CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-869

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-869
Original

NDA 20-869
M.O. Review #1

Submission: 6/25/97
Review completed: 11/23/97
Revised date: 12/ 1/97

Proposed trade name: Cosopt™

Established name: Dorzolamide hydrochloride/timolol maleate ophthalmic solution

Chemical name: (4S-*trans*)-4-(ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride, (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol maleate (1:1) (salt)

Active ingredients: Dorzolamide hydrochloride (22.26 mg/mL)
Timolol maleate (6.83 mg/mL)

Inactive ingredients: Sodium citrate dihydrate USP (2.94 mg/mL), hydroxyethyl cellulose (5 mg/mL), mannitol (16 mg/mL), sodium hydroxide to adjust to pH 5.65.

Preservative: 0.075 mg/mL benzalkonium chloride (BAK)

Applicant: Merck Research Laboratories
Merck & Co., Inc.
West Point, PA 19486
(215) 397-2905

Pharmacologic Category: Combination carbonic anhydrase inhibitor (CAI) and β-blocker

Proposed Indication(s): Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma when concomitant therapy is appropriate.

Dosage Form(s): Ophthalmic Solution
Route(s) of Administration: Topical ophthalmic
NDA Drug Classification: 4 S
Related NDAs: **NDA 20-408** **Trusopt**
NDA 18-086 **Timoptic**

2 Table of Contents

3 Material Reviewed

NDA Volumes 1.1,2, 10 through 61
CD ROM Volumes 1-3

4 Chemistry/Manufacturing Controls

Reviewer's Comments: *See Chemistry/Manufacturing Review. The following areas are of particular clinical concern:*

Specifications

Reviewer's Comments:

Stability

Data for 11 batches of dorzolamide hydrochloride and timolol maleate ophthalmic solution stored for two years at 25°C and 30°C and 6 batches for 18 months (4 batches) and 12 months (2 batches) at 25°C/60%RH and 30°C/35%RH are within specifications for all parameters studied.

Reviewer's Comments: *The relative humidity (RH) for the 25°C conditions should be 40% or lower.*

5 **Animal Pharmacology/Toxicology** *No specific issues noted.*

6 **Clinical Background**

6.1 **Relevant human experience**

Timoptic and Trusopt have each been used separately and in combination together (dosed separately) in clinical studies leading to the approval of Trusopt. Events similar to the use of either alone have been observed when the combination is used.

6.2 **Important information from related INDs and NDAs**

See MOR for NDA 20-408 dated 5/28/94

6.3 **Foreign experience**

Cosopt is not currently marketed in any country in the world and has not been withdrawn from marketing in any country.

6.4 **Human Pharmacology, pharmacokinetics, pharmacodynamics**

See MOR for NDA 20-408

6.6 **Proposed Directions for Use**

When used as monotherapy, the dose is one drop of TRUSOPT Ophthalmic Solution in the affected eye(s) three times daily. When used as adjunctive therapy with an ophthalmic beta-blocker, the dose is one drop of TRUSOPT in the affected eye(s) two times daily. When substituting TRUSOPT for another ophthalmic antiglaucoma agent, discontinue the other agent after proper dosing on one day, and start TRUSOPT on the next day. If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

Reviewer's Comments: *Disagree. Studies in this application and previously have demonstrated the need for tid administration of dorzolamide when used adjunctively with a beta-blocker.*

APPEARS THIS WAY
ON ORIGINAL

7 Description of Principal Clinical Data Sources

Review Number	US vs Non-US Number of sites	Protocol Number	Design	Doses	Enrolled	Completed (Drop out)	Age Range [years]
1	Non-US 22 European sites	44	Multiple dose Double masked Parallel 3 months + 12 month extension	Combo bid Dorzolamide 2% tid Timolol 0.5% bid	48♂ 67♀ 71♂ 47♀ 55♂ 62♀	99 (16) 102 (16) 100 (17)	31-80 36-79 21-84
2	US 27 sites	47	Multiple dose Double masked Parallel 3 months	Combo bid Dorzolamide 2% tid Timolol 0.5% bid	54♂ 60♀ 55♂ 54♀ 62♂ 50♀	105 (9) 98 (11) 101 (11)	28-83 27-84 36-83
3	US 23 sites	63	Multiple dose Double masked Parallel 3 months	Combo bid Dorzolamide 2% tid Timolol 0.5% bid	42♂ 62♀ 22♂ 29♀ 47♂ 51♀	94 (10) 49 (2) 89 (9)	37-86 22-88 30-88
4	US 23 sites	64	Multiple dose Double masked Parallel 3 months	Combo bid Dorzolamide 2% tid Timolol 0.5% bid	54♂ 47♀ 32♂ 17♀ 44♂ 53♀	97 (4) 47 (2) 91 (6)	34-80 34-85 32-84
5	US 19 sites	43	Multiple dose Double masked Parallel 3 months + 9 month extension	Combo bid Concomitant tid	50♂ 71♀ 71♂ 50♀	99 (22) 104 (17)	22-81 25-84
6	Non-US Multiple continents 16 sites	58	Multiple dose Double masked Parallel 3 months	Combo bid Concomitant bid	65♂ 86♀ 48♂ 100♀	145 (6) 145 (3)	23-83 28-84
Not presented in this review	US Single Site	30	Multiple dose Parallel Two week	Combo bid Placebo	3♂ 7♀ 2♂ 3♀	10 (0) 5 (0)	28-48 26-54
Not presented in this review	Multicenter	32	Multiple dose Parallel Two week	Combo bid Timolol bid	25♂ 23♀ 30♂ 23♀	48 (0) 53 (0)	37-83 28-84

Reviewer's Comments: *There were no significant findings with respect to safety or efficacy in protocols 30 and 32. Since the duration of the protocols (2 weeks) is insufficient, the studies have been reviewed but not presented in full in this report.*

8 Clinical Studies

8.1 Indication Reduction of Intraocular Pressure

8.1.1 Reviewer's Trial # 1 **Applicant's protocol # 44**

A Randomized, Double-Masked, Parallel Study Comparing the 0.5% Timolol/2.0% MK-0507 Combination Ophthalmic Solution to 0.5% Timolol Ophthalmic Solution or 2.0% MK-0507 Ophthalmic Solution in Patients With Elevated Intraocular Pressure #044

8.1.1.1 Objective/Rationale

1) To compare the IOP-lowering effect of the 0.5% timolol/2.0% MK-0507 combination (administered b.i.d.) to that of 0.5% timolol (b.i.d.) and to that of 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 in their usual monotherapy dose regimens over a 3-month period.

3) To evaluate the safety of the 0.5% timolol/2.0% MK-0507 combination administered b.i.d. for 1 year.

8.1.1.2 Design Parallel, randomized, double-masked, active-controlled, multicenter study followed by an open-label extension.

8.1.1.3 Protocol

	Prestudy Screening Days -21 to -2	Day 1, Week 2, Months 1, 2, 3			Months 6, 9, 12 and 15			Month 3 and Poststudy
		Pre-dose	Post-dose	2 Hours	Pre-dose	Post-dose	2 Hours	
General Ocular and Medical History	X							
Physical Examination	X							X
Laboratory Tests	X							X
Symptomatology	X	X	X	X	X	X	X	
Anterior Segment Exam	X	X		X	X		X	
Visual Acuity	X	X			X			
IOP Measurement	X	X		X	X		X	
Lens and Ophthalmoscopy	X							X
Visual Field	X							X
Gonioscopy	X							

8.1.1.3.1 Population

Male or female (postmenopausal or sterilized) patients ranging in age from 21 to 85 years with a diagnosis of open-angle glaucoma or ocular hypertension in both eyes with IOP ≥24 mmHg in at least one eye at hour 0 and hour 2, following washout of ocular hypotensive medication. The length of the washout was dependent upon the medication: 72 hours for pilocarpine, carbachol, and aceclidine; one week for dipivefrin and epinephrine; and three weeks for all others.

8.1.1.3.2 Endpoints

Efficacy - IOP

Safety - Cup to disc ratio, visual acuity, visual field, blood pressure, heart rate, ocular signs and symptoms, and incidence of adverse experiences.

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

			Combo	Dorz	Timolol
1	Welsh, N.	Johannesburg, South Africa	5	4	3
2	Morel, M.	Brussels, Belgium	5	5	6
3	Meyer, D.	Tygerberg, South Africa	3	3	2
4	Kara Jose, N.	Sao Paulo, Brazil	5	6	6
5	Bron, A.M.	Dijon, France	2	3	3
6	NONE				
7	Langmann, G.	Graz, Austria	6	6	6
8	Abrantes, P.	Sao Paulo, Brazil	6	6	6
9	George, J.	Nancy, France	6	5	6
10	Vargas, E.	Lima, Peru	12	12	12
11	Huber-Spitzy, V.	Vienna, Austria	7	7	7
12	Gottinger, W.	Innsbruck, Austria	4	3	3
13	Antillon, C.F.	San Jose, Costa Rica	6	6	6
14	Best, Stephen J.	Auckland, New Zealand	5	6	6
15	Metzner-Serra, L.	Lisbon, Portugal	6	6	6
16	Johann, D.	Munich, Germany	4	4	4
17	Richter, G.	Berlin, Germany	2	3	3
18	Arenas, E.	Bogata, Colombia	6	6	6
19	Correa, A.	Bogata, Colombia	6	6	6
20	Gillies, W.	Melbourne, Australia	5	6	6
21	van der Pol, B.A.E.	Leeuwarden, Netherlands	6	6	6
22	Lerner, S.F.	Buenos Aires, Argentina	6	6	6
23	Sirbat, D.	Nancy, France	2	3	2
Total			115	118	117

Baseline Demographic Characteristics by Treatment Group

	Combination (N=115) N (%)	MK-0507 (N=118) N (%)	Timolol (N=117) N (%)
Gender			
Male	48 (42)	71 (60)	55 (47)
Female	67 (58)	47 (40)	62 (53)
Race			
White	89 (77)	96 (81)	93 (79)
Black	4 (3)	2 (2)	3 (3)
Hispanic	9 (8)	10 (8)	9 (8)
Mestizo	9 (8)	8 (7)	11 (9)
Other	4 (3)	2 (2)	1 (1)
Iris Color			
Dark Brown	9 (8)	11 (9)	8 (7)
Brown	54 (47)	49 (42)	45 (38)
Hazel	17 (15)	24 (20)	22 (19)
Green	6 (5)	9 (8)	12 (10)
Blue	29 (25)	25 (21)	30 (26)
Age (Years)			
N	115	118	117
Mean [SD]	62.5 [11.4]	61.7 [9.9]	61.4 [12.0]
Median	65	64	63
Range	31-80	36-79	21-84

Significantly more males in the MK-0507 group than in the combination group, p=0.006.

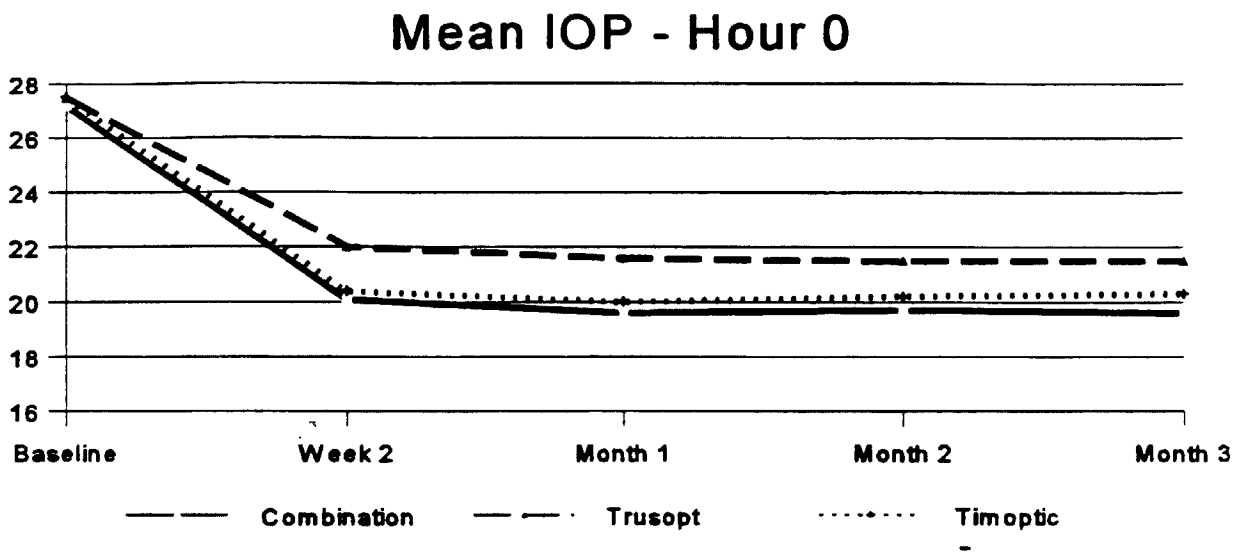
Patient Accounting

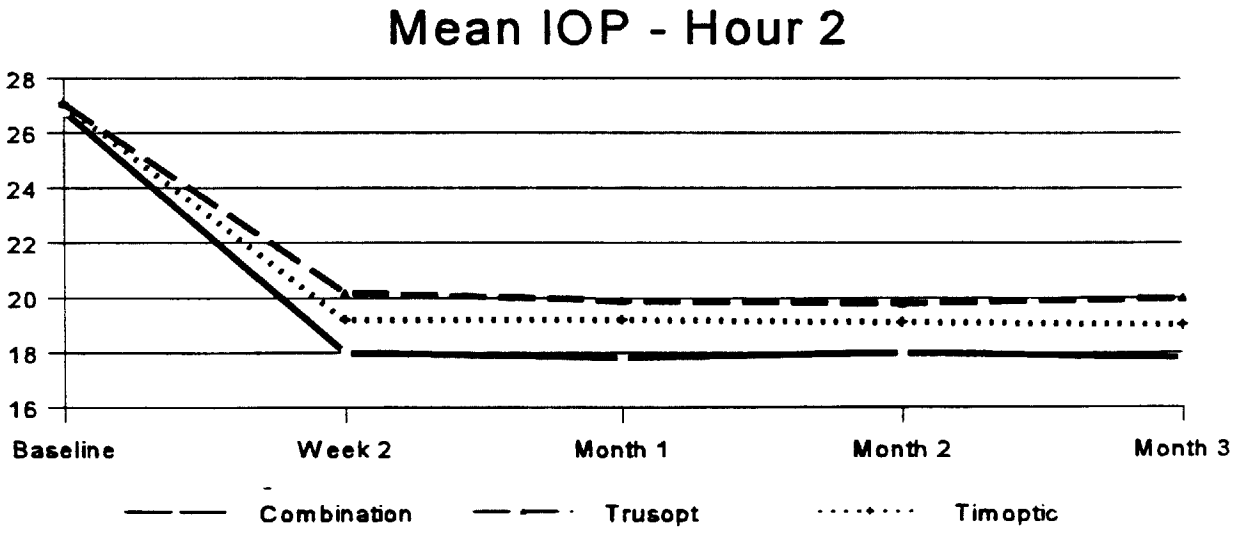
	Combination	Dorzolamide	Timolol
Entered Masked Phase	115	118	117
Completed Masked Phase	110	110	106
Entered Open Label Phase	110	110	106
Completed Open Label Phase	99	102	100
Discontinued - Masked Phase			
Clinical Adverse Experience	5	8	11
Protocol Deviation	2	0	3
Therapy Ineffective	0	6	6
Patient Withdrew	1	0	1
Lost to Follow-up	2	0	0
Discontinued - Open Label			
Clinical Adverse Experience	9	5	2
Therapy Ineffective	2	1	1
Patient Withdrew	0	0	1
Lost to Follow-up	0	2	2

Discontinued for Adverse Experiences

Group	Number	Gender	Age	Day of Onset	Adverse Experience	Duration (Days)	Day Discontinued
Combination	7226	F	66	80	Blurred Vision, Foreign Body Sensation, Burning/Stinging	3	80
Combination	7026	M	70	70	Conjunctivitis O.U.	12	71
Timolol	7325	M	64	5	Asthma	1hr	4
Timolol	7241	F	60	79	Meningitis/Death	2	64
Timolol	7143	M	82	86	Eyelid inflammation	6	85
Combination	7012	M	34	328	Visual Field Defect	66	329
Combination	7017	M	65	407	Rash	23	412
Combination	7018	M	74	364	Atherosclerosis	1	364
Combination	7044	F	62	90	Retinal vascular occlusion	29	118
Combination	7024	F	71	133	CVA	3	133
Combination	7062	M	48	331	Scotoma	1	331
Combination	7069	F	67	187	Taste Perversion, Dyspnea, Nausea, Vertigo	72	257
Combination	7077	M	62	98	Eyelid Inflammation	52	120
Combination	7096	M	55	443	Intestinal obstruction, peritonitis	1	435
Combination	7108	M	66	330	Conjunctival injection, edema	47	330
Combination	7123	F	59	163	Eyelid edema and inflammation	26	182
Combination	7165	F	69	216	Conjunctivitis	62	273
Combination	7178	M	66	210	Myocardial Infarction	1	210
Combination	7221	F	53	125	Conjunctival injection, itching	15	135
Combination	7311	F	62	104	Optic Disc Hemorrhage, VF defect	8	104
Combination	7346	F	68	156	Myocardial infarction	3	156

8.1.1.4.2 **Efficacy endpoint outcomes**





Reviewer's Comments: *The combination is statistically superior to Trusopt at both Hour 0 and Hour 2. The combination is statistically superior to Timoptic in lowering intraocular pressure at Hour 2 only. This is probably due to the shorter duration of effect of the combination.*

