CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-816

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-816
Original

NDA # 20-816		Submission:	1/26/97
		Receive date:	1/28/97
M.O. Review # 1		Review started:	4/24/97
		Review completed:	8/05/97

Drug name:	Brinzolamide Ophthalmic Suspension, 1%
Generic name:	Brinzolamide Ophthalmic Suspension
Proposed trade name:	AZOPT
Chemical name:	(R)-(+)-4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thienol[3,2-e]thiazine-6-sulfonamide-1,1-dioxide
Sponsor:	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, TX 76134-2099
Pharmacologic Category:	Carbonic anhydrase inhibitor
Proposed Indication(s):	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Dosage Form and Route of Administration:	Topical, ophthalmic suspension
NDA Drug Classification:	1S
Related Drugs:	TRUSOPT
Related Applications:	NDA 20-408 TRUSOPT, Merck & Co., Inc.
Related Reviews:	Statistical Review dated: May 28, 1997 Biopharm dated: June 4, 1997

2 Table of Contents

3 Material Reviewed
NDA Volumes #1; # 54-75

4 Chemistry/Manufacturing Controls
See Chemist's Review

5 Animal Pharmacology/Toxicology
See Pharmacology and Toxicology Reviews

6.1 Relevant human experience
Oral carbonic anhydrase inhibitors have been used since the 1950's to lower intraocular pressure by reducing aqueous humor formation. One of the major problems with this class of drugs is the significant incidence of adverse side effects, occurring in 30% to 60% of patients treated. The most common of these adverse effects are fatigue, malaise, depression, GI disturbances, taste perversion, paresthesia and diminished sexual functioning. Additionally, there is an increased incidence of renal calculi associated with chronic use of oral CAI's. In rare instances, accounting for at least 26 deaths, various types of blood dyscrasias have been induced by oral CAI's.

Given the significant systemic side effects of oral CAI's, there have been numerous attempts to develop a topical formulation of a CAI. In 1995, the first topical CAI was approved by the FDA (Trusopt (NDA 20-408) Merck & Co., Inc.).

6.2 Important information from related INDs and NDAs
See statement above re: NDA 20-408, TRUSOPT

6.3 Foreign Experience
Brinzolamide ophthalmic suspension 1% has not been registered or marketed in any country outside the United States. It has not been withdrawn from any market for safety or efficacy reasons. Marketing applications are not pending approval in any other country at this time.

6.4 Human Pharmacology
Brinzolamide is an inhibitor of carbonic anhydrase II (CA-II), found primarily in red blood cells, but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

After topical ocular administration, (3% t.i.d. for 2 weeks), the concentration in plasma is below the assay quantitation limit In blood, brinzolamide distributes almost entirely into RBC's due to its high affinity for CA-II. This contributes to the long whole

blood half-life of 111 days. Plasma protein binding of brinzolamide in humans is approximately 60%. N-Desmethyl-brinzolamide is the only metabolite detected in human blood following topical and oral administration. Preliminary data indicate the parent drug is the predominant component found in human urine.

Following oral administration of 1 mg capsules twice per day, brinzolamide accumulates after 2-4 weeks in concentrations in the RBC's which saturate CA-II (approximately 20uM). The N-desethyl metabolite also accumulates in RBC's. This compound appears to reach steady-state levels generally after 20-28 weeks of dosing. In the oral study, CA-II was inhibited by about 95-96% and total CA by approximately 70% at steady-state.

In the ongoing, long-term, topical study with b.i.d. and t.i.d dosed 1% brinzolamide, the systemic drug absorption is lower than with oral-dosed 1 mg b.i.d. Accumulation to concentrations of brinzolamide sufficient to saturate RBC CA-II appears to be requiring 6-9 months. Metabolite levels are lower at the 6-9 month point than those observed in the oral study. Total CA inhibition appears to be leveling at approximately 40-70% (oral study approximately 70%).

6.6 Proposed Directions for Use

The recommended starting dose is one drop of AZOPT Ophthalmic Suspension in the affected eye(s) two times daily. If the clinical response is not adequate after 4 weeks, the dosage may be increased to three times daily. AZOPT may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

7 Description of Clinical Data Sources

Principal Studies

Protocol Type	Study Design	Treatment Duration	Patient Population	Dosing Regimen	No. of Sites	No. Patients (Intent to Treat)	Status
Phase I							
Oral PK (C-95-76)	Double-masked, randomized, placebo-controlled	32 weeks + 12 week washout	Normal volunteers	• 1 mg ALØ4862 PO BID • Placebo PO BID	1	24 Total 20 ALØ4862 4 Placebo	Completed Washout ongoing
Oral PK (C-96-59)	Double-masked, randomized, placebo-controlled	40 weeks + 12 week washout	Renally impaired volunteers	• 1 mg ALØ4862 PO BID • Placebo PO BID	5	20 Expected 16 ALØ4862 4 Placebo	Ongoing
Phase II							
Dose Response (C-92-25)	Double-masked, randomized, placebo-controlled	15 days	Primary open-angle glaucoma or ocular hypertension	• ALØ4862 (0.3,1,2,3%): 1 drop BID • Placebo: 1 drop BID	20	157 Total 126 ALØ4862 31 Placebo	Completed
BID/TID Dosing (C-94-49)	Triple-masked, randomized, active-controlled	28 days	Primary open-angle glaucoma or ocular hypertension	• 1% ALØ4862: 1-2 drops BID • 1% ALØ4862: 1-2 drops TID	6	105 Total 51 BID 54 TID	Completed

Phase III							
Pivotal No. 1 Primary Therapy (C-95-46)	Triple-masked, randomized, placebo-controlled	3 months	Primary open-angle glaucoma or ocular hypertension	• 1% ALØ4862: 1 drop BID • 1% ALØ4862: 1 drop TID • 2% TRUSOPT: 1 drop TID • Placebo: 1 drop TID	29	463 Total 134 ALØ4862 133 ALØ4862 131 TRUSOPT 65 Placebo	Completed
Pivotal No. 2 Primary Therapy (C-95-48)	Triple-masked, randomized, active- controlled	3 months	Primary open-angle glaucoma or ocular hypertension	• 1% ALØ4862: 1 drop BID • 1% ALØ4862: 1 drop TID • 2% TRUSOPT: 1 drop TID • 0.5% TIMOPTIC: 1 drop BID	46 21 (US) 25 (EU)	572 Total 165 ALØ4862 169 ALØ4862 165 TRUSOPT 73 TIMOPTIC	Completed
Pivotal No. 3 Adjunctive Therapy (C-95-38)	Triple-masked, randomized, placebo-controlled	3 months	Primary open-angle glaucoma or ocular hypertension	• 1% ALØ4862: 1 drop TID • Placebo: 1 drop TID (dosing adjunctive to TIMOPTIC 0.5%)	23	132 Total 65 ALØ4862 67 Placebo	Completed
Comfort No. 1 (C-96-29)	Triple-masked, randomized, active-controlled	1 week	Primary open-angle glaucoma or ocular hypertension	• 1% ALØ4862: 1 drop TID • 2% TRUSOPT: 1 drop TID	3	109 Total 55 ALØ4862 54 TRUSOPT	Completed
Comfort No. 2 (C-96-40)	Triple-masked, randomized, active-controlled	1 week	Primary open-angle glaucoma or ocular hypertension	• 1% ALØ4862: 1 drop TID • 2% TRUSOPT: 1 drop TID	3	104 Total 52 ALØ4862 52 TRUSOPT	Completed
Long-Term Therapy (C-95-47)	Triple-masked, randomized, active-controlled	18 months	Primary open-angle glaucoma or ocular hypertension	• 1% ALØ4862: 1 drop BID • 1% ALØ4862: 1 drop TID • 0.5% TIMOPTIC: 1 drop BID	16	250 Expected 100 ALØ4862 100 ALØ4862 50 TIMOPTIC	Ongoing

Abbreviations and drug names used include the following: BID (twice-daily); TID (three-times daily); QID (four-times daily); PO (by mouth); NLO (nasolacrimal occlusion); US (United States); EU (Europe); ALØ4862 (Brinzolamide); BETOPTIC S (betaxolol suspension 0.25%); TIMOPTIC 0.5% (timolol 0.5%); TIMOPTOL 0.5% (timolol 0.5%) and TRUSOPT 2.0% (Dorzolamide 2.0%).

8 Clinical Studies

8.1 Indication Reduction of Intraocular Pressure

8.1.1 Reviewer's Trial # 1
Sponsor's Protocol # C-92-25

15-Day Dose-Response Study of 4 Concentrations of AL04862 (Brinzolamide Ophthalmic Suspension, 1%)

8.1.1.1 Objective/Rationale

To evaluate the dose-response and the duration of ocular hypotensive effect produced by AL04862, 0.3%, 1.0%, 2.0% and 3.0% relative to its vehicle

8.1.1.2 Design

Parallel, randomized, double-masked, placebo-controlled, multicenter, 15-day, dose-response study

8.1.1.3 Protocol

Study Plan

Activity	Screening Exam	Eligibility Exam		Baseline Exam					Day 1 Exam					Day 2 Exam	Day 8 Exam					Day 15 Exam				
		8 a.m.	4 p.m.	8 a.m.	+2	+4	+8	+12 Hrs	8 a.m.	+2	+4	+8	+12 Hrs	8 a.m.	8 a.m.	+2	+4	+8	+12 Hrs	8 a.m.	+2	+4	+8	+12 Hrs
Screen Patients	X																							
Withdraw Rx	X																							
Document Withdrawal of Nonstudy Meds.		X		X																				
Informed Consent	X																							
Biomicroscopy		X		X					X					X	X					X				
Visual Acuity		X		X					X					X	X					X				
IOP		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmoscopy	X																							
Perimetry		X																						
Gonioscopy		X																						
BP/Pulse		X		X					X					X	X					X				
Demographics		X																						
Medical History		X																						
Instill Medications									X					X	X					X				
Instruct Patient*		X							X					X	X					X				
Collect Medications																							X	
Complete Exit Form																								X
Dismiss Patient																								X

8.1.1.3.1 Population

Adult patients of any race or gender, between the ages of 21-70 with a diagnosis of primary open-angle glaucoma or ocular hypertension with IOP between 23-36 mmHg, inclusive, following washout of ocular hypotensive medications

8.1.1.3.2 Endpoints

Efficacy: IOP change off-therapy from baseline

Safety: Adverse events, ocular signs and symptoms, visual acuity, heart rate and blood pressure

8.1.1.3.3 Statistical Considerations

Data Sets

The dose response of AL04862 was evaluated with two separate data sets: 1) the intent-to-treat data set and 2) the efficacy data set. All patients who received study medication were included in the intent-to-treat data set. Only patients who had at least one eye meet the IOP criteria at the eligibility exam were included in the efficacy data set. Patients with both eyes meeting IOP criteria were also efficacy evaluable; however, IOP for these patients was defined as the average IOP of both eyes.

Primary Efficacy Endpoint

Percent change from baseline in IOP observed at 8:00 a.m., 10:00 a.m., 12:00 noon, 4:00 p.m., and 8:00 p.m. was used as the primary efficacy endpoint. The average of the IOP readings taken at 8:00 a.m. on the Eligibility Day, Baseline Day, and Day 1 was used as baseline for the 8:00 a.m. IOP. The average IOP readings taken at 4:00 p.m. on the Eligibility Day and Baseline Day was used as baseline for the 4:00 p.m. IOP. For the remaining time points (10:00 a.m., 12:00 noon, and 8:00 p.m.) the IOP reading on the Baseline Day was used as baseline.

Comparability of IOP at Baseline

The comparability of IOP data at baseline was assessed with the analysis of variance model. The patients nested within treatment groups effect was considered a random effect to account for correlation between repeated measures on patients. If no treatment or treatment by time effect was detected, then the treatment groups were considered comparable at baseline with respect to IOP.

Analysis of Primary Efficacy Endpoint

Protocol C-92-25 proposed that the dose-response relationship between AL04862 and percent change from baseline in IOP be evaluated using linear regression with percent change from baseline as the response and log of dose of AL04862 as the predictor.

The dose response of AL04862 was evaluated using an analysis of variance model, which does not assume a linear relationship between reduction of IOP and concentration of AL04862.

Demographics

Differences in treatment groups with respect to age, sex, race, and iris color were investigated with a chi-square test.

Descriptive statistics were calculated for the percent change from baseline in IOP for subclassifications of sex, iris color, race, and age (65 years or younger vs. over 65 years of age). No statistical comparisons were conducted on IOP based on subclassifications.

Safety

Changes in ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, vitreous), visual acuity, heart rate, and blood pressure were evaluated for safety. Ocular signs were investigated for clinically meaningful changes from baseline (i.e., no statistical comparisons were made). Visual acuity was categorized into maximum (across visits) lines of change on a Snellen chart. Categories were improvement or no lines of change, a one line decrease on the Snellen chart, and a two line decrease on the Snellen chart. Comparisons between dose groups were then analyzed with a Cochran-Mantel-Haenszel rank score test on the categorized maximum lines of change data. Dose comparisons with respect to heart rate and mean blood pressure were conducted using a t-test on the maximum decrease (across visits) in heart rate and blood pressure.

