CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 204-251
Drug Name:	Simbrinza (brinzolamide 1%/ brimonidine tartrate 0.2%) ophthalmic suspension
Indication(s):	The reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Applicant:	Alcon
Date(s):	Stamp date: June 19, 2012 PDUFA date: April 19, 2013 Review date: March 15, 2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
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Keywords: clinical studies, mixed linear model, reduction of intraocular pressure

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1 EXECUTIVE SUMMARY

In this submission, the Applicant is seeking the approval of a fixed dose combination ophthalmic suspension of brinzolamide 1% and brimonidine tartrate 0.2% for the indication of the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The individual active components of the product are currently approved products in the United States for the above indication. Since many patients often require 2 medications to allow for a clinically meaningful reduction in IOP, development of the fixed dose combination product was considered in order to reduce treatment burden since both drugs would be given in a single formulation.

The primary evidence of efficacy of the brinzolamide/brimonidine combination is based on two Phase 3 trials: C-10-033 and C-10-039. Both of the trials were randomized, multicenter, parallel group, active controlled trials designed to evaluate the safety and efficacy of the fixed combination of brinzolamide/brimonidine in lowering IOP relative to each of its individual components in patients with open-angle glaucoma or ocular hypertension. The primary objectives of the trials were to demonstrate that brinzolamide/brimonidine was superior to brinzolamide with respect to IOP-lowering and that brinzolamide/brimonidine was superior to brimonidine with respect to IOP-lowering. The primary efficacy endpoint was mean IOP assessed at 3 visits (Week 2, Week 6, and Month 3) at 4 time points (8 AM, 10 AM, 3 PM, and 5 PM). The primary analysis of IOP was based on the differences in mean IOP between treatment groups (brinzolamide/brimonidine – brinzolamide and brinzolamide/brimonidine - brimonidine) at each assessment time point determined using a pairwise test based on the least square means derived from a linear mixed model that accounts for correlated IOP measurements within patient.

In C-10-033, 660 patients were randomized into the study and approximately 90% of the patients completed the study. The Intent-to-Treat population consisted of 209 brinzolamide/brimonidine patients, 224 brinzolamide patients, and 216 brimonidine patients. The mean IOP measurements were statistically significantly lower in the brinzolamide/brimonidine group compared to both the brinzolamide alone and brimonidine alone groups at all visits and time points (refer to Table 6). The mean differences between treatment groups were greater than 1.0 mmHg at all assessment time points and greater than 1.5 mmHg for the majority of assessment time points, including all assessment time points for the brinzolamide/brimonidine group compared to the brimonidine alone group.

In C-10-039, 690 patients were randomized into the study and approximately 90% of the patients completed the study. The Intent-to-Treat population consisted of 218 brinzolamide/brimonidine patients, 229 brinzolamide patients, and 232 brimonidine patients. The mean IOP measurements were statistically significantly lower in the brinzolamide/brimonidine group compared to both the brinzolamide alone and brimonidine alone groups at all visits and time points (refer to Table 12). The mean difference between the brinzolamide/brimonidine group and the brinzolamide treatment group was greater than 1.0 mmHg at all but 1 assessment time point and was greater than 1.5 mmHg for the majority of the assessment time points. The mean difference between the brinzolamide/brimonidine group and the brimonidine group was greater than 1.5 mmHg for all of the assessment time points.

Based on the results of the two pivotal Phase 3 trials, both trials met the stated primary objectives in that mean IOP was statistically significantly reduced at all assessment time points with treatment with the fixed combination of brinzolamide/brimonidine when compared to each of the individual components alone. Therefore, there is adequate evidence of efficacy to support the indication of the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension for the fixed combination of brinzolamide/brimonidine.

2 INTRODUCTION

2.1 Overview

This is an NDA submission for Simbrinza™, a fixed dose combination ophthalmic suspension of brinzolamide 1% and brimonidine tartrate 0.2% (brinz/brim). The indication being sought by the Applicant is the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The individual active components of the product are both approved products in the United States for the above indication. Brinzolamide 1% (brinz) is a carbonic anhydrase inhibitor and is the active ingredient in Azopt eye drops, suspension. Brimonidine 0.2% (brim) is an alpha 2-adrenergic agonist and is the active ingredient in Alphagan. The individual components both decrease elevated IOP by reducing aqueous humor secretion but do so by different mechanisms of action. Many patients require 2 medications to allow for a clinically meaningful reduction in IOP. Therefore, the Applicant has developed the fixed dose combination, brinzolamide/brimonidine.

The development program for brinzolamide/brimonidine consisted of a single Phase 1 pharmacokinetic study in healthy adults, a Phase 2 proof of concept study, a Phase 2 study to assess the comfort upon installation of the product, and two Phase 3 trials. Primary support of the efficacy of brinzolamide/brimonidine is based on the two Phase 3 trials: C-10-033 and C-10-039. Both of the Phase 3 trials were randomized, multicenter, parallel group, active controlled trials designed to demonstrate the contribution of elements, i.e., designed to show a meaningful contribution to the efficacy of the fixed combination to each of the individual components. The focus of this review will be the two pivotal Phase 3 efficacy trials.

An End of Phase 2 meeting was held with the Medical Division on November 15, 2010 to obtain guidance on the development plan for brinzolamide/brimonidine tartrate ophthalmic suspension. At this meeting, the Medical Division agreed that the two contribution of elements trials (C-10-033 and C-10-039) of three months duration as proposed by the Applicant were acceptable to demonstrate superiority of the combination product to each of the individual components for lowering of intraocular pressure. The Medical Division stated that measurement of IOP at 8 AM, 10 AM, 3 PM and 5 PM at two Eligibility Visits and at three on-therapy visits (Week 2, Week 6, and Month 3) was appropriate. These measurements were to be analyzed separately as well as compared to baseline. The Medical Division also requested that safety information from at least 100 patients treated for at least 6 months be collected. Therefore, C-10-039 was designed to collect an additional 3 months of safety information.

Table 1
Listing of Studies Included in Review

Protocol	Phase and Design	Dosing Regimen	Dosing Duration	# of Subjects per Arm	Study Population
C-10-033	Phase 3 multi center, randomized, double-masked, parallel group, active controlled	1 drop in each eye 3 times daily	3 months	214 brinz/brim 226 brinz 220 brim	Patients diagnosed with open angle-glaucoma or ocular hypertension
C-10-039	Phase 3 multi center, randomized, double-masked, parallel group, active controlled	1 drop in each eye 3 times daily	3 months with additional 3 months for safety	221 brinz/brim 234 brinz 235 brim	Patients diagnosed with open angle-glaucoma or ocular hypertension

2.2 Data Sources

The data analyzed in this review comes from the Phase 3 trials submitted as the pivotal evidence to support the efficacy of brinzolamide/brimonidine. The final C-10-033 study report, the 3-month C-10-039 study report, and datasets for the two studies provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\cdsesub1\EVSPROD\NDA204251\0000.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets submitted were of acceptable quality. Minimal programming was necessary to reproduce the results presented by the Applicant.

Reviewer's Comment: *Unless otherwise indicated, tables presented in this review are based on analyses conducted by this reviewer using the analysis datasets submitted by the Applicant and confirm the results of those presented by the Applicant in the C-10-033 and C-10-039 Study Reports.*

Initially, there was an issue converting the XPT files with file names that included hyphens for example "-iop-01.xpt" to SAS datasets. The Applicant was asked to provide the code necessary to convert these files or provide an acceptable alternative that would address this issue. The Applicant provided the appropriate code in a response dated August 10, 2012 located at: \\cdsesub1\EVSPROD\NDA204251\0005. They also indicated that there should not have been any hyphens in the files names they sent unless perhaps the underscores that were used were converted to hyphens in the final publishing process.

Reviewer's Comment: *It should be noted that the file names in the EDR do contain hyphens rather than underscores. It is unsure if this happened before or after the submission was loaded into the EDR. The electronic document room staff should relook at the original submission to see if the file names had hyphens or underscores. If they had hyphens to begin with, the Applicant should be made aware of that so for the next time they can know to look for it. If it is something that happened on this end of the submission, then it should be made sure it is known that this is happening and something should be done to make sure it doesn't happen.*

3.2 Evaluation of Efficacy

3.2.1 Study C-10-033

3.2.1.1 Study Design and Endpoints

C-10-033 was a Phase 3, multicenter, randomized, double-masked, parallel group, active controlled study designed to evaluate the safety and efficacy of a fixed combination of brinzolamide/brimonidine in lowering IOP relative to each of its individual components in patients with open-angle glaucoma or ocular hypertension. The study was conducted at 68 investigational centers in the United States. Patients were screened for eligibility during a screening and 2 eligibility visits. Initial screening procedures were performed at the screening visit. Patients were to discontinue all ocular hypotensive agents according to the recommended washout schedule. Following the washout period, patients returned for the Eligibility 1 Visit and then 3 to 8 days later for the Eligibility 2 visit. At both of the Eligibility Visits, IOP was measured in both eyes at 8 AM, 10 AM, 3 PM, and 5 PM. Patients who had IOP measurements within the specified range were randomized in a 1:1:1 ratio to receive treatment with either the fixed combination of brinzolamide/brimonidine, brinzolamide alone, or brimonidine alone. The criterion for the IOP measurements was as follows: mean IOP measurements in at least 1 eye and the same eye must have been:

- Greater than or equal to 24 mmHg and less than or equal to 36 mmHg at the 8 AM time point for both Eligibility visits
- Greater than or equal to 21 mmHg and less than or equal to 36 mmHg at the 10 AM time point for both Eligibility visits
- The mean IOP in either eye must not have been greater than 36 mmHg at any time point.

The randomization was stratified by the 8 AM baseline IOP of the study eye (24 to 27 mmHg, 28 to 36 mmHg) to ensure balanced baseline IOP measurements between the treatment groups.

Patients were dispensed study drug and instructed to instill 1 drop of study drug in both eyes TID at approximately 8 AM, 3 PM, and 10 PM for 3 months. The patients were instructed not to dose on the morning of the scheduled on-therapy study visits. The on-therapy study visits were scheduled to occur at Week 2 (Day 14 ± 3 days), Week 6 (Day 42 ± 3 days), and Month 3 (Day 90 ± 4 days). During these visits, all patients underwent slit-lamp examinations and BCVA assessments of both eyes at 8 AM, had their pulse and blood pressures measured at 8 AM and 2 hours later, and had IOP measurements taken in both eyes at 8 AM and 2, 7, and 9 hours later. Designated personnel at each investigational center instilled the study drugs at 8 AM and 3 PM (approximately 15 minutes after conducting the IOP measurements), while the patients self-

administered the third dose of study drug in the evening at home. Adverse events (AEs) were recorded at all on-therapy study visits and patients provided updates of their medical histories and concomitant medication uses at all post-Screening study visits.

The study was double-masked and neither the patient nor the study personnel had knowledge of the assigned treatment. The study drugs were packaged and labeled identically. However due to the differences in the appearance of the eye drops (suspension versus solution), the individuals who instilled the study drug during the on-therapy study visits were not allowed to conduct the IOP measurements and were instructed not to discuss the study drugs with study personnel. Minimization of inter- and intra-rater variability in the evaluation of IOP was achieved by the use of calibrated tonometers and the same 2 individuals (an operator and reader) measured the IOP for each individual patient using the same method for measuring IOP at all study visits.

The primary objectives of the study were to demonstrate that brinzolamide/brimonidine was superior to brinzolamide with respect to IOP-lowering efficacy and that brinzolamide/brimonidine was superior to brimonidine with respect to IOP-lowering efficacy. The primary efficacy endpoint was the IOP. The protocol stated that the primary efficacy endpoint was to be assessed at each of the assessment time points (8 AM, 10 AM, 3 PM, and 5 PM) at Month 3 and supportive efficacy endpoints were at each of the assessment time points at Week 2 and Week 6.