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

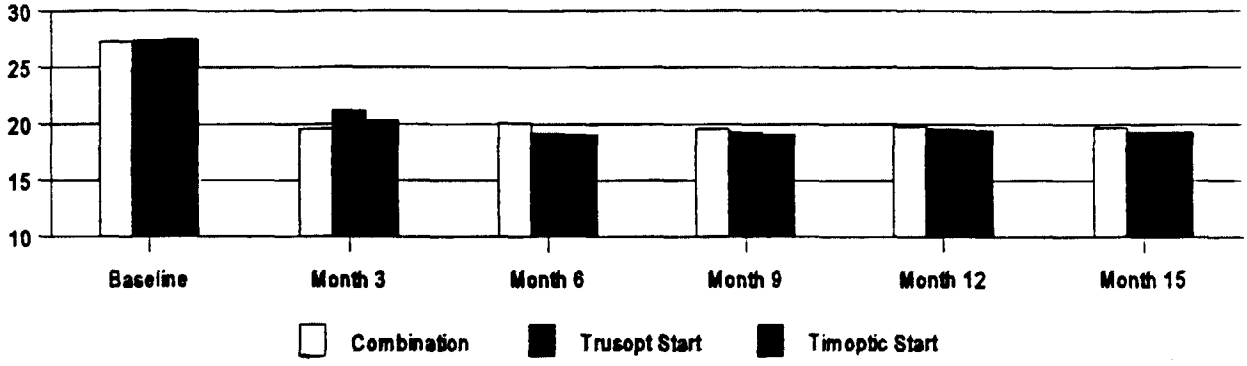
Exam	Treatment	N	Baseline Mean	Baseline SD	Treatment Mean	Treatment SD	Change Mean	Change SD	Percent Change Mean	Percent Change Median
Hour 0										
Week 2	Combination	113	27.2	3.4	20.1	3.6	-7.1	3.3	-25.9	-26.7
	Trusopt	117	27.5	4.6	22.0	4.2	-5.5	3.8	-19.7	-19.2
	Timoptic	116	27.5	4.6	20.4	4.4	-7.1	4.1	-25.5	-25.0
Month 1	Combination	114	27.3	3.4	19.6	3.6	-7.6	4.3	-27.4	-26.6
	Trusopt	118	27.6	4.7	21.6	4.3	-6.0	4.0	-21.3	-20.8
	Timoptic	117	27.5	4.5	20.0	4.2	-7.5	4.3	-26.9	-25.7
Month 2	Combination	114	27.3	3.4	19.7	3.3	-7.6	3.8	-27.3	-26.5
	Trusopt	118	27.6	4.7	21.5	4.9	-6.1	4.7	-21.8	-23.1
	Timoptic	117	27.5	4.5	20.2	3.9	-7.4	4.1	-26.3	-25.9
Month 3	Combination	114	27.3	3.4	19.6	3.2	-7.7	3.7	-27.6	-26.9
	Trusopt	118	27.6	4.7	21.5	4.9	-6.1	4.4	-21.8	-23.1
	Timoptic	117	27.5	4.5	20.3	4.2	-7.2	4.5	-25.6	-25.0
Hour 2										
Week 2	Combination	113	26.8	3.6	18.0	3.3	-8.8	3.4	-32.6	-33.3
	Trusopt	117	27.1	4.5	20.2	4.3	-6.9	3.1	-25.4	-25.0
	Timoptic	116	27.1	4.3	19.2	4.4	-7.9	4.4	-28.7	-30.1
Month 1	Combination	114	26.8	3.6	17.8	3.3	-9.0	4.0	-33.2	-31.7
	Trusopt	118	27.2	4.6	19.9	4.5	-7.2	3.6	-26.6	-27.3
	Timoptic	117	27.1	4.3	19.2	4.5	-7.9	4.1	-29.0	-30.8
Month 2	Combination	114	26.8	3.6	18.0	2.9	-8.8	4.0	-32.1	-31.5
	Trusopt	118	27.2	4.6	19.8	4.8	-7.3	4.3	-26.8	-27.3
	Timoptic	117	27.1	4.3	19.1	4.5	-7.9	4.2	-29.0	-32.0
Month 3	Combination	114	26.8	3.6	17.8	2.8	-9.0	3.5	-33.1	-34.3
	Trusopt	118	27.2	4.6	20.0	4.8	-7.1	4.1	-26.2	-28.6
	Timoptic	117	27.1	4.3	19.0	4.2	-8.0	4.2	-29.3	-30.8

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

	Treatment Group	Difference	Std Error	95% Conf Interval
Hour 0				
Week 2	Combination (113) - MK-0507 (117)	-6.2	1.41	(-9.0, -3.5)
	Combination (113) - Timolol (116)	-0.5	1.41	(-3.3, 2.3)
	Timolol (116) - MK-0507 (117)	-5.7	1.40	(-8.5, -3.0)
Month 1	Combination (114) - MK-0507 (118)	-6.0	1.47	(-8.9, -3.1)
	Combination (114) - Timolol (117)	-0.7	1.48	(-3.7, 2.2)
	Timolol (117) - MK-0507 (118)	-5.6	1.46	(-8.4, -2.7)
Month 2	Combination (114) - MK-0507 (118)	-5.6	1.52	(-8.6, -2.6)
	Combination (114) - Timolol (117)	-1.2	1.52	(-4.2, 1.8)
	Timolol (117) - MK-0507 (118)	-4.5	1.50	(-7.5, -1.6)
Month 3	Combination (114) - MK-0507 (118)	-5.8	1.53	(-8.8, -2.8)
	Combination (114) - Timolol (117)	-2.0	1.53	(-5.1, 1.0)
	Timolol (117) - MK-0507 (118)	-3.9	1.52	(-6.9, -0.9)
Hour 2				
Week 2	Combination (113) - MK-0507 (117)	-7.1	1.33	(-9.7, -4.5)
	Combination (113) - Timolol (116)	-4.0	1.33	(-6.6, -1.4)
	Timolol (116) - MK-0507 (117)	-3.2	1.32	(-5.8, -0.6)
Month 1	Combination (114) - MK-0507 (118)	-6.4	1.35	(-9.1, -3.8)
	Combination (114) - Timolol (117)	-4.4	1.35	(-7.1, -1.7)
	Timolol (117) - MK-0507 (118)	-2.3	1.34	(-5.0, 0.3)
Month 2	Combination (114) - MK-0507 (118)	-5.2	1.35	(-7.9, -2.6)
	Combination (114) - Timolol (117)	-3.2	1.36	(-5.9, -0.5)
	Timolol (117) - MK-0507 (118)	-2.3	1.34	(-4.9, 0.4)
Month 3	Combination (114) - MK-0507 (118)	-6.9	1.32	(-9.5, -4.3)
	Combination (114) - Timolol (117)	-4.0	1.32	(-6.6, -1.3)
	Timolol (117) - MK-0507 (118)	-3.1	1.31	(-5.7, -0.6)

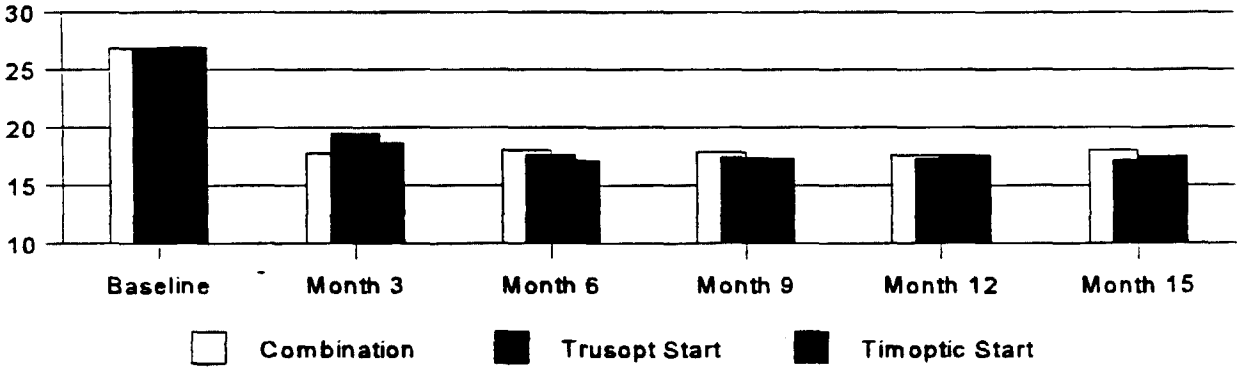
The estimated difference between treatments was a weighted average of the mean difference within each clinic based on the number of patients entered at each clinic. All-Patients-Treated Analysis (Last-Observation-Carried-Forward) -- Worse Eye.

Open Extension - Mean IOP, Hour 0



Combination	27.3	19.6	20.1	19.6	19.8	19.7
Trusopt Start	27.4	21.2	19.2	19.3	19.6	19.3
Timoptic Start	27.5	20.3	19.1	19.1	19.5	19.3

Open Extension -Mean IOP, Hour 2



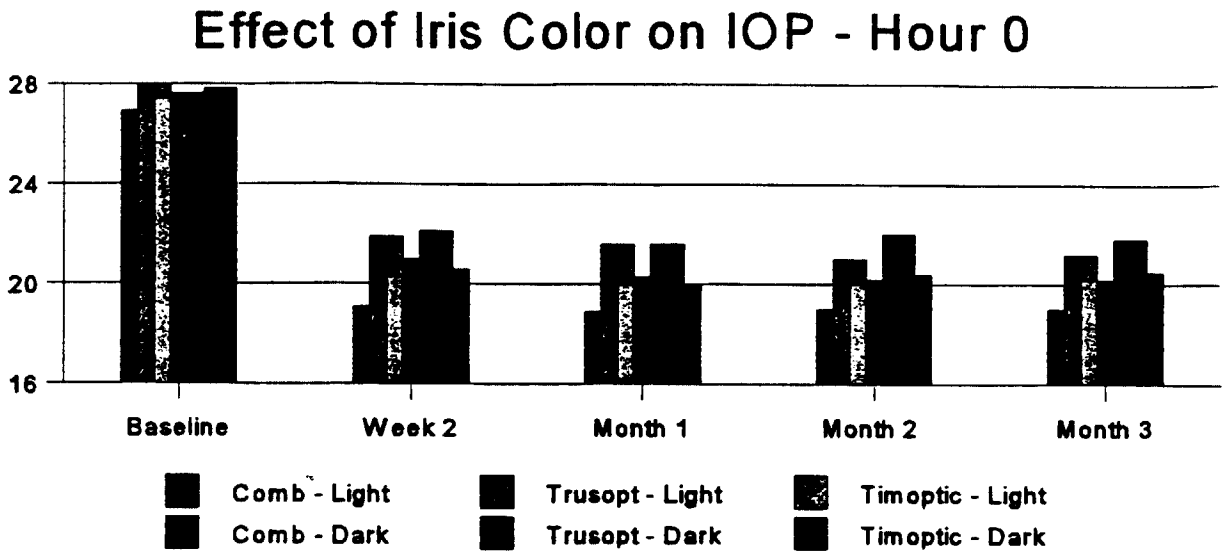
Combination	26.9	17.8	18.1	17.9	17.8	18.1
Trusopt Start	26.9	19.5	17.6	17.4	17.3	17.1
Timoptic Start	27	18.7	17.2	17.3	17.6	17.5

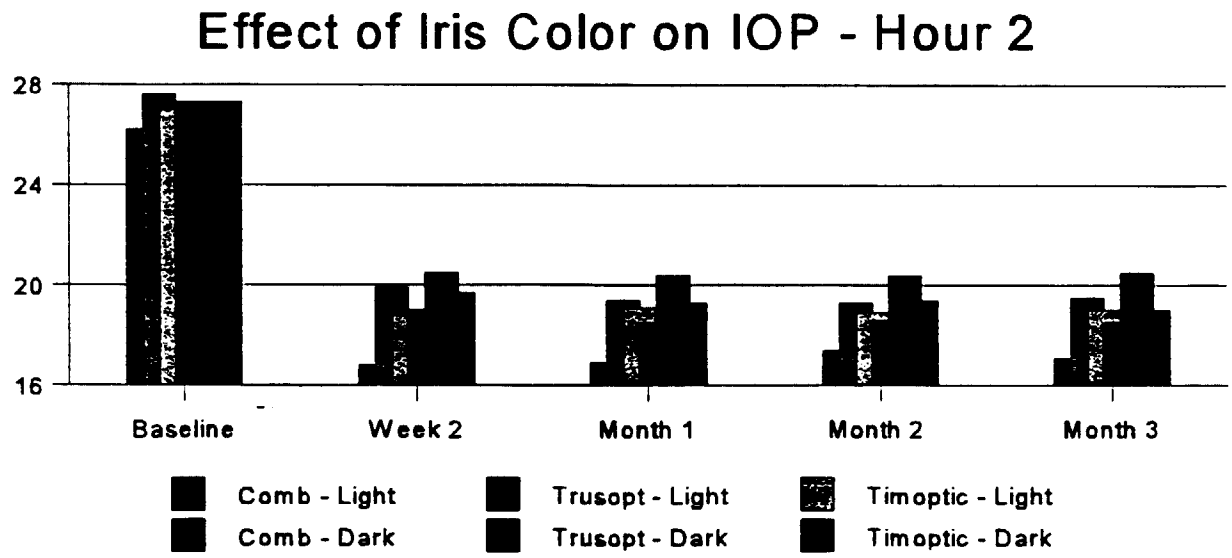
Reviewer's Comments: *The IOP showed only a small amount of variation throughout the one year follow-up.*

Additional Analyzes:
Significant (or nearly significant) interaction between treatment and age was also observed for each hour and visit; the percent reduction in IOP was greater for patients ≥65 years of age than for patients <65 in the timolol and MK-0507 treatment groups; however, the percent reduction in IOP for the combination group was greater in general for patients <65 years of age as compared to patients ≥65. Since Gail and Simonís test failed to detect a significant qualitative interaction between treatment and age, the analysis proceeded as if there were no interaction between treatment and age.

A significant independent effect on percent reduction in IOP due to race was observed; there was a greater percent reduction in IOP for whites as compared to nonwhites. A significant independent effect on percent reduction in IOP due to iris color was also observed; there was a greater percent reduction in IOP for light irides as compared to dark irides. No consistent independent effect of gender across the time points was observed.

Reviewer's Comments: *The difference in race is likely to be due to the difference in iris color. The higher percent reduction in light colored irides has been observed before with several IOP reducing medications including timolol.*





Reviewer's Comments: *There is more IOP reduction in the light colored irides.*

8.1.1.4.3 Safety outcomes

Laboratory Experiences:

Reviewer's Comments: *There were no clinically significant laboratory adverse experiences. There were not enough patients treated to rule out the possibility of a rare incidence of aplastic anemia.*

Pupil Diameter:(mm)	Combination	Dorzolamide	Timolol
Baseline	4.0	4.0	4.0
Treatment	4.1	4.2	4.2

Reviewer's Comments: *The differences (increases) noted above will require replication.*

Visual Acuity and Visual Fields:

Reviewer's Comments: *No specific differences between groups were noted. It would have been preferable for visual acuity to be reported as the number of lines increased by 1, 2 and more than 2, and the number of lines decreased by 1, 2 and more than 2.*

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

Treatment Group	Study	AN	Eye	Horizontal	Vertical	Horizontal	Vertical
Combination	4	7233	L	.40	NA	.60	NA
(n=112)	7	7049	R	.40	.40	.60	.60
	14	7153	L	NA	.10	NA	.30
	14	7155	L	.30	.30	.50	.70
	14	7160	R	NA	.50	NA	.70
	14	7160	L	.60	.60	.80	.80
	18	7250	R	.30	NA	.50	NA
MK-0507	7	7040	R	.60	NA	.80	NA
(n=118)							
Timolol	4	7231	L	.40	.40	.70	.70
(N=114)	7	7043	R	.80	NA	1.00	NA
	10	7317	R	.30	NA	.50	NA

Reviewer's comments: *An explanation is needed for the apparent imbalance in enlarged cup/disc ratio.*

Number (%) of Patients with Clinical Adverse Experiences (>1% in Any Treatment Group)

Adverse Experience	Combination (N=115) N %	Dorzolamide (N=118) N %	Timolol (N=117) N %	Combination Open Label (N=326) N %
Patients With Any Adverse Experience	55 (48)	47 (40)	48 (41)	181 (56)
Body as a Whole/Site Unspecified	5 (4)	3 (3)	5 (4)	20 (6)
Flu-Like Illness	0	0	2 (2)	
Cardiovascular System	2 (2)	6 (5)	3 (3)	29 (9)
Hypertension	1 (1)	3 (3)	1 (1)	8 (2)
Digestive System	3 (3)	2 (2)	5 (4)	25 (8)
Diarrhea	1 (1)	0	2 (2)	
Gastritis				4 (1)
Nausea				4 (1)
Endocrine System	0	1 (1)	1 (1)	3 (1)
Metabolic/Nutritional/Immune	0	0	1 (1)	7 (2)
Hypercholesterolemia				6 (2)
Musculoskeletal System	3 (3)	1 (1)	6 (5)	34 (10)
Arthralgia				4 (1)
Arthritis				4 (1)
Cramp, Muscle				4 (1)
Myalgia				4 (1)
Pain, Back				7 (2)
Nervous System & Psychiatric	7 (6)	9 (8)	8 (7)	28 (9)
Headache	4 (3)	4 (3)	7 (6)	15 (5)
Paresthesia	0	2 (2)	0	
Vertigo				4 (1)
Respiratory System	14 (12)	9 (8)	5 (4)	50 (15)
Bronchitis	4 (3)	0	0	9 (3)
Infection, Respiratory, Upper	4 (3)	1 (1)	1 (1)	15 (5)
Influenza	2 (2)	4 (3)	1 (1)	10 (3)
Pharyngitis	2 (2)	2 (2)	0	6 (2)
Dyspnea				5 (2)
Skin & Skin Appendage	6 (5)	4 (3)	6 (5)	21 (6)
Eczema				4 (1)
Erythema	0	0	2 (2)	
Herpes Zoster	2 (2)	0	0	
Special Senses	37 (32)	29 (25)	32 (27)	118 (36)
Blepharitis				6 (2)
Blurred Vision	5 (4)	1 (1)	2 (2)	7 (2)
Burning and/or Stinging, Eye	7 (6)	9 (8)	3 (3)	10 (3)
Chalazion				4 (1)
Conjunctivitis	2 (2)	2 (2)	0	11 (3)
Conjunctivitis, Follicular				5 (2)
Cupping, Optic Disc	2 (2)	0	0	
Constriction, Visual Field				6 (2)
Defect, Nasal Step				8 (2)

Defect, Visual Field	0	2 (2)	2 (2)	23 (7)
Degeneration, Macular				4 (1)
Degeneration, Vitreous	2 (2)	3 (3)	3 (3)	
Dry Eyes	2 (2)	0	0	
Edema, Eyelid	2 (2)	0	0	5 (2)
Epiphora	0	1 (1)	2 (2)	
Erosion, Corneal				7 (2)
Foreign Body Sensation	4 (3)	2 (2)	1 (1)	
Hemorrhage, Optic Disc	2 (2)	1 (1)	0	
Hemorrhage, Retinal	1 (1)	2 (2)	1 (1)	
Hemorrhage, Subconjunctival	3 (3)	0	1 (1)	
Inflammation, Eyelid	3 (3)	1 (1)	1 (1)	
Injection, Conjunctival	4 (3)	10 (8)	2 (2)	15 (5)
Itching, Eye	2 (2)	2 (2)	0	6 (2)
Opacity, Lens	1 (1)	4 (3)	2 (2)	10 (3)
Opacity, Vitreous	0	2 (2)	0	
Pain, Eye	3 (3)	1 (1)	2 (2)	8 (2)
Perversion, Taste	1 (1)	3 (3)	2 (2)	6 (2)
Scotoma	0	0	2 (2)	
Scotoma, Arcuate	2 (2)	0	1 (1)	4 (1)
Staining, Corneal	4 (3)	3 (3)	5 (4)	11 (3)
Tearing	0	3 (3)	0	
Urogenital System	4 (3)	3 (3)	4 (3)	14 (4)
Cystitis	0	0	2 (2)	
Infection, Urinary Tract				4 (1)
Pyelonephritis	0	2 (2)	0	

Note: 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.

