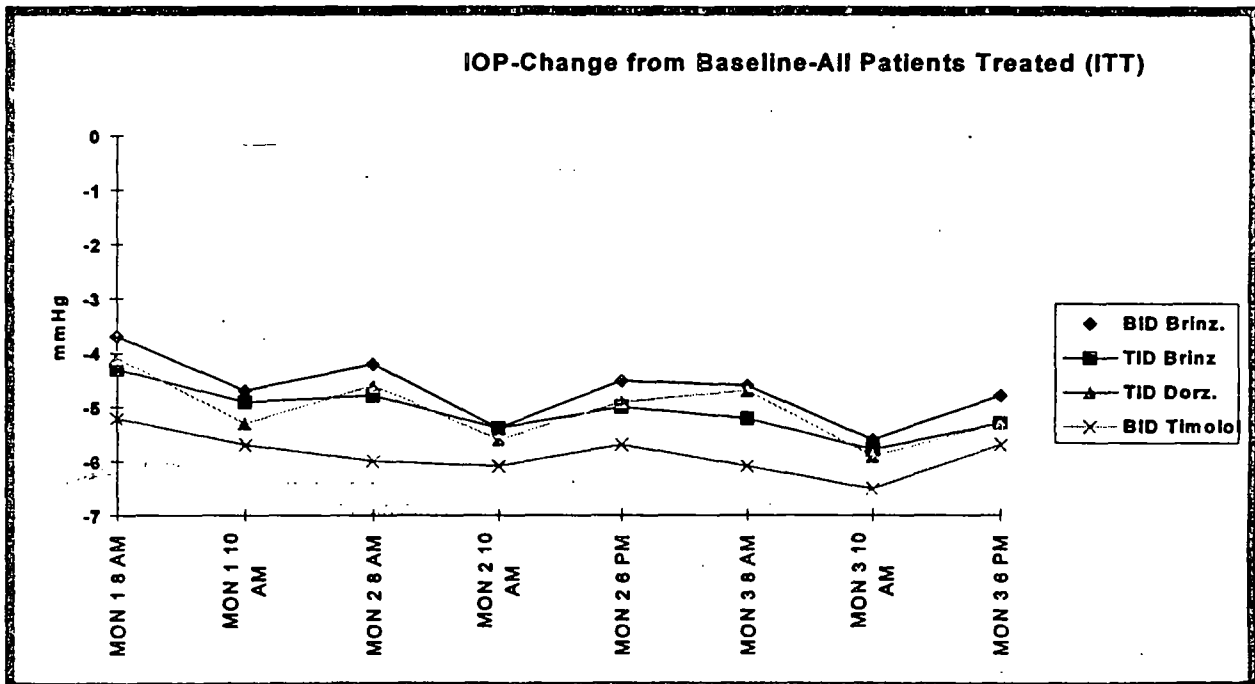
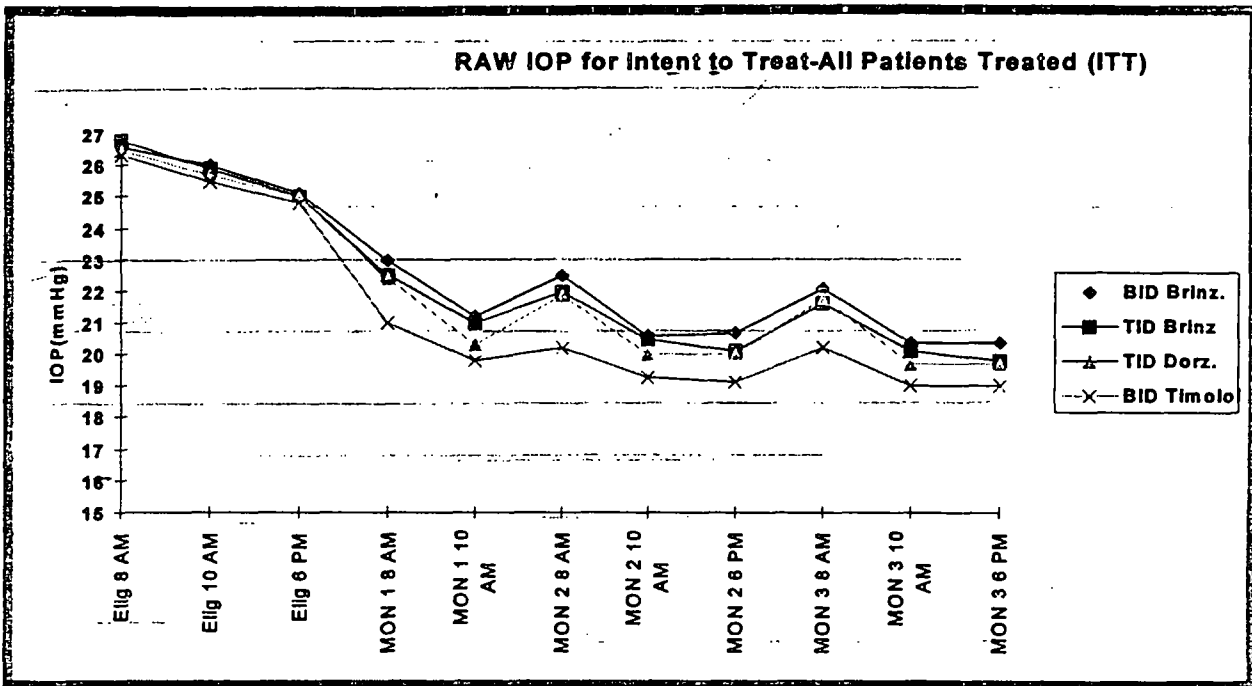


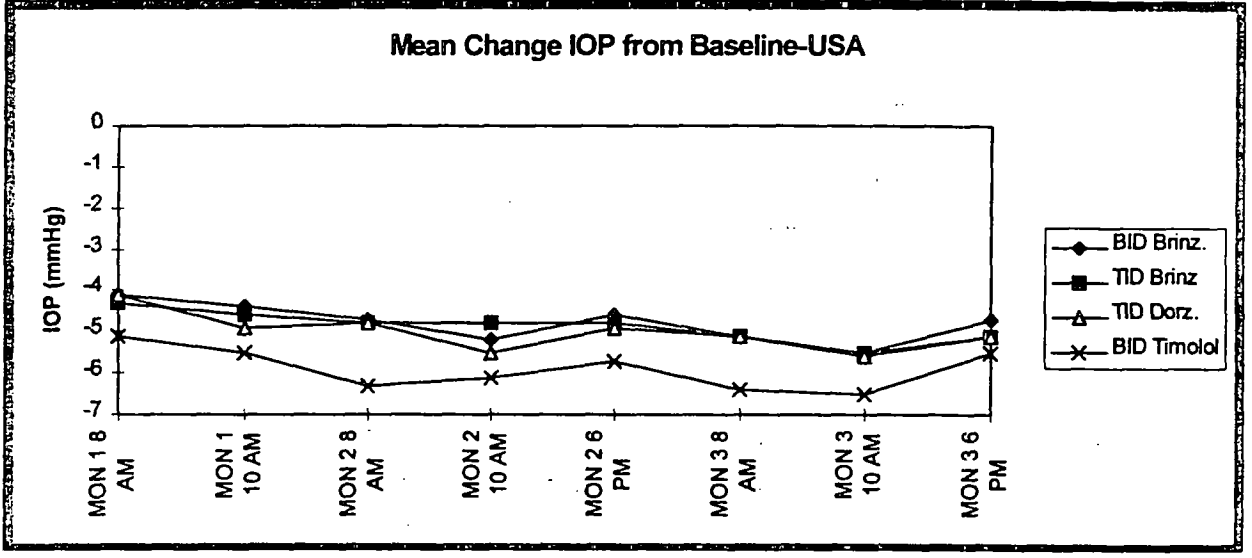
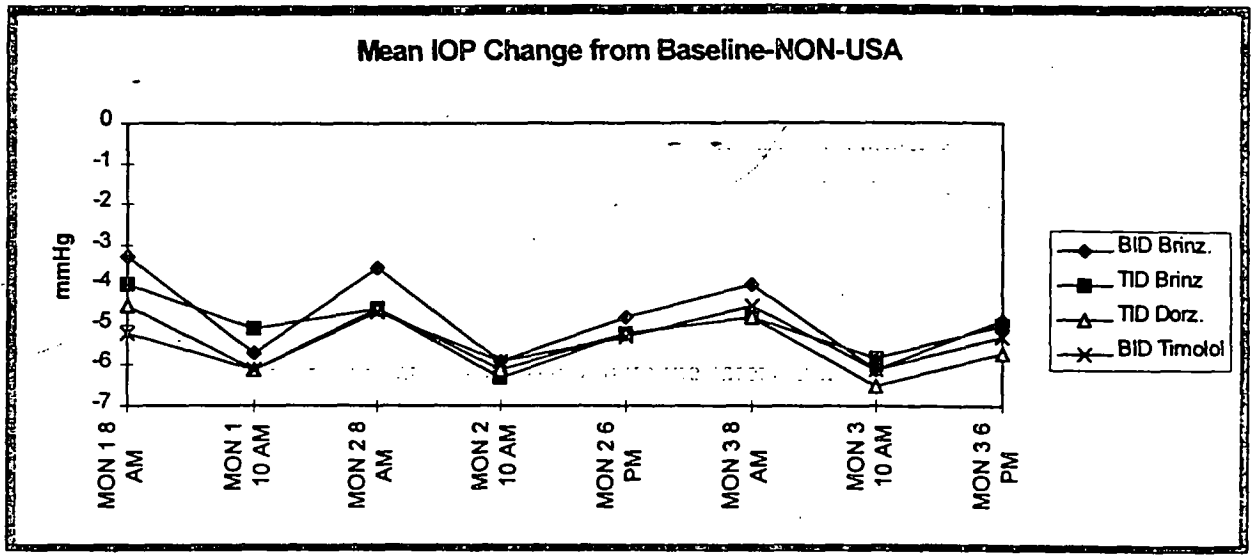
8.1.4.4.2 Efficacy Endpoint Outcomes



**Reviewer's Comments:** *B.i.d.-dosed Brinzolamide 1% lowers IOP from baseline by approximately 5.2 mmHg at peak. T.i.d.-dosed Brinzolamide 1% lowers IOP from baseline by approximately 5.4 mmHg at peak. Dorzolamide 2% lowers IOP from baseline by approximately 5.6 mmHg. Timolol 0.5% lowers IOP from baseline by approximately 6.1 mmHg. From the graphs, it is clear that the IOPs in the b.i.d.-dosed Brinzolamide group are consistently lower at each time point than any other group with the exception of timepoint 10 a.m. in Month 2, where it is equivalent to t.i.d.-dosed Brinzolamide 1%.*