Reviewer's Comment: *As indicated to the Applicant at the end of phase 2 meeting, the comparisons of mean IOP at all visits (Week 2, Week 6 and Month 3) and assessment time points (8 AM, 10 AM, 3 PM, and 5 PM) are to be considered primary efficacy comparisons.*

3.2.1.2 Statistical Methodologies

The primary analysis of IOP was based on the difference in mean IOP between treatment groups (brinzolamide/brimonidine – brinzolamide alone and brinzolamide/brimonidine – brimonidine alone) at each assessment time point. The treatment difference in the mean IOP was determined using a pairwise test at each assessment time point. The pairwise tests were based on the least square means derived from a linear mixed model that accounts for correlated IOP measurements within patient. The model is:

$$IOP_{ijklm} = \mu + T_i + V_j + H_k + S_l + TV_{ij} + TH_{ik} + VHj_k + TVH_{ijk} + \rho\,(T)_{m(i)} + \varepsilon_{ijklm}$$

where μ is the overall mean, T_i is the fixed effect due to i^{th} treatment group, V_j is the fixed effect due to the j^{th} visit, H_k is the fixed effect due to k^{th} time point, S_l is the fixed effect due to the l^{th} stratum for 8AM baseline IOP (strata: 24 to 27 mmHg, 28 to 36 mmHg), TV_{ij} is the treatment by visit interaction, TH_{ik} is the treatment by time interaction, VH_{jk} is the visit by time interaction, TVH_{ijk} is the treatment by visit by time interaction, $\rho(T)_{m(i)}$ is the random effect due to m^{th} patient within the i^{th} treatment group and ε_{ijklm} is the measurement error associated with the individual patient. The effect ρ is considered random in order to account for repeated observations on patients. Results based on the linear mixed model are robust for data that is missing at random. In addition, descriptive statistics were calculated for IOP, IOP change from baseline, and IOP percent change from baseline.

A sensitivity analysis for the primary endpoint was performed using a last observation carried forward (LOCF) approach to handle missing data. If a patient missed a visit, the most recently measured IOP for the same time of day was used to impute the missing IOP value.

Reviewer's Comment: *Although LOCF is not an ideal method for handling missing data, this has been the preferred approach of the Medical Division.*

Three data sets were used for analysis. The intent-to-treat (ITT) population included all patents that received study drug and completed at least 1 on-therapy study visit. The ITT population was the primary analysis population for efficacy. The per protocol (PP) population included all patients who satisfied pre-randomization inclusion/exclusion criteria, received study drug, and completed at least 1 on-therapy study visit. The PP population was used as a supportive analysis of the primary efficacy endpoint. The safety analysis set included all patients who received study drug.

One eye from each patient was chosen as the study eye and only data from the study eye was used in the efficacy analyses. In cases where only one eye was dosed, this was the study eye. In cases where both eyes were dosed, the worst eye was the study eye. The worse eye was defined as the eye with the higher IOP at 8 AM averaged across the two Eligibility visits. If both eyes had equal measurements, then the 10 AM measurement was used to determine the worse eye. If both eyes still had equal measurements, then the right eye was selected for analysis.

The study was designed to contribute no fewer than 200 patients per treatment group to the assessment of safety at Month 3. Additionally, assuming a two-sided type I error rate of 5%, a common standard deviation for mean IOP as small as 3.5 mmHg and as large as 3.9 mmHg, 143 evaluable patients per treatment group would provide at least 90% power to detect a difference in mean IOP of 1.5 mmHg between any 2 groups.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 660 patients were randomized into the study: 216 to the brinzolamide/brimonidine group, 225 to the brinzolamide group, and 219 to the brimonidine group. Approximately 90% of the randomized patients completed the study. The most common reason for discontinuation across all treatment groups was adverse event. Reasons for discontinuation are reported in Table 2.

Table 2
C-10-033
Patient Disposition

	Brinz/Brim	Brinz	Brim
Randomized	216	225	219
Completed Study	189 (87.5)	213 (94.7)	192 (87.7)
Discontinued Study	27 (12.5)	12 (5.3)	27 (12.3)
Adverse Event	21	7	16
Lost to Follow-up	1	0	1
Patient's Decision	2	3	7
Noncompliance	1	0	0
Protocol Violation	1	1	1
Inadequate Control of IOP	1	1	2

The Safety Population is comprised of all 660 patients. It should be noted, however, that 4 patients did not receive their randomized study treatment: 1 patient randomized to brimonidine received brinzolamide/brimonidine instead, 2 patients randomized to brinzolamide/brimonidine received brimonidine instead, and 1 patient randomized to brinzolamide/brimonidine received brinzolamide instead. These patients are analyzed according to the randomized treatment assigned in all efficacy analyses but they are analyzed according to the treatment they actually received in the Safety Population. Seven patients in the brinzolamide/brimonidine group, 1 patient in the brinzolamide group, and 3 patients in the brimonidine group had no on-therapy follow-up data and were excluded from the ITT population. An additional 29 patients (10 brinzolamide/brimonidine, 9 brinzolamide, and 10 brimonidine) were excluded from the PP population due to protocol violations.

Table 3
C-10-033
Analysis Populations

	Brinz/Brim	Brinz	Brim
Randomized	216	225	219
Safety Population*	214	226	220
ITT Population**	209	224	216
PP Population**	199	215	206

*Patients analyzed according to actual treatment received
**Patients analyzed according to randomized treatment

Reviewer's Comment: *The efficacy analyses presented in this review will focus on the ITT population.*

Table 4 summarizes the demographic and baseline characteristics of the ITT population. There were no significant differences across treatment groups. Overall, 61% of the study population was female and 68% was white. The mean age of the patients was 64 years. The majority of the patients had brown eyes and a diagnosis of open-angle glaucoma. Approximately 69% were included in the baseline IOP stratum of 24-27 mmHg. Mean corneal thickness at baseline was approximately 0.55 mm.

Table 4
C-10-033
Demographic and Baseline Characteristics (ITT)

	Treatment Group		
	Brinz/Brim	**Brinz**	**Brim**
# Patients	209	224	216
Gender			
Male	73 (34.9)	97 (43.3)	84 (38.9)
Female	136 (65.1)	127 (56.7)	132 (61.1)
Age mean (SD)	63.9 (11.3)	65.0 (10.0)	64.3 (10.8)
Min, max	18, 91	33, 88	25, 92
Race			
White	143 (68.4)	141 (62.9)	155 (71.8)
Black	62 (29.7)	75 (33.5)	59 (27.3)
Asian	3 (1.4)	5 (2.2)	0
Other	1 (0.5)	3 (1.3)	2 (0.9)
Iris Color			
Blue	44 (21.1)	43 (19.2)	47 (21.8)
Brown	129 (61.7)	147 (65.6)	131 (60.6)
Green	8 (3.8)	8 (3.6)	10 (4.6)
Grey	3 (1.4)	2 (0.9)	5 (2.3)
Hazel	25 (12.0)	24 (10.7)	23 (10.6)
Diagnosis			
Ocular Hypertension	81 (38.8)	71 (31.7)	65 (30.1)
Open-Angle Glaucoma	123 (58.9)	149 (66.5)	147 (68.1)
Open-Angle Glaucoma with Pigment Dispersion	4 (1.9)	3 (1.3)	3 (1.4)
Open-Angle Glaucoma with Pseudoexfoliation	1 (0.5)	1 (0.4)	1 (0.5)
Baseline IOP Stratum			
24-27 mmHg	144 (68.9)	154 (68.8)	151 (69.9)
28-36 mmHg	65 (31.1)	70 (31.3)	65 (30.1)
Study (Worse) Eye			
Right	118 (56.5)	132 (58.9)	110 (50.9)
Left	91 (43.5)	92 (41.1)	106 (49.1)
Corneal Thickness(mm) mean (SD)	0.553 (0.032)	0.550 (0.035)	0.550 (0.035)
Min, max	(0.462, 0.613)	(0.452, 0.615)	(0.442, 0.617)

Table 5 presents the mean baseline IOP for each time point. There are no significant differences among the 3 treatment groups at any of the 4 time points. The highest IOP measurements were seen at the 8 AM visit and decreased throughout the day.

Table 5
C-10-033
Baseline IOP (mmHg) (ITT)

		Brinz/Brim (n=209)	Brinz (n=224)	Brim (n=216)
8 AM	mean (SD)	26.9 (2.63)	27.1 (2.64)	27.0 (2.56)
	min, max	24, 35	24, 35	24, 35
10 AM	mean (SD)	25.3 (2.76)	25.4 (2.74)	25.4 (2.78)
	min, max	21, 35	21, 35	21, 36
3 PM	mean (SD)	23.7 (2.98)	23.8 (3.24)	24.0 (3.27)
	min, max	15, 33	17, 35	16, 34
5 PM	mean (SD)	23.2 (3.08)	23.6 (3.39)	23.7 (3.30)
	min, max	15, 34	17, 35	16, 35

3.2.1.4 Results and Conclusions

Mean IOP measurements at each visit (Week 2, Week 6, and Month 3) at each time point (8 AM, 10 AM, 3 PM and 5 PM) are presented in Table 6. The mean IOP measurements were statistically significantly lower in the brinzolamide/brimonidine group compared to both the brinzolamide alone and brimonidine alone groups at all visits and time points. The mean differences between treatment groups (brinzolamide/brimonidine- brinzolamide and brinzolamide/brimonidine –brimonidine) were greater than 1.0 mmHg at all assessment time points and greater than 1.5 mmHg for the majority of assessment time points, this included all of the assessment time points for the brinzolamide/brimonidine group compared to the brimonidine alone group.

Table 6
C-10-033
Mean IOP (mmHg) (ITT) at Week 2, Week 6, and Month 3

			Brinz/Brim (n=209)	Brinz (n=224)	Brim (n=216)
Week 2	**8 AM**	Mean* (SE)	20.4 (0.29)	22.0 (0.27)	22.4 (0.28)
		Mean difference**		-1.6	-2.0
		95% CI		(-2.3, -0.9)	(-2.7, -1.3)
		p-value		<0.0001	<0.0001
	10 AM	Mean (SE)	17.1 (0.29)	20.5 (0.28)	19.4 (0.28)
		Mean difference		-3.4	-2.3
		95% CI		(-4.1, -2.7)	(-3.0, -1.6)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	18.4 (0.29)	20.4 (0.28)	20.6 (0.28)
		Mean difference		-1.9	-2.2
		95% CI		(-2.6, -1.3)	(-2.9, -1.5)
		p-value		<0.0001	<0.0001
	5 PM	Mean (SE)	16.6 (0.29)	19.7 (0.28)	18.4 (0.28)
		Mean difference		-3.2	-1.9
		95% CI		(-3.9, -2.5)	(-2.6, -1.2)
		p-value		<0.0001	<0.0001

			Brinz/Brim (n=209)	Brinz (n=224)	Brim (n=216)
Week 6	**8 AM**	Mean (SE)	20.4 (0.29)	21.9 (0.28)	22.6 (0.28)
		Mean difference		-1.5	-2.3
		95% CI		(-2.2, -0.8)	(-3.0, -1.6)
		p-value		<0.0001	<0.0001
	10 AM	Mean (SE)	17.5 (0.29)	20.2 (0.28)	19.5 (0.28)
		Mean difference		-2.7	-2.0
		95% CI		(-3.4, -2.0)	(-2.7, -1.3)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	18.9 (0.29)	20.2 (0.28)	21.1 (0.28)
		Mean difference		-1.2	-2.1
		95% CI		(-1.9, -0.5)	(-2.8, -1.4)
		p-value		0.0007	<0.0001
	5 PM	Mean (SE)	17.0 (0.29)	19.7 (0.28)	18.6 (0.28)
		Mean difference		-2.6	-1.5
		95% CI		(-3.3, -1.9)	(-2.2, -0.8)
		p-value		<0.0001	<0.0001
Month 3	**8 AM**	Mean (SE)	20.5 (0.29)	21.6 (0.28)	23.3 (0.29)
		Mean difference		-1.1	-2.8
		95% CI		(-1.8, -0.4)	(-3.5, -2.1)
		p-value		0.0016	<0.0001
	10 AM	Mean (SE)	17.2 (0.29)	20.4 (0.28)	19.7 (0.29)
		Mean difference		-3.2	-2.5
		95% CI		(-3.9, -2.5)	(-3.2, -1.8)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	18.7 (0.29)	20.4 (0.28)	21.3 (0.29)
		Mean difference		-1.8	-2.6
		95% CI		(-2.5, -1.1)	(-3.3, -1.9)
		p-value		<0.0001	<0.0001
	5 PM	Mean (SE)	17.0 (0.29)	20.0 (0.28)	18.8 (0.29)
		Mean difference		-3.0	-1.8
		95% CI		(-3.7, -2.3)	(-2.5, -1.1)
		p-value		<0.0001	<0.0001

*Estimates are based on least square means derived from a linear mixed model that accounts for correlated IOP measurements within patient.
**Difference is brinzolamide/brimonidine – individual component

The amount of missing data at each visit was relatively small and fairly consistent across treatment groups. Missing data per treatment group at Week 2 ranged from 1.8% to 2.4%, at Week 6 ranged from 4.5% to 7.9%, and at Month 3 ranged from 5.4% to 12.0%. Thus, the results based on the analysis using LOCF (see Supplemental Table S-1) are very similar to those presented in Table 6.