Emergent or Worsening Ocular Symptoms

Experience	Combination (N=115) N %	Dorzolamide (N=118) N %	Timolol (N=117) N %	Combination Open Label (N=326) N %
Patients with any ocular symptoms	42 (37)	49 (42)	37 (32)	86 (27)
Blurred vision	10 (9)	7 (6)	7 (6)	22 (7)
Burning eye	23 (20)	20 (17)	19 (16)	37 (12)
Dryness of eye	3 (3)	0 (0)	1 (1)	
Eye Discomfort	1 (1)	1 (1)	2 (2)	
Eye pain	1 (1)	2 (2)	2 (2)	4 (1)
Eyelid pain or discomfort	3 (3)	2 (2)	3 (3)	8 (3)
Foreign body sensation	4 (4)	2 (2)	1 (1)	9 (3)
Heaviness, eye	1 (1)	2 (2)	2 (2)	
Itching, eye	8 (7)	5 (4)	4 (3)	14 (4)
Stinging eye	7 (6)	15 (13)	4 (3)	14 (4)
Tearing eye	3 (3)	7 (6)	0 (0)	14 (4)
Vision cloudy	0	3 (3)	2 (2)	
Patients with nonocular symptoms	38 (33)	47 (40)	7 (6)	78 (24)
Taste, Bitter	28 (25)	35 (30)	6 (5)	64 (20)
Taste, Sour	13 (11)	10 (9)	0 (0)	15 (5)
Taste, Sweet	1 (1)	2 (2)	1 (1)	2 (1)

Emergent or Worsening Ocular Signs

Experience	Combination (N=115) N %	Dorzolamide (N=118) N %	Timolol (N=117) N %	Combination Open Label (N=326) N %
Conjunctiva (any sign)	21 (18)	22 (19)	15 (13)	66 (20)
Conjunctival discharge				4 (1)
Conjunctival edema	2 (2)	2 (2)	1 (1)	4 (1)
Conjunctivitis	1 (1)	2 (2)	0 (0)	
Conjunctivitis, Follicular	1 (1)	3 (3)	2 (2)	10 (3)
Hemorrhage, Subconjunctival	3 (3)	0 (0)	0 (0)	
Hyperemia, Conjunctival	17 (15)	17 (14)	12 (10)	53 (16)
Cornea (any sign)	14 (12)	10 (9)	14 (12)	45 (14)
Punct. epith. erosions or SPK	6 (5)	6 (5)	6 (5)	26 (8)
Staining, Fluorescein	11 (10)	8 (7)	10 (9)	25 (8)
Lens (any sign)	1 (1)	4 (3)	2 (2)	36 (11)
Coloration, Lens nucleus	0 (0)	2 (2)	1 (1)	10 (3)
Lens, Cortical opacity	1 (1)	2 (2)	1 (1)	19 (6)
Lens, Nuclear				8 (3)
Lens, Posterior subcapsular				5 (2)
Lids (any sign)	8 (7)	6 (5)	10 (9)	24 (7)
Blepharitis				6 (2)
Erythema, Eyelid	5 (4)	4 (3)	5 (4)	6 (2)
Edema, Eyelid				6 (2)
Hordeolum	1 (<1)	0 (0)	3 (3)	
Papillae, Eyelid				4 (1)
Optic Nerve (any sign)	4 (4)	2 (2)	3 (3)	24 (8)
Atrophy, Optic				4 (1)
Glaucomatous cupping	2 (2)	1 (1)	1 (1)	19 (6)
Hemorrhage, Optic disc	2 (2)	1 (1)	0 (0)	
Retina (any sign)	3 (3)	4 (3)	1 (1)	20 (6)
Hemorrhage, Retina	1 (1)	2 (2)	1 (1)	
Vitreous (any sign)	3 (3)	4 (3)	5 (4)	20 (6)
Degeneration, Vitreous				6 (2)
Detachment, Vitreous	2 (2)	3 (3)	4 (4)	14 (4)
Opacity, Vitreous	1 (1)	2 (2)	0 (0)	

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

Study #1 Summary

1. The study demonstrates that the combination is more effective in lowering IOP at 2 hours after dosing and not after 12 hours.

2. The combination demonstrates a combination of adverse events equal to or greater than each component alone.

3. There is an unexplained increase in larger cup/disc ratios in the combination group.

4. The IOP lowering effect is consistent throughout the 1 year study period.

8.1.2 Reviewer's Trial # 2 Applicant's protocol # 47

A Parallel, Randomized, Double-Masked Study Comparing the 0.5% Timolol/2.0% MK-0507 Combination Ophthalmic Solution to 0.5% Timolol Ophthalmic Solution or 2.0% MK-0507 Ophthalmic Solution in Patients With Elevated Intraocular Pressure #047

8.1.2.1 Objective/Rationale - *Same as study #1 without 1 year follow-up*

8.1.2.2 Design - *Same as study #1 without 1 year follow-up*

8.1.2.3 Protocol

	Prestudy Screening Days -21 to -2	Days 1, 15, 30, 60 & 90			Poststudy
		Pre-dose	Post-dose	2 Hours	
General Ocular and Medical History	X				
Physical Examination	X				X
Laboratory Tests	X				X
Symptomatology	X	X	X	X	
External and Anterior Segment Exam	X	X		X	
Visual Acuity	X	X			
IOP Measurement	X	X		X	
Lens and Ophthalmoscopy	X				X
Visual Field	X				X
Gonioscopy	X				

8.1.2.3.1 Population *Same as study #1*

8.1.2.3.2 Endpoints *Same as study #1 without 1 year follow-up*

8.1.2.4 Results

8.1.2.4.1 Populations enrolled/analyzed

			Combo	Dorz	Timolol
1	Barnebey, Howard	Seattle, WA	3	2	3
2	Blitzer, Ronald J.	Rahway, NJ	4	4	4
3	Bowe, Brian E.	Wenatchee, WA	7	6	7
4	Campbell, Charles B.	Winston-Salem, NC	6	6	6
5	Cacioppo, Leonard R.	Brooksville, FL	6	6	6
6	Cioffi, George A.	Portland, OR	4	3	3
7	Cohen, John S.	Cincinnati, OH	3	3	3
8	Cyrlin, Marshall N.	Southfield, MI	3	3	3
10	Friedman, Robert	S. Sunrise, FL	5	5	5
11	Geiser, David K.	Wheaton, IL	4	4	5
12	Gottlieb, Louis N.	Winston-Salem, NC	5	5	5
13	Grady, Frank	Lake Jackson, TX	2	3	2
14	Guber, Donald	Altamonte Springs, FL	2	3	2
15	Hodes, Barton L.	Tucson, AZ	0	1	1
16	Jolson, Alfred	Altamonte Springs, FL	3	4	3
17	Karas, Stefen	Honolulu, Hawaii	0	0	1
18	Karp, David W.	Louisville, KY	5	3	4
19	Kunesh-Part, Kristine	Dayton, OH	2	0	1
20	Laibovitz, Robert A.	Austin, TX	10	10	10
21	Lewis, Richard A.	Sacramento, CA	6	5	5
22	McMahon, Charles D.	Colorado Springs, CO	1	1	0
23	Mundorf, Thomas	Charlotte, NC	7	8	8
24	Parver, Leonard M.	Washington, DC	5	4	4
25	Rotberg, Michael	Charlotte, NC	7	7	8
26	Schuman, Joel S.	Boston, MA	4	3	4
27	Stabile, John R.	Tenafly, NJ	6	6	5
28	Wilensky, Jacob	Chicago, IL	4	4	4
Total			114	109	112

Baseline Demographic Characteristics by Treatment Group

	Combination (N=114) N (%)	MK-0507 (N=109) N (%)	Timolol (N=112) N (%)
Gender			
Male	54 (47)	55 (50)	62 (55)
Female	60 (53)	54 (50)	50 (45)
Race			
White	94 (82)	94 (86)	88 (79)
Black	18 (16)	12 (11)	19 (17)
Hispanic	1 (1)	2 (2)	3 (3)
Other	1 (1)	1 (1)	2 (2)
Iris Color			
Dark Brown	18 (16)	15 (14)	18 (16)
Brown	31 (27)	31 (28)	27 (24)
Hazel	24 (21)	21 (19)	31 (28)
Green	5 (4)	8 (7)	5 (4)
Blue	36 (32)	34 (31)	31 (28)
Age (Years)			
N	114	109	112
Mean [SD]	62.4 [11.7]	61.3 [11.8]	62.4 [11.5]
Median	65	62	63
Range	28-83	27-84	36-83

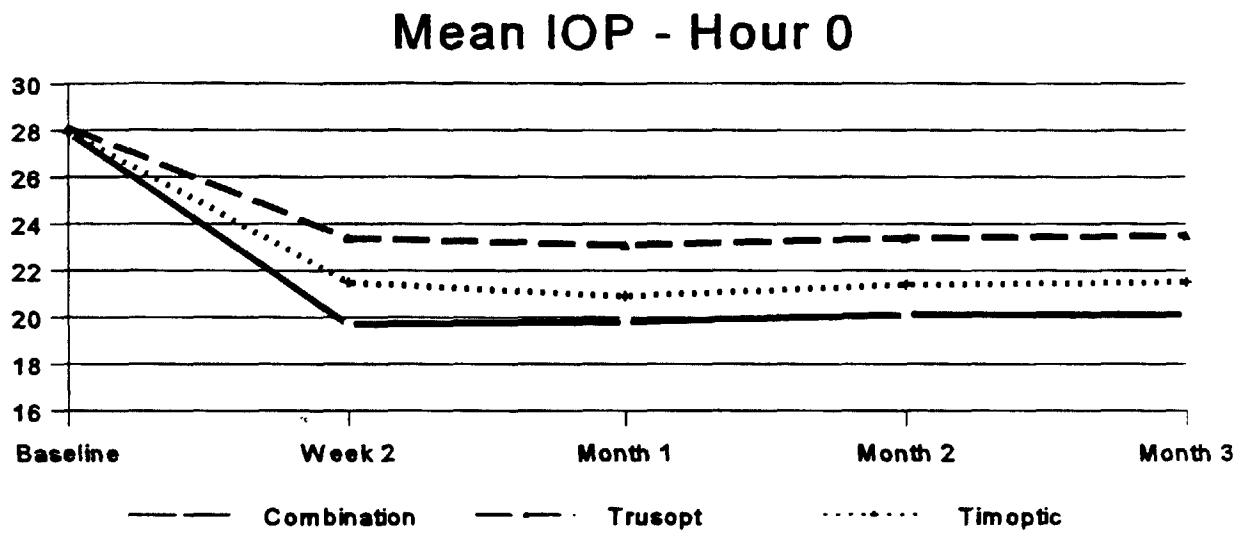
Patient Accounting

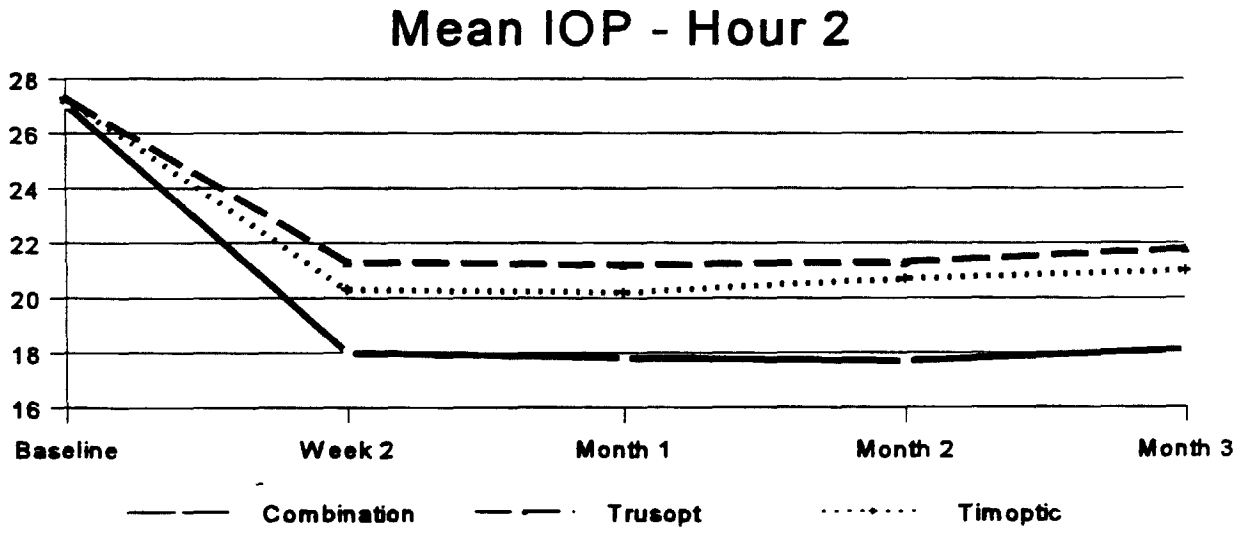
	Combination	Dorzolamide	Timolol
Entered	114	109	112
Completed Masked Phase	105	98	101
Discontinued			
Clinical Adverse Experience	8	4	1
Protocol Deviation	1	2	4
Therapy Ineffective	0	3	4
Patient Withdrew	0	0	1
Lost to Follow-up	0	2	1

Discontinued for Adverse Experiences

Group	Number	Gender	Age	Day of Onset	Adverse Experience	Duration (Days)	Day Discontinued
Combination	7543	M	74	23	Nausea, Dyspepsia, Anorexia, Tinnitus	43	24
Combination	7582	M	71	7	Myasthenia Gravis	393	47
Combination	7677	F	53	1	Nasal Congestion	12	6
Combination	7688	F	60	2	Ocular swelling, burning/stinging and injection	36	34
Combination	7784	M	78	8	Foreign body sensation, visual disturbance	8	15
Combination	7861	F	49	1	Eye pain, photosensitivity, burning/stinging	7	3
Combination	7882	M	81	81	Diabetes, Pneumonia	21	98
Combination	7888	F	64	22	Pancreatitis, abscess	37	63
Dorzolamide	7724	F	44	2	Nausea, Flatulence, Abdominal pain	25	23
Dorzolamide	7798	F	64	22	Headache	3	22
Dorzolamide	7831	M	33	24	Pain, Chest	13	24
Dorzolamide	7525	M	42	79	Uveitis	12	78
Timolol	7620	M	67	48	Diarrhea	12 hrs	48

8.1.2.4.2 **Efficacy endpoint outcomes**





Reviewer's Comments: *The combination is statistically superior to Trusopt and Timoptic at Hour 0 and Hour 2, although the clinical difference is minimal.*

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

Exam	Treatment	N	Baseline Mean	SD	Treatment Mean	SD	Change Mean	SD	Percent Change Mean	Median
Hour 0										
Wk 2	Combination	113	27.9	5.0	19.7	4.1	-8.1	4.6	-28.5	-28.0
	MK-0507	109	28.1	4.7	23.4	4.4	-4.6	3.7	-16.1	-16.7
	Timolol	111	27.9	4.6	21.5	3.8	-6.4	4.0	-22.4	-23.1
Mo 1	Combination	114	27.8	5.0	19.8	4.3	-8.0	4.5	-28.2	-28.8
	MK-0507	109	28.1	4.7	23.1	4.2	-5.0	3.8	-17.4	-17.2
	Timolol	111	27.9	4.6	20.9	4.0	-7.0	3.9	-24.6	-24.0
Mo 2	Combination	114	27.8	5.0	20.1	4.5	-7.7	4.2	-27.3	-28.0
	2% MK-0507	109	28.1	4.7	23.4	4.3	-4.7	3.9	-16.3	-16.7
	Timolol	111	27.9	4.6	21.4	4.6	-6.5	3.8	-23.2	-23.3
Mo 3	Combination	114	27.8	5.0	20.1	4.5	-7.7	4.2	-27.4	-29.4
	MK-0507	109	28.1	4.7	23.5	4.2	-4.6	4.3	-15.5	-16.7
	Timolol	111	27.9	4.6	21.5	4.0	-6.4	4.1	-22.2	-22.2
Hour 2										
Wk 2	Combination	111	27.1	4.4	18.0	3.5	-9.1	3.9	-33.1	-32.0
	MK-0507	109	27.3	3.8	21.3	3.9	-6.0	3.1	-21.9	-22.2
	Timolol	110	27.3	4.4	20.3	3.5	-7.0	4.9	-24.6	-25.0
Mo 1	Combination	112	27.1	4.3	17.8	3.7	-9.3	4.4	-33.7	-35.4
	MK-0507	109	27.3	3.8	21.2	3.9	-6.1	3.3	-22.1	-22.2
	Timolol	110	27.3	4.4	20.2	3.9	-7.0	4.9	-24.8	-25.0
Mo 2	Combination	112	27.1	4.3	17.7	3.7	-9.4	4.4	-34.1	-34.5
	MK-0507	109	27.3	3.8	21.3	3.8	-5.9	3.3	-21.5	-20.8
	Timolol	110	27.3	4.4	20.7	4.4	-6.6	5.2	-23.3	-25.0
Mo 3	Combination	112	27.1	4.3	18.1	3.8	-9.0	4.3	-32.7	-33.3
	MK-0507	109	27.3	3.8	21.8	4.3	-5.4	3.6	-19.8	-20.8
	Timolol	110	27.3	4.4	21.0	4.7	-6.3	4.7	-22.6	-23.5

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

8.1.2.4.3 Safety outcomes

Laboratory Experiences:

Reviewer's Comments: *There were no clinically significant laboratory adverse experiences. There were not enough patients treated to rule out the possibility of a rare incidence of aplastic anemia.*

Pupil Diameter:(mm)	Combination	Dorzolamide	Timolol
Baseline	3.9	3.9	3.9
Treatment	3.9	3.9	3.9

Reviewer's Comments: *No differences were observed.*

Visual Acuity and Visual Fields:

Reviewer's Comments: *No specific differences between groups were noted. It would have been preferable for visual acuity to be reported as the number of lines increased by 1, 2 and more than 2, and the number of lines decreased by 1, 2 and more than 2.*

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

Treatment Group	Study	AN	Eye	Horizontal	Vertical	Horizontal	Vertical
Combination	12	7582	L	.40	.40	.60	.60
	12	7582	R	.40	.40	.60	.60
	12	7743	L	.40	.40	.60	.40
Dorzolamide	13	7569	L	.40	.40	.60	.60
	13	7571	L	.55	.55	.90	.90
			R	.55	.55	.85	.85

Reviewer's comments: *No difference between groups.*

Number (%) of Patients with Clinical Adverse Experiences (>1% in Any Treatment Group)