MAC  
absolute value

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**Reviewer's Comments:** *In general, the results of the US study groups were similar to the results of the non-US study groups.*

**IOP Descriptive Statistics for Intent to Treat Data****VISIT**

Raw IOP			ELIG 8AM	ELIG 10AM	ELI G 6PM	MON1 8AM	MON1 10AM	MON2 8AM	MON2 10AM	MON2 6PM	MON3 8AM	MON3 10AM	MON3 6PM
<b>Treatment</b>													
BID Brin 1%	IOP	Mean	26.6	26.0	25.1	23.0	21.2	22.5	20.6	20.7	22.1	20.4	20.4
		n	165	165	165	164	163	156	156	155	155	155	154
TID Brin 1%	IOP	Mean	26.8	25.9	25.0	22.5	21.0	22.0	20.5	20.1	21.6	20.1	19.8
		n	169	169	169	166	166	158	158	156	153	152	151
TID Dorz 2%	IOP	Mean	26.5	25.7	25.0	22.4	20.3	21.9	20.0	20.0	21.8	19.7	19.7
		n	165	165	165	160	160	156	156	154	155	155	155
BID Timolol	IOP	Mean	26.3	25.5	24.8	21.0	19.8	20.2	19.3	19.1	20.2	19.0	19.0
		n	73	73	73	73	73	70	71	70	69	69	69

**VISIT**

IOP Change from Baseline		ELIG 8AM	ELIG 10AM	ELIG 6PM	MON1 8AM	MON1 10AM	MON2 8AM	MON2 10AM	MON2 6PM	MON3 8AM	MON3 10AM	MON3 6PM
<b>Treatment</b>												
BID Brin 1%	DecIOP Mean	.	.	.	-3.7	-4.7	-4.2	-5.4	-4.5	-4.6	-5.6	-4.8
	n	0	0	0	164	163	156	156	155	155	155	154
TID Brin 1%	DecIOP Mean	.	.	.	-4.3	-4.9	-4.8	-5.4	-5.0	-5.2	-5.8	-5.3
	n	0	0	0	166	166	158	158	156	153	152	151
TID Dorz 2%	DecIOP Mean	.	.	.	-4.1	-5.3	-4.6	-5.6	-4.9	-4.7	-5.9	-5.3
	n	0	0	0	160	160	156	156	154	155	155	155
BID Timolol	DecIOP Mean	.	.	.	-5.2	-5.7	-6.0	-6.1	-5.7	-6.1	-6.5	-5.7
	n	0	0	0	73	73	70	71	70	69	69	69

**Comparison of TID Brinzolamide to Dorzolamide for Intent to Treat Data**

Month Time	1		2			3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
TID Brinzolamide 1.0%	-4.3	-4.9	-4.8	-5.4	-4.9	-5.2	-5.8	-5.3
TID Dorzolamide 2.0%	-4.1	-5.3	-4.5	-5.6	-4.9	-4.7	-5.9	-5.2
TID-DORZ	-0.2	0.4	-0.2	0.2	0.0	-0.5	0.1	-0.0
Upper 95% CL	0.42	<u>1.09</u>	0.41	0.83	0.68	0.19	0.75	0.64
Lower 95% CL	-0.88	-0.21	-0.90	-0.49	-0.65	-1.13	-0.58	-0.68

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

Month Time	1		2			3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
BID Brinzolamide 1.0%	-3.7	-4.7	-4.1	-5.3	-4.4	-4.5	-5.5	-4.7
TID Dorzolamide 2.0%	-4.1	-5.3	-4.5	-5.6	-4.9	-4.7	-5.9	-5.2
BID-DORZ	0.4	0.6	0.4	0.3	0.5	0.2	0.3	0.6
Upper 95% CL	<u>1.05</u>	<u>1.24</u>	<u>1.07</u>	0.93	<u>1.21</u>	0.87	1.00	<u>1.22</u>
Lower 95% CL	-0.25	-0.07	-0.26	-0.39	-0.11	-0.46	-0.33	-0.11

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

Month Time	1		2			3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
BID Brinzolamide 1.0%	-3.7	-4.7	-4.1	-5.3	-4.4	-4.5	-5.5	-4.7
TID Brinzolamide 1.0%	-4.3	-4.9	-4.8	-5.4	-4.9	-5.2	-5.8	-5.3
BID-TID	0.6	0.1	0.6	0.1	0.5	0.7	0.3	0.6
Upper 95% CL	<u>1.28</u>	0.79	<u>1.31</u>	0.76	<u>1.19</u>	<u>1.34</u>	0.91	<u>1.24</u>
Lower 95% CL	-0.02	-0.51	-0.01	-0.56	-0.13	0.02	-0.41	-0.09

**Reviewer's Comments:** To demonstrate equivalence, the 95% confidence interval must be within 1.5 mmHg for all time points and within 1 mmHg for the majority of time points measured. Equivalence between t.i.d.-dosed Brinzolamide and t.i.d.-dosed Dorzolamide has been demonstrated, as all but one of the upper 95% confidence limits are within 1 mmHg.

Equivalence has not been demonstrated for b.i.d.-dosed Brinzolamide and t.i.d.-dosed Dorzolamide, nor for b.i.d.-dosed Brinzolamide and t.i.d.-dosed Brinzolamide, as it is clear from the above tables that the majority of the upper 95% confidence limits are not within 1 mmHg.

**Comparison of Mean IOP Changes to Timolol by Visit and Time of Day**

Treatment	Month 1		Month 2			Month 3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Brinzolamide 1.0% BID	-3.8	-4.8	-4.3	-5.4	-4.7	-4.7	-5.7	-4.8
Timolol 0.5% BID	-5.2	-5.7	-5.8	-6.0	-5.6	-5.8	-6.3	-5.4
Brinzolamide 1.0% TID	-4.2	-4.8	-4.7	-5.3	-4.9	-5.0	-5.6	-5.1
Timolol 0.5% BID	-5.2	-5.7	-5.8	-6.0	-5.6	-5.8	-6.3	-5.4
Dorzolamide 2.0% TID	-4.3	-5.3	-4.7	-5.7	-5.0	-4.8	-5.9	-5.3
Timolol 0.5% BID	-5.2	-5.7	-5.8	-6.0	-5.6	-5.8	-6.3	-5.4

**Reviewer's Comments:** *None of the CAI groups is equivalent to timolol.*

**8.1.4.4.3 Safety Outcomes**  
**Frequency and Incidence of Adverse Events**

Coded Adverse Events	Brinzolamide 1% BID N=165		Brinzolamide 1% TID N=169		Dorzolamide 2% TID N=165		Timolol 0.5% BID N=73	
	N	%	N	%	N	%	N	%
	<b>OCULAR</b>							
Blurred Vision	5	3	6	4	1	1	0	
Discomfort	3	2	5	3	27	16	2	3
Hyperemia	3	2	3	2	2	1	1	1
Foreign Body Sensation	1	1	3	2	1	1	0	
Pruritus	0		3	2	4	2	0	
Conjunctivitis	0		1	1	3	2	1	1
<b>NONOCULAR</b>								
<b>Body as a Whole</b>								
Surgical/Medical Procedure	4	2	0		2	1	0	
Headache	3	2	1	1	3	2	1	1
Infection	2	1	3	2	4	2	1	1
Pain	2	1	3	2	0		0	

Cold Syndrome	1	1	3	2	1	1	1	1
Accidental Injury	0		3	2	0		0	
Asthenia	1	1	0		3	2	1	1
<u>Respiratory</u> Rhinitis	1	1	2	1	3	2	0	
Sinusitis	2	1	0		4	2	2	3
Dyspnea	0		0		3	2	0	
<u>Special Senses</u> Taste Perversion	5	3	13	8	7	4	0	
<u>Urogenital</u> Urinary Tract Infection	0		0		4	2	0	
Prostate Neoplasm	0		0		4	2	0	

**Reviewer's Comments:** The above chart lists the adverse events occurring in >1% of patients. The most common adverse events were discomfort, blurred vision and taste perversion.

#### Visual Acuity

**Reviewer's Comments:** There were no significant differences between treatment groups with respect to worsening from baseline of visual acuity.

#### Ocular Signs

**Reviewer's Comments:** There were no significant differences between treatment groups with respect to worsening from baseline of ocular signs.

#### Dilated Fundus Exam

**Reviewer's Comments:** There were no significant differences between treatment groups with respect to worsening from baseline of dilated fundus exam.

#### Visual Fields

**Reviewer's Comments:** There were no significant differences between treatment groups with respect to worsening from baseline of visual fields.

#### Cardiovascular Data

##### Heart Rate

**Reviewer's Comments:** There were decreases in heart rate for each group, in particular for t.i.d. Brinzolamide 1% and Timolol. There were no clinically significant differences between groups.

##### Blood Pressure

**Reviewer's Comments:** There were no statistically or clinically significant changes in systolic or diastolic blood pressure within groups or between groups.

#### Laboratory Data

**Reviewer's Comments:** There were no clinically significant changes from baseline laboratory values either within groups or between groups.

**8.1.4.5 Reviewer's Conclusions of Study # 4 Results**

1. Equivalence was demonstrated for t.i.d.-dosed Brinzolamide, 1% and t.i.d.-dosed Dorzolamide, 2%. Equivalence was not demonstrated between either b.i.d.-dosed Brinzolamide, 1% and t.i.d.-dosed Brinzolamide, 1% or between b.i.d.-dosed Brinzolamide, 1% and t.i.d.-dosed Dorzolamide, 2%.
2. Only one of eighteen US centers met the recommended minimum requirement of ten patients per arm per center and none of the twenty-four non-US centers met this requirement. ~~It would have been preferable to have more patients per arm per center.~~

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**8.1.5 Reviewer's Study # 5  
Sponsor's Protocol C-95-39**

**A Three-month, Multicenter, Triple-Masked, Placebo-Controlled, Adjunctive Study of the Safety and Efficacy of TID-Dosed Brinzolamide 1% Ophthalmic Suspension in the Treatment of Patients With Primary Open-Angle Glaucoma or Ocular Hypertension Maintained on Timolol Therapy**

**8.1.5.1 Objective**

The primary objective was to evaluate the safety and IOP-lowering efficacy of t.i.d.-dosed Brinzolamide 1% compared to placebo, when used adjunctively to Timolol 0.5% b.i.d., in patients with primary open-angle glaucoma or ocular hypertension.

**8.1.5.2 Design**

Randomized, triple-masked, placebo-controlled, multicenter, parallel group study.

**8.1.5.3 Protocol**

Patients were randomized into one of two treatment groups (Brinzolamide 1% t.i.d. or Placebo t.i.d.) in an equal 1:1 ratio. The study design included a three-week run-in phase in which all patients were placed on open-label Timolol 0.5% b.i.d. followed by two diurnal IOP eligibility examinations. Treatment with masked test medications was adjunctive to the open-label Timolol 0.5% and was for three months. IOP evaluations were conducted at 8:00 a.m. and 10:00 a.m. at months 1, 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. and 10:00 a.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 diurnally-corrected IOP reduction from baseline at the 8:00 a.m. and 10:00 a.m. time points. Analysis of variance was used to compare the average IOP reduction between the treatment groups.

