CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-816

STATISTICAL REVIEW(S)

NDA 20-816

MAY 28 1997

Statistical Review and Evaluation

NDA 20-816
Name of Drug: AZOPT (Brinzolamide) Sterile Ophthalmic Suspension Topical 1.0%
Applicant: Alcon Laboratories, Inc.
Indication: Reduction of Intraocular Pressure (IOP)
Document Reviewed: Statistical Section of NDA 20-816 (Vol. 51-Vol.75) Dated 1/28/97 by CDER
Reviewer: Laura Lu, Ph.D.
Date of Review: 5/28/97

I. Introduction of Clinical Development Plan

The primary object of the Brinzolamide clinical development plan was to establish safety and IOP-lowing efficacy of Brinzolamide Ophthalmic Suspension 1.0% when used as primary and adjunctive therapy. A secondary objective was to demonstrate clinically relevant advantages versus Dorzolamide Ophthalmic Solution 2%, the only marketed topical carbonic anhydrase inhibitors. Such advantages included a favorable dosing regimen (1.0% BID) and a distinct comfort advantage (ocular burning and stinging) compared to Dorzolamide Ophthalmic Solution 2%. The pivotal primary therapy studies (C-95-46 and C-95-48) were designed as equivalency studies with sufficient statistical power to compare directly the Brinzolamide Ophthalmic Suspension 1% dosing regimens (BID and TID) to each other and also to Dorzolamide Ophthalmic Solution 2% TID. The placebo arm in one of primary therapy studies (C-95-46) was included as a control in order to provide both clinical and statistical assessment between the Brinzolamide and Dorzolamide treatment groups of the diurnally-corrected IOP reductions from baseline. The Timolol Ophthalmic Solution 0.5% treatment arm in the other primary therapy study (C-95-48) was included as an active control to validate the design of the equivalency study and to provide a comparison to a commonly used and well accepted therapeutic agent ('gold standard') against which the IOP-lowing efficacy of Brinzolamide Ophthalmic Suspension 1% and and Dorzolamide Ophthalmic Solution 2% could be evaluated. The third pivotal study (C-95-38) was designed as a TID adjunctive therapy study to a beta-blocker (Timolol) to provide the safety experience to support both BID or TID adjunctive therapy. Additionally, two well-controlled, multiple-dose studies (C-96-26 and C-96-40) was conducted to demonstrate a distinct comfort advantage of Brinzolamide TID over Dorzolamide TID.

II. Protocol C-95-46

1. Description of Study Protocol

This is a randomized, triple-masked, parallel group, multi-center, both placebo and active controlled clinical study. The objective of the study is to compare the safety and IOP-lowing efficacy of BID-dosed 1.0% Brinzolamide, TID-dosed 1.0% Brinzolamide, TID-dosed 2.0% Dorzolamide and placebo in patients with primary open-angle glaucoma or ocular hypertension. A total of 385 patients will be enrolled in the study with 110 patients in each of the active treatment groups and 55 patients in the placebo group. After appropriate washout of glaucoma medication(s), patients must have an 8:00 a.m. IOP of 24 to 36 mmHg, inclusive, in at least one eye, with no greater than a 5 mmHg difference between eyes, at both Eligibility Visits 1 and 2. In addition, patients must have an IOP of 21 to 36 mmHg, inclusive, in at least one eye (the same eye), with no greater than a 5 mmHg difference between eyes, at the 10:00 a.m. and 6:00 p.m. measurements at both Eligibility Visits 1 and 2. If these IOP criteria are met, patients will be randomized to receive Brinzolamide 1.0% BID, Brinzolamide 1.0% TID, Dorzolamide 2.0% TID and placebo. Patients will instill masked medication in both eyes at 8:00 a.m., 4:00 p.m. and 10:00 p.m. during a three month treatment phase. Patients will return at Month 1, at which time bilateral IOP measurements will be made at 8:00 a.m. and 10:00 p.m. Patients will then be seen again at Month 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. 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.

2. Primary Statistical Methods

Efficacy Analysis

The statistical objective of this study was to demonstrate the equivalence of BID and TID-dosed Brinzolamide 1.0% and TID-dosed Dorzolamide 2.0% and to demonstrate superiority to placebo. The efficacy analysis was based on the mean IOP change from baseline in the per protocol data set. The safety and intent-to-treat data sets consisted of all patients who received study medications. The per protocol

data set consisted of patients who met the evaluability criteria and the inclusion/exclusion criteria of the protocol. Data from eyes that met the IOP range evaluability criteria at all measurements during both eligibility visits were included in the per-protocol data set. The per-protocol analysis is the primary analysis and the last observation will be carried forward for patients discontinuing due to treatment failure.

The following comparisons of means were planned to demonstrate the equivalence of BID and TID-dosed Brinzolamide 1.0% and TID-dosed Dorzolamide 2.0% and to demonstrate superiority to placebo.

Treatment 1	Treatment 2	Purpose of Comparison
Brinzolamide BID	Placebo	Superiority
Brinzolamide BID	Brinzolamide TID	Equivalence
Brinzolamide BID	Dorzolamide TID	Equivalence
Brinzolamide TID	Placebo	Superiority
Brinzolamide TID	Dorzolamide TID	Equivalence
Dorzolamide TID	Placebo	Superiority

Superiority was declared if the p-value of the comparison was less than 0.05 and the active compound had a better reduction in IOP than placebo. Therapeutic equivalence was declared if a two sided 95% confidence interval of the difference in IOP reduction between treatments fell within ± 1.5 mmHg. The following analysis of variance model (proc Mixed, SAS Version 6.10) was used:

$$Y_{ijklm}=\mu+T_i+M_j+TM_{ij}+D_k+TD_{ik}+TMD_{ijk}+P(T)_{(i)}+\epsilon_{ijklm}$$

where Y stands for IOP change from baseline, T stands for treatments, M stands for months, D stands for time of day, P(T) stands for patients nested within treatment. Patient was considered a random effect to account for the correlation of repeated measures on a patient.

Safety Analysis

Visual Acuity

Descriptive statistics (N, %) for Snellen lines of change from baseline were calculated by treatment group, and the Cochran-Mantel-Haenszel test (proc Freq., SAS version 6.10) was used to compare treatments. Baseline visual acuity was defined as the pre-dosing measurement taken closest to initial dosing (Eligibility Visit 2 when available). For each patient, the eye showing the largest decrease in Snellen lines from baseline to the last study visit was used in the analysis.

Cardiovascular (Pulse and Blood Pressure)

Changes from baseline for pulse, diastolic blood pressure, and systolic blood pressure were analyzed via repeated measures analysis of variance. Change from baseline was calculated at each study visit. Baseline was defined as the pre-dosing measurement taken closest to initial dosing (Eligibility Visit 2 when available). The following statistical model (proc Mixed, SAS Version 6.10) was used to compare treatments:

$$Y_{ijk} = \mu + T_i + V_j + TV_{ij} + P(T)_{k(i)} + \epsilon_{ijk}$$

where Y represents change from baseline for pulse, diastolic blood pressure, or systolic blood pressure, T represents treatments, V represents visits and P(T) represents patients nested within treatments. Patient was considered a random effect to account for the correlation of repeated measures on a patient.

Dilated Fundus

Descriptive statistics (N, %) for Retina/Macula/Choroid, Optic Nerve, and Disc Pallor are presented by treatment group for patients with a clinical worsening in either eye. Clinical worsening was defined as an increase in fundus score from baseline to the last study visit. Baseline values were collected at the Screening exam. The Chi-square test (proc Freq., SAS version 6.10) was used to compare treatment groups for each fundus score.

For Cup/Disc Ratio, one-way analysis of variance (proc Mixed, SAS Version 6.10) was used to analyze change from baseline to end of study. Baseline values were collected at the Screening exam. For each patient, the average of the patient's two eyes was used in the analysis.

Ocular Signs

Descriptive statistics (N, %) for Eyelids/Conjunctiva, Cornea, Iris/Anterior Chamber, Lens, and Vitreous are presented by treatment group for patients with a clinical worsening in either eye. Clinical worsening was defined as an increase in ocular sign score from baseline to any follow-up visit. Baseline was defined as the pre-dosing measurement taken closest to initial dosing (Eligibility Visit 2 when available). The Chi-square test (proc Freq., SAS Version 6.10) was used to compare treatment groups for each ocular sign.