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

Number of Patients Entered into Study

Inv. #	Investigator	Location	Vehicle	0.3%	1.0%	2.0%	3.0%	Total
271	Robert Stewart,M.D	Houston, TX	3	4	4	4	4	19
331	Alan Mandell, M.D.	Memphis, TN	0	0	1	1	1	3
358	Thom Zimmerman,M.D.	KY Lions Eye Inst. Lousiville, KY	0	1	1	1	1	1
447	Bruce Shields, M.D.	Duke Univ. Durham, NC	2	2	2	2	2	10
453	Alan Crandall, M.D.	Univ. Utah Salt Lake City, UT	1	1	0	1	0	3
470	Donald Brotherman, M.D.	Dallas, TX	2	3	3	3	2	13
479	Robert Allen, M.D.	Univ. Va. Health Ctr Charlottesville, VA	2	1	2	2	0	7
543	Robert Ritch, M.D.	NY Eye & Ear Infirm. New York, NY	1	0	2	0	2	5
648	Alan Robin, M.D.	Baltimore, MD	4	4	4	4	4	20
649	Rick Lewis, M.D.	Sacramento, CA	0	1	1	0	0	2
861	Saul Ullman, M.D.	Pensacola, FL	4	2	3	2	4	15
961	Ronald Gross, M.D.	Houston, TX	1	1	2	1	2	7
970	Robert Lehmann, M.D.	Nacogkoches, TX	2	2	2	3	2	11
1074	Joseph Caprioli, M.D.	Yale Univ. New Haven, CT	0	0	0	0	1	1
1237	Lawrence Hurvitz, M.D.	Sarasota, FL	0	0	0	1	1	2
1409	Dong Shin, M.D.	Kresge Eye Inst. Detroit, MI	2	2	2	2	2	10
1473	Thomas Mundorf, M.D.	Charlotte, NC	2	2	2	2	2	10
1515	???	???	1	0	1	1	0	3
1551	Barbara Smythe, M.D.	Fort Worth, TX	2	2	2	1	2	9
1565	Louis Cantor, M.D.	Indiana Univ. Indianapolis, IN	2	1	1	0	2	6
Totals	20		31	29	34	30	33	157

Reviewer's Comment: *There is no name or location listed for investigator 1515.*

Demographic Characteristics of All Patients Included in the Primary Efficacy Analysis

AGE		Treatment 0.0% N=27	0.3% N=24	1.0% N=32	2.0% N=28	3.0% N=31
All Ages	Mean	59.4	62.7	59.6	57.9	58.2
	STD	11.8	13.7	10.2	11.8	10.1
	N	27	24	32	28	31
	Min	29	32	41	35	37
	Max	74	87	78	76	75
13-64	N	15	10	22	18	22
	%	56	42	69	64	71
> 64	N	12	14	10	10	9
	%	44	58	31	36	29

SEX		Treatment 0.0%	0.3%	1.0%	2.0%	3.0%
Male	N	13	12	16	12	14
	%	48	50	50	43	45
Female	N	14	12	16	16	17
	%	52	50	50	57	55

RACE		Treatment 0.0%	0.3%	1.0%	2.0%	3.0%
Cauc	N	19	18	25	20	24
	%	70	75	78	71	77
Black	N	7	6	4	7	7
	%	26	25	13	25	23
Asian	N	1	-	-	1	-
	%	4	-	-	4	-
Other	N	-	-	3	-	-
	%	-	-	9	-	-

IRIS		Treatment 0.0%	0.3%	1.0%	2.0%	3.0%
Brown	N	15	13	17	16	15
	%	56	54	53	57	48
Hazel	N	5	5	5	2	5
	%	19	21	16	7	16
Green	N	1	-	1	-	-
	%	4	-	3	-	-
Blue	N	6	5	9	10	10
	%	22	21	28	36	32
Grey	N	-	1	-	-	1
	%	-	4	-	-	3

Baseline IOP Values for Patients in Primary Efficacy Analysis

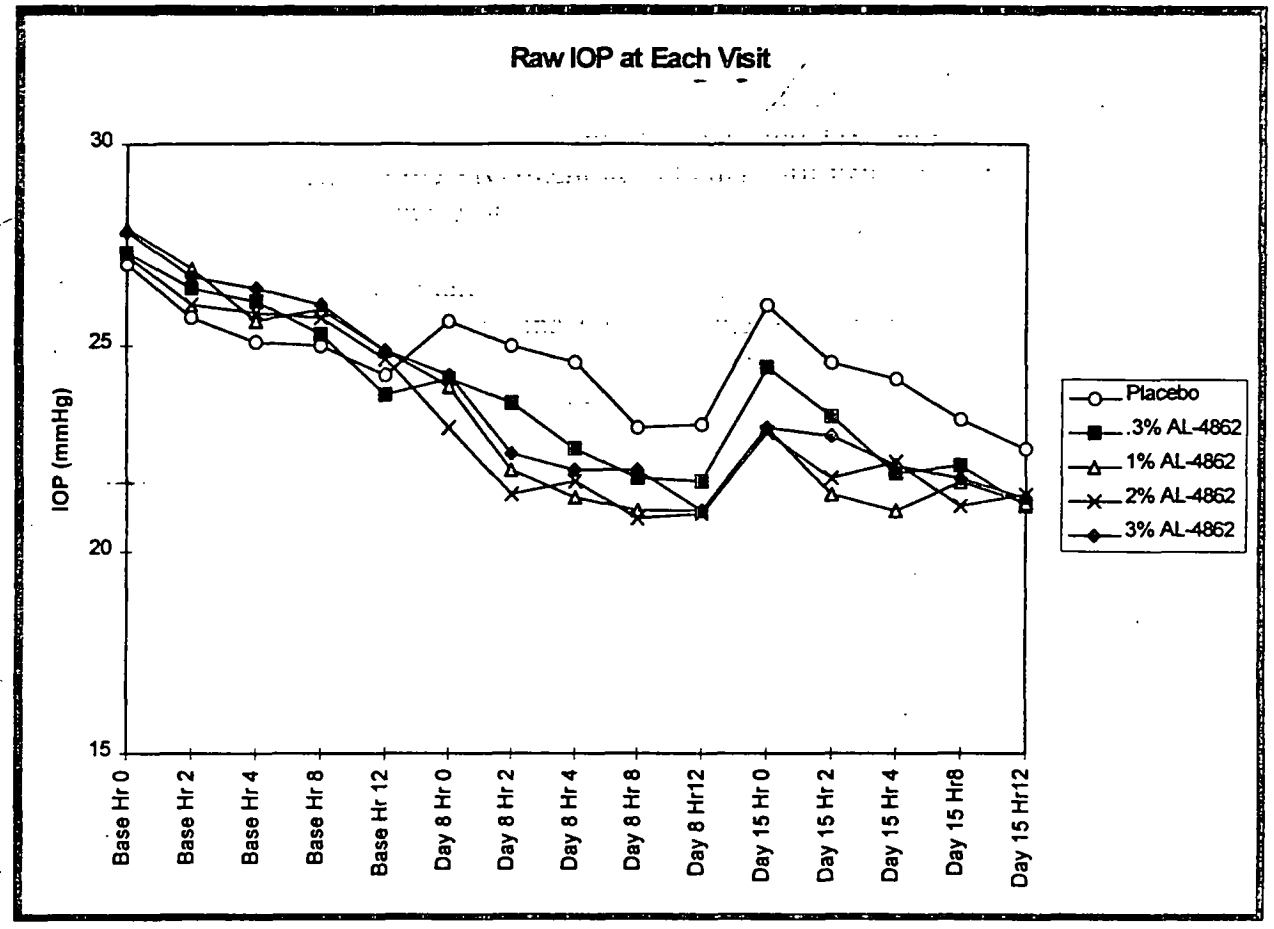
	Treatment				
	0.0%	0.3%	1.0%	2.0%	3.0%
Time=Hour 0					
N	27	24	32	28	31
Mean	27.5	27.7	28.2	28.0	28.2
[S.D.]	[3.0]	[2.7]	[2.7]	[3.1]	[3.4]
Time=Hour 2					
N	27	24	32	28	31
Mean	26.5	26.7	27.1	27.2	26.9
[S.D.]	[2.9]	[3.5]	[3.3]	[3.4]	[3.5]
Time=Hour 4					
N	27	24	32	28	31
Mean	25.7	25.8	25.9	26.7	26.6
[S.D.]	[2.6]	[3.0]	[3.0]	[3.6]	[3.1]
Time=Hour 8					
N	27	24	32	28	31
Mean	25.5	25.6	26.0	26.6	26.4
[S.D.]	[2.2]	[2.7]	[2.9]	[3.5]	[3.4]
Time=Hour 12					
N	27	24	31	28	29
Mean	24.6	24.7	25.1	25.6	25.1
[S.D.]	[2.4]	[2.6]	[2.8]	[3.7]	[2.8]

Distribution By Reason and Treatment of Patients Discontinued From the Study

Reason	Randomized Treatment Group					Total
	Placebo	AL-4862 0.3%	AL-4862 1.0%	AL-4862 2.0%	AL-4862 3.0%	
Inadequate IOP Control	1	0	0	0	0	1
Protocol Violation	0	0	1	0	0	1
Patient Unable to Keep Visit Schedule	0	0	0	0	1	1
TOTALS	1	0	1	0	1	3

Reviewer's Comments: *No patients were discontinued from the study due to adverse events.*

8.1.1.4.2 Efficacy endpoint outcomes



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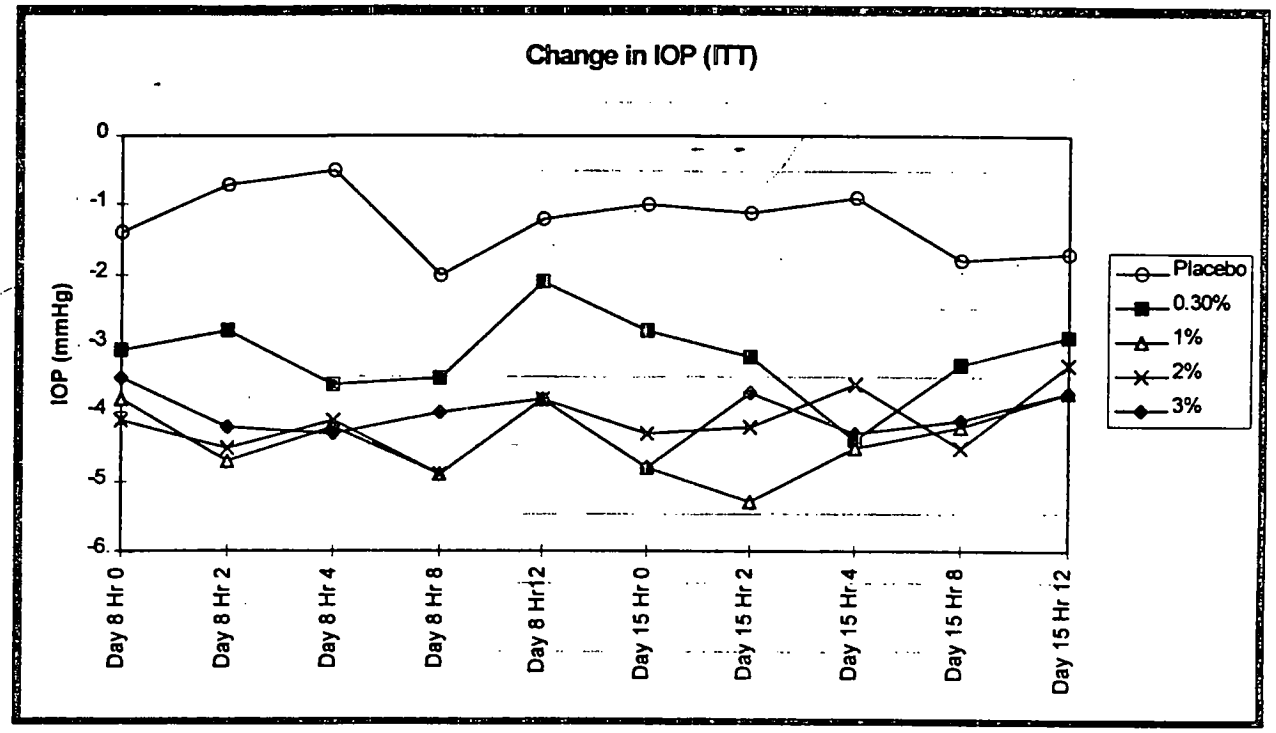

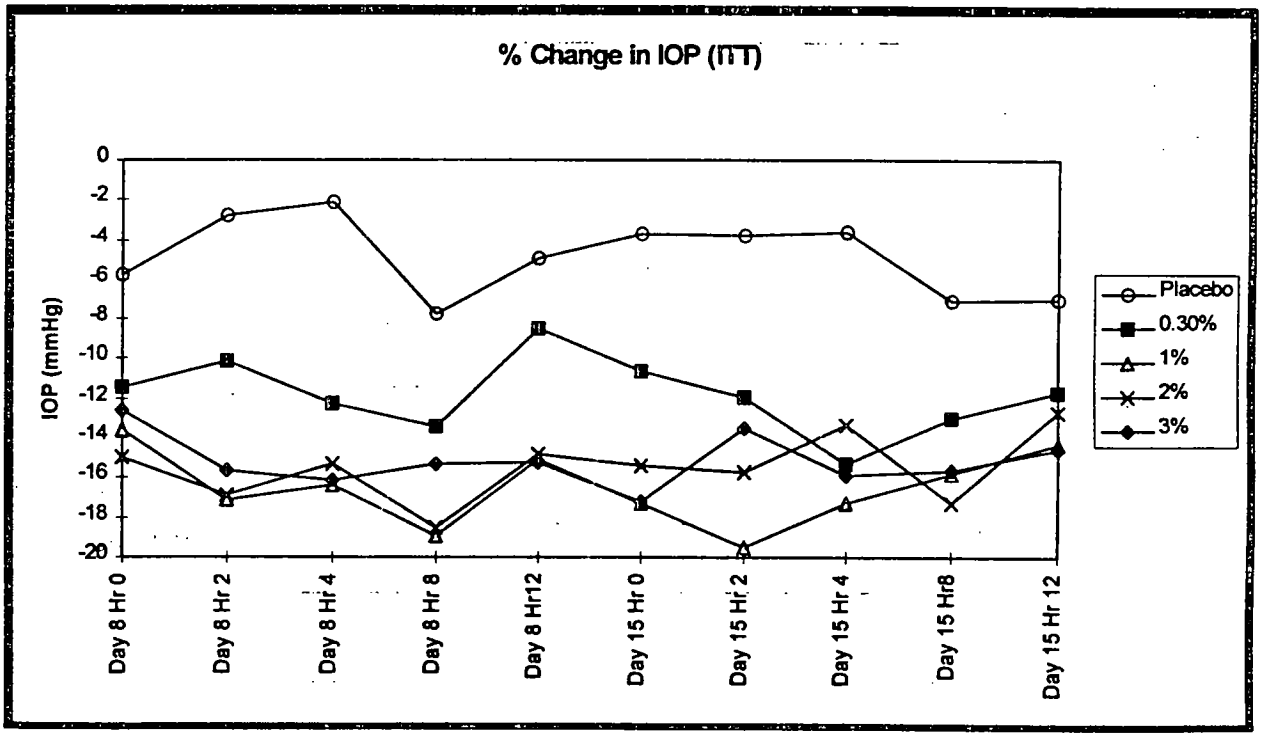

Reviewer's Comments: *AL04862 does not show a linear concentration-dependent response. Both the 1% and 2% concentrations were more effective than the 0.3% and the 3% concentrations*

and placebo. The IOP-lowering effect of the 1% and 2% concentrations is approximately equal, however, when the effect of the diurnal variation of IOP is taken into account, the 1% concentration is slightly more effective than the 2% concentration. The maximum IOP-lowering effect of the 1% concentration was 5.5 mmHg from baseline; the minimum was 3.7 mmHg from baseline. The 2% concentration lowered IOPs by a maximum of 4.9 mmHg and a minimum of 3.3 mmHg. The placebo group showed a reduction of approximately 2 mmHg from baseline.

Due to the small numbers of patients in each demographic subset (age, gender, iris color and race), no valid conclusions could be drawn with respect to the effect of these variables on efficacy of the various concentrations. This could have been avoided by enrolling more patients in this dose-ranging study. Additionally, enrolling more patients in this study would have provided determination of peak and trough time points. There were no significant differences between the intent-to-treat and per protocol analyses.