**8.1.5.3.1 Population**

Adult patients of any race and either gender with a diagnosis of primary open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension. Qualifying IOPs 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., with no greater than a 5-mmHg difference between eyes, during Eligibility Visits 1 and 2.

<u>Inv. No.</u>	<u>Investigator</u>	<u>#Enrolled</u>	<u>#Completed</u>
1986	Walter Atlas, M.D. Nalle Clinic 1918 Randolph Road Charlotte, NC 28226	7	6
470	Donald Brotheman, M.D. 10 Medical Pkwy, Suite-102 Dallas, TX 75234	9	7
1208	Robert Caine, M.D. 110 Cambridge Street Fredericksburg, VA 22405	9	8
1236	Randy Craven, M.D. 850 East Harvard, Suite 205 Denver, CO 80210	6	3
1912	Louis Gottlieb, M.D. Piedmont Research Associates 1901 South Hawthorn, Suite 306 Winston-Salem, NC 27103	6	4
1980	Colman Kraff, M.D. Kraff Eye Institute 25 East Washington St., Suite 606 Chicago, IL 60602	4	3
1987	Christopher Kranemann, M.D. 3000 Lawrence East, Suite 104 Scarborough, Ontario M1P 2V1	4	2
156	Theodore, Krupin, M.D. Dept. of Ophthalmology Tarry Building 5-715 300 East Superior Street Chicago, IL 60611	4	3
331	Alan Mandell, M.D. 6005 Park Avenue, Suite 926B Memphis, TN 38119	13	13
1733	Donald McCurdy, M.D. University of Alabama 1716 University Boulevard Birmingham, AL 35294	15	14
1979	John Owen, M.D. SORRA Research Center Medical Forum 950 22nd St. North, Suite 550 Birmingham, AL 35203	7	4

1914	Leonard Parver, M.D. 1145 19th Street, Suite 500 Washington, D.C. 20036	3	3
733	E. George Rosanelli, Jr., M.D. 508 Habana Avenue, Suite 140 Tampa, FL 33609	2	2
1806	Kenneth Sall, M.D. 9604 E. Artesia Blvd., Suite 203 Bellflower, CA 90706	18	15
1409	Dong Shin, M.D. 4717 St. Antoine Detroit, MI 48201	5	3
1976	Jerry Shuster, M.D. Central Florida Eye Associates 1900 North Orange Avenue Orlando, FL 32804	3	3
1964	Ramesh Tripathi, MD, Ph.D Dept. of Ophthalmology University of South Carolina SCEI, Four Richland Medical Park Dr. Suite 100 Columbia, SC 29203	1	1
1923	James Tsai, M.D. Vanderbilt University Eye Center 8018 Medical Center East Nashville, TN 37232	5	5
1913	Jeffrey Wasserstrom, M.D. 5565 Grossmont Center Drive Bldg. 3, Suite 551 La Mesa, CA 91942	11	9

#### 8.1.5.3.2 Endpoints-Same as Study # 3

#### 8.1.5.3.3 Statistical Considerations

The key efficacy analysis was based on the mean IOP change from baseline in the per-protocol data set. The statistical objective of this study was to demonstrate the superiority of Brinzolamide 1.0% t.i.d., used adjunctively to Timolol 0.5% b.i.d., to Placebo.

### IOP Calculation

Each IOP measurement was performed with the following procedure: IOP was measured twice on an eye, and if the measurements differed by more than 4 mmHg, a third IOP measurement was taken. If a third IOP was collected when the first two differed by 4 mmHg or less, then the third measurement was not used and the IOP for that measurement was the average of the first two. If the first two measurements differed by more than 4 mmHg, then the IOP was the average of the nearest two measurements. If two pairs of the three measurements differed by the same amount, then all three measurements were averaged. The final average was rounded up to the nearest integer.

The measurement procedure above was repeated for both eyes. If the IOP in both eyes differed by more than 5 mmHg, both eyes were considered unevaluable for efficacy. In the per-protocol data set, an eye was determined to be evaluable for efficacy if it was  $24 \leq \text{IOP} \leq 36$  mmHg at 8:00 a.m. and was  $21 \leq \text{IOP} \leq 36$  mmHg at 10:00 a.m. These criteria were required to be met on both eligibility visit days. If both eyes were considered evaluable at baseline, the IOP was the average of the two values during all follow-up visits. If only one eye met the baseline criteria, then only data from that eye was used.

In the intent-to-treat analysis, IOP was the average of both eyes at all follow-up visits (i.e., both eyes were considered evaluable in the intent-to-treat data set).

Baseline IOP was the average of the IOP's for the evaluable eyes across both eligibility days. Change from baseline was the diurnally corrected change from this average baseline.

### Efficacy Analysis

#### Primary Efficacy Analysis

The statistical objective of this study was to demonstrate superiority to Placebo.

The following analysis of variance model was used:

Since the treatment differences were homogeneous across months, comparisons were also made on the time of day treatment means after collapsing over months. Comparisons were based on the treatment by time least squares means because the treatment by month interaction term and the treatment by month by time interaction term were not significant at the 0.10 level.

**Reviewer's Comments:** *Evaluations in different months should not be collapsed.*

#### Subgroup Analyses

Subgroup descriptive statistics were calculated for mean IOP. The demographic subgroups are age (<65, >= 65), sex, race, iris color (brown vs. others) and ocular

diagnosis.

The 95% confidence limits for each demographic subgroup were graphed for the intent-to-treat data. Each graph contains the means and confidence limits for each subgroup for a treatment group. The confidence limits were constructed using the t-distribution for this mean using variances and arithmetic mean observed at each visit.

#### Assessment of Consistency of Results Across Sites

Homogeneity of the treatment effect among investigators was analyzed using a repeated measures analysis of variance model.

The test for homogeneity of investigators on the treatment effect was conducted using an estimate of the treatment effect within a site. The estimate was based on the difference in means, the treatment nested within investigator effect, and patient nested within the treatment by investigator interaction effect. Confidence intervals on the treatment effects within each site were graphed.

A treatment difference was considered homogeneous among sites if the site treatment differences were symmetrically, distributed about the grand mean for the treatment difference.

Reviewer's Comments: *There were too few patients per site to do this analysis correctly.*

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## 8.1.5.4 Results

## 8.1.5.4.1 - Populations enrolled/analyzed

Demographic Statistics for Intent to Treat Data

	Mean	Std	Age	N	Min	Max
Treatment						
TID Brinzolamide 1.0% <i>{ + 1000000}</i>	62.0	12.4		65	37	89
Placebo	63.1	12.3		67	34	85

	TID Brinzol 1%		Placebo	
	N	%	N	%
<u>Age</u>				
< 65	34	52.3	34	50.7
≥ 65	31	47.7	33	49.3
<u>Sex</u>				
MALE	36	55.4	27	40.3
FEMALE	29	44.6	40	59.7
<u>Race</u>				
CAUCASIAN	37	56.9	45	67.2
BLACK	19	29.2	17	25.4
ASIAN	2	3.1		
OTHER	7	10.8	5	7.5
<u>Iris Color</u>				
BROWN	38	58.5	39	58.2
HAZEL	7	10.8	2	3.0
GREEN	1	1.5	5	7.5
BLUE	18	27.7	19	28.4
GREY	1	1.5	2	3.0
<u>Diagnosis</u>				
OH	24	36.9	12	17.9
POAG	41	63.1	53	79.1
Pigm Disp			2	3.0

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**Discontinued Subjects:****List of Patients Excluded From the Primary Efficacy Analyses**

Investigator No.	Patient No.	Treatment Group	Reason For Exclusion	
156	2003	Briazolamide 1% TID	IOP asymmetry	
1236	402		IOP asymmetry	
1912	1102		IOP asymmetry	
1987	2203		IOP asymmetry	
1208	2304		Contraindicated concomitant medication	
1733	212		Contraindicated concomitant medication	
1980	1904		Contraindicated concomitant medication	
1986	2104		Contraindicated concomitant medication	
470	102		No on-therapy IOP data	
1236	405		No on-therapy IOP data	
1979	1807		No on-therapy IOP data	
470	101		Inadequate timolol run-in period	
1236	403		Placebo	IOP asymmetry
1409	1502			IOP asymmetry
1912	1103	IOP asymmetry		
1987	2204	IOP asymmetry		
1806	2401	No on-therapy IOP data		
1806	2411	No on-therapy IOP data		
1806	2413	No on-therapy IOP data		
1979	1802	No on-therapy IOP data		
1409	1501	Non-compliance to study medication		
1913	2511	Non-compliance to study medication		
1913	2502	Inadequate timolol run-in period		
1979	1805	Non-qualifying IOP		

**Distribution by Reason and Treatment Group of Patients Excluded  
From the Efficacy Analyses**

Reason	Randomized Treatment Group		Total
	Brinzolamide 1% TID	Placebo	
IOP asymmetry	4	4	8
No on-therapy IOP data	3	4	7
Contraindicated concomitant medication	4	0	4
Inadequate timolol run-in period	1	1	2
Non-compliance to study medication	0	2	2
Non-qualifying IOP	0	1	1
<b>TOTALS</b>	<b>12</b>	<b>12</b>	<b>24</b>

