CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204251Orig1s000

MEDICAL REVIEW(S)

Deputy Division Director Review of NDA 204251

Date	April 19, 2013
From	Wiley A. Chambers, M.D.
NDA	204251
Applicant	Alcon Research, Ltd.
Date of Submission	June 19, 2012
Name	Simbrinza (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2%
Dosage forms / Strength	Topical ophthalmic suspension, 1%/0.2%
Proposed Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Recommended for Approval

1. Introduction/Background

The active components in this combination of brinzolamide/brimonidine ophthalmic suspension 1%/0.2% were previously approved as monotherapeutic agents for the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension. This 505(b)(2) application lists the following drug products as the basis for the submission: NDA 20-816 [Azopt (brinzolamide ophthalmic suspension) 1%], NDA 20-613[Alphagan (brimonidine tartrate ophthalmic solution) 0.2%], and ANDA 76260 [Brimonidine Tartrate Ophthalmic Solution, 0.2%]. Clinical studies for this new drug application were conducted under IND 106293.

Brimonidine tartrate at a concentration of 0.2% was approved by the United States FDA on September 6, 1996, for the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Brinzolamide was approved in the United States on April 1, 1998, for the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The application has been submitted as a 505(b)(2) application because the applicant (Alcon) does not have a right to reference some of the non-clinical studies used to support the Pregnancy, Nursing Mothers, and Carcinogenesis, Mutagenesis, Impairment of Fertility sections of the labeling. Alcon also does not have a right to reference some of the studies which support the labeling references to brimonidine ophthalmic solution. The drug product which is the subject of this application (Simbrinza (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2%) is linked to the non-clinical studies by chemical analyses which confirm that brimonidine tartrate is a component of both Simbrinza and the oral drug product that was used in the non-clinical studies. The drug product used for the non-clinical studies is not Simbrinza, but is instead an oral product given to exaggerate the potential exposure of brimonidine. The use of this different oral product is necessary to exaggerate the potential exposure. The oral product used to exaggerate the potential exposure is the same as was used to exaggerate the exposure of the reference drug product in NDA 20-613. References to brimonidine ophthalmic solution in the labeling do not refer to Simbrinza, but instead refer to the reference drug product in NDA 20-613. They are included in the labeling of Simbrinza because the regulations require the inclusion of relevant Warnings/Precautions/Adverse Events associated with products in the same class as the drug product which is the subject of this application. Adequate and well controlled trials supporting the proposed drug product in this application were conducted by the applicant.

2. Product Quality

Each mL of Simbrinza (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2% contains:
Active ingredients: brinzolamide 1%, brimonidine tartrate: 0.2%.
Preservative used in the combination: benzalkonium chloride (0.003 %).
Inactive ingredients include: propylene glycol, carbomer 974P, boric acid, mannitol, sodium chloride, tyloxapol and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

Brimonidine tartrate is manufactured by two drug substance manufacturers: (b) (4) and (b) (4) Both are the approved manufacturers for Alcon's Brimonidine Tartrate Ophthalmic Solution (ANDA 76254). Brinzolamide is also manufactured two drug substance manufacturers: (b) (4) and (b) (4) the same manufacturers of brinzolamide for Alcon's approved Azopt (brinzolamide ophthalmic suspension) 1% in NDA 20-816.

The drug product will be packaged in an opaque, white, low density polyethylene (LDPE) bottle with a natural LDPE dispensing plug and white polypropylene (PP) closure filled with either 8 mL in a 10 mL bottle (for trade) (b) (4) of the suspension.

Quantitative Composition:

Component	% w/v	Function	Compendial Status
Brinzolamide	1.0 [b,c]	Active ingredient	USP [d]
Brimonidine Tartrate	0.2 [b]	Active ingredient	NOC [e]
Carbomer 974P [f]	(b) (4)		NF
Sodium Chloride			USP
Mannitol			USP
Propylene Glycol			USP
Tyloxapol			USP
Boric Acid			NF
Benzalkonium Chloride	0.003 [g]	Preservative	NF
Sodium Hydroxide and/or Hydrochloric Acid	Adjust pH to approximately 6.5	pH Adjustment	NF
Purified Water	(b) (4)		USP

[b] Amount added based on purity of the raw material.
(b) (4)
[d] Although brinzolamide is a compendial (USP) material, the drug substance will be tested according to the currently approved AZOPT (NDA 20-816) specifications.
[e] NOC = Non-official Compendia.
(b) (4)