8.1.1.4.3 Safety Outcomes

Frequency and Incidence of Adverse Events

Coded Adverse Events	AL04862 0.3% N=29		AL04862 1.0% N=34		AL04862 2.0% N=30		AL04862 3.0% N=33		Placebo N=31	
	N	%	N	%	N	%	N	%	N	%
OCULAR										
Pruritus	1	3	1	3	2	7	0		1	3
Discomfort	0		3	9	1	3	1	3	2	7
Dry Eye	0		1	3	0		0		0	
Eye Fatigue	0		1	3	0		1	3	0	
Blurred Vision	0		0		2	7	3	9	1	3
Keratitis	0		0		1	3	1	3	0	
Precipitate	0		0		0		2	6	0	
Pain	0		0		1	3	1	3	0	
Lid Margin Crusting	0		0		0		1	3	0	
Hyperemia	1	3	0		1	3	1	3	1	3
Conjunctival Edema	1	3	0		0		0		0	
Corneal Striae	1	3	0		0		0		0	
Photophobia	0		1	3	0		0		0	
Corneal Staining	0		1	3	0		0		0	

Coded Adverse Events	AL04862 0.3% N=29		AL04862 1.0% N=34		AL04862 2.0% N=30		AL04862 3.0% N=33		Placebo N=31	
	N	%	N	%	N	%	N	%	N	%
Lid Disorder	0		0		1	3	0		0	
Lid Erythema	0		0		1	3	0		0	
Lid Edema	0		0		1	3	0		0	
Corneal Abrasion	0		0		0		0		1	3
Discharge NOS	0		0		0		0		1	3
NONOCULAR										
Cardiovascular Hypotension	1	3	0		0		2	6	0	
Hypertension	1	3	0		0		0		1	3
Bradycardia	0		1	3	1	3	1	3	5	16
Digestive Dry Mouth	0		2	6	0		0		0	
Nausea	0		0		0		1	3	0	
Respiratory Rhinitis	1	3	0		2	7	0		0	
Increased Cough	1	3	0		0		0		0	
Pharyngitis	0		0		0		0		1	3
Skin and Appendages Erythema	1	3	0		0		0		0	
Special Senses Taste Perversion	2	7	5	15	5	17	8	24	1	3
Body as a Whole Back Pain	1	3	0		0		0		0	
Neck Pain	1	3	0		0		0		0	
Allergy	0		1	3	0		0		0	
Cold Syndrome	0		1	3	0		0		0	
Headache	0		0		1	3	2	6	0	
Flu Syndrome	0		0		0		0		1	3
Urogenital Urinary Frequency	0		0		0		1	3	0	

Reviewer's Comment: *The most frequent ocular adverse events were discomfort, blurred vision and pruritus. The most frequent non-ocular adverse events were taste perversion and bradycardia.*

Visual Acuity

There were no clinically significant differences between the groups with respect to visual acuity.

Heart Rate

There were slight decreases in heart rate for each group, but between groups, the differences were not considered clinically significant. The incidence of bradycardia was 15% in the placebo group as compared to 3% in the active groups.

Blood Pressure

There was a slight decrease in blood pressure for each group, but no clinically significant differences between groups.

Ocular Signs

There were no clinically significant differences in ocular signs (eyelids, conjunctiva, cornea, iris, anterior chamber, lens, vitreous) between the groups.

8.1.1.5 Reviewer's Conclusions of Study # 1 Results

1. AL04862 does not show a linear concentration-dependent response. The 1% concentration was the most effective concentration with maximal IOP-lowering of 5.5 mmHg from baseline and minimal IOP-lowering of 3.7 mmHg from baseline. The placebo group showed a reduction of approximately 2 mmHg from baseline.

2. The most commonly reported adverse events in the brinzolamide groups were discomfort, pruritus, blurred vision and taste perversion.

3. The sponsor should provide the name and address of investigator # 1515.

4. Enrolling more patients in this study could have provided information regarding efficacy of the various concentrations with respect to demographic subsets (age, gender, iris color, and race), as well as determination of peak and trough time points and a better safety profile.

8.1.2 Reviewer's Trial # 2
Sponsor's Protocol # C-94-49

A Four-Week, Multicenter, Triple-Masked, Parallel, Group, Dosing-Frequency Study of the Efficacy and Safety of BID and TID Dosed AL-4862 Ophthalmic Suspension in the Treatment of Patients with Primary Open-Angle Glaucoma or Ocular Hypertension

8.1.2.1 Objective/Rationale
To evaluate the safety and IOP-lowering efficacy of b.i.d. versus t.i.d.- dosed topical AL04862 1.0% Ophthalmic Suspension in patients with primary open-angle glaucoma or ocular hypertension

8.1.2.2 Design
Multicenter, triple-masked, randomized, parallel group study

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ON ORIGINAL

8.1.2.3 Protocol Study Plan

Activity	PHASE I											PHASE II									
	Eligibility Phase											Triple-Masked Treatment Phase									
	Screening Exam	Eligibility No. 1 Examinations					Eligibility No. 2 Examinations					Week 2 Examinations					Week 4 Examinations				
		8 a.m.	12 noon	4 p.m.	6 p.m.	8 p.m.	8 a.m.	12 noon	4 p.m.	6 p.m.	8 p.m.	8 a.m.	12 noon	4 p.m.	6 p.m.	8 p.m.	8 a.m.	12 noon	4 p.m.	6 p.m.	8 p.m.
Screen Patients	X																				
Informed Consent	X																				
Demographics	X																				
Medical History	X																				
IOP		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Best Corrected Visual Acuity	X	X					X					X					X				
Biomicroscopy	X	X					X					X					X				
Resting Pulse	X																				
Resting Blood Pressure	X																				
Dilated Ophthalmoscopy	X																				
Automated Perimetry							X[2]														
Gonioscopy	X[3]																				
Discontinue All Glaucoma Medication	X																				
Dispense Masked Medication	X										X	X[4]									
Instill Masked Medication		X[5]		X[5]			X[5]		X[5]			X[5]		X[5]			X[5]		X[5]		
Collect Medications											X										X
Complete Exit Form																					X
Dismiss Patient																					X

[1]All IOP measurements should be ± 30 minutes of the required time.
[2]Automated Perimetry (non-dilated) is to be conducted between the 8:00 a.m. and 8:00 p.m. IOP measurements at the Eligibility #2 visit (i.e., it must be after the 8:00 a.m. IOP measurement). A visual field evaluation will not be performed at the Eligibility No. 2 visit only if the following criteria have been satisfied: evaluation conducted within the last twelve (12) months with normal or full results; or evaluation conducted within the past six (6) months with glaucomatous field loss within the acceptable guidelines as stated in the Exclusion Criteria (page 7) and Automated Perimetry section (page 19).
[3]Gonioscopy is to be conducted only if this procedure has not been performed within the last 6 months.
[4]Dispense medications as necessary.
[5]Instill medication 30 minutes after the 8:00 a.m. and 4:00 p.m. IOP measurements

8.1.2.3.1 Population

Patients 21 years of age or older, of any race, of either gender, with a diagnosis of primary open-angle glaucoma (with or without a pseudoexfoliation or pigment dispersion component) or ocular hypertension. All eligible patients were required to have post-washout IOP measurements of 24 mmHg to 36 mmHg inclusive, in at least one eye (same eye), at the 8:00 a.m. IOP measurements on two eligibility visits separated by one week.

Investigators

Inv. No.	Name/Address	#enrolled	#completed
1028	Mark B. Abelson, M.D. Ophthalmic Research Associates, Inc. 863 Turnpike Street North Andover, MA 01845 Andover Eye Associates 138 Haverhill Street Andover, MA 01810	3	3
470	Donald P. Brotherman, M.D. Professional Plaza 3 10 Medical Parkway Dallas, TX 75234	12	12
1709	Amber Dobler, M.D. 1350 South Main Street Suite 1600 Fort Worth, TX 76104	16	15
943	Robert A. Laibovitz, M.D. Eye Research Associates 3307 Northland Drive Austin, TX 78731	21	21
386	Wayne F. March, M.D. University of Texas Medical Branch Department of Ophthalmology Galveston, TX 77550	18	18
271	Robert H. Stewart, M.D. Houston Eye Associates 2855 Gramercy Houston, Texas 77025	35	33
	Totals	105	102

8.1.2.3.2 Endpoints

Efficacy: IOP change in mmHg from diurnal baseline
Safety: Visual acuity, ocular signs

8.1.2.3.3 Statistical Considerations

Analysis of variance was used to compare average IOP reductions between the b.i.d. and t.i.d.- dosed groups.

The planned sample size of 48 patients per group provided 80% power for detecting a 7 % difference between the two groups in mean percent decrease in IOP, assuming $\sigma = 12\%$ and $\alpha = 0.5$, two-tailed.

8.1.2.4 Results

8.1.2.4.1 Populations enrolled/analyzed

Demographic Statistics for Per Protocol Patients

	AGE				
	MEAN	STD	N	MIN	MAX
TRT					
BID-ALØ4862	61.9	10.6	48	36	83
TID-ALØ4862	61.2	11.5	54	34	82

	Treatment			
	BID-ALØ4862		TID-ALØ4862	
	N	%	N	%
Age				
<65	23	47.9	32	59.3
>=65	25	52.1	22	40.7
Sex				
MALE	18	37.5	20	37.0
FEMALE	30	62.5	34	63.0
Race				
CAUCASIAN	32	66.7	40	74.1
BLACK	15	31.3	12	22.2
OTHER	1	2.1	2	3.7
Iris				
BROWN	30	62.5	31	57.4
HAZEL	6	12.5	13	24.1
GREEN	1	2.1	1	1.9
BLUE	11	22.9	8	14.8
GREY	.	.	1	1.9
Diagnosis				
OH	20	41.7	19	35.2
POAG	28	58.3	35	64.8

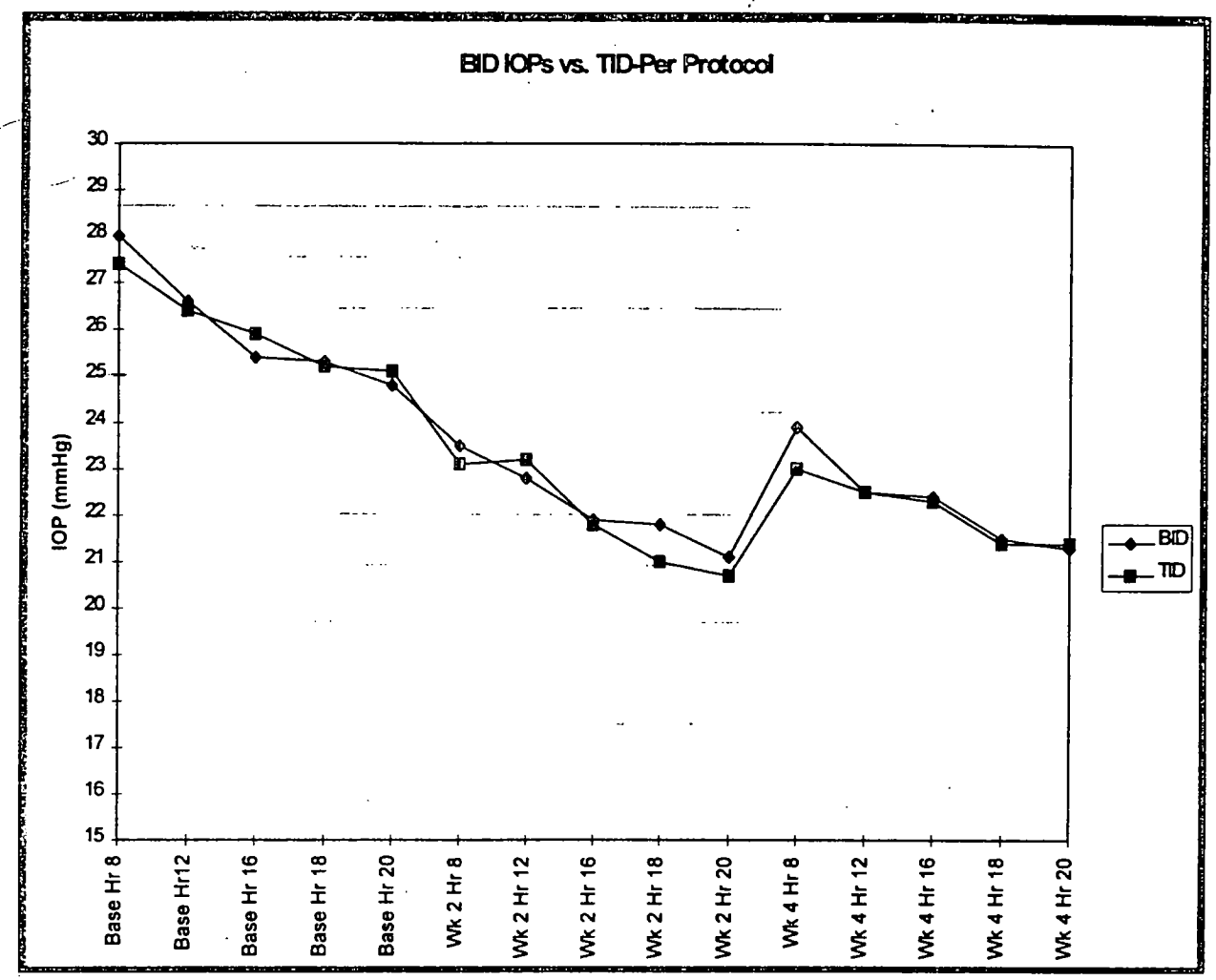
Discontinued Subjects

Patients Discontinued Following Randomization

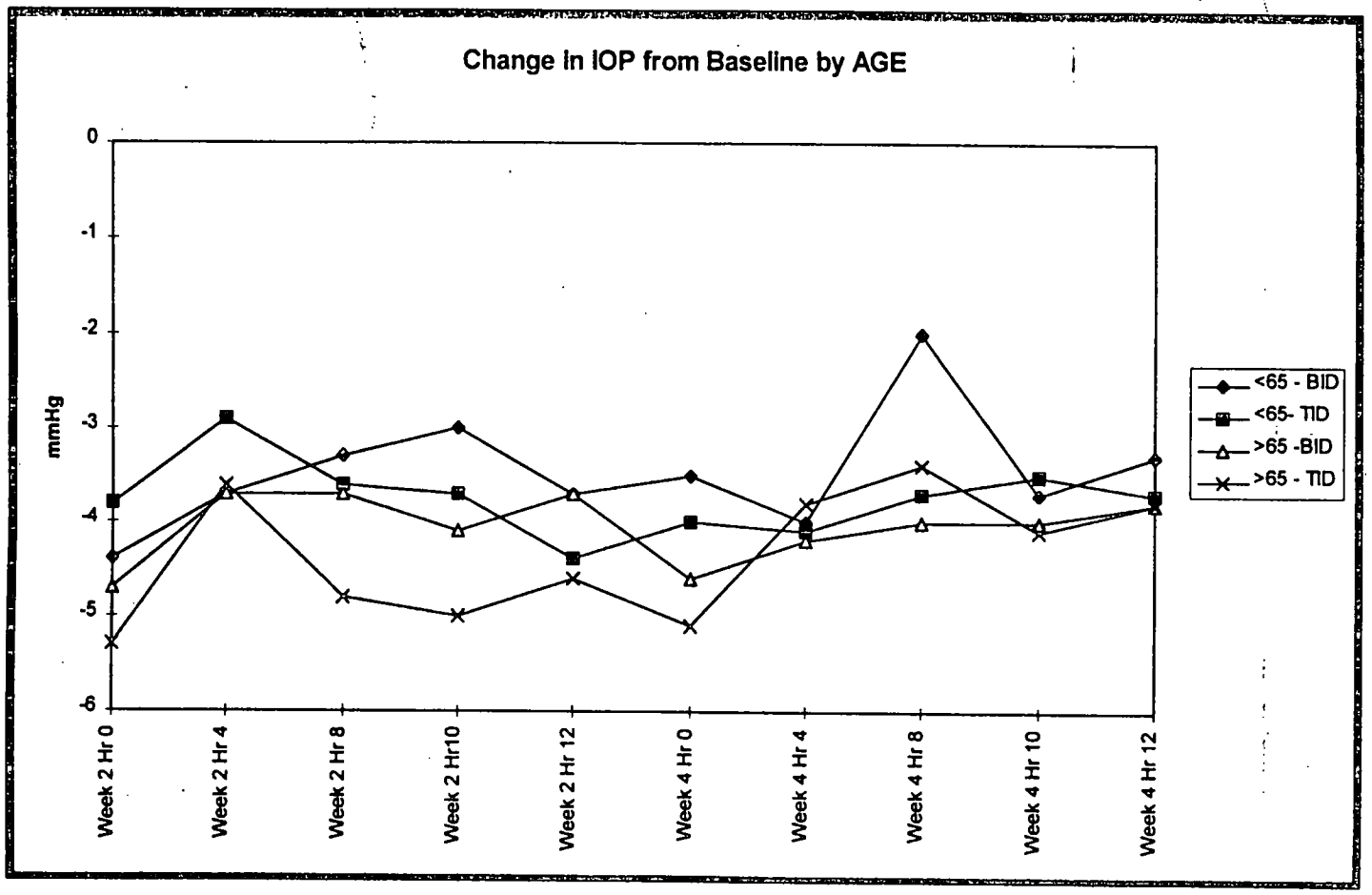
Investigator Number	Patient Number	Treatment	Duration of Treatment	Reason Discontinued
271	508*	ALØ4862 1.0% BID	Unknown	Lost to follow-up No follow-up IOP data.
271	523*	ALØ4862 1.0% BID	7 days	Drug-related adverse event (keratitis). No follow-up IOP data.
386	317	ALØ4862 1.0% BID	4 weeks	Noncompliance. Week 4 data not evaluable.
1709	402*	ALØ4862 1.0% BID	Unknown	Patient decision not to continue. No follow-up IOP data.