Table 7 presents the change from baseline in mean IOP at each assessment time point. Similar to the results seen for mean IOP, the change from baseline in mean IOP was significantly better (greater decrease from baseline) for the brinzolamide/brimonidine group compared to both the brinzolamide alone and brimonidine alone groups at all visits and time points.

Table 7
Study C-10-033
Change from baseline IOP (mmHg) (ITT) at Week 2, Week 6, and Month 3

			Brinz/Brim (n=209)	Brinz (n=224)	Brim (n=216)
Week 2	**8 AM**	Mean* (SE)	-7.3 (0.27)	-5.9 (0.26)	-5.5 (0.26)
		Mean difference**		-1.4	-1.8
		95% CI		(-2.0, -0.8)	(-2.4, -1.2)
		p-value		<0.0001	<0.0001
	10 AM	Mean (SE)	-9.0 (0.27)	-5.7 (0.26)	-6.9 (0.26)
		Mean difference		-3.2	-2.1
		95% CI		(-3.9, -2.6)	(-2.7, -1.4)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	-6.1 (0.27)	-4.3 (0.26)	-4.3 (0.26)
		Mean difference		-1.7	-1.8
		95% CI		(-2.4, -1.1)	(-2.4, -1.1)
		p-value		<0.0001	<0.0001
	5 PM	Mean (SE)	-7.4 (0.27)	-4.7 (0.26)	-6.3 (0.26)
		Mean difference		-2.7	-1.1
		95% CI		(-3.4, -2.1)	(-1.8, -0.5)
		p-value		<0.0001	0.0006
Week 6	**8 AM**	Mean (SE)	-7.3 (0.27)	-6.1 (0.26)	-5.3 (0.27)
		Mean difference		-1.3	-2.0
		95% CI		(-1.9, -0.6)	(-2.7, -1.4)
		p-value		0.0001	<0.0001
	10 AM	Mean (SE)	-8.7 (0.27)	-6.1 (0.26)	-6.9 (0.27)
		Mean difference		-2.6	-1.8
		95% CI		(-3.2, -2.0)	(-2.4, -1.1)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	-5.6 (0.27)	-4.5 (0.26)	-3.9 (0.27)
		Mean difference		-1.0	-1.7
		95% CI		(-1.6, -0.4)	(-2.3, -1.0)
		p-value		0.0021	<0.0001
	5 PM	Mean (SE)	-7.0 (0.27)	-4.8 (0.26)	-6.1 (0.27)
		Mean difference		-2.2	-0.9
		95% CI		(-2.8, -1.5)	(-1.5, -0.2)
		p-value		<0.0001	0.0102
Month 3	**8 AM**	Mean (SE)	-7.2 (0.27)	-6.3 (0.26)	-4.7 (0.27)
		Mean difference		-0.9	-2.5
		95% CI		(-1.6, -0.3)	(-3.2, -1.9)
		p-value		0.0045	<0.0001
	10 AM	Mean (SE)	-8.9 (0.27)	-5.8 (0.26)	-6.7 (0.27)
		Mean difference		-3.1	-2.2
		95% CI		(-3.7, -2.4)	(-2.9, -1.5)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	-5.9 (0.27)	-4.3 (0.26)	-3.7 (0.27)
		Mean difference		-1.6	-2.2
		95% CI		(-2.2, -0.9)	(-2.8, -1.5)
		p-value		<.00001	<0.0001
	5 PM	Mean (SE)	-7.0 (0.27)	-4.5 (0.26)	-5.9 (0.27)
		Mean difference		-2.6	-1.1
		95% CI		(-3.2, -1.9)	(-1.8, -0.5)
		p-value		<0.0001	0.0008

*Estimates are based on least square means derived from a linear mixed model that accounts for correlated IOP measurements within patient.
**Difference is brinzolamide/brimonidine – individual component

3.2.2 Study C-10-039

3.2.2.1 Study Design and Endpoints

The study design and endpoints for Study C-10-039 are identical to that of Study C-10-033 (refer to Section 3.2.1.1 for details) with the exception that Study C-10-039 had an additional follow-up visit at Month 6. The primary assessments of efficacy were through Month 3 and the additional 3 months of study drug exposure was intended to provide further safety data. The study was conducted at 64 sites in the United States.

Reviewer's Comment: *The study report for C-10-039 included in the submission includes complete Month 3 data and is the focus of this review. The results of the additional 3 months of study drug use are to be reported once all patients complete the study. Treatment assignments were broken for analysis purposes following the completion of the Month 3 visit only after database lock. The mask was maintained for all individuals associated with the conduct of the study including the patients, the investigators, and the clinical trial monitors.*

3.2.2.2 Statistical Methodologies

The statistical methodologies for Study C-10-039 are identical to that of Study C-10-033 (refer to Section 3.2.1.2 for details).

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 690 patients were randomized into the study: 221 to the brinzolamide/brimonidine group, 233 to the brinzolamide group, and 236 to the brimonidine group. Approximately 90% of the randomized patients completed the study. The most common reason for discontinuation across all treatment groups was adverse event. The next most common reason for discontinuation was inadequate IOP control which occurred more often in the brimonidine alone group. Reasons for discontinuation are reported in Table 8.

Table 8
C-10-039
Patient Disposition

	Brinz/Brim	Brinz	Brim
Randomized	221	233	236
Completed Study	196 (88.7)	216 (92.7)	203 (86.0)
Discontinued Study	25 (11.3)	17 (7.3)	33 (14.0)
Adverse Event	19	8	19
Patient's Decision	2	0	1
Noncompliance	1	0	0
Protocol Violation	1	2	0
Inadequate Control of IOP	1	7	13
Patient did not meet entrance criteria	1	0	0

The Safety Population is comprised of all 690 patients. It should be noted, however, that 3 patients did not receive their randomized study treatment: 1 patient randomized to brimonidine received brinzolamide instead, 1 patient randomized to brinzolamide/brimonidine received brimonidine instead, and 1 patient randomized to brimonidine received brinzolamide/brimonidine instead. These patients are analyzed according to the randomized treatment assigned in all efficacy analyses but they are analyzed according to the treatment they actually received in the Safety Population. Three patients in the brinzolamide/brimonidine group, 4 patients in the brinzolamide group and 4 patients in the brimonidine group had no on-therapy follow-up data and were excluded from the ITT population. An additional 33 patients (10 brinzolamide/brimonidine, 12 brinzolamide, and 11 brimonidine) were excluded from the PP population due to protocol violations.

Table 9
C-10-039
Analysis Populations

	Brinz/Brim	Brinz	Brim
Randomized	221	233	236
Safety Population*	221	234	235
ITT Population**	218	229	232
PP Population**	208	217	221

*Patients analyzed according to actual treatment received
**Patients analyzed according to randomized treatment

Table 10 summarizes the demographic and baseline characteristics of the ITT population. There were no significant differences across treatment groups. Overall, 56% of the study population was female and 78% was white. The mean age of the patients was 65 years. The majority of the patients had brown eyes and a diagnosis of open-angle glaucoma. Approximately 63% were included in the baseline IOP stratum of 24-27 mmHg. Mean corneal thickness at baseline was approximately 0.55 mm.

Table 10
C-10-039
Demographic and Baseline Characteristics (ITT)

	Treatment Group		
	Brinz/Brim	**Brinz**	**Brim**
# Patients	218	229	232
Gender			
Male	100 (45.9)	97 (42.4)	101 (43.5)
Female	118 (54.1)	132 (57.6)	131 (56.5)
Age mean (SD)	65.7 (10.3)	64.2 (10.3)	64.9 (10.5)
Min, max	34, 95	22, 87	33, 92
Race			
White	174 (79.8)	179 (78.2)	176 (75.9)
Black	36 (16.5)	42 (18.3)	52 (22.4)
Asian	3 (1.4)	5 (2.2)	1 (0.4)
Other	5 (2.3)	3 (1.3)	3 (1.3)
Iris Color			
Blue	55 (25.2)	60 (26.2)	53 (22.8)
Brown	118 (54.1)	126 (55.0)	125 (53.9)
Green	9 (4.1)	13 (5.7)	17 (7.3)
Grey	0	1 (0.4)	0
Hazel	35 (16.1)	28 (12.2)	36 (15.5)
Other	1 (0.5)	1 (0.4)	1 (0.4)
Diagnosis			
Ocular Hypertension	51 (23.4)	59 (25.8)	58 (25.0)
Open-Angle Glaucoma	160 (73.4)	165 (72.1)	169 (72.8)
Open-Angle Glaucoma with Pigment Dispersion	6 (2.8)	2 (0.9)	5 (2.2)
Open-Angle Glaucoma with Pseudoexfoliation	1 (0.5)	3 (1.3)	0
Baseline IOP Stratum			
24-27 mmHg	139 (63.8)	145 (63.3)	145 (62.5)
28-36 mmHg	79 (36.2)	84 (36.7)	87 (37.5)
Study (Worse) Eye			
Right	120 (55.0)	111 (48.5)	124 (53.4)
Left	98 (45.0)	118 (51.5)	108 (46.6)
Corneal Thickness(mm) mean (SD)	0.553 (0.034)	0.557 (0.032)	0.554 (0.032)
Min, max	(0.465, 0.653)	(0.467, 0.617)	(0.469, 0.614)

Table 11 presents the mean baseline IOP for each time point. There are no significant differences among the 3 treatment groups at any of the 4 time points. The highest IOP measurements were seen at the 8 AM visit and decreased throughout the day.

Table 11
C-10-039
Baseline IOP (mmHg) (ITT)

		Brinz/Brim (n=218)	Brinz (n=229)	Brim (n=232)
8 AM	mean (SD)	27.2 (2.75)	27.2 (2.72)	27.3 (2.73)
	min, max	24, 36	24, 36	24, 36
10 AM	mean (SD)	25.8 (3.09)	26.0 (3.20)	25.8 (3.02)
	min, max	21, 34	21, 36	21, 35
3 PM	mean (SD)	24.4 (3.67)	24.4 (3.58)	24.0 (3.39)
	min, max	16, 36	15, 36	17, 36
5 PM	mean (SD)	24.1 (3.71)	24.2 (3.86)	23.7 (3.58)
	min, max	13, 35	15, 36	16, 36

3.2.2.4 Results and Conclusions

Mean IOP measurements at each visit (Week 2, Week 6, and Month 3) at each time point (8 AM, 10 AM, 3 PM and 5 PM) are presented in Table 12. The mean IOP measurements were statistically significantly lower in the brinzolamide/brimonidine group compared to both the brinzolamide alone and brimonidine alone groups at all visits and time points. The mean difference between the brinzolamide/brimonidine group and the brinzolamide treatment group was greater than 1.0 mmHg at all but 1 assessment time point and was greater than 1.5 mmHg for the majority of the assessment time points. The mean difference between the brinzolamide/brimonidine group and the brimonidine group was greater than 1.5 mmHg for all of the assessment time points.