REGULATORY SPECIFICATIONS:

Brinzolamide Identity (TLC)	(b) (4)
Brinzolamide Identity (HPLC)	
Brinzolamide Assay	
Brimonidine Tartrate Identity (TLC)	
Brimonidine Tartrate Identity (HPLC)	
Brimonidine Tartrate Assay	
(b) (4)	
(b) (4)	
(b) (4)	
Any Single Unspecified Impurity	
Total Impurities	
Benzalkonium Chloride Identity	
Benzalkonium Chloride Assay	
Boric Acid Identity	
Boric Acid Assay	
pH	
Osmolality	
Viscosity (b) (4)	
Color	White to off-white
Uniformity	Uniform suspension
Redispersibility	(b) (4)
Particle Size (b) (4)	
Bacterial Endotoxins Test	
Sterility	

INSPECTIONS:
An "Acceptable" site recommendation from the Office of Compliance was entered into EES on April 17, 2013.

3. Nonclinical Pharmacology/Toxicology

Pharmacology Toxicology did not identify substantial new safety issues. While a waiver for conducting carcinogenicity studies was granted, a brinzolamide carcinogenicity study was completed, but has not yet been submitted. This study will be reviewed when submitted.

4. Clinical Pharmacology/Biopharmaceutics

Clinical Study C-10-010 was conducted to describe the steady-state PK of brimonidine and brinzolamide in plasma, and the red blood cell (RBC) saturation of brinzolamide and N-desethyl brinzolamide following topical ocular administration of the fixed dose combination Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension compared to its individual active components alone (Brinzolamide 1% Ophthalmic Suspension and Brimonidine Tartrate 0.2% Ophthalmic solution, respectively) in 142 healthy adult subjects.

The overall conclusion from these results showed that the RBC saturation of brinzolamide and N-desethyl brinzolamide, plasma concentration of brinzolamide, and steady-state plasma PK of brimonidine following topical ocular administration of the fixed dose combination of Brinzolamide/Brimonidine dosed TID or BID, were comparable to those observed after administration of the individual active components alone (Brinzolamide and Brimonidine, respectively).

5. Sterility Assurance

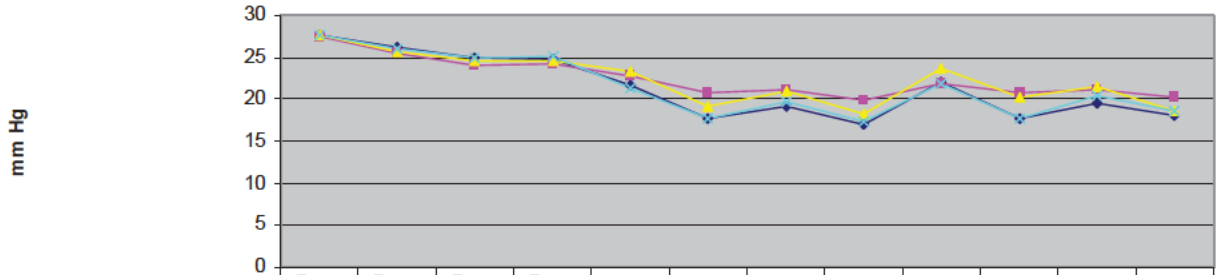
Brinzolamide/Brimonidine Suspension will be packaged in Alcon's standard white low density polyethylene (LDPE) DROP-TAINER bottles with fill volumes of [redacted] (b) (4) nd 8 mL (in the 10 mL bottle) with natural LDPE dispensing plug and a white polypropylene (PP) closure. No product quality microbiology deficiencies were identified based upon the information provided.

6. Clinical/Statistical - Efficacy

The primary sources for efficacy data for this application came from three trials: C-09-038 (Phase 2), C-10-033 (Phase 3), and C-10-039 (Phase 3). For each study, the mean IOP was assessed in the morning time 0 and at + 2 hrs, + 7 hrs, and + 9 hrs) on each of the following days, Baseline, Week 2, Week 6 and Month 3. IOP measurements were done at 8AM, 10AM, 3PM, and 5PM. Study C-10-039 had an additional 3 months of follow-up (total trial length was 6 months).