*Excluded from all analyses of efficacy

8.1.2.4.2 Efficacy endpoint outcomes



Reviewer's Comments: *T.i.d.-dosing reduces IOP to a greater extent than b.i.d.- dosing at more time points. The difference in the amount of reduction of IOP is not clinically or statistically significant. In this study, b.i.d. and t.i.d. dosing appear to be equivalent with respect to IOP lowering, however, the number of subjects in each group is relatively low and the study is short. (4 weeks). It would have been helpful to have measurements at the 2-hour time point, as this appeared to be the peak time point in the dose-ranging study.*

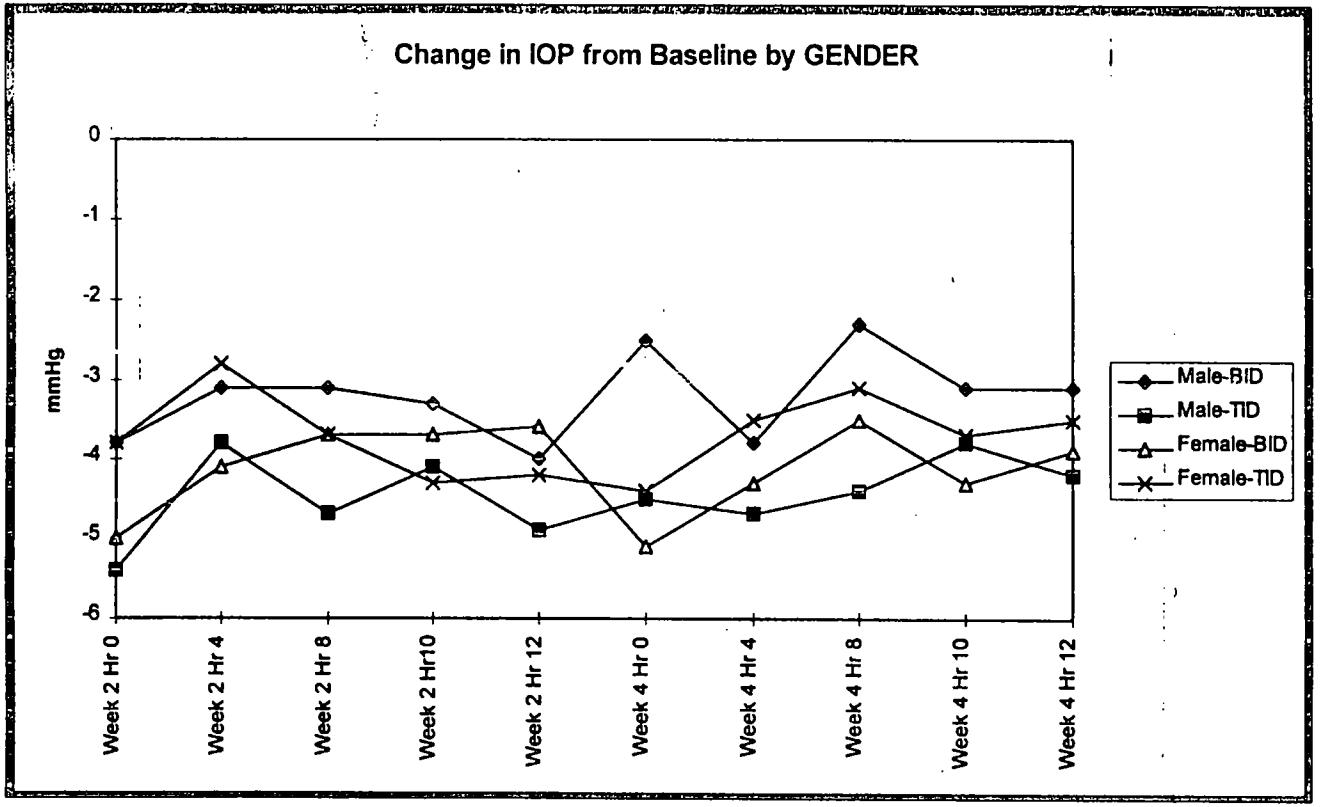


at which clinical significance was reached.

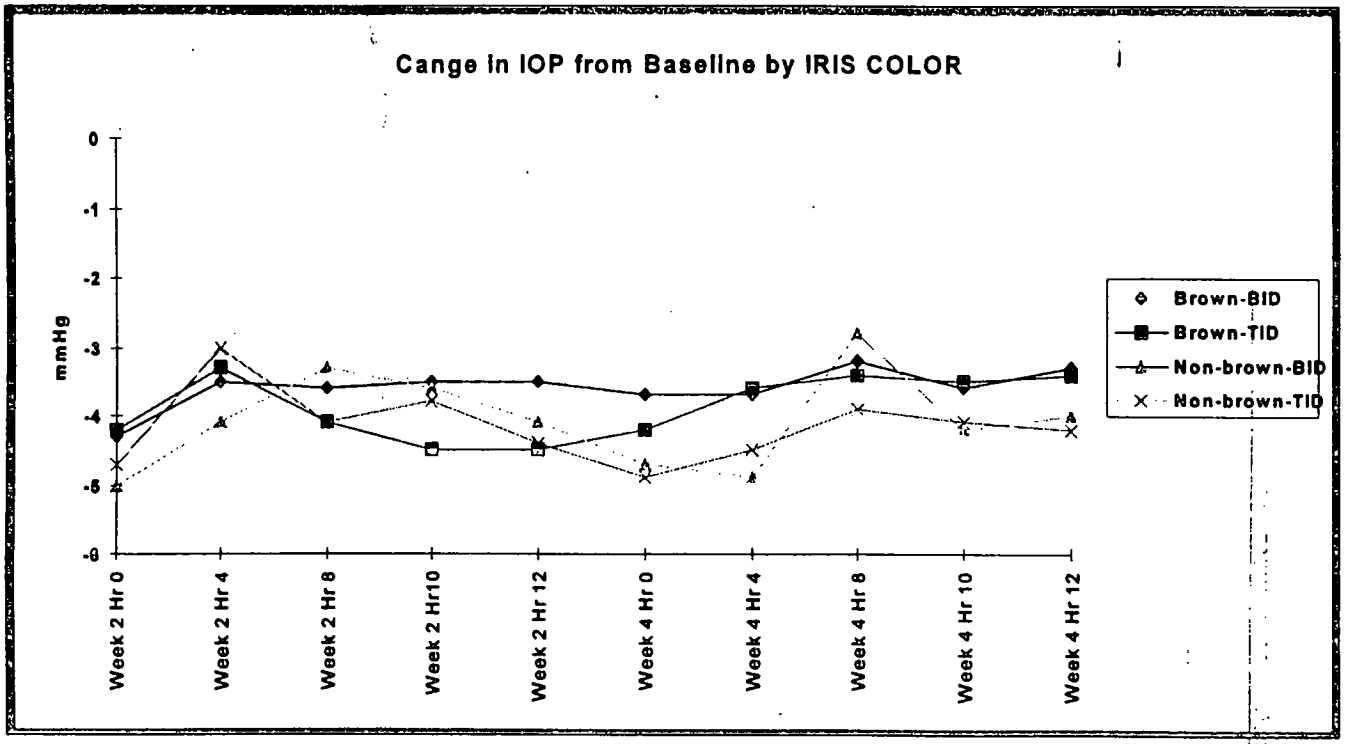
Reviewer's Comments:

NDA 20-816 AZOPT

T.i.d. dosing was slightly more effective than b.i.d. dosing for all ages, however, there were only two time points



Reviewer's Comments: *T.i.d. dosing was more effective than b.i.d. dosing in males. Five of ten time points reached clinical significance. B.i.d. dosing was slightly more effective than t.i.d. dosing in females, however, only two of ten time points reached clinical significance. As previously mentioned, the numbers of subjects in each group is low.*



Reviewer's Comments: *T.i.d. dosing was slightly more effective than b.i.d. dosing in both brown and non-brown irides, however, the differences were not clinically significant. There were not enough patients enrolled in each racial subset to make any valid conclusions regarding differences in efficacy due to race.*

8.1.2.4.3 Safety Comparisons

Frequency and Incidence of Adverse Events

Coded Adverse Events	ALØ4862 1.0% Ophthalmic Suspension (BID) N=51		ALØ4862 1.0% Ophthalmic Suspension (TID) N=54	
OCULAR	**N**	**%**	**N**	**%**
Hyperemia	1	2	1	2
Foreign Body Sensation	1	2	0	
Keratitis	1	2	1	2
Diplopia	0		1	2
Hordeolum	1	2	0	
Chalazion	0		2	4
Lid Edema	0		1	2
Conjunctival Hemorrhage	0		1	2
NONOCULAR				
Body as a Whole Accidental Injury	1	2	1	2
Cardiovascular Arrhythmia	1	2	0	
Metabolic and Nutritional Gout	0		1	2
Face Edema	0		1	2
Nervous Dizziness	1	2	0	
Nervousness	1	2	0	
Respiratory Dyspnea	1	2	0	
Skin and Appendages Urticaria	1	2	0	
Dermatitis	0		1	2

Visual Acuity

Maximum Change in Visual Acuity at Final Visit

Change in Visual Acuity (Snellen Lines)	No Change or Improvement		One Line Decrease		Two Line Decrease	
	N	%	N	%	N	%
ALØ4862 1.0% (BID) N=49	40	81.6	5	10.2	4	8.2
ALØ4862 1.0% (TID) N=54	43	79.6	8	14.8	3	5.6

Reviewer's Comments: *No clinically significant decrease in visual acuity was observed for either group.*

Ocular Signs

Worsening in Ocular Signs

Treatment Groups	Eyelids/ Conjunctiva		Cornea		Iris/Anterior Chamber		Lens		Vitreous	
	N	%	N	%	N	%	N	%	N	%
ALØ4862 1.0% BID N=51	1	2	1	2	0		0		0	
ALØ4862 1.0% TID N=54	2	4	1	2	0		0		0	

Reviewer's Comments: *There were two cases of keratitis; one in each of the treatment groups. In the b.i.d.- dosed group there was one case of hordeolum and in the t.i.d.- dosed group, there were two cases of chalazion. It is unlikely that the hordeolum and chalazion were treatment-related.*

Overall Frequency and Incidence of Adverse Events

	ALØ4862 1% BID Total		ALØ4862 1% TID Total	
Ocular	**N**	**%**	**N**	**%**
Hyperemia	1	2	1	2
Foreign Body Sensation	1	2	0	
Keratitis	1	2	1	2
Diplopia	0		1	2
Hordeolum	1	2	0	
Chalazion	0		2	4
Lid Edema	0		1	2
Conjunctival Hemorrhage	0		1	2
Nonocular				
Accidental Injury	1	2	1	2
Arrhythmia	1	2	0	
Gout	0		1	2
Urticaria	1	2	0	
Face Edema	0		1	2
Dizziness	1	2	0	
Nervousness	1	2	0	
Dyspnea	1	2	0	
Dermatitis	0		1	2

Reviewer's Comment: *The most common adverse ocular event was chalazion which occurred in 4% of patients in the t.i.d. group. It is unlikely that this adverse event was treatment-related. One case of diplopia was reported in the t.i.d. group (resolved). The remainder of the ocular and nonocular adverse events occurred with a frequency of 2% or less and were nonserious. The adverse event profile was essentially the same for the b.i.d. and t.i.d. groups.*

8.1.2.5 Reviewer's Conclusions of Study # 2 Results:

1. In this study, b.i.d. and t.i.d. dosing appear to be clinically equivalent with respect to IOP lowering, however, it would have been more informative to have more patients in each group, as well as IOP measurements at the 2-hour time point, since this appeared to be the peak timepoint in the dose-ranging study.

2. The incidence of adverse events were low and nonserious, with the b.i.d.- dosed group and the t.i.d.- dosed groups having essentially the same adverse event profile.

3. In order to make any valid conclusions regarding efficacy, more patients would have had to have been enrolled.

8.1.3 Reviewer's Trial # 3
Sponsor's Protocol C-95-46

A Three-Month Multicenter, Triple-Masked, Primary Therapy Study of the Efficacy and Safety of BID and TID-Dosed Brinzolamide 1% Ophthalmic Solution Compared to TID-Dosed Dorzolamide 2% and TID-Dosed Placebo in the Treatment of Patients With Primary Open-Angle Glaucoma or Ocular Hypertension

8.1.3.1 Objectives/Rationale

The primary objective was to compare the safety and IOP-lowering efficacy of b.i.d.-dosed brinzolamide 1%, t.i.d.-dosed brinzolamide 1%, t.i.d.-dosed dorzolamide 2% and t.i.d.-dosed placebo in patients with primary open-angle glaucoma or ocular hypertension.

8.1.3.2 Study Design

This study was a multi center (29 sites), triple-masked, efficacy trial in which data obtained from 463 patients with open-angle glaucoma or ocular hypertension. The patients were randomized into one of four treatment groups:

-1% brinzolamide b.i.d.
-1% brinzolamide t.i.d.
-2% dorzolamide t.i.d.
-placebo t.i.d.

Randomization was 2:2:2:1 respectively. There was a five-day to three-week run-in phase, in which all patients underwent a washout from all ocular hypotensive therapy, followed by two diurnal IOP eligibility examinations. Treatment with masked test medications was for three months with IOP evaluations at 8:00 a.m. and 10:00 a.m. at Month 1 and 8:00 a.m., 10:00 a.m., and 6:00 p.m. at Months 2 and 3.

8.1.3.3 Protocol:

Phase I - Run-in (Washout and Eligibility Visits 1 and 2)

Following an initial screening visit, patients will enter a Run-In Phase during which they will discontinue all glaucoma medication(s) as follows: at least three (3) weeks for topical beta-blockers; at least two (2) weeks for topical sympathomimetics or alpha agonists; at least five (5) days for miotics; and at least five (5) days for topical or oral carbonic anhydrase inhibitors. In order to minimize potential risk to the patient due to IOP elevations during the washout period, investigators may substitute a miotic in place of a beta-blocker, sympathomimetic or alpha agonist. However, patients must be washed out of medications for the minimum period described above.

After a washout period ranging from five (5) days to three (3) weeks, patients will return for the Eligibility Visit 1, and one week later, the Eligibility Visit 2. At these visits, bilateral IOP measurements will be obtained at 8:00 a.m., 10:00 a.m. and 6:00 p.m. Patients that qualify for randomization into Phase II of the study must have an 8:00 a.m. IOP of **24 to 36 mmHg, inclusive**, and 10:00 a.m. and 6:00 p.m. IOPs of **21 to 36 mmHg, inclusive**, in at least one eye. The IOP criteria must be met by at least one eye and it must be the same eye at each of the qualifying IOP measurements during Eligibility Visits 1 and 2. In addition, there must be no greater than a 5 mmHg difference between eyes at Eligibility Visits 1 and 2.

Phase II - Triple-Masked Treatment Phase (Months 1, 2 and 3)

A three (3) month, triple-masked, efficacy phase will follow during which patients will be randomized to either AL04862 1.0% b.i.d., AL04862 1.0% t.i.d., Dorzolamide 2.0% t.i.d. or placebo t.i.d.. Patients will return at Month 1, at which time bilateral IOP measurements will be made at 8:00 a.m. and 10:00 a.m. Patients will then be seen again at Months 2 and 3 at which time bilateral IOP measurements will be obtained at 8:00 a.m., 10:00 a.m. and 6:00 p.m. Visual acuity and biomicroscopy will be assessed at all 8:00 a.m. examinations.

8.1.3.3.1 Population

Adult patients, 21 years or older, of any race or gender diagnosed with primary open-angle glaucoma or ocular hypertension. Qualifying IOPs following wash-out, were 24 to 36 mmHg, inclusive, in at least one eye, at the 8:00 a.m. measurement and 21 to 36 mmHg, inclusive, at 10:00 a.m. and 6:00 p.m., with no greater than a 5 mmHg difference between eyes during eligibility visits 1 and 2.

APPEARS THIS WAY
ON ORIGINAL

Study Plan

Activity	PHASE I							PHASE II							
	Run-In and Eligibility Phase							Triple-Masked Treatment Phase							
	Screening Exam	Eligibility #1 Examinations			Eligibility #2 Examinations			Month 1 Examinations		Month 2 Examinations			Month 3 Examinations		
		8 a.m.	10 a.m.	6 p.m.	8 a.m.	10 a.m.	6 p.m.	8 a.m.	10 a.m.	8 a.m.	10 a.m.	6 p.m.	8 a.m.	10 a.m.	6 p.m.
Screen Patients	X														
Informed Consent	X														
Demographics	X														
Medical History	X														
Urine Pregnancy Test	X[1]												X[1]		
IOP		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Best Corrected Visual Acuity	X	X			X			X		X			X		
Biomicroscopy	X	X			X			X		X			X		
Resting Pulse	X	X			X			X		X			X		
Resting Blood Pressure	X	X			X			X		X			X		
Dilated Ophthalmoscopy	X														X[6]
Automated Perimetry					X[3]								X[3]		
Gonioscopy	X[4]														
Hematology		X											X		
Blood Chemistry		X											X		
Urinalysis		X											X		
Dispense Masked Medication							X	X[5]		X[5]					
Instill Masked Medication								X		X			X		
Collect Medications															X
Complete Exit Form															X

[1] Urine pregnancy test to be performed on women of childbearing potential.
[2] All IOP measurements should be ±30 minutes of the required time.
[3] Automated Perimetry (non-dilated) is to be conducted between the 8:00 a.m. and 6:00 p.m. IOP measurements at the Eligibility No. 2 and Month 3 Examinations. A visual field evaluation will not be performed at the Eligibility No. 2 visit only if the following criteria have been satisfied: evaluation conducted within the past three (3) months with normal or full results; or evaluation conducted within the past three (3) months with glaucomatous field loss but within acceptable guidelines.
[4] Gonioscopy is to be conducted only if this procedure has not been performed within the last 6 months.
[5] Dispense medications as necessary.
[6] Dilated ophthalmoscopy can be performed ± three (3) days of the actual Month 3 Examination.

Investigators:

Inv. No.	Name/Address	# enrolled	# completed
1300	Kerry K . Assil, M.D. 2232 Santa Monica Blvd Santa Monica, CA 90411	20	17
1973	Cecil C. Beehler, M.D. Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL 33901	19	16
1946	Leonard Cacioppo, M.D. 14543 Cortez Boulevard Brooksville, FL 34613	7	7
1208	Robert Caine, M.D. 110 Cambridge Street Fredericksburg, VA 22405	41	37
1985	Margaret DiGaetano, M.D. Daytona Ophthalmic Services, P.A. 1620 Mason Avenue, Suite A Daytona Beach, FL 32117	14	13
501	Mitchell H. Friedlaender, M.D. 10666 North Torrey Pines Road La Jolla, CA 92037	12	10
1948	Beth Friedland, M.D. 10 Park Plaza, Suite 3 P.O. Box 12765 Research Triangle Park, NC 27709	14	13
1952	Kevin Greenidge, M.D. NY Eye and Ear Infirmary 310 E. 14th Street, Room 401 New York, NY 10003	15	10
961	Ronald L . Gross, M.D. 6550 Fannin, Suite 1401 Houston, TX 77030	6	4
1098	Harold A. Helms, Jr., M.D. 1100 23rd Street South Birmingham, AL 35205	0	0

Inv.	Name/Address	# enrolled	# completed
1929	Eve Higginbotham, M.D. 419 West Redwood St., Suite 420 Baltimore, MD 21201	4	3
1008	Barry Horwitz, M.D. 8945 Longpoint Road, Suite 111 Houston, TX 77055	14	14
1932	Andrew Iwach, M.D. 490 Post Street, Suite 640 San Francisco, CA 94102	2	2
1941	Robert L. Kantor, M.D. 2111 Bee Ridge Road Sarasota, FL 34239	1	1
1515	L. Jay Katz, M.D. Wills Eye Hospital 900 Walnut Street Philadelphia, PA 19107	0	0
338	Edwin U. Keates, M.D. 500 Old York Road Jenkintown, PA 19046	8	8
1999	Marta Lopatynsky, M.D. Ophthalmic Surgical Associates, P.C. 124 Avenue B Bayonne, NJ 07002	10	7
1735	George M. Lowry, M.D. 8123 Broadway San Antonio, TX 78209	12	12
647	Robert M. Mandelkorn, M.D. 6315 Forbes Ave, Suite L122 Pittsburgh, PA 15217	0	0
1068	Sam Maskett, M.D. 7320 Woodlake Avenue, No. 380 West Hills, CA 91307	0	0
1403	Jeffrey B. Morris, M.D. 477 N El Camino Real, Suite A 210 Encinitas, CA 92024	75	70

Inv.	Name/Address	# enrolled	# completed
1806	Kenneth Sall, M.D. 9604 E Artesia Blvd, Suite 203 Bellflower, CA 90706	92	81
701	John Samples, M.D. 3375 S W Terwilliger Blvd. Portland, OR 97201	6	5
1340	Joseph W. Spadafora, D.O. 21275 Olean Blvd Port Charlotte, FL 33952	0	0
1972	Onex D. Stevenson, M.D. Stevenson Medical/Surgical Eye Ctr 3535 Brenville St., Suite 325 New Orleans, LA 70119	30	27
415	Stuart A. Terry, M.D. 215 East Quincy, Suite 200 San Antonio, TX 78215-2030	1	1
1975	Carl B. Tubbs, M.D. Associated Eye Physicians & Surgeons 232 North Main Street Stillwater, MN 55083	11	8
1007	Thomas R. Walters, M.D. 1700 South Mopac Austin, TX 78746	31	29
394	Mark J. Weiss, M.D. 1717 South Utica, Suite 102 Tulsa, OK 74104	18	14

Reviewer's Comment: *There were no patients randomized for investigator 1941, yet it is stated that one patient completed the study.*

Total # Investigators	# Patients	Avg. # Pts. Per Inv.	Avg. #Pts. Per Arm	#Enrolled	#Completed
24 (all U.S.)	463	19	5 - -	463	409

Reviewer's Comments: *Only one-eighth (3 of 24) of the centers met the recommended minimum criterion for Phase 3 studies, of 10 patients per arm per center. Only one-fourth (6 of 24) of the centers met the recommended minimum criterion (for Phase 2 studies), of five patients per arm per center.*

8.1.3.3.2 Endpoints

Efficacy: Measurement of IOP.

Safety: Visual acuity, blood pressure, heart rate, cup to disc ratio, visual field, ocular signs and symptoms, pupil diameter, adverse events and laboratory values (10-hematology, 19-chemistry, 2-urinalyses).

8.1.3.3.3 Statistical Considerations

A. Evaluability

All patients receiving treatment will be considered evaluable for safety and analyzed for intent-to-treat. The primary analysis will be performed on only those patients who meet the protocol inclusion/exclusion criteria and on all data points ruled evaluable.

B. Analysis

The statistical objectives of this study are to demonstrate therapeutic equivalence between b.i.d. and t.i.d.- dosed AL04862 and t.i.d.- dosed Dorzolamide, and to demonstrate superiority of AL04862 to placebo.

The primary efficacy endpoint will be the diurnally corrected IOP reduction from baseline at the 8:00 a.m., 10:00 a.m. and 6:00 p.m. time points. Statistical analysis will be based on the average of evaluable eyes. In the primary analysis, the last observation will be carried forward for patients discontinuing due to treatment failure. Analysis of variance will be used to compare the IOP reduction between treatment arms.

C. Power

With 110 evaluable patients per treatment arm, there is greater than an 80% chance that the confidence limits for the pairwise differences between b.i.d.- dosed AL04862, t.i.d.- dosed AL04862 and t.i.d.- dosed Dorzolamide will be less than 1.5 mmHg. This sample size is based upon confidence intervals assuming there is no difference between treatments and a standard deviation of 3.4 mmHg.

With 110 evaluable patients in each of the CAI treatment arms this study will have greater than 90% power to detect a 1.5 mmHg or greater difference between the three CAI treatment arms. With 55 evaluable patients in the placebo treatment arm this study will also have greater than 90% power to detect a difference of 2.0 mmHg or greater between placebo and any of the three CAI treatment arms (2 tailed t-test, alpha=0.05, std=3.4).

8.1.3.4 Results

8.1.3.4.1 Populations enrolled/analyzed

Demographics

	Age				
	Mean	**Std**	**N**	**Min**	**Max**
Treatment					
BID Brinzolamide 1.0%	61	14	115	30	88
TID Brinzolamide 1.0%	64	12	124	28	84
TID Dorzolamide 2.0%	64	13	114	26	88
Placebo	63	13	56	32	85

Treatment

	Bid Brinzol		Tid Brinzol		Tid Dorzol		Placebo	
	N	%	N	%	N	%	N	%
Age								
< 65	60	52	54	44	51	45	25	45
>=65	55	48	70	57	63	55	31	55
Sex								
MALE	55	48	47	38	54	47	30	54
FEMALE	60	52	77	62	60	53	26	47
Race								
CAUCASIAN	92	80	92	74	86	75	41	73
BLACK	11	10	14	11	6	5	6	11
ASIAN	1	1	.	.	1	1	.	.
OTHER	11	10	18	15	21	18	9	16
Iris Color								
BROWN	52	45	58	47	61	54	31	55
HAZEL	17	15	21	17	20	18	5	9
GREEN	9	8	6	5	5	4	2	4
BLUE	34	30	36	29	26	23	18	32
GREY	3	3	3	2	2	2	.	.
Diagnosis								
OH	24	21	33	27	26	23	11	20
POAG	90	78	86	69	87	76	44	79
Pigm Disp	1	1	4	3	.	.	1	2
PsdExFol	.	.	1	1	1	1	.	.

Discontinued Subjects

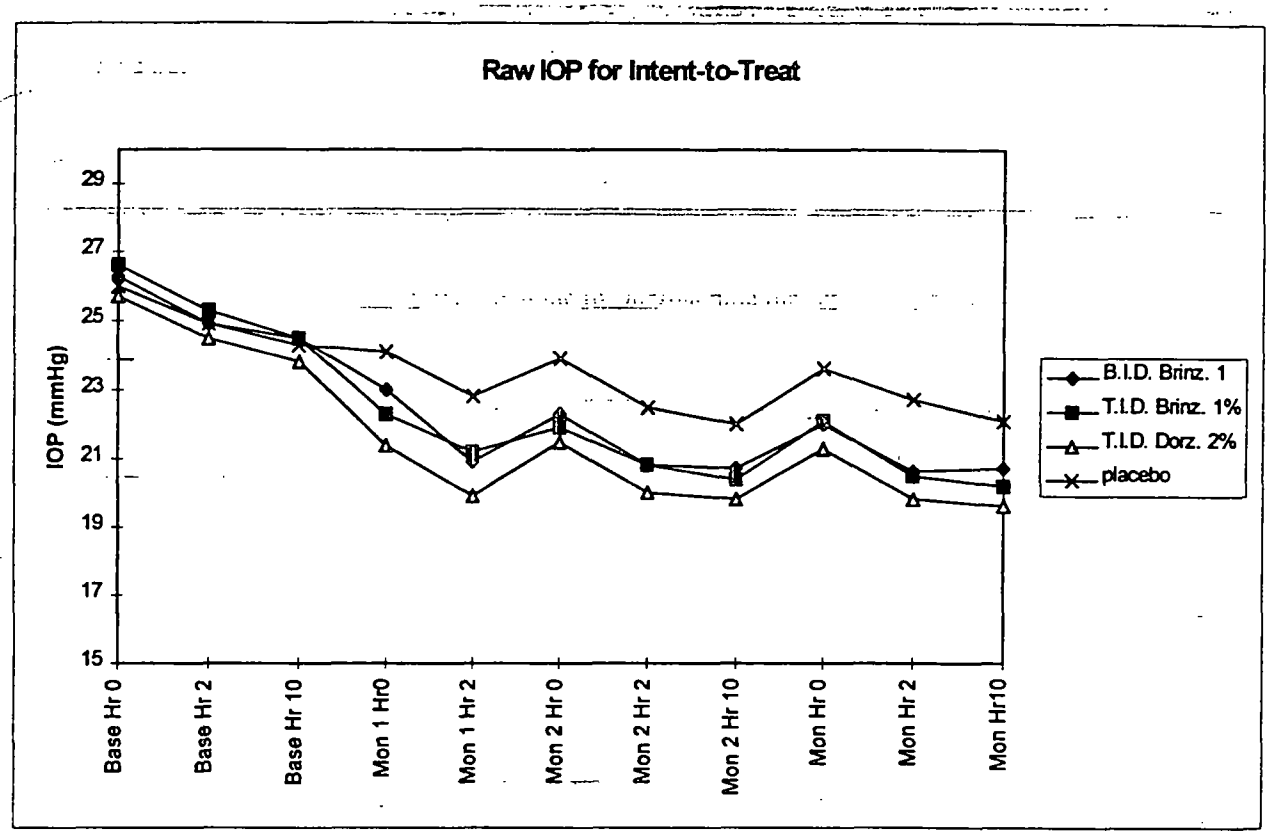
Distribution by Reason and Treatment Group of Patients Discontinued Following Randomization