Table 12
C-10-039
Mean IOP (mmHg) at Week 2, Week 6 and Month 3 (ITT)

			Brinz/Brim (n=218)	Brinz (n=229)	Brim (n=232)
Week 2	**8 AM**	Mean* (SE)	20.5 (0.29)	22.2 (0.29)	22.8 (0.29)
		Mean difference**		-1.7	-2.4
		95% CI		(-2.4, -1.0)	(-3.1, -1.7)
		p-value		<0.0001	<0.0001
	10 AM	Mean (SE)	17.4 (0.30)	20.7 (0.29)	19.2 (0.29)
		Mean difference		-3.3	-1.8
		95% CI		(-4.0, -2.6)	(-2.5, -1.2)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	18.7 (0.30)	20.5 (0.29)	21.1 (0.29)
		Mean difference		-1.7	-2.3
		95% CI		(-2.4, -1.1)	(-3.0, -1.6)
		p-value		<0.0001	<0.0001
	5 PM	Mean (SE)	16.5 (0.30)	20.1 (0.29)	18.3 (0.29)
		Mean difference		-3.6	-1.8
		95% CI		(-4.3, -2.9)	(-2.4, -1.1)
		p-value		<0.0001	<0.0001

			Brinz/Brim (n=218)	Brinz (n=229)	Brim (n=232)
Week 6	**8 AM**	Mean (SE)	20.7 (0.30)	21.9 (0.29)	23.2 (0.29)
		Mean difference		-1.2	-2.5
		95% CI		(-1.9, -0.5)	(-3.2, -1.8)
		p-value		0.0007	<0.0001
	10 AM	Mean (SE)	17.4 (0.30)	20.5 (0.29)	19.7 (0.29)
		Mean difference		-3.1	-2.3
		95% CI		(-3.8, -2.4)	(-3.0, -1.6)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	19.3 (0.30)	20.2 (0.29)	21.2 (0.29)
		Mean difference		-0.8	-1.9
		95% CI		(-1.5, -0.2)	(-2.6, -1.2)
		p-value		0.0146	<0.0001
	5 PM	Mean (SE)	16.9 (0.30)	19.9 (0.29)	18.5 (0.29)
		Mean difference		-3.0	-1.7
		95% CI		(-3.7, -2.3)	(-2.4, -1.0)
		p-value		<0.0001	<0.0001
Month 3	**8 AM**	Mean (SE)	21.1 (0.30)	22.0 (0.29)	23.2 (0.30)
		Mean difference		-1.0	-2.2
		95% CI		(-1.7, -0.3)	(-2.9, -1.5)
		p-value		0.0054	<0.0001
	10 AM	Mean (SE)	18.0 (0.30)	20.8 (0.29)	19.9 (0.30)
		Mean difference		-2.8	-1.9
		95% CI		(-3.5, -2.1)	(-2.6, -1.2)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	19.5 (0.30)	20.7 (0.29)	21.5 (0.30)
		Mean difference		-1.2	-2.0
		95% CI		(-1.9, -0.5)	(-2.7, -1.3)
		p-value		0.0008	<0.0001
	5 PM	Mean (SE)	17.2 (0.30)	20.4 (0.29)	18.9 (0.30)
		Mean difference		-3.2	-1.7
		95% CI		(-3.9, -2.5)	(-2.4, -1.0)
		p-value		<0.0001	<0.0001

*Estimates are based on least square means derived from a linear mixed model that accounts for correlated IOP measurements within patient.
**Difference is brinzolamide/brimonidine – individual component

The amount of missing data at each visit was relatively small and fairly consistent across treatment groups. Missing data per treatment group at Week 2 ranged from 0.8% to 4.3%, at Week 6 ranged from 3.9% to 9.1%, and at Month 3 ranged from 7.4% to 14.2%. Thus, the results based on the analysis using LOCF (see Supplemental Table S-2) are very similar to those presented in Table 12.

Table 13 presents the change from baseline in mean IOP at each assessment time point. Similar to the results seen for mean IOP, the change from baseline in mean IOP was significantly better (greater decrease from baseline) for the brinzolamide/brimonidine group compared to both the brinzolamide alone and brimonidine alone groups at all visits and time points.

Table 13
Study C-10-039
Change from baseline IOP (mmHg) (ITT) at Week 2, Week 6, and Month 3

			Brinz/Brim (n=209)	**Brinz** (n=224)	**Brim** (n=216)
Week 2	**8 AM**	Mean* (SE)	-7.4 (0.26)	-5.6 (0.25)	-5.0 (0.25)
		Mean difference**		-1.7	-2.3
		95% CI		(-2.4, -1.1)	(-3.0, -1.7)
		p-value		<0.0001	<0.0001
	10 AM	Mean (SE)	-9.1 (0.26)	-6.0 (0.25)	-7.2 (0.26)
		Mean difference		-3.1	-1.9
		95% CI		(-3.7, -2.5)	(-2.5, -1.2)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	-6.3 (0.26)	-4.5 (0.25)	-3.6 (0.25)
		Mean difference		-1.7	-2.7
		95% CI		(-2.3, -1.1)	(-3.3, -2.1)
		p-value		<0.0001	<0.0001
	5 PM	Mean (SE)	-8.3 (0.27)	-4.7 (0.25)	-6.0 (0.26)
		Mean difference		-3.6	-2.3
		95% CI		(-4.2, -2.9)	(-2.9, -1.6)
		p-value		<0.0001	<0.0001
Week 6	**8 AM**	Mean (SE)	-7.4 (0.26)	-5.9 (0.26)	-4.7 (0.26)
		Mean difference		-1.2	-2.5
		95% CI		(-1.8, -0.6)	(-3.1, -1.8)
		p-value		0.0002	<0.0001
	10 AM	Mean (SE)	-9.1 (0.26)	-6.1 (0.26)	-6.7 (0.26)
		Mean difference		-3.0	-2.4
		95% CI		(-3.6, -2.3)	(-3.0, -1.7)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	-5.7 (0.26)	-4.8 (0.26)	-3.5 (0.26)
		Mean difference		-0.9	-2.2
		95% CI		(-1.5, -0.2)	(-2.9, -1.6)
		p-value		0.0081	<0.0001
	5 PM	Mean (SE)	-8.0 (0.26)	-4.9 (0.26)	-5.8 (0.26)
		Mean difference		-3.0	-2.2
		95% CI		(-3.6, -2.4)	(-2.8, -1.5)
		p-value		<0.0001	<0.0001
Month 3	**8 AM**	Mean (SE)	-6.8 (0.27)	-5.8 (0.26)	-4.6 (0.26)
		Mean difference		-1.0	-2.1
		95% CI		(-1.6, -0.4)	(-2.8, -1.5)
		p-value		0.0022	<0.0001
	10 AM	Mean (SE)	-8.5 (0.27)	-5.8 (0.26)	-6.5 (0.26)
		Mean difference		-2.6	-1.9
		95% CI		(-3.3, -2.0)	(-2.6, -1.3)
		p-value		<.0001	<.0001
	3 PM	Mean (SE)	-5.5 (0.27)	-4.3 (0.26)	-3.1 (0.26)
		Mean difference		-1.1	-2.3
		95% CI		(-1.8, -0.5)	(-3.0, -1.7)
		p-value		0.0005	<.0001
	5 PM	Mean (SE)	-7.6 (0.27)	-4.4 (0.26)	-5.4 (0.26)
		Mean difference		-3.3	-2.2
		95% CI		(-3.9, -2.6)	(-2.9, -1.6)
		p-value		<.0001	<0.0001

*Estimates are based on least square means derived from a linear mixed model that accounts for correlated IOP measurements within patient.
**Difference is brinzolamide/brimonidine – individual component

3.3 Evaluation of Safety

The individual components of the combination are both approved products with known safety profiles. The majority of the adverse events reported in the pivotal Phase 3 trials were for local ocular side effects with known causal association with the individual components. No new or increased incidence of topical ocular events with the use of brimonidine/brinzolamide relative to the individual components was identified. No patients died during the Phase 3 clinical trials. Tables 14 and 15 include a brief summary of the treatment emergent adverse event from Studies C-10-033 and C-10-039, respectively. For a detailed review of the safety data, please see the Medical Officer's review.

Table 14
C-10-033
Overall Adverse Events
Safety Population

	Treatment Group		
	Brinz/Brim	**Brinz**	**Brim**
# Patients	214	226	220
Any Treatment Emergent Adverse Event	80 (37.4)	74 (32.7)	74 (33.6)
Serious Treatment Emergent Adverse Event	2 (0.9)	6 (2.7)	2 (0.9)
Occular Reactions (occurring at an incidence ≥1%)			
Vision Blurred	13 (6.1)	14 (6.2)	1 (0.5)
Occular hyperaemia	7 (3.3)	2 (0.9)	9 (4.1)
Eye irritation	6 (2.8)	2 (0.9)	4 (1.8)
Conjunctival hyperaemia	3 (1.4)	4 (1.8)	3 (1.4)
Dry eye	2 (0.9)	2 (0.9)	6 (2.7)
Eye pain	3 (1.4)	4 (1.8)	2 (0.9)
Conjunctivitis allergic	4 (1.9)	1 (0.4)	2 (0.9)
Eye puritus	2 (0.9)	2 (0.9)	3 (1.4)
Foreign body sensation in eyes	3 (1.4)	2 (0.9)	1 (0.5)
Punctate keratitis	1 (0.5)	1 (0.4)	3 (1.4)
Eye allergy	1 (0.5)	0	3 (1.4)
Eye discharge	1 (0.5)	3 (1.3)	0

Adapted from Tables 12.2.2-1 and 12.2.3.1-1 of C-10-033 Study Report

Table 15
C-10-039
Overall Adverse Events
Safety Population

	Treatment Group		
	Brinz/Brim	**Brinz**	**Brim**
# Patients	221	234	235
Any Treatment Emergent Adverse Event	95 (43.0)	85 (36.3)	73 (31.1
Serious Treatment Emergent Adverse Event	4 (1.8)	1 (0.4)	5 (2.1)
Occular Reactions (occurring at an incidence ≥1%)			
Vision Blurred	10 (4.5)	16 (6.8)	0
Eye irritation	12 (5.4)	4 (1.7)	6 (2.6)
Eye pain	6 (2.7)	4 (1.7)	3 (1.3)
Eye allergy	10 (4.5)	0	2 (0.9)
Conjunctivitis	4 (1.8)	0	7 (3.0)
Conjunctivitis allergic	4 (1.8)	1 (0.4)	5 (2.1)
Occular hyperaemia	2 (0.9)	1 (0.4)	6 (2.6)
Eye puritus	5 (2.3)	3 (1.3)	0
Conjunctival hyperaemia	4 (1.8)	1 (0.4)	2 (0.9)
Dry eye	4 (1.8)	2 (0.9)	1 (0.4)
Lacrimation increased	3 (1.4)	1 (0.4)	1 (0.4)
Conjunctival follicles	1 (0.5)	0	3 (1.3)

Adapted from Tables 12.2.2-1 and 12.2.3.1-1 of C-10-030 Study Report

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Descriptive analyses by gender, race and age were conducted for mean IOP at Week 2, Week 6, and Month 3 at each assessment time point (see Supplemental Tables S-3 to S-8) for both studies. Overall, the results were similar to those seen for the overall population for each demographic subgroup. The results for the Other Race subgroup should be interpreted with caution due to the small sample sizes. Analyses by geographic region were not conducted since all clinical sites were in the United States.

4.2 Other Special/Subgroup Populations

Both trials were stratified by the 8 AM baseline IOP measurement. Supplemental Tables S-9 and S-10 summarize the descriptive results by baseline IOP stratum for mean IOP at Week 2, Week 6, and Month 3 at each assessment time point for each study, respectively. As would be expected, the mean IOP estimates at all assessment time points are higher for the baseline 28-36 mmHg stratum than the 24-27 mmHg stratum. In both stratums, the mean IOP estimates at all assessment time points for each treatment group are lower than the original baseline stratum values. As seen for the overall population, the differences in mean IOP favored the brinzolamide/brimonidine group compared to each of the individual components.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues for this submission. Although the primary efficacy endpoint was stated in the protocols to be IOP assessed at Month 3 at each assessment time point (8 AM, 10 AM, 3 PM, 5 PM) and each assessment time point at the Week 2 and Week 6 visits were to be supportive efficacy endpoints, the Applicant was told at the End of Phase 2 meeting that comparison of IOP at all visits and assessment time points would be considered primary efficacy comparisons. Since all comparisons were necessary to claim significance, there is no adjustment to the type I error for multiple endpoints (i.e., each comparison was assessed at an alpha level of 0.05). Additionally, since the brinzolamide/brimonidine group needed to be superior to each of the individual components, no adjustment to the type I error was needed for multiple treatment comparisons.