Visual Field

One-way analysis of variance (proc Mixed, SAS Version 6.10) was used to compare change from baseline among treatments at the last study visit for these parameters. Baseline values were obtained at Eligibility Visit 2. For each patient, the average of the two eyes was used in the analysis.

Pupil Diameter

One-way analysis of variance (proc Mixed, SAS Version 6.10) was used to compare change from baseline among treatments at the last study visit for pupil diameter. Baseline values were obtained at Eligibility Visit 2. For each patient, the average of the two eyes was used in the analysis.

3. Sponsor's Results

Patient Disposition and Evaluability

A total of 463 patients across 24 investigational sites was randomized to treatments. Fifty-four (54) of the 463 patients randomized to treatments were not evaluable for efficacy and thus excluded from the primary per protocol efficacy analysis but included in the intent-to-treat analysis. The distribution by reason and treatment group of patients excluded from the efficacy analysis is listed in Table 3, Page 8-02502 of NDA 20-816, with the most common reasons being IOP asymmetry (17 patients), no on-therapy IOP data (14 patients) and non-qualifying IOP (13 patients). The overall number of patients included in efficacy analysis at each treatment visit ranged from 409 to 389 as summarized below.

Number of Patients Included in Per Protocol Analysis at Each Visit

Explanation	Treatment	baseline	Month 1		Month 2			Month 3		
			8am	10am	8am	10am	6pm	8am	10am	6pm
Observed Data	Brinzolamide 1.0% BID	115	115	115	110	110	109	107	106	106
	Brinzolamide 1.0% TID	124	124	124	122	122	122	120	120	120
	Dorzolamide 2.0% TID	114	113	113	113	113	113	112	112	111
	Placebo	56	55	55	50	50	50	51	51	51
	Total Visits Observed	409	407	407	395	395	394	390	389	388
Data Carried Forward for Treatment Failures	Brinzolamide 1.0% BID	0	0	0	2	2	0	3	3	1
	Brinzolamide 1.0% TID	0	0	0	1	1	0	1	1	0
	Dorzolamide 2.0% TID	0	0	0	0	0	0	0	0	0
	Placebo	0	0	0	1	1	0	1	1	0
	Total Visits Carried	0	0	0	4	4	0	5	5	1
	Total Visits	409	407	407	399	399	394	395	394	389
Discontinuation [1]	Brinzolamide 1.0% BID	0	0	0	3	3	3	3	3	5
	Brinzolamide 1.0% TID	0	0	0	0	0	0	1	1	2
	Dorzolamide 2.0% TID	0	0	0	0	0	0	1	1	1
	Placebo	0	0	0	2	2	2	2	2	3
	Total	0	0	0	5	5	5	7	7	11
Visits not Evaluable for Ongoing Patients	Brinzolamide 1.0% BID	0	0	0	0	0	3	2	3	3
	Brinzolamide 1.0% TID	0	0	0	1	1	2	2	2	2
	Dorzolamide 2.0% TID	0	1	1	1	1	1	1	1	2
	Placebo	0	1	1	3	3	4	2	2	2
	Total	0	2	2	5	5	10	7	8	9
Total Not Evaluable		0	2	2	10	10	15	14	15	20
Total Patients		409	409	409	409	409	409	409	409	409

[1]Note that 13 patients discontinued in the per protocol data set. Eleven (11) of these discontinued before Month 3, 1 patient had data carried forward from Month 2, and Patient 1355 had Month 3 data but did not complete the study as planned.

Patient Demographics and Baseline Characteristics

No significant differences (all $p \geq 0.13$) were observed between treatment groups with respect to baseline IOP, mean age, age distribution (elderly vs non-elderly), sex distribution, iris color distribution, race distribution and ocular diagnosis distribution. For detailed information see Tables 6 and 8, Pages 8-02506 and 8-02508 of NDA 20-816.

Efficacy

The efficacy results showed below were all from per protocol analysis, and were also confirmed by intent-to-treat analysis.

IOP Changes From Baseline

The mean changes from baseline for Brinzolamide 1.0% were approximately -4.0 mmHg in the BID treatment group and approximately -4.5 mmHg in the TID treatment group. The changes from baseline were statistically significant (all $p < 0.001$) for both the BID and the TID groups at all times of day (8 a.m., 10 a.m. and 6 p.m.) at all visits (Months 1,2 and 3). Likewise, the mean changes from baseline for Dorzolamide 2.0% TID were approximately -4.5 mmHg and were also statistically significant (all $p < 0.001$) at all times of day (8 a.m., 10 a.m. and 6 p.m.) at all visits (Months 1, 2 and 3). Detailed results are in Tables 7 and 8, Pages 8-02507 and 8-02508 of NDA 20-816.

Placebo Comparisons

The following results demonstrated that IOP changes following both BID (-3.4 to -4.1 mmHg) and TID-dosing(-4.1 to -4.8 mmHg) with Brinzolamide and TID-dosing with Dorzolamide (-4.3 to -4.9 mmHg) were all clinically and statistically significant (all $p \leq 0.0177$) compared to placebo.

Comparison of Mean IOP Changes to Placebo by Visit and Time of Day

	Month 1		Month 2			Month 3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
Brinzolamide 1.0% BID[1]	-3.4	-3.9	-3.9	-3.9	-3.4	-4.1	-4.1	-3.6
Placebo[1]	-2.2	-2.3	-2.0	-2.6	-2.3	-2.3	-2.2	-2.2
p-value[2]	0.0101	0.0007	0.0001	0.0090	0.0177	0.0004	0.0001	0.0058
Brinzolamide 1.0% TID[1]	-4.5	-4.3	-4.8	-4.6	-4.1	-4.6	-4.8	-4.2
Placebo[1]	-2.2	-2.3	-2.0	-2.6	-2.3	-2.3	-2.2	-2.2
p-value[2]	0.0000	0.0000	0.0000	0.0001	0.0002	0.0000	0.0000	0.0000
Dorzolamide 2.0% TID[1]	-4.3	-4.6	-4.5	-4.7	-4.3	-4.4	-4.9	-4.3
Placebo[1]	-2.2	-2.3	-2.0	-2.6	-2.3	-2.3	-2.2	-2.2
p-value[2]	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

[1]All IOP changes are LSMEANS (in mmHg) from corresponding diurnal baseline.
[2]P value for the difference in LSMEAN IOP between the treatment groups.

Clinical Utility of BID and TID Brinzolamide

The IOP-lowering efficacy of Brinzolamide was further evaluated by an analysis of those patients that either responded (IOP reduction ≥ 5.0 mmHg) or were controlled (IOP ≤ 21.0 mmHg) following treatment.

Analysis of Patients That Responded or Were Controlled by Visit and Time of Day[1]

		Month 1		Month 2			Month 3		
		8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment									
Brinzolamide 1.0% BID	%	38.3	60.0	49.1	65.2	62.4	50.0	67.0	62.6
	n	115	115	112	112	109	110	109	107
Brinzolamide 1.0% TID	%	52.4	64.5	56.1	69.1	69.7	60.3	68.6	72.5
	n	124	124	123	123	122	121	121	120
Dorzolamide 2.0% TID	%	54.0	70.8	58.4	67.3	73.5	54.5	76.8	73.9
	n	113	113	113	113	113	112	112	111
Placebo	%	23.6	32.7	33.3	45.1	42.0	25.0	42.3	52.9
	n	55	55	51	51	50	52	52	51

[1]Response is defined as having an IOP reduction ≥ 5.0 mmHg from corresponding diurnal baseline. Control is defined as having an IOP ≤ 21.0 mmHg.

The above results show that 38.3% to 67.0% of the patients either responded (IOP reduction ≥ 5.0 mmHg) or were controlled (IOP ≤ 21.0 mmHg) in BID Brinzolamide group, 52.4% to 72.5% of the patients either responded or were controlled in TID Brinzolamide group, and 54.0% tp 76.8% of the patients either responded or were controlled in TID Dorzolamide group. Smaller percentages of placebo patients (23.6% to 52.9%) either responded or were controlled.

EQUIVALENCE COMPARISON

Brinzolamide 1.0% TID vs Dorzolamide 2.0% TID

The following results showed that the upper 95% confidence limits for the difference in IOP reduction between the treatment groups were less than 1.5 mmHg at all time points. Thus, TID-dosing with Brinzolamide 1.0% produced IOP reductions both clinically and statistically equivalent to the IOP reductions produced by TID-dosing with Dorzolamide 2.0%.

Comparison of Mean IOP Changes and Confidence Limit By Visit and Time of Day (TID Brinzolamide vs TID Dorzolamide)

	Month 1		Month 2			Month 3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
Brinzolamide 1.0% TID[1]	-4.5	-4.3	-4.8	-4.6	-4.1	-4.6	-4.8	-4.2
Dorzolamide 2.0% TID[1]	-4.3	-4.6	-4.5	-4.7	-4.3	-4.4	-4.9	-4.3
TID-DORZ	-0.3	0.3	-0.3	0.1	0.2	-0.2	0.1	0.1
Upper 95% CL[2]	0.50	1.08	0.41	0.86	0.96	0.60	0.81	0.83

[1]All IOP changes are LSMEANS (in mmHg) from corresponding diurnal baseline.
[2]Upper 95% confidence limit for the difference between Brinzolamide and Dorzolamide.

Brinzolamide 1.0% BID vs Dorzolamide 2.0% TID

The results at each individual visits show that the upper 95% confidence limits for the difference in IOP reduction between treatment groups were less than or equal to 1.5 mmHg at four (4) of the eight (8) time points.

Comparison of Mean IOP Changes and Confidence Limit By Visit and Time of Day (BID Brinzolamide vs TID Dorzolamide)

Month	1		2			3		
Time	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
Brinzolamide 1.0% BID[1]	-3.4	-3.9	-3.9	-3.9	-3.4	-4.1	-4.1	-3.6
Dorzolamide 2.0% TID[1]	-4.3	-4.6	-4.5	-4.7	-4.3	-4.4	-4.9	-4.3
BID-DORZ	0.8	0.7	0.6	0.8	0.9	0.4	0.8	0.7
Upper 95% CL[2]	1.62	1.49	1.33	1.54	1.63	1.13	1.54	1.50

[1]All IOP changes are LSMEANS (in mmHg) from corresponding diurnal baseline.
[2]Upper 95% confidence limit for the difference between Brinzolamide and Dorzolamide.

Brinzolamide 1.0% BID vs Brinzolamide 1.0% TID.

The results at each individual visits showed that the upper 95% confidence limits for the difference in IOP reduction between treatment groups were less than 1.5 mmHg at six (6) of the eight (8) time points.

Comparison of Mean IOP Changes and Confidence Limit by Visit and Time of Day (BID Brinzolamide vs TID Brinzolamide)

Month	1		2			3		
Time	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
Brinzolamide 1.0% BID[1]	-3.4	-3.9	-3.9	-3.9	-3.4	-4.1	-4.1	-3.6
Brinzolamide 1.0% TID[1]	-4.5	-4.3	-4.8	-4.6	-4.1	-4.6	-4.8	-4.2
BID-TID	1.1	0.4	0.9	0.7	0.7	0.5	0.7	0.6
Upper 95% CL[2]	1.85	1.14	1.67	1.42	1.41	1.28	1.48	1.41

[1]All IOP changes are LSMEANS (in mmHg) from corresponding diurnal baseline.
[2]Upper 95% confidence limit for the difference between Brinzolamide and Dorzolamide.

Subgroup Analysis

The subgroup analysis (sex, age, race and iris color) results were consistent with the whole group results.

Safety

Ocular Events Related to Therapy

Most Frequent Ocular-Related Events

Ocular Events	Brinzolamide 1% BID N=134		Brinzolamide 1% TID N=133		Dorzolamide 2% TID N=131		Placebo N=65	
	N	%	N	%	N	%	N	%
Discomfort	4	3.0	4	3.0	14	10.7	1	1.5
Blurred Vision	4	3.0	3	2.3	0	0	1	1.5

Nonocular Events Related to Therapy

Most Frequent Nonocular-Related Events

Nonocular Events	Brinzolamide 1% BID N=134		Brinzolamide 1% TID N=133		Dorzolamide 2% TID N=131		Placebo N=65	
	N	%	N	%	N	%	N	%
Taste Perversion	5	3.7	9	6.8	7	5.3	0	0

Serious Events Related to Therapy
No serious events related to therapy were reported during the study (Table 27, Page 8-02539 of NDA 20-816).

Other Safety Parameters

There was no statistically significant difference in worsening from baseline in visual acuity, ocular signs, dilated fundus, visual fields and change in pulse for any treatment group. Analysis of variance indicated a statistically significant ($p = 0.0018$) effect on systolic pressure between Brinzolamide 1.0% BID and Dorzolamide 2.0%, and a statistically significant ($p = 0.0063$) effect between Placebo and Dorzolamide 2.0%.

Summary Statistics for Systolic Blood Pressure Change from Baseline

			Change from Baseline		
Treatment		**Baseline**	**Month 1**	**Month 2**	**Month 3**
BID BRINZOL	MEAN	131.8	0.9	1.6	2.1
	STD	16.0	14.7	13.8	14.6
	N	134	127	121	118
	MIN				
	MAX				
TID BRINZOL	MEAN	134.4	-1.2	-0.6	-1.7
	STD	17.4	14.1	15.7	16.4
	N	133	127	126	124
	MIN				
	MAX				
TID DORZOL	MEAN	137.3	-3.2	-4.1	-4.0
	STD	16.7	16.1	16.6	16.7
	N	131	126	125	125
	MIN				
	MAX				
PLACEBO	MEAN	132.6	1.1	2.4	1.5
	STD	16.5	13.4	13.0	14.9
	N	65	62	60	59
	MIN				
	MAX				

$p = 0.0058$ from repeated measures analysis of variance comparing treatment groups. Pairwise comparisons showed a significant difference between BID BRINZOL and TID DORZOL ($p = 0.0018$) and between PLACEBO and TID DORZOL ($p = 0.0063$).

4. Reviewer's Comments

IOP Reduction from Baseline.

The mean IOP reductions were 3.5 mmHg to 4.0 mmHg (13.0% to 16.7%) for Brinzolamide BID, 4.0 mmHg to 4.6 mmHg (16.6% to 19.1%) for Brinzolamide TID, 4.2 mmHg to 4.7 mmHg (16.9% to 20.1%) for Dorzolamide TID and 2.1 mmHg to 2.4 mmHg (9.1% to 11.6%) for placebo. IOP was significantly (statistically) reduced from baseline in all four groups including the placebo group (2.2 to 2.6 mmHg). The net gain of IOP reduction for Brinzolamide BID, TID and Dorzolamide TID over placebo were 1.2 mmHg to 1.7 mmHg, 1.7 mmHg to 2.5 mmHg and 1.9 mmHg to 2.3 mmHg.

Equivalence Comparison

In 'General Guidance for Glaucoma/IOP lowing Clinical Trials', the statistical consideration for equivalence recommended by FDA is '95% confidence interval within 1.5 mmHg for all time points and within 1 mmHg for the majority of time points measured.'.

The equivalence comparison results of Brinzolamide BID vs. Dorzolamide TID showed that all the upper limits of the 95% confidence intervals were above 1 mmHg, and 5 of the 8 upper limits were at least 1.5 mmHg.

The equivalence comparison results of Brinzolamide BID vs. Brinzolamide TID showed that all the upper limits of the 95% confidence intervals were above 1 mmHg, and 2 of the 8 upper limits were at least 1.5 mmHg.

The above results do not support the sponsor's claim of the equivalence of Brinzolamide BID to Brinzolamide TID and Dorzolamide TID. However, the Brinzolamide TID was shown to be equivalent to Dorzolamide TID.

Clinical Utility of BID and TID Brinzolamide

The results in the sponsor's 'Clinical Utility of BID and TID Brinzolamide' section were all referring to the respond/control rate of patients at each individual time point. The rates of patients who consistently responded or were under control in 1 month, 2 months and 3 months are listed in the following table.

The Rates of Patients That Responded or Were Controlled in Different Periods

	Periods		
	In All 3 Months	In Both Months 2 and 3	In Month 3
BID Brinzolamide	15.9%(17/107)	26.1%(28/107)	42.0%(45/107)
TID Brinzolamide	24.1%(29/120)	34.1%(41/120)	49.1%(59/120)
TID Dorzolamide	25.2%(28/111)	31.5%(35/111)	49.5%(55/111)
Placebo	8.0%(4/50)	10.0%(5/50)	15.6%(8/51)

Results at Different Study Sites

Only 2 of 24 sites had more than 10 patients at all treatment arms. No systematic differences among investigators are assessable due to the small sample sizes.

III. Protocol C-95-48

1. Description of Study Protocol

This is a randomized, triple-masked, parallel group, multi-center, and active controlled clinical study. The objective of the study is to compare the safety and IOP-lowing efficacy of BID-dosed 1.0% Brinzolamide, TID-dosed 1.0% Brinzolamide, TID-dosed 2.0% Dorzolamide and BID-dosed Timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. The design of this study is identical to Protocol C-95-46 with placebo replaced by Timolol BID.

2. Primary Statistical Analyses

The efficacy and safety analyses in Protocol C-95-48 are the same as those in Protocol C-95-46.

3. Sponsor's Results

Patient Disposition and Evaluability

A total of 572 patients across 46 investigational sites was randomized to treatments. Sixty (60) of the 572 patients randomized to treatments were not evaluable for efficacy and thus excluded from the primary per protocol efficacy analysis but included in the intent-to-treat analysis. The

distribution by reason and treatment group of patients excluded from the efficacy analysis is listed in Table 3, Page 8-04859 of NDA 20-816, with the most common reasons being IOP asymmetry (20 patient), non-qualifying IOP (16 patients) and contraindicated concomitant medication (15 patients). The overall number of patients included in the efficacy analysis at each treatment visit ranged from 483 to 512 as summarized below.

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Number of Patients Included in Per Protocol Analysis at Each Visit

Explanation	Treatment	Baseline	Month 1		Month 2			Month 3		
			8a	10a	8a	10a	6p	8a	10a	6p
Observed Data	Brinzolamide 1.0% BID	150	150	149	143	143	143	143	143	142
	Brinzolamide 1.0% TID	148	148	148	139	139	139	137	136	135
	Dorzolamide 2.0% TID	149	148	148	144	144	142	145	145	145
	Timolol 0.5% BID	65	65	65	60	61	61	58	58	58
	Total Visits Observed	512	511	510	486	487	485	483	482	480
Data Carried Forward for Treatment Failures	Brinzolamide 1.0% BID	0	0	0	2	1	0	2	1	0
	Brinzolamide 1.0% TID	0	0	0	3	3	0	4	4	1
	Dorzolamide 2.0% TID	0	0	0	1	1	0	1	1	0
	Timolol 0.5% BID	0	0	0	1	1	0	3	3	2
	Total Visits Carried	0	0	0	7	6	0	10	9	3
	Total Visits	**512**	**511**	**510**	**493**	**493**	**485**	**493**	**491**	**483**

Number of Patients Not Included in Per Protocol Analysis at Each Visit

Explanation	Treatment	Baseline	Month 1		Month 2			Month 3		
			8a	10a	8a	10a	6p	8a	10a	6p
Discontinuation [1]	Brinzolamide 1.0% BID	0	0	0	0	0	0	0	1	2
	Brinzolamide 1.0% TID	0	0	0	0	0	0	0	0	3
	Dorzolamide 2.0% TID	0	0	0	0	0	0	0	0	1
	Timolol 0.5% BID	0	0	0	0	0	0	0	0	1
	Total	0	0	0	0	0	0	0	1	7
Visits not Evaluable for Ongoing Patients	Brinzolamide 1.0% BID	0	0	1	5	6	7	5	5	6
	Brinzolamide 1.0% TID	0	1	0	6	6	9	7	8	9
	Dorzolamide 2.0% TID	0	0	1	4	4	7	3	3	3
	Timolol 0.5% BID	0	0	0	4	3	4	4	4	4
	Total	0	1	2	19	19	27	19	20	22
Total Not Evaluable		0	1	2	19	19	27	19	21	29
Total Patients		**512**	**512**	**512**	**512**	**512**	**512**	**512**	**512**	**512**

[1]Note that 10 patients discontinued in the per protocol data set. Seven (7) of these patients discontinued before Month 3, and 3 patients had data carried forward from previous visits.

Patient Demographics and Baseline Characteristics

No significant differences (all $p \geq 0.34$) were observed between treatment groups with respect to baseline IOP, mean age, age distribution (elderly vs non-elderly), sex distribution, iris color distribution, race distribution and ocular diagnosis distribution. Detailed results were listed in Tables 6 and 8, Pages 8-04863 and 8-04865 of NDA 20-816.

Efficacy

The efficacy results showed below were all from per protocol analysis, and were also confirmed by intent-to-treat analysis.

IOP Changes From Baseline

The mean changes from baseline for Brinzolamide 1.0% were approximately -4.8 mmHg in the BID treatment group and approximately -5.0 mmHg in the TID treatment group. The changes from baseline were statistically significant (all $p < 0.001$) for both the BID and the TID groups at all times of day (8 a.m., 10 a.m. and 6 p.m.) at all visits (Months 1, 2 and 3). Likewise, the mean changes from baseline for Dorzolamide 1.0% TID were approximately -5.0 mmHg and were also statistically significant (all $p < 0.001$) at all times of day (8 a.m., 10 a.m. and 6 p.m.) at all visits (Months 1, 2 and 3). Detailed results are in Table 7 and Table 8, Pages 8-04864 and 8-04865 of NDA 20-816.

Timolol Comparisons

The results of IOP reduction from baseline at each individual time points are listed as follows.

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

	Month 1		Month 2			Month 3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
Brinzolamide 1.0% BID[1]	-3.8	-4.8	-4.3	-5.4	-4.7	-4.7	-5.7	-4.8
Timolol 0.5% BID[1]	-5.2	-5.7	-5.8	-6.0	-5.6	-5.8	-6.3	-5.4
p-value[2]	0.0027	0.0625	0.0009	0.2044	0.0495	0.0244	0.1451	0.1540
Brinzolamide 1.0% TID[1]	-4.2	-4.8	-4.7	-5.3	-4.9	-5.0	-5.6	-5.1
Timolol 0.5% BID[1]	-5.2	-5.7	-5.8	-6.0	-5.6	-5.8	-6.3	-5.4
p-value[2]	0.0301	0.0434	0.0142	0.1350	0.1476	0.1017	0.1034	0.4261
Dorzolamide 2.0% TID[1]	-4.3	-5.3	-4.7	-5.7	-5.0	-4.8	-5.9	-5.3
Timolol 0.5% BID[1]	-5.2	-5.7	-5.8	-6.0	-5.6	-5.8	-6.3	-5.4
p-value[2]	0.0498	0.4198	0.0127	0.4815	0.2102	0.0359	0.3623	0.8508

[1]All IOP changes are LSMEANS (in mmHg) from corresponding diurnal baseline.
[2]P value for the difference in LSMEAN IOP between the treatment groups.

Clinical Utility of BID and TID Brinzolamide

The rates of patients who responded (IOP reduction ≥ 5.0 mmHg) or were controlled (IOP ≤ 21.0 mmHg) are listed in the following table.

Analyses of Patients That Responded or Were Controlled by Visit and Time of Day[1]

		Month 1		Month 2			Month 3		
		8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment									
Brinzolamide 1.0% BID	%	42.7	69.1	51.7	74.3	70.6	53.8	75.7	72.5
	n	150	149	145	144	143	145	144	142
Brinzolamide 1.0% TID	%	48.0	67.6	54.2	73.2	77.7	60.3	77.9	80.1
	n	148	148	142	142	139	141	140	136
Dorzolamide 2.0% TID	%	45.3	65.5	52.4	72.4	74.6	55.5	78.1	80.0
	n	148	148	145	145	142	146	146	145
Timolol 0.5% BID	%	63.1	67.7	68.9	77.4	90.2	73.8	82.0	76.7
	n	65	65	61	62	61	61	61	60

[1]Response is defined as having an IOP reduction ≥ 5.0 mmHg from corresponding diurnal baseline. Control is defined as having an IOP ≤ 21.0 mmHg.

The results show that 42.7% to 75.7% of the patients who took BID Brinzolamide either responded (IOP reduction ≥ 5.0 mmHg) or were controlled (IOP ≤ 21.0 mmHg). This compares with results obtained with TID-dosing with Brinzolamide 1.0% (48.0% to 80.1%) and TID-dosing with Dorzolamide 2.0% (45.3% to 80.0%). Higher percentages of Timolol 0.5% BID patients (63.1% to 90.2%) either responded or were controlled.

Equivalence Comparison

Brinzolamide 1.0% TID vs Dorzolamide 2.0% TID

The results of IOP reduction from baseline at each individual time points are listed as follows.

Comparison of Mean IOP Changes and Confidence Limit By Visit and Time of Day (TID Brinzolamide vs TID Dorzolamide)

	Month 1		Month 2			Month 3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
Brinzolamide 1.0% TID [1]	-4.2	-4.8	-4.7	-5.3	-4.9	-5.0	-5.6	-5.1
Dorzolamide 2.0% TID[1]	-4.3	-5.3	-4.7	-5.7	-5.0	-4.8	-5.9	-5.3
TID-DORZ	0.1	0.6	-0.0	0.4	0.1	-0.2	0.3	0.3
Upper 95% CL[2]	0.79	1.24	0.69	1 07	0.80	0.49	1.04	0.99

[1]All IOP changes are LSMEANS (in mmHg) from corresponding diurnal baseline.
[2]Upper 95% confidence limit for the difference between Brinzolamide and Dorzolamide.

In summary, TID-dosing with Brinzolamide was clinically and statistically (confidence limit ≤ 1.5 mmHg) equivalent to TID-dosing with Dorzolamide in reducing IOP.

Brinzolamide 1.0% BID vs Dorzolamide 2.0% TID

The results of IOP reduction from baseline at each individual time points are listed as follows.

Comparison of Mean IOP Changes and Confidence Limit By Visit and Time of Day
(BID Brinzolamide vs TID Dorzolamide)

	Month 1		Month 2			Month 3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
Brinzolamide 1.0% BID[1]	-3.8	-4.8	-4.3	-5.4	-4.7	-4.7	-5.7	-4.8
Dorzolamide 2.0% TID[1]	-4.3	-5.3	-4.7	-5.7	-5.0	-4.8	-5.9	-5.3
BID-DORZ	0.5	0.5	0.4	0.3	0.3	0.1	0.3	0.6
Upper 95% CL[2]	1.16	1.17	1.08	0.96	1.03	0.77	0.95	1.27

[1]All IOP changes are LSMEANS (in mmHg) from corresponding diurnal baseline.
[2]Upper 95% confidence limit for the difference between Brinzolamide and Dorzolamide.

Brinzolamide 1.0% BID vs Brinzolamide 1.0% TID

The results of IOP reduction from baseline at each individual visit are as follows.

Comparison of Mean IOP Changes and Confidence Limit by Visit and Time of Day
(BID Brinzolamide vs TID Brinzolamide)

	Month 1		Month 2			Month 3		
	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Treatment								
Brinzolamide 1.0% BID[1]	-3.8	-4.8	-4.3	-5.4	-4.7	-4.7	-5.7	-4.8
Brinzolamide 1.0% TID[1]	-4.2	-4.8	-4.7	-5.3	-4.9	-5.0	-5.6	-5.1
BID-TID	0.4	-0.1	0.4	-0.1	0.2	0.3	-0.1	0.3
Upper 95% CL[2]	1.07	0.62	1.09	0.60	0.94	0.98	0.62	1.00

[1]All IOP changes are LSMEANS (in mmHg) from corresponding diurnal baseline.
[2]Upper 95% confidence limit for the difference between Brinzolamide and Dorzolamide.

Subgroup Analysis

The subgroup analysis (sex, age, race and iris color) results were consistent with the whole group results.

Safety

Ocular Events Related to Therapy

Most Frequent Ocular-Related Events

Ocular 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	%
Blurred Vision	5	3.0	5	3.0	1	0.6	0	0
Discomfort	3	1.8	4	2.4	27	16.4	2	2.7

Nonocular Events Related to Therapy

Most Frequent Nonocular-Related Events

Nonocular 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	%
Taste Perversion	5	3.0	13	7.7	7	4.2	0	0

Serious Events Related to Therapy

No serious events related to therapy were reported during the study (Table 27, Page 8-04894 of NDA 20-816).

Other Safety Parameters

There was no statistically significant difference in worsening from baseline in visual acuity, ocular signs, dilated fundus, visual fields and change in blood pressure for any treatment group. Statistically significant differences from baseline in pulse change were noted for Brinzolamide BID and Timolol, Brinzolamide TID and Timolol. Detailed results are listed below.

Summary Statistics for Pulse Change From Baseline

Treatment		Baseline	Change from Baseline Month 1	Month 2	Month 3
BID BRINZOL	MEAN	73.0	0.7	-0.3	-0.6
	STD	9.8	8.2	9.3	9.3
	N	164	163	155	154
	MIN				
	MAX				
TID BRINZOL	MEAN	73.7	-0.4	-1.1	-2.3
	STD	8.7	8.7	8.5	8.5
	N	169	166	159	152
	MIN				
	MAX				
TID DORZOL	MEAN	73.9	0.4	-0.6	-1.2
	STD	8.9	7.1	8.7	7.5
	N	165	159	155	154
	MIN				
	MAX				
BID TIMOLOL	MEAN	74.2	-2.5	-3.3	-3.9
	STD	9.0	7.5	8.9	9.3
	N	73	73	71	69
	MIN				
	MAX				

P = 0.0073 from repeated measures analysis of variance comparing treatment groups. Pairwise comparisons showed a significant difference between BID BRINZOL and BID TIMOLOL (p = 0.0011), and between TID DORZOL and BID TIMOLOL (p = 0.0047). Analysis of variance results and supporting data are located in Appendix V, page 351.

4. Reviewer's Comments

Timolol Comparison

Although the IOP deductions of BID Brinzolamide and TID Brinzolamide were not statistically smaller than that of Timolol at all 8 time points (4 of 8 in BID and Timolol comparison and 3 of 8 in TID and Timolol comparison), the magnitude of the IOP deductions of BID Brinzolamide and TID Brinzolamide were consistently smaller than that of Timolol

<= Timolol-BID <= <= Timolol-

TID <=

Clinical Utility of BID and TID Brinzolamide

The results in the sponsor's 'Clinical Utility of BID and TID Brinzolamide' section were all referring to the respond/control rate of patients at each individual time point. The rates of patients who consistently responded or were under control in 1 month, 2 months and 3 months are listed in the following table.

The Rates of Patients That Responded or Were Controlled in Different Periods

	Periods		
	In All 3 Months	In Both Months 2 and 3	In Month 3
BID Brinzolamide	19.0%(27/142)	28.9%(41/142)	44.4%(63/142)
TID Brinzolamide	24.3%(33/136)	36.8%(50/136)	49.3%(67/136)
TID Dorzolamide	22.8%(33/145)	31.7%(45/142)	46.5%(66/142)
Timolol	41.7%(25/60)	50.0%(30/60)	61.7%(37/60)

Equivalence Comparison

The sponsor's results showed that the upper limits of 95% confidence intervals of mean(BID-DORZ) were all less than 1.5 mmHg, but the majority (5 of the 8) of them were over 1 mmHg, and the other three were close to 1 mmHg. These results do not support the equivalence claim of BID Brinzolamide and TID Dorzolamide. However, Brinzolamide TID was shown to be equivalent to Dorzolamide TID.

Results at Different Study Sites

Only 1 of the 42 investigators had more than 10 patients at all treatment arms. Differences between investigator sites are not statistically assessable due to the small sample sizes. As suggested by the medical officer, the statistical reviewer summarized the IOP changes from baseline separately for domestic patients (n=3594) and European patients (n=1901). The mean IOP changes are presented in the following tables and figures. Figure 1 shows that, among the domestic patients, the Timolol group has a higher mean IOP

reduction than other treatment groups consistently along all time points, which confirms the result in the overall group. Figure 2 shows that, among European patients, none of the four treatments are consistently more effective in IOP reduction than other groups. The IOP reductions at 10am are higher than that at 8am and 6pm among European patients.

Comparison of Mean IOP Changes to Timolol by Visit and Time of Day
(Domestic Patients Only)

	Month 1		Month 2			Month 3		
Treatment	8 am	10 am	8 am	10 am	6 pm	8 am	10 am	6 pm
Brinzolamide 1.0% BID[1] (n=1033)	-4.1	-4.4	-4.7	-5.2	-4.6	-5.1	-5.5	-4.7
Brinzolamide 1.0% TID[1] (n=1054)	-4.3	-4.6	-4.8	-4.8	-4.8	-5.1	-5.5	-5.1
Dorzolamide 2.0% TID[1] (n=1033)	-4.1	-4.9	-4.8	-5.5	-4.9	-5.1	-5.6	-5.1
Timolol 0.5% BID[1] (n=474)	-5.1	-5.5	-6.3	-6.1	-5.7	-6.4	-6.5	-5.5

Comparison of Mean IOP Changes to Timolol by Visit and Time of Day
(European Patients Only)

	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[1] (n=579)	-3.3	-5.7	-3.6	-5.9	-4.8	-4.0	-6.1	-4.9
Brinzolamide 1.0% TID[1] (n=526)	-4.0	-5.1	-4.6	-6.3	-5.2	-4.8	-5.8	-5.0
Dorzolamide 2.0% TID[1] (n=579)	-4.5	-6.1	-4.6	-6.1	-5.2	-4.8	-6.5	-5.7
Timolol 0.5% BID[1] (n=217)	-5.2	-6.1	-4.7	-5.9	-5.3	-4.5	-6.1	-5.3

Figure 1. Mean IOP Change (Domestic Patients Only)

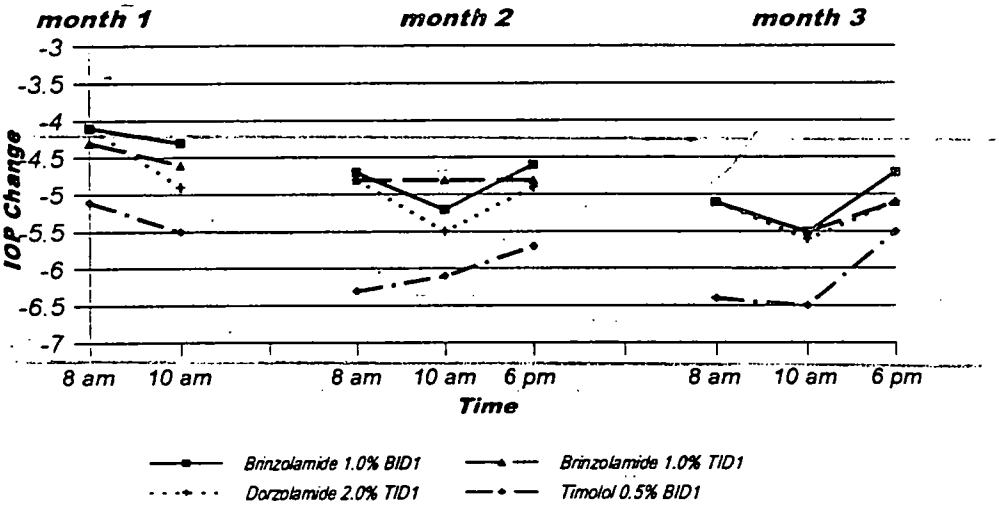
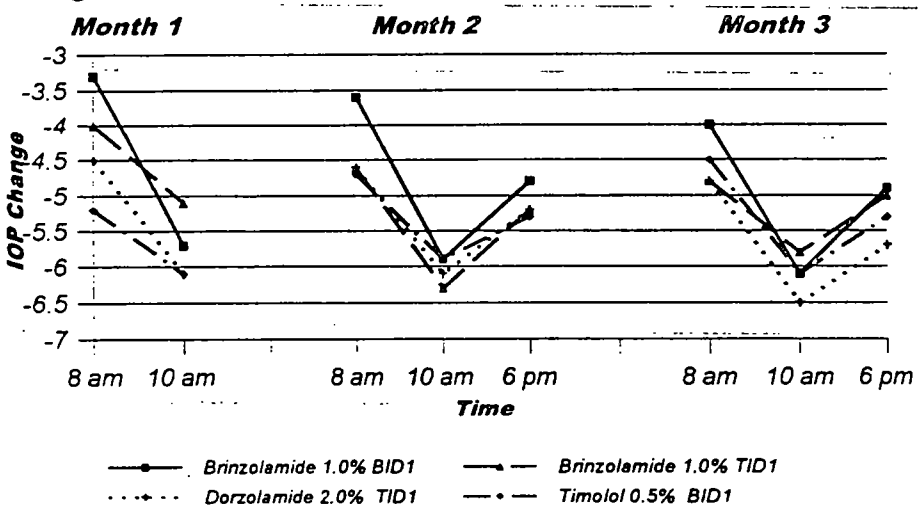


Figure 2. Mean IOP Change (European Patients Only)



IV. Protocol C-95-38

1. Description of Study Protocol

This is a randomized, triple-masked, parallel group, multi-center, placebo controlled clinical study. The objective of the study is to compare the safety and IOP-lowing efficacy of TID-dosed 1.0% Brinzolamide to placebo, when used adjunctively to Timolol 0.5% BID, in patients with primary

open-angle glaucoma or ocular hypertension. A total of 100 patients will be enrolled in the study with 50 patients in the active treatment group and 50 patients in the placebo group. After 3 weeks' Timolol stabilization period, patients must have an 8:00 a.m. IOP of 24 to 36 mmHg, inclusive, in at least one eye, with no greater than a 5 mmHg difference between eyes, at both Eligibility Visits 1 and 2. In addition, patients must have an IOP of 21 to 36 mmHg, inclusive, in at least one eye (the same eye), with no greater than a 5 mmHg difference between eyes, at the 10:00 a.m. and 6:00 p.m. measurements at both Eligibility Visits 1 and 2. If these IOP criteria are met, patients will be randomized to receive either Brinzolamide TID or placebo TID in addition to open-label Timolol BID. Patients will be instructed to instill one drop of masked, study medication into each eye at 8:00 a.m., 4:00 p.m. and 10:00 p.m. and Timolol 0.5% dosing will be continued at 8:00 a.m. and 10:00 p.m. Patients will be instructed to instill the masked study medication 5 to 10 minutes after the 8:00 a.m. and 10:00 p.m. Timolol 0.5% dose. Patients will be then scheduled to return at monthly intervals for three (3) months to have their IOP measurements and other tests done at 8:00 a.m. and 10:00 a.m.

2. Primary Statistical Analyses

The efficacy and safety analyses in Protocol C-95-38 are the same as those in Protocol C-95-46.

3. Sponsor's Results

Patient Evaluability and Disposition

A total of 132 patients across 19 investigational sites was randomized to treatments. Among them 24 patients were not evaluable for efficacy and thus excluded from the primary per protocol efficacy analysis but included in the intent-to-treat analysis. The distribution by reason and treatment group of patients excluded from the efficacy analysis is listed in Table 3, Page 8-07463 of NDA 20-816, with the most common reasons being IOP asymmetry (8 patients), no on-therapy IOP data (7 patients) and contraindicated concomitant medication (4 patients). The overall number of patients included in efficacy analysis at each treatment visit ranged from 100 to 108 as summarized below.

Number of Patients Included in Per Protocol Analysis at Each Visit

Explanation	Treatment	Baseline	Month 1 8am	Month 1 10am	Month 2 8am	Month 2 10am	Month 3 8am	Month 3 10am
Observed at Visit	Brinzolamide 1.0% TID	53	52	52	53	53	51	51
	Placebo	55	55	55	47	46	46	46
	Total	108	107	107	100	99	97	97
Data Carried Forward for Treatment Failures	Brinzolamide 1.0% TID	0	0	0	0	0	0	0
	Placebo	0	0	0	2	3	3	3
	Total	0	0	0	2	3	3	3
Data Available for Analysis	Brinzolamide 1.0% TID	53	52	52	53	53	51	51
	Placebo	55	55	55	49	49	49	49
	Total	108	107	107	102	102	100	100

Number of Patients Not Included in Per Protocol Analysis at Each Visit

Explanation	Treatment	Baseline	Month 1 8am	Month 1 10am	Month 2 8am	Month 2 10am	Month 3 8am	Month 3 10am
Discontinuation [1]	Brinzolamide 1.0% TID	0	0	0	0	0	0	0
	Placebo	0	0	0	5	5	5	5
	Total	0	0	0	5	5	5	5
Visits not Evaluable for Ongoing Patients	Brinzolamide 1.0% TID	0	1	1	0	0	2	2
	Placebo	0	0	0	1	1	1	1
	Total	0	1	1	1	1	3	3
Total Visits Not Available For Analysis	Brinzolamide 1.0% TID	0	1	1	0	0	2	2
	Placebo	0	0	0	6	6	6	6
	Total	0	1	1	6	6	8	8
Total Patients	Brinzolamide 1.0% TID	53	53	53	53	53	53	53
	Placebo	55	55	55	55	55	55	55
	Total	108	108	108	108	108	108	108

Note 9 patients from the per protocol data set discontinued. Five of the patients discontinued before month 3, three patients had data carried forward from previous visits, and patient 1503 had data at Month 3 but did not complete the study as planned.

Patient Demographics and Baseline Characteristics

No significant differences (all $p \geq 0.181$) were observed between treatment groups with respect to baseline IOP, mean age, age distribution (elderly vs non-elderly), sex distribution, iris color distribution and race distribution. There was a statistically significant difference ($p = 0.043$) between the treatment groups in the percentage of patients with primary open-angle glaucoma (58.5% vs 74.5%) and ocular hypertension (41.5% vs 21.8%). However these differences were not clinically meaningful since the IOP reductions were similar between treatment groups within each ocular diagnosis. These results are presented in Tables 6 and 8,

Pages 8-07466 and 8-07468 of NDA 20-816.

Efficacy

The efficacy results showed below were all from per protocol analysis, and were also confirmed by intent-to-treat analysis.

IOP Changes From Baseline

The mean changes from baseline for Brinzolamide 1.0% TID were approximately -3.6 mmHg compared to approximately -1.8 mmHg in the placebo group. The changes from baseline were statistically significant (all $p < 0.001$) for both the Brinzolamide 1.0% TID and Placebo groups at all visits. These results are presented in Table 7, Page 8-07467 of NDA 20-816.

Placebo Comparisons

The IOP reductions in the Brinzolamide 1.0% TID treatment group compared to Placebo were significant (all $p \leq 0.0329$) when the differences were analyzed separately at each study visit as presented in the following table. These results demonstrated that IOP changes following TID-dosing with Brinzolamide 1.0% (-3.2 to -4.1 mmHg) were all statistically significant (all $p \leq 0.0329$) compared to placebo.

Comparison of Mean IOP Changes to Placebo by Visit and Time of Day

	Month 1		Month 2		Month 3	
	8a	10a	8a	10a	8a	10a
Treatment						
Brinzolamide 1.0% TID[1]	-3.2	-3.3	-3.7	-3.8	-4.1	-3.3
Placebo[1]	-2.1	-1.1	-2.6	-1.5	-2.6	-1.0
p-value[2]	0.0329	0.0000	0.0291	0.0000	0.0044	0.0000

[1]All IOP changes are LSMEANS (in mmHg) from corresponding diurnal baseline.
[2]P value for the difference in LSMEAN IOP between the treatment groups.

Subgroup Analysis

The results of subgroup analysis were consistent with that of the whole group analysis.

Safety

Ocular Events Related to Therapy

Most Frequent Ocular-Related Events

Ocular Events	Brinzolamide 1.0% TID + Timolol 0.5% BID N = 65		Placebo TID + Timolol 0.5% BID N = 67	
	N	%	N	%
Blurred Vision	3	4.6	1	1.5
Discomfort	0	0	3	4.5
Hyperemia	0	0	2	3.0
Keratitis	0	0	2	3.0
Pruritus	0	0	2	3.0

Nonocular Events Related to Therapy

Most Frequent Nonocular-Related Events

Ocular Events	Brinzolamide 1.0% TID + Timolol 0.5% BID N = 65		Placebo TID + Timolol 0.5% BID N = 67	
	N	%	N	%
Special Senses Taste Perversion	5	7.7	0	0

Serious Events Related to Therapy

No serious events related to therapy were reported during the study (Table 17, Page 8-07481 of NDA 20-816).

Other Safety Parameters

There was no statistically significant difference in worsening from baseline in visual acuity, ocular signs, dilated fundus, visual fields and changes of pulse and blood

pressures for any treatment group.

4. Reviewer's Comment

None of the investigators' sites had more than 10 patients at all treatment arms. The differences between investigators' results are not assessable due to the small sample sizes.

V. Protocol C-96-29

1. Description of Study Protocol

This study is a multi-center, triple-masked, active-controlled, parallel trial in which data is obtained from approximately 88 patients. The primary objective is to evaluate the ocular discomfort, based on burning and stinging, of Brinzolamide 1.0% Ophthalmic Suspension dosed TID, compared to Dorzolamide 2.0% Ophthalmic Solution dosed TID, following multiple dosing in patients with primary open-angle glaucoma or ocular hypertension. Patients will be randomized into one of two treatment groups with 1:1 ratio. The study design includes a one-week treatment phase with TID dosing. Comfort evaluations will be conducted at the screening examination to familiarize patients with the use of the discomfort scale and at the end of one week of treatment at 8:00 a.m. The criteria for evaluation is ocular discomfort utilizing a 4 unit scale. The principal statistical methods are ANOVA, Fisher's Exact test, and two-sample t-test.

2. Sponsor's Results

Patient Demographics

A total of 109 patients was randomized into the two treatments with 55 patients in the Brinzolamide group and 54 patients in the Dorzolamide group. Among them, 6 patients were not evaluable for efficacy and thus excluded from the primary per protocol efficacy analysis but included in the intent-to-treat analysis. There were no statistical difference in the distributions of sex, age, race and iris color between the two treatments.

Efficacy

The per protocol analysis results, which were confirmed by

the intent-to-treat analysis results, of ocular discomfort are listed in the following table.

Ocular Discomfort Evaluation

	Brinzolamide 1.0% (N = 52)	Dorzolamide 2.0% (N = 51)	P-Value
Mean Score[1]	0.4	1.7	0.0001[2]
No Discomfort[3]	71.2%	19.6%	< 0.001[3]

[1] Mean score is based upon an ocular discomfort scale of 0 (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe).
[2] Based upon a comparison of mean scores at the end of Week 1.
[3] Based upon a comparison of percentage of patients with no ocular discomfort at the end of Week 1.

Distribution of Ocular Discomfort Scores[1]

Discomfort Score	Brinzolamide		Dorzolamide		P-Value
	N	%	N	%	
None (0)	37	71.2	10	19.6	0.001[2]
Mild (1)	10	19.2	10	19.6	
Moderate (2)	3	5.8	19	37.3	
Severe (3)	2	3.8	10	19.6	
Very Severe (4)	0	0	2	3.9	

[1] Ocular discomfort scores are based upon the evaluation obtained at the end of Week 1.
[2] P value of 0.001 based upon a comparison of the distribution of scores using a Cochran-Mantel - Haenszel rank score test.

In summary, Brinzolamide TID was both clinically and statistically more comfortable than Dorzolamide TID.

Safety

Adverse events related to Brinzolamide 1.0% were nonserious, usually mild, generally occurred with each instillation, resolved without treatment, and usually did not interrupt continuation in the study. No serious events related or unrelated to therapy were reported during the study, and no

patient was discontinued from the study due to a serious treatment-related event. The most frequent ocular events related to Brinzolamide TID was blurred vision (20.0%). The most frequent nonocular event related to Brinzolamide TID was taste perversion (14.5%).

3. Reviewer's Comments

Subgroup Analysis

The following subgroup analysis results performed by this reviewer are consistent with the sponsor's whole group results. Race subgroup analysis is only done for Caucasian and Black due to the small sample sizes of other races. For the same reason, iris color subgroup analysis is only performed for the brown color.

Ocular Discomfort Mean Score by Sex

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
Male	0.5 (n=20)	1.6 (n=27)	0.0002
Female	0.4 (n=32)	1.7 (n=24)	< 0.001

Ocular Discomfort Mean Score by Age

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
13< =Age<65	0.5 (n=25)	2.1 (n=25)	0.0001
Age> =65	0.4 (n=27)	1.3 (n=26)	0.004

Ocular Discomfort Mean Score by Race

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
Caucasian	0.5 (n=29)	1.8 (n=37)	<0.0001
Black	0.4 (n=17)	1.4 (n=11)	0.05

Ocular Discomfort Mean Score of Brown Iris Color

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
Brown	0.4 (n=34)	1.6 (n=27)	0.0001

Results at Different Investigators' Sites

The following table shows that the ocular discomfort results at different investigators' sites are consistent with the sponsor's whole group results.

Ocular Discomfort Evaluation by Investigator

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
Investigator 271	0.3 (n=19)	1.5 (n=20)	0.0006
Investigator 1007	0.5 (n=23)	2.0 (n=21)	<0.0001
Investigator 1208	0.4 (n=10)	1.4 (n=10)	0.05

VI. Protocol C-96-40

1. Description of Study Protocol

The study design of protocol C-96-40 is identical to C-96-29.

2. Sponsor's Results

Patient Demographics

A total of 104 patients was randomized into the two treatments with 52 patients in the Brinzolamide group and 52 patients in the Dorzolamide group. Among them 9 patients were not evaluable for efficacy and thus excluded from the primary per protocol efficacy analysis but included in the intent-to-treat analysis. There were no statistically significant difference in the distributions of sex, age, race and iris color between the two treatments.

Efficacy

The per protocol analysis results, which were confirmed by the intent-to-treat analysis results, of ocular discomfort are listed in the following table.

Ocular Discomfort Evaluation

	Brinzolamide 1.0% (N = 48)	Dorzolamide 2.0% (N = 47)	P-Value
Mean Score[1]	0.2	1.5	0.0001[2]
No Discomfort[3]	81.3%	17.0%	< 0.001[3]

[1] Mean score is based upon an ocular discomfort scale of 0 (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe).
[2] Based upon a comparison of mean scores at the end of Week 1.
[3] Based upon a comparison of percentage of patients with no ocular discomfort at the end of Week 1.

Distribution of Ocular Discomfort Scores[1]

Discomfort Score	Brinzolamide		Dorzolamide		P-Value
	N	%	N	%	
None (0)	39	81.3	8	17.0	0.001[2]
Mild (1)	9	18.7	13	27.7	
Moderate (2)	0	0	21	44.7	
Severe (3)	0	0	4	8.5	
Very Severe (4)	0	0	1	2.1	

[1] Ocular discomfort scores are based upon the evaluation obtained at the end of Week 1.
[2] P value of 0.001 based upon a comparison of the distribution of scores using a Cochran-Mantel - Haenszel rank score test.

In summary, Brinzolamide TID is statistically more comfortable than Dorzolamide TID.

Safety

Adverse events related to Brinzolamide 1.0% were nonserious, usually mild, generally occurred with each instillation, resolved without treatment, and usually did not interrupt

continuation in the study. No serious events related or unrelated to therapy were reported during the study, and no patient was discontinued from the study due to a serious treatment-related event. The most frequent ocular events related to Brinzolamide TID was blurred vision (25.0%). The most frequent nonocular event related to Brinzolamide TID was taste perversion (9.6%).

3. Reviewer's Comments

Subgroup Analysis

The following subgroup analysis results performed by this reviewer are consistent with the sponsor's whole group results. Race subgroup analysis is only done for Caucasian due to the small sample sizes of other races. For the same reason, iris color subgroup analysis is only performed for brown, hazel and blue color.

Ocular Discomfort Mean Score by Sex

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
Male	0.2 (n=14)	1.4 (n=20)	0.0003
Female	0.2 (n=34)	1.6 (n=27)	< 0.001

Ocular Discomfort Mean Score by Age

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
13< =Age<65	0.2 (n=19)	1.9 (n=14)	0.0001
Age> =65	0.2 (n=29)	1.4 (n=33)	0.0001

Ocular Discomfort Mean Score by Race

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
Caucasian	0.2 (n=43)	1.5 (n=42)	0.0001

Ocular Discomfort Mean Score of Brown Iris Color

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
Brown	0.4 (n=17)	1.8 (n=17)	0.0001
hazel	0.1 (n=13)	1.5 (n=8)	0.0031
blue	0.1 (n=18)	1.2 (n=19)	0.0001

Results at Different Investigators' Sites

The following table shows that the ocular discomfort results at different investigators' sites are consistent with the sponsor's whole group results.

Ocular Discomfort Evaluation by Investigator

	Brinzolamide 1.0%	Dorzolamide 2.0%	P-Value
Investigator 470	0.2 (n=28)	1.6 (n=27)	0.0001
Investigator 1892	0.2 (n=9)	1.4 (n=10)	0.0016
Investigator 1913	0.1 (n=11)	1.2 (n=10)	0.0133

VII. Overall Conclusions

The following conclusions are based on the results in the five phase III studies above.

1. Brinzolamide TID produced statistically significant reduction in IOP (4.1 to 5.6 mmHg, or 16.6% to 19.1% from baseline). These IOP reductions were statistically equivalent to the reductions (4.3 to 5.9 mmHg, or 16.9% to 20.1% from baseline) observed with Dorzolamide TID. (Study C-95-46)

2. Brinzolamide TID, used adjunctively with Timolol, provided additional statistically significant IOP reduction (3.2 to 4.1 mmHg, or 13.2% to 16.6% from baseline). (Study C-95-38)

3. Brinzolamide TID, based on burning and stinging, was more comfortable than Dorzolamide TID. The proportion of patients

with 1 week's Brinzolamide TID experiencing no burning and stinging was 71.2% to 81.3% as compared to 17.0% to 19.6% with Dorzolamide TID. (Study C-96-29, Study C-96-40)

4. Brinzolamide BID was not statistically equivalent to Brinzolamide TID and Dorzolamide TID. In Study C-95-46, the equivalence comparison results of BID Brinzolamide vs. TID Dorzolamide showed that all the upper limits of the 95% confidence intervals were above 1 mmHg, and 5 of the 8 upper limits at individual time points were at least 1.5 mmHg. In Study C-95-48, all the upper limits of 95% confidence intervals of mean(BID-DORZ) were less than 1.5 mmHg, but the majority (5 of the 8) of them were over 1 mmHg, and the other three were close to 1 mmHg. (Study C-95-46)

5. The IOP reductions (4.1 to 5.6 mmHg, or 16.6% to 19.1% from baseline) by Brinzolamide TID were consistently smaller than those by Timolol BID (5.2 to 6.3 mmHg) at all individual visits. (Study C-95-48)

6. The respond/control rates (38% to 75% for Brinzolamide BID, 48% to 80% for Brinzolamide TID) in the labeling of NDA 20-816 referred to the rates at each individual time point. The rates of patients who consistently responded or were under control in all 3 months are 15.9% to 19%. (Study C-95-46, Study C-95-48)

7. It is a noticeable phenomena that the IOP reduction with placebo (2.2 to 2.6 mmHg, or 9.1% to 11.6% from baseline) was also statistically significant (all $p<=0.001$). (Study C-95-46)

8. In the three pivotal studies (Study C-95-38, Study C-95-46, Study C-95-48), only 3 of the 85 investigators' sites had more than 10 patients at all the study arms. Differences between investigator sites were not statistically assessable due to the small sample sizes. The separate analyses for the American patients and European patients in Study C-95-48 showed that, among European patients, none of the four treatments were consistently more effective in IOP reduction than other groups. These results are not consistent with the American patients' and the whole group results which showed that Timolol was consistently more effective in IOP reduction than other treatments. (Study C-95-38, Study C-95-46, Study C-95-48)

/S/

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Archival: NDA 20-816

CC:

HFD-550/MO/Ludwig
HFD-550/Act. Dir./Chambers
HFD-550/PM/Holmes
HFD-550/Div. File
HFD-340/Div. Sci. Inv.
HFD-725/Lu
HFD-725/Leung
HFD-725/Div. File

APPEARS THIS WAY
ON ORIGINAL