Analysis of Efficacy Endpoint(s)

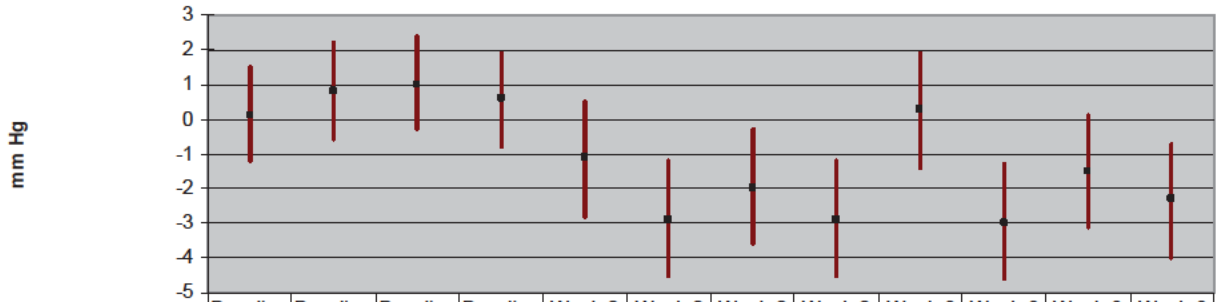
Study C-09-038 ITT Population, LOCF



	Base line 8AM	Base line 10AM	Base line 3PM	Base line 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Brinz 1%/Brim 0.2%	27.6	26.2	25	24.8	21.7	17.8	19.1	17	22.1	17.7	19.6	18
Brinz 1%	27.5	25.4	24	24.2	22.8	20.7	21.1	19.9	21.8	20.7	21.1	20.3
Brim 0.2%	27.7	25.6	24.5	24.6	23.4	19.2	20.9	18.2	23.6	20.3	21.5	18.6
Brinz 1%+Brim 0.2%	27.7	26.1	25	25.2	21.3	17.8	19.7	17.3	21.8	17.7	20.4	18.7

Baseline mean IOP of the four treatment groups is similar. The mean IOP of the fixed combination is similar to the brimonidine 0.2% and brinzolamide 1% given concomitantly. The mean IOP of the fixed combination is numerically lower than brimonidine 0.2% given alone and is lower than brinzolamide 1% given alone.

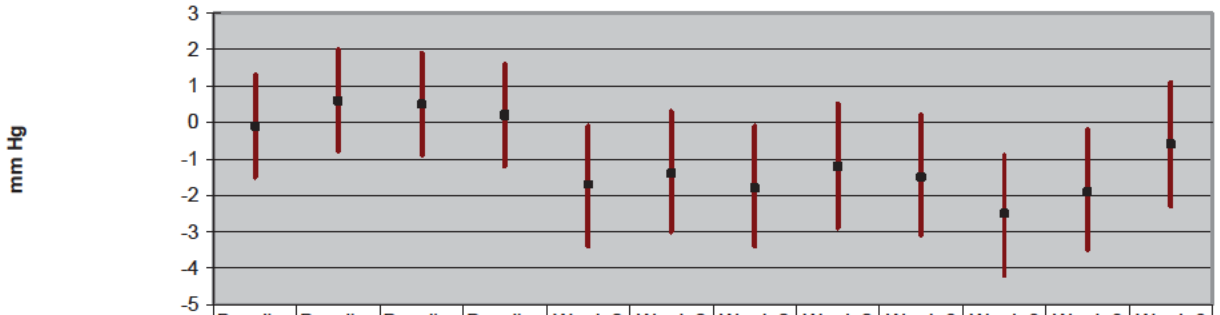
Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1%) with 95% Confidence Intervals



	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Lower CI	-1.2	-0.6	-0.3	-0.8	-2.8	-4.5	-3.6	-4.5	-1.4	-4.6	-3.1	-4
Upper CI	1.5	2.2	2.4	1.9	0.5	-1.2	-0.3	-1.2	1.9	-1.3	0.1	-0.7
■ Mean Difference	0.1	0.8	1	0.6	-1.1	-2.9	-2	-2.9	0.3	-3	-1.5	-2.3

The mean IOP at baseline for the two treatment groups is comparable. The mean difference between the fixed combination and brinzolamide 1% is not statistically significant at all time points. The 95% confidence intervals cross zero at Week 2 (8AM) and Week 6 (8AM, 3PM). The mean difference ranges from 0.3 to -3.0 mm Hg.

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals

