.040). There were no other statistically significant differences between the treatment groups.

Table 7 presents the number (%) of patients with prior therapy by drug category and by specific drug. Only the specific therapies with an observed incidence ≥3% in either group are shown. A significantly greater proportion of patients in the combination group took anti-inflammatories compared to the concomitant group (13% vs. 5%; p=0.042). There were no other statistically significant differences between the treatment groups.

Table 8 presents the number (%) of patients with concomitant therapy, by drug category and by specific drug, for the double-masked phase of the study. Only the specific therapies with an observed incidence ≥3% in either group are shown. A significantly greater proportion of patients in the combination group took hormones and synthetic substitutes compared to the concomitant group (33% vs. 20%; p=0.028). There were no other statistically significant differences between the treatment groups.

Table 9 presents the number (%) of patients with concomitant therapy, by drug category and by specific drug, for the open-label phase of the study. Only the specific therapies with an observed incidence ≥3% in either group are shown. A significantly greater proportion of patients in the combination group took anti-inflammatories compared to the concomitant group (20% vs. 7%; p=0.008). A significantly greater proportion of patients in the concomitant group took the cardiovascular medication enalapril maleate compared to the combination group (7% vs. 1%; p=0.036). A significantly greater proportion of patients in the combination group took hormones and synthetic substitutes compared to the concomitant group (39% vs. 23%; p=0.013). There were no other statistically significant differences between the treatment groups.

1. Patient Characteristics (Cont.)

Table 6

Number (%) of Patients With Secondary Diagnoses by Body System and by Specific Secondary Diagnosis (Incidence ≥3% in Any Treatment Group)

	Combination (N=121)	Concomitant (N=121)
	N (%)	N (%)
Number of Patients With A Secondary Diagnosis	121 (100)	121 (100)
Body As A Whole/Site Unspecified	15 (12)	6 (5)
Hernia, Diaphragmatic	6 (5)	2 (2)
Cardiovascular System Disorders	61 (50)	56 (46)
Atherosclerosis	4 (3)	2 (2)
Hypertension	50 (41)	52 (43)
Digestive System Disorders	9 (7)	12 (10)
Endocrine Disorders	26 (21)	15 (12)
Diabetes Mellitus	16 (13)	13 (11)
Hypothyroidism	6 (5)	2 (2)
Hematologic/Lymphatic Disorders	0	1 (1)
Metabolic, Nutritional, Immune Disorders	29 (24)	21 (17)
Allergy, Drug	8 (7)	6 (5)
Allergy, Nondrug	7 (6)	6 (5)
Hypercholesterolemia	12 (10)	6 (5)
Musculoskeletal Disorders[a]	35 (29)	19 (16)
Arthritis	20 (17)	13 (11)
Osteoarthritis	5 (4)	0
Nervous System/Psychiatric Disorders	23 (19)	23 (19)
Anxiety	1 (1)	5 (4)
Depression	4 (3)	2 (2)
Headache	8 (7)	6 (5)
Insomnia	4 (3)	3 (2)
Migraine	4 (3)	2 (2)
Respiratory System Disorders[b]	19 (16)	8 (7)
Sinus Disorder	6 (5)	1 (1)
Tonsillectomy	4 (3)	0
Skin/Skin Appendage Disorders	6 (5)	3 (2)

1. **Patient Characteristics (Cont.)**

Table 6 (Cont.)

Number (%) of Patients With Secondary Diagnoses by Body System and by Specific Secondary Diagnosis (Incidence ≥3% in Any Treatment Group)

	Combination (N=121)	Concomitant (N=121)
	N (%)	N (%)
Special Sense Disorders	121 (100)	121 (100)
Allergy, Ocular	2 (2)	4 (3)
Blepharitis	5 (4)	3 (2)
Cataract	27 (22)	26 (21)
Degeneration, Macular	0	4 (3)
Degeneration, Vitreous	4 (3)	2 (2)
Glaucoma, Open-Angle	102 (84)	100 (83)
Hypertension, Ocular	20 (17)	23 (19)
Surgery, Glaucoma	10 (8)	12 (10)
Urogenital System Disorders	20 (17)	25 (21)
Benign Prostatic Hypertrophy	0	5 (4)
Hysterectomy	8 (7)	7 (6)
Menopausal Disorder	5 (4)	4 (3)
Surgery, Prostate	1 (1)	4 (3)

[a]p=0.020, significantly greater incidence in the combination group.
[b]p=0.040, significantly greater incidence in the combination group.

Patients with more than one secondary diagnosis in a body system are counted only once in that body system total and in the overall total.

All body systems in which at least 1 patient had a secondary diagnosis are listed.

Data Source: [4.8]

1. Patient Characteristics (Cont.)

Table 7

Number (%) of Patients With Prior Drug Therapy by Drug Category and by Specific Drug Therapy (Incidence ≥3% in Any Treatment Group)

	Combination (N=121)	Concomitant (N=121)
	N (%)	N (%)
Number of Patients With Any Prior Therapy	121 (100)	121 (100)
Anti-Benign Prostatic Hyperplasia Agents	0	2 (2)
Antihistamines	4 (3)	6 (5)
Anti-infective Agents	8 (7)	8 (7)
Anti-inflammatories[a]	16 (13)	6 (5)
Ibuprofen	8 (7)	4 (3)
Antineoplastic Agents	2 (2)	0
Antiparkinsonian Agents	1 (1)	0
Autonomic Drugs	121 (100)	121 (100)
Atenolol	4 (3)	1 (1)
Betaxolol Hydrochloride	6 (5)	2 (2)
Carteolol Hydrochloride	2 (2)	4 (3)
Dipivefrin	10 (8)	14 (12)
Levobunolol Hydrochloride	17 (14)	19 (16)
Timolol Maleate	121 (100)	121 (100)
Blood Formation & Coagulation Agents	1 (1)	1 (1)
Cardiovascular Drugs	49 (40)	49 (40)
Diltiazem Hydrochloride	4 (3)	5 (4)
Enalapril Maleate	3 (2)	7 (6)
Hydrochlorothiazide/Triamterene	11 (9)	9 (7)
Lisinopril	8 (7)	4 (3)
Lovastatin	5 (4)	2 (2)
Nifedipine	5 (4)	10 (8)
Verapamil	4 (3)	10 (8)
Central Nervous System Drugs	35 (29)	30 (25)
Acetaminophen	6 (5)	4 (3)
Aspirin	16 (13)	13 (11)
Cold Remedies	1 (1)	0
Electrolyte/Caloric/Water Balance Agents	14 (12)	15 (12)
Furosemide	1 (1)	5 (4)
Hydrochlorothiazide	6 (5)	6 (5)

1. **Patient Characteristics (Cont.)**

Table 7 (Cont.)

Number (%) of Patients With Prior Drug Therapy by Drug Category and by Specific Drug Therapy (Incidence ≥3% in Any Treatment Group)

	Combination (N=121)	Concomitant (N=121)
	N (%)	N (%)
Gastrointestinal Drugs	8 (7)	8 (7)
Hormones & Synthetic Substitutes	38 (31)	24 (20)
Estrogens, Conjugated	12 (10)	7 (6)
Glipizide	1 (1)	5 (4)
Glyburide	8 (7)	3 (2)
Insulin	4 (3)	2 (2)
Levothyroxine Sodium	8 (7)	2 (2)
Muscle Relaxants	1 (1)	1 (1)
Nasal Decongestants	1 (1)	2 (2)
Ophthalmic Preparations	43 (36)	49 (40)
Pilocarpine	33 (27)	41 (34)
Pilocarpine Gel	6 (5)	4 (3)
Pharmaceutical Adjuncts	1 (1)	0
Skin & Mucous Membrane Preparations	0	1 (1)
Vitamins & Minerals	9 (7)	5 (4)
Classification Undetermined	2 (2)	2 (2)

[a]p=0.042, significantly greater incidence in the combination group.

Patients with more than one prior therapy in a drug category are counted only once in that category total and in the overall total.

All drug categories in which at least 1 patient had a prior therapy are listed.

Data Source: [4.9]

1. Patient Characteristics (Cont.)

Table 8

Number (%) of Patients With Concomitant Drug Therapy by Drug Category and by Specific Drug Therapy (Incidence ≥3% in Any Treatment Group)
Double-Masked Phase

	Combination (N=121)	Concomitant (N=121)
	N (%)	N (%)
Number of Patients With Any Concomitant Therapy	94 (78)	91 (75)
Anti-Benign Prostatic Hyperplasia Agents	0	3 (2)
Antihistamines	4 (3)	6 (5)
Anti-infective Agents	17 (14)	9 (7)
Ciprofloxacin	4 (3)	1 (1)
Sulfamethoxazole/Trimethoprim	4 (3)	1 (1)
Anti-inflammatories	17 (14)	7 (6)
Ibuprofen	8 (7)	4 (3)
Antineoplastic Agents	2 (2)	0
Antiparkinsonian Agents	1 (1)	0
Antitussives	3 (2)	1 (1)
Autonomic Drugs	14 (12)	6 (5)
Atenolol	4 (3)	1 (1)
Pseudoephedrine Hydrochloride	4 (3)	2 (2)
Blood Formation & Coagulation Agents	1 (1)	1 (1)
Cardiovascular Drugs	49 (40)	50 (41)
Diltiazem Hydrochloride	4 (3)	5 (4)
Enalapril Maleate	3 (2)	7 (6)
Hydrochlorothiazide/Triamterene	11 (9)	9 (7)
Lisinopril	8 (7)	4 (3)
Lovastatin	5 (4)	2 (2)
Nifedipine	5 (4)	10 (8)
Verapamil	5 (4)	10 (8)
Central Nervous System Drugs	36 (30)	32 (26)
Acetaminophen	9 (7)	5 (4)
Aspirin	15 (12)	14 (12)
Cold Remedies	1 (1)	0
Electrolyte/Caloric/Water Balance Agents	14 (12)	15 (12)
Furosemide	1 (1)	5 (4)
Hydrochlorothiazide	6 (5)	6 (5)
Expectorants	0	1 (1)

1. Patient Characteristics (Cont.)

Table 8 (Cont.)

Number (%) of Patients With Concomitant Drug Therapy by Drug Category and by Specific Drug Therapy (Incidence ≥3% in Any Treatment Group)

Double-Masked Phase

	Combination (N=121)	Concomitant (N=121)
	N (%)	N (%)
Gastrointestinal Drugs	9 (7)	8 (7)
Ranitidine	4 (3)	3 (2)
Hormones & Synthetic Substitutes[a]	40 (33)	24 (20)
Estrogens, Conjugated	12 (10)	7 (6)
Glipizide	1 (1)	5 (4)
Glyburide	8 (7)	4 (3)
Insulin	4 (3)	2 (2)
Levothyroxine Sodium	8 (7)	2 (2)
Immunologic Substances	1 (1)	0
Local Anesthetics	0	1 (1)
Mast Cell Stabilizers	0	1 (1)
Muscle Relaxants	1 (1)	1 (1)
Nasal Decongestants	2 (2)	3 (2)
Ophthalmic Preparations	5 (4)	4 (3)
Pharmaceutical Adjuncts	1 (1)	0
Skin & Mucous Membrane Preparations	1 (1)	1 (1)
Vitamins & Minerals	9 (7)	5 (4)

[a]p=0.028, significantly greater incidence in the combination group.

Patients with more than one concomitant therapy in a drug category are counted only once in that category total and in the overall total.

All drug categories in which at least 1 patient had a concomitant therapy are listed.

Data Source: [4.9]

1. Patient Characteristics (Cont.)

Table 9

Number (%) of Patients With Concomitant Drug Therapy by Drug Category and by Specific Drug Therapy (Incidence ≥3% in Any Treatment Group)

Open-Label Phase

	Combination (N=107)	Concomitant (N=113)
	N (%)	N (%)
Patients With Any Concomitant Therapy	87 (81)	84 (74)
Anti-Benign Prostatic Hyperplasia Agents	0	3 (3)
Antihistamines	3 (3)	7 (6)
Anti-infective Agents	15 (14)	22 (19)
Erythromycin	2 (2)	4 (4)
Sulfamethoxazole/Trimethoprim	4 (4)	2 (2)
Anti-inflammatories[a]	21 (20)	8 (7)
Ibuprofen	8 (7)	4 (4)
Antineoplastic Agents	3 (3)	0
Antiparkinsonian Agents	1 (1)	1 (1)
Antitussives	2 (2)	1 (1)
Autonomic Drugs	15 (14)	7 (6)
Atenolol	4 (4)	1 (1)
Pseudoephedrine Hydrochloride	4 (4)	2 (2)
Blood Formation & Coagulation Agents	6 (6)	4 (4)
Cardiovascular Drugs	45 (42)	47 (42)
Digoxin	2 (2)	4 (4)
Diltiazem Hydrochloride	4 (4)	6 (5)
Enalapril Maleate[b]	1 (1)	8 (7)
Hydrochlorothiazide/Triamterene	11 (10)	8 (7)
Lisinopril	9 (8)	4 (4)
Lovastatin	4 (4)	0
Nifedipine	6 (6)	11 (10)
Pravastatin	2 (2)	4 (4)
Ramipril	4 (4)	0
Verapamil	3 (3)	10 (9)
Central Nervous System Drugs	34 (32)	33 (29)
Acetaminophen	8 (7)	5 (4)
Aspirin	16 (15)	14 (12)

1. **Patient Characteristics (Cont.)**

Table 9 (Cont.)

Number (%) of Patients With Concomitant Drug Therapy by Drug Category and by Specific Drug Therapy (Incidence ≥3% in Any Treatment Group)

Open-Label Phase

	Combination (N=107)	Concomitant (N=113)
	N (%)	N (%)
Cold Remedies	0	1 (1)
Electrolyte/Caloric/Water Balance Agents	13 (12)	17 (15)
Furosemide	1 (1)	6 (5)
Hydrochlorothiazide	5 (5)	6 (5)
Potassium Chloride	3 (3)	4 (4)
Expectorants	0	2 (2)
Gastrointestinal Drugs	12 (11)	10 (9)
Cimetidine	5 (5)	3 (3)
Ranitidine	4 (4)	1 (1)
Hormones & Synthetic Substitutes[c]	42 (39)	26 (23)
Estrogens, Conjugated	12 (11)	6 (5)
Glipizide	2 (2)	5 (4)
Glyburide	7 (7)	4 (4)
Insulin	4 (4)	3 (3)
Levothyroxine Sodium	7 (7)	2 (2)
Immunologic Substances	0	1 (1)
Local Anesthetics	1 (1)	1 (1)
Muscle Relaxants	1 (1)	2 (2)
Nasal Decongestants	1 (1)	2 (2)
Ophthalmic Preparations	3 (3)	6 (5)
Pharmaceutical Adjuncts	0	1 (1)
Vitamins & Minerals	7 (7)	5 (4)
Multivitamins	4 (4)	1 (1)

[a]p=0.008, significantly greater incidence in the combination group.
[b]p=0.036, significantly greater incidence in the concomitant group.
[c]p=0.013, significantly greater incidence in the combination group.
Patients with more than one concomitant therapy in a drug category are counted only once in that category total and in the overall total.
All drug categories in which at least 1 patient had a concomitant therapy are listed.
Combination and concomitant refer to the initial treatment-group assignments; all patients received 0.5% timolol/2.0% MK-0507 fixed combination b.i.d. during the open-label phase.

Data Source: [4.9]

2. Patient Accounting

a. Accounting for Patients in the Study

1) Double-Masked Phase

Two hundred forty-two patients were randomized to the two treatment groups. Of this number, 220 (91%) completed the double-masked phase of the study. Table 10 presents the number (%) of patients who entered, completed, and discontinued the double-masked phase. For each reason causing discontinuation, the proportion of patients did not differ significantly between treatment groups. However, more patients in the combination group discontinued (n=14) compared to the concomitant group (n=8) and this difference can be attributed primarily to more discontinuations due to clinical adverse experiences in the combination group. The patients who discontinued from the double-masked phase are listed in [4.4].

Table 10

Patient Accounting
Double-Masked Phase

	Combination	Concomitant	Total
	N (%)	N (%)	N (%)
Entered Masked Phase	121	121	242
Completed Masked Phase	107 (88)	113 (93)	220 (91)
Discontinued Masked Phase	14 (12)	8 (7)	22 (9)
Clinical Adverse Experience	7 (6)	3 (2)	10 (4)
Laboratory Adverse Experience	0 (0)	0 (0)	0 (0)
Protocol Deviation	1 (1)	2 (2)	3 (1)
Patient Withdrew	1 (1)	0 (0)	1 (<1)
Therapy Ineffective	5 (4)	3 (2)	8 (3)

Data Source: [4.10]

2. Patient Accounting (Cont.)

2) Open-Label Phase

After completing the double-masked phase of the study, patients were eligible to enter the open-label phase and receive 0.5% timolol/2.0% MK-0507 fixed combination b.i.d. Of the 220 patients who entered the open-label phase, 203 (92%) completed it. Table 11 presents the number (%) of patients who entered, completed, and discontinued the open-label phase. For each reason causing discontinuation, the proportion of patients did not differ significantly between the groups defined by the initial treatment assignment in the double-masked phase. The patients who discontinued from the open-label phase are listed in [4.5].