Reason	Randomized Treatment Group				Total
	Brinzolamide 1% BID	Brinzolamide 1% TID	Dorzolamide 2% TID	Placebo	
Adverse event	4	2	1	2	9
Protocol violation	3	1	3	0	7
Inadequate IOP control	4	2	0	1	7
Lost to follow-up	0	0	1	2	3
Patient decision	0	1	2	0	3
Non-compliance to visit schedule	1	1	0	0	2
Non-compliance to study medication	1	0	0	1	2
Intercurrent illness	1	0	0	0	1
Patient relocation	1	0	0	0	1
TOTALS	15	7	7	6	35

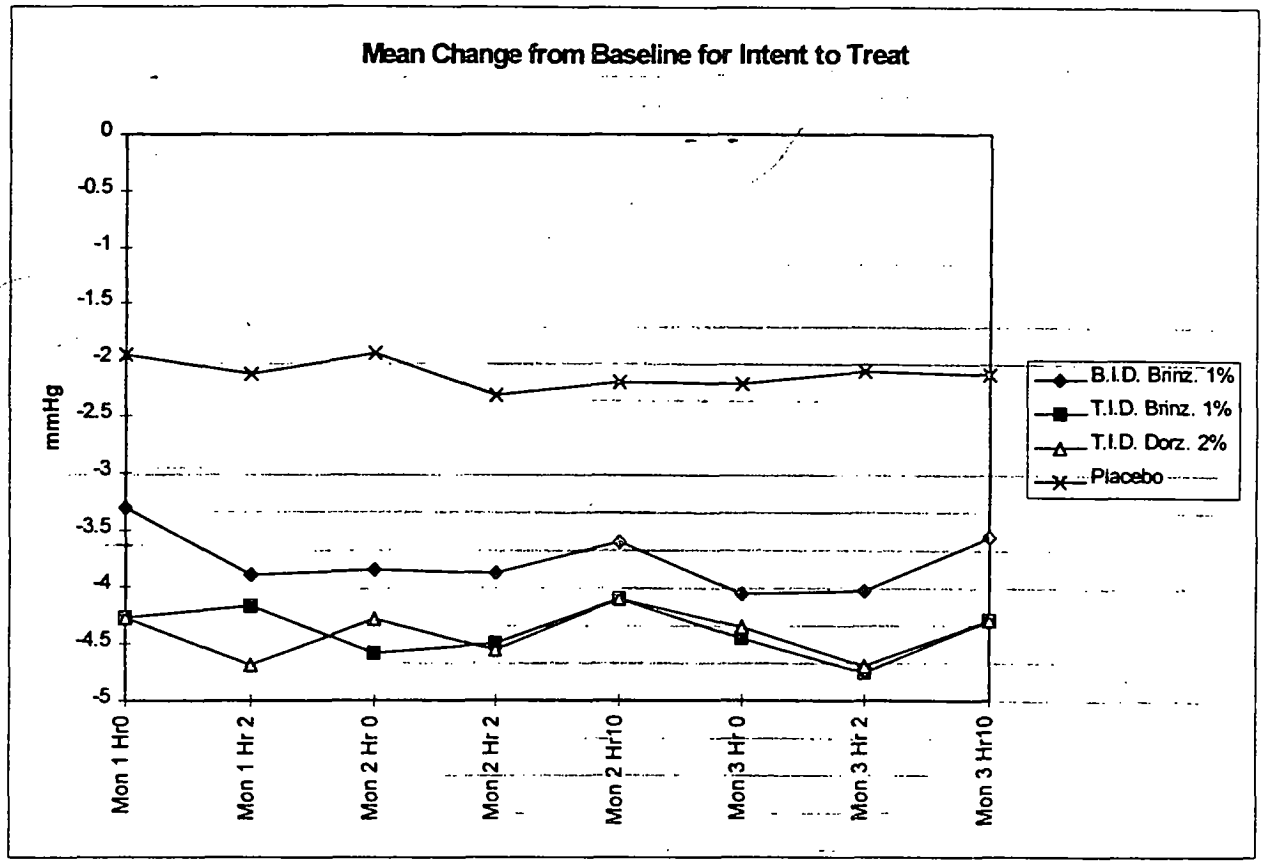
Patients Discontinued Due to Adverse Events

Treatment Group	Investigator #	Patient #	Adverse Event
Brinzolamide 1% B.I.D	394	2002	pain, dyspepsia
	1806	1046	retinal detachment, visual acuity
	1929	1076	reduction
	1973	3306	eye discomfort, blurred vision, eye pain ocular hyperemia, pruritus, foreign body sensation
Brinzolamide 1% T.I.D	1806	1084	myocardial infarction
	1985	3705	dermatitis, urticaria
Dorzolamide 2% T.I.D.	1972	3616	death-motor vehicle accident
Placebo	1208	1205	corneal abrasion
	1208	1230	pneumonia

8.1.3.4.2 Efficacy Endpoint Outcomes



APPEARS THIS WAY
ON ORIGINAL



Reviewer's Comments: *The IOP lowering effect of t.i.d. Brinzolamide and t.i.d. Dorzolamide are statistically and clinically equivalent reducing IOP by approximately 4.7 mmHg at peak and by 4.3 mmHg at trough. B.i.d Brinzolamide lowered IOP by approximately 4.2 mmHg at peak and by 3.7 mmHg at trough. The IOP lowering effect of b.i.d. Brinzolamide is clearly less than that of either t.i.d. Brinzolamide or t.i.d. Dorzolamide at every time point. Placebo reduced IOP by approximately 2.2 mmHg, which is greater than is usually seen with placebo.*

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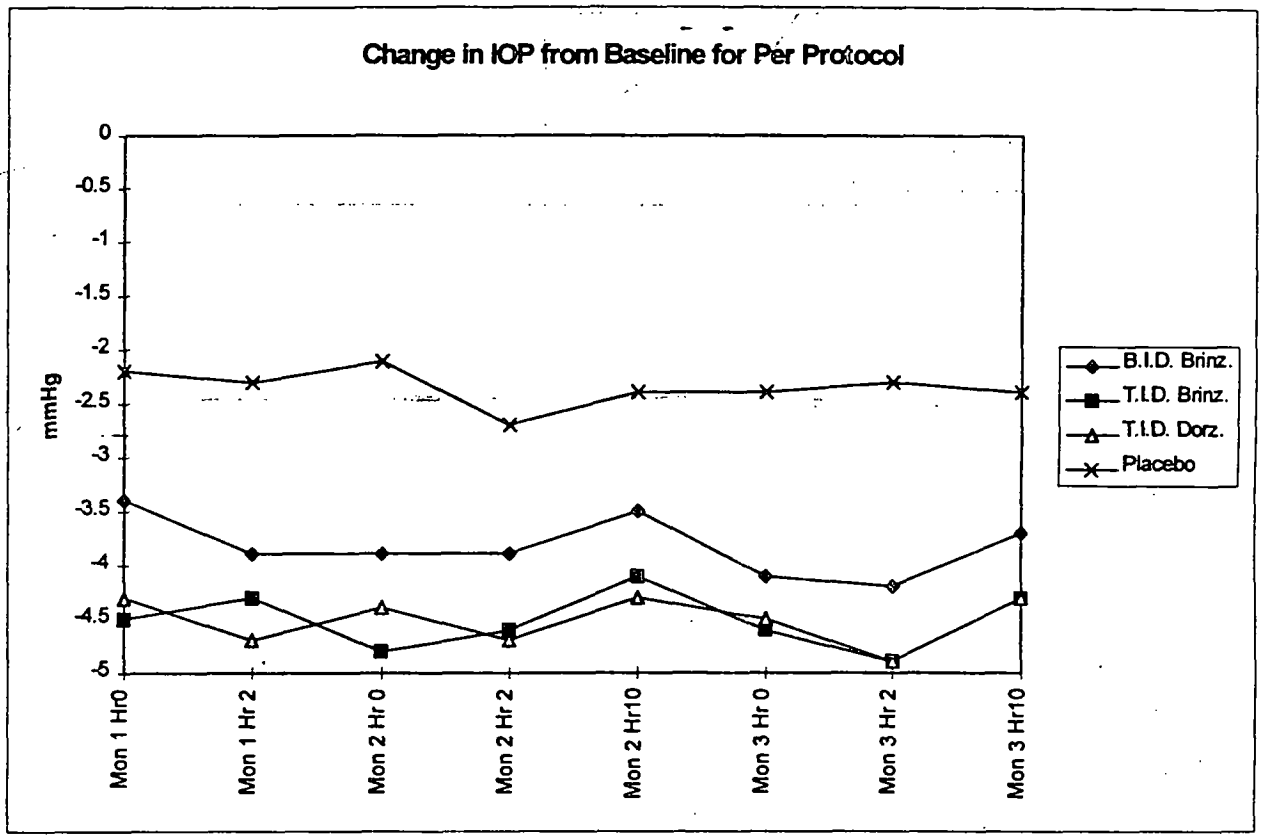
ON ORIGINAL



Reviewer's Comments: *There were no significant differences between the intent-to-treat and the per protocol analyses.*

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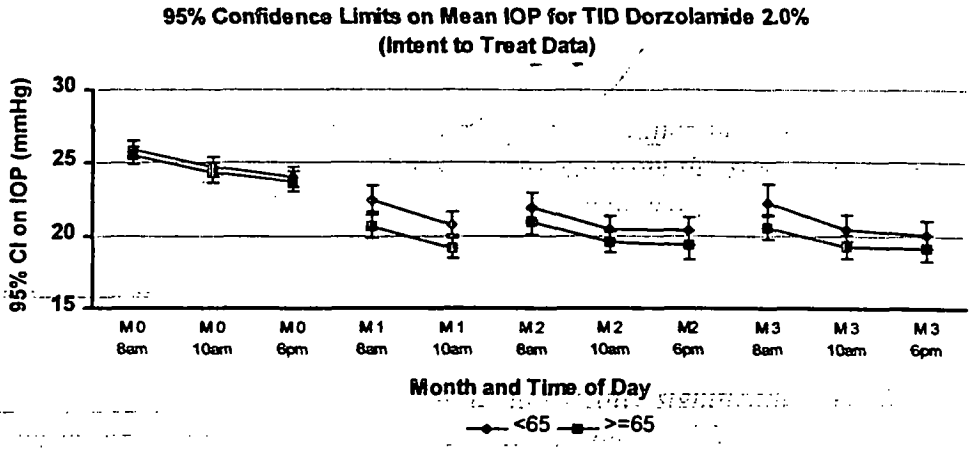
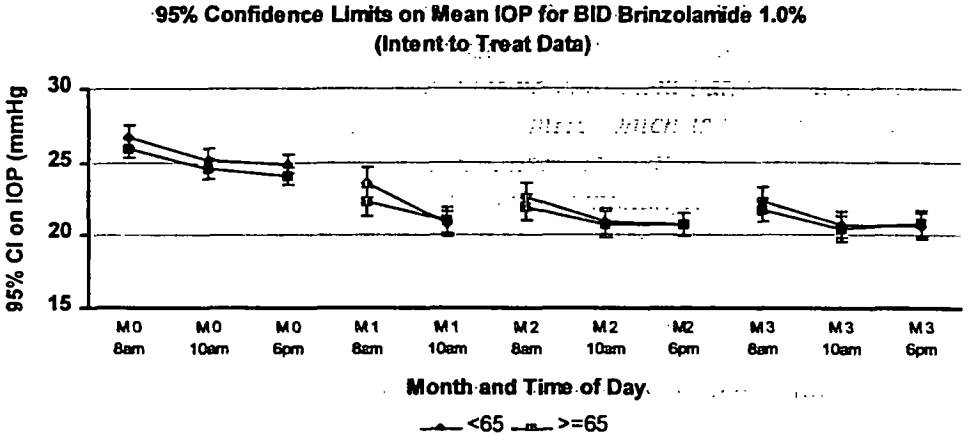
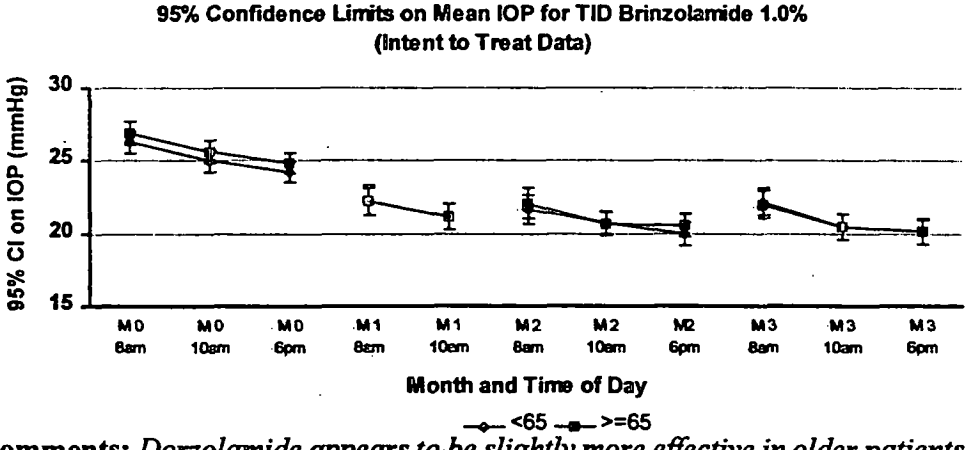
ON ORIGINAL