### List of Patients Discontinued Following Randomization

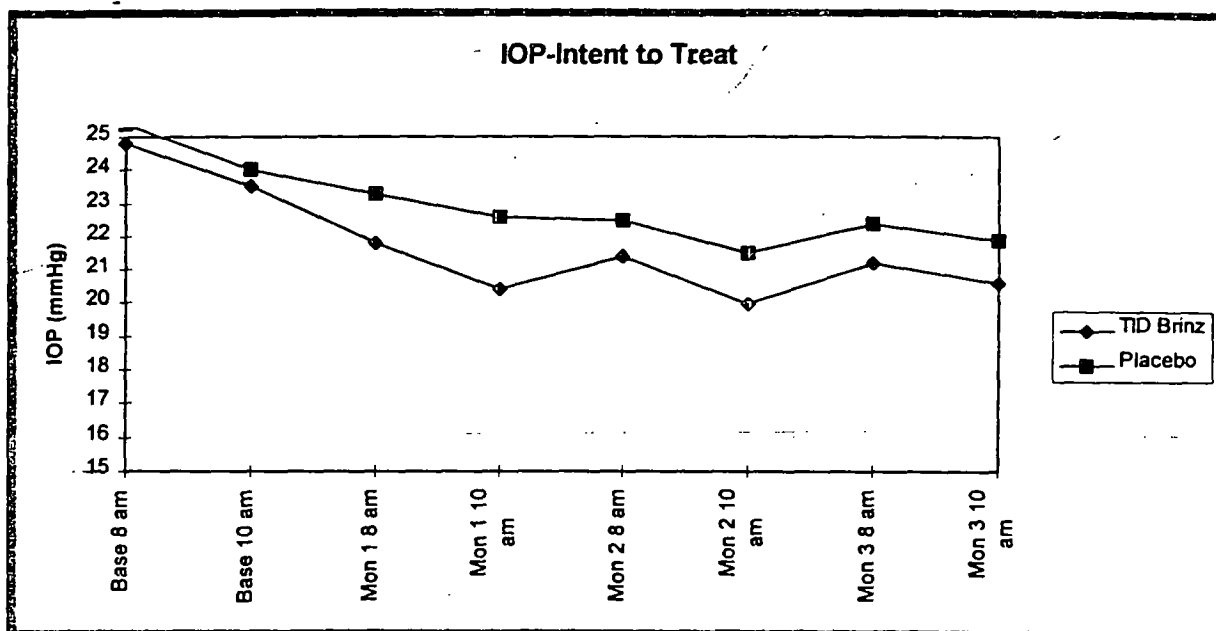
Investigator No.	Patient No.	Treatment Group	Reason
1979	1807	Brinzolamide 1% TID	Protocol violation: non-qualifying visual field
1986	2104		Protocol violation: contraindicated concomitant medication
1987	2203		Protocol violation: IOP asymmetry
470	102		Protocol violation: non-qualifying visual field
1236	405		Adverse event (cough, pharyngitis, taste perversion)
1409	1503		Non-compliance to study medication
1806	2401	Placebo	Inadequate IOP control
1806	2411		Inadequate IOP control
1806	2418		Inadequate IOP control
1914	803		Inadequate IOP control
1976	1702		Inadequate IOP control
331	604		Adverse event (ocular discomfort, keratitis)
1806	2407		Adverse event (emergency surgery due to ruptured stomach ulcer)
1806	2413		Adverse event (ocular hyperemia, pruritus and pain)
1979	1802		Adverse event (ocular hyperemia, discomfort and pruritus)
1979	1805		Protocol violation: non-qualifying IOP
1987	2204		Protocol violation: IOP asymmetry
1733	203		Lost to follow-up
1806	2412		Lost to follow-up
470	109		Patient relocation

### Distribution by Reason and Treatment Group of Patients Discontinued Following Randomization

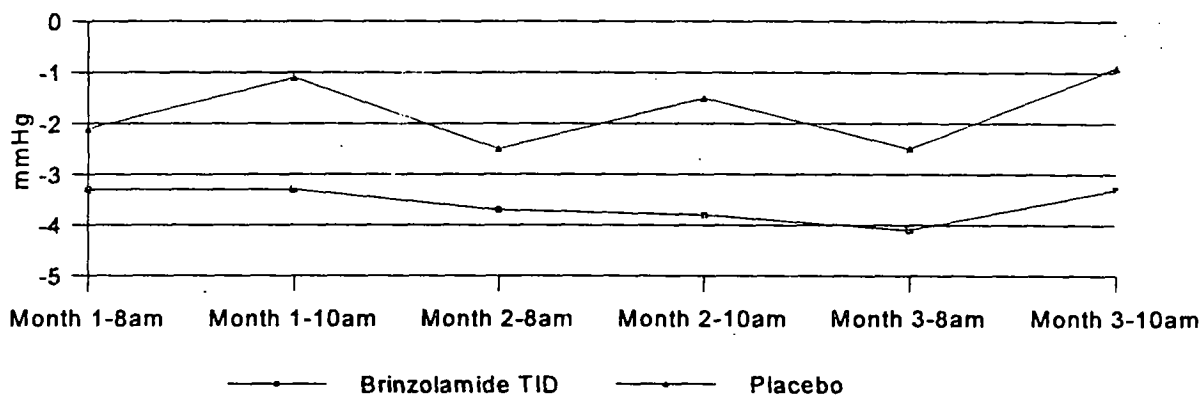
Reason	Randomized Treatment Group		Total
	Brinzolamide 1% TID	Placebo	
Protocol violation	4	2	6
Inadequate IOP control	0	5	5
Adverse event	1	4	5
Lost to follow-up	0	2	2
Non-compliance to study medication	1	0	1
Patient relocation	0	1	1
<b>TOTALS</b>	<b>6</b>	<b>14</b>	<b>20</b>



## 8.1.5.4.2 Efficacy Endpoint Outcomes



## Change from Baseline



Brinzolamide TID	-3.3	-3.3	-3.7	-3.8	-4.1	-3.3
Placebo	-2.1	-1.1	-2.5	-1.5	-2.5	-0.9

**Reviewer's Comments:** The IOP reduction of the t.i.d. Brinzolamide group was greater than placebo at each time point. At peak, the differences ranged from 2.2 to 2.4 mmHg. At trough, the differences ranged from 1.2 to 1.6 mmHg. Clinical efficacy for adjunctive therapy of t.i.d.-dosed Brinzolamide 1% with b.i.d. Timolol 0.5% is minimal.

**Subgroup Analyses**

**Reviewer's Comments:** In general, there were no clinically significant differences in IOP-lowering in the Brinzolamide 1% treatment group when evaluated according to gender, race, iris color or ocular diagnosis.

**8.1.5.4.3 Safety Outcomes:  
Frequency and Incidence of Adverse Events**

Coded Adverse Events	Brinzolamide 1.0% TID + Timolol 0.5% BID N=65		Placebo BID + Timolol 0.5% BID N=67	
	N	%	N	%
<b>Ocular</b>				
Blurred Vision	4	6	1	2
Discomfort	0		3	5
Hyperemia	0		4	6
Keratitis	2	3	3	4
Pruritus	0		4	6
Lid Edema	0		1	2
Pain	0		2	3
Abnormal Vision	0		2	3
Decreased Visual Acuity	1	2	1	2
Blepharitis	1	2	0	
Conjunctivitis	1	2	0	
Corneal Abrasion	0		1	2
Increased IOP	0		1	2
Corneal Staining	0		1	2
Corneal Edema	0		1	2
<b>NONOCULAR</b>				
<b>Body as a Whole</b>				
Headache	3	5	1	2
Cold Syndrome	1	2	1	2
Infection	1	2	2	3
<b>Special Senses</b>				
Taste Perversion	5	8	0	
Ear Disorder	0		1	2
<b>Surgical/Medical Procedure</b>				
	0		4	6
Carcinoma	0		1	2
Accidental Injury	0		1	2
Pain	0		1	2
Back Pain	0		1	2
<b>Digestive</b>				
Diarrhea	2	3	0	
Esophagitis	1	2	0	

Coded Adverse Events	Brinzolamide 1.0% TID + Timolol 0.5% BID N=65		Placebo BID + Timolol 0.5% BID N=67	
Gastrointestinal Disorder	1	2	0	
Tooth Disorder	1	2	0	
Stomach Ulcer	0		1	2
Dry Mouth	0		1	2
Cardiovascular Hypertension	1	2	0	
Respiratory Increased Cough	2	3	1	2
Sinusitis	2	3	1	2
Rhinitis	1	2	0	
Pharyngitis	1	2	1	2
Skin and Appendages Skin Discoloration	0		1	2
Urticaria	1	2	0	
Metabolic and Nutritional Peripheral Edema	1	2	1	2
Musculo-Skeletal Arthralgia	1	2	0	
Spontaneous Bone Fracture	1	2	0	
Nervous Anxiety	1	2	0	
Urogenital Dysuria	2	3	0	

**Reviewer's Comments:** *The most frequent ocular adverse events were blurred vision, discomfort, hyperemia, pruritus and keratitis. The most frequent nonocular adverse event was taste perversion, occurring only in the active treatment group.*

#### Other Safety Parameters

**Reviewer's Comments:** *There was no clinically significant worsening from baseline in visual acuity, ocular signs, dilated fundus examination, visual fields, blood pressure or heart rate. Additionally, laboratory studies revealed no clinically significant changes either within groups or between groups.*



**8.1.6 Reviewer's Trial # 6  
Sponsor's Protocol # C-96-29**

**A One-Week, Triple-Masked, Multiple-Dose Study of TID-Dosed 1.0% AL04862 Ophthalmic Suspension Compared to TID-Dosed 2% Dorzolamide Ophthalmic Solution in Patients With Primary Open-Angle Glaucoma or Ocular Hypertension**

**8.1.6.1 Objective**

The primary objective was to evaluate the ocular discomfort, based on burning and stinging, of Brinzolamide 1% Ophthalmic Suspension dosed t.i.d., compared to Dorzolamide 2% Ophthalmic Solution (TRUSOPT) dosed t.i.d., following multiple dosing inpatients with primary open-angle glaucoma or ocular hypertension.

**8.1.6.2 Design**

Multicenter, triple-masked, randomized, parallel study

**8.1.6.3 Protocol**

**Study Plan**

Activity	Screening Phase	Treatment Phase
	Screening Exam	Week I Examination
	8 a.m.	8 a.m.
Screen Patients	X	
Informed Consent	X	
Demographics	X	
Medical History	X	
Urine Pregnancy Test	X <sup>1</sup>	X <sup>1</sup>
Best Corrected Visual Acuity	X	X
Biomicroscopy	X	X
Gonioscopy	X <sup>2</sup>	
Instill Current Ocular Hypotensive Agent	X	
Comfort Evaluation	X	X
Dispense Masked Medication	X	
Instill Masked Medication		X
Collect Medications		X
Complete Exit Form		X
Dismiss Patient From Study		X

### Study Procedure

This study is designed as a one-week, triple-masked, parallel trial with two treatment groups: 1.0% AL04862 dosed TID; and 2.0% Dorzolamide dosed TID.- It consisted of two (2) study visits. The first visit was a Screening Exam. A Week 1 Exam was conducted after the one-week, masked, treatment phase as shown below. An ocular comfort evaluation will be performed at the Screening Exam and at the Week 1 Exam visit following instillation of the 8:00 a.m. dose at the study site.

#### 8.1.6.3.1 Population

Adult patients of any race, either gender, 21 years of age or older, with a diagnosis of primary open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension who are on bilateral, single, topical, ocular hypotensive agents.