Table 11

Patient Accounting
Open-Label Phase

	Combination	Concomitant	Total
	N (%)	N (%)	N (%)
Entered Open-Label Phase	107	113	220
Completed Open-Label Phase	99 (93)	104 (92)	203 (92)
Discontinued Open-Label Phase	8 (7)	9 (8)	17 (8)
Clinical Adverse Experience	6 (6)	3 (3)	9 (4)
Laboratory Adverse Experience	0 (0)	0 (0)	0 (0)
Protocol Deviation	0 (0)	1 (1)	1 (<1)
Patient Withdrew	0 (0)	2 (2)	2 (1)
Therapy Ineffective	2 (2)	1 (1)	3 (1)
Lost to Follow-up	0 (0)	2 (2)	2 (1)

Combination and concomitant refer to the initial treatment group assignments; all patients received 0.5% timolol/2.0% MK-0507 fixed combination b.i.d. during the open-label phase.

Data Source: [4.10]

2. Patient Accounting (Cont.)

b. Accounting for Patients in the Analysis

Table 12 shows the number (%) of patients in the primary efficacy analysis. The number (%) of patients in the efficacy analyses at secondary time points is provided in [4.25]. One patient (AN 6196) did not have an IOP measurement after baseline and, therefore, was not included in any of the efficacy analyses. Of the remaining 241 patients, 224 contributed IOP data for the primary analysis of efficacy.

Table 12

Number (%) of Patients in the Primary Efficacy Analysis

	Average of Month 2 and Month 3 at Hour 8	
	Combination	Concomitant
Total Entered	121	121
Excluded[a]		
Did Not Meet IOP Entrance Criteria	1	1
Prohibited Prior Therapy	2	6
Prohibited Concomitant Therapy	1	5
Prohibited Secondary Diagnosis	0	1
Total Excluded[b]	3 (2)	7 (6)
Missing		
Estimable	6 (5)	4 (3)
Non-Estimable[c]	5 (4)	3 (2)
Total Missing	11 (9)	7 (6)
Total Per-Protocol Analysis[d]	107 (88)	107 (88)
Total All-Patients-Treated Analysis (OC)[e]	110 (91)	114 (94)

[a] Only applies to patients with data for Hour 8 at either Month 2 or Month 3.
[b] Patients excluded for more than one reason are only counted once in the total
[c] No IOP exams past baseline for Hour 8
[d] Number of patients in the Per-Protocol Analysis = Total entered - total excluded - total missing
[e] Number of patients in the All-Patients-Treated Observed Cases Analysis = Total entered -total missing

Data Source: [4.6]

One patient (AN 6188) did not start masked therapy until the day after randomization. Coding guidelines specified that the baseline visit be coded with a Relative Day of -1. This patient was not regarded as a protocol violator and was included in all analyses of efficacy.

The protocol specified a 2-week run-in period during which all patients were to receive only 0.5% timolol b.i.d. The following 5 patients received 0.5% timolol for less than 14 days prior to Day 1: AN 6215 (11 days), AN 6271 (12 days), AN 6072 (13 days), AN 6077 (13 days), and AN 6099 (12 days). These patients were not excluded because 11 days is sufficient time for the IOP-lowering effect of timolol to be established.

2. **Patient Accounting (Cont.)**

Some or all of the examinations from a total of 35 patients (18 patients in the combination group and 17 patients in the concomitant therapy group) were excluded from the "Per-Protocol" analysis of the double-masked phase [4.6]. IOP data were excluded at one or more visits (Hours 0, 2, and 8 unless otherwise noted) for the following reasons:

a. Patient did not meet the intraocular pressure entrance criterion. This violation resulted in all data being excluded. The intraocular pressure criterion was as follows: An IOP measurement of ≥22 mm Hg in one eye (the same eye) at Hours 0 and 2 at the baseline evaluation (following the 2-week timolol run-in period).

b. Patient took prohibited prior therapy during the run-in period. During the run-in period, patients were prohibited from taking any other therapy that might have an effect on IOP. Therefore, patients were excluded if they had taken any of the following medications during the 14 days immediately preceding Day 1 of the study: topical adrenergic agents, topical β-blockers, pilocarpine, aceclidine, clonidine, topical steroids, oral CAIs, topical prostaglandins.

c. Use of concomitant therapy that may have had an effect on intraocular pressure. An examination was excluded if the patient had taken any of the following medications during the 14 days preceding the examination: topical adrenergic agents, topical beta-blockers, pilocarpine, aceclidine, clonidine, topical steroids, oral carbonic anhydrase inhibitors, topical prostaglandins.

d. Failure to instill all doses of study medication the day prior to, or the morning and afternoon of, an examination. If the morning dose was taken but the afternoon dose was missed on the day of the examination then only the Hour 8 data was excluded.

e. Instillation of study medication prior to the Hour 0 measurement of intraocular pressure. It was assumed that since all patients were required to report to the clinic on the day of a study examination before study medication was administered, this violation did not occur.

f. Only one eye treated. This violation did not occur.

g. A secondary diagnosis that was prohibited in the protocol. Only 1 patient, with chronic obstructive pulmonary disease, was excluded for this reason.

2. Patient Accounting (Cont.)

h. Oral β-blocking agents were permitted if their administration remained constant over time. A change in dose or frequency resulted in the exclusion of data from all subsequent examinations.

Table 13 presents the relative day ranges that were established since not all patients returned to the clinic for examinations on the exact day specified in the protocol. In all cases, the last examination within a relative day range was used in the analysis. Data were not carried forward from one phase of the study to estimate missing data from the next phase, in other words, baseline data were not carried forward to the double-masked phase, and data from the double-masked phase were not carried forward to the open-label phase.

All 242 patients were included in the evaluation of clinical and laboratory adverse experiences.

Table 13

Relative Day Ranges for Last-Observation-Carried-Forward and Observed-Cases Approaches to the Analysis

Phase	Exam	Specified Day	Last-Observation-Carried-Forward Approach	Observed-Cases Approach
Baseline	Day 1	1	-1,1	-1,1
Double-Masked	Week 2	15	2 to 22	2 to 22
	Month 1	30	2 to 45	23 to 45
	Month 2	60	2 to 75	46 to 75
	Month 3	90	2 to 135	76 to 135
Open-Label	Month 6	180	2 to 225*	136 to 225
	Month 9	270	2 to 315*	226 to 315
	Month 12	365	2 to 410*	316 to 410

Days in Baseline, Double-Masked, and Open-Label Phases are relative to study start.
The last exam in each relative day range is used for the analysis indicated.
* Values from the double-masked phase were not carried forward to the open-label phase.

Data Source: Not Applicable

3. Efficacy

a. Double-Masked Phase

The principal objective of the masked phase of the study was to compare the IOP-lowering effect of the 0.5% timolol/2.0% MK-0507 combination solution (b.i.d.) to that of the concomitant administration of 0.5% timolol (b.i.d.) plus 2.0% MK-0507 (t.i.d.) for up to 3 months of therapy. IOP measurements were obtained at Hour 0 (0830 hours), Hour 2 (1030 hours), and Hour 8 (1630 hours) on Day 1 (baseline), Week 2, Month 1, Month 2, and Month 3. In the discussion that follows, time point refers to one of the three Hour examinations while visit refers to one of the scheduled days that the patient returned to the clinic.

1) Descriptive Summaries

Table 14 presents IOP summary statistics for each visit in the double-masked phase using an APT-LOCF approach. Changes from baseline for the combination group ranged from -3.1 mm Hg to -5.0 mm Hg and for the concomitant therapy group, from -3.9 mm Hg to -5.2 mm Hg. For each visit, mean reductions in IOP at Hour 2 were roughly 1.0 mm Hg greater than reductions in IOP at Hour 0 or Hour 8. Percent changes from baseline ranged from -12.0 to -19.9 for the combination group and from -14.6 to -20.3 for the concomitant therapy group. For each visit, percent reductions in IOP were approximately 4.5 percentage points greater at Hour 2 than at Hour 0, and they were approximately 3.0 percentage points greater at Hour 2 than at Hour 8.

Figure 1 displays the IOP treatment means and standard errors by treatment group across visits in the double-masked phase. Estimates were based on an APT-LOCF population. The two treatment groups were, in general, comparable over time. Apparent treatment-group differences at Hour 8 are explained in part by the lower mean baseline IOP seen in the concomitant therapy group (the mean baseline IOP at Hour 8 was approximately 0.4 mm Hg lower for the concomitant therapy group than the combination group).

3. **Efficacy (Cont.)**

Table 14

IOP Summary Statistics† (mm Hg) -- Double-Masked Phase

Exam	Treatment	N	Baseline			Treatment			Change			Percent Change		
			Mean	Std	Med	Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Hour 0														
Wk 2	Combination	115	26.0	3.0	25.0	22.9	4.2	22.0	-3.1	3.1	-3.0	-12.0	11.8	-12.5
	Concomitant	120	26.1	3.8	26.0	22.2	3.6	22.0	-3.9	3.0	-4.0	-14.6	10.6	-14.8
Mo 1	Combination	120	26.1	3.0	25.0	22.3	4.1	22.0	-3.8	3.0	-4.0	-14.8	11.5	-16.0
	Concomitant	121	26.1	3.8	26.0	21.8	3.7	22.0	-4.2	3.1	-4.0	-15.9	11.1	-16.7
Mo 2	Combination	120	26.1	3.0	25.0	22.4	3.8	22.0	-3.7	2.7	-4.0	-14.3	10.3	-14.5
	Concomitant	121	26.1	3.8	26.0	21.6	3.9	21.0	-4.4	3.6	-4.0	-16.6	12.6	-16.7
Mo 3	Combination	120	26.1	3.0	25.0	22.5	4.1	22.0	-3.6	3.0	-4.0	-13.8	11.1	-15.4
	Concomitant	121	26.1	3.8	26.0	22.0	4.4	22.0	-4.1	3.7	-4.0	-15.5	13.8	-15.4
Hour 2														
Wk 2	Combination	114	25.1	3.3	24.0	20.5	3.9	20.0	-4.6	3.2	-4.0	-18.1	12.2	-17.6
	Concomitant	119	25.1	3.7	24.0	20.2	3.7	20.0	-4.8	3.5	-4.0	-18.9	12.8	-17.4
Mo 1	Combination	119	25.1	3.3	24.0	20.1	3.5	20.0	-5.0	3.3	-5.0	-19.6	12.1	-19.2
	Concomitant	120	25.0	3.7	24.0	19.9	3.7	19.0	-5.2	3.1	-5.0	-20.3	11.3	-21.7
Mo 2	Combination	119	25.1	3.3	24.0	20.0	3.8	20.0	-5.0	3.4	-5.0	-19.9	12.3	-20.0
	Concomitant	120	25.0	3.7	24.0	19.9	3.5	19.0	-5.2	3.3	-5.0	-20.2	11.8	-21.7
Mo 3	Combination	119	25.1	3.3	24.0	20.1	3.8	20.0	-5.0	3.5	-5.0	-19.7	12.9	-20.0
	Concomitant	120	25.0	3.7	24.0	20.2	4.2	20.0	-4.9	3.8	-5.0	-19.1	14.4	-21.7

3. Efficacy (Cont.)

Table 14 (Cont.)

IOP Summary Statistics[†] (mm Hg) -- Double-Masked Phase

Exam	Treatment	N	Baseline			Treatment			Change			Percent Change		
			Mean	Std	Med	Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Hour 8														
Wk 2	Combination	111	23.6	3.9	23.0	19.8	3.8	19.0	-3.8	3.3	-4.0	-15.5	12.9	-15.0
	Concomitant	115	23.3	4.2	23.0	19.4	3.6	19.0	-3.9	3.9	-4.0	-15.6	15.3	-17.6
Mo 1	Combination	116	23.7	3.9	23.0	19.9	3.6	19.5	-3.8	3.3	-4.0	-15.2	12.8	-15.1
	Concomitant	118	23.3	4.2	23.0	18.8	3.6	18.0	-4.5	3.4	-4.0	-18.5	13.0	-19.0
Mo 2	Combination	116	23.7	3.9	23.0	19.8	3.7	19.0	-3.9	3.4	-4.0	-15.6	13.4	-17.0
	Concomitant	118	23.3	4.2	23.0	19.1	3.9	19.0	-4.3	3.9	-4.0	-17.3	15.2	-19.1
Mo 3	Combination	116	23.7	3.9	23.0	20.0	3.9	19.0	-3.7	3.4	-3.5	-14.9	13.2	-16.3
	Concomitant	118	23.3	4.2	23.0	19.0	3.5	19.0	-4.3	3.8	-4.0	-17.4	14.8	-18.9

[†]All-Patients-Treated Analysis (Last Observation Carried Forward) -- Worse Eye.

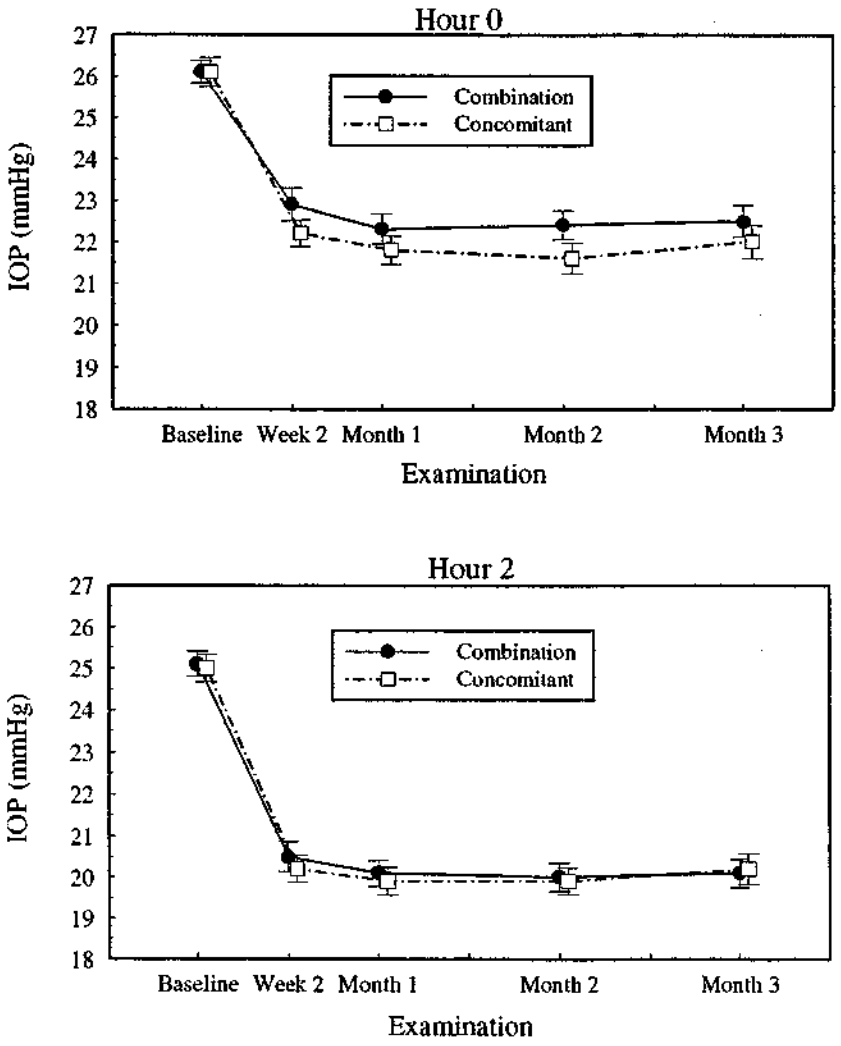
Data Source: [4.11]

3. **Efficacy (Cont.)**

Figure 1

IOP Treatment Means and Standard Errors+

Double-Masked Phase



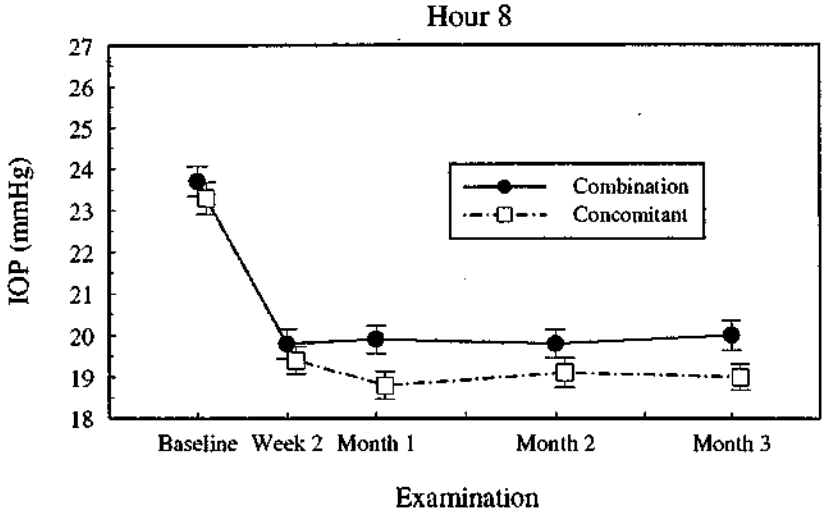
+ "All-Patients-Treated" Analysis (Last Observation Carried Forward) - Worse Eye

Data Source: [4.11]

3. Efficacy (Cont.)

Figure 1 (Cont.)

IOP Treatment Means and Standard Errors+
Double-Masked Phase



+ "All-Patients-Treated" Analysis (Last Observation Carried Forward) - Worse Eye

Data Source: [4.11]

3. **Efficacy (Cont.)**

2) **Primary Efficacy Analysis**

The primary efficacy hypothesis concerns whether the two treatments are equivalent at Hour 8 in their IOP-lowering ability following 2 to 3 months of therapy. The criterion for determining treatment equivalence was specified in the data analysis plan [3.3] as follows: the confidence must be 95% or better that the absolute difference between mean change in IOP from baseline for the treatment groups is <1.5 mm Hg. The data analysis plan required that change be assessed with a simple average of IOP at Month 2 and Month 3 using an APT-OC approach.

Summary statistics for IOP using an APT-OC approach are presented in Table 1 of [4.1]. Although fewer observations are included (because no data are estimated), the mean changes are nearly identical to those given in Table 14 for the APT-LOCF approach.

Table 15 shows the IOP estimates and confidence levels for the difference between treatments in the mean change in IOP from baseline, averaged over the Month 2 and Month 3 visits. Results for each time point are shown along with the estimated confidence (probability) that the true difference lies between -1.5 mm Hg and 1.5 mm Hg. The Hour 0 and Hour 2 estimates are provided for comparative purposes only and are not considered part of the primary hypothesis. The estimated difference between treatments is a weighted average of the mean difference within each clinic, based on the number of patients entered at each clinic. The 2 patients enrolled by investigator Spirn were combined with the 6 patients enrolled by investigator Cyrlin in this analysis and all other analyses of efficacy. Details on how point and interval estimates were calculated can be found in the data analysis plan [3.3].

As shown in Table 15, there is 97.1% confidence that the difference between treatment group means at Hour 8 is within -1.5 and 1.5 mm Hg. The point estimate for the treatment difference is -0.73 mm Hg. The negative difference indicates that the IOP-reduction in the concomitant group was greater on average than the IOP-reduction in the combination group. The 95% confidence interval for the difference in treatment-group means is (-1.53 mm Hg, 0.07 mm Hg) and zero is included as an interior point.

3. **Efficacy (Cont.)**

Table 15

IOP Estimates and Confidence Levels for the Difference Between Treatments (mm Hg) — Mean Change in IOP from Baseline Averaged Over the Month 2 and Month 3 Visits†

Double-Masked Phase

Exam	Sample Size		Difference Between Treatments	Standard Error of Difference	95% Conf. Int. for Difference Between Means	Confidence Difference Lies Between -1.5 and 1.5
	Combination	Concomitant				
Hour 0	112	116	-0.67 mm Hg	0.37	(-1.41, 0.06)	0.986*
Hour 2	112	115	-0.05 mm Hg	0.39	(-0.81, 0.71)	>0.999*
Hour 8	110	114	-0.73 mm Hg	0.41	(-1.53, 0.07)	0.971*

* The confidence is 0.950 or more that the difference between treatment means lies between -1.5 and 1.5 mm Hg.

† "All-Patients-Treated" Analysis (Observed Cases) -- Worse Eye.
The difference between treatments (Concomitant - Combination) is a weighted average of the mean difference within each clinic based on the number of patients entered at each clinic.

Data Source: [4.11]

3. **Efficacy (Cont.)**

The data analysis plan required that two diagnostic checks be performed before drawing inference with regard to treatment equivalence at Hour 8. First, the validity of averaging Month 2 and Month 3 data must be checked by comparing changes at the two visits separately within each treatment group. The criterion for determining whether the IOP changes were comparable was as follows: for each treatment group there must be ≥95.0% confidence (probability) that the difference in the mean change in IOP between the two visits is within -1.5 and 1.5 mm Hg. Table 2 in [4.1] gives estimates of the mean difference in IOP between the Month 2 and Month 3 visits (Month 3 minus Month 2). There is >99% confidence that the mean change is within -1.5 and 1.5 mm Hg for each treatment group estimate at Hour 8 (0.24 mm Hg for the combination group and -0.08 mm Hg for the concomitant group). Therefore, averaging Month 2 and Month 3 data is reasonable.

The second diagnostic check investigates the possible interaction between investigative site and treatment effect. Based on a SAS® Type II Sums of Squares ANOVA model, no significant interactions between investigative site and treatment effect were found.

In summary, the treatment groups have been demonstrated to be equivalent in their ability to reduce IOP at Hour 8 after 2 to 3 months of treatment, based on a definition that limits the treatment difference to be within -1.5 and 1.5 mm Hg.

3) Secondary Evaluations of Efficacy

The following secondary analyses, with regard to treatment equivalence, were also performed:

1. The same approach used for the primary analysis but with respect to the Hour 0 and Hour 2 time points.

2. An APT-LOCF approach to evaluate treatment equivalence at each visit for the Hour 0, Hour 2 and Hour 8 time points.

3. A PP-OC approach to all analyses.

3. **Efficacy (Cont.)**

Table 15 shows the IOP estimates and confidence levels for the difference between treatments in the mean change in IOP from baseline, averaged over the Month 2 and Month 3 visits, for the Hour 0 and Hour 2 time points. At Hour 0, the difference between treatment groups was -0.67 mm Hg, with a 95% confidence interval given by (-1.41 mm Hg, 0.06 mm Hg). At Hour 2, the difference was -0.05 mm Hg, with a 95% confidence interval given by (-0.81 mm Hg, 0.71 mm Hg). At both time points, the confidence is >98% that the groups are equivalent. Diagnostic checks indicate that it is reasonable to average Month 2 and Month 3 data at Hour 0 and Hour 2 (see Table 2, [4.1]) and that there is no interaction between treatment and clinic at these two time points (see Table 3, [4.1]).

Table 16 shows the IOP estimates and confidence levels for the difference between treatments in the mean change in IOP from baseline for each visit in the double-masked phase. Calculations were based on an "All-Patients-Treated," Last-Observation-Carried Forward approach and the difference was estimated with the same "weighting by clinic size" scheme as was used in the primary analysis of equivalence. The estimated confidence level associated with treatment equivalence is also shown. All confidence levels are greater than 0.950. Although the 95% confidence interval for Hour 0, Week 2 does not include zero, there is 96.7% confidence that the treatments are equivalent. Figure 2 displays the estimated difference in treatment means with 95% confidence intervals for the IOP change from baseline for the double-masked phase.

3. **Efficacy (Cont.)**

Table 16

IOP Estimates and Confidence Levels for Difference Between Treatments (mm Hg) — Mean Change in IOP from Baseline†
Double-Masked Phase

Exam	Sample Size		Difference Between Treatments	Standard Error of Difference	95% Conf. Int. for Diff. Between Means	Conf. Diff. Lies between -1.5 and 1.5
	Combination	Concomitant				
Hour 0						
Wk 2	115	120	-0.78 mm Hg	0.39	(-1.55,-0.02)	0.967 *
Mo 1	120	121	-0.42 mm Hg	0.37	(-1.15, 0.32)	0.998 *
Mo 2	120	121	-0.72 mm Hg	0.40	(-1.50, 0.07)	0.975 *
Mo 3	120	121	-0.52 mm Hg	0.42	(-1.34, 0.31)	0.990 *
Hour 2						
Wk 2	114	119	-0.23 mm Hg	0.43	(-1.08, 0.62)	0.998 *
Mo 1	119	120	-0.11 mm Hg	0.41	(-0.92, 0.69)	>0.999 *
Mo 2	119	120	-0.14 mm Hg	0.43	(-0.98, 0.71)	0.999 *
Mo 3	119	120	0.17 mm Hg	0.47	(-0.75, 1.10)	0.997 *
Hour 8						
Wk 2	111	115	-0.15 mm Hg	0.47	(-1.08, 0.79)	0.997 *
Mo 1	116	118	-0.74 mm Hg	0.43	(-1.58, 0.10)	0.963 *
Mo 2	116	118	-0.44 mm Hg	0.46	(-1.34, 0.46)	0.989 *
Mo 3	116	118	-0.69 mm Hg	0.44	(-1.55, 0.18)	0.967 *

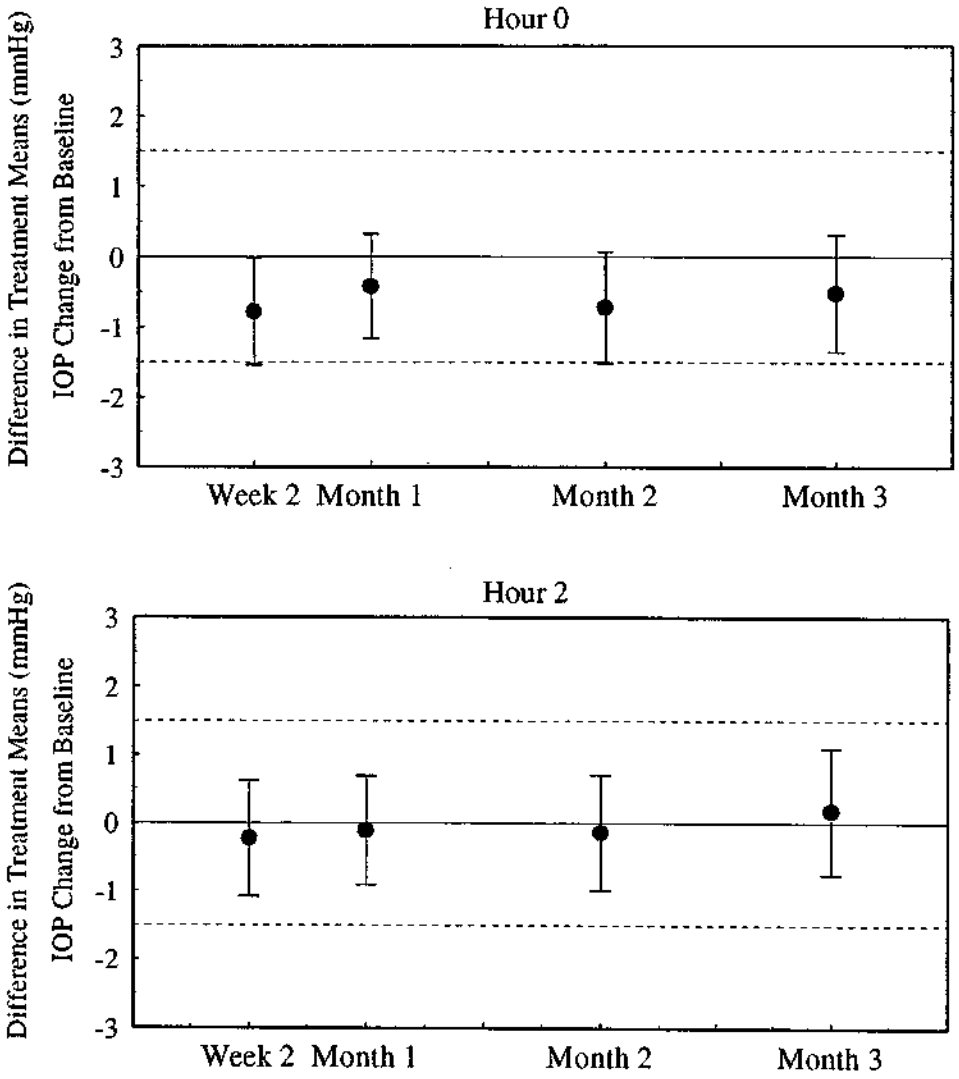
* The confidence is 0.950 or more that the difference between treatment means lies between -1.5 and 1.5 mm Hg.
† All-Patients-Treated Analysis (Last Observation Carried Forward) -- Worse Eye.
The difference between treatments is a weighted average of the mean difference within each clinic based on the number of patients entered at each clinic.

Data Source: [4.11]

3. **Efficacy** (Cont.)

Figure 2

Estimated Difference in Treatment Means with 95% Confidence Interval†
IOP Change from Baseline -- Double-Masked Phase



Concomitant-Combination; a negative difference indicates a greater decrease in IOP in the concomitant group. The difference between treatment groups is a weighted average of the mean difference within each clinic based on the number of patients enrolled at each clinic.

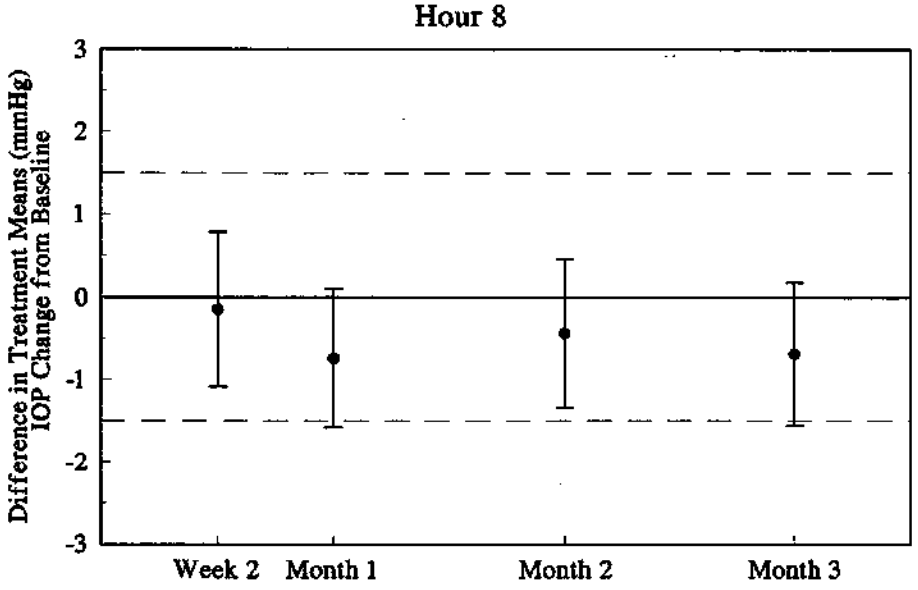
† "All-Patients-Treated" Analysis (Last Observation Carried Forward) -- Worse Eye.

Data Source: [4.11]

3. **Efficacy (Cont.)**

Figure 2 (Cont.)

Estimated Difference in Treatment Means with 95% Confidence Interval†
IOP Change from Baseline -- Double-Masked Phase



Concomitant - Combination; a negative difference indicates a greater decrease in IOP in the concomitant group. The difference between treatment groups is a weighted average of the mean difference within each clinic based on the number of patients enrolled at each clinic.

† "All-Patients-Treated" Analysis (Last Observation Carried Forward) -- Worse Eye.

Data Source: [4.11]

The results of the "per-protocol observed cases" analyses are provided in [4.2]. When the primary analysis for Hour 8 is performed on this data set, equivalence no longer holds; the estimated confidence of 0.942 is below 0.95 (see Table 2, [4.2]). While treatment equivalence is demonstrated at Hour 2, it is not demonstrated at Hour 0, when the average of the Month 2 and Month 3 data are used. When individual visits are considered, all of the Hour 2 confidence estimates, one half (Week 2 and Month 2) of the Hour 8 confidence estimates, and one half (Months 1 and 3) of the Hour 0 confidence estimates exceed 0.950 (see Table 3, [4.2]). In all cases, the point estimate for treatment difference suggests that the IOP-lowering effect of the concomitant group does not exceed 1.0 mm Hg more than the IOP-lowering effect of the combination group.

3. **Efficacy** (Cont.)

4) **Effect of Baseline Covariates on IOP**

The effect of baseline covariates on change in IOP from baseline was explored along with their interaction with treatment. The response that was used was the average of Month 2 and Month 3 changes in IOP, which is consistent with the approach taken for the primary analysis. The following baseline factors were examined:

- Investigator
- Age (<65, ≥65)
- Race (White, Other)
- Sex
- Iris Color (Dark, Light)

Table 3 in [4.1] lists p-values that were obtained for treatment, factor (covariate), and treatment-by-factor interaction from ANOVA models using SAS® Type II Sums of Squares. A significant effect due to Investigator was observed at the Hour 0, Hour 2 and Hour 8 time points. No other covariates were significant and there were no significant interactions.

Summary statistics for these covariates are also provided in [4.3]. They are based on an APT-LOCF population.

b. **Open-Label Phase**

The principal objective of the open-label phase of the study was to demonstrate that the IOP-lowering effect of 0.5% timolol/2.0% MK-0507 combination solution (b.i.d.) was maintained for up to 12 months. An additional objective of the open-label phase of the study was to compare the IOP-lowering effect of the 0.5% timolol/2.0% MK-0507 combination solution (b.i.d.) for up to 12 months between patients who continued on 0.5% timolol/2.0% MK-0507 combination solution (b.i.d.) and those patients who were switched from concomitant administration of 0.5% timolol (b.i.d.) plus 2.0% MK-0507 (t.i.d.) after the 3-month double-masked phase.

After completing the double-masked phase of the study, patients were eligible to enter the open-label phase and receive the 0.5% timolol/2.0% MK-0507 combination solution (b.i.d.). Patients in the open-label phase were scheduled to return to the clinic for Month 6, Month 9, and Month 12 evaluations of IOP. IOP measurements were obtained at Hour 0 (0830 hours) and Hour 2 (1030 hours) at each of these visits. All 220 patients who completed the double-masked phase entered the open-label phase.

3. **Efficacy (Cont.)**

1) **Descriptive Summaries**

Table 17 presents IOP summary statistics (by initial treatment assignment) for each visit in the open-label phase using an APT-LOCF approach. Also presented, for reference, are IOP summary statistics for Month 3 (the final visit of the double-masked phase) for the patients who continued into the open-label phase. Changes from baseline for the combination group ranged from -3.5 to -5.4 mm Hg and for the concomitant therapy group, from -3.2 to -5.2 mm Hg. For each visit, mean reductions in IOP at Hour 2 were approximately 1.5 mm Hg greater than the reductions at Hour 0. Percent changes from baseline for the combination group ranged from -13.7 to -21.4 and for the concomitant therapy group, from -12.1 to -20.7. For each visit, percent reductions in IOP at Hour 2 were approximately 6.5 percentage points greater than the percent reductions at Hour 0. Figure 3 displays the IOP treatment means and standard errors for each treatment group across visits in the open-label phase. Estimates were based on an APT-LOCF approach.

2) **Evaluations of Efficacy**

Two evaluations of efficacy during the open-label phase were performed. First, to assess whether the IOP-lowering effect of the fixed combination (b.i.d.) was maintained for up to 12 months, 95% confidence intervals were calculated for the change in IOP from the time-matched baseline at Hour 0 and Hour 2 at Months 6, 9, and 12 for the group of patients who remained on the fixed combination (b.i.d.) during the open-label phase of the study. Second, comparisons of the change in IOP from baseline were made between patients who received the fixed combination (b.i.d.) during both phases and those who switched from the concomitant group during the double-masked phase to the combination during the open-label phase. An APT-LOCF approach was used for both analyses.

3. **Efficacy** (Cont.)

Table 17

IOP Summary Statistics† (mm Hg) — Open-Label Phase

Exam	Treatment	N	Baseline			Treatment			Change			Percent Change		
			Mean	Std	Med	Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Hour 0														
Mo 3*	Combination	107	25.9	2.9	25.0	22.1	3.8	22.0	-3.8	2.8	-4.0	-14.6	10.7	-15.4
	Concomitant	113	25.8	3.3	25.0	21.5	3.8	21.0	-4.4	3.4	-4.0	-16.6	12.8	-16.0
Mo 6	Combination	105	26.0	2.9	25.0	22.2	4.3	22.0	-3.8	3.2	-4.0	-14.8	12.6	-16.7
	Concomitant	111	25.8	3.3	25.0	22.3	3.5	22.0	-3.5	3.7	-4.0	-12.9	13.3	-14.3
Mo 9	Combination	105	26.0	2.9	25.0	22.3	3.9	22.0	-3.6	3.1	-4.0	-13.9	11.6	-14.3
	Concomitant	112	25.8	3.3	25.0	21.7	3.7	21.0	-4.1	3.5	-4.0	-15.6	13.0	-15.7
Mo 12	Combination	105	26.0	2.9	25.0	22.4	5.1	22.0	-3.5	4.3	-4.0	-13.7	15.5	-14.3
	Concomitant	112	25.8	3.3	25.0	22.6	4.2	22.0	-3.2	4.1	-3.0	-12.1	14.8	-13.3
Hour 2														
Mo 3*	Combination	107	24.8	2.9	24.0	19.7	3.5	19.0	-5.1	3.4	-5.0	-20.3	12.8	-21.7
	Concomitant	113	24.8	2.9	24.0	19.7	3.2	19.0	-5.1	3.4	-5.0	-20.2	12.4	-21.7
Mo 6	Combination	105	24.9	2.9	24.0	19.5	3.4	20.0	-5.4	3.4	-5.0	-21.4	12.5	-21.7
	Concomitant	108	24.6	2.5	24.0	19.5	3.3	19.0	-5.2	3.4	-5.0	-20.7	13.1	-21.7
Mo 9	Combination	105	24.9	2.9	24.0	19.9	3.3	20.0	-5.0	3.3	-5.0	-19.7	12.7	-20.8
	Concomitant	108	24.6	2.5	24.0	19.6	3.5	20.0	-5.1	3.2	-5.0	-20.5	12.5	-21.1
Mo 12	Combination	105	24.9	2.9	24.0	19.8	5.1	19.0	-5.1	4.5	-6.0	-20.5	16.4	-21.7
	Concomitant	108	24.6	2.5	24.0	19.7	3.5	19.0	-5.0	3.5	-5.0	-20.0	12.9	-20.0

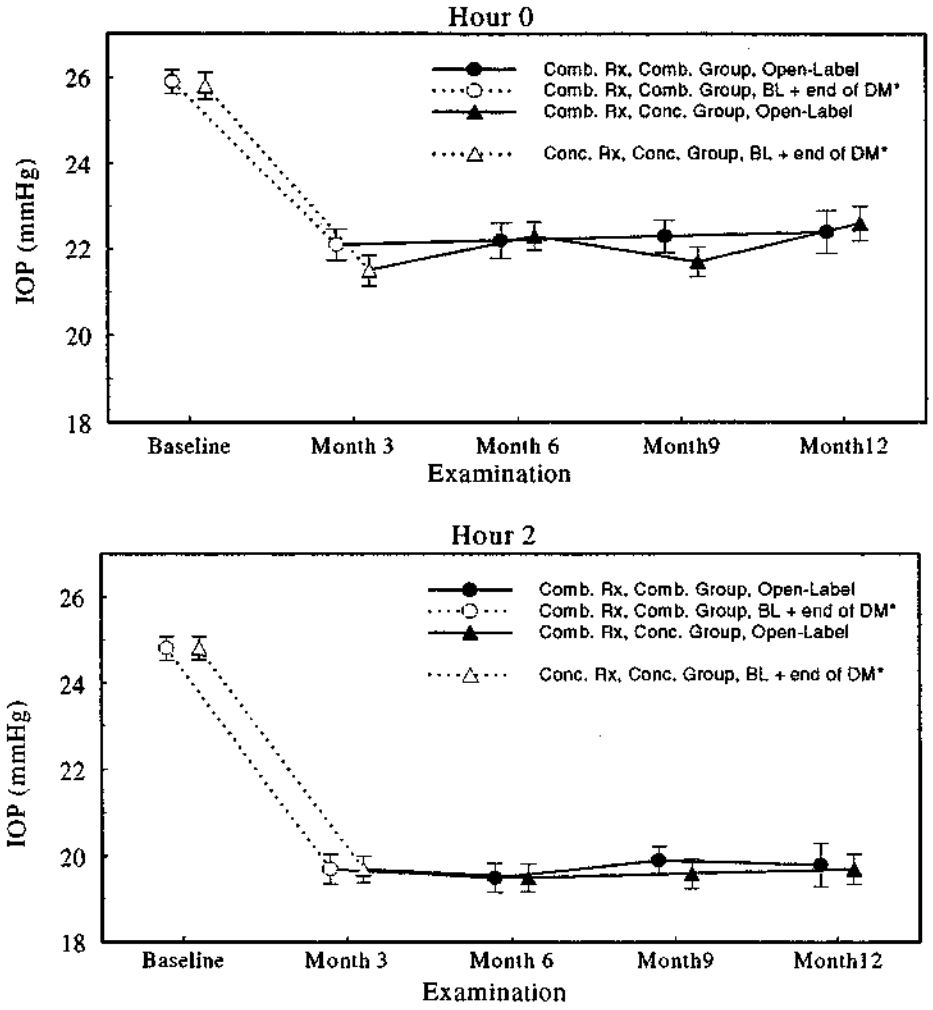
† "All-Patients-Treated" Analysis (Last Observation Carried Forward) - Worse Eye.
* Summary statistics for Month 3 (final visit of the double-masked phase) for patients who continued into the open-label phase are included for reference.
Combination and concomitant refer to the initial treatment-group assignments; all patients received 0.5% timolol/2.0% MK-0507 fixed combination b.i.d. during the open-label phase.

Data Source: [4.11]

3. **Efficacy (Cont.)**

Figure 3

IOP Treatment Means and Standard Errors+
Open-Label Phase



Combination and concomitant refer to the initial treatment group assignments; all patients received 0.5% Timolol/2.0% MK-0507 fixed combination (b.i.d.) during the open-label phase.

+ "All-Patients-Treated" (Last Observation Carried Forward) - Worse Eye

* Baseline (BL) and end of double-masked (DM) phase provided for reference.

Data Source: [4.11]

3. **Efficacy (Cont.)**

Table 18 presents the mean change in IOP from baseline and the corresponding 95% confidence interval for each visit in the open-label phase, for patients who received the combination during both phases of the study. All mean changes from baseline displayed in Table 18 are significantly different from 0 since all of the 95% confidence intervals exclude 0 as an interior point. The mean changes from baseline for Hour 0 during the open-label phase range from -3.8 to -3.5 mm Hg. These changes are similar in magnitude to the mean change from baseline of -3.8 mm Hg observed at the end of the double-masked phase in the combination group. The mean changes from baseline for Hour 2 during the open-label phase range from -5.4 to -5.0 mm Hg. These changes are similar in magnitude to the mean change from baseline of -5.1 mm Hg observed at the end of the double-masked phase. The magnitude of the difference in mean change in IOP from baseline between the Month 3 visit in the double-masked phase and each visit in the open-label phase did not exceed 0.3 mm Hg at Hour 0 or at Hour 2. Hence, it is concluded that the IOP-lowering effect of the fixed combination (b.i.d.) was maintained for up to 12 months.

Table 18

Mean Change in IOP (mm Hg) From Baseline and 95% Confidence Intervals†
Open-Label Phase

		Initial Treatment Assignment		
		Combination (N=107)		
Hour	Exam	N	Mean Change	95% C.I.
0	Mo 6	105	-3.8	(-4.4, -3.2)
	Mo 9	105	-3.6	(-4.2, -3.0)
	Mo 12	105	-3.5	(-4.3, -2.7)
2	Mo 6	105	-5.4	(-6.1, -4.7)
	Mo 9	105	-5.0	(-5.6, -4.4)
	Mo 12	105	-5.1	(-6.0, -4.2)

† "All-Patients-Treated" Analysis (Last Observation Carried Forward) - Worse Eye.

Data Source: [4.11]

3. **Efficacy (Cont.)**

Table 19 presents IOP estimates and confidence levels for the difference between initial treatment groups in the mean change in IOP from baseline at Hour 0 and Hour 2 for each visit in the open-label phase. Comparisons between treatment groups (defined by initial treatment assignment) were assessed with the estimated confidence level (probability) that the difference between the means of each group was <1.5 mm Hg. A 95% confidence interval for each estimated difference is also shown. At all time points, the confidence is >98% that the treatment groups are equivalent. Figure 4 displays the estimated difference in treatment means with 95% confidence intervals for the IOP change from baseline during the open-label phase. These data show that the initial treatment assignment did not affect efficacy during the open-label phase.

Table 19

IOP Estimates and Confidence Levels for Difference
Between Initial Treatment Groups
Mean Change in IOP (mm Hg) From Baseline†

Open-Label Phase

Exam	Sample Size		Difference Between Treatments	Standard Error of Difference	95% Conf. Int. for Diff. Between Means	Conf. Diff. Lies between -1.5 and 1.5
	Combination	Concomitant				
Hour 0						
Mo 6	105	111	0.32 mm Hg	0.45	(-0.57, 1.22)	0.995 *
Mo 9	105	112	-0.47 mm Hg	0.42	(-1.30, 0.36)	0.992 *
Mo 12	105	112	0.36 mm Hg	0.53	(-0.67, 1.40)	0.984 *
Hour 2						
Mo 6	105	108	0.23 mm Hg	0.46	(-0.69, 1.14)	0.997 *
Mo 9	105	108	-0.05 mm Hg	0.45	(-0.93, 0.84)	0.999 *
Mo 12	105	108	0.11 mm Hg	0.55	(-0.97, 1.19)	0.992 *

* The confidence is 0.950 or more that the difference between treatment means lies between -1.5 and 1.5 mm Hg.

† "All-Patients-Treated" Analysis (Last Observation Carried Forward) -- Worse Eye.

The difference between treatments is a weighted average of the mean difference within each clinic based on the number of patients entered at each clinic.

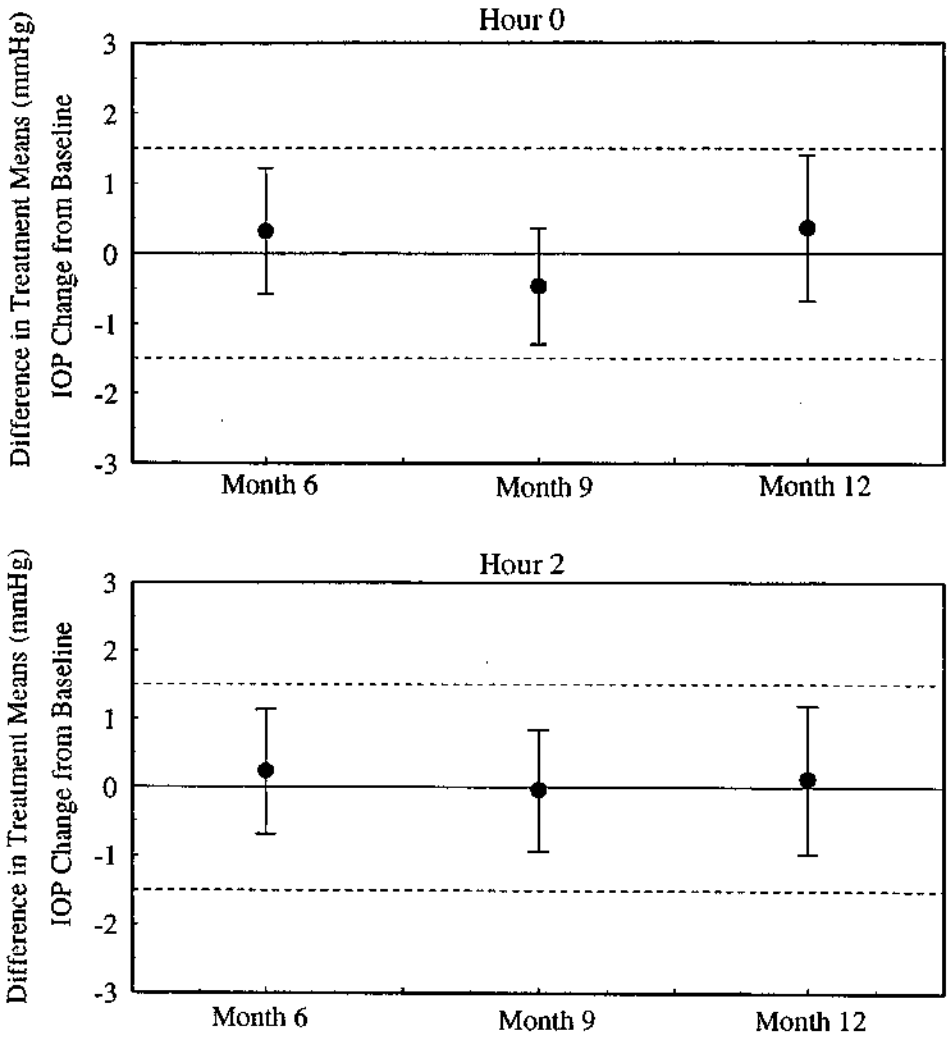
Combination and concomitant refer to the initial treatment group assignments; all patients received 0.5% timolol/2.0% MK-0507 fixed combination b.i.d. during the open-label phase.

Data Source: [4.11]

3. **Efficacy (Cont.)**

Figure 4

Estimated Difference in Treatment Means with 95% Confidence Interval†
IOP Change from Baseline — Open-Label Phase



Concomitant-Combination; a negative difference indicates a greater decrease in IOP in the concomitant group. The difference between treatment groups is a weighted average of the mean difference within each clinic based on the number of patients enrolled at each clinic.

† "All-Patients-Treated" Analysis (Last Observation Carried Forward) -- Worse Eye.

Data Source: [4.11]

4. Safety

a. Adverse Experiences—Clinical

The analysis of clinical adverse experiences included all 242 patients who received study medication in the double-masked phase and all 220 patients who received study medication in the open-label phase. The incidence rates for adverse experiences in the two treatment groups were compared using Fisher's exact test (two-tailed).

1) Overall Assessment of Clinical Adverse Experiences

Table 20 presents a summary of the clinical adverse experiences reported during this study. Of the 242 patients who entered the double-masked phase, 73 (30%) had a clinical adverse experience: 41 (34%) in the combination group and 32 (26%) in the concomitant group. There were no statistically significant differences between the treatment groups in the proportion of patients with any adverse experience, with drug-related adverse experiences, or with serious adverse experiences. There were also no statistically significant differences between the treatment groups in the proportion of patients who died or were discontinued due to an adverse experience during the double-masked phase.

Tables 21 presents the number (%) of patients with clinical adverse experiences, by body system and by specific adverse experience, during the double-masked phase of the study. Only the specific adverse experiences with an observed incidence ≥1% in either treatment group are shown. There were no significant differences between the treatment groups for any body system or for any specific adverse experience. Similarly, there were no significant differences between the treatment groups, either by body system or by specific adverse experience, in the proportion of patients with an adverse experience that was considered possibly, probably, or definitely drug related. The most frequently reported adverse experiences during the double-masked phase were headache (3%) and eye discharge (3%) in the combination group and eye irritation (3%) in the concomitant group.

4. Safety (Cont.)

Table 22 presents the number (%) of patients with clinical adverse experiences, by body system and by specific adverse experience, during the open-label phase. Only the specific adverse experiences with an observed incidence ≥1% are shown. Clinical adverse experiences were reported by 101 (46%) of the 220 patients who entered the open-label phase of the study. The most frequently reported adverse experiences during this phase were upper respiratory infection (6%) and lens opacity (5%); none of these adverse experiences was considered drug related.

Table 20

Clinical Adverse Experience Summary

Number (%) of Patients	Combination (N=121)		Concomitant (N=121)	
	N	(%)	N	(%)
Double-Masked Phase				
Patients evaluated	121		121	
With any adverse experience	41	(34)	32	(26)
Drug-related adverse experience†	12	(10)	12	(10)
Serious adverse experience	3	(2)	0	(0)
Patients who died	1	(1)	0	(0)
Discontinued due to adverse experience	7	(6)	3	(2)

	Combination (N=220)	
	N	(%)
Open-Label Phase		
Patients evaluated	220	
With any adverse experience	101	(46)
Drug-related adverse experience†	14	(6)
Serious adverse experience	26	(12)
Patients who died	2	(1)
Discontinued due to adverse experience	9	(4)

No significant differences between treatment groups were found.
†Drug-related implies possibly, probably, or definitely caused by the test drug.

Data Source: [4.12] and [4.26]

4. Safety (Cont.)

Table 21

Number (%) of Patients With Clinical Adverse Experiences
by Body System and by Specific Adverse Experience
(Incidence ≥1% in Any Treatment Group)

Double-Masked Phase

Adverse Experience	Combination (N=121)			Concomitant (N=121)		
	N	(%)		N	(%)	
Patients with any adverse experience	41	(34)	[12]	32	(26)	[12]
Body as a whole/site unspecified	3	(2)	[0]	2	(2)	[0]
Cardiovascular System	2	(2)	[0]	2	(2)	[1]
Hypertension	0	(0)	[0]	2	(2)	[1]
Digestive System	7	(6)	[3]	1	(1)	[1]
Dry Mouth	3	(2)	[3]	1	(1)	[1]
Nausea	2	(2)	[1]	0	(0)	[0]
Endocrine System	1	(1)	[0]	1	(1)	[0]
Metabolic/Nutritional/Immune	2	(2)	[0]	0	(0)	[0]
Musculoskeletal System	2	(2)	[1]	0	(0)	[0]
Nervous System & Psychiatric	8	(7)	[2]	4	(3)	[1]
Depression	2	(2)	[0]	1	(1)	[0]
Dizziness	2	(2)	[0]	0	(0)	[0]
Headache	4	(3)	[1]	1	(1)	[0]
Respiratory System	10	(8)	[1]	3	(2)	[0]
Cough	3	(2)	[1]	0	(0)	[0]
Infection, Respiratory, Upper	2	(2)	[0]	1	(1)	[0]

4. Safety (Cont.)

Table 21 (Cont.)

Numbers (%) of Patients With Clinical Adverse Experiences
by Body System and by Specific Adverse Experience
(Incidence ≥1% in Any Treatment Group)

Double-Masked Phase

Adverse Experience	Combination (N=121)			Concomitant (N=121)		
	N	(%)		N	(%)	
Skin & Skin Appendage	2	(2)	[0]	1	(1)	[0]
Special Senses	23	(19)	[7]	20	(17)	[8]
Blurred Vision	1	(1)	[1]	3	(2)	[1]
Burning and/or Stinging, Eye	1	(1)	[0]	2	(2)	[2]
Conjunctivitis	1	(1)	[0]	2	(2)	[1]
Defect, Visual Field	2	(2)	[0]	1	(1)	[0]
Discharge, Eye	4	(3)	[2]	2	(2)	[0]
Foreign Body Sensation	2	(2)	[2]	0	(0)	[0]
Irritation, Eye	1	(1)	[0]	4	(3)	[2]
Itching, Eye	0	(0)	[0]	2	(2)	[0]
Opacity, Lens	2	(2)	[0]	1	(1)	[0]
Retinopathy, Diabetic	2	(2)	[0]	0	(0)	[0]
Urogenital System	2	(2)	[1]	2	(2)	[1]
Urolithiasis	2	(2)	[1]	0	(0)	[0]

[ ] Number of patients with adverse experiences possibly, probably, or definitely drug related.

If a patient reported a particular adverse experience more than once, the patient was counted only once with that adverse experience. Patients with more than one adverse experience in a body system category are counted only once in that body system total and in the overall total.

All body systems in which at least 1 patient had an adverse experience are listed.

No significant differences between treatment groups were found.

Data Source: [4.12]

4. Safety (Cont.)

Table 22

Number (%) of Patients With Clinical Adverse Experiences
by Body System and by Specific Adverse Experience
(Incidence ≥1%)

Open-Label Phase

Adverse Experience	Combination (N=220)		
	N	(%)	
Patients with any AE	101	(46)	[14]
Body As A Whole/Site Unspecified	17	(8)	[1]
Edema/Swelling	3	(1)	[0]
Pain, Abdominal	4	(2)	[0]
Pain, Chest	3	(1)	[1]
Cardiovascular System	16	(7)	[0]
Hypertension Increased	3	(1)	[0]
Digestive System	15	(7)	[2]
Dyspepsia	3	(1)	[0]
Vomiting	3	(1)	[0]
Endocrine System	6	(3)	[0]
Diabetes Mellitus	3	(1)	[0]
Diabetes, Loss of Control	3	(1)	[0]
Hemic & Lymphatic System	3	(1)	[0]
Metabolic/Nutritional/Immune	3	(1)	[1]
Musculoskeletal System	15	(7)	[0]
Tendinitis	3	(1)	[0]

4. Safety (Cont.)

Table 22 (Cont.)

Number (%) of Patients With Clinical Adverse Experiences
by Body System and by Specific Adverse Experience
(Incidence ≥1%)

Open-Label Phase

Adverse Experience	Combination (N=220)		
	N	(%)	
Nervous System & Psychiatric	15	(7)	[3]
Anxiety	4	(2)	[0]
Depression	3	(1)	[1]
Headache	4	(2)	[0]
Respiratory System	30	(14)	[2]
Bronchitis	4	(2)	[1]
Cough	3	(1)	[0]
Infection, Respiratory, Upper	13	(6)	[0]
Influenza	5	(2)	[0]
Sinus Disorder	3	(1)	[1]
Sinusitis	3	(1)	[0]
Skin & Skin Appendage	10	(5)	[0]
Neoplasm, Skin, Malignant	3	(1)	[0]
Special Senses	43	(20)	[8]
Conjunctivitis	4	(2)	[1]
Defect, Visual Field	5	(2)	[0]
Opacity, Lens	11	(5)	[0]
Urogenital System	8	(4)	[1]

[ ] Number of patients with adverse experiences possibly, probably, or definitely drug related.

If a patient reported a particular adverse experience more than once, the patient was counted only once with that adverse experience. Patients with more than one adverse experience in a body system category are counted only once in that body system total and in the overall total.

All body systems in which at least 1 patient had an adverse experience are listed.

Data Source: [4.12]

4. Safety (Cont.)

2) Serious Clinical Adverse Experiences

Table 23 lists the patients with serious clinical adverse experiences during the double-masked phase of the study. There were three such patients, all of whom were in the combination group. None of these experiences was considered drug related. One of these patients died and is described below; the remaining patients are described in [4.7].

Patient AN 6133 was a 73-year-old white male with open-angle glaucoma, diabetes, hypertension, and poor circulation. Concomitant medications included Glynase, Dyazide, and aspirin. On Study Day 29, he was hospitalized because of jaundice secondary to a pancreatic blockage, which was biopsied and found to be malignant and inoperable. The patient developed pneumonia on Study Day 35, and the timolol/MK-0507 combination was discontinued on Study Day 47. The patient died on Study Day 58. These adverse experiences were considered definitely not related to the study medication.

Table 24 lists the 26 patients with serious clinical adverse experiences during the open-label phase of the study. One serious adverse experience (urolithiasis) was considered possibly drug related; this patient (AN 6174) recovered without treatment and completed the study with no further problems. Two patients died as the result of adverse experiences that occurred during the open-label phase of the study and are described below. The remaining patients with serious adverse experiences are described in [4.7].

Patient #6103 was a 66-year-old black female with open-angle glaucoma, hypertension, arthritis, and elevated cholesterol. She completed the double-masked phase of the study on Day 84 and began receiving open-label 0.5% timolol/2.0% MK-0507 b.i.d. Concomitant medications were trichlormethiazide, piroxicam, and lovastatin. On Day 140, the patient was hospitalized due to severe headache. She did not have her study medication with her, so timolol 0.5% b.i.d. was initiated. Subarachnoid hemorrhage and cerebral aneurysm were discovered and treated surgically. The patient required artificial ventilation and was nonverbal with multiple neurological problems after surgery. Approximately 2 months later, the patient developed pneumonia followed by sepsis. She died of these complications approximately 3 months after timolol/MK-0507 was

4. Safety (Cont.)

stopped. None of these events was considered related to the study medication. (Note: Because the onset of pneumonia and sepsis was more than 14 days after study medication was stopped, they are not included in any of the adverse experience tables presented in this report. Because the patient's death was caused by complications secondary to the subarachnoid hemorrhage experienced during the open-label phase of the study, the death is included in the adverse experience tables in this report.)

Patient AN 6143 was a 73-year-old white male with open-angle glaucoma and a history of prostate cancer and seborrheic keratosis. He completed the double-masked phase of the study on Day 92 and began receiving open-label 0.5% timolol/2.0% MK-0507 b.i.d. There were no concomitant medications. On Day 264, colon cancer and liver cancer were diagnosed and the patient was hospitalized. The timolol/MK-0507 combination was discontinued on Day 284 because the patient became comatose. The patient died on Day 286. None of these events was considered related to the study medication.

4. Safety (Cont.)

Table 23

Listing of Patients With Serious Clinical Adverse Experiences

Double-Masked Phase

Allocation Number	Study Number	Sex	Age	Day of Onset	Adverse Experience	Duration	Intensity	Drug Related	Action Taken	Outcome
Combination (N=121)										
6133	043003	M	73	29	Jaundice	30 days	Severe	Definitely Not	None	Still present
				32	Neoplasm, Pancreas	27 days	Severe	Definitely Not	None	Still present
				35	Pneumonia	24 days	Severe	Definitely Not	Discon	Still present
				58	Death		Severe	Definitely Not		
6138	043003	M	74	11	Hematuria	13 days	Moderate	Probably Not	None	Recovered
				11	Dysuria	13 days	Moderate	Probably Not	None	Recovered
				20	Urolithiasis	4 days	Moderate	Definitely Not	Discon	Recovered
6183	043003	M	75	99	Lesion, Skin	37 days	Mild	Definitely Not	None	Recovered

Data Source: [4.12]

4. Safety (Cont.)

Table 24

Listing of Patients With Serious Clinical Adverse Experiences

Open-Label Phase

Allocation Number	Study Number	Sex	Age	Day of Onset	Adverse Experience	Duration	Intensity	Drug Related	Action Taken	Outcome
Combination (N=220)										
6103	043002	F	66	140	Hemorrhage, Subarachnoid	42 days	Severe	Probably Not	Discon	Still Present
				140	Headache	42 days	Severe	Probably Not	Discon	Still Present
				235	Death		Severe	Probably Not		
6183	043003	M	75	372	Neoplasm, Skin, Malignant	65 days	Mild	Definitely Not	None	Recovered
6254	043005	F	54	167	Angina Pectoris	7 days	Moderate	Probably Not	None	Recovered
				167	Cardiomyopathy	7 days	Moderate	Probably Not	None	Recovered
6082	043006	F	70	269	Myocardial Infarction	1 days	Severe	Probably Not	None	Recovered
6128	043007	F	64	358	Erysipelas	8 days	Moderate	Definitely Not	None	Recovered
6130	043007	F	59	229	Neoplasm, Breast, Malignant	19 days	Moderate	Definitely Not	Discon	Recovered
6256	043007	M	62	268	Neoplasm, Skin, Malignant	1 days	Mild	Definitely Not	None	Recovered
6072	043009	F	57	225	Neoplasm, Sinus, Benign	1 days	Severe	Definitely Not	None	Recovered
6075	043009	M	67	338	CVA	6 days	Moderate	Definitely Not	None	Recovered
6274	043009	M	59	264	CVA	202 days	Severe	Probably Not	None	Recovered
6004	043012	F	63	184	Cystocele	120 days	Severe	Probably Not	None	Recovered
				289	Neoplasm, Lung	269 days	Mild	Probably Not	None	Still Present

4. Safety (Cont.)

Table 24 (Cont.)

Listing of Patients With Serious Clinical Adverse Experiences

Open-Label Phase

Allocation Number	Study Number	Sex	Age	Day of Onset	Adverse Experience	Duration	Intensity	Drug Related	Action Taken	Outcome
6143	043012	M	73	264	Neoplasm, Intestinal, Malignant	23 days	Severe	Probably Not	Discon	Still Present
				264	Neoplasm, Liver, Malignant	23 days	Severe	Probably Not	Discon	Still Present
				286	Death		Severe	Probably Not		
6243	043012	M	62	140	Myocardial Infarction	1 days	Severe	Probably Not	None	Recovered
				216	Deformity, Chest	2 days	Moderate	Definitely Not	None	Recovered
6134	043003	F	72	182	Pain, Chest	3 days	Severe	Definitely Not	None	Recovered
				182	Dyspepsia	2 days	Severe	Definitely Not	None	Recovered
6135	043003	F	81	125	Syncope	2 min	Severe	Definitely Not	None	Recovered
6033	043004	M	70	356	Neoplasm, Skin, Malignant	42 days	Mild	DefinitelyNot	None	Recovered
6026	043010	F	54	156	Neoplasm, Breast, Malignant	1 days	Mild	Definitely Not	None	Recovered
6155	043010	M	42	290	Displacement, Disc, Intervertebral	1 days	Severe	Definitely Not	None	Recovered
6168	043013	M	44	160	Appendicitis	5 days		Definitely Not	None	Recovered

4. Safety (Cont.)

Table 24 (Cont.)

Listing of Patients With Serious Clinical Adverse Experiences

Open-Label Phase

Allocation Number	Study Number	Sex	Age	Day of Onset	Adverse Experience	Duration	Intensity	Drug Related	Action Taken	Outcome
6260	043013	F	41	127	Neoplasm, Vaginal, Malignant	61 days	Severe	Definitely Not	None	Recovered
				364	Embolism/ Infarction, Pulmonary	10 days	Severe	Definitely Not	None	Recovered
6055	043015	F	70	242	Syncope	3 min	Severe	Probably Not	None	Recovered
6061	043016	M	75	173	Arrhythmia	22 days	Moderate	Definitely Not	Discon	Recovered
6174	043017	F	65	130	Urolithiasis	8 days	Severe	Possibly	None	Recovered
6223	043017	F	66	229	Fracture, Patella	38 days	Severe	Definitely Not	None	Recovered
6118	043018	F	44	108	Pneumonia	3 days	Moderate	Definitely Not	None	Recovered
6120	043018	F	48	339	Depressive Disorder	19 days	Severe	Probably Not	None	Recovered

Data Source: [4.12] and [4.26]

4. Safety (Cont.)

3) **Patients Discontinued Due to Clinical Adverse Experiences**

Table 25 lists the 10 patients who were discontinued due to clinical adverse experiences during the double-masked phase. Seven patients were in the combination group, and three were in the concomitant group.

Five of the seven patients who were discontinued from the combination group had drug-related adverse experiences. In 3 patients the adverse experience was ocular (eyelid irritation, eyelid edema, and ocular allergy, respectively), and in 2 patients it was nonocular (urolithiasis in 1 patient and insomnia, nausea, cough, dry mouth, and pharyngeal discomfort in the other). All 5 patients recovered after the timolol/MK-0507 combination was stopped. The remaining 2 patients discontinued the timolol/MK-0507 combination because of serious nonocular adverse experiences that were not drug related; these patients are described in [4.7].

Two of the three patients who were discontinued from the concomitant group had drug-related adverse experiences. In both patients the adverse experience was ocular (conjunctivitis and ocular allergy, respectively). Both patients recovered after timolol and MK-0507 were stopped. The remaining patient discontinued timolol and MK-0507 because of an ocular adverse experience (visual field defect) that was not drug related.

Table 26 lists the 9 patients who were discontinued due to clinical adverse experiences during the open-label phase. Four patients discontinued the timolol/MK-0507 combination because of drug-related adverse experiences. Three of these patients had ocular adverse experiences (blurred vision in 1, conjunctivitis in 1, and blepharitis and eyelid inflammation in 1); the fourth patient had a nonocular adverse experience (depression). The ocular adverse experiences resolved after the timolol/MK-0507 combination was stopped, but the depression did not. Of the remaining 5 patients who discontinued open-label therapy, 1 had a visual field defect that was definitely not drug related, and 4 had serious nonocular adverse experiences that were not drug related; the patients with serious adverse experiences are described in [4.7].