Adverse Experience	Combination (N=114) N %	Dorzolamide (N=109) N %	Timolol (N=112) N %
Patients With Any Adverse Experience	57 (50)	63 (58)	53 (47)
Body As A Whole/Site Unspecified	5 (4)	10 (9)	3 (3)
Asthenia/Fatigue	0	1 (1)	2 (2)
Flu-Like Illness	1 (1)	3 (3)	0
Pain, Abdominal	3 (3)	4 (4)	0
Pain, Chest	0	2 (2)	0
Cardiovascular System	0	5 (5)	6 (5)
Hypertension	0	1 (1)	2 (2)
Hypertension Increased	0	2 (2)	1 (1)
Digestive System	10 (9)	8 (7)	7 (6)
Diarrhea	3 (3)	0	1 (1)
Dry Mouth	1 (1)	1 (1)	2 (2)
Dyspepsia	2 (2)	1 (1)	0
Nausea	1 (1)	2 (2)	1 (1)
Endocrine System	2 (2)	0	1 (1)
Diabetes Mellitus	2 (2)	0	1 (1)
Metabolic/Nutritional/Immune	1 (1)	1 (1)	1 (1)
Musculoskeletal System	7 (6)	8 (7)	13 (12)
Arthritis	0	0	2 (2)
Cramp, Muscle	0	0	2 (2)
Myalgia	1 (1)	0	2 (2)
Pain, Back	1 (1)	4 (4)	1 (1)
Pain, Knee	0	0	2 (2)
Pain, Neck	2 (2)	0	1 (1)
Nervous System & Psychiatric	14 (12)	12 (11)	12 (11)
Depression	0	0	3 (3)
Dizziness	2 (2)	1 (1)	2 (2)
Headache	8 (7)	7 (6)	4 (4)
Paresthesia	1 (1)	1 (1)	2 (2)
Somnolence	0	0	2 (2)
Respiratory System	15 (13)	25 (23)	17 (15)
Bronchitis	0	3 (3)	1 (1)
Congestion, Nasal	3 (3)	1 (1)	1 (1)
Cough	2 (2)	2 (2)	2 (2)
Infection, Respiratory, Upper	8 (7)	11 (10)	7 (6)

Influenza	0	1 (1)	2 (2)
Pharyngitis	1 (1)	2 (2)	2 (2)
Rhinorrhea	1 (1)	0	2 (2)
Sinus Disorder	1 (1)	3 (3)	0
Sinusitis	2 (2)	3 (3)	1 (1)
Skin & Skin Appendage	5 (4)	4 (4)	5 (4)
Rash	1 (1)	2 (2)	0
Urticaria	0	0	2 (2)
Special Senses	38 (33)	39 (36)	24 (21)
Blurred Vision	5 (4)	4 (4)	5 (4)
Burning and/or Stinging, Eye	21 (18)	15 (14)	7 (6)
Cataract	2 (2)	1 (1)	1 (1)
Discharge, Eye	1 (1)	1 (1)	4 (4)
Dry Eyes	0	2 (2)	2 (2)
Erosion, Corneal	0	1 (1)	2 (2)
Foreign Body Sensation	2 (2)	3 (3)	1 (1)
Hemorrhage, Subconjunctival	1 (1)	2 (2)	0
Injection, Ocular	3 (3)	4 (4)	1 (1)
Irritation, Eyelid	1 (1)	2 (2)	0
Itching, Eye	4 (4)	3 (3)	0
Opacity, Lens	0	2 (2)	0
Opacity, Vitreous	0	0	2 (2)
Pain, Eye	1 (1)	1 (1)	2 (2)
Perversion, Taste	9 (8)	11 (10)	1 (1)
Photopsia	0	0	2 (2)
Tearing	3 (3)	3 (3)	1 (1)
Visual Disturbance	2 (2)	1 (1)	0
Urogenital System	3 (3)	2 (2)	6 (5)
Infection, Urinary Tract	2 (2)	2 (2)	2 (2)

Note: All body systems in which at least 1 patient had an adverse experience are listed. 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 clinical adverse experience in a body system category are counted only once in that body system total and in the overall total.

Emergent or Worsening Ocular Symptoms

Experience	Combination (N=114) N %	Dorzolamide (N=109) N %	Timolol (N=112) N %
Patients with any ocular symptoms	70 (61)	63 (58)	34 (31)
Blurred vision	23 (20)	19 (17)	10 (9)
Burning eye	30 (26)	31 (28)	10 (9)
Dryness of eye	2 (2)	7 (6)	8 (7)
Eye pain	4 (4)	0 (0)	2 (2)
Eyelid pain or discomfort	1 (1)	2 (2)	1 (1)
Foreign body sensation	4 (4)	2 (2)	4 (4)
Itching, eye	8 (7)	9 (8)	4 (4)
Photophobia	1 (1)	1 (1)	2 (2)
Redness, eye	2 (2)	2 (2)	1 (1)
Stickiness, eye	4 (4)	1 (1)	0 (0)
Stinging eye	25 (22)	19 (17)	9 (8)
Tearing eye	11 (10)	6 (6)	1 (1)
Vision cloudy	6 (5)	6 (6)	4 (4)
Patients with any nonocular symptoms	32 (28)	40 (37)	6 (5)
Taste, Bitter	22 (19)	34 (31)	5 (5)
Taste, Sour	5 (4)	2 (2)	1 (1)
Taste, Sweet	7 (6)	7 (6)	1 (1)

Emergent or Worsening Ocular Signs

Experience	Combination (N=114) N %	Dorzolamide (N=109) N %	Timolol (N=112) N %
Anterior Chamber (any sign)	2 (2)	1 (1)	0 (0)
Conjunctiva (any sign)	11 (10)	15 (14)	13 (12)
Conjunctival Edema	2 (2)	3 (3)	3 (3)
Conjunctival Follicles	3 (3)	1 (1)	0 (0)
Conjunctival Hyperemia	6 (5)	11 (10)	9 (8)
Cornea (any sign)	8 (7)	6 (6)	11 (10)
Punct. epith. erosions or SPK	5 (4)	4 (4)	7 (6)
Staining, fluorescein	5 (4)	2 (2)	8 (7)
Lens (any sign)	10 (9)	7 (7)	7 (6)
Cataract, Subcapsular	1 (1)	2 (2)	1 (1)
Coloration, Lens Nucleus	3 (3)	1 (1)	4 (4)
Lens, Cortical opacity	2 (2)	1 (1)	0 (0)
Nuclear Opacity, Lens	4 (4)	3 (3)	4 (4)
Lids (any sign)	7 (6)	7 (6)	5 (5)
Blepharitis	3 (3)	3 (3)	2 (2)
Edema, Eyelid	1 (1)	2 (2)	2 (2)
Erythema, Eyelid	1 (1)	2 (2)	0 (0)
Optic Nerve (any sign)	4 (4)	6 (6)	1 (1)
Glaucomatous, Cupping	3 (3)	5 (5)	0 (0)
Retina (any sign)	1 (1)	0 (0)	1 (1)
Vitreous (any sign)	1 (1)	1 (1)	4 (4)
Opacity, Vitreous	0 (0)	0 (0)	3 (3)

Reviewer's Comments: *There were no significant differences between groups.*

Study #2 Summary

1. The study demonstrates that the combination is statistically more effective in lowering IOP.

2. The combination demonstrates a combination of adverse events equal to or greater than each component alone.

8.1.3 Reviewer's Trial # 3 Applicant's protocol # 63

A Parallel, Randomized, Double-Masked Study Comparing the 0.5% Timolol/2.0% MK-0507 Combination Ophthalmic Solution b.i.d. to 0.5% Timolol Ophthalmic Solution b.i.d. or 2.0% MK-0507 Ophthalmic Solution t.i.d. in Patients With Elevated Intraocular Pressure who are Inadequately Controlled on Timolol Alone #063

8.1.3.1 Objective/Rationale

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

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

8.1.3.2 Design Same as Study #2

8.1.3.3 Protocol

	Timolol Run-In Day -21 to -1 Prestudy Screening Days -21 to -2	Days 1, 15, 30, 60 & 90		Poststudy (with 5 days of completing or discontinuing)
		Immediately Pre-dose	2 Hours Post-dose	
General Ocular and Medical History	X			
External and anterior segment examination	X	X	X	
Visual Acuity	X	X		
IOP Measurement	X	X	X	
Symptoms	X	X	X	
Lens and Ophthalmoscopy	X			X
Visual Field	X			X
Gonioscopy	(within 6 months)			
β-HCG (urine) (women of child bearing potential	X			X

8.1.3.3.1 Population

Male or female patients above 21 years of age with a diagnosis of open-angle glaucoma or ocular hypertension in both eyes with IOP ≥22 mmHg in at least one eye at hour 0 and hour 2, at baseline following the 3 week run-in period..

8.1.3.3.2 Endpoints

Efficacy - IOP

Safety - Cup to disc ratio, visual acuity, visual field, ocular signs and symptoms, and incidence of adverse experiences.

8.1.3.4 Results

8.1.3.4.1 Populations enrolled/analyzed

Study Num	Investigator	Location	Combination	MK-0507	Timolol
001	Abelson, Mark	North Andover, MA	5	3	4
002	Barnebey, Howard	Seattle, WA	6	2	6
003	Bernstein, Michael	Birmingham, AL	2	1	1
004	Brown, Reay	Atlanta, GA	6	3	6
005	Cacioppo, Leonard	Brooksville, FL	6	3	6
006	George, Roger	Tacoma, WA	4	3	6
007	Cohen, John	Cincinnati, OH	1	0	1
008	DuBiner, Harvey	Morrow, GA	6	3	6
009	Gieser, David	Wheaton, IL	6	3	5
010	Greenberg, Marvin	Tamarac, FL	8	4	7
011	Harbin, Thomas	Atlanta, GA	5	3	5
012	Horwitz, Barry	Houston, TX	2	1	2
013	Johnstone, Murray	Seattle, WA	1	1	1
014	Karp, David	Louisville, KY	6	3	5
015	Kolodner, Harry	Clearwater, FL	2	1	2
016	Laibovitz, Robert	Austin, TX	8	4	8
017	Lewis, Richard	Sacramento, CA	2	0	0
018	Mundorf, Thomas	Charlotte, NC	6	2	5
019	Ostrov, Charles	Minneapolis, MN	4	2	4
020	Rotberg, Michael	Charlotte, NC	4	2	4
021	Schultz, Jeffrey	Bronx, NY	0	0	0
022	Turner, Jerald	Clearwater, FL	4	2	4
023	Williams, Robert	Louisville, KY	10	5	10
Total			104	51	98

Baseline Demographic Characteristics by Treatment Group

	Combination (N=104) N (%)	MK-0507 (N=51) N (%)	Timolol (N=98) N (%)
Gender			
Male	42 (40)	22 (43)	47 (48)
Female	62 (60)	29 (57)	51 (52)
Race			
White	90 (87)	40 (78)	78 (80)
Black	13 (13)	9 (18)	17 (17)
Asian	1 (1)	0	0
Hispanic	0	1 (2)	2 (2)
Filipino	0	1 (2)	0
East Indian	0	0	1 (1)
Iris Color			
Dark Brown	14 (13)	7 (14)	15 (15)
Brown	30 (29)	16 (31)	30 (31)
Hazel	19 (18)	6 (12)	15 (15)
Green	2 (2)	5 (10)	3 (3)
Blue	39 (38)	17 (33)	35 (36)
Age (Years)			
Mean [SD]	63.6 [12.4]	64.4 [15.0]	63.4 [13.0]
Median	64.5	66	65. 5
Range	37-86	28-88	30-88

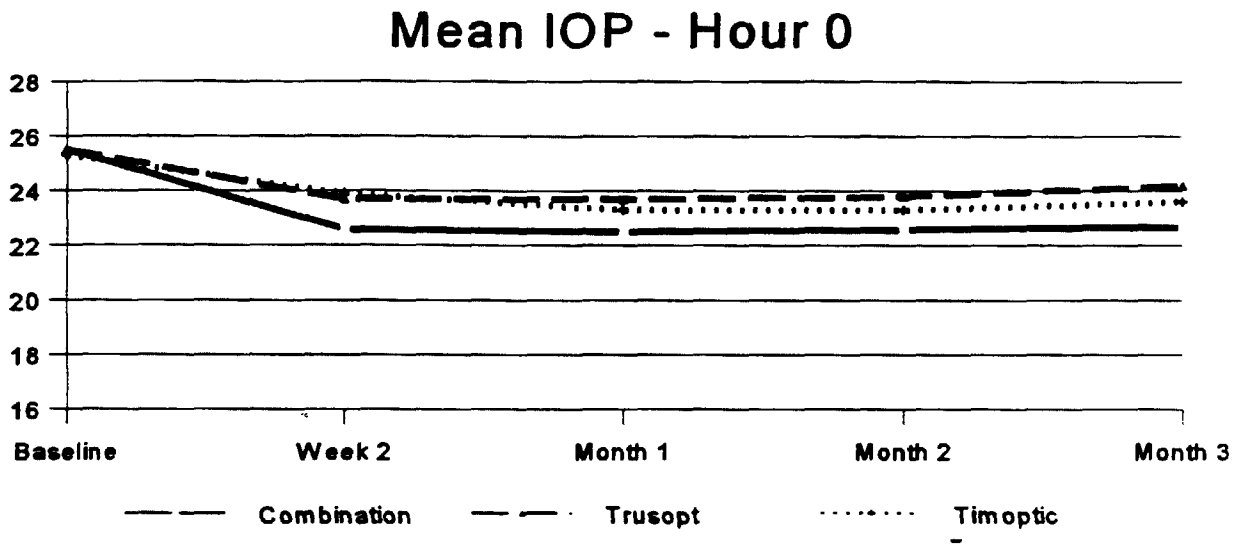
Patient Accounting

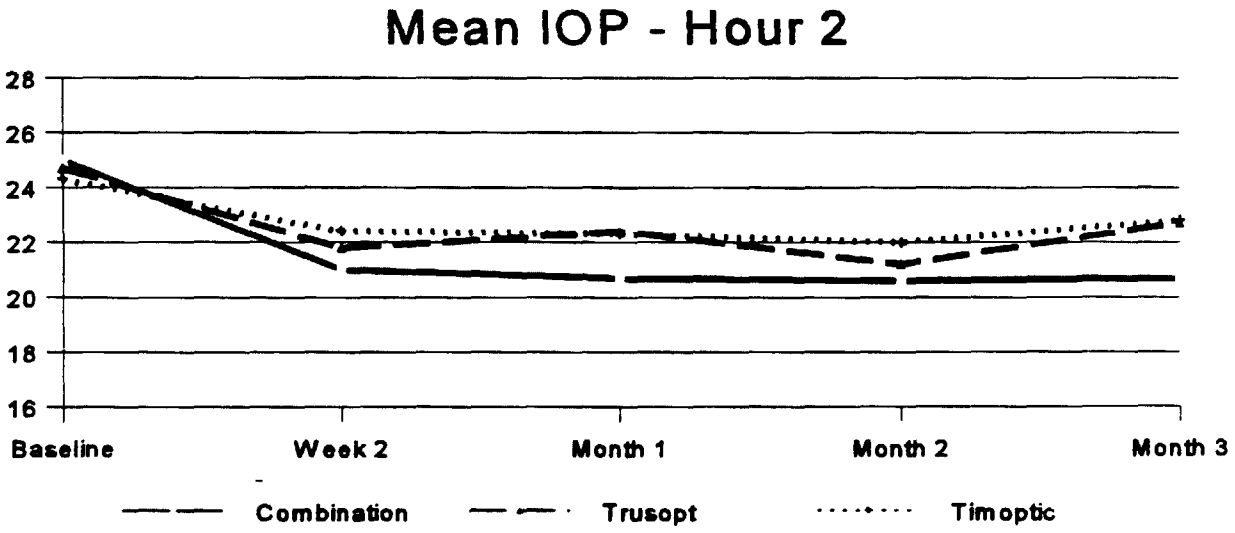
	Combination	Dorzolamide	Timolol
Entered Masked Phase	104	51	98
Completed Masked Phase	94	49	89
Discontinued			
Clinical Adverse Experience	3	0	1
Protocol Deviation	2	0	3
Therapy Ineffective	4	2	3
Patient Withdrew	1	0	2

Discontinued for Adverse Experiences

Group	Number	Gender	Age	Day of Onset	Adverse Experience	Duration (Days)	Day Discontinued
Combination	8150	F	71	53	Dizziness, Nausea and Tremors	22	72
Combination	8219	F	60	80	Plasmacytoma/Death	142	80
Combination	8213	F	45	2	Eye Pain	18	19
Timolol	8342	F	80	11	Urinary Frequency	23	27

8.1.3.4.2 Efficacy endpoint outcomes





Reviewer's Comments: *The combination is statistically superior to Trusopt at both Hour 0 and Hour 2 at most, but not all time points. The combination is statistically superior to Timoptic in lowering intraocular pressure at most, but not all time points.*

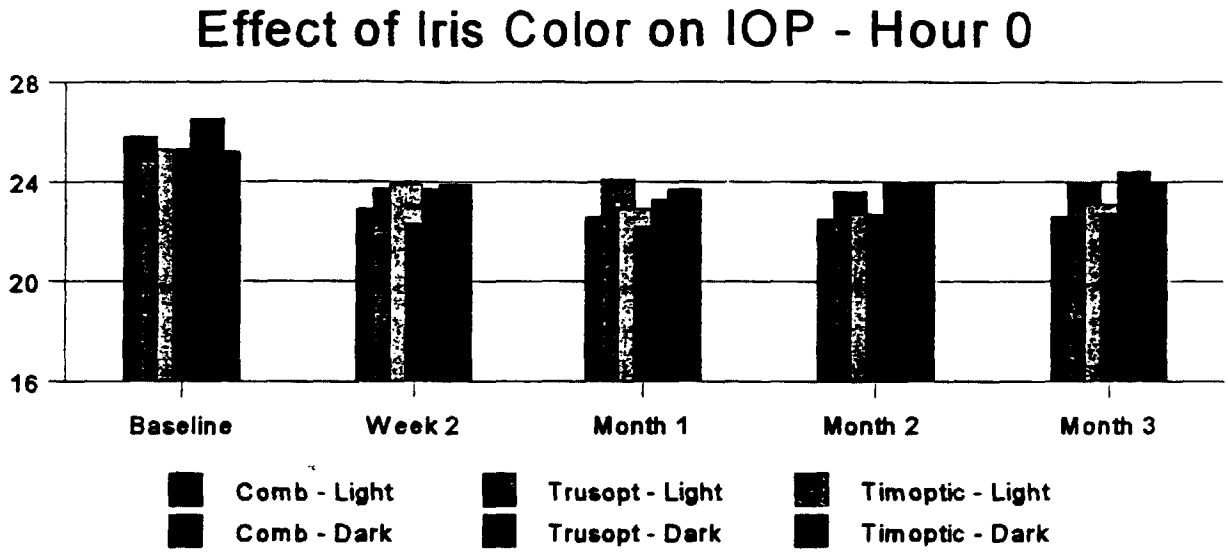
IOP Summary Statistics (mm Hg) -- Double-Masked Phase