5.2 Collective Evidence

The pivotal evidence to support the efficacy of brinzolamide/brimonidine for the reduction of elevated IOP was based on two relatively identically designed Phase 3 trials (C-10-033 and C-10-039). Both trials showed that treatment with brinzolamide/brimonidine led to significantly lower mean IOP measurements at each visit (Week 2, Week 4, Month 3) and each time point (8 AM, 10 AM, 3 PM, and 5 PM) when compared to both the brinzolamide alone and brimonidine alone groups. In study C-10-033, the differences in mean IOP between brinzolamide/brimonidine and each of the individual components was greater than 1 mmHg at all assessment time points. Furthermore, the differences in mean IOP between brinzolamide/brimonidine and brinzolamide alone were at least 1.5 mmHg for 10 of 12 assessment time points and differences in mean IOP between brinzolamide/brimonidine and brimonidine alone were at least 1.5 mmHg for all 12 of 12 assessment time points. In study C-10-039, the differences in mean IOP between brinzolamide/brimonidine and each of the individual components was greater than 1 mmHg at all but one assessment time point. Furthermore, the differences in mean IOP between brinzolamide/brimonidine and brinzolamide alone were at least 1.5 mmHg for 8 of 12 assessment time points and differences in mean IOP between brinzolamide/brimonidine and brimonidine alone were at least 1.5 mmHg for all 12 of 12 assessment time points.

5.3 Conclusions and Recommendations

Based on the results of the two pivotal Phase 3 trials, mean IOP was statistically significantly reduced at all assessment time points with treatment with the fixed combination of brinzolamide/brimonidine when compared to each of the individual components alone. Therefore, there is adequate evidence of efficacy to support the indication of the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension for the fixed combination of brinzolamide/brimonidine.

5.4 Labeling Recommendations

In Section 14 Clinical Studies, the Applicant is proposing (b) (4) It is recommended that the data be presented for each study individually (b) (4) It is further recommended that the point estimate of mean IOP for each treatment group be presented along with the point estimate of the difference in means between treatment groups (brinz/brim – brinz alone and brinz/brim – brim alone). Additionally, the 95% confidence interval about the difference in mean IOP should be presented along with the point estimate of the difference in mean IOP. A table similar to the following is recommended for presenting the mean IOP data at Month 3.

Study	Time Point		Brinz/Brim	Brinz	Brim
Study 1			(n=209)	(n=224)	(n=216)
	8 AM	Mean (SE)*	20.5 (0.29)	21.6 (0.28)	23.3 (0.29)
		Mean difference**		-1.1	-2.8
		95% CI		(-1.8, -0.4)	(-3.5, -2.1)
	10 AM	Mean (SE)	17.2 (0.29)	20.4 (0.28)	19.7 (0.29)
		Mean difference		-3.2	-2.5
		95% CI		(-3.9, -2.5)	(-3.2, -1.8)
	3 PM	Mean (SE)	18.7 (0.29)	20.4 (0.28)	21.3 (0.29)
		Mean difference		-1.8	-2.6
		95% CI		(-2.5, -1.1)	(-3.3, -1.9)
	5 PM	Mean (SE)	17.0 (0.29)	20.0 (0.28)	18.8 (0.29)
		Mean difference		-3.0	-1.8
		95% CI		(-3.7, -2.3)	(-2.5, -1.1)
Study 2			(n=218)	(n=229)	(n=232)
	8 AM	Mean (SE)	21.1 (0.30)	22.0 (0.29)	23.2 (0.30)
		Mean difference		-1.0	-2.2
		95% CI		(-1.7, -0.3)	(-2.9, -1.5)
	10 AM	Mean (SE)	18.0 (0.30)	20.8 (0.29)	19.9 (0.30)
		Mean difference		-2.8	-1.9
		95% CI		(-3.5, -2.1)	(-2.6, -1.2)
	3 PM	Mean (SE)	19.5 (0.30)	20.7 (0.29)	21.5 (0.30)
		Mean difference		-1.2	-2.0
		95% CI		(-1.9, -0.5)	(-2.7, -1.3)
	5 PM	Mean (SE)	17.2 (0.30)	20.4 (0.29)	18.9 (0.30)
		Mean difference		-3.2	-1.7
		95% CI		(-3.9, -2.5)	(-2.4, -1.0)

*Estimates are based on least square means derived from a linear mixed model that accounts for correlated IOP measurements within patient.
**Difference is brinzolamide/brimonidine – individual component
Intent-To Treat Population defined as all patients who received study drug and completed at least 1 on-therapy study visit.

If the Medical Division determines that the pooled data is acceptable, the 95% confidence interval about the point estimate of the mean difference should be included. These can be found in Supplemental Table S-11 for mean IOP.

Supplemental Tables

Table S-1
C-10-033
Mean IOP (mmHg) (ITT- LOCF) at Week 2, Week 6, and Month 3

			Brinz/Brim	Brinz	Brim
Week 2	**8 AM**	Mean (SE)	19.7 (0.24)	21.3 (0.25)	21.6 (0.28)
		N	209	223	216
		Mean difference		-1.6	-1.9
		95% CI		(-2.3, -0.9)	(-2.6, -1.2)
		p-value*		<0.0001	<0.0001
	10 AM	Mean (SE)	16.4 (0.21)	19.9 (0.23)	18.6 (0.25)
		N	205	221	212
		Mean difference		-3.4	-2.23
		95% CI		(-4.0, -2.8)	(-2.8, -1.5)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	17.8 (0.21)	19.7 (0.24)	19.8 (0.27)
		N	205	220	212
		Mean difference		-1.9	-2.1
		95% CI		(-2.6, -1.3)	(-2.7, -1.4)
		p-value		<0.0001	<0.0001
	5 PM	Mean (SE)	15.9 (0.20)	19.1 (0.22)	17.6 (0.22)
		N	204	220	212
		Mean difference		-3.2	-1.7
		95% CI		(-3.8, -2.6)	(-2.3, -1.1)
		p-value		<0.0001	<0.0001
Week 6	**8 AM**	Mean (SE)	19.7 (0.27)	21.2 (0.28)	21.8 (0.30)
		N	209	224	216
		Mean difference		-1.5	-2.1
		95% CI		(-2.2, -0.7)	(-2.8, -1.3)
		p-value		0.0002	<0.0001
	10 AM	Mean (SE)	16.8 (0.24)	19.6 (0.25)	18.6 (0.24)
		N	205	222	212
		Mean difference		-2.8	-1.9
		95% CI		(-3.5, -2.1)	(-2.5, -1.2)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	18.3 (0.25)	19.5 (0.22)	20.3 (0.27)
		N	205	222	212
		Mean difference		-1.2	-2.0
		95% CI		(-1.9, -0.6)	(-2.8, -1.3)
		p-value		0.0003	<0.0001
	5 PM	Mean (SE)	16.4 (0.23)	19.0 (0.23)	17.8 (0.23)
		N	204	222	212
		Mean difference		-2.6	-1.4
		95% CI		(-3.2, -1.9)	(-2.1, -0.8)
		p-value		<0.0001	<0.0001
Month 3	**8 AM**	Mean (SE)	19.8 (0.28)	21.0 (0.30)	22.4 (0.31)
		N	209	224	216
		Mean difference		-1.2	-2.6
		95% CI		(-2.0, -0.4)	(-3.4, -1.7)
		p-value		0.0031	<0.0001
	10 AM	Mean (SE)	16.6 (0.25)	19.8 (0.26)	18.8 (0.26)
		N	205	222	212

		Brinz/Brim	Brinz	Brim
	Mean difference		-3.2	-2.3
	95% CI		(-3.9, -2.5)	(-3.0, -1.6)
	p-value		<0.0001	<0.0001
3 PM	Mean (SE)	18.0 (0.26)	19.7 (0.24)	20.5 (0.27)
	N	205	222	212
	Mean difference		-1.7	-2.5
	95% CI		(-2.4, -1.0)	(-3.2, -1.7)
	p-value		<0.0001	<0.0001
5 PM	Mean (SE)	16.3 (0.26)	19.3 (0.25)	18.0 (0.24)
	N	204	222	212
	Mean difference		-3.0	-1.7
	95% CI		(-3.7, -2.3)	(-2.4, -1.0)
	p-value		<0.0001	<0.0001

*p-value based on two-sample t-test
Table adapted from C-10-033: Table 1 and C-10-033 Table 2 of December 20, 2012 submission

Table S-2
C-10-039
Mean IOP (mmHg) at Week 2, Week 6 and Month 3 (ITT- LOCF)

			Brinz/Brim	Brinz	Brim
Week 2	**8 AM**	Mean (SE)	20.0 (0.269)	21.7 (0.29)	22.5 (0.27)
		N	218	229	230
		Mean difference		-1.7	-2.5
		95% CI		(-2.5, -1.0)	(-3.2, -1.7)
		p-value		<0.0001	<0.0001
	10 AM	Mean (SE)	16.9 (0.24)	20.3 (0.24)	18.8 (0.26)
		N	214	227	226
		Mean difference		-3.4	-1.9
		95% CI		(-4.0, -2.7)	(-2.6, -1.2)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	18.3 (0.27)	20.1 (0.24)	20.6 (0.26)
		N	212	227	226
		Mean difference		-1.8	-2.4
		95% CI		(-2.5, -1.1)	(-3.1, -1.6)
		p-value		<0.0001	<0.0001
	5 PM	Mean (SE)	16.0 (0.24)	19.7 (0.24)	17.8 (0.25)
		N	211	227	222
		Mean difference		-3.7	-1.8
		95% CI		(-4.3, -3.0)	(-2.5, -1.1)
		p-value		<0.0001	<0.0001
Week 6	**8 AM**	Mean (SE)	20.2 (0.27)	21.5 (0.28)	22.8 (0.30)
		N	218	229	228
		Mean difference		-1.3	-2.3
		95% CI		(-2.1, -0.5)	(-3.0, -1.6)
		p-value		0.0009	<0.0001
	10 AM	Mean (SE)	16.9 (0.25)	20.1 (0.26)	19.2 (0.28)
		N	214	227	228
		Mean difference		-3.2	-2.3
		95% CI		(-3.9, -2.5)	(-3.0, -1.6)
		p-value		<0.0001	<0.0001
	3 PM	Mean (SE)	18.8 (0.26)	19.8 (0.25)	20.7 (0.29)
		N	213	227	228
		Mean difference		-0.9	-1.9
		95% CI		(-1.6, -0.2)	(-2.7, -1.1)
		p-value		0.0091	<0.0001
	5 PM	Mean (SE)	16.4 (0.25)	19.5 (0.25)	18.0 (0.26)
		N	212	227	225
		Mean difference		-3.1	-1.7
		95% CI		(-3.8, -2.4)	(-2.4, -0.9)
		p-value		<0.0001	<0.0001
Month 3	**8 AM**	Mean (SE)	20.5 (0.27)	21.7 (0.29)	23.1 (0.30)
		N	218	229	232
		Mean difference		-1.2	-2.6
		95% CI		(-1.9, -0.4)	(-3.4, -1.8)
		p-value		0.0036	<0.0001
	10 AM	Mean (SE)	17.5 (0.26)	20.4 (0.26)	19.5 (0.27)
		N	214	227	228
		Mean difference		-2.9	-2.0
		95% CI		(-3.6, -2.2)	(-2.8, -1.3)

		Brinz/Brim	Brinz	Brim
	p-value		<0.0001	<0.0001
3 PM	Mean (SE)	19.1 (0.26)	20.3 (0.28)	21.1 (0.30)
	N	213	227	228
	Mean difference		-1.3	-2.0
	95% CI		(-2.0, -0.5)	(-2.8, -1.2)
	p-value		0.0009	<0.0001
5 PM	Mean (SE)	16.7 (0.26)	20.0 (0.27)	18.4 (0.29)
	N	212	227	225
	Mean difference		-3.3	-1.6
	95% CI		(-4.0, -2.6)	(-2.4, -0.9)
	p-value		<0.0001	<0.0001

*p-value based on two-sample t-test
Table adapted from C-10-039: Table 1 and C-10-039 Table 2 of December 20, 2012 submission

Table S-3
C-10-033
Mean IOP (mmHg) by Age (ITT)

Age	Visit	Time		Brinz/Brim	Brinz	Brim
< 65 years	**Week 2**	**8 AM**	Mean (SD)	19.9 (3.1)	22.2 (4.0)	21.6 (4.1)
			N	104	98	115
		10 AM	Mean (SD)	16.7 (3.2)	20.4 (3.3)	18.7 (3.7)
			N	103	98	114
		3 PM	Mean (SD)	17.9 (3.1)	20.1 (3.5)	19.8 (4.0)
			N	103	98	114
		5 PM	Mean (SD)	16.1 (3.0)	19.4 (3.4)	17.6 (3.3)
			N	102	98	114
	Week 6	**8 AM**	Mean (SD)	19.9 (3.8)	22.0 (4.1)	21.7 (4.3)
			N	99	96	109
		10 AM	Mean (SD)	16.9 (3.4)	20.1 (3.8)	18.6 (3.5)
			N	98	96	108
		3 PM	Mean (SD)	18.2 (3.5)	19.6 (3.5)	20.1 (3.8)
			N	97	96	108
		5 PM	Mean (SD)	16.5 (3.3)	19.5 (3.5)	17.7 (3.3)
			N	97	96	108
	Month 3	**8 AM**	Mean (SD)	19.8 (4.4)	21.8 (4.3)	22.3 (4.4)
			N	92	95	104
		10 AM	Mean (SD)	16.8 (3.8)	20.3 (4.2)	19.1 (4.1)
			N	92	95	104
		3 PM	Mean (SD)	18.1 (4.1)	20.3 (3.7)	20.5 (4.2)
			N	92	95	104
		5 PM	Mean (SD)	16.5 (4.0)	19.8 (3.8)	18.0 (3.5)
			N	92	95	103
≥ 65 years	**Week 2**	**8 AM**	Mean (SD)	19.6 (3.7)	20.7 (3.4)	21.6 (4.2)
			N	105	125	101
		10 AM	Mean (SD)	16.2 (2.8)	19.4 (3.4)	18.6 (3.4)
			N	102	123	98
		3 PM	Mean (SD)	17.6 (2.8)	19.4 (3.6)	19.9 (3.7)
			N	102	122	98
		5 PM	Mean (SD)	15.7 (2.9)	18.7 (3.2)	17.7 (3.1)
			N	102	122	98
	Week 6	**8 AM**	Mean (SD)	19.5 (3.9)	20.6 (4.3)	21.9 (4.3)
			N	99	119	94
		10 AM	Mean (SD)	16.7 (3.4)	19.0 (3.5)	18.6 (3.3)
			N	99	118	93
		3 PM	Mean (SD)	18.3 (3.7)	19.3 (3.2)	20.3 (4.0)
			N	99	118	92
		5 PM	Mean (SD)	16.2 (3.4)	18.6 (3.4)	17.7 (3.1)
			N	99	118	91
	Month 3	**8 AM**	Mean (SD)	19.9 (3.9)	20.2 (3.9)	22.6 (4.5)
			N	97	118	88
		10 AM	Mean (SD)	16.3 (3.5)	19.2 (3.7)	18.6 (3.1)
			N	97	118	88
		3 PM	Mean (SD)	17.9 (3.3)	19.3 (3.5)	20.5 (3.3)
			N	97	117	88
		5 PM	Mean (SD)	16.1 (3.4)	18.8 (3.5)	17.7 (3.1)
			N	97	117	87

Table S-4
C-10-033
Mean IOP (mmHg) by Gender (ITT)

Gender	Visit	Time		Brinz/Brim	Brinz	Brim
Male	**Week 2**	**8 AM**	Mean (SD)	19.3 (3.7)	21.2 (3.8)	22.5 (4.1)
			N	73	97	84
		10 AM	Mean (SD)	16.2 (2.9)	20.1 (3.4)	19.6 (4.1)
			N	72	96	83
		3 PM	Mean (SD)	17.3 (2.8)	20.0 (3.6)	20.9 (4.4)
			N	72	95	83
		5 PM	Mean (SD)	15.6 (2.9)	19.2 (3.4)	18.1 (3.7)
			N	72	95	83
	Week 6	**8 AM**	Mean (SD)	19.4 (3.8)	21.2 (4.3)	22.5 (4.2)
			N	72	94	80
		10 AM	Mean (SD)	16.9 (3.2)	19.7 (3.9)	19.3 (3.4)
			N	72	94	80
		3 PM	Mean (SD)	18.1 (3.7)	19.7 (3.2)	20.4 (4.2)
			N	72	94	80
		5 PM	Mean (SD)	16.0 (3.2)	18.9 (3.4)	18.1 (3.6)
			N	72	94	80
	Month 3	**8 AM**	Mean (SD)	19.9 (4.1)	20.9 (4.3)	22.9 (4.7)
			N	72	94	77
		10 AM	Mean (SD)	16.6 (3.6)	19.4 (4.2)	19.6 (4.1)
			N	72	94	77
		3 PM	Mean (SD)	18.2 (3.9)	19.7 (3.7)	20.6 (3.9)
			N	72	93	77
		5 PM	Mean (SD)	16.3 (3.8)	19.1 (3.7)	18.2 (3.0)
			N	72	93	75
Female	**Week 2**	**8 AM**	Mean (SD)	19.9 (3.3)	21.4 (3.7)	21.0 (4.1)
			N	136	126	132
		10 AM	Mean (SD)	16.6 (3.1)	19.7 (3.3)	18.0 (3.0)
			N	133	125	129
		3 PM	Mean (SD)	18.0 (3.0)	19.5 (3.5)	19.2 (3.3)
			N	133	125	129
		5 PM	Mean (SD)	16.1 (2.9)	19.0 (3.2)	17.3 (2.8)
			N	132	125	129
	Week 6	**8 AM**	Mean (SD)	19.9 (3.9)	21.2 (4.3)	21.4 (4.4)
			N	126	121	123
		10 AM	Mean (SD)	16.7 (3.5)	19.3 (3.6)	18.1 (3.4)
			N	125	120	121
		3 PM	Mean (SD)	18.3 (3.6)	19.3 (3.4)	20.1 (3.7)
			N	124	120	120
		5 PM	Mean (SD)	16.6 (3.4)	19.0 (3.5)	17.5 (2.9)
			N	124	120	119
	Month 3	**8 AM**	Mean (SD)	19.8 (4.2)	20.9 (4.1)	22.2 (4.2)
			N	117	119	115
		10 AM	Mean (SD)	16.5 (3.6)	20.0 (3.8)	18.4 (3.3)
			N	117	119	115
		3 PM	Mean (SD)	17.9 (3.6)	19.8 (3.6)	20.4 (3.8)
			N	117	119	115
		5 PM	Mean (SD)	16.3 (3.7)	19.4 (3.7)	17.7 (3.5)
			N	117	119	115

Table S-5
C-10-033
Mean IOP (mmHg) by Race (ITT)

Race	Visit	Time		Brinz/Brim	Brinz	Brim
White	**Week 2**	**8 AM**	Mean (SD)	19.8 (3.7)	21.3 (3.7)	21.8 (3.9)
			N	143	141	155
		10 AM	Mean (SD)	16.4 (3.1)	19.7 (3.2)	18.6 (3.5)
			N	139	139	152
		3 PM	Mean (SD)	18.0 (3.0)	19.8 (3.3)	20.1 (3.7)
			N	139	138	152
		5 PM	Mean (SD)	15.8 (2.9)	19.1 (3.0)	17.7 (3.0)
			N	138	138	152
	Week 6	**8 AM**	Mean (SD)	19.9 (3.9)	21.4(4.5)	22.0 (4.5)
			N	133	132	145
		10 AM	Mean (SD)	16.8 (3.4)	19.5 (3.6)	18.7 (3.4)
			N	132	131	143
		3 PM	Mean (SD)	18.4 (3.3)	19.5 (3.1)	20.7 (3.9)
			N	131	131	142
		5 PM	Mean (SD)	16.2 (3.1)	19.0 (3.3)	17.9 (3.2)
			N	131	131	141
	Month 3	**8 AM**	Mean (SD)	20.3 (3.9)	20.8 (3.9)	22.7 (4.3)
			N	127	130	134
		10 AM	Mean (SD)	16.8 (3.6)	19.7 (3.8)	18.7 (3.5)
			N	127	130	134
		3 PM	Mean (SD)	18.3 (3.6)	19.6 (3.6)	20.6 (3.6)
			N	127	129	134
		5 PM	Mean (SD)	16.3 (3.7)	19.0 (3.4)	17.6 (3.2)
			N	127	129	132
Black	**Week 2**	**8 AM**	Mean (SD)	19.5 (3.0)	21.3 (3.8)	21.2 (4.6)
			N	62	74	59
		10 AM	Mean (SD)	16.6 (2.9)	20.1 (3.7)	18.6 (3.8)
			N	62	74	58
		3 PM	Mean (SD)	17.1 (2.9)	19.4 (3.9)	19.3 (4.3)
			N	62	74	58
		5 PM	Mean (SD)	16.0 (2.9)	18.7 (3.5)	17.5 (3.7)
			N	62	74	58
	Week 6	**8 AM**	Mean (SD)	19.4 (3.7)	20.9 (3.9)	21.4 (3.8)
			N	61	75	56
		10 AM	Mean (SD)	17.1 (3.3)	19.5 (4.0)	18.3 (3.4)
			N	61	75	56
		3 PM	Mean (SD)	18.1 (4.2)	19.3 (3.7)	19.0 (3.4)
			N	61	75	56
		5 PM	Mean (SD)	16.9 (3.8)	18.7 (3.6)	17.4 (3.2)
			N	61	75	56
	Month 3	**8 AM**	Mean (SD)	18.9 (4.6)	21.1 (4.7)	21.8 (4.4)
			N	58	75	56
		10 AM	Mean (SD)	15.9 (3.6)	19.5 (4.3)	18.9 (3.7)
			N	58	75	56
		3 PM	Mean (SD)	17.3 (3.8)	19.8 (3.6)	20.0 (4.0)
			N	58	75	56
		5 PM	Mean (SD)	16.2 (3.9)	19.6 (4.0)	18.4 (3.4)
			N	58	75	56
Other	**Week 2**	**8 AM**	Mean (SD)	19.8 (2.1)	21.9 (3.8)	19.5 (6.4)

Race	Visit	Time		Brinz/Brim	Brinz	Brim
			N	4	8	2
		10 AM	Mean (SD)	16.3 (1.7)	21.0 (3.7)	19.0 (4.2)
			N	4	8	2
		3 PM	Mean (SD)	18.8 (3.0)	21.3 (4.1)	16.5 (0.7)
			N	4	8	2
		5 PM	Mean (SD)	17.3 (2.2)	21.8 (4.6)	16.0 (0)
			N	4	8	2
	Week 6	**8 AM**	Mean (SD)	19.0 (2.9)	20.8 (3.8)	18.0 (0)
			N	4	8	2
		10 AM	Mean (SD)	14.0 (2.9)	19.8 (3.0)	17.5 (3.5)
			N	4	8	2
		3 PM	Mean (SD)	16.5 (2.6)	19.9 (2.5)	18.0 (5.7)
			N	4	8	2
		5 PM	Mean (SD)	15.0 (4.2)	21.3 (3.9)	17.5 (2.1)
			N	4	8	2
	Month 3	**8 AM**	Mean (SD)	18.0 (2.2)	20.9 (3.4)	27.5 (9.2)
			N	4	8	2
		10 AM	Mean (SD)	16.8 (1.5)	20.4 (4.1)	26.5 (9.2)
			N	4	8	2
		3 PM	Mean (SD)	17.8 (3.6)	20.9 (4.9)	27.5 (7.8)
			N	4	8	2
		5 PM	Mean (SD)	16.3 (3.3)	20.5 (4.7)	23.0 (5.7)
			N	4	8	2

Table S-6
C-10-039
Mean IOP (mmHg) by Age (ITT)

Age	Visit	Time		Brinz/Brim	Brinz	Brim
< 65 years	**Week 2**	**8 AM**	Mean (SD)	20.4 (4.0)	22.2 (3.7)	22.9 (3.8)
			N	98	110	115
		10 AM	Mean (SD)	17.4 (4.0)	20.7 (3.4)	19.4 (4.1)
			N	97	109	113
		3 PM	Mean (SD)	18.4 (4.4)	20.7 (3.5)	20.9 (4.0)
			N	97	109	113
		5 PM	Mean (SD)	16.1 (3.7)	20.1 (3.4)	18.3 (3.8)
			N	96	109	112
	Week 6	**8 AM**	Mean (SD)	20.4 (4.2)	21.9 (3.8)	22.7 (4.4)
			N	93	106	107
		10 AM	Mean (SD)	17.2 (3.9)	20.5 (3.8)	19.4 (4.1)
			N	92	105	105
		3 PM	Mean (SD)	18.8 (3.9)	20.2 (3.8)	20.5 (4.1)
			N	92	105	104
		5 PM	Mean (SD)	16.4 (3.9)	19.6 (3.8)	18.2 (3.8)
			N	92	105	104
	Month 3	**8 AM**	Mean (SD)	20.9 (4.2)	22.2 (3.5)	22.5 (3.7)
			N	88	102	101
		10 AM	Mean (SD)	17.8 (4.0)	21.1 (3.6)	19.1 (3.8)
			N	88	100	99
		3 PM	Mean (SD)	19.1 (3.7)	20.9 (3.8)	20.4 (3.9)
			N	88	100	99
		5 PM	Mean (SD)	16.6 (3.8)	20.3 (3.7)	18.0 (4.1)
			N	88	100	99
≥ 65 years	**Week 2**	**8 AM**	Mean (SD)	19.7 (3.6)	21.3 (4.9)	22.0 (4.2)
			N	120	119	115
		10 AM	Mean (SD)	16.5 (3.0)	19.8 (3.8)	18.2 (3.5)
			N	117	118	113
		3 PM	Mean (SD)	18.1 (3.4)	19.5 (3.7)	20.3 (3.9)
			N	115	118	113
		5 PM	Mean (SD)	15.9 (3.3)	19.3 (3.8)	17.4 (3.7)
			N	115	118	110
	Week 6	**8 AM**	Mean (SD)	20.0 (3.8)	21.0(4.2)	22.6 (4.7)
			N	114	117	110
		10 AM	Mean (SD)	16.7 (3.4)	195 (3.8)	18.9 (4.1)
			N	113	115	110
		3 PM	Mean (SD)	18.8 (3.7)	19.1 (3.5)	20.6 (4.4)
			N	114	115	108
		5 PM	Mean (SD)	16.3 (3.4)	19.1 (3.8)	17.6 (3.7)
			N	112	115	107
	Month 3	**8 AM**	Mean (SD)	20.2 (3.7)	20.8 (4.5)	22.4 (4.5)
			N	108	114	102
		10 AM	Mean (SD)	17.2 (3.6)	19.3 (3.8)	19.0 (3.6)
			N	106	113	102
		3 PM	Mean (SD)	19.0 (3.8)	19.4 (4.0)	21.0 (4.5)
			N	106	112	101
		5 PM	Mean (SD)	16.7 (3.9)	19.3 (4.0)	18.0 (4.3)
			N	106	112	100

Table S-7
C-10-039
Mean IOP (mmHg) by Gender (ITT)

Gender	Visit	Time		Brinz/Brim	Brinz	Brim
Male	**Week 2**	**8 AM**	Mean (SD)	19.8 (3.5)	21.1 (4.1)	22.6 (4.1)
			N	100	97	99
		10 AM	Mean (SD)	16.7 (3.3)	20.0 (3.8)	18.8 (3.5)
			N	97	96	98
		3 PM	Mean (SD)	17.9 (3.6)	19.9 (4.0)	20.5 (3.8)
			N	96	96	98
		5 PM	Mean (SD)	15.7 (3.2)	19.5 (3.9)	17.7 (3.9)
			N	96	96	95
	Week 6	**8 AM**	Mean (SD)	19.7 (3.9)	21.1 (3.9)	22.8 (4.4)
			N	96	95	95
		10 AM	Mean (SD)	16.8 (3.6)	19.8 (4.1)	19.4 (4.1)
			N	95	95	95
		3 PM	Mean (SD)	18.4 (3.5)	19.4 (4.2)	20.9 (4.6)
			N	95	95	94
		5 PM	Mean (SD)	16.0 (3.6)	19.5 (4.2)	18.3 (4.0)
			N	94	95	93
	Month 3	**8 AM**	Mean (SD)	20.6 (4.1)	21.0 (4.5)	22.9 (4.4)
			N	93	93	91
		10 AM	Mean (SD)	17.4 (3.7)	20.0 (4.1)	19.6 (3.9)
			N	93	92	90
		3 PM	Mean (SD)	18.7 (3.4)	19.8 (4.3)	21.0 (4.6)
			N	92	91	90
		5 PM	Mean (SD)	16.6 (3.6)	19.6 (4.1)	18.4 (4.3)
			N	92	91	89
Female	**Week 2**	**8 AM**	Mean (SD)	20.2 (4.0)	22.2 (4.5)	22.3 (4.0)
			N	118	132	131
		10 AM	Mean (SD)	17.1 (3.6)	20.4 (3.5)	18.8 (4.1)
			N	117	131	128
		3 PM	Mean (SD)	18.5 (4.1)	20.2 (3.4)	20.7 (4.1)
			N	116	131	128
		5 PM	Mean (SD)	16.3 (3.7)	19.9 (3.3)	17.9 (3.7)
			N	115	131	127
	Week 6	**8 AM**	Mean (SD)	20.6 (4.1)	21.6 (4.1)	22.5 (4.7)
			N	111	128	122
		10 AM	Mean (SD)	17.0 (3.7)	20.1 (3.7)	18.9 (4.1)
			N	110	125	120
		3 PM	Mean (SD)	19.3 (4.0)	19.9 (3.2)	20.2 (3.9)
			N	111	125	118
		5 PM	Mean (SD)	16.6 (3.7)	19.3 (3.4)	17.6 (3.6)
			N	110	125	118
	Month 3	**8 AM**	Mean (SD)	20.5 (3.8)	21.8 (3.9)	22.1 (3.9)
			N	117	123	112
		10 AM	Mean (SD)	17.6 (3.9)	20.3 (3.6)	18.5 (3.4)
			N	101	121	111
		3 PM	Mean (SD)	19.3 (4.1)	20.3 (3.8)	20.5 (3.8)
			N	102	121	110
		5 PM	Mean (SD)	16.7 (4.1)	19.9 (3.7)	17.7 (4.1)
			N	102	121	110

Table S-8
C-10-039
Mean IOP (mmHg) by Race (ITT)

Race	Visit	Time		Brinz/Brim	Brinz	Brim
White	**Week 2**	**8 AM**	Mean (SD)	19.9 (3.6)	21.6 (4.3)	22.7 (4.0)
			N	174	179	175
		10 AM	Mean (SD)	16.8 (3.5)	20.2 (3.5)	19.1 (3.7)
			N	171	178	172
		3 PM	Mean (SD)	18.2 (3.6)	20.0 (3.6)	20.7 (3.8)
			N	170	178	172
		5 PM	Mean (SD)	15.8 (3.3)	19.7 (3.4)	17.9 (3.8)
			N	169	178	169
	Week 6	**8 AM**	Mean (SD)	20.1 (3.8)	21.4 (3.9)	22.9 (4.5)
			N	165	174	166
		10 AM	Mean (SD)	16.8 (3.5)	20.0 (3.7)	19.2 (4.0)
			N	164	172	164
		3 PM	Mean (SD)	18.8 (4.5)	19.7 (3.7)	20.6 (4.1)
			N	164	172	161
		5 PM	Mean (SD)	16.2 (3.4)	19.5 (3.8)	17.9 (3.7)
			N	163	172	160
	Month 3	**8 AM**	Mean (SD)	20.5 (3.8)	21.3 (4.1)	22.6 (3.8)
			N	154	169	154
		10 AM	Mean (SD)	17.1 (3.7)	20.1 (3.7)	19.1 (3.4)
			N	153	167	152
		3 PM	Mean (SD)	19.1 (3.6)	20.1 (3.9)	20.8 (4.0)
			N	153	166	152
		5 PM	Mean (SD)	16.6 (3.7)	19.8 (3.9)	17.9 (3.9)
			N	153	166	151
Black	**Week 2**	**8 AM**	Mean (SD)	20.5 (4.8)	22.5 (4.5)	21.5 (4.1)
			N	36	42	52
		10 AM	Mean (SD)	17.3 (3.8)	20.9 (4.4)	18.0 (4.3)
			N	36	41	51
		3 PM	Mean (SD)	18.5 (5.0)	20.6 (4.0)	20.2 (4.6)
			N	35	41	51
		5 PM	Mean (SD)	16.8 (4.4)	20.0 (4.1)	17.7 (4.0)
			N	35	41	50
	Week 6	**8 AM**	Mean (SD)	20.2 (4.6)	22.0 (4.7)	21.7 (4.8)
			N	35	41	47
		10 AM	Mean (SD)	17.3 (4.2)	20.4 (4.7)	19.0 (4.5)
			N	34	40	47
		3 PM	Mean (SD)	18.8 (5.0)	19.7 (3.6)	20.1 (4.8)
			N	35	40	47
		5 PM	Mean (SD)	16.9 (4.7)	19.0 (3.5)	17.7 (4.1)
			N	34	40	47
	Month 3	**8 AM**	Mean (SD)	20.5 (4.9)	22.3 (4.3)	21.9 (4.7)
			N	35	39	47
		10 AM	Mean (SD)	18.2 (4.5)	20.5 (4.2)	18.8 (5.7)
			N	34	38	45
		3 PM	Mean (SD)	18.7 (4.6)	20.3 (4.7)	20.4 (4.8)
			N	34	38	44
		5 PM	Mean (SD)	17.0 (4.9)	20.1 (3.9)	18.6 (5.2)
			N	34	38	44
Other	**Week 2**	**8 AM**	Mean (SD)	19.8 (3.1)	20.0 (5.2)	23.7 (2.1)

Race	Visit	Time		Brinz/Brim	Brinz	Brim
			N	8	8	3
		10 AM	Mean (SD)	17.0 (2.4)	18.9 (2.8)	16.3 (3.2)
			N	7	8	3
		3 PM	Mean (SD)	19.4 (2.5)	18.5 (3.8)	22.0 (4.6)
			N	7	8	3
		5 PM	Mean (SD)	17.9 (1.7)	18.9 (4.9)	17.7 (1.2)
			N	7	8	3
	Week 6	**8 AM**	Mean (SD)	22.3 (5.2)	19.6 (3.2)	23.5 (3.9)
			N	7	8	4
		10 AM	Mean (SD)	18.1 (2.8)	18.0 (3.1)	16.3 (3.4)
			N	7	8	4
		3 PM	Mean (SD)	21.1 (2.8)	18.9 (3.1)	23.3 (2.2)
			N	7	8	4
		5 PM	Mean (SD)	17.6 (1.5)	17.9 (3.4)	19.5 (2.4)
			N	7	8	4
	Month 3	**8 AM**	Mean (SD)	20.9 (2.3)	20.4 (3.6)	23.8 (7.6)
			N	7	8	4
		10 AM	Mean (SD)	17.6 (2.4)	19.4 (3.9)	18.0 (2.9)
			N	7	8	4
		3 PM	Mean (SD)	18.7 (2.4)	19.8 (3.1)	20.8 (5.5)
			N	7	8	4
		5 PM	Mean (SD)	16.7 (2.4)	18.4 (2.9)	16.8 (3.5)
			N	7	8	4

Table S-9

C-10-033

Mean IOP (mmHg) by Baseline IOP Stratum (ITT)