4. Safety (Cont.)

Table 25

Listing of Patients Who Discontinued Due to Clinical Adverse Experiences

Double-Masked Phase

Allocation Number	Study Number	Sex	Age	Day of Onset	Adverse Experience	Duration (Days)	Day Discontinued	Intensity	Drug Related	Serious	Outcome
Combination (N=121)											
6228	043001	M	56	75	Urolithiasis	32	85	Mild	Possibly	No	Recovered
6133	043003	M	73	35	Pneumonia	24	47	Severe	Definitely Not	Yes	Still present
6138	043003	M	74	20	Urolithiasis	4	15	Moderate	Definitely Not	Yes	Recovered
6025	043010	M	30	60	Irritation, Eyelid	36	93	Moderate	Possibly	No	Recovered
6157	043010	F	43	2	Diarrhea	76	15	Mild	Probably Not	No	Recovered
				2	Dizziness	16		Mild	Probably Not	No	Recovered
				2	Insomnia	71		Mild	Possibly	No	Recovered
				2	Nausea	15		Mild	Possibly	No	Recovered
				2	Weight Loss	20		Mild	Probably Not	No	Recovered
				2	Cough	62		Mild	Possibly	No	Recovered
				2	Dry Mouth	26		Mild	Possibly	No	Recovered
				2	Discomfort, Pharyngeal	20		Mild	Possibly	No	Recovered
				10	Arthritis	7		Mild	Probably Not	No	Recovered
				13	Otorrhagia	3		Mild	Probably Not	No	Recovered
6098	043011	F	56	2	Edema, Eyelid	58	11	Mild	Definitely	No	Recovered
6163	043011	M	79	32	Allergy, Ocular	7	33	Moderate	Definitely	No	Recovered
Concomitant (N=121)											
6076	043009	M	58	1	Conjunctivitis	15	13	Moderate	Probably	No	Recovered
6279	043011	M	65	46	Allergy, Ocular	8	49	Moderate	Definitely	No	Recovered
6262	043013	M	62	97	Defect, Visual Field	1	97	—	Definitely Not	No	Still present

Data Source: [4.12]

4. Safety (Cont.)

Table 26

Listing of Patients Who Discontinued Due to Clinical Adverse Experiences

Open-Label Phase

Allocation Number	Study Number	Sex	Age	Day of Onset	Adverse Experience	Duration (Days)	Day Discontinued	Intensity	Drug Related	Serious	Outcome
Combination (N=220)											
6269	043001	F	60	84	Depression	93	176	Moderate	Probably	No	Still Present
6103	043002	F	66	140	Hemorrhage, Subarachnoid	42	139	Severe	Probably Not	Yes	Still Present
				140	Headache	42		Severe	Probably Not	Yes	Still Present
6130	043007	F	59	229	Neoplasm, Breast Malignant	19	272	Moderate	Definitely Not	Yes	Recovered
6029	043010	F	55	189	Blurred Vision	304	252	Moderate	Possibly	No	Recovered
6143	043012	M	73	264	Neoplasm, Intestinal, Malignant	23	284	Severe	Probably Not	Yes	Still Present
				264	Neoplasm, Liver, Malignant	23		Severe	Probably Not	Yes	Still Present
6057	043015	M	70	273	Defect, Visual Field	10	273	Mild	Definitely Not	No	Still Present
6104	043002	F	62	119	Conjunctivitis	51	169	Moderate	Probably	No	Recovered
6054	043015	M	61	185	Blepharitis	11	190	Mild	Probably	No	Recovered
				185	Inflammation, Eyelid	11		Mild	Probably	No	Recovered
6061	043016	M	75	173	Arrhythmia	22	173	Moderate	Definitely Not	Yes	Recovered

Data Source: [4.12]

4. Safety (Cont.)

b. Adverse Experiences—Laboratory

All patients who had a laboratory examination were included in the analysis of laboratory adverse experiences. The number of patients evaluated for each phase refers to the number of patients with a laboratory examination during that phase.

1) Overall Assessment of Laboratory Adverse Experiences

Table 27 presents a summary of the laboratory adverse experiences reported during the study. Of the 236 patients evaluated in the double-masked phase, 10 (4%) had a laboratory adverse experience: 5 (4%) in the combination group and 5 (4%) in the concomitant group. The groups did not differ significantly with regard to the incidence of drug-related laboratory adverse experiences. None of the patients in either group had a serious laboratory adverse experience or discontinued the study due to a laboratory adverse experience.

Table 28 presents the number (%) of patients with laboratory adverse experiences, by category and by specific adverse experience, during the double-masked phase of the study. There were no statistically significant differences between the groups with regard to any specific adverse experience or category. The most common laboratory adverse experiences during this phase were increased leukocyte count (3%) in the combination group and hyperglycemia (2%) in the concomitant group. Three patients in the combination group had laboratory adverse experiences that were considered possibly drug related: increased leukocyte count (AN 6202), decreased RBC count (AN 6029), and decreased serum bicarbonate (AN 6023). In each case, the patient continued in the study and the laboratory adverse experience had resolved by the end of the open-label phase.

Table 29 presents the number (%) of patients with laboratory adverse experiences, by category and by specific adverse experience, during the open-label phase of the study. Of the 211 patients evaluated, 11 (5%) had a laboratory adverse experience. The most common laboratory adverse experience during this phase was hyperglycemia (2%). Two patients had laboratory adverse experiences that were considered drug related: crystalluria (AN 6200) and oxaluria (AN 6164). Both patients had a history of urine crystals prior to the study, and in both cases the adverse experience resolved within 2 weeks after the timolol/MK-0507 combination was stopped.

4. **Safety (Cont.)**

Table 27

Laboratory Adverse Experience Summary

Number (%) of Patients	Combination (N=121)		Concomitant (N=121)	
	N	(%)	N	(%)
Double-Masked Phase				
Patients evaluated	115	(95)	121	(100)
With any adverse experience	5	(4)	5	(4)
Drug-related adverse experience†	3	(3)	0	(0)
Serious adverse experience	0	(0)	0	(0)
Patients who died	0	(0)	0	(0)
Discontinued due to adverse experience	0	(0)	0	(0)
	Combination (N=220)			
	N	(%)		
Open-Label Phase				
Patients evaluated	211	(96)		
With any adverse experience	11	(5)		
Drug-related adverse experience†	2	(1)		
Serious adverse experience	0	(0)		
Patients who died	0	(0)		
Discontinued due to adverse experience	0	(0)		

No significant differences between treatment groups were found.
†Drug-related implies possibly, probably, or definitely caused by the test drug.

Data Source: [4.12]

4. **Safety (Cont.)**

Table 28

Number (%) of Patients With Laboratory Adverse Experiences
by Category and by Specific Adverse Experience

Double-Masked Phase

Adverse Experience	Combination (N=121)			Concomitant (N=121)		
	N	(%)		N	(%)	
Patients with any adverse experience	5/115	(4)	[3]	5/121	(4)	[0]
Hematology	5/113	(4)	[2]	1/120	(1)	[0]
Basophils Increased	0/113	(0)	[0]	1/120	(1)	[0]
Eosinophils Increased	0/113	(0)	[0]	1/120	(1)	[0]
Leukocyte Count Increased	3/113	(3)	[1]	0/120	(0)	[0]
Monocytes Increased	1/113	(1)	[0]	0/120	(0)	[0]
RBC Count Decreased	1/113	(1)	[1]	0/120	(0)	[0]
Thrombocytosis	1/112	(1)	[0]	0/119	(0)	[0]
Blood Chemistry	2/115	(2)	[1]	3/121	(2)	[0]
Alk. Phosphatase Increased	0/114	(0)	[0]	1/121	(1)	[0]
ALT Increased	1/115	(1)	[0]	0/121	(0)	[0]
AST Increased	1/115	(1)	[0]	0/121	(0)	[0]
Bicarbonate Decreased	1/115	(1)	[1]	0/121	(0)	[0]
Hyperglycemia	0/115	(0)	[0]	3/121	(2)	[0]
Urinalysis	0/112	(0)	[0]	3/120	(3)	[0]
Glycosuria	0/112	(0)	[0]	1/120	(1)	[0]
Hemoglobinuria	0/112	(0)	[0]	1/120	(1)	[0]
Proteinuria	0/112	(0)	[0]	1/120	(1)	[0]

[ ] Number of patients with adverse experiences possibly, probably, or definitely drug related.

This table presents counts of patients having specific laboratory adverse experiences in the following format: number of patients with experience/number of patients tested. If a patient had a particular adverse experience more than once, the patient was counted only once with that adverse experience. Patients with more than one adverse experience in a category are counted only once in that category total and in the overall total.

No significant differences between treatment groups were found.

Data Source: [4.12]

4. **Safety** (Cont.)

Table 29

Number (%) of Patients With Laboratory Adverse Experiences by Category and by Specific Adverse Experience

Open-Label Phase

Adverse Experience	Combination (N=220)		
	N	(%)	
Patients with any adverse experience	11/211	(5)	[2]
Hematology	3/208	(1)	[0]
Basophils Increased	1/207	(<1)	[0]
Eosinophils Increased	1/207	(<1)	[0]
Hematocrit Decreased	1/207	(<1)	[0]
Hemoglobin Decreased	2/208	(1)	[0]
Blood Chemistry	6/209	(3)	[0]
Hyperglycemia	5/209	(2)	[0]
Hypoglycemia	1/209	(<1)	[0]
Urinalysis	5/210	(2)	[2]
Crystalluria	1/210	(<1)	[1]
Glycosuria	2/210	(1)	[0]
Hematuria	1/210	(<1)	[0]
Hemoglobinuria	1/210	(<1)	[0]
Oxaluria	1/210	(<1)	[1]

[ ] Number of patients with adverse experiences considered possibly, probably, or definitely drug related.

This table presents counts of patients having specific laboratory adverse experiences in the following format: number of patients with experience/number of patients tested. If a patient had a particular adverse experience more than once, the patient was counted only once with that adverse experience. Patients with more than one adverse experience in a category are counted only once in that category total and in the overall total.

Data Source: [4.12]

4. Safety (Cont.)

2) Serious Laboratory Adverse Experiences

There were no serious laboratory adverse experiences during either phase of this study.

3) Patients Discontinued due to Laboratory Adverse Experiences

No patients discontinued due to a laboratory adverse experience during either phase of this study.

c. Adverse Experiences—Other (Special Examinations)

Table 30 lists the physical examination adverse experiences reported during the study. Three patients had adverse experiences that were discovered on physical examination at the end of the double-masked phase. All 3 patients were in the concomitant therapy group. None of these adverse experiences was serious, drug related, or caused the patient to discontinue the study.

Four patients had physical examination adverse experiences at the end of the open-label phase. One of these adverse experiences (seborrheic keratosis) was considered drug related (possibly). None was serious or caused the patient to discontinue the study.

4. Safety (Cont.)

Table 30

Listing of Patients With Physical Examination Adverse Experiences

Treatment	Allocation Number	Study Number	Sex	Age	Day	Adverse Experience	Serious	Drug Related	Action Taken
Double-Masked Phase									
Concomitant	6135	043003	F	81	91	Bruit, carotid	No	Definitely Not	None
(N=121)	6252	043005	F	58	86	Murmur, systolic	No	Probably Not	None
	6164	043011	M	72	93	Blood pressure elevated	No	Definitely Not	None
Open-Label Phase									
Combination	6092	043011	F	75	359	Peripheral pulse decreased	No	Definitely Not	None
(N=220)					359	Bruit, systolic	No	Definitely Not	None
					359	Systolic murmur	No	Definitely Not	None
	6095	043011	F	51	360	Bruit, carotid	No	Definitely Not	None
	6162	043011	M	69	381	Keratosis, Seborrheic	No	Possibly	None
	6282	043011	M	67	194	Bruit, carotid	No	Definitely Not	None

Data Source: [4.12]

4. Safety (Cont.)

d. Clinical Safety Measurements

1) Ocular Symptoms

Table 31 presents the number (%) of patients with emergent or worsening ocular symptoms during the double-masked phase of the study. Only the symptoms with an observed incidence ≥1% in either treatment group are shown. Of the 241 patients evaluated, 89 (37%) reported an ocular symptom that emerged or became worse: 43 (36%) in the combination group and 46 (38%) in the concomitant group. A significantly greater proportion of patients in the combination group reported eyelid pain or discomfort as compared to the concomitant group (6% vs. 1%, p=0.036). There were no other significant differences between treatment groups in the proportion of patients reporting a specific symptom. The most frequently reported ocular symptoms were burning eye (14% in the combination group, 10% in the concomitant group), blurred vision (12% in both groups), and stinging eye (12% in both groups).

Table 32 presents the number (%) of patients with emergent or worsening ocular symptoms during the open-label phase of the study. Only the symptoms with an observed incidence ≥1% are shown. Of the 217 patients evaluated, 56 (26%) reported an ocular symptom that emerged or became worse. The most frequently reported ocular symptoms were burning eye (9%), blurred vision (7%), and itching eye (5%).

4. Safety (Cont.)

Table 31

Number (%) of Patients With Emergent or Worsening Ocular Symptoms
(Incidence ≥1% in Any Treatment Group)

Double-Masked Phase

	Combination (N=121)		Concomitant (N=121)	
	N	(%)	N	(%)
Patients evaluated	120	(99)	121	(100)
Patients with any ocular symptoms	43	(36)	46	(38)
Aching, eye	2	(2)	0	(0)
Blurred vision	14	(12)	15	(12)
Burning eye	17	(14)	12	(10)
Dryness of eye	4	(3)	4	(3)
Eye pain	2	(2)	2	(2)
Eyelid pain or discomfort[a]	7	(6)	1	(1)
Foreign body sensation	3	(3)	3	(2)
Heaviness, eye	3	(3)	0	(0)
Itching, eye	9	(8)	8	(7)
Stinging eye	14	(12)	15	(12)
Tearing eye	7	(6)	4	(3)
Vision cloudy	4	(3)	2	(2)

[a]p=0.036, significantly greater incidence in the combination group.

Data Source: [4.13]

4. Safety (Cont.)

Table 32

Number (%) of Patients with Emergent or Worsening Ocular Symptoms
(Incidence ≥1%)

Open-Label Phase

	Combination (N=220)	
	N	(%)
Patients evaluated	217	(99)
Patients with any ocular symptoms	56	(26)
Blurred vision	16	(7)
Burning eye	20	(9)
Dryness of eye	7	(3)
Eye pain	5	(2)
Eyelid pain or discomfort	5	(2)
Foreign body sensation	3	(1)
Itching, eye	11	(5)
Stinging eye	9	(4)
Tearing eye	8	(4)
Vision cloudy	5	(2)

Data Source: [4.13]

4. **Safety (Cont.)**

2) **Nonocular Symptoms**

Table 33 presents the number (%) of patients with emergent or worsening nonocular symptoms during the double-masked phase. Bitter taste was the most commonly reported nonocular symptom in the combination group (32%) and in the concomitant group (35%). There were no statistically significant differences between the groups with regard to the incidence of these nonocular symptoms.

Table 34 presents the number (%) of patients with emergent or worsening nonocular symptoms during the open-label phase. Bitter taste remained the most commonly reported nonocular symptom (17%).

Table 33

Number (%) of Patients With Emergent or Worsening Nonocular Symptoms
Double-Masked Phase

	Combination (N=121)		Concomitant (N=121)	
	N	(%)	N	(%)
Patients evaluated	120	(99)	121	(100)
Patients with nonocular symptoms	41	(34)	46	(38)
Taste, Bitter	38	(32)	42	(35)
Taste, Sour	5	(4)	6	(5)
Taste, Sweet	0	(0)	2	(2)
No significant differences between treatment groups were found.				

Data Source: [4.14]

Table 34

Number (%) of Patients With Emergent or Worsening Nonocular Symptoms
Open-Label Phase

	Combination (N=220)	
	N	(%)
Patients evaluated	217	(99)
Patients with any nonocular symptoms	39	(18)
Taste, Bitter	36	(17)
Taste, Sour	2	(1)
Taste, Sweet	3	(1)

Data Source: [4.14]

4. **Safety (Cont.)**

3) **Ocular Signs**

Ocular signs represent changes noted by the investigator during examination of the eye, specifically the lids, anterior chamber, conjunctiva, cornea, lens, optic nerve, retina, and vitreous.

Table 35 presents the number (%) of patients with emergent or worsening ocular signs during the double-masked phase of the study. Only the specific signs with an observed incidence ≥1% in either treatment group are shown. There were no statistically significant differences between the treatment groups with regard to the incidence of any ocular sign. The ocular signs reported most frequently were conjunctival hyperemia (12% in the combination group, 14% in the concomitant group) and punctate epithelial erosions or SPK (13% in both groups).

Table 36 presents the number (%) of patients with emergent or worsening ocular signs during the open-label phase of the study. Only the specific signs with an observed incidence ≥1% are shown. The ocular signs reported most frequently were punctate epithelial erosions or SPK (9%), fluorescein staining (5%), conjunctival hyperemia (5%), and nuclear opacity of the lens (5%).

4. Safety (Cont.)

Table 35

Number (%) of Patients With Emergent or Worsening Ocular Signs
(Incidence ≥1% in Any Treatment Group)

Double-Masked Phase

	Combination (N=121)		Concomitant (N=121)	
	N	(%)	N	(%)
Anterior Chamber				
Patients evaluated	120	(99)	121	(100)
Patients with any ocular sign	4	(3)	7	(6)
Anterior chamber cells	2	(2)	7	(6)
Conjunctiva				
Patients evaluated	120	(99)	121	(100)
Patients with any ocular sign	16	(13)	23	(19)
Conjunctival discharge	3	(3)	0	(0)
Conjunctival follicles	1	(1)	4	(3)
Follicular conjunctivitis	0	(0)	2	(2)
Conjunctival hyperemia	14	(12)	17	(14)
Cornea				
Patients evaluated	120	(99)	121	(100)
Patients with any ocular sign	22	(18)	21	(17)
Corneal epithelial defect	3	(3)	0	(0)
Punct. epith. erosions or SPK	16	(13)	16	(13)
Staining, fluorescein	5	(4)	6	(5)
Lens				
Patients evaluated	117	(97)	121	(100)
Patients with any ocular sign	3	(3)	2	(2)
Lens, cortical opacity	2	(2)	0	(0)

4. Safety (Cont.)

Table 35 (Cont.)

Number (%) of Patients With Emergent or Worsening Ocular Signs
(Incidence ≥1% in Any Treatment Group)

Double-Masked Phase

	Combination (N=121)		Concomitant (N=121)	
	N	(%)	N	(%)
Lids				
Patients evaluated	120	(99)	121	(100)
Patients with any ocular sign	13	(11)	10	(8)
Blepharitis	3	(3)	3	(3)
Debris, eye	6	(5)	6	(5)
Scurf	2	(2)	2	(2)
Optic Nerve				
Patients evaluated	117	(97)	121	(100)
Patients with any ocular sign	1	(1)	1	(1)
Retina				
Patients evaluated	117	(97)	121	(100)
Patients with any ocular sign	3	(3)	0	(0)
Retinopathy, diabetic	2	(2)	0	(0)
Vitreous				
Patients evaluated	117	(97)	121	(100)
Patients with any ocular sign	2	(2)	0	(0)

All categories in which at least 1 patient had an emergent or worsening ocular sign are listed.

No significant differences between treatment groups were found.

Data Source: [4.15] and [4.16]

4. Safety (Cont.)

Table 36

Number (%) of Patients With Emergent or Worsening Ocular Signs
(Incidence ≥1%)

Open-Label Phase

	Combination (N=220)	
	N	(%)
Anterior Chamber		
Patients evaluated	217	(99)
Patients with any ocular sign	2	(1)
Conjunctiva		
Patients evaluated	217	(99)
Patients with any ocular sign	26	(12)
Conjunctival follicles	9	(4)
Conjunctival hyperemia	11	(5)
Cornea		
Patients evaluated	217	(99)
Patients with any ocular sign	30	(14)
Punct epith. erosions or SPK	19	(9)
Staining, fluorescein	10	(5)
Lens		
Patients evaluated	212	(96)
Patients with any ocular sign	21	(10)
Coloration lens nucleus	7	(3)
Lens, cortical opacity	4	(2)
Lens, nuclear opacity	10	(5)
Lids		
Patients evaluated	217	(99)
Patients with any ocular sign	17	(8)
Blepharitis	6	(3)
Debris, eye	6	(3)
Optic Nerve		
Patients evaluated	212	(96)
Patients with any ocular sign	2	(1)
Retina		
Patients evaluated	212	(96)
Patients with any ocular sign	6	(3)
Hemorrhage, retina	3	(1)
Vitreous		
Patients evaluated	212	(96)
Patients with any ocular sign	2	(1)

All categories in which at least 1 patient had an emergent or worsening ocular sign are listed.

Data Source: [4.15] and [4.16]

4. Safety (Cont.)

4) Pupil Diameter

Table 37 presents summary statistics for pupil diameter. Summary statistics are shown for the baseline examination (Day 1), the last examination during the indicated phase of the study, and the change from baseline.

During the double-masked phase, the change in pupil diameter from baseline was not significantly different between the treatment groups. During the open-label phase, there was no change in pupil diameter from baseline.

Table 37

Pupil Diameter Summary Statistics

		Baseline			Treatment			Change		
Treatment	N	Mean	SD	Med	Mean	SD	Med	Mean	SD	Med
Double-Masked Phase										
Combination	111	4.4	1.4	4.0	4.3	1.4	4.0	-0.1	0.6	0.0
Concomitant	113	4.3	1.6	4.0	4.2	1.3	4.0	-0.1	0.9	0.0
Open-Label Phase										
Combination	206	4.4	1.5	4.0	4.4	1.4	4.0	0.0	0.9	0.0

Data Source: [4.24]

5) Visual Acuity

Table 38 presents the number (%) of patients by the baseline visual acuity of their better eye. Over 75% of the patients in each treatment group had a baseline visual acuity of 20/25 or better.

Table 39 lists the patients with a doubling of the visual angle from their baseline examination to their final examination within the indicated phase of the study. Three patients experienced a doubling of the visual angle during the double-masked phase (2 in the combination group and 1 in the concomitant group). Six patients experienced a doubling of the visual angle during the open-label phase.

4. **Safety (Cont.)**

Table 38

Number (%) of Patients by Baseline Visual Acuity
Better Eye

Snellen Visual Acuity	Combination (N=121)		Concomitant (N=121)	
	N	(%)	N	(%)
20/20 or better	73	(60)	66	(55)
20/25	25	(21)	26	(21)
20/30	13	(11)	19	(16)
20/40 or worse	10	(8)	10	(8)

Data Source: [4.17]

Table 39

Listing of Patients With a Doubling of the Visual Angle

Treatment Group	Study	Investigator	AN	Eye	Baseline	Treatment*
Double-Masked Phase†						
Combination (N=120)	13	Samples	6167	R	20/30	20/60
	13	Samples	6170	L	20/30	20/60
Concomitant (N=120)	11	McMahon	6279	R	20/20	20/50
Open-Label Phase						
Combination (N=217)	01	Allen	6216	L	20/25	20/50
	08	Karp	6041	R	20/30	20/80
	10	Lewis	6029	R	20/15	20/40
	13	Samples	6167	R	20/30	20/70
	13	Samples	6169	R	20/40	20/80
	15	Shrader	6057	L	20/30	20/60

*Final examination within the indicated study phase.
†No significant difference between treatment groups was found.

Data Source: [4.17]

4. Safety (Cont.)

6) Visual Field Examination

The visual field examination provided three types of data: (1) the investigator's assessment of the intensity and location of any visual field defect, (2) the investigator's assessment of whether there had been a clinically significant progression since the baseline examination, and (3) the global indices for those patients who underwent a static visual field examination by Humphrey Program 24-2 or Octopus Program G1.

Visual Field Defects

Table 40 presents the number (%) of patients with baseline visual field defects. Only the defects with an observed incidence ≥1% in either treatment group are shown. Overall, 124 (52%) of the 238 patients evaluated had a visual field defect at baseline. There were no significant differences between the treatment groups in the proportion of patients with any of the defects indicated.

Table 40

Number (%) of Patients With Baseline Visual Field Defects
(Incidence ≥1% in Any Treatment Group)

	Combination (N=121)		Concomitant (N=121)	
	N	(%)	N	(%)
Patients evaluated	119	(98)	119	(98)
Patients with any defect	58	(49)	66	(55)
Blind spot enlarged	2	(2)	1	(1)
Scotoma, arcuate	37	(31)	35	(29)
Scotoma, paracentral	8	(7)	12	(10)
Nasal depression	2	(2)	0	(0)
Depression, nonspecific	25	(21)	27	(23)
Nasal depression, sup.	2	(2)	1	(1)
Nasal step	23	(19)	26	(22)
General constriction	11	(9)	11	(9)
Localized peripheral constriction	16	(13)	16	(13)
No significant differences between treatment groups were found.				

Data Source: [4.18]

4. Safety (Cont.)

Table 41 presents the number (%) of patients with emergent or worsening visual field defects at the end of the double-masked phase. Only the defects with an observed incidence ≥1% in either treatment group are shown. Of the 225 patients evaluated, 30 (13%) had emergent or worsening visual field defects: 17 (16%) in the combination group and 13 (11%) in the concomitant group. There were no significant differences between the treatment groups in the proportion of patients with any of the defects indicated. The most frequently reported defects were nonspecific depression (6% in the combination group, 4% in the concomitant group), nasal step (4%, 4%), and arcuate scotoma (3%, 5%).

Table 41

Number (%) of Patients With Emergent or Worsening Visual Field Defects
(Incidence ≥1% in Any Treatment Group)

Double-Masked Phase

	Combination (N=121)		Concomitant (N=121)	
	N	(%)	N	(%)
Patients evaluated	110	(91)	115	(95)
Patients with any defect	17	(16)	13	(11)
Scotoma, arcuate	3	(3)	6	(5)
Scotoma, paracentral	4	(4)	3	(3)
Depression, nonspecific	6	(6)	4	(4)
Nasal depression, sup.	2	(2)	1	(1)
Nasal step	4	(4)	4	(4)
Nasal depression, inferior	2	(2)	0	(0)
General constriction	3	(3)	4	(4)
Localized peripheral constriction	3	(3)	3	(3)
No significant differences between treatment groups were found.				

Data Source: [4.18]

4. **Safety** (Cont.)

Table 42 presents the number (%) of patients with emergent or worsening visual field defects at the end of the open-label phase. Only the defects with an observed incidence ≥1% are shown. Of the 210 patients evaluated, 36 (17%) had emergent or worsening visual field defects. The most frequently reported defects were nonspecific depression (8%) and arcuate scotoma (7%).

Table 42

Number (%) of Patients With Emergent or Worsening Visual Field Defects
(Incidence ≥1%)

Open-Label Phase

	Combination (N=220)	
	N	(%)
Patients evaluated	210	(95)
Patients with any defect	36	(17)
Scotoma, arcuate	14	(7)
Scotoma, paracentral	4	(2)
Depression, nonspecific	16	(8)
Nasal step	9	(4)
General constriction	8	(4)
Localized peripheral constriction	4	(2)

Data Source: [4.18]

Clinically Significant Progression

Table 43 lists the patients with clinically significant progression since the baseline visual field examination. At the end of the double-masked phase, 7 (3%) of the 225 patients evaluated had a clinically significant progression: 3 (2%) in the combination group and 4 (3%) in the concomitant group. This difference in incidence between treatment groups was not statistically significant. At the end of the open-label phase, 9 (4%) of the 210 patients evaluated had a clinically significant progression of their visual field defects.

4. Safety (Cont.)

Table 43

Listing of Patients with Clinically Significant Progression
Since the Baseline Visual Field Examination

Treatment	Study	Investigator	AN	Eye
Double-Masked Phase*				
Combination (N=110)	5	DuBiner	6019	B
	6	Greenberg	6090	L
	19	Greenidge	6194	L
Concomitant (N=115)	5	DuBiner	6017	R
	6	Greenberg	6085	R
	11	McMahon	6159	R
	13	Samples	6262	R
Open-Label Phase				
Combination (N=210)	01	Allen	6213	R
	05	DuBiner	6017	R
	06	Greenberg	6088	B
	07	Hoff	6255	R
	11	McMahon	6159	B
	14	Schuman	6208	L
	15	Shrader	6057	L
	17	Vela-Thomas	6175	L
	17	Vela-Thomas	6177	L
*No significant difference between treatment groups was found.				

Data Source: [4.18]

Global Indices

Table 44 presents summary statistics for the visual field global indices for each phase of the study. No clinically meaningful changes in the visual field global indices were observed in either phase. No statistical tests were performed on these parameters.

4. Safety (Cont.)

Table 44

Summary Statistics - Visual Field Global Indices

			Baseline			Treatment			Change		
Study Phase	Treatment	N	Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Mean Defect, P1, Octopus G1 (Decibels)											
Double-Masked	Combination	14	7.6	8.8	3.5	5.5	7.0	3.7	-2.1	4.4	-0.9
	Concomitant	14	7.3	8.1	4.1	7.4	8.5	3.0	0.1	3.9	0.4
Open Label	Combination	26	7.8	8.5	4.1	3.5	3.9	2.2	-4.3	8.5	-1.5
Loss Variance P1, Octopus G1 (Decibels)											
Double Masked	Combination	14	5.8	5.6	4.9	12.0	10.4	8.1	6.2	12.2	3.5
	Concomitant	14	6.6	3.2	5.2	6.6	5.8	6.5	0.1	5.2	0.4
Open Label	Combination	26	6.4	4.6	5.2	13.0	14.4	7.1	6.6	14.8	0.8
Corrected Loss Variance, Octopus G1 (Decibels)											
Double Masked	Combination	14	7.5	11.1	2.9	11.3	11.2	9.3	3.8	10.0	2.2
	Concomitant	14	7.0	9.0	3.6	8.1	11.1	3.4	1.2	5.2	0.7
Open Label	Combination	26	7.7	10.2	3.3	9.5	13.3	3.5	1.8	8.9	0.2
Short Term Fluctuation, Octopus G1 (Decibels)											
Double Masked	Combination	14	1.8	0.5	1.7	2.1	0.6	1.9	0.3	0.7	0.4
	Concomitant	13	1.7	0.4	1.7	1.9	0.7	1.8	0.1	0.6	0.0
Open Label	Combination	25	1.8	0.5	1.7	2.0	0.6	1.8	0.2	0.6	0.2
Mean Defect, P2, Octopus G1 (Decibels)											
Double Masked	Combination	14	7.8	8.6	4.4	5.8	6.6	4.7	-2.1	4.3	-1.2
	Concomitant	14	8.0	7.7	4.5	7.6	7.8	3.8	-0.4	3.7	0.3
Open Label	Combination	26	8.3	8.1	5.0	4.2	4.3	3.2	-4.1	7.8	-1.5

4. Safety (Cont.)

Table 44 (Cont.)

Summary Statistics - Visual Field Global Indices

Study Phase	Treatment	N	Baseline			Treatment			Change		
			Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Loss Variance, P2, Octopus G1 (Decibels)											
Double Masked	Combination	14	6.0	5.8	5.2	12.6	11.6	8.5	6.7	13.4	3.7
	Concomitant	14	8.4	6.6	7.0	8.0	6.2	5.5	-0.4	4.7	-0.9
Open Label	Combination	26	7.5	6.3	6.5	13.3	14.9	7.1	5.8	15.7	0.8
Mean Defect, Humphrey 24-2 (Decibels)											
Double Masked	Combination	94	-2.6	4.8	-1.2	-2.5	5.1	-1.1	0.2	1.9	0.1
	Concomitant	97	-3.1	4.1	-1.6	-3.0	4.2	-1.8	0.0	2.2	0.3
Open Label	Combination	170	-2.9	4.5	-1.4	-3.2	4.7	-1.7	-0.2	2.1	0.0
Pattern Standard Deviation, Humphrey 24-2 (Decibels)											
Double Masked	Combination	94	3.1	2.2	2.2	3.4	2.7	2.3	0.2	1.4	0.0
	Concomitant	97	3.8	3.4	2.3	3.6	3.1	2.3	-0.3	1.8	-0.1
Open Label	Combination	170	3.5	3.0	2.2	3.6	3.0	2.1	0.0	1.7	0.0
Corrected Pattern Standard Deviation, Humphrey 24-2 (Decibels)											
Double Masked	Combination	94	2.3	2.3	1.7	2.4	2.8	1.4	0.1	1.6	-0.1
	Concomitant	96	2.9	3.4	1.6	2.9	3.3	1.6	-0.2	1.8	0.0
Open Label	Combination	170	2.7	3.0	1.6	2.7	3.2	1.4	-0.1	1.8	0.0
Short Term Fluctuation, Humphrey 24-2 (Decibels)											
Double Masked	Combination	94	1.6	0.8	1.5	1.7	1.2	1.5	0.1	1.1	0.1
	Concomitant	96	1.8	0.9	1.5	1.7	0.8	1.5	-0.1	0.8	0.0
Open Label	Combination	170	1.7	0.9	1.5	1.8	1.0	1.5	0.0	1.0	0.1

Data Source: [4.19]

4. Safety (Cont.)

7) Cup-to-Disc Ratio

Table 45 lists the patients who had a worsening of 0.2 or greater in the cup-to-disc ratio of the optic nerve. At the end of the double-masked phase, 3 (3%) of the 117 patients evaluated in the combination group had this degree of worsening. Although all 3 patients were in the combination group, the observed difference in proportion of patients for the two treatment groups (i.e., 3% vs. 0%) was not statistically significant. At the end of the open-label phase, 3 (1%) of the 212 patients evaluated had a worsening of 0.2 or greater in the cup-to-disc ratio.

Table 45

Listing of Patients with Worsening of 0.2 or Greater in the Cup-to-Disc Ratio

Treatment Group	Study	AN	Eye	Baseline		Treatment	
				Horizontal	Vertical	Horizontal	Vertical
Double-Masked Phase*							
Combination (N=117)	19	6191	R	0.60	0.60	0.80	0.80
	19	6197	R	0.40	0.40	0.60	0.60
	19	6200	L	0.50	0.50	0.80	0.80
			R	0.30	0.30	0.70	0.70
Open-Label Phase							
Combination (N=212)	13	6261	L	0.40	0.40	0.60	0.70
	07	6126	L	0.50	NA	0.70	NA
	17	6171	R	0.50	NA	0.70	NA

*No significant difference between treatment groups was found.
NA=not applicable (change was <0.2).

Data Source: [4.20]

4. Safety (Cont.)

8) Blood Pressure and Pulse Rate

Table 46 presents summary statistics for blood pressure and pulse rate for each phase of the study.

At the end of the double-masked phase, the two treatment groups were comparable with regard to mean change from baseline in systolic pressure, diastolic pressure, and pulse rate. The mean change in systolic blood pressure for the combination group was -1.2 mm Hg compared to 0.1 mm Hg for the concomitant group. The mean change in diastolic pressure for the combination group was -1.1 mm Hg compared to -1.0 mm Hg for the concomitant group. The mean change in pulse rate for the combination group was 0.1 beats/min compared to -0.4 beats/min for the concomitant group. None of the differences noted achieved statistical significance.

At the end of the open-label phase, the following mean changes from baseline were observed: systolic pressure -0.9 mm Hg, diastolic pressure -1.7 mm Hg, and pulse rate -0.7 beats/min.