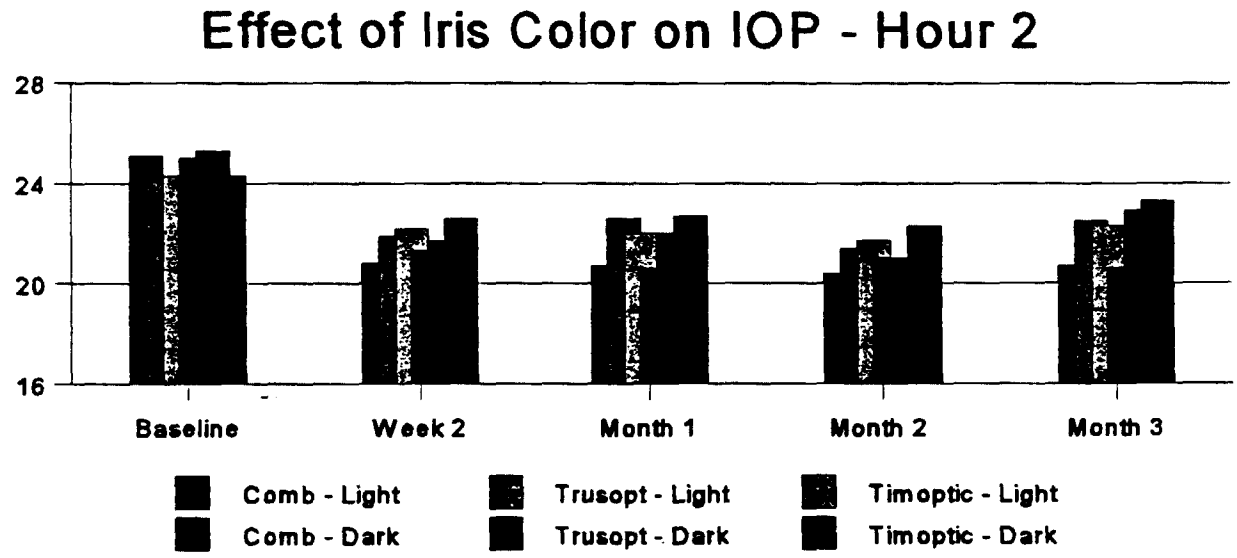
Exam	Treatment	N	Baseline Mean	SD	Treatment Mean	SD	Change Mean	SD	Percent Change Mean	Median
Hour 0										
Week 2	Combination	99	25.5	3.4	22.6	3.4	-2.9	3.3	-10.9	-10.0
	MK-0507	51	25.5	3.8	23.7	3.6	-1.9	3.4	-6.6	-4.5
	Timolol	96	25.3	3.2	23.9	4.2	-1.4	3.2	-5.4	-4.5
Month 1	Combination	102	25.5	3.4	22.5	3.5	-3.0	3.4	-11.3	-11.9
	MK-0507	51	25.5	3.8	23.7	4.0	-1.8	3.9	-6.3	-4.0
	Timolol	98	25.2	3.1	23.3	4.4	-2.0	3.0	-7.9	-7.7
Month 2	Combination	102	25.5	3.4	22.6	3.8	-2.9	3.1	-11.0	-12.8
	MK-0507	51	25.5	3.8	23.8	4.2	-1.8	4.3	-6.0	-7.4
	Timolol	98	25.2	3.1	23.3	4.2	-1.9	3.1	-7.5	-8.5
Month 3	Combination	102	25.5	3.4	22.7	3.9	-2.8	3.4	-10.6	-10.4
	MK-0507	51	25.5	3.8	24.2	5.1	-1.4	4.3	-4.9	-4.5
	Timolol	98	25.2	3.1	23.6	4.3	-1.7	3.1	-6.7	-7.3
Hour 2										
Week 2	Combination	100	25.0	4.0	21.0	4.0	-4.0	3.1	-15.8	-16.7
	MK-0507	51	24.7	3.3	21.8	3.4	-2.8	3.8	-10.8	-9.1
	Timolol	93	24.3	2.6	22.4	3.7	-1.9	2.5	-8.1	-8.7
Month 1	Combination	103	25.0	3.9	20.7	4.3	-4.4	3.0	-17.3	-18.4
	MK-0507	51	24.7	3.3	22.4	3.8	-2.3	4.5	-8.5	-8.7
	Timolol	95	24.3	2.6	22.3	4.6	-2.0	3.3	-8.7	-9.5
Month 2	Combination	103	25.0	3.9	20.6	4.2	-4.4	3.3	-17.1	-16.7
	MK-0507	51	24.7	3.3	21.2	3.5	-3.5	4.3	-13.3	-9.1
	Timolol	95	24.3	2.6	22.0	4.2	-2.4	3.2	-9.8	-12.0
Month 3	Combination	103	25.0	3.9	20.7	4.5	-4.4	3.3	-17.3	-18.2
	MK-0507	51	24.7	3.3	22.7	3.8	-2.0	4.1	-7.4	-6.7
	Timolol	95	24.3	2.6	22.8	4.6	-1.6	3.7	-6.6	-8.7

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

Additional Analyzes:

Reviewer's Comments: *Additional analyzes (not presented in this review) were consistent with respect to subgroups based on age, race, gender or iris color.*


Effect of Iris Color on IOP - Hour 0
28
24
20
16
Baseline
Week 2
Month 1
Month 2
Month 3
Comb - Light
Comb - Dark
Trusopt - Light
Trusopt - Dark
Timoptic - Light
Timoptic - Dark


Effect of Iris Color on IOP - Hour 2
28
24
20
16
Baseline
Week 2
Month 1
Month 2
Month 3
Comb - Light
Comb - Dark
Trusopt - Light
Trusopt - Dark
Timoptic - Light
Timoptic - Dark

8.1.3.4.3 Safety outcomes

Laboratory Experiences:

Reviewer's Comments: *There were no laboratory evaluations performed.*

Pupil Diameter:(mm)	Combination	Dorzolamide	Timolol
Baseline	3.8	3.9	3.7
Treatment	3.7	3.7	3.7

Reviewer's Comments: *The differences (decreases) noted above will require replication.*

Visual Acuity and Visual Fields:

Reviewer's Comments: *No specific differences between groups were noted. It would have been preferable for visual acuity to be reported as the number of lines increased by 1, 2 and more than 2, and the number of lines decreased by 1, 2 and more than 2.*

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

Treatment Group	Study	AN	Eye	Horiz	Vert	Horiz	Vert

None

Reviewer's comments: *This is unusual for a study of this type.*

Number (%) of Patients with Clinical Adverse Experiences (>1% in Combination Group)

Adverse Experience	Combination (N=104) n (%)	Dorzolamide (N=51) n (%)	Timolol (N=98) n (%)
Patients with any adverse experiences [a]	65 (63)	30 (59)	42 (43)
Body as a Whole/Site Unspecified	7 (7)	3 (6)	7 (7)
Pain, chest	3 (3)	0	0
Cardiovascular System	2 (2)	0	1 (1)
Digestive System	3 (3)	3 (6)	4 (4)
Nausea	2 (2)	0	0
Endocrine System	2 (2)	2 (4)	1 (1)
Musculoskeletal System	7 (7)	5 (10)	1 (1)
Pain, back	2 (2)	2 (4)	1 (1)
Nervous System and Psychiatric	9 (9)	3 (6)	7 (7)
Dizziness	4 (4)	1 (2)	1 (1)
Headache	3 (3)	1 (2)	3 (3)
Respiratory System	7 (7)	8 (16)	10 (10)
Infection, respiratory, upper [b]	2 (2)	5 (10)	4 (4)
Sinusitis	2 (2)	1 (2)	1 (1)
Skin and Skin Appendage	4 (4)	3 (6)	1 (1)
Eczema	2 (2)	0	0
Special Senses [c]	47 (45)	23 (45)	26 (27)
Blurred vision	2 (2)	2 (4)	7 (7)
Burning and/or stinging, eye [d]	31 (30)	12 (24)	8 (8)
Foreign body sensation	3 (3)	0	2 (2)
Injection, conjunctival	2 (2)	1 (2)	0
Itching, eye	2 (2)	1 (2)	3 (3)
Opacity, vitreous	2 (2)	0	1 (1)
Pain, eye	4 (4)	0	0
Perversion, taste	8 (8)	7 (14)	2 (2)
Photopsia	2 (2)	0	0
Tearing	3 (3)	1 (2)	2 (2)
Urogenital System	3 (3)	1 (2)	3 (3)

[a] Significantly greater incidence in the combination group (vs. timolol), p =0.007.
[b] Significantly greater incidence in the MK-0507 group (vs. combination), p =0.039.
[c] Significantly greater incidence in the combination group (vs. timolol), p =0.008.
[d] Significantly greater incidence in the combination group (vs. timolol), p=0.001.
[e] Significantly greater incidence in the MK-0507 group (vs. combination), p =0.034.

Note: All body systems in which at least 1 patient had an adverse experience are listed.
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 clinical adverse experience in a body system category are counted only once in that body system total and in the overall total.

Emergent or Worsening Ocular Symptoms

Adverse Experience	Combination (N=104) n (%)	Dorzolamide (N=51) n (%)	Timolol (N=98) n (%)
Patients with any ocular symptoms	17 (17)	8 (16)	13 (13)
Blurred vision	2 (2)	3 (6)	5 (5)
Burning eye	5 (5)	0	2 (2)
Dryness of eye	0	0	3 (3)
Foreign body sensation	4 (4)	0	4 (4)
Heaviness, eye	0	0	1 (1)
Itching, eye	2 (2)	2 (4)	1 (1)
Mattering, eye	0	1 (2)	1 (1)
Eyelid pain or discomfort	1 (1)	1 (2)	0
Photophobia	2 (2)	2 (4)	0
Stinging eye	1 (1)	0	1 (1)
Tearing eye	3 (3)	2 (4)	2 (2)
Taste, bitter [b]	16 (16)	6 (12)	5 (5)
Taste, sour	2 (2)	0	1 (1)
Taste, sweet	1 (1)	0	0
Taste, unusual	2 (2)	0	0

[b] Significantly greater incidence in the combination group (vs. timolol), $p<0.020$.

Emergent or Worsening Ocular Signs

Adverse Experience	Combination (N=104) n (%)	Dorzolamide (N=51) n (%)	Timolol (N=98) n (%)
Anterior Chamber (any ocular sign)	2 (2)	0	0
Conjunctiva (any ocular sign)	11 (11)	6 (12)	10 (10)
Conjunctival edema	1 (1)	0	2 (2)
Dilated episcleral vessels	2 (2)	0	0
Conjunctival hyperemia	9 (9)	6 (12)	8 (8)
Mucus Discharge	1 (1)	0	1 (1)
Cornea (any ocular sign)	13 (13)	4 (8)	11 (11)
Punct. epith. erosions or SPK	7 (7)	3 (6)	7 (7)
Staining, fluorescein	6 (6)	1 (2)	4 (4)
Lens (any ocular sign)	2 (2)	0	2 (2)
Cataract, Subcapsular	1 (1)	0	1 (1)
Lens, Cortical opacity	1 (1)	0	1 (1)
Lids (any ocular sign)	6 (6)	5 (10)	5 (5)
Blepharitis	0	1 (2)	0
Debris, eye	1 (1)	3 (6)	3 (3)
Discharge, ocular	0	0	1 (1)
Edema, eyelid	1 (1)	0	1 (1)
Exudate/scales, eyelid	1 (1)	0	1 (1)
Impacted meibomian glands	1 (1)	0	1 (1)
Seborrhea, Eye	0	1 (2)	0
Optic Nerve (any ocular sign)	1 (1)	0	0
Retina (any ocular sign)	1 (1)	0	1 (1)
Atherosclerotic vascular disease	0	0	1 (1)
Vitreous, degeneration	0	0	1 (1)

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

Study #3 Summary

1. The study demonstrates that the combination is usually more effective in lowering IOP at 2 hours after dosing and after 12 hours.

2. The combination demonstrates a combination of adverse events equal to or greater than each component alone.

3. The protocol was not directly followed for pupil measurements (i.e., estimates were made to a quarter of a millimeter instead of whole millimeters).

8.1.4 Reviewer's Trial # 4 Applicant's protocol # 64

A Parallel, Randomized, Double-Masked Study Comparing the 0.5% Timolol/2.0% MK-0507 Combination Ophthalmic Solution b.i.d. to 0.5% Timolol Ophthalmic Solution b.i.d. or 2.0% MK-0507 Ophthalmic Solution t.i.d. in Patients With Elevated Intraocular Pressure who are Inadequately Controlled on Timolol Alone #064

8.1.4.1 Objective/Rationale - *Same as Study #3*
8.1.4.2 Design - *Same as Study #3*
8.1.4.3 Protocol - *Same as Study #3*
8.1.4.3.1 Population - *Same as Study #3*
8.1.4.3.2 Endpoints - *Same as Study #3*

8.1.4.4 Results
8.1.4.4.1 Populations enrolled/analyzed

Study Num	Investigator	Location	Combination	MK-0507	Timolol
001	Atlas, Walter	Charlotte, NC	6	3	5
002	Baerveldt, George	Cleveland, OH	6	3	6
003	Bennion, Richard	Wenatchee, WA	4	1	3
004	Dagianis, John	Nashua, NH	2	0	2
005	Dirks, Monte	Aurora, CO	8	4	8
006	Evans, Richard	San Antonio, TX	8	4	8
007	Hedstrom, Peter	Portland, ME	4	1	4
008	Hodes, Barton	Tucson, AZ	2	1	0
009	Kalenak, Jeffrey	Milwaukee, WI	0	0	0
010	Korn, Elliott	St. Louis, MO	6	3	6
011	Lozier, Jeffrey	San Diego, CA	6	3	6
012	Michael, Andrew	Denver, CO	4	2	3
013	McDonald, Marguerite	New Orleans, LA	0	0	0
014	OfConnor, Daniel	Plymouth, MA	2	1	2
015	Piltz, Jodie	Philadelphia, PA	2	1	2
016	Sall, Kenneth	Bellflower, CA	8	4	8
017	Schenker, Howard	Rochester, NY	6	3	6
018	Schuman, Joel	Boston, MA	2	1	2
019	Stewart, William	Charleston, SC	6	3	6
020	Vela, Angela	Atlanta, GA	2	2	3
021	Walters, Thomas	Austin, TX	8	4	8
022	Baker, Doug	Columbus, OH	3	2	3
023	Singer, Michael	San Antonio, TX	6	3	6
Total			101	49	97

Baseline Demographic Characteristics by Treatment Group

	Combination (N=101) N (%)	MK-0507 (N=49) N (%)	Timolol (N=97) N (%)
Gender			
Male	54 (53)	32 (65)	44 (45)
Female	47 (47)	17 (35)	53 (55)
Race			
White	73 (72)	35 (71)	69 (71)
Black	16 (16)	6 (12)	18 (19)
Asian	1 (1)	0	0
Hispanic	11 (11)	7 (14)	10 (10)
Indian	0	1 (2)	0
Iris Color			
Dark Brown	17 (17)	5 (10)	20 (21)
Brown	25 (25)	15 (31)	26 (27)
Hazel	15 (15)	8 (16)	20 (21)
Green	4 (4)	2 (4)	5 (5)
Blue	40 (40)	19 (39)	26 (27)
Age (Years)			
Mean [SD]	61.2 [11.1]	62.0 [12.6]	63.1 [12.3]
Median	63.0	63.0	66.0
Range	34-80	34-85	32-84

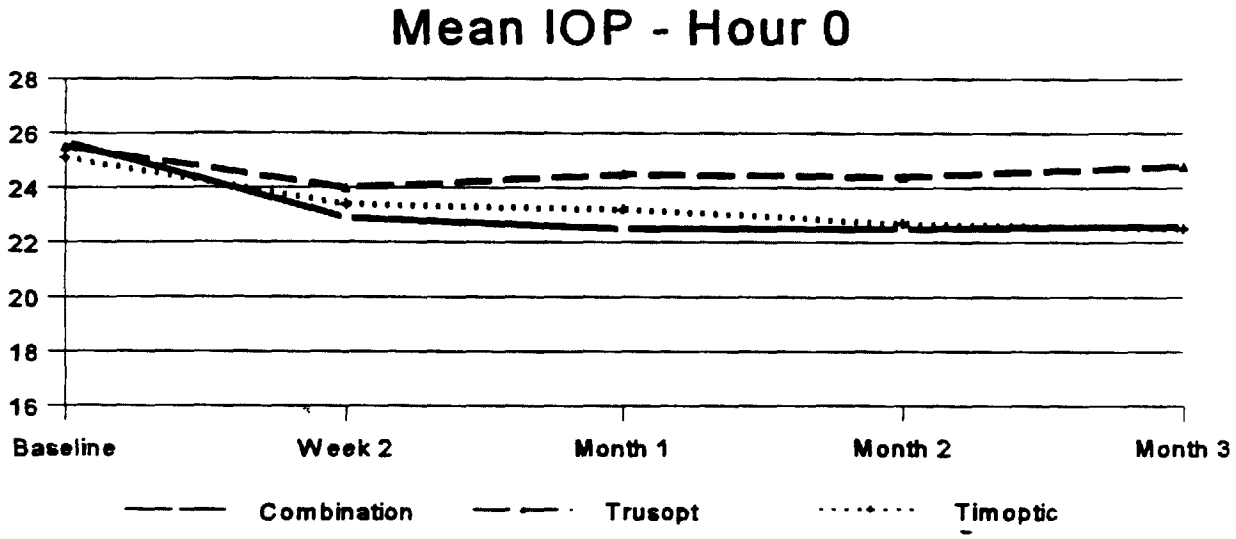
Patient Accounting

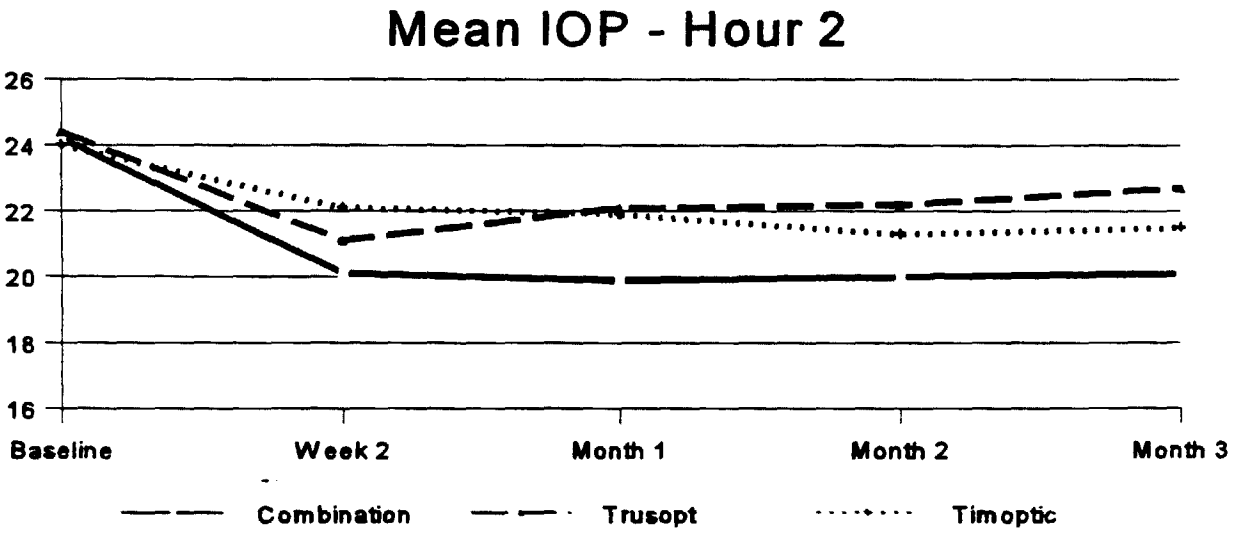
	Combination	Dorzolamide	Timolol
Entered Masked Phase	101	49	97
Completed Masked Phase	97	47	91
Discontinued			
Clinical Adverse Experience	1	0	0
Protocol Deviation	0	0	0
Therapy Ineffective	3	2	5
Patient Withdrew	0	0	1

Discontinued for Adverse Experiences

Group	Number	Gender	Age	Day of Onset	Adverse Experience	Duration (Days)	Day Discontinued
Combination	8411	M	43	3	Pharyngeal Discomfort, Cough	8	8

8.1.4.4.2 Efficacy endpoint outcomes





Reviewer's Comments: *The combination is statistically superior to Trusopt at both Hour 0 and Hour 2. The combination is statistically superior to Timoptic in lowering intraocular pressure at most, but not all time points.*

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

Exam	Treatment	N	Baseline Mean	Baseline SD	Treatment Mean	Treatment SD	Change Mean	Change SD	Percent Change Mean	Percent Change Median
Hour 0										
Week 2	Combination	99	25.7	3.0	22.9	3.4	-2.9	3.7	-10.6	-9.1
	MK-0507	49	25.5	3.1	24.0	3.3	-1.4	3.8	-4.9	-4.3
	Timolol	96	25.1	2.6	23.4	3.9	-1.7	3.1	-6.7	-7.5
Month 1	Combination	100	25.7	3.0	22.5	3.6	-3.2	3.7	-12.0	-11.8
	MK-0507	49	25.5	3.1	24.5	4.5	-1.0	4.2	-3.5	-6.7
	Timolol	96	25.1	2.6	23.2	3.3	-1.8	2.4	-7.3	-8.3
Month 2	Combination	100	25.7	3.0	22.5	4.1	-3.2	3.8	-12.2	-12.3
	MK-0507	49	25.5	3.1	24.4	4.1	-1.1	3.9	-3.8	-4.2
	Timolol	96	25.1	2.6	22.7	3.5	-2.4	2.6	-9.5	-11.2
Month 3	Combination	100	25.7	3.0	22.6	4.0	-3.2	3.3	-12.1	-12.0
	MK-0507	49	25.5	3.1	24.8	4.2	-0.7	3.9	-2.1	-4.3
	Timolol	96	25.1	2.6	22.5	3.4	-2.6	3.0	-10.1	-11.1
Hour 2										
Week 2	Combination	99	24.2	2.6	20.1	3.0	-4.1	2.7	-16.7	-17.4
	MK-0507	49	24.4	3.1	21.1	3.5	-3.2	4.1	-12.6	-13.6
	Timolol	96	24.0	2.3	22.1	3.4	-1.9	2.7	-7.8	-8.2
Month 1	Combination	100	24.2	2.6	19.9	3.0	-4.2	2.6	-17.4	-17.4
	MK-0507	49	24.4	3.1	22.1	4.3	-2.2	3.3	-9.2	-8.3
	Timolol	96	24.0	2.3	21.9	3.7	-2.1	3.0	-8.8	-9.0
Month 2	Combination	100	24.2	2.6	20.0	3.2	-4.2	2.7	-17.3	-16.3
	MK-0507	49	24.4	3.1	22.2	4.3	-2.2	3.8	-8.8	-11.1
	Timolol	96	24.0	2.3	21.3	3.4	-2.7	2.8	-11.1	-10.7
Month 3	Combination	100	24.2	2.6	20.1	3.9	-4.0	3.0	-16.8	-16.7
	MK-0507	49	24.4	3.1	22.7	4.0	-1.7	3.2	-6.8	-3.8
	Timolol	96	24.0	2.3	21.5	3.5	-2.5	3.3	-10.1	-12.5

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

Additional Analyzes:

Although some covariate-by-treatment interactions had small p-values at certain time points and examinations, overall there was no evidence of a covariate-by-treatment interaction. Significant effects due to investigator were observed at Hour 0 (Month 2, Month 3) and at Hour 2 (Week 2, Month 2, Month 3). Significant effects due to patient age were observed at Hour 0 (Week 2, and Month 2) and at Hour 2 (Week 2). A significant effect due to iris color was observed at Hour 2, Month 2. No other covariates were significant at any time point.

Reviewer's Comments: *The analyzes were consistent with respect to subgroups based on age, race, gender or iris color.*

8.1.4.4.3 Safety outcomes

Laboratory Experiences:

Reviewer's Comments: *There were no laboratory evaluations performed.*

Pupil Diameter:(mm)	Combination	Dorzolamide	Timolol
Baseline	4.0	4.0	4.2
Treatment	4.2	4.1	4.0

Reviewer's Comments: *The differences (increases) above will require replication.*

Visual Acuity and Visual Fields:

Reviewer's Comments: *No specific differences between groups were noted. It would have been preferable for visual acuity to be reported as the number of lines increased by 1, 2 and more than 2, and the number of lines decreased by 1, 2 and more than 2.*

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

Treatment Group	Study	AN	Eye	Horiz	Vert	Horiz	Vert
Timolol	5	8507	L	NA	.30	NA	.50
	17	8455	L	.40	.60	.70	.80
			R	.50	.60	.70	.80

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Number (%) of Patients with Clinical Adverse Experiences (>1% in Combination Group)

Adverse Experience	Combination (N=101) n (%)	Dorzolamide (N=49) n (%)	Timolol (N=97) n (%)
Any adverse experience	75 (74)	38 (78)	58 (60)
Body As A Whole/Site Unspecified	6 (6)	1 (2)	3 (3)
Flu-like illness	2 (2)	0	1 (1)
Hyperemia	2 (2)	0	1 (1)
Cardiovascular System	2 (2)	1 (2)	0
Digestive System	9 (9)	1 (2)	5 (5)
Dyspepsia	2 (2)	0	0
Nausea	2 (2)	0	1 (1)
Vomiting	2 (2)	0	0
Metabolic/Nutritional/Immune	3 (3)	0	1 (1)
Musculoskeletal System	3 (3)	1 (2)	2 (2)
Nervous System and Psychiatric	4 (4)	5 (10)	11 (11)
Dizziness	2 (2)	0	0
Headache	3 (3)	4 (8)	9 (9)
Respiratory System	14 (14)	7 (14)	13 (13)
Cough	2 (2)	1 (2)	0
Discomfort, pharyngeal	2 (2)	0	0
Infection, respiratory, upper	5 (5)	3 (6)	7 (7)
Influenza	3 (3)	0	0
Sinus disorder	2 (2)	1 (2)	0
Skin and Skin Appendage	3 (3)	2 (4)	1 (1)
Special Senses[a]	66 (65)	31 (63)	46 (47)
Blurred vision	5 (5)	1 (2)	5 (5)
Burning and/or stinging, eye[b]	31 (31)	14 (29)	13 (13)
Chalazion	2 (2)	0	1 (1)
Discharge, eye	2 (2)	0	2 (2)
Discomfort, visual	2 (2)	0	0
Erosion, corneal	13 (13)	5 (10)	9 (9)
Injection, conjunctival	6 (6)	2 (4)	5 (5)
Itching, eye	3 (3)	0	6 (6)
Opacity, vitreous	2 (2)	1 (2)	0
Pain, eye	3 (3)	2 (4)	0
Perversion, taste[c]	22 (22)	13 (27)	2 (2)
Tearing	4 (4)	1 (2)	1 (1)

a Significantly greater incidence in the combination group (vs timolol), p =0.015; Significantly greater incidence for drug-related events in the combination group (vs timolol), p = 0.002.

b Significantly greater incidence in the combination group (vs timolol), p =0.004; Significantly greater incidence for drug-related events in the combination group (vs timolol), p = 0.004.

c Significantly greater incidence in the combination group (vs timolol), p<0.001; Significantly greater incidence for drug-related events in the combination group (vs timolol), p<0.001.

Emergent or Worsening Ocular Symptoms

Adverse Experience	Combination (N=101) n (%)	Dorzolamide (N=49) n (%)	Timolol (N=97) n (%)
Any ocular symptoms	21 (21)	14 (29)	22 (23)
Blurred vision	4 (4)	2 (4)	4 (4)
Burning eye	10 (10)	7 (14)	7 (7)
Dryness of eye	0 (0)	1 (2)	3 (3)
Eye discomfort	0 (0)	1 (2)	0 (0)
Eye pain	2 (2)	1 (2)	0 (0)
Eyelids puffy	1 (1)	0 (0)	0 (0)
Floaters	0 (0)	1 (2)	0 (0)
Foreign body sensation	0 (0)	0 (0)	2 (2)
Hyperemia, conjunctiva	1 (1)	0 (0)	1 (1)
Irritation, eyelid	0 (0)	0 (0)	1 (1)
Itching, eye	4 (4)	1 (2)	6 (6)
Redness, eye	1 (1)	0 (0)	0 (0)
Stickiness, eye	0 (0)	0 (0)	1 (1)
Stinging eye	3 (3)	4 (8)	1 (1)
Tearing eye	3 (3)	1 (2)	1 (1)
Vision cloudy	0 (0)	0 (0)	1 (1)
Any nonocular symptoms[a]	20 (20)	12 (25)	2 (2)
Taste, bitter[b]	13 (13)	9 (18)	1 (1)
Taste, sour	3 (3)	2 (4)	0 (0)
Taste, sweet	0 (0)	2 (4)	0 (0)
Taste, unusual	5 (5)	0 (0)	1 (1)

[a] Significantly greater incidence in the combination group (vs timolol), $p<0.001$.
[b] Significantly greater incidence in the combination group (vs timolol), $p=0.001$.

Emergent or Worsening Ocular Signs

Adverse Experience	Combination (N=101) n (%)	Dorzolamide (N=49) n (%)	Timolol (N=97) n (%)
Any Conjunctival Sign	13 (13)	2 (4)	12 (12)
Chemosis	1 (1)	0 (0)	0 (0)
Conjunctival follicles	0 (0)	0 (0)	1 (1)
Conjunctivitis, allergic	1 (1)	0 (0)	0 (0)
Conjunctivitis, follicular	0 (0)	0 (0)	1 (1)
Episcleritis	1 (1)	0 (0)	0 (0)
Follicular reaction, conjunctiva	2 (2)	0 (0)	2 (2)
Hyperemia, conjunctiva	10 (10)	2 (4)	8 (8)
Irritation, conjunctiva	0 (0)	1 (2)	0 (0)
Redness, eye	0 (0)	0 (0)	1 (1)
Any Corneal sign	18 (18)	13 (27)	17 (18)
Cornea, dry	1 (1)	0 (0)	0 (0)
Corneal epith. stain	0 (0)	0 (0)	1 (1)
Corneal epith. defect	1 (1)	0 (0)	0 (0)
Dystrophy, cornea	0 (0)	0 (0)	1 (1)
Flush, ciliary	0 (0)	1 (2)	0 (0)
Guttata, cornea	1 (1)	0 (0)	0 (0)
Kruckenberg spindle	0 (0)	0 (0)	1 (1)
Precipitate, keratic	0 (0)	1 (2)	0 (0)
Punct. epith. erosions or spk	16 (16)	10 (20)	14 (14)
Staining, fluorescein	0 (0)	2 (4)	3 (3)
Any Lens sign	5 (5)	1 (2)	1 (1)
Cataract, subcapsular, posterior	1 (1)	0 (0)	0 (0)
Coloration, lens nucleus	0 (0)	1 (2)	0 (0)
Lens, cortical opacity	3 (3)	0 (0)	0 (0)
Nuclear opacity, lens	2 (2)	1 (2)	1 (1)
Pseudoexfoliation, lens capsule	1 (1)	0 (0)	0 (0)
Any Lid sign	11 (11)	1 (2)	5 (5)
Blepharitis	4 (4)	0 (0)	1 (1)
Chalazion	2 (2)	0 (0)	1 (1)
Ecchymosis, eyelid	0 (0)	1 (2)	0 (0)
Edema, eyelid	0 (0)	1 (2)	0 (0)
Edema, nasal	0 (0)	0 (0)	1 (1)
Erythema, eyelid	4 (4)	0 (0)	0 (0)
Exudate/scales, eyelid	2 (2)	0 (0)	2 (2)
Stye	0 (0)	0 (0)	1 (1)

Any Optic Nerve sign	2 (2)	0 (0)	1 (1)
Glaucomatous, cupping	1 (1)	0 (0)	1 (1)
Hemorrhage, optic disc	0 (0)	0 (0)	1 (1)
Optic disc, saucerized	1 (1)	0 (0)	0 (0)
Any Retinal sign	1 (1)	0 (0)	4 (4)
AV nicking	1 (1)	0 (0)	0 (0)
Edema, retinal	0 (0)	0 (0)	1 (1)
Hemorrhage, retinal	0 (0)	0 (0)	2 (2)
Macular degeneration, age related	0 (0)	0 (0)	1 (1)
Any Vitreous sign	3 (3)	0 (0)	0 (0)
Detachment, vitreous	3 (3)	0 (0)	0 (0)
Opacity, vitreous	1 (1)	0 (0)	0 (0)

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

Study #4 Summary

1. The study demonstrates that the combination is usually more effective in lowering IOP at 2 and 12 hours after dosing.

2. The combination demonstrates a combination of adverse events equal to or greater than each component alone.

3. Procedures for pupil measurements appear to have been inconsistently applied. For example, pupil measurements for patients 8435, 8437, 8438, 8439, 8587, 8588, 8590, 8596, 8597, 8598 and 8599 have sometimes been recorded to the nearest tenth of a millimeter instead of a millimeter as described in the protocol and appear to sometimes have been measured as stated in the protocol and sometimes taken from the perimeter.

4. There is a question about the accuracy of the reporting of patients discontinued for adverse events. Patient 8435 was discontinued due to elevated IOP, however the patient also had a disc hemorrhage as an adverse event.

8.1.5 Reviewer's Trial # 5 Applicant's protocol # 43

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

8.1.5.1 Objective/Rationale

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.

8.1.5.2 Design

Parallel, randomized, double-masked, active-controlled, multicenter study (90 days) followed by an open-label extension (9 months).

8.1.5.3 Protocol

	Prestudy Screening Days -21 to -14	Day -7			Days 1*, 15*, 30*, 60*, 90*, 180, 270, 365				Day 90 and Poststudy
		Pre-dose	Post-dose	2 Hours	Pre-dose	Post-dose	2 Hours	8 Hours (only * days)	
General Ocular and Medical History	X								
Physical Examination	X								X
Laboratory Tests	X								X
Symptomatology	X	X	X	X	X	X	X	X	
Anterior Segment Exam	X				X		X	X	
Visual Acuity	X	X			X				
IOP Measurement	X	X		X	X		X	X	
Lens and Ophthalmoscopy	X								X
Visual Field	X								X

8.1.5.3.1 Population

Male or female (postmenopausal or sterilized) patients ranging in age from 21 to 85 years with a diagnosis of open-angle glaucoma or ocular hypertension in both eyes with IOP ≥22 mmHg in at least one eye at hour 0 and hour 2 on Day 1 after receiving 0.5% timolol b.i.d. alone for 2 weeks.

8.1.5.3.2 Endpoints - Same as Study #1

8.1.5.4 Results

8.1.5.4.1 Populations enrolled/analyzed

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

Baseline Demographic Characteristics by Treatment Group

	Combination (N=121) N (%)	Concomitant (N=121) N (%)
Sex[a]		
Male	50 (41)	71 (59)
Female	71 (59)	50 (41)
Race		
White	88 (73)	92 (76)
Black	29 (24)	29 (24)
Hispanic	3 (2)	0 (0)
Chinese	1 (1)	0 (0)
Iris Color		
Dark Brown	30 (25)	24 (20)
Brown	29 (24)	33 (27)
Hazel	17 (14)	19 (16)
Green	3 (2)	5 (4)
Blue	42 (35)	40 (33)
Age (Years)		
Mean [SD]	60.7 [11.6]	61.7 [13.0]
Median	63	65
Range	22-81	25-84

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

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Patient Accounting

	Combination	Concomitant
Entered Masked Phase	121	121
Completed Masked Phase	107	113
Entered Open Label Phase	107	113
Completed Open Label Phase	99	104
Discontinued - Masked Phase		
Clinical Adverse Experience	7	3
Protocol Deviation	1	2
Therapy Ineffective	5	3
Patient Withdrew	1	0
Lost to Follow-up		
Discontinued - Open Label		
Clinical Adverse Experience	6	3
Therapy Ineffective	2	1
Patient Withdrew	0	2
Lost to Follow-up -	0	2
Protocol Deviation	0	1

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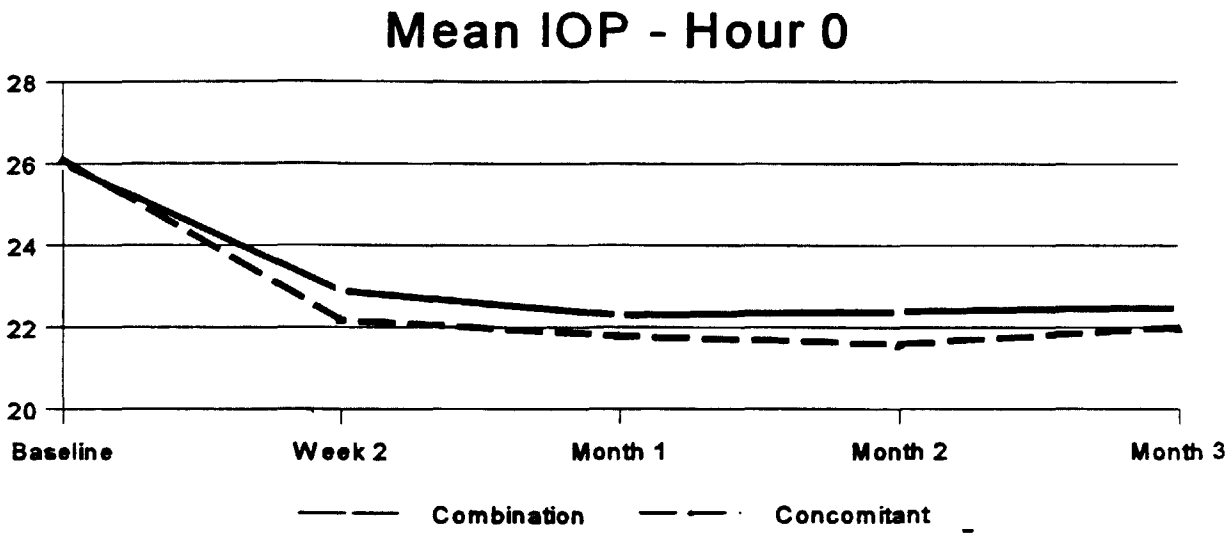
Discontinued for Adverse Experiences- Double Masked Phase