Mean IOP and Confidence Limit According to Age

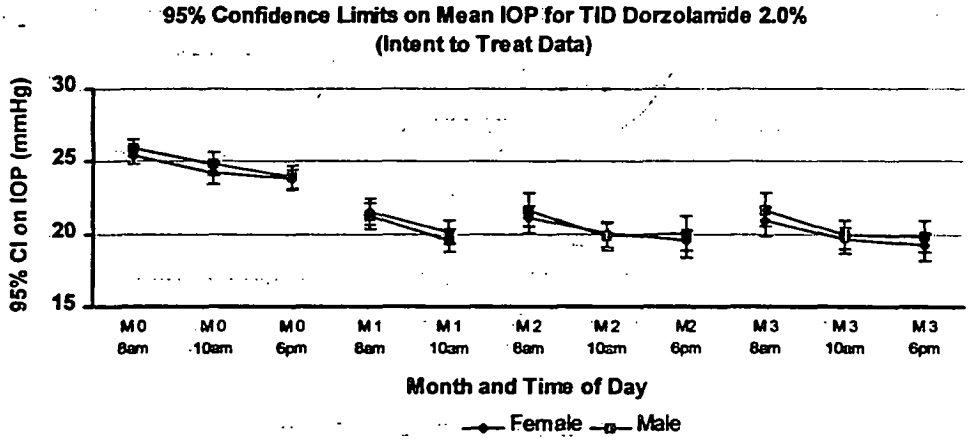


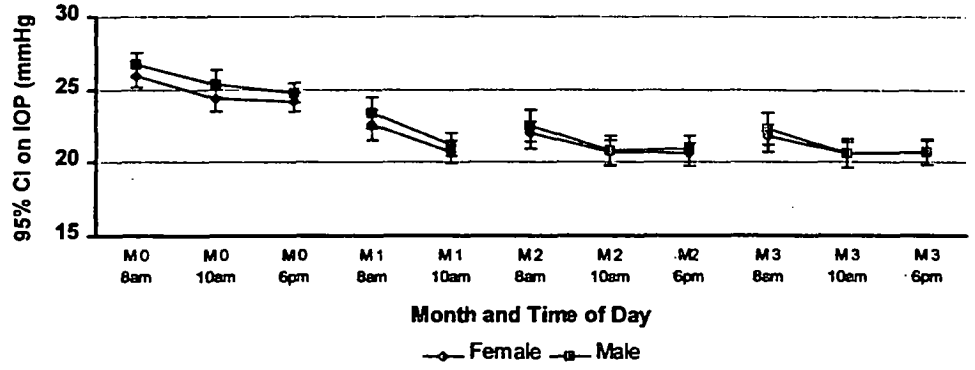


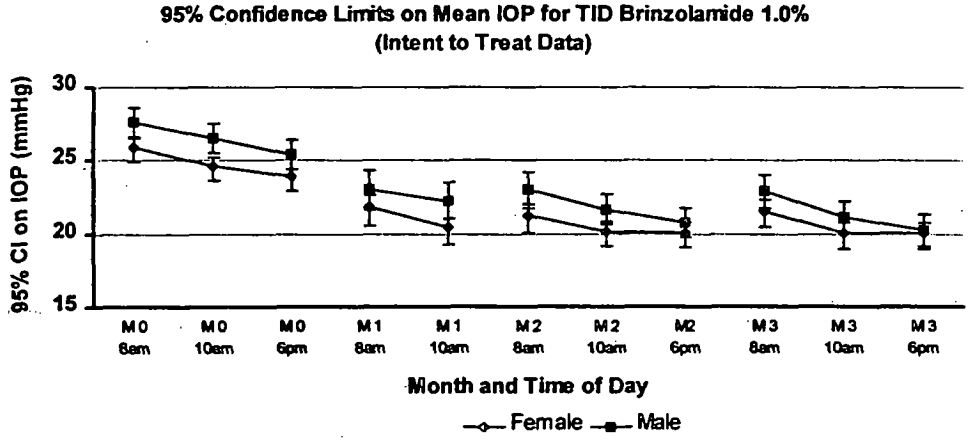


Reviewer's Comments: *Dorzolamide appears to be slightly more effective in older patients and this difference appears to be clinically significant. Brinzolamide does not differentiate between older and younger patients.*

Mean IOP and Confidence Limit According to Gender

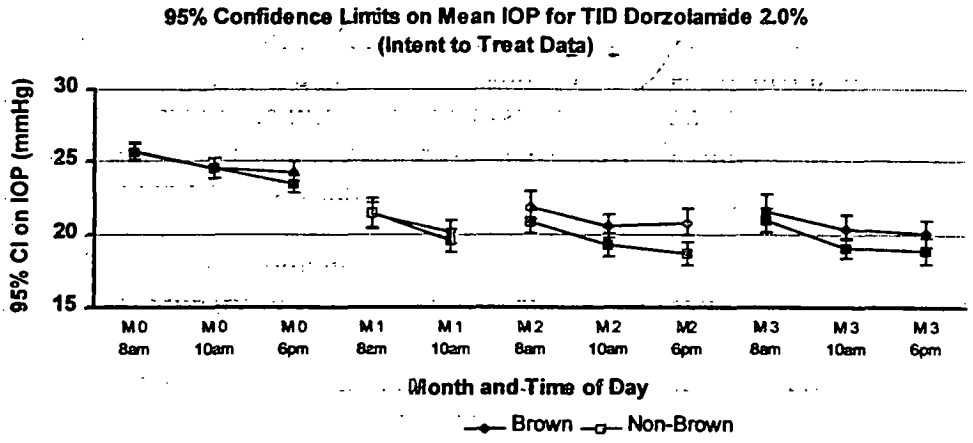


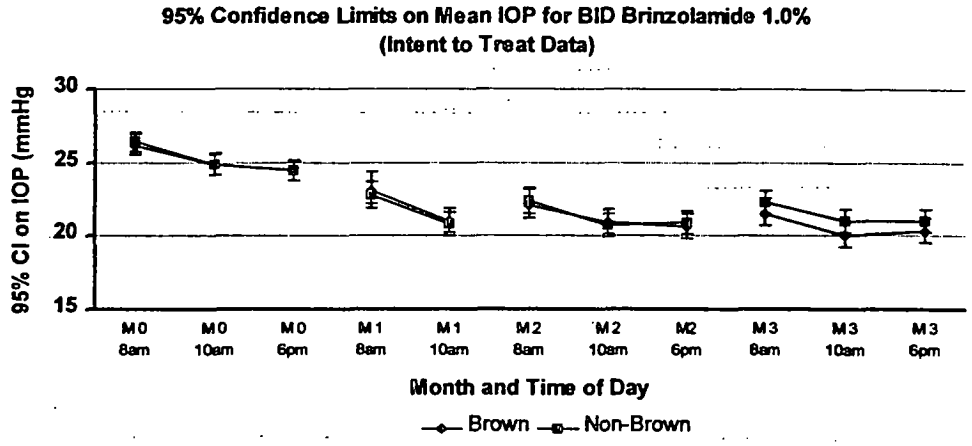


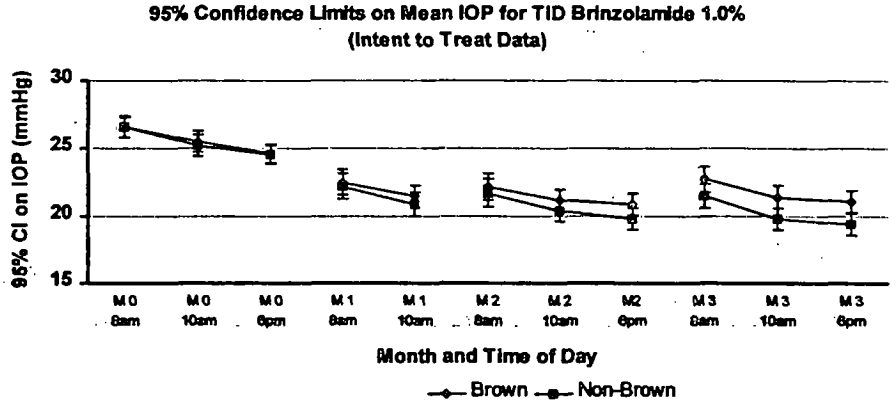


Reviewer's Comments: *With respect to gender, t.i.d.-dosed Brinzolamide appears to be more effective in females and the difference is clinically significant. Dorzolamide does not make a differentiation with respect to gender.*

Mean IOP and Confidence Limit According to Iris Color







Reviewer's Comments: *IOPs were reduced more in light colored irides as compared to dark colored irides and the difference was clinically significant. The exception was the b.i.d.-dosed Brinzolamide group where the reverse was true.*

Analysis of Variance for Intent To Treat Data

Comparison of TID Brinzolamide to Dorzolamide for Intent to Treat Data

Month	1			2			3	
Time	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
TID Brinzolamide 1.0%	-4.3	-4.2	-4.6	-4.5	-4.1	-4.5	-4.8	-4.3
TID Dorzolamide 2.0%	-4.3	-4.7	-4.3	-4.6	-4.1	-4.4	-4.7	-4.3
TID-DORZ	0.0	-0.5	-0.3	-0.1	-0.0	-0.1	-0.1	-0.0
Upper 95% CL	0.71	1.24	0.40	0.76	0.71	0.61	0.65	0.71
Lower 95% CL	-0.70	-0.18	-1.02	-0.66	-0.71	-0.81	-0.77	-0.71

Comparison of BID Brinzolamide to Dorzolamide for Intent to Treat Data

Month	1			2			3	
Time	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
BID Brinzolamide 1.0%	-3.3	-3.9	-3.9	-3.9	-3.6	-4.1	-4.0	-3.6
TID Dorzolamide 2.0%	-4.3	-4.7	-4.3	-4.6	-4.1	-4.4	-4.7	-4.3
BID-DORZ	1.0	-0.8	-0.4	-0.7	0.5	0.3	0.7	0.7
Upper 95% CL	**1.68**	**1.50**	**1.14**	**1.38**	**1.23**	**1.01**	**1.37**	**1.44**
Lower 95% CL	0.27	0.09	-0.29	-0.05	-0.20	-0.43	-0.07	-0.00

Comparison of BID Brinzolamide to TID Brinzolamide for Intent to Treat Data

Month	1			2			3	
Time	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
BID Brinzolamide 1.0%	-3.3	-3.9	-3.9	-3.9	-3.6	-4.1	-4.0	-3.6
TID Brinzolamide 1.0%	-4.3	-4.2	-4.6	-4.5	-4.1	-4.5	-4.8	-4.3
BID-TID	1.0	0.3	0.7	0.6	0.5	0.4	0.7	0.7
Upper 95% CL	**1.68**	0.97	**1.45**	**1.33**	**1.23**	**1.11**	**1.43**	**1.44**
Lower 95% CL	0.27	-0.44	0.02	-0.10	-0.20	-0.33	-0.01	0.00

Reviewer's Comments: *To show equivalence, the 95% confidence interval should be within 1.5 mmHg for **all** time points and within 1 mmHg for the **majority** of time points measured. When one looks at the confidence intervals for comparison of t.i.d.-dosed Brinzolamide and t.i.d.-dosed Dorzolamide, this is the case, hence, in this study, equivalence between the two has been established. This is clearly not the case when b.i.d.-dosed Brinzolamide is compared to either t.i.d.-dosed Brinzolamide or t.i.d.-dosed Dorzolamide. Therefore, in this study, equivalence has not been established between either b.i.d.-dosed Brinzolamide and t.i.d.-dosed Brinzolamide or b.i.d.-dosed Brinzolamide and t.i.d.-dosed Dorzolamide. B.i.d.-dosed Brinzolamide is inferior to both t.i.d.-dosed Brinzolamide and t.i.d-dosed Dorzolamide with respect to IOP lowering effect.*

8.1.3.4.3 Safety Comparisons

Coded Adverse Events	Brinzolamide 1.0% BID N=134		Brinzolamide 1.0% TID N=133		Dorzolamide 2.0% TID N=131		Placebo TID N=65	
	N	%	N	%	N	%	N	%
OCULAR								
Discomfort	4	3	4	3	16	12	1	2
Blurred Vision	4	3	6	5	1	<1	1	2
Discharge NOS	3	2	1	<1	0		0	
Foreign Body Sensation	3	2	1	<1	0		0	
Pruritus	2	2	2	2	0		1	2
Hyperemia	3	2	0		3	2	1	2
Sticky Sensation	2	2	0		0		1	2
Vitreous Disorder	2	2	1	<1	0		1	2
Optic Nerve Disorder	2	2	0		1	<1	0	
Decreased Visual Acuity	2	2	0		0		0	
Dry Eye	2	2	3	2	0		1	2
Pain	2	2	0		0		2	3
Subjunctival Hemorrhage	0		2	2	1	<1	0	
Conjunctivitis	0		1	<1	0		1	2
Corneal Abrasion	0		1	<1	0		1	2
Hemorrhage	0		0		0		1	2
Accidental Injury	0		0		0		1	2
Retinal Tear	0		0		0		1	2
Vision Change	0		0		1	<1	2	4
Vitreous Detachment	0		0		0		1	2
Keratitis	1	<1	2	2	0		1	2
Blepharitis	0		0		0		1	2
Ocular Disorder	0		0		0		1	2
NONOCULAR								
Body as a Whole								
Headache	3	2	4	3	2	2	3	5
Pain	2	2	4	3	2	2	3	5
Infection	3	2	3	2	7	5	1	2
Digestive								
Diarrhea	3	2	2	2	2	2	0	
Nausea	3	2	1	<1	0		0	
Dry Mouth	2	2	1	<1	0		0	
Special Senses								
Taste Perversion	5	4	9	7	7	5	0	

Reviewer's Comments: *The above table represents percentage of patients reporting ocular and nonocular adverse events occurring with overall incidence greater than 1%. The most common adverse events were discomfort, blurred vision and taste perversion.*

Summary Statistics for Visual Acuity Change from Baseline to Last Visit

	No Change or Improvement		One Snellen Line Decrease		Two Snellen Line Decrease		Greater than Two Snellen Line Decrease		Total
Treatment	N	%	N	%	N	%	N	%	N
BID BRINZOL	84	63.6	40	30.3	5	3.8	3	2.3	132
TID BRINZOL	78	59.1	46	34.8	7	5.3	1	0.8	132
TID DORZOL	89	69.5	36	28.1	2	1.6	1	0.8	128
PLACEBO	44	71.0	14	22.6	4	6.5	0	0	62
Total	295	65.0	136	30.0	18	4.0	5	1.1	454

Reviewer's Comments: *There were no clinically significant differences in change in visual acuity from baseline to last visit between the groups.*

Ocular Signs

Eyelids/Conjunctiva, Cornea, Iris/Anterior Chamber, Lens, Vitreous

Reviewer's Comments: *There were no significant differences between groups with respect to these areas of the eye, however, comparative data was unavailable for 7 patients. (2% of evaluable patients)*

Pupil

Reviewer's Comments: *There were no significant differences within groups or between groups with respect to change in pupil diameter from baseline to exit of the study.*

Dilated Fundus Exam

Reviewer's Comments: *There were no significant differences between treatment groups in the*

dilated fundus exam which includes and examination of the retina/macula/choroid, vitreous, lens, optic nerve, disc pallor, and cup/disc ratio. However, comparable data was unavailable for 20 patients. (4% of evaluable patients)

Visual Fields

Reviewer's Comments: *There were no clinically significant differences between treatment groups with respect to change in visual field from baseline to exit from the study, however, comparative data was unavailable on 38 patients. (8% of evaluable patients)*

Cardiovascular Data

Blood Pressure

Reviewer's Comments: *The sponsor reported a statistically significant effect on systolic blood pressure between Brinzolamide 1% b.i.d. and Dorzolamide 2% and between placebo and Dorzolamide 2%; Dorzolamide slightly decreasing systolic blood pressure and Brinzolamide 1% and placebo slightly increasing systolic blood pressure. However, when individual patient listings for systolic blood pressure were looked at, there was no consistent pattern found. The differences reported by the sponsor were differences of a few mmHg which is within acceptable limits for variability of blood pressure due to the inherent imprecise nature of the sphygmomanometer, combined with the human error or variability from technician to technician. Hence, in this reviewer's opinion, there are no significant differences between treatment groups with respect to systolic or diastolic blood pressure.*

Heart Rate

Reviewer's Comments: *There were no significant differences in heart rate between treatment groups and no significant adverse results.*

Laboratory Data

Reviewer's Comments: *There were no clinically significant trends within or between treatment groups.*

8.1.3.5 Reviewer's Conclusions of Study # 3 Results

1. In this study, equivalence was demonstrated between t.i.d.-dosed Brinzolamide 1% and Dorzolamide 2%. B.i.d.-dosed Brinzolamide 1% was not shown to be equivalent to t.i.d.-dosed Brinzolamide 1% or Dorzolamide 2% and had less effect on IOP-lowering than either.