4. Safety (Cont.)

Table 46

Summary Statistics - Blood Pressure and Pulse

Study Phase	Treatment	N	Baseline			Treatment			Percent Change			Change		
			Mean	Std	Med	Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Systolic BP (mm Hg)														
Double Masked*	Combination	110	138.7	19.6	140.0	137.2	17.9	137.0	-0.3	9.7	0.0	-1.2	14.1	0.0
	Concomitant	113	138.2	18.6	140.0	138.3	18.4	136.0	0.5	10.0	0.0	0.1	13.7	0.0
Open Label	Combination	202	138.6	20.2	140.0	137.8	19.2	138.0	0.1	11.4	0.0	-0.9	16.8	0.0
Diastolic BP (mm Hg)														
Double Masked*	Combination	110	82.2	8.9	80.0	81.0	8.3	80.0	-0.8	9.6	0.0	-1.1	7.8	0.0
	Concomitant	113	83.6	8.8	82.0	82.5	8.7	82.0	-0.8	9.2	0.0	-1.0	7.7	0.0
Open Label	Combination	202	82.5	8.8	82.0	80.8	9.1	80.0	-1.4	11.4	0.0	-1.7	9.2	0.0
Pulse (beats/min)														
Double Masked*	Combination	108	73.0	9.4	73.5	72.9	9.9	74.5	0.8	12.8	0.0	0.1	9.3	0.0
	Concomitant	110	71.4	9.6	72.0	71.0	9.9	72.0	0.3	13.3	0.0	-0.4	9.7	0.0
Open Label	Combination	201	72.0	9.3	72.0	71.4	9.4	72.0	-0.2	13.2	0.0	-0.7	9.4	0.0

*No significant difference between treatment groups was found.

Data Source: [4.21]

4. Safety (Cont.)

e. Laboratory Safety Measurements

1) Hematology

Table 47 presents summary statistics for hematology. There were no clinically meaningful mean changes in hematology in either phase of the study.

2) Blood Chemistry

Table 48 presents summary statistics for blood chemistry. There were no clinically meaningful mean changes in blood chemistry in either phase of the study.

3) Urinalysis

Table 49 presents summary statistics for urine pH. There was no clinically meaningful mean change in urine pH in either phase of the study. Other urinalysis results are presented in [4.22].

4. Safety (Cont.)

Table 47

Summary Statistics - Hematology

				Baseline			Treatment			Change		
Parameter	Study Phase	Treatment	N	Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Hemoglobin (gm/dl)	Double Masked	Combination	112	14.15	1.42	14.15	14.02	1.45	14.10	-0.13	0.59	-0.10
		Concomitant	119	14.47	1.28	14.50	14.31	1.46	14.30	-0.16	0.75	-0.10
	Open Label	Combination	206	14.30	1.32	14.40	14.27	1.40	14.30	-0.03	0.74	0.00
Hematocrit (%)	Double Masked	Combination	112	42.60	4.01	42.00	41.62	4.13	41.00	-0.98	2.45	-1.00
		Concomitant	119	43.55	3.66	43.00	42.35	4.26	43.00	-1.19	2.75	-1.00
	Open Label	Combination	205	43.07	3.79	43.00	42.47	4.19	42.00	-0.60	2.82	-1.00
WBC Count (Ths/mm^3)	Double Masked	Combination	112	6.64	1.70	6.40	6.71	1.96	6.42	0.08	1.44	-0.12
		Concomitant	119	6.55	1.81	6.42	6.45	1.90	6.20	-0.09	1.14	-0.21
	Open Label	Combination	206	6.59	1.78	6.37	6.34	1.73	6.06	-0.25	1.26	-0.15
Neutrophils (%)	Double Masked	Combination	112	58.65	8.33	59.00	58.82	8.41	59.40	0.17	6.37	0.40
		Concomitant	119	58.25	9.09	57.60	58.77	8.78	59.20	0.52	6.84	-0.10
	Open Label	Combination	205	58.35	8.77	58.20	59.52	8.24	59.30	1.17	6.73	0.90
Lymphocytes (%)	Double Masked	Combination	112	31.03	8.12	30.55	30.78	7.96	29.50	-0.25	5.69	-0.05
		Concomitant	119	31.29	8.30	32.10	30.81	8.23	31.00	-0.48	6.60	0.00
	Open Label	Combination	205	31.18	8.25	30.90	30.54	8.09	30.20	-0.65	6.52	-0.40
Monocytes (%)	Double Masked	Combination	112	7.25	1.89	7.00	7.34	2.14	6.80	0.09	2.05	0.05
		Concomitant	119	7.37	1.97	7.10	7.21	1.91	6.80	-0.16	1.98	-0.10
	Open Label	Combination	205	7.33	1.91	7.00	6.96	1.73	6.70	-0.37	1.85	-0.30
Eosinophils (%)	Double Masked	Combination	112	2.20	1.43	1.95	2.22	1.52	1.80	0.03	1.15	-0.10
		Concomitant	119	2.25	1.79	1.80	2.38	1.62	1.90	0.13	1.28	0.10
	Open Label	Combination	205	2.27	1.80	1.80	2.13	1.61	1.80	-0.14	1.19	-0.10

4. Safety (Cont.)

Table 47 (Cont.)

Summary Statistics - Hematology

				Baseline			Treatment			Change		
Parameter	Study Phase	Treatment	N	Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Basophils (%)	Double Masked	Combination	112	0.87	0.35	0.80	0.84	0.32	0.80	-0.03	0.35	0.00
		Concomitant	119	0.83	0.38	0.80	0.83	0.33	0.80	0.00	0.34	0.00
	Open Label	Combination	205	0.87	0.37	0.80	0.86	0.38	0.80	-0.01	0.40	0.00
Platelet Count (Ths/mm^3)	Double Masked	Combination	110	258.6	60.8	251.5	258.8	59.7	256.5	0.2	42.0	1.0
		Concomitant	117	254.9	59.0	250.0	252.4	60.3	249.0	-2.6	42.8	-2.0
	Open Label	Combination	202	257.0	61.1	251.5	254.1	57.7	250.5	-2.9	37.0	-1.0
RBC Count (Mil/mm^3)	Double Masked	Combination	112	4.67	0.45	4.65	4.63	0.46	4.60	-0.04	0.19	0.00
		Concomitant	119	4.73	0.44	4.70	4.67	0.51	4.70	-0.06	0.26	0.00
	Open Label	Combination	206	4.71	0.43	4.70	4.69	0.43	4.70	-0.02	0.24	0.00
MCV (fl)	Double Masked	Combination	112	91.31	5.28	91.00	89.88	5.28	89.00	-1.44	3.57	-1.50
		Concomitant	119	92.33	5.44	92.00	91.03	5.48	91.00	-1.30	3.98	-1.00
	Open Label	Combination	205	91.60	5.54	92.00	90.77	5.55	91.00	-0.83	4.06	-1.00

Data Source: [4.22]

4. Safety (Cont.)

Table 48

Summary Statistics - Blood Chemistry

Parameter	Study Phase	Treatment	N	Baseline			Treatment			Change		
				Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
BUN (mg/dL)	Double Masked	Combination	114	14.86	4.34	15.00	14.62	3.96	15.00	-0.24	3.40	0.00
		Concomitant	120	15.78	4.67	15.00	15.99	5.01	15.00	0.21	3.73	0.00
	Open Label	Combination	208	15.26	4.44	15.00	15.43	4.59	15.00	0.17	3.31	1.00
Serum Creatinine (mg/dL)	Double Masked	Combination	114	1.13	0.18	1.10	1.14	0.19	1.10	0.01	0.12	0.00
		Concomitant	120	1.18	0.21	1.20	1.21	0.22	1.20	0.02	0.14	0.00
	Open Label	Combination	208	1.15	0.19	1.10	1.15	0.20	1.10	0.00	0.12	0.00
AST (u/l)	Double Masked	Combination	114	20.30	5.91	19.00	20.50	6.40	19.50	0.20	4.63	0.00
		Concomitant	120	20.98	8.56	18.00	20.77	11.96	19.00	-0.22	11.40	-1.00
	Open Label	Combination	208	20.70	7.64	19.00	19.99	5.10	19.00	-0.71	5.67	0.00
ALT (u/l)	Double Masked	Combination	114	20.74	10.39	18.00	20.22	10.13	18.00	-0.52	6.93	-0.50
		Concomitant	120	21.07	13.71	17.00	19.56	10.90	17.00	-1.51	11.82	-1.00
	Open Label	Combination	208	21.16	12.63	18.00	19.75	8.92	17.50	-1.41	9.57	0.00
Serum Alk. Phos. (u/l)	Double Masked	Combination	113	74.2	22.4	71.0	72.8	21.8	71.0	-1.3	9.9	-1.0
		Concomitant	120	73.1	20.9	70.0	72.5	22.4	69.5	-0.6	11.2	-0.50
	Open Label	Combination	208	73.5	21.9	70.5	71.7	22.1	69.0	-1.8	11.2	-1.0
Serum Glucose (mg/dL)	Double Masked	Combination	114	117.4	55.8	99.0	111.9	48.0	97.0	-5.4	32.4	-2.0
		Concomitant	120	106.0	42.5	93.0	113.1	51.1	95.0	7.1	29.8	2.0
	Open Label	Combination	207	112.0	49.2	96.0	115.9	45.9	100.0	3.9	39.9	2.0
Serum Proteins (gm/dL)	Double Masked	Combination	114	7.20	0.47	7.20	7.25	0.54	7.20	0.04	0.43	0.05
		Concomitant	120	7.15	0.50	7.10	7.11	0.46	7.10	-0.05	0.43	-0.05
	Open Label	Combination	208	7.18	0.49	7.10	7.26	0.49	7.25	0.08	0.40	0.10

4. Safety (Cont.)

Table 48 (Cont.)

Summary Statistics - Blood Chemistry

Parameter	Study Phase	Treatment	N	Baseline			Treatment			Change		
				Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Serum Albumin (gm/dL)	Double Masked	Combination	114	4.02	0.30	4.00	4.00	0.27	4.00	-0.02	0.21	0.00
		Concomitant	120	4.05	0.34	4.00	3.99	0.31	4.00	-0.06	0.23	-0.10
	Open Label	Combination	208	4.03	0.32	4.00	4.04	0.31	4.10	0.01	0.26	0.00
Serum Sodium (mEq/l)	Double Masked	Combination	114	139.5	2.5	140.0	139.7	2.4	140.0	0.2	2.3	1.0
		Concomitant	120	139.7	2.3	139.5	139.8	2.6	140.0	0.2	2.7	0.0
	Open Label	Combination	208	139.6	2.3	139.5	139.3	2.3	139.0	-0.2	2.4	0.0
Serum Potassium (mEq/l)	Double Masked	Combination	113	4.38	0.43	4.40	4.28	0.45	4.30	-0.10	0.37	-0.10
		Concomitant	120	4.39	0.39	4.40	4.31	0.36	4.30	-0.08	0.39	-0.10
	Open Label	Combination	207	4.38	0.43	4.40	4.33	0.39	4.30	-0.05	0.46	0.00
Serum Chloride (mEq/l)	Double Masked	Combination	114	104.1	3.6	105.0	104.5	3.2	105.0	0.4	3.4	1.0
		Concomitant	120	104.1	3.3	104.0	104.7	3.4	105.0	0.6	3.4	1.0
	Open Label	Combination	208	104.1	3.3	104.0	104.4	3.5	105.0	0.3	4.1	0.0
Serum HCO3 (mEq/l)	Double Masked	Combination	114	26.30	2.34	26.40	26.62	2.57	26.80	0.32	3.00	0.10
		Concomitant	120	26.51	2.35	26.70	26.18	2.76	26.25	-0.33	2.78	-0.35
	Open Label	Combination	208	26.41	2.36	26.60	25.23	2.44	25.20	-1.18	2.66	-1.00

Data Source: [4.22]

4. Safety (Cont.)

Table 49

Summary Statistics - Urine pH

Study Phase	Treatment	N	Baseline			Treatment			Change		
			Mean	Std	Med	Mean	Std	Med	Mean	Std	Med
Double Masked	Combination	111	6.02	0.82	6.00	5.92	0.85	6.00	-0.10	1.07	0.00
	Concomitant	119	5.92	0.81	6.00	5.96	0.85	6.00	0.03	1.03	0.00
Open Label	Combination	208	5.96	0.82	6.00	6.00	0.80	6.00	0.04	0.94	0.00

Data Source: [4.22]

D. DISCUSSION

The primary objective of this study was to evaluate whether the IOP-lowering effect of the 0.5% timolol/2.0% MK-0507 combination given b.i.d. was equivalent to that of its components (0.5% timolol b.i.d. and 2% MK-0507 t.i.d.) administered concomitantly for a period of up to 3 months. Secondary efficacy objectives included evaluating whether the IOP effect of the combination was maintained for up to 12 months, and whether IOP control was maintained in patients who were switched to combination therapy after 3 months of concomitant therapy. This study was conducted in patients whose IOP was not adequately controlled on 0.5% timolol b.i.d. The results of this study have been published as meeting abstracts [1.1.1; 1.1.2; 1.1.3].

The data analysis plan stated that the treatment regimens would be considered equivalent if the confidence level was greater than 0.950 that the absolute difference between the mean change in IOP from baseline for the two treatment groups was less than 1.5 mm Hg. This criterion had to be fulfilled at the primary endpoint which was Hour 8, averaged over the Month 2 and Month 3 visits, using the "All-Patients-Treated," Observed Cases (APT-OC) approach. Analysis of the study results found that, at the primary endpoint, the confidence level was 0.971 that the absolute difference between the two treatment groups was less than 1.5 mm Hg. The point estimate for the difference between the IOP-lowering effect of the two treatment groups was -0.73 mm Hg; the concomitant group had a slightly greater IOP reduction than the combination group, as might be expected since they received an extra dose of MK-0507. Nevertheless, from a statistical and clinical perspective, this study demonstrated equivalent efficacy between the two therapy regimens at the primary endpoint.

Equivalent efficacy was also demonstrated at the secondary time points (Hour 0 and Hour 2) using the average of the Month 2 and Month 3 visits and the APT-OC approach, as well as at all three time points (Hours 0, 2, and 8) using the individual visits and the "All-Patients-Treated," Last Observation Carried Forward (APT-LOCF) approach. The results of the "Per-Protocol," Observed Cases (PP-OC) analysis are also supportive of equivalent efficacy; although the confidence level was slightly below 0.950 for Hour 0 and Hour 8, the point estimate for the treatment difference was less than 1.0 mm Hg when the average of the Month 2 and Month 3 data was used, and when the individual visits were considered.

The study results also showed that the IOP-lowering effect of the combination was maintained for up to 1 year. During the open-label phase, the mean change in IOP from baseline ranged from -3.8 to -3.5 mm Hg at Hour 0 and from -5.4 to -5.0 at Hour 2. These changes are similar in magnitude to those observed at the end of the double-masked phase (-3.8 mm Hg at Hour 0 and -5.1 mm Hg at Hour 2). Furthermore, IOP

D. DISCUSSION (CONT.)

control was maintained in those patients who were switched to combination therapy after 3 months of concomitant therapy. At each time point in the open-label phase the confidence level was >98% that the two treatment groups (i.e., those initially assigned to concomitant therapy and those initially assigned to combination therapy) were equivalent.

The study objectives also included comparing the safety profiles of combination therapy and concomitant therapy for up to 3 months and evaluating the tolerability of combination therapy when taken for up to 12 months. There were no statistically significant differences between the treatment groups during the 3-month double-masked phase in the proportion of patients with any adverse experiences, with drug-related adverse experiences, or with serious adverse experiences. There were also no statistically significant differences between the treatment groups in the proportion of patients who were discontinued due to a clinical adverse experience.

Ocular and nonocular symptoms generally occurred with similar frequencies in both treatment groups. Ocular symptoms occurred with similar frequency in the open-label extension of the study as in the double-masked phase. Bitter taste was the most common nonocular symptom in both treatment groups (32% in the combination group and 35% in the concomitant group) during the double-masked phase. Bitter taste remained the most common nonocular symptom during the open-label phase but was reported less frequently (17%) than during the initial masked treatment phase. This suggests that the bitter taste becomes less noticeable to patients as therapy continues.

There were no statistically significant differences between the two treatment groups when they were compared for emergent or worsening ocular signs, visual acuity, visual field results, optic nerve cup-to-disc ratio, blood pressure and pulse rate, or laboratory measures. Furthermore, combination therapy for up to 12 months continued to be generally well tolerated.

In summary, this study has demonstrated that b.i.d. administration of the 0.5% timolol/2.0% MK-0507 combination has an IOP-lowering effect equivalent to that of b.i.d. administration of 0.5% timolol given concomitantly with t.i.d. administration of 2.0% MK-0507. Additionally, combination therapy maintains its IOP-lowering effect and is generally well tolerated for up to 1 year.

E. CONCLUSIONS

In the treatment of elevated IOP in patients with glaucoma or ocular hypertension:

1. The IOP-lowering effect of the 0.5% timolol/2.0% MK-0507 fixed combination administered b.i.d. is equivalent to that of the concomitant administration of 0.5% timolol b.i.d. and 2.0% MK-0507 t.i.d. for up to 3 months.

2. The IOP-lowering effect of 0.5% timolol/2.0% MK-0507 is maintained for up to 1 year.

3. The fixed combination of 0.5% timolol/2.0% MK-0507 is generally well tolerated compared to concomitant administration of 0.5% timolol given b.i.d. and 2.0% MK-0507 given t.i.d.

4. The 0.5% timolol/2.0% MK-0507 fixed combination is generally well tolerated for up to 1 year.

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1.1.2	Clineschmidt CM, Strahlman ER, Anderson K, the Timolol/MK–507 Combination Study Group. Comparison of a fixed combination of dorzolamide and timolol (b.i.d.) to concomitant administration of dorzolamide (t.i.d) plus timolol (b.i.d.) in patients with open-angle glaucoma for three months. Invest Ophthalmol Vis Sci 1995;36(4):S736.	2391
1.1.3	Strohmaier K, Snyder E, Adamsons I. Long-term safety and efficacy of COSOPT, a fixed combination of dorzolamide and timolol. Invest Ophthalmol Vis Sci 1996;37(3):S1102.	2392
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