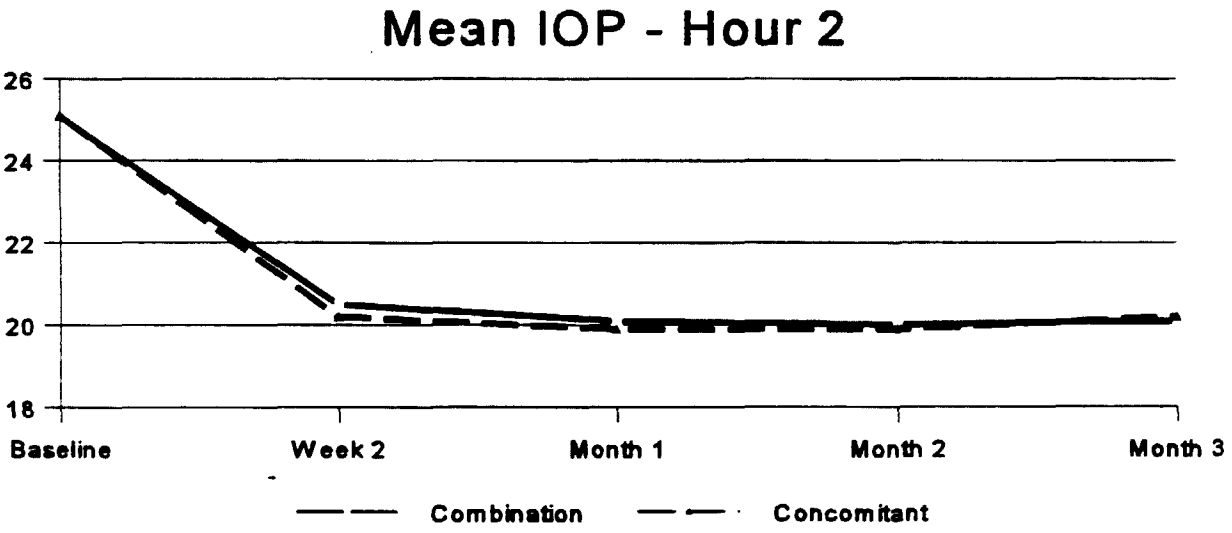
Group	Number	Gender	Age	Day of Onset	Adverse Experience	Duration (Days)	Day Discontinued
Combination	6228	M	56	75	Urolithiasis	32	85
Combination	6133	M	73	35	Pancreas neoplasm, Pneumonia	24	47
Combination	6138	M	74	20	Urolithiasis	4	15
Combination	6025	M	30	60	Eyelid irritation	36	93
Combination	6157	F	43	2	Diarrhea, Dizziness, Insomnia, Nausea, Weight loss, Cough, Dry Mouth, Arthritis, Otorrhagia	15-76	15
Combination	6098	F	56	2	Eyelid edema	58	11
Combination	6163	M	79	32	Ocular Allergy	7	33
Concomitant	6076	M	58	1	Conjunctivitis	15	13
Concomitant	6279	M	65	46	Ocular Allergy	8	49
Concomitant	6262	M	62	97	Visual Field Defect	1	97

Discontinued for Adverse Experiences- Open Label

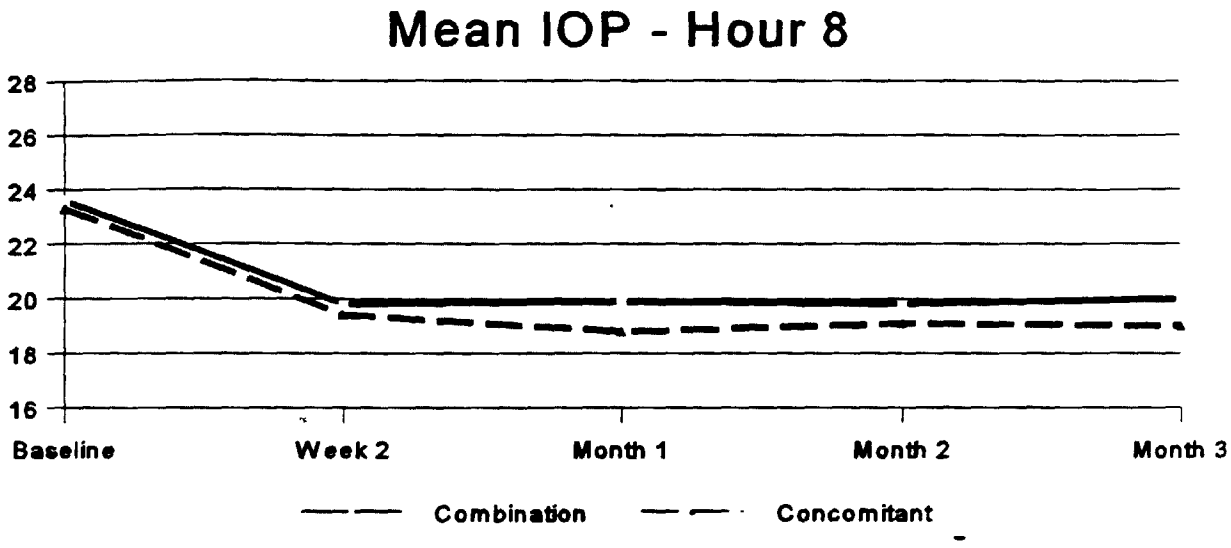
Group	Number	Gender	Age	Day of Onset	Adverse Experience	Duration (Days)	Day Discontinued
Combination	6269	F	60	84	Depression	93	176
Combination	6103	F	66	140	Subarachnoid hemorrhage, Headache	42	139
Combination	6130	F	59	229	Breast Neoplasm	19	272
Combination	6029	F	55	189	Blurred Vision	304	252
Combination	6143	M	73	264	Intestinal and liver neoplasm	23	284
Combination	6057	M	70	273	Visual Field Defect	10	273
Combination	6104	F	62	119	Conjunctivitis	51	169
Concomitant	6054	M	61	185	Eyelid inflamation, Blepharitis	11	190
Concomitant	6061	M	75	173	Arrhythmia	22	173

8.1.5.4.2 Efficacy endpoint outcomes





Reviewer's Comments: *The combination is inferior to the concomitant at hour 0 (12 hours after dosing). This is probably due to the shorter duration of effect of the combination.*



Reviewer's Comments: *The combination is inferior to concomitant administration.*

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

Exam	Treatment	N	Baseline Mean	Baseline SD	Treatment Mean	Treatment SD	Change Mean	Change SD	Percent Change Mean	Percent Change Median
Hour 0										
Wk 2	Combination	115	26.0	3.0	22.9	4.2	-3.1	3.1	-12.0	-12.5
	Concomitant	120	26.1	3.8	22.2	3.6	-3.9	3.0	-14.6	-14.8
Mo 1	Combination	120	26.1	3.0	22.3	4.1	-3.8	3.0	-14.8	-16.0
	Concomitant	121	26.1	3.8	21.8	3.7	-4.2	3.1	-15.9	-16.7
Mo 2	Combination	120	26.1	3.0	22.4	3.8	-3.7	2.7	-14.3	-14.5
	Concomitant	121	26.1	3.8	21.6	3.9	-4.4	3.6	-16.6	-16.7
Mo 3	Combination	120	26.1	3.0	22.5	4.1	-3.6	3.0	-13.8	-15.4
	Concomitant	121	26.1	3.8	22.0	4.4	-4.1	3.7	-15.5	-15.4
Hour 2										
Wk 2	Combination	114	25.1	3.3	20.5	3.9	-4.6	3.2	-18.1	-17.6
	Concomitant	119	25.1	3.7	20.2	3.7	-4.8	3.5	-18.9	-17.4
Mo 1	Combination	119	25.1	3.3	20.1	3.5	-5.0	3.3	-19.6	-19.2
	Concomitant	120	25.0	3.7	19.9	3.7	-5.2	3.1	-20.3	-21.7
Mo 2	Combination	119	25.1	3.3	20.0	3.8	-5.0	3.4	-19.9	-20.0
	Concomitant	120	25.0	3.7	19.9	3.5	-5.2	3.3	-20.2	-21.7
Mo 3	Combination	119	25.1	3.3	20.1	3.8	-5.0	3.5	-19.7	-20.0
	Concomitant	120	25.0	3.7	20.2	4.2	-4.9	3.8	-19.1	-21.7
Hour 8										
Wk 2	Combination	111	23.6	3.9	19.8	3.8	-3.8	3.3	-15.5	-15.0
	Concomitant	115	23.3	4.2	19.4	3.6	-3.9	3.9	-15.6	-17.6
Mo 1	Combination	116	23.7	3.9	19.9	3.6	-3.8	3.3	-15.2	-15.1
	Concomitant	118	23.3	4.2	18.8	3.6	-4.5	3.4	-18.5	-19.0
Mo 2	Combination	116	23.7	3.9	19.8	3.7	-3.9	3.4	-15.6	-17.0
	Concomitant	118	23.3	4.2	19.1	3.9	-4.3	3.9	-17.3	-19.1
Mo 3	Combination	116	23.7	3.9	20.0	3.9	-3.7	3.4	-14.9	-16.3
	Concomitant	118	23.3	4.2	19.0	3.5	-4.3	3.8	-17.4	-18.9

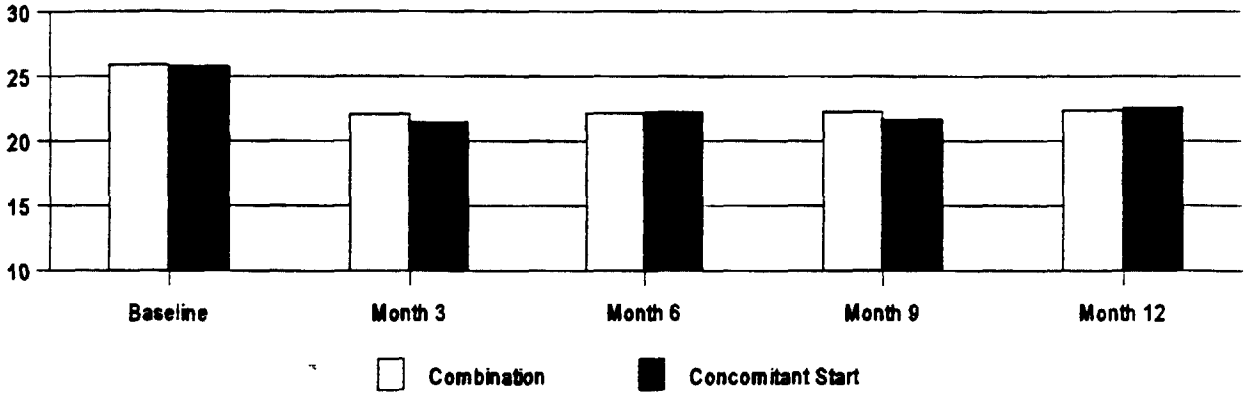
All-Patients-Treated Analysis (Last Observation Carried Forward) – Worse Eye.

Exam		Combination	Concomitant	Difference Between Treatments	95% Conf. Int. for Difference
Hour 0					
	Wk 2	115	120	-0.78 mm Hg	(-1.55,-0.02)
	Mo 1	120	121	-0.42 mm Hg	(-1.15, 0.32)
	Mo 2	120	121	-0.72 mm Hg	(-1.50, 0.07)
	Mo 3	120	121	-0.52 mm Hg	(-1.34, 0.31)
Hour 2					
	Wk 2	114	119	-0.23 mm Hg	(-1.08, 0.62)
	Mo 1	119	120	-0.11 mm Hg	(-0.92, 0.69)
	Mo 2	119	120	-0.14 mm Hg	(-0.98, 0.71)
	Mo 3	119	120	0.17 mm Hg	(-0.75, 1.10)
Hour 8					
	Wk 2	111	115	-0.15 mm Hg	(-1.08, 0.79)
	Mo 1	116	118	-0.74 mm Hg	(-1.58, 0.10)
	Mo 2	116	118	-0.44 mm Hg	(-1.34, 0.46)
	Mo 3	116	118	-0.69 mm Hg	(-1.55, 0.18)

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.

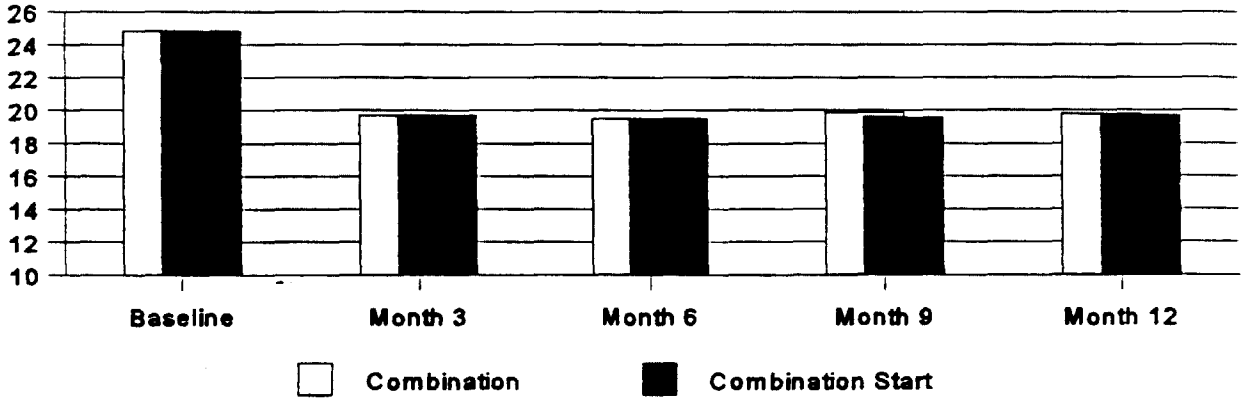
Reviewer's Comments: *The 95% confidence interval is not within 1 for the majority of time points and is not always within 1.5. The combination is therefore not considered equivalent to concomitant therapy and was generally observed to be inferior.*

Open Extension - Mean IOP, Hour 0



Combination	25.9	22.1	22.2	22.3	22.4
Concomitant Start	25.8	21.5	22.3	21.7	22.6

Open Extension -Mean IOP, Hour 2



Combination	24.8	19.7	19.5	19.9	19.8
Combination Start	24.8	19.7	19.5	19.8	19.7

Reviewer's Comments: *IOP is consistent throughout the 12 month period.*

8.1.5.4.3 Safety outcomes

Laboratory Experiences:

Reviewer's Comments: *There were no consistent trends in laboratory adverse experiences. There were not enough patients treated to rule out the possibility of a rare incidence of aplastic anemia.*

Pupil Diameter:(mm)	Combination	Concomitant
Baseline	4.4	4.3
Treatment	4.3	4.2

Reviewer's Comments: *The differences (decreases) noted above will require replication.*

Visual Acuity and Visual Fields:

Reviewer's Comments: *No specific differences between groups were noted. It would have been preferable for visual acuity to be reported as the number of lines increased by 1, 2 and more than 2, and the number of lines decreased by 1, 2 and more than 2.*

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

Treatment Group	Study	AN	Eye	Horizontal	Vertical	Horizontal	Vertical
Combination	19	6191	R	.60	.60	.80	.80
(n=117)	19	6197	R	.40	.40	.60	.60
	19	6200	L	.50	.50	.80	.80
	19	6200	R	.30	.30	.70	.70
Concomitant	None						
(n=121)							
Open label Combination							
(N=212)	13	6261	L	.40	.40	.60	.70
	7	6126	L	.50	NA	.70	NA
	17	6171	R	.50	NA	.70	NA

Reviewer's comments: *An explanation is needed for the apparent imbalance in enlarged cup/disc ratio.*

Number (%) of Patients with Clinical Adverse Experiences (>1% in Any Treatment Group)

Adverse Experience	Combination (N=121) N %	Combination Concomitant (N=121) N %	Open Label (N=220) N %
Patients with any adverse experience	41 (34)	32 (26)	101 (46)
Body as a whole/site unspecified	3 (2)	2 (2)	17 (8)
Edema/Swelling			3 (1)
Abdominal Pain			4 (2)
Chest Pain			3 (1)
Cardiovascular System	2 (2)	2 (2)	16 (7)
Hypertension	0 (0)	2 (2)	3 (1)
Digestive System	7 (6)	1 (1)	15 (7)
Dry Mouth	3 (2)	1 (1)	
Nausea	2 (2)	0 (0)	
Dyspepsia			3 (1)
Vomiting			3 (1)
Endocrine System	1 (1)	1 (1)	6 (3)
Diabetes			3 (1)
Diabetes, loss of control			3 (1)
Hemic & Lymphatic System			3 (1)
Metabolic/Nutritional/Immune	2 (2)	0 (0)	3 (1)
Musculoskeletal System	2 (2)	0 (0)	15 (7)
Tendinitis			3 (1)
Nervous System & Psychiatric	8 (7)	4 (3)	15 (7)
Depression	2 (2)	1 (1)	3 (1)
Dizziness	2 (2)	0 (0)	
Headache	4 (3)	1 (1)	4 (2)
Anxiety			4 (2)
Respiratory System	10 (8)	3 (2)	30 (14)
Cough	3 (2)	0 (0)	3 (1)
Infection, Respiratory, Upper	2 (2)	1 (1)	13 (6)
Bronchitis			4 (2)
Influenza			5 (2)
Sinus Disorder			3 (1)
Sinusitis			3 (1)
Skin & Skin Appendage	2 (2)	1 (1)	10 (5)
Skin malignant neoplasm			3 (1)
Special Senses	23 (19)	20 (17)	43 (20)
Blurred Vision	1 (1)	3 (2)	

Burning and/or Stinging, Eye	1 (1)	2 (2)	
Conjunctivitis	1 (1)	2 (2)	4 (2)
Defect, Visual Field	2 (2)	1 (1)	5 (2)
Discharge, Eye	4 (3)	2 (2)	
Foreign Body Sensation	2 (2)	0 (0)	
Irritation, Eye	1 (1)	4 (3)	
Itching, Eye	0 (0)	2 (2)	
Opacity, Lens	2 (2)	1 (1)	11 (5)
Retinopathy, Diabetic	2 (2)	0 (0)	
Urogenital System	2 (2)	2 (2)	8 (4)
Urolithiasis	2 (2)	0 (0)	

Note: 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.