2. With only 3 of the 24 study sites meeting the recommended minimum requirement of 10 patients per arm per center, it would have been desirable to have fewer study sites with more patients enrolled per site or more patients enrolled in the 24 existing sites.

3. The sponsor should provide an explanation for the role of Investigator # 1941 in the study. As previously mentioned, it was stated that no patients were randomized to this investigator, yet, it was reported that one patient completed the study under Inv. # 1941.

4. The most commonly reported adverse experiences were discomfort, blurred vision, and taste perversion.

8.1.4 **Reviewer's Trial # 4**
Sponsor's Protocol C-95-48

A Three-Month, Multicenter, Triple-Masked, Primary Therapy Study of the Efficacy and Safety of BID and TID Dosed Brinzolamide 1% Ophthalmic Suspension Compared to TID Dosed Dorzolamide 2% and BID Dosed Timolol 0.5% in the Treatment of Patients With Primary Open-Angle Glaucoma or Ocular Hypertension

8.1.4.1 **Objective/Rationale**

The primary objective was to compare the safety and IOP-lowering efficacy of b.i.d.-dosed brinzolamide 1%, t.i.d.-dosed Brinzolamide 1%, t.i.d.-dosed Dorzolamide 2%, and b.i.d.-dosed Timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension.

8.1.4.2 **Design**

This study was a multicenter (46 sites), triple-masked, pivotal, efficacy trial in which data from 572 and 512 patients were included in the safety and efficacy analyses, respectively. The patients were randomized into one of four (4) treatment groups (Brinzolamide 1.0% b.i.d., Brinzolamide 1.0% t.i.d., Dorzolamide 2.0% t.i.d. or Timolol 0.5% b.i.d.) in an unequal 2:2:2:1 ratio, respectively. The study design included a five day to three-week run-in phase in which all patients underwent a washout from all ocular hypotensive therapy, followed by two diurnal IOP eligibility examinations. Treatment with masked test medications was for three (3) months with IOP evaluations at 8:00 a.m. and 10:00 a.m. at Month 1 and 8:00 a.m., 10:00 a.m. and 6:00 p.m. at Months 2 and 3. Efficacy data was obtained by comparing on-therapy IOP measurements to the average baseline corresponding IOP values obtained at Eligibility Visits 1 and 2 (i.e., 8:00 a.m., 10:00 a.m. and 6:00 p.m.). Safety data was generated from adverse events, visual acuity, biomicroscopic exams, heart rate, blood pressure and laboratory (blood chemistry, hematology and urinalysis) evaluations.

The primary efficacy endpoint was the diurnally-corrected IOP reduction from baseline at the 8:00 a.m., 10:00 a.m. and 6:00 p.m. time points. Analysis of variance was used to compare the average IOP reduction between the treatment groups. Confidence intervals (95%) were used to establish statistical equivalence between the treatment groups.

8.1.4.3 Protocol

General Study Design

Group	Study Phase		
	Run-In Phase		Triple-Masked Treatment Phase
	Washout	Eligibility	(Months 1, 2 and 3)
Brinzolamide 1.0% BID	5 Days - 3 Weeks	2 Visits (1 Week Apart)	Brinzolamide 1.0% BID
Brinzolamide 1.0% TID			Brinzolamide 1.0% TID
Dorzolamide 2.0% TID			Dorzolamide 2.0% TID
Timolol 0.5% BID			Timolol 0.5% BID

Phase I - Run-in (Washout and Eligibility Visits 1 and 2)-Same as Study # 3

Phase II - Triple-Masked Treatment Phase (Months 1, 2 and 3)-Same as Study # 3

Study Plan-Same as Study # 3

8.1.4.3.1 Population-Same as Study # 3

8.1.4.3.2 Endpoints-Same as Study # 3

8.1.4.3.3 Statistical Considerations-Same as Study # 3

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8.1.4.4 Results

8.1.4.4.1 Populations enrolled/analyzed

Demographics Statistics for Intent to Treat Data

	Age				
	Mean	Std	N	Min	Max
Treatment					
BID Brinzolamide 1.0%	62.7	11.9	165	27	86
TID Brinzolamide 1.0%	61.1	12.2	169	31	83
TID Dorzolamide 2.0%	62.5	12.8	165	19	86
BID Timolol 0.5%	60.6	11.2	73	39	85

	Treatment							
	BID Brinzol 1%		TID Brinzol 1%		TID Dorzol 2%		BID Timolol 0.5%	
	N	%	N	%	N	%	N	%
Age								
< 65	87	52.7	88	52.1	79	47.9	40	54.8
> =65	78	47.3	81	47.9	86	52.1	33	45.2
Sex								
MALE	74	44.8	87	51.5	76	46.1	35	47.9
FEMALE	91	55.2	82	48.5	89	53.9	38	52.1
Race								
CAUCASIAN	133	80.6	140	82.8	135	81.8	55	75.3
BLACK	24	14.5	23	13.6	22	13.3	16	21.9
ASIAN	.	.	1	0.6	.	.	.	.
OTHER	8	4.8	5	3.0	8	4.8	2	2.7
Iris Color [1]								
BROWN	82	50.0	77	45.6	80	48.5	36	49.3
HAZEL	21	12.8	15	8.9	27	16.4	9	12.3
GREEN	11	6.7	9	5.3	7	4.2	3	4.1
BLUE	45	27.4	57	33.7	45	27.3	21	28.8
GREY	5	3.0	11	6.5	6	3.6	4	5.5
Diagnosis								
OH	61	37.0	76	45.0	64	38.8	25	34.2
POAG	102	61.8	92	54.4	97	58.8	47	64.4
Pigm Disp	1	0.6	1	0.6	2	1.2	1	1.4
PsdExFol	1	0.6	.	.	2	1.2	.	.

Patient 6502 had a missing value for iris color.

US-Investigators:

Inv. No.	Name/Address	# Enrolled	# Completed
479	Robert Allen, M.D. 1101 East Marshall Street Sanger Hall, Room 8020 Richmond, VA 23298-0262	1	1
1404	Charles B. Campbell, III, M.D. Piedmont Research Associates 1902 S. Hawthorn Road, Suite 306 Winston-Salem, NC 27103	26	23
1552	Carl Camras, M.D. Univ. of Nebraska Medical Center 600 South 42nd Street Omaha, NE 68198	20	18
1971	G. Richard Cohen, M.D. West Boca Professional Building 9988 Central Park Blvd., N. Suite 204 Boca Raton, FL 33428	14	9
1974	David L. Cook, M.D. 2848 Niles Road St. Joseph, MI 49085	21	21
1709	Amber Dobler, M.D. Ophthalmology Associates 1201 Summit Avenue Ft. Worth, TX 76102	27	25
1930	Robert Friedman, M.D. 7800 W. Oakland Park Blvd., #206 Sunrise, FL 33351	13	12
1945	Barrett Haik, M.D. Univ. of TN, Dept. of Ophthalmology 956 Court Avenue, Room D-223 Memphis, TN 38163	3	3
1736	Kenneth Haik, M.D. 1407 Carrollton Avenue New Orleans, LA 70118	16	14

Investigators Cont'd:		# Enrolled	# Completed
1944	David Karp, M.D. 4004 Dupont Circle Louisville, KY 40207	16	12
943	Robert A. Laibovitz, M.D. 3307 Northland, Suite 470 Austin, TX 78731	34	34
432	Norman S. Levy, M.D. 7106 NW 11th Place, Suite B Gainesville, FL 32605-3192	7	7
1473	Thomas K. Mundorf, M.D. 1718 East 4th Street, Suite 902 Charlotte, NC 28204	21	21
1978	Earl L. Nelson, M.D. Eye Surgery Center of Louisiana 560 Read Blvd., Suite 900 New Orleans, LA 70127	21	19
1915	Steven R. Shields, M.D. 1755 South Grand Blvd. Saint Louis, MO 63104	3	2
1990	Peter Skov, M.D. West Bank Medical Clinic Suite 407 Marrero, LA 70072	16	11
271	Robert H. Stewart, M.D. 2855 Gramercy Houston, TX 77025	77	74
1913	Jeffrey Wasserstrom, M.D. 5565 Grossmont Center Drive Building 3, Suite 551 La Mesa, CA 91942-3024	33	29

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Non-US Investigators:

Inv. No	Name/Address	# Enrolled	# Completed
1729	Dr. Hans-Joachim Belger Domhof 15 - 21 D-48683 Ahaus GERMANY	5	5
1487	Prof. Alain Bron Service d'ophtalmologie Hôpital Général 3 rue du Faubourg Raines F - 21030 Dijon FRANCE	14	13
1969	Dr. Howard Cohn 23, Bld. Delessert F-75116 Paris FRANCE	10	9
707	Dr. Jacqueline Collignon CHU Sart Tilman Service d'Ophthalmologie Domaine du Sart Tilman B-4000 Liège BELGIUM	6	4
906	Prof. Jose Cunha-Vaz Clinica Optalmologica Hospital da Universidade P-3049 Coimbra	6	3
1989	Dr. Jean-Claude Dascotte 84, Bd de la République F-59120 Loos FRANCE	2	2
645	Dr. Philippe Demailly Institut du Glaucome 7, Rue Pierre Larousse F-75015 Paris FRANCE	20	20
1906	Dr. Michèle Detry Hôpital Saint Luc Service d'Ophthalmologie Av. Hippocrate 10 B-1000 Bruxelles BELGIUM	7	4

1940	Dr. Pieter De Waard Oogziekenhuis Rotterdam Schiedamse Vest 180 NL-3011 BH Rotterdam NETHERLANDS	7	7
1898	Prof. Jean-Luc George Service d'Ophtalmologie Hôpital Brabois Rue du Morvan F - 54511 Vandoeuvre FRANCE	18	16
1988	Dr. Denis Gruber 34, Place de l'Hôtel de Ville F-76600 Le Havre FRANCE	3	2
1686	Dr. Pascale Hamard Service II Hôpital des XV - XX 28 rue de Charenton F - 75571 Paris Cedex 12 FRANCE	14	14
1824	Prof. Philippe Kestelyn Universitair Ziekenhuis Dienst Oogheelkunde De Pintelaan 185 B-9000 Gent BELGIUM	6	5
1896	Dr. Gilles Lesieur 4 rue Patus Crémat F - 81000 Albi FRANCE	9	9
1895	Prof. François Malecaze Service d'Ophtalmologie Hôpital Purpan place du Dr. Baylac F - 31059 Toulouse Cedex FRANCE	2	1
866	Dr. Andrews Matt Am Weidenbruch 145 D-51061 Köln GERMANY	10	10

1711	Prof. Ulrich Mester Knappschaftskrankenhaus Sulzbach Augenklinik In der Klinik 10 D-66280 Sulzbach/Saar GERMANY	22	20
1732	Prof. Jean-Philippe Nordmann Service d'Ophtalmologie Hôpital Tenon 4, rue de la chine F - 75970 Paris Cedex 20 FRANCE	2	2
1897	Prof. Jean-Paul Renard Hôpital du Val de Grace 74, Bd. de Port Royal F - 75230 Paris Cedex 05 FRANCE	4	4
1829	Dr. Danièle Sangers Esdoornenlaan 14 B-3090 Overijse BELGIUM	6	4
1961	Prof. Einar Stefansson Clinic of Ophthalmology Öldugata 17 Landakot Hospital ICE-101 Reykjavik ICELAND	20	15
1730	Prof. Marie-José Tassignon Universitair Ziekenhuis Dienst Oogheelkunde Wilrijkstraat 10 B-2560 Edegem BELGIUM	5	3
1497	Prof. Wulf-Dieter Ulrich Roßmarktsche Straße 16 D-04552 Borna GERMANY	2	2
1917	Dr. Carl Verdonck Tolstraat 64 B-2000 Antwerpen BELGIUM	3	3

Total # Investigators	# Patients	Avg.# Pts. Per Inv.	Avg. # Pts. Per Arm	#Enrolled	#Completed
U.S.-18	369	21	5	369	335
Non-US-24	203	9	2	203	177

Reviewer's Comments: *Only one of the U.S. centers met the recommended minimum criterion of 10 patients per arm per center for Phase 3 studies. Only one-half (9 of 18)of the U.S centers met the recommended minimum criterion (for Phase 2 studies) of 5 patients per arm per center. None of the European centers met the recommended minimum criterion of 10 patients per arm per center for Phase 3 studies and only one-eighth (3 of 24) of the European centers met the recommended minimum criterion (for Phase 2 studies) of 5 patients per arm per center.*

Discontinued Subjects

Distribution by Reason and Treatment Group of Patients Discontinued Post Randomization

Randomized Treatment Group					
Reason	Brinzolamide 1% BID	Brinzolamide 1% TID	Dorzolamide 2% TID	Timolol 0.5% BID	Total
Adverse Event	3	5	5	0	13
Inadequate IOP Control	2	4	1	3	10
Patient Decision	3	2	0	0	5
Lost to Follow-up	0	1	1	0	2
Non-compliance to Study Medication	0	0	0	1	1
Protocol Violation	2	4	3	0	9
TOTALS	**10**	**16**	**10**	**4**	**40**

Patients Discontinued Due to Adverse Events

Investigator No.	Patient No.	Treatment Group	Reason for Discontinuation
1711	5409	Brinzolamide 1% BID	Adverse event (keratoconjunctivitis)
1895	6502		Adverse event (kidney pain)
1913	4107		Adverse event (headache)
1473	3319	Brinzolamide 1% TID	Adverse event (depression)
1709	4821		Adverse event (bronchitis, asthma, infection)
1709	4827		Adverse event (dermatitis)
1736	3502		Adverse event (carcinoma)
1898	5814		Adverse event (blurred vision)
1709	4817	Dorzolamide 2% TID	Adverse event (asthma, dyspnea, infection)
1709	4818		Adverse event (dyspnea, chest pain, tachycardia, anxiety)
1711	5403		Adverse event (eye discomfort)
1898	5802		Adverse event (eye discomfort, hyperemia and pruritus, lid edema, headache)
1944	4209		Adverse event (periorbital edema and erythema)

Distribution by Reason and Treatment Group of Patients Excluded From Efficacy Analysis

Reason	Randomized Treatment Group				Total
	Brinzolamide 1% BID	Brinzolamide 1% TID	Dorzolamide 2% TID	Timolol 0.5% BID	
IOP asymmetry	5	6	5	4	20
Non-qualifying IOP	4	6	4	2	16
Contraindicated concomitant medication	5	6	2	2	15
No on-therapy IOP data	1	3	4	0	8
Patient discontinued prior to using study drug	0	0	1	1	2
Inadequate washout	0	0	1	0	1
TOTALS	**15**	**21**	**17**	**9**	**62**

Evaluated for Efficacy	**150**	**148**	**149**	**65**	**512**
Evaluated for Safety	**165**	**169**	**165**	**73**	**572**

Reviewer's Comments: *Two patients were excluded from both analyses because they discontinued prior to utilizing any test medication. (1 pt. from Dorz. 2% group; one from Timolol 0.5% group.)*

APPEARS THIS WAY
ON ORIGINAL