#### Investigators:

<u>Inv. No.</u>	<u>Name/Address</u>	<u># Enrolled</u>	<u># Completed</u>
271	Robert Stewart, M.D. Houston Eye Associates Houston, TX 77025	43	39
1007	Thomas Walters, M.D. Austin, TX 78746	46	44
1208	Robert Caine, M.D. Eye Associates of Virginia Fredericksburg, VA 22405	20	20
	<b>Total</b>	<b>109</b>	<b>103</b>

#### 8.1.6.3.2 Endpoints

Efficacy: Ocular discomfort (burning/stinging)-4-unit scale

Safety: Visual acuity, ocular signs, adverse events

#### 8.1.6.3.3 Statistical Considerations

The key efficacy analyses were based on the evaluation of ocular discomfort. The score for ocular discomfort in the Brinzolamide 1% group was compared to the score in the Dorzolamide 2% treatment group using a two-sample t-test. Additional analyses of ocular comfort were performed using Fisher's Exact test and a Cochran-Mantel-Haenszel rank score test to compare the distribution of ocular discomfort between the treatment groups.

## 8.1.6.4 Results

## 8.1.6.4.1 - Populations enrolled/analyzed

Demographics for Intent-to-Treat Patients

Treatment	Sex			
	Male		Female	
	N	%	N	%
Brinzolamide	21	38.18	34	61.82
Dorzolamide	27	50.00	27	50.00

Treatment	Race							
	Caucasian		Black		Asian		Other	
	N	%	N	%	N	%	N	%
Brinzolamide	30	54.55	18	32.73	1	1.82	6	10.91
Dorzolamide	40	74.07	11	20.37	1	1.85	2	3.70

Treatment	Iris									
	Brown		Hazel		Green		Blue		Grey	
	N	%	N	%	N	%	N	%	N	%
Brinzolamide	37	67.27	10	18.18	1	1.82	7	12.73	.	.
Dorzolamide	28	51.85	7	12.96	3	5.56	15	27.78	1	1.85

Treatment	Mean	Std	Age		
			N	Min	Max
Brinzolamide	62.5	11.45	55	31	82
Dorzolamide	61.1	12.43	54	40	81

Treatment	Age Category			
	<=65		>= 65	
	N	%	N	%
Brinzolamide	26	47.27	29	52.73
Dorzolamide	26	48.15	28	51.85

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**Distribution by Investigator of Randomized, Safety-Evaluated and Efficacy-Evaluated Patients**

Patients Randomized and Safety-Evaluated			
Inv. No.	Brinzolamide	Dorzolamide	Total
271	22	21	43
1007	23	23	46
1208	10	10	20
<b>TOTALS</b>	<b>55</b>	<b>54</b>	<b>109</b>

Patients Randomized and Efficacy-Evaluated		
Brinzolamide	Dorzolamide	Total
19	20	39
23	21	44
10	10	20
<b>52</b>	<b>51</b>	<b>103</b>

**List of Patients Discontinued Following Randomization and Not Evaluable for Efficacy**

Investigator Number	Patient Number	Treatment Group	Duration of Treatment	Reason for Discontinuation
271	209	Brinzolamide	7 days	Protocol violation (non-compliance to dosing)
	215	Brinzolamide	7 days	Protocol violation (non-compliance to dosing)
	234	Brinzolamide	7 days	Protocol violation (non-compliance to dosing)
	235	Dorzolamide	7 day	Protocol violation (non-compliance to dosing)
1007	126	Dorzolamide	6 days	Adverse events (ocular hyperemia, tearing, ocular discomfort, conjunctival edema and conjunctival follicles)
	141	Dorzolamide	1 day	Adverse event (dyspepsia)

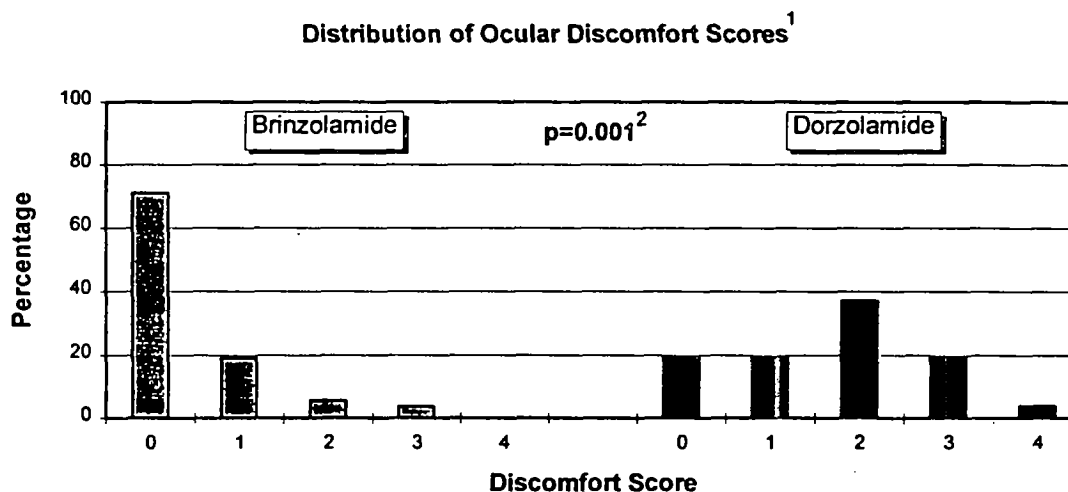


## 8.1.6.4.2 Efficacy endpoint outcomes

Mean Ocular Discomfort for Intent-to-Treat Patients at Week 1

Treatment	Ocular Discomfort Week 1	
Brinzolamide	Mean	0.4
	Std	0.78
	N	52
Dorzolamide	Mean	1.7
	Std	1.12
	N	51
	p-value*	0.0001

**Reviewer's Comments:** *Brinzolamide shows a difference in mean ocular discomfort (burning/stinging) of 1.3 units less than Dorzolamide. It is unclear what clinical meaning this has.*



<sup>1</sup> Ocular discomfort scores of 0 (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) are based upon the evaluation obtained at the end of Week 1.

<sup>2</sup> P value of 0.001 based upon a comparison of the distribution of scores using a Cochran - Mantel - Haenszel rank score test.

**Reviewer's Comments:** *The Brinzolamide group of patients had a greater percentage of patients who described no ocular discomfort (burning/stinging) as compared to the Dorzolamide group. The Dorzolamide group had a greater percentage of patients experiencing moderate, severe and very severe ocular discomfort as compared to the Brinzolamide group.*

## 8.1.6.4.3 Safety Outcomes

**Frequency and Incidence of Adverse Events**

Coded Adverse Events	Brinzolamide 1% TID N=55		Dorzolamide 2% TID N=54	
	N	%	N	%
<b>Ocular</b>				
Blurred Vision	11	20	2	4
Foreign Body Sensation	2	4	1	2
Pain	2	4	1	2
Abnormal Vision	1	2	1	2
Dry Eye	1	2	0	
Hyperemia	0		4	7
Tearing	0		2	4
Discomfort	0		1	2
Conjunctival Edema	0		1	2
Decreased Visual Acuity	0		1	2
Hordeolum	0		1	2
Conjunctival Follicles	0		1	2
<b>Nonocular</b>				
<u>Special Senses</u>				
Taste Perversion	8	15	5	9
<u>Body as a Whole</u>				
Cold Syndrome	0		1	2
Headache	1	2	0	
Infection	0		1	2
Mucous Membrane Disorder	0		1	2
Pain	0		1	2
Back Pain	0		1	2
<u>Respiratory</u>				
Rhinitis	0		1	2
<u>Digestive</u>				
Nausea	1	2	0	
Dyspepsia	0		1	2
<u>Musculoskeletal</u>				
Arthralgia	1	2	0	
<u>Skin and Appendages</u>				
Skin Disorder	0		1	2

**Reviewer's Comments:** *The most common ocular adverse events were blurred vision, foreign body sensation, pain, hyperemia, tearing. The most common non-ocular adverse event was taste perversion. It is confusing to have "discomfort" listed in the adverse events when it is an endpoint in this study, in addition to which, the percentages do not match the rest of the study results. An explanation should be provided as to what is meant by "discomfort" in this situation.*

**Other Safety Parameters**

**Reviewer's Comments:** *No clinically significant worsening from baseline in visual acuity or ocular signs were noted within or between either group.*

**8.1.6.5 Reviewer's Conclusions of Study # 6 Results**

1. In this study, Brinzolamide had less discomfort (stinging/burning) associated with its use than Dorzolamide.

It is the opinion of this reviewer, however, that the term "ocular discomfort" encompasses more than just stinging and burning as it is used in this study. Certainly, an experience of pain or foreign body sensation would fall into the category of "ocular discomfort". It is misleading to use the term "discomfort" solely for stinging and burning. Particularly with respect to the labeling, the words "stinging and burning" should be used in place of "discomfort" to avoid misinterpretation.

2. The term "discomfort" was used in the list of adverse events. "Discomfort" was an endpoint in this study, connoting stinging/burning. An explanation should be provided as to what was meant by the adverse event of "discomfort".
3. The most frequent adverse events for each study group are listed below:

	<u>Brinzolamide</u>	<u>Dorzolamide</u>
Blurred vision	20%	4%
Foreign body sensation	4%	2%
Pain	4%	2%
Hyperemia	0%	7%
Tearing	0%	4%
Taste Perversion	15%	9%

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**8.1.7 Reviewer' Trial # 7**  
**Sponsor's Protocol # C-96-40**

**A One-Week, Triple-Masked, Multiple-Dose Comfort Study of TID-Dosed 1% Brinzolamide Ophthalmic Suspension Compared to TID-Dosed 2% Dorzolamide Ophthalmic Solution in Patients With Primary Open-Angle Glaucoma or Ocular Hypertension**

**8.1.7.1 Objective**

The primary objective was to evaluate the ocular discomfort based on burning and stinging of Brinzolamide 1% Ophthalmic Suspension dosed t.i.d., compared to Dorzolamide 2% Ophthalmic Solution (TRUSOPT) dosed t.i.d., following multiple dosing in patients with primary open-angle glaucoma or ocular hypertension.

<b>8.1.7.2</b>	<b>Design</b>	Same as Study # 6
<b>8.1.7.3</b>	<b>Protocol</b>	Same as Study # 6
<b>8.1.7.3.1</b>	<b>Population</b>	Same as Study # 6
<b>8.1.7.3.2</b>	<b>Endpoints</b>	Same as Study # 6
<b>8.1.7.3.3</b>	<b>Statistical Considerations</b>	Same as Study # 6

**Investigators:**

<b><u>Inv. No.</u></b>	<b><u>Name/Address</u></b>	<b><u># Enrolled</u></b>	<b><u># Completed</u></b>
470	Donald P. Brotheman, M.D. Dallas, TX 75234	59	55
1892	Shannon Smith, M.D. Lehmann Eye Associates Nacogdoches, TX 75961	22	19
1913	Jeffrey Wasserstrom, M.D. La Mesa, CA 91942	23	21
	<b><u>Total</u></b>	104	95

## 8.1.7.4 Results

## 8.1.7.4.1 Populations enrolled/analyzed

## Distribution by Investigator of Randomized, Safety-Evaluated and Efficacy-Evaluated Patients

Patients Randomized and Safety-Evaluated			
Inv. No.	Brinzolamide	Dorzolamide	Total
470	30	29	59
1892	11	11	22
1913	11	12	23
<b>TOTALS</b>	<b>52</b>	<b>52</b>	<b>104</b>

Patients Randomized and Efficacy-Evaluated		
Brinzolamide	Dorzolamide	Total
28	27	55
9	10	19
11	10	21
<b>48</b>	<b>47</b>	<b>95</b>

## - List of Patients Not Evaluable for Efficacy

Investigator Number	Patient Number	Treatment Group	Reason Patient Not Evaluable
470	504	Brinzolamide	Protocol violation: concomitant medication (steroid)
	509	Dorzolamide	Protocol violation: concomitant medication (steroid)
	522	Dorzolamide	No follow-up data. Patient discontinued due to an adverse event (nausea, diarrhea)
	546	Brinzolamide	No follow-up data. Patient lost to follow-up.
1892	606	Dorzolamide	No follow-up data. Patient discontinued due to an adverse event (ocular hyperemia and fatigue, headache)
	614	Brinzolamide	No follow-up data. Patient discontinued due to an adverse event (dizziness)
	618	Brinzolamide	Protocol violation: concomitant medication (steroid)
1913	406	Dorzolamide	Protocol violation: non-compliance to visit schedule and dosing
	420	Dorzolamide	No follow-up data. Patient discontinued due to an adverse event (dizziness)

**Demographics**

Treatment	Sex			
	Male		Female	
	N	%	N	%
Brinzolamide	17	32.69	35	67.31
Dorzolamide	21	40.38	31	59.62

Treatment	Race					
	Caucasian		Black		Other	
	N	%	N	%	N	%
Brinzolamide	45	86.54	5	9.62	2	3.85
Dorzolamide	46	88.46	2	3.85	4	7.69

Treatment	Iris							
	Brown		Hazel		Green		Blue	
	N	%	N	%	N	%	N	%
Brinzolamide	19	36.54	13	25.00	.	.	20	38.46
Dorzolamide	19	36.54	10	19.23	3	5.77	20	38.46

Treatment	Age					
	Mean	Std	N	Min	Max	
Brinzolamide	68.6	10.72	52	41	92	
Dorzolamide	68.5	12.45	52	36	90	

Treatment	Age Category			
	<=65		>= 65	
	N	%	N	%
Brinzolamide	21	40.38	31	59.62
Dorzolamide	16	30.77	36	69.23

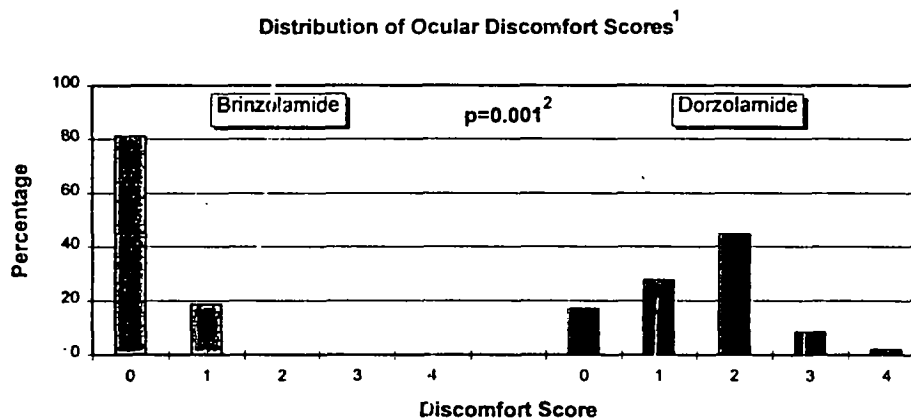
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### 8.1.7.4.2 Efficacy endpoint outcomes

#### Mean Ocular Discomfort for Intent-to-Treat Patients at Week 1

Treatment		Ocular Discomfort	
		Week 1	
Brinzolamide	Mean	0.2	
	Std	0.42	
	N	51	
Dorzolamide	Mean	1.5	
	Std	0.93	
	N	50	
p-value		0.0001	

**Reviewer's Comments:** *Brinzolamide shows a difference in mean ocular discomfort (burning/stinging), of 1.3 units less than Dorzolamide. It is unclear what clinical meaning this has.*



- Ocular discomfort scores of 0 (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) are based upon the evaluation obtained at the end of Week 1.
- P value of 0.001 based upon a comparison of the distribution of scores using a Cochran - Mantel - Haenszel rank score test.

**Reviewer's Comments:** *In the Brinzolamide group, there were a greater percentage of patients who experienced no stinging or burning as compared to the patients in the Dorzolamide group. Additionally, there were greater percentages of patients experiencing mild, moderate, severe and very severe ocular discomfort (stinging/burning) in the Dorzolamide group as compared to the Brinzolamide group.*

8.1.7.4.3 - Safety Outcomes  
Frequency and Incidence of Adverse Events

Coded Adverse Events	Brinzolamide (ALØ4862) 1% TID N=52		Dorzolamide 2% TID N=52	
	N	%	N	%
<b>OCULAR</b>				
Blurred Vision	13	25	2	4
Foreign Body Sensation	5	10	1	2
Hyperemia	1	2	1	2
Pain	1	2	1	2
Dry Eye	0		1	2
Eye Fatigue	0		1	2
<b>NONOCULAR</b>				
<u>Body as a Whole</u>				
Headache	1	2	6	12
<u>Digestive</u>				
Nausea	1	2	2	4
Diarrhea	0		1	2
<u>Nervous</u>				
Dizziness	1	2	1	2
<u>Respiratory</u>				
Rhinitis	1	2	1	2
<u>Special Senses</u>				
Taste Perversion	5	10	4	8
<u>Musculoskeletal</u>				
Joint Disorder	1	2	0	

**Reviewer's Comments:** *The most common ocular adverse events were blurred vision and foreign body sensation. The most common nonocular adverse events were taste perversion and headache.*

**Other Safety Parameters**

**Reviewer's Comments:** *No clinically significant worsening from baseline in visual acuity or ocular signs were noted within or between groups.*



**8.1.7.5 Reviewer's Conclusions of Study # 7 Results**

1. Brinzolamide had statistically and clinically less discomfort (stinging/burning) associated with its use as compared to Dorzolamide.
2. The most frequent adverse events for each study group are listed below:

	<u>Brinzolamide</u>	<u>Dorzolamide</u>
Blurred vision	25%	4%
Foreign body sensation	10%	2%
Taste perversion	10%	8%
Headache	2%	10%

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ON ORIGINAL

**8.1.8 Reviewer's Study # 8  
Sponsor's Protocol C-95-47**

**A Eighteen-Month, Multicenter, Triple-Masked, Parallel Study of the Efficacy and Safety of BID and TID-Dosed Brinzolamide 1.0% Ophthalmic Suspension Compared to BID-Dosed Timolol 0.5% in the Treatment of Patients with Primary Open-Angle Glaucoma or Ocular Hypertension**

**8.1.8.1 Objective/Rationale**

To evaluate the safety (adverse events, laboratory data and endothelial cell density) and efficacy (IOP-lowering) of b.i.d. and t.i.d.-dosed brinzolamide 1% and Timoptic 0.5% b.i.d. over an 18 month period.

**8.1.8.2 Design**

Parallel, triple-masked, randomized, active-controlled, multicenter study

**8.1.8.3 Protocol**

This is an ongoing long-term safety and efficacy study. The patients were randomized into one of the following three treatment groups in a 2:2:1 ratio, respectively:

-brinzolamide ophthalmic suspension 1%, b.i.d.

-brinzolamide ophthalmic suspension 1%. t.i.d.

-Timolol ophthalmic solution 0.5%, b.i.d.

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 one 8:00 a.m. eligibility examination. Treatment with masked test medications will be for eighteen months with IOP evaluations at 8:00 a.m. at months 1, 3, 6, 9, 12, 15 and 18. Efficacy data will be obtained by comparing on-therapy IOP measurements to the average baseline corresponding IOP values obtained at the 8:00 a.m. eligibility visit. Safety data will be generated from adverse events, visual acuity, biomicroscopic exams, heart rate, blood pressure, laboratory (blood chemistry, hematology and urinalysis evaluations), endothelial cell density and corneal thickness.

**Reviewer's Comments:** *Study should include at least two peak and two trough measurements over time.*

**8.1.8.3.1 Population**

Patients with primary open-angle glaucoma or ocular hypertension

**8.1.8.3.2 Endpoints**

Efficacy: Measurement of IOP

Safety: Adverse events, visual acuity, biomicroscopic exams, heart rate, blood pressure, endothelial cell density, corneal thickness, and laboratory evaluations (blood chemistry, hematology and urinalysis evaluations)

**8.1.8.4 Results**

Study is ongoing therefore only masked adverse events from this study are to be reported in this NDA for evaluation of safety.

**8.1.8.4.1 Statistical Considerations**

Analysis of variance will be used to compare the average IOP reduction between the treatment groups. Summary statistics will be calculated for the safety parameters.

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## 8.1.8.4.2 Safety Outcomes

**Incidence of Adverse Events Occuring with Frequency of > 1% in Any Treatment Group**

Coded Adverse Events	Treatment A N=150		Treatment B N=154		Treatment C N=76	
	N	%	N	%	N	%
<b>OCULAR</b>						
Blurred Vision	7	5	6	4	3	4
Pain	5	3	1	<1	1	1
Discomfort	3	2	5	3	4	5
Discharge NOS	3	2	3	2	0	
Keratitis	3	2	2	1	1	1
Hyperemia	1	<1	4	3	0	
Corneal Staining	1	<1	0		2	3
<b>NONOCULAR</b>						
Body as a Whole Headache	2	1	1	<1	2	3
Infection	5	3	1	<1	0	
Surgical/Medical Procedure	3	2	1	<1	1	1
Cold Syndrome	2	1	1	<1	4	5
Chest Pain	1	<1	1	<1	2	3
Flu Syndrome	0		0		2	3
<u>Respiratory</u> Rhinitis	4	3	0		1	1
Dyspnea	1	<1	4	3	0	
Pharyngitis	3	2	0		1	1
Sinusitis	2	1	1	<1	2	3
<u>Special Senses</u> Taste Perversion	3	2	9	6	0	
<u>Cardiovascular</u> Hypertension	1	<1	0		2	3

**Reviewer's Comments:** *The most frequent ocular adverse events were discomfort and blurred vision. The most frequent nonocular event was taste perversion.*

### 8.1.8.5 Reviewer's Conclusions of Study # 8 Results

1. The most frequent adverse events in this ongoing study were as follows:

	<u>Trt. A</u>	<u>Trt. B</u>	<u>Trt. C</u>
Blurred vision	5%	4%	4%
Discomfort	2%	3%	5%
Taste Perversion	2%	6%	0%

The findings of this ongoing, long-term study are consistent with those of the three-month primary therapy studies in this application.

2. The study should have included two peak and trough measurements.

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## 9 Overview of Efficacy

1. The drug does not show a linear concentration-dependent response. The 1% concentration appears to be the most effective.
2. Brinzolamide 1% is equivalent to Dorzolamide 2% when dosed t.i.d. B.i.d.-dosing of Brinzolamide 1% was not shown to be equivalent to either t.i.d.-dosed Brinzolamide 1% or to t.i.d.-dosed Dorzolamide 2%.
3. Brinzolamide 1% dosed t.i.d. lowers IOP by approximately 4.3-4.8 mean mmHg.
4. The reductions in IOP with Brinzolamide 1% are less than those with Timoptic 0.5%.
5. Adjunctive therapy of t.i.d.-dosed Brinzolamide 1% with b.i.d.-dosed Timoptic 0.5% demonstrated minimal efficacy. The IOP lowering differences between the adjunctive therapy group and the placebo group ranged from 1.5-2.1 mmHg at peak and 1-1.2 mmHg at trough.

## 10 Overview of Safety

### 10.1 Significant/Potentially Significant Events

#### 10.1.1 Deaths

Reviewer's Comments: *One death was reported due to a motor vehicle accident.*

### 10.1.2 Other Significant/Potentially Significant Events

Clinical Adverse Events in > 1% of Patients in Any Treatment Group, Phase 3 Studies

Coded Adverse Events	Brinzolamide 1.0% N=870		Brinzolamide 1.0% + Timolol 0.5% N=88 <sup>c</sup>		Dorzolamide 2.0% N=402		Timolol 0.5% N=147 <sup>d</sup>		Placebo N=101	
	N	%	N	%	N	%	N	%	N	%
<b>Nonocular</b>										
<u>Body as a Whole</u>										
Headache	13	1.5	3	3.4	11	2.7	2	1.4	3	3.0
Infection	11	1.3	4	4.6	12	3.0	3	2.0	1	1.0
Pain	9	1.0	1	1.1	4	1.0	1	0.7	0	
Cold Syndrome	9	1.0	1	1.1	6	1.5	2	1.4	1	1.0
Accidental Injury	8	0.9	1	1.1	3	0.7	1	0.7	0	
Surgical/Medical Procedure	7	0.8	0		3	0.7	5	3.4	0	
Allergy	4	0.5	1	1.1	1	0.2	0		4	4.0
Back Pain	4	0.5	0		2	0.5	2	1.4	0	
<u>Special Senses</u>										
Taste Perversion	50	5.7	6	6.8	23	5.7	0		1	1.0
<u>Cardiovascular</u>										
Hypertension	6	0.7	1	1.1	1	0.2	1	0.7	1	1.0
Angina Pectoris	0		1	1.1	0		0		0	
Bradycardia	1	0.1	0		0		0		5	5.0
<u>Digestive</u>										
Diarrhea	7	0.8	2	2.3	3	0.7	1	0.7	0	
Tooth Disorder	4	0.5	1	1.1	2	0.5	0		0	
GI Disorder	3	0.3	1	1.1	0		0		0	
Esophagitis	0		1	1.1	0		0		0	
<u>Hemic and Lymphatic</u>										
Echymosis	1	0.1	1	1.1	0		0		0	
<u>Metabolic and Nutritional</u>										
Peripheral Edema	0		1	1.1	0		1	0.7	0	
<u>Musculoskeletal</u>										
Myalgia	3	0.3	1	1.1	0		0		0	
Arthralgia	2	0.2	1	1.1	0		0		0	
Spontaneous Bone Fracture	1	0.1	1	1.1	0		0		0	
<u>Nervous</u>										
Anxiety	0		1	1.1	1	0.2	0		0	
Insomnia	0		1	1.1	1	0.2	0		0	
Vertigo	0		0		0		0		2	2.0
<u>Respiratory</u>										
Rhinitis	9	1.0	1	1.1	6	1.5	0		2	2.0

Pharyngitis	6	0.7	1	1.1	0		1	0.7	2	2.0
Sinusitis	3	0.3	2	2.3	5	1.2	3	2.0	0	
Increased Cough	3	0.3	2	2.3	1	0.2	1	0.7	0	
Asthma	1	0.1	1	1.1	1	0.2	0		0	
<u>Skin and Appendages</u> Dermatitis										
	7	0.8	0		3	0.7	0		0	
Urticaria	2	0.2	1	1.1	0		0		0	
<u>Urogenital</u> Urinary Tract Infection	4	0.5	0		5	1.2	0		0	
Dysuria	0		2	2.3	0		0		0	

**Reviewer's Comments:** *With the exception of taste perversion, headache and pain, these adverse events do not appear to be frequent events.*

Coded Adverse Events	Brinzolamide 1.0% N=870		Brinzolamide 1.0% + Timolol 0.5% N=88*		Dorzolamide 2.0% N=402		Timolol 0.5% N=147 <sup>d</sup>		Placebo N=101	
	N	%	N	%	N	%	N	%	N	%
<b>Ocular</b>										
Blurred Vision	45	5.1	9	10.2	6	1.5	3	2.0	2	2.0
Discomfort	19	2.2	6	6.8	44	10.9	6	4.1	3	3.0
Foreign Body Sensation	16	1.8	2	2.3	3	0.7	0		0	
Pruritus	8	1.0	0		4	1.0	4	2.7	2	2.0
Dry Eye	9	1.0	0		2	0.5	0		1	1.0
Hyperemia	12	1.4	1	1.1	10	2.5	5	3.4	2	2.0
Pain	7	0.8	0		2	0.5	2	1.4	2	2.0
Discharge NOS	4	0.5	1	1.1	0		0		1	1.0
Keratitis	8	1.0	2	2.3	1	0.2	3	2.0	1	1.0
Corneal Stainig	1	0.1	1	1.1	0		1	0.7	0	
Tearing <sup>†</sup>	2	0.2	0		4	1.0	0		0	
Corneal Abrasion	1	0.1	0		0		1	0.7	2	2.0
Abnormal Vision	2	0.2	0		2	0.5	3	2.0	1	1.0
Diplopia	1	0.1	0		0		0		0	
Conjunctivitis	2	0.2	1	1.1	3	0.7	1	0.7	1	1.0
Decreased Vision	0		1	1.1	0		1	0.7	0	

**Reviewer's Comments:** *The most frequent adverse events associated with Brinzolamide 1%, were blurred vision (5%) and taste perversion (6%).*



10.1.3 Overdose Experience - None

10.2 Other Safety Findings

10.2.1 Laboratory Findings, Vital Signs, ECG's

**Reviewer's Comments:** *There were no clinically significant changes in laboratory values, heart rate, blood pressure, visual acuity, or ocular signs in patients receiving Brinzolamide 1%, however, Brinzolamide does accumulate in red blood cells, as mentioned in the human pharmacology section.*

APPEARS THIS WAY  
ON ORIGINAL

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**12 Conclusions**

1. AZOPT (brinzolamide ophthalmic suspension, 1%) lowers intraocular pressure approximately 4-5 mmHg.
2. AZOPT is equivalent to TRUSOPT only when dosed t.i.d. Neither drug lowers IOP to the extent of Timoptic 0.5%.
3. AZOPT has been shown to have less ocular stinging and burning associated with its use as compared to TRUSOPT.
4. The full safety risks cannot be adequately studied prior to approval, because expected frequency of severe sulfonamide reactions is relatively low.

**Deficiencies**

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.

APPEARS THIS WAY  
ON ORIGINAL

**13 Recommendations**

AZOPT (NDA 20-816) is recommended for approval **contingent** upon incorporation into the labeling of the recommended changes and a response from the sponsor addressing the issues listed in the Deficiencies Section.

**/S/***MD*

Elizabeth N. Ludwig, M.D.  
Medical Officer, Ophthalmology

cc: HFD-550  
HFD-550/Supervisory CSO/LoBianco  
HFD-550/CSO/Gunter  
HFD-550/CHEM/Yaciw  
HFD-550/MICRO/Sweeney  
HFD-550/PHARM/Coulter  
HFD-550/BIOPHARM/Kumi  
HFD-550/BIOSTAT/Lu  
HFD-550/MO/Ludwig  
HFD-550/SMO/Chambers *wac 9/1/97*

**APPEARS THIS WAY  
ON ORIGINAL**

Clinical Review of NDA 20-816  
Amendment

**NDA 20-816**  
**Review #2**

**Submission Date:** 12/15/97  
**Review Date:** 1/22/98

**Applicant:**

Alcon Laboratories  
6201 South Freeway  
Fort-Worth, TX 76134

**Applicant's  
Representative:**

Richard P. Gural  
Vice-President, Regulatory Affairs  
817-551-4630

**Drug:**

AZOPT™ (brinzolamide ophthalmic suspension) 1%

**Pharmacologic Category:**

Carbonic Anhydrase Inhibitor

**Submitted:**

Response to the Approvable letter dated December 4, 1997.  
Includes the response the chemistry and clinical issues, and revised  
draft labeling. Only the clinical issues and the labeling are  
included in this review.

Item numbers are consistent with the items listed on the approvable  
letter.

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NDA 20-816

Page 2

18. **The submitted draft labeling will need to be revised. Please submit revised draft labeling consistent with the enclosed draft labeling, with the addition of osmolality of the drug product added to the Description section. In the submission, please include carton and container labeling consistent with the enclosed draft labeling.**

**Response:** The revised proposed Package Insert is attached. The carton and container labeling will be revised once the proposed Package Insert is approved.

**Reviewer's Comments:**

*Reviewer recommended deletions are noted by ~~strikeout~~ and additions by ~~adding~~ within the review. Note that only revised package insert labeling has been submitted. Alcon states in this submission that the carton and container labeling will be revised when the package insert is approved. This is not acceptable.*

**Reviewer's comments:** *The osmolality was added as requested.*

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NOT  
TO BE  
RELEASABLE

5 pages

NDA 20-816

**Reviewer's comments:** *The NDC numbers were revised. Acceptable.*

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Clinical Issues

27. **There were less than ten patients per arm per center in the major clinical studies. Please provide an explanation.**

Response: All of the sites that participated in the three multicenter Phase 3 studies were recruited and initiated with the intent of enrolling enough patients to complete 10 patients per arm per center. The sites indicated they could enroll approximately two patients per week which would result in enrollment of sufficient patients over a six month period to fulfill the 10 patients per arm per center guidance. However, many of the sites enrolled far fewer patients than anticipated which resulted in less than 10 patients per arm per center at the time when the overall study enrollment was completed. Attempts are always made to select sites that can fulfill the 10 patient per arm per center guidance, however, it is often difficult for sites to accomplish this in a manner consistent with timely completion of the multicenter studies.

**Reviewer's Comment:** *Acknowledged, but not preferable.*

28. **Please provide a time table for the submission of the study report data and conclusions of study C-95-47, regarding drug product's effect on the corneal endothelium.**

Response

Study C-95-47 is an ongoing, long-term, multicenter study evaluating the safety and efficacy of Brinzolamide 1 % (BID and TID) compared to Timolol 0.5% solution (BID). The protocol was amended, subsequent to study initiation, as discussed at the preNDA meeting, to increase the study duration from 12 to 18 months to obtain longer term safety data. This study will be completed in December, 1997 and the final study report will be submitted to the FDA no later than March, 1998.

Consistent with the protocol amendment, an analysis was performed when all patients completed the Month 12 visit. A repeated measures analysis of variance was used to assess differences between treatments over time. The results from the safety analysis demonstrated that there were no adverse effects on corneal health. An assessment of the endothelial cell density change from baseline demonstrated no clinically relevant or statistically significant differences comparing BID Brinzolamide 1% vs BID Timolol 0.5% solution at Month 6 or Month 12 and comparing TID Brinzolamide 1% vs BID Timolol 0.5% solution at

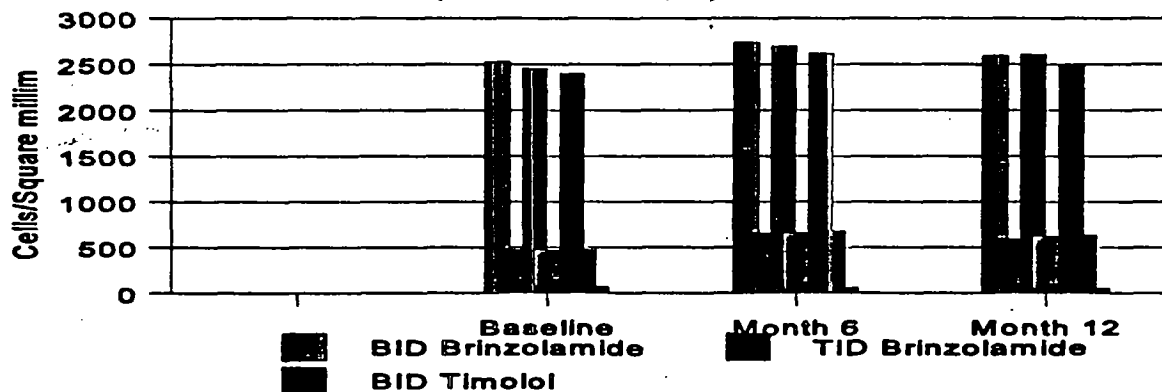
Month 6 or Month 12. In addition, an assessment of the central corneal thickness change from baseline demonstrated no clinically relevant or statistically significant differences comparing BID Brinzolamide 1% vs BID Timolol 0.5% solution at Month 6 ( $p = 0.0859$ ) or Month 12 and comparing TID Brinzolamide 1% vs BID Timolol 0.5% solution at Month 6 or Month 12. These results are presented in the following tables and figures.

**Corneal Endothelial Cell Density**

Group		Baseline	Month 6	Month 12
BID Brinzolamide	Mean	2528	2736	2591
	Std	475	655	589
	N	145	115	106
TID Brinzolamide	Mean	2459	2699	2609
	Std	474	655	622
	N	146	115	102
BID Timolol	Mean	2405	2623	2504
	Std	478	682	639
	N	75	63	56

**Endothelial Cell Density**

(Standard Dev, N)



Reviewer's Comments: *Acceptable.*

29. Please provide an explanation as to why IOP measurements at the "peak time periods" were not included in the ongoing study, C-95-47. -

**Response**

The peak effect of brinzolamide on IOP reduction was obtained in two (2) large multicenter, Phase III primary therapy studies. As reported in the NDA, peak (10 AM) mean IOP reductions across both of these studies ranged from 3.9 to 5.7 mmHg with BID-dosing 4.3 to 5.6 mmHg with TID-dosing.

Study C-95-47 is an ongoing, multicenter, three-arm parallel study whose primary objective is to evaluate the long-term safety of Brinzolamide 1% (BID and TID) compared to Timolol 0.5% solution (BID). Overall safety is being evaluated based upon an assessment of adverse events, laboratory parameters (blood chemistry, hematology and uranalysis), endothelial cell density and corneal thickness.

Efficacy is a secondary endpoint and is being evaluated as an 8 AM trough IOP. Since long-term safety is the focus of the study, only trough IOP measurements are being obtained. The 8 AM trough IOP is probably the most critical IOP measurement to obtain in assessing long-term stability of IOP reduction since this measurement time is at the end of the dosing interval following evening dosing and also the time when the IOP usually increases as a result of normal diurnal variation.

**Reviewer's Comments:** *The IOP information from this study is only minimally helpful because the IOP was not also collected at peak.*

30. Please provide an explanation for the role of Investigator # 1941. It was stated that no patients were randomized to Investigator # 1941, yet, it is reported that one patient completed the study under this investigator.

**Response**

Investigator #1941 (Robert L. Kantor, M.D.) participated in Study C-95-46 and (1) patient at this site was randomized to study drug (Brinzolamide 1 % BID). This patient was discontinued at the Month 1 visit and was included in both the efficacy and safety analyses. The statement in the study report indicating that no patients were randomized at this site was made in error.

**Reviewer's Comments:** *Acceptable.*

NDA 20-816

Page 12

31. The name and address of Investigator 1515 of Study C-92-25 was not provided. Please provide this information.

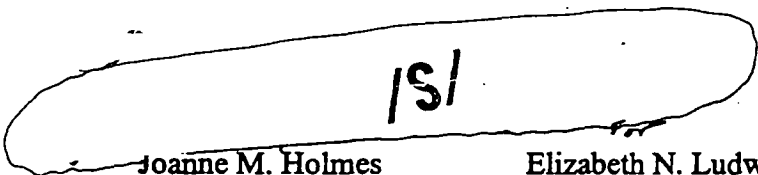
**Response:**

The name and address of Investigator #1515 that participated in Study C-92-25 was omitted in error in the study report. This investigator is as follows: Jay Katz, M.D., Wills Eye Hospital, 900 Walnut Street, Philadelphia, PA 19107.

**Reviewer's Comments:** *Acceptable.*

**Recommendation:**

It is recommended that the labeling be revised as identified above.

 /S/

Joanne M. Holmes

Elizabeth N. Ludwig, MD

 /S/

Wiley A. Chambers, M.D.

cc:

NDA 20-816

HFD-550

HFD-550/Clin Rev/Holmes

HFD-550/Proj Mgr/LoBianco

HFD-550/Chem/Yaciw

HFD-550/Pharm/Coulter

HFD-880/Biopharm/Wang

HFD-550/MO/Ludwig

HFD-550/Dep Dir/Chambers

1335

Clinical Review of NDA 20-816  
Amendment

NDA 20-816  
Review #3

Submission Dates: 1/27 & 28/98  
Review Date: 2/4/98

**Applicant:** Alcon Laboratories  
6201 South Freeway  
Fort Worth, TX 76134

**Applicant's  
Representative:** Scott Krueger  
Director, Regulatory Affairs  
817-551-4630

**Drug:** AZOPT™ (brinzolamide ophthalmic suspension) 1%

**Pharmacologic Category:** Carbonic Anhydrase Inhibitor

**Submitted:** Revised labeling based on previous reviews.

**Reviewer's Comments:**

*Reviewer recommended deletions are noted by ~~strikeout~~ and additions by shading within the review.*

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NDA 20-816

**Recommendation:**

The application is recommended for approval with the revision of the labeling as identified above, reduction of the expiration dating to 18 months for all containers except the 2.5 mL (which should be 12 months), a revised limit for residual solvents and a revised stability protocol for testing inverted samples every six months.

/S/

Wiley A. Chambers, M.D.

cc:

NDA 20-816

HFD-550

HFD-550/Clin Rev/Holmes

HFD-550/Proj Mgr/LoBianco

HFD-550/Chem/Yaciw

HFD-550/Pharm/Coulter

HFD-880/Biopharm/Wang

HFD-550/MO/Ludwig

HFD-550/Dep Dir/Chambers

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ON ORIGINAL

Clinical Review of NDA 20-816  
Amendment

**NDA 20-816**  
**Review #4**

**Submission Dates:** 2/4/98  
**Review Date:** 2/6/98

**Applicant:** Alcon Laboratories  
6201 South Freeway  
Fort Worth, TX 76134

**Applicant's**  
**Representative:** Scott Krueger  
Director, Regulatory Affairs  
817-551-4630

**Drug:** AZOPT™ (brinzolamide ophthalmic suspension) 1%

**Pharmacologic Category:** Carbonic Anhydrase Inhibitor

**Submitted:** Revised labeling based on previous reviews.



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NDA 20-816

**Reviewer's Comments:** — *Acceptable. Carton and container labeling has also been revised to be consistent and is acceptable.*

NDA 20-816

**Recommendation:**

NDA 20-816, Azopt (brinzolamide ophthalmic suspension) is recommended for approval for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

/s/

Wiley A. Chambers, M.D.

cc:

NDA 20-816

HFD-550

HFD-550/Clin Rev/Holmes

HFD-550/Proj Mgr/LoBianco

HFD-550/Chem/Yaciw

HFD-550/Pharm/Coulter

HFD-880/Biopharm/Wang

HFD-550/MO/Ludwig

HFD-550/Dep Dir/Chambers

APPEARS THIS WAY  
ON ORIGINAL

Clinical Review of NDA 20-816  
Amendment

**NDA 20-816**  
**Review #5**

**Submission Dates:** 4/1/98  
**Review Date:** 4/1/98

**Applicant:** Alcon Laboratories  
6201 South Freeway  
Fort Worth, TX 76134

**Applicant's Representative:** Scott Krueger  
Director, Regulatory Affairs  
817-551-4630

**Drug:** AZOPT™ (brinzolamide ophthalmic suspension) 1%

**Pharmacologic Category:** Carbonic Anhydrase Inhibitor

**Submitted:** Revised labeling based on recommendations from the Director of ODE V.

**Labeling:**  
AZOPT™ (brinzolamide ophthalmic suspension) 1%

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**Reviewer's Comments:**

*Acceptable. The labeling has been revised to be consistent with the recommendations.*

**Recommendation:**

NDA 20-816, Azopt (brinzolamide ophthalmic suspension) is recommended for approval for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

/S/

Wiley A. Chambers, M.D.

cc: Orig NDA 20-816  
HFD-550/Clin Rev/Holmes  
HFD-550/Proj Mgr/Gorski  
HFD-550/Chem/Yaciw  
HFD-550/Pharm/Coulter  
HFD-880/Biopharm/Wang  
HFD-550/MO/Ludwig  
HFD-550/Dep Dir/Chambers

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