Emergent or Worsening Ocular Symptoms

Experience	Combination (N=121) N %	Concomitant (N=121) N %	Combination Open Label (N=220) N %
Patients with any ocular symptoms	43 (36)	46 (38)	56 (26)
Aching, eye	2 (2)	0 (0)	
Blurred vision	14 (12)	15 (12)	16 (7)
Burning eye	17 (14)	12 (10)	20 (9)
Dryness of eye	4 (3)	4 (3)	7 (3)
Eye pain	2 (2)	2 (2)	5 (2)
Eyelid pain or discomfort[a]	7 (6)	1 (1)	5 (2)
Foreign body sensation	3 (3)	3 (2)	3 (1)
Heaviness, eye	3 (3)	0 (0)	
Itching, eye	9 (8)	8 (7)	11 (5)
Stinging eye	14 (12)	15 (12)	9 (4)
Tearing eye	7 (6)	4 (3)	8 (4)
Vision cloudy	4 (3)	2 (2)	5 (2)
Bitter taste	38 (32)	42 (35)	37 (17)
Sour taste	5 (4)	6 (5)	2 (1)
Sweet taste	0 (0)	2 (2)	3 (1)

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

Emergent or Worsening Ocular Signs

Experience	Combination (N=121) N %	Concomitant (N=121) N %	Combination Open Label (N=220) N %
Anterior Chamber sign	4 (3)	7 (6)	2 (1)
Anterior chamber cells	2 (2)	7 (6)	
Conjunctival sign	16 (13)	23 (19)	26 (12)
Conjunctival discharge	3 (3)	0 (0)	
Conjunctival follicles	1 (1)	4 (3)	9 (4)
Follicular conjunctivitis	0 (0)	2 (2)	
Conjunctival hyperemia	14 (12)	17 (14)	11 (5)
Corneal sign	22 (18)	21 (17)	30 (14)
Corneal epithelial defect	3 (3)	0 (0)	
Punct. epith. erosions or SPK	16 (13)	16 (13)	19 (9)
Staining, fluorescein	5 (4)	6 (5)	10 (5)
Lens sign	3 (3)	2 (2)	21 (10)
Lens, cortical opacity	2 (2)	0 (0)	4 (2)
Lens, nuclear opacity			10 (5)
Lid sign	13 (11)	10 (8)	17 (8)
Blepharitis	3 (3)	3 (3)	6 (3)
Debris, eye	6 (5)	6 (5)	6 (3)
Scurf	2 (2)	2 (2)	
Optic Nerve sign	1 (1)	1 (1)	2 (1)
Retina sign	3 (3)	0 (0)	6 (3)
Retinopathy, diabetic	2 (2)	0 (0)	
Retinal hemorrhage			3 (1)
Vitreous sign	2 (2)	0 (0)	2 (1)

Study #5 Summary

1. The study demonstrates that the combination is less effective than concomitant administration in lowering IOP.

2. The combination demonstrates a combination of adverse events equal to or greater than concomitant use of timolol and dorzolamide.

3. There is an unexplained increase in larger cup/disc ratios in the combination group.

4. The IOP lowering effect is consistent throughout the 1 year study period.

8.1.6 Reviewer's Trial # 6 Applicant's protocol # 58

A 3-Month, Parallel, Randomized, Double-Masked, Study Comparing the IOP-lowering effect of 0.5% Timolol/2.0% MK-0507 Combination B.I.D. to the Concomitant Administration of 0.5% Timolol Ophthalmic Solution B.I.D. and 2% MK-0507 B.I.D. #058

8.1.6.1 Objective/Rationale

1. To determine if the IOP-lowering effect at trough (Hour 0) of the 0.5% timolol/2.0% MK-0507 combination b.i.d. was equivalent to that of the concomitant administration of 0.5% timolol b.i.d. plus 2.0% MK-0507 b.i.d. for up to 3 months.

2. To determine if the IOP-lowering effect at peak (Hour 2) of the 0.5% timolol/2.0% MK-0507 combination b.i.d. was equivalent to that of the concomitant administration of 0.5% timolol b.i.d. plus 2.0% MK-0507 b.i.d. for up to 3 months.

3. To compare the safety profile of the 0.5% timolol/2.0% MK-0507 combination to that of its components administered concomitantly b.i.d. over a 3-month period.

8.1.6.2 Design

Parallel, randomized, double-masked, active-controlled, multicenter study (90 days).

8.1.6.3 Protocol

	Prestudy Screening Days -21 to -1	Timolol Run-in Day -14 to Day -1 Day -7			Days 1, 15, 30, 60, 90			Day 90 and Poststudy
	-	Pre-dose	Post-dose	2 Hours	Pre-dose	Post-dose	2 Hours	2 Hours
General Ocular and Medical History	X							
Visual Acuity	X				X			X
External and anterior segment exam	X				X		X	
IOP	X	X		X	X		X	
Lens and ophthalmoscopy	X							X
Visual Field	X							X

8.1.6.3.1 Population - Same as Study #5

8.1.6.3.2 Endpoints - Same as Study #1

8.1.6.4 Results

8.1.6.4.1 Populations enrolled/analyzed

			Combination	Concomitant
01	Best, Stephen	Auckland, New Zealand	3	3
02	Brooks, Anne	East Melbourne, Australia	8	8
03	Lusky, Moshe	Petah, Tikva, Israel	12	12
04	Correa, Antonio	Medellin, Columbia	12	12
05	Arenas, Eduardo	Bogata, Columbia	9	9
06	Kara Jose, Newton	Sao Paulo, Brazil	10	8
07	Gil-Carrasco, Felix	Coyoacan, Mexico	12	12
08	Torres, Joaquim	Oporto, Portugal	10	9
09	Jiminez-Antillon	San Jose, Costa Rica	6	6
10	Portocarrero, Carlos	Guatemala, Guatemala	6	6
11	Renard, Jean-Paul	Paris, France	8	7
12	Vargas, Enrique M.	Lima, Peru	17	18
13	Eggers, Andres	Santiago, Chile	7	8
14	Theodosiadis,George	Athens, Greece	10	10
15	Lerner, Simon Fabian	Buenos Aires, Argentina	12	12
16	Babayan Mena,Juan	Mexico City, Mexico	9	8
Total			151	148

Baseline Demographic Characteristics by Treatment Group

	Combination (N=151) N (%)	Concomitant (N=148) N (%)
Gender		
Male	65 (43)	48 (32)
Female	86 (57)	100 (68)
Race		
White	79 (52)	76 (51)
Black	7 (5)	8 (5)
Asian	0 (0)	1 (1)
Hispanic	29 (19)	28 (19)
Indian	1 (1)	0 (0)
Mestizo	33 (22)	35 (24)
Mulatto	2 (1)	0 (0)
Iris Color		
Dark Brown	31 (21)	22 (15)
Brown	82 (54)	87 (59)
Hazel	22 (15)	19 (13)
Green	4 (3)	8 (5)
Blue	12 (8)	12 (8)
Age (Years)		
Mean [S.D.]	62.6 [11.4]	63.6 [10.6]
Median	65.0	64.0
Range	23 to 83	28 to 84

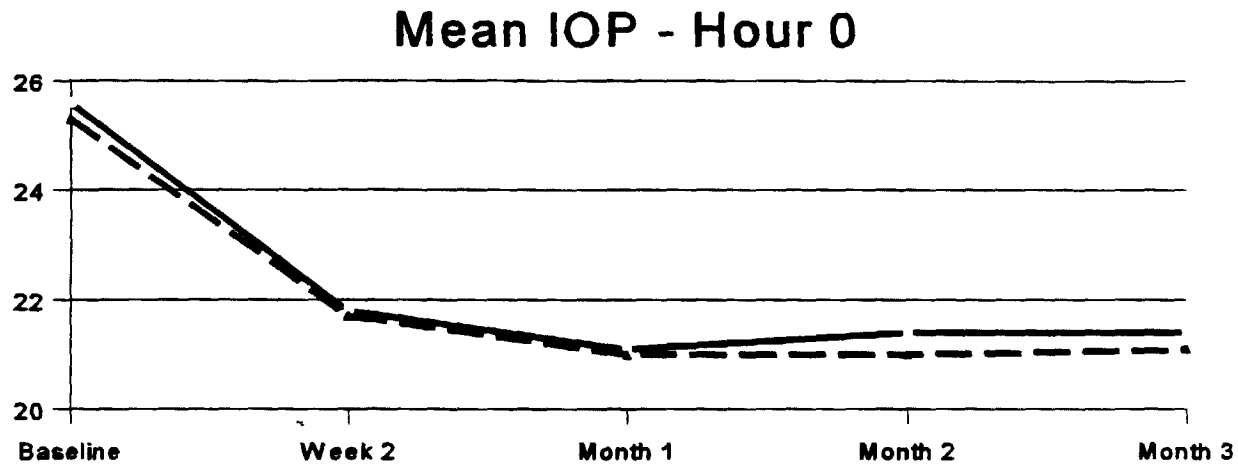
Patient Accounting

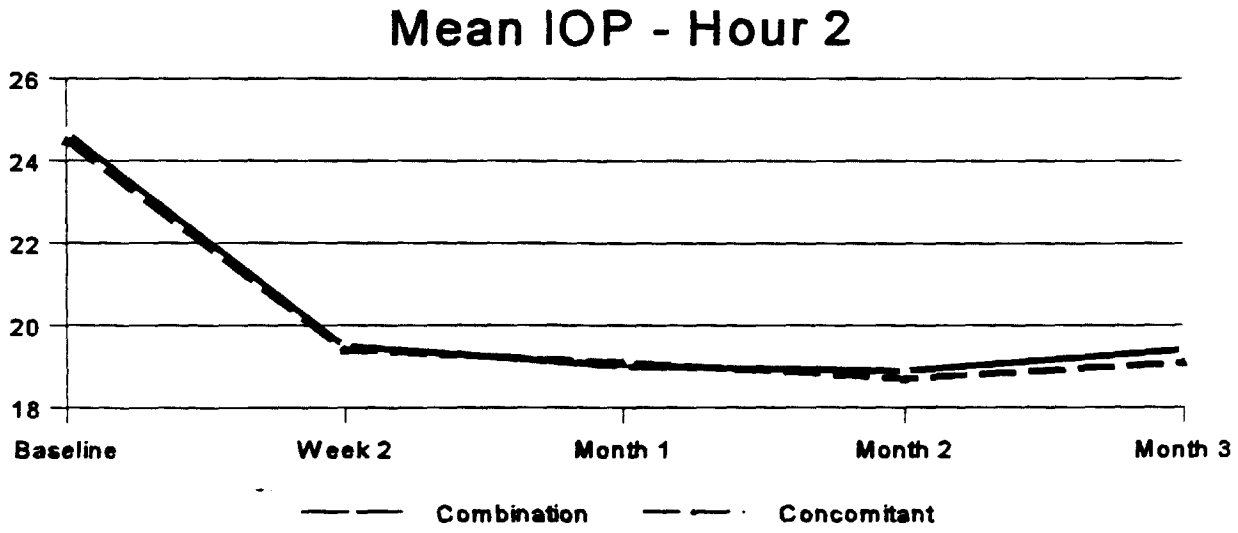
	Combination	Concomitant
Entered Masked Phase	151	148
Completed Masked Phase	145	145
Discontinued		
Clinical Adverse Experience	2	1
Protocol Deviation	1	0
Therapy Ineffective	3	1
Lost to Follow-up	0	1

Discontinued for Adverse Experiences

Group	Number	Gender	Age	Day of Onset	Adverse Experience	Duration (Days)	Day Discontinued
Combination	9502	F	81	15	Ocular discharge, injection	2	15
Combination	9476	M	71	15	Corneal staining, photophobia, itching, tearing, inflammation	15	29
Concomitant	9717	F	62	9	Burning, corneal staining, eyelid irritation	70	57

8.1.6.4.2 Efficacy endpoint outcomes





Reviewer's Comments: *The combination bid is equivalent to the concomitant use bid, however, the dorzolamide is indicated as a tid medication.*

IOP Summary Statistics (mm Hg)

Exam	Treatment	N	Baseline Mean	Baseline SD	Treatment Mean	Treatment SD	Change Mean	Change SD	Percent Change Mean	Percent Change Median
Hour 0										
Week 2	Combination	150	25.6	3.1	21.8	4.0	-3.8	3.2	-14.6	-14.8
	Concomitant	147	25.3	3.2	21.7	3.8	-3.6	3.3	-14.0	-13.0
Month 1	Combination	151	25.6	3.1	21.1	3.9	-4.5	3.3	-17.2	-16.7
	Concomitant	148	25.3	3.2	21.0	3.8	-4.3	3.3	-16.9	-16.7
Month 2	Combination	151	25.6	3.1	21.4	4.1	-4.1	3.3	-16.1	-16.7
	Concomitant	148	25.3	3.2	21.0	4.0	-4.3	3.3	-17.0	-16.3
Month 3	Combination	151	25.6	3.1	21.4	4.1	-4.2	3.3	-16.3	-16.7
	Concomitant	148	25.3	3.2	21.1	3.7	-4.2	3.1	-16.3	-15.4
Hour 2										
Week 2	Combination	151	24.7	3.2	19.5	3.6	-5.2	2.9	-20.9	-22.2
	Concomitant	148	24.5	3.2	19.4	3.5	-5.1	3.3	-20.6	-19.6
Month 1	Combination	151	24.7	3.2	19.0	3.9	-5.7	3.2	-23.1	-25.0
	Concomitant	148	24.5	3.2	19.1	3.5	-5.4	3.5	-21.7	-22.4
Month 2	Combination	151	24.7	3.2	18.9	3.6	-5.8	3.0	-23.3	-24.0
	Concomitant	148	24.5	3.2	18.7	3.6	-5.8	3.4	-23.2	-22.4
Month 3	Combination	151	24.7	3.2	19.4	3.7	-5.4	3.1	-21.6	-22.2
	Concomitant	148	24.5	3.2	19.1	3.5	-5.4	3.3	-21.8	-22.6

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

Exam		Combination	Concomitant	Diff Between Treatments	95% Conf. Int. for Diff.
Hour 0					
	Week 2	150	147	0.15	(-0.43, 0.74)
	Month 1	151	148	0.12	(-0.47, 0.71)
	Month 2	151	148	-0.17	(-0.75, 0.41)
	Month 3	151	148	-0.02	(-0.59, 0.56)
Hour 2					
	Week 2	151	148	0.08	(-0.47, 0.63)
	Month 1	151	148	0.30	(-0.31, 0.90)
	Month 2	151	148	0.01	(-0.56, 0.57)
	Month 3	151	148	-0.08	(-0.65, 0.48)

All-Patients-Treated Analysis (Last-Observation-Carried-Forward) - 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 enrolled at each clinic.

Reviewer's Comments: *The 95% confidence interval is within 1 for the majority of time points and is always within 1.5. The combination bid is therefore considered equivalent to concomitant therapy bid.*

8.1.5.4.3 Safety outcomes

Laboratory Experiences:

Reviewer's Comments: *There were no consistent trends in laboratory adverse experiences. There were not enough patients treated to rule out the possibility of a rare incidence of aplastic anemia.*

Pupil Diameter:(mm)	Combination	Concomitant
Baseline	4.1	4.2
Treatment	4.2	4.3

Reviewer's Comments: *The differences (increases) noted above will require replication.*

Visual Acuity and Visual Fields:

Reviewer's Comments: *No specific differences between groups were noted. It would have been preferable for visual acuity to be reported as the number of lines increased by 1, 2 and more than 2, and the number of lines decreased by 1, 2 and more than 2.*

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

Treatment Group	Study	AN	Eye	Horizontal	Vertical	Horizontal	Vertical
Combination (N=151)	1	9528	L	0.30	0.30	0.60	0.60
	3	9594	L	NA	0.60	NA	0.80
	6	9461	R	0.20	0.20	0.40	0.60
	12	9739	R	0.60	NA	0.80	NA
	14	9695	R	0.20	0.20	0.40	0.40
	14	9701	R	NA	0.60	NA	0.80
Concomitant (N=147)	2	9501	R	0.30	NA	0.50	NA
	7	9608	L	NA	0.60	NA	0.80

NA = Not applicable (change was <0.2)

Reviewer's comments: *An explanation is needed for the apparent imbalance in enlarged cup/disc ratio.*

Number (%) of Patients with Clinical Adverse Experiences (>1% in Any Treatment Group)

Adverse Experience	Combination (N=151) N %	Concomitant (N=148) N %
Number of patients with any adverse experience	72 (48)	76 (51)
Body As a Whole/Site Unspecified	4 (3)	4 (3)
Pain, abdominal	1 (1)	2 (1)
Cardiovascular System	4 (3)	4 (3)
Blood pressure increased	2 (1)	1 (1)
Hypertension	2 (1)	0
Hypotension	0	2 (1)
Digestive System	3 (2)	6 (4)
Diarrhea	0	2 (1)
Pain, dental	0	2 (1)
Endocrine System	0	2 (1)
Metabolic/Nutritional/Immune	1 (1)	0
Musculoskeletal System	1 (1)	3 (2)
Nervous System and Psychiatric	4 (3)	9 (6)
Headache	2 (1)	7 (5)
Paresthesia	0	2 (1)
Respiratory System	16 (11)	17 (11)
Bronchitis	3 (2)	3 (2)
Cough	2 (1)	3 (2)
Infection, respiratory	2 (1)	2 (1)
Infection, respiratory, upper	4 (3)	3 (2)
Influenza	6 (4)	4 (3)
Pharyngitis	1 (1)	3 (2)
Sinusitis	2 (1)	0
Skin and Skin Appendage	4 (3)	4 (3)
Pruritus	0	2 (1)
Special Senses	54 (36)	54 (36)
Blepharitis	2 (1)	1 (1)
Blurred vision	2 (1)	6 (4)
Burning and/or stinging, eye	18 (12)	12 (8)
Chalazion	2 (1)	2 (1)
Defect, visual field	4 (3)	4 (3)
Discharge, eye	2 (1)	1 (1)
Edema, conjunctival	4 (3)	4 (3)
Edema, eyelid	2 (1)	0

Erosion, corneal	1 (1)	2 (1)
Foreign body sensation	1 (1)	3 (2)
Injection, conjunctival	4 (3)	4 (3)
Irritation, eyelid	2 (1)	1 (1)
Itching, eye	4 (3)	2 (1)
Opacity, lens	0	2 (1)
Pain, eye	2 (1)	3 (2)
Perversion, taste	16 (11)	18 (12)
Staining, corneal	6 (4)	9 (6)
Tearing	2 (1)	1 (1)
Visual acuity decreased	4 (3)	3 (2)
Visual disturbance	2 (1)	1 (1)
Urogenital System	1 (1)	3 (2)
Infection, urinary tract	0	3 (2)

Note: 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.