Stratum	Visit	Time		Brinz/Brim	Brinz	Brim
24-27	**Week 2**	**8 AM**	Mean (SD)	18.8 (3.1)	19.9 (2.7)	20.3 (3.4)
			N	144	153	151
		10 AM	Mean (SD)	15.9 (2.9)	18.8 (2.9)	18.0 (3.1)
			N	140	151	148
		3 PM	Mean (SD)	17.0 (2.6)	18.6 (3.1)	18.8 (3.1)
			N	140	151	148
		5 PM	Mean (SD)	15.3 (2.5)	18.1 (2.7)	17.1 (2.8)
			N	139	151	148
	Week 6	**8 AM**	Mean (SD)	18.7 (3.4)	19.8 (3.4)	20.4 (3.5)
			N	135	147	141
		10 AM	Mean (SD)	16.0 (2.8)	18.5 (3.4)	17.7 (2.8)
			N	134	147	140
		3 PM	Mean (SD)	17.4 (3.2)	18.5 (2.8)	19.2 (3.5)
			N	133	147	139
		5 PM	Mean (SD)	15.8 (3.0)	18.0 (2.9)	17.2 (2.8)
			N	133	147	138
	Month 3	**8 AM**	Mean (SD)	18.4 (3.0)	19.7 (3.6)	20.9 (3.7)
			N	127	147	132
		10 AM	Mean (SD)	15.4 (2.9)	18.5 (3.0)	17.9 (3.1)
			N	127	147	132
		3 PM	Mean (SD)	16.7 (2.8)	18.7 (3.1)	19.4 (3.5)
			N	127	146	132
		5 PM	Mean (SD)	15.3 (3.0)	18.2 (3.1)	17.3 (3.1)
			N	127	147	132
28-36	**Week 2**	**8 AM**	Mean (SD)	21.7 (3.2)	24.5 (3.6)	24.6 (4.2)
			N	65	70	65
		10 AM	Mean (SD)	17.7 (2.9)	22.3 (3.1)	20.2 (4.2)
			N	65	70	64
		3 PM	Mean (SD)	19.4 (3.0)	22.2 (3.3)	22.3 (4.3)
			N	65	69	64
		5 PM	Mean (SD)	17.2 (3.2)	21.2 (3.3)	18.9 (3.7)
			N	65	69	64
	Week 6	**8 AM**	Mean (SD)	21.9 (3.9)	24.2 (4.3)	24.9 (4.3)
			N	63	68	62
		10 AM	Mean (SD)	18.5 (3.8)	21.8 (3.4)	20.8 (3.7)
			N	63	67	61
		3 PM	Mean (SD)	20.1 (3.7)	21.6 (3.3)	22.6 (3.6)
			N	63	67	61
		5 PM	Mean (SD)	17.5 (3.7)	21.1 (3.6)	18.9 (2.7)
			N	63	67	61
	Month 3	**8 AM**	Mean (SD)	22.9 (4.6)	23.5 (4.1)	26.0 (3.8)
			N	62	66	60
		10 AM	Mean (SD)	18.6 (3.8)	22.4 (4.5)	21.1 (4.0)
			N	62	66	60
		3 PM	Mean (SD)	20.6 (3.9)	22.1 (3.4)	22.9 (3.4)
			N	62	65	60
		5 PM	Mean (SD)	18.4 (4.2)	21.8 (3.4)	19.4 (3.4)
			N	62	65	58

Table S-10
C-10-039
Mean IOP (mmHg) by Baseline IOP Stratum (ITT)

Stratum	Visit	Time		Brinz/Brim	Brinz	Brim
24-27	**Week 2**	**8 AM**	Mean (SD)	18.8 (3.1)	20.2 (3.5)	20.8 (3.0)
			N	139	145	143
		10 AM	Mean (SD)	16.1 (2.9)	19.2 (3.0)	17.6 (3.1)
			N	137	143	143
		3 PM	Mean (SD)	17.4 (3.3)	18.9 (3.3)	19.5 (3.1)
			N	135	143	143
		5 PM	Mean (SD)	15.3 (3.1)	18.5 (3.1)	17.1 (3.4)
			N	134	143	141
	Week 6	**8 AM**	Mean (SD)	19.0 (3.4)	19.9 (3.4)	21.1 (3.6)
			N	132	141	140
		10 AM	Mean (SD)	16.1 (3.0)	18.8 (3.4)	17.8 (3.3)
			N	130	140	139
		3 PM	Mean (SD)	18.0 (3.1)	18.6 (3.2)	19.4 (3.7)
			N	131	140	138
		5 PM	Mean (SD)	15.7 (3.1)	18.5 (3.5)	17.1 (3.0)
			N	131	140	137
	Month 3	**8 AM**	Mean (SD)	19.2 (3.2)	20.2 (3.8)	21.2 (3.3)
			N	126	140	134
		10 AM	Mean (SD)	16.6 (3.3)	19.2 (3.5)	18.3 (3.4)
			N	124	137	133
		3 PM	Mean (SD)	18.1 (3.3)	19.0 (3.7)	19.9 (4.1)
			N	124	137	132
		5 PM	Mean (SD)	15.8 (3.1)	18.8 (3.6)	17.4 (3.8)
			N	127	137	132
28-36	**Week 2**	**8 AM**	Mean (SD)	22.2 (3.9)	24.3 (4.5)	25.3 (3.9)
			N	79	84	87
		10 AM	Mean (SD)	18.4 (4.0)	22.1 (3.8)	20.8 (4.1)
			N	77	84	83
		3 PM	Mean (SD)	19.8 (4.3)	21.5 (3.2)	22.6 (4.5)
			N	77	84	83
		5 PM	Mean (SD)	17.3 (3.7)	21.8 (3.4)	19.1 (4.1)
			N	77	84	81
	Week 6	**8 AM**	Mean (SD)	22.3 (4.1)	24.0 (3.8)	22.3 (4.1)
			N	75	82	77
		10 AM	Mean (SD)	18.4 (4.0)	22.1 (3.7)	21.4 (4.4)
			N	75	80	76
		3 PM	Mean (SD)	20.4 (4.3)	22.1 (3.7)	22.6 (74)
			N	75	80	74
		5 PM	Mean (SD)	17.4 (4.3)	20.9 (3.8)	19.3 (4.6)
			N	73	80	74
	Month 3	**8 AM**	Mean (SD)	23.0 (3.9)	23.7 (3.9)	25.0 (4.4)
			N	70	76	69
		10 AM	Mean (SD)	19.1 (4.2)	22.0 (3.7)	20.4 (3.8)
			N	70	76	68
		3 PM	Mean (SD)	20.7 (4.0)	22.1 (3.8)	22.3 (4.0)
			N	70	75	68
		5 PM	Mean (SD)	18.2 (4.5)	21.5 (3.8)	19.2 (4.7)
			N	70	75	67

Table S-11
Studies C-10-033 and C-10-039 Pooled
Mean IOP (mmHg) at Week 2, Week 6, and Month 3 (ITT)

			Brinz/Brim (n=427)	**Brinz** (n=452)	**Brim** (n=446)
Week 2	**8 AM**	Mean* (SE)	20.5 (0.20)	22.1 (0.19)	22.6 (0.20)
		Mean difference**		-1.6	-2.1
		95% CI		(-2.1, -1.2)	(-2.6, -1.7)
		p-value		<0.0001	<0.0001
	10 AM	mean (SE)	17.3 (0.20)	20.6 (0.19)	19.3 (0.20)
		Mean difference		-3.3	-2.0
		95% CI		(-3.8, -2.9)	(-2.4, -1.5)
		p-value		<0.0001	<0.0001
	3 PM	mean (SE)	18.6 (0.20)	20.4 (0.19)	20.8 (0.20)
		Mean difference		-1.8	-2.2
		95% CI		(-2.3, -1.4)	(-2.6, -1.7)
		p-value		<0.0001	<0.0001
	5 PM	mean (SE)	16.6 (0.20)	19.9 (0.19)	18.3 (0.20)
		Mean difference		-3.4	-1.7
		95% CI		(-3.8, -2.9)	(-2.2, -1.3)
		p-value		<0.0001	<0.0001
Week 6	**8 AM**	mean (SE)	20.6 (0.20)	21.9 (0.19)	22.9 (0.20)
		Mean difference		-1.3	-2.3
		95% CI		(-1.8, -0.9)	(-2.7, -1.8)
		p-value		<0.0001	<0.0001
	10 AM	mean (SE)	17.5 (0.20)	20.4 (0.19)	19.5 (0.20)
		Mean difference		-2.9	-2.1
		95% CI		(-3.3, -2.5)	(-2.5, -1.6)
		p-value		<0.0001	<0.0001
	3 PM	mean (SE)	19.2 (0.20)	20.2 (0.19)	21.1 (0.20)
		Mean difference		-1.0	-1.9
		95% CI		(-1.4, -0.6)	(-2.4, -1.5)
		p-value		<0.0001	<0.0001
	5 PM	mean (SE)	17.0 (0.20)	19.8 (0.19)	18.5 (0.20)
		Mean difference		-2.8	-1.5
		95% CI		(-3.2, /2.3)	(-2.0, -1.1)
		p-value		<0.0001	<0.0001
Month 3	**8 AM**	mean (SE)	20.8 (0.20)	21.8 (0.20)	23.2 (0.20)
		Mean difference		-1.0	-2.4
		95% CI		(-1.5, -0.6)	(-2.8, -1.9)
		p-value		<0.0001	<0.0001
	10 AM	mean (SE)	17.6 (0.20)	20.6 (0.20)	19.7 (0.20)
		Mean difference		-3.0	-2.1
		95% CI		(-3.4, -2.5)	(-2.5, -1.6)
		p-value		<0.0001	<0.0001
	3 PM	mean (SE)	19.1 (0.20)	20.6 (0.20)	21.4 (0.20)
		Mean difference		-1.4	-2.2
		95% CI		(-1.9, -1.0)	(-2.7, -1.7)
		p-value		<0.0001	<0.0001
	5 PM	mean (SE)	17.1 (0.20)	20.2 (0.20)	18.8 (0.20)
		Mean difference		-3.1	-1.7
		95% CI		(-3.6, -2.6)	(-2.1, -1.2)
		p-value		<0.0001	<0.0001

*Estimates are based on least square means derived from a linear mixed model that accounts for correlated IOP measurements within patient.
**Difference is brinzolamide/brimonidine – individual component

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/s/

CHERYL A DIXON
03/15/2013

YAN WANG
03/15/2013
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204251 **Applicant:** Alcon **Stamp Date:** 6/19/12

Drug Name: Brinzolamide 1%/ Brimonidine Tartrate 0.2% **NDA/BLA Type:** Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			• Analysis datasets appear to contain variables necessary to reproduce Sponsor's analyses with minimal additional programming necessary. • Problems converting xpt files to sas datasets due to file names including hyphens i.e. -iop-01.xpt. Renaming the files with underbars rather than hyphens allows for the conversion.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __ Yes**_____**
If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant. N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are issues with converting xpt files with file names that include hyphens i.e. -iop-01.xpt to sas datasets. The hyphens are not recognized in a manually programmed Proc Copy statement. Please provide the code necessary to convert xpt files with file names that include hyphens to sas datasets or any appropriate alternative that will address this issue. (***Reviewer's Comment:*** *Comment to be sent to Applicant prior to 74-day letter*.)

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	Study C-0-039 is ongoing through 6 month for safety. The primary endpoint for efficacy was 3 months.
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

The submission contains two pivotal phase 3 trials- C-10-033 and C-10-039. Both trials were multicenter, randomized, double-masked, parallel, active-controlled studies in male and females patients aged 18 years of age or older with open-angle glaucoma or ocular hypertension. Subjects in C-10-033 were dosed for 3 months. Subjects in C-10-039 were dosed for 3 months for assessing efficacy with an additional 3 months of dosing for assessing safety only. The submission contains all data through 3 months. The Month 6 safety analysis of Study C-10-039 is intended to be provided during the review cycle when all patients have completed the study and the data are available. The trials were designed to demonstrate the superior efficacy of the fixed combination, brinzolamide/brimonidine, compared to each of the individual components alone. The primary efficacy endpoint was intraocular pressure (IOP) measured at Month 3 at 8 AM, 10 AM, 3PM, and 5PM. Supportive efficacy endpoints were IOP measured at Week 2 and Week 6 at each of assessment time points as for Month 3. Based on the Applicant's summary of the results, mean IOP was significantly lower in the brinzolamide/brimonidine group compared to each of the individual components at all visits (Week 2, Week 6, and Month 3) at all assessment time points (8 AM, 10 AM, 3PM, and 5PM). Treatment differences were at least 1 mmHg lower for the combination than that observed for either of the components at the same visit and timepoint. Additionally, at every assessment timepoint at all visits, the combination reduced then mean IOP by 2 mmHg or more compared with at least one of the components.

Cheryl Dixon, Ph.D.	8/7/12
Reviewing Statistician	Date
Yan Wang, Ph.D.	8/7/12
Supervisor/Team Leader	Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

CHERYL A DIXON
08/07/2012

YAN WANG
08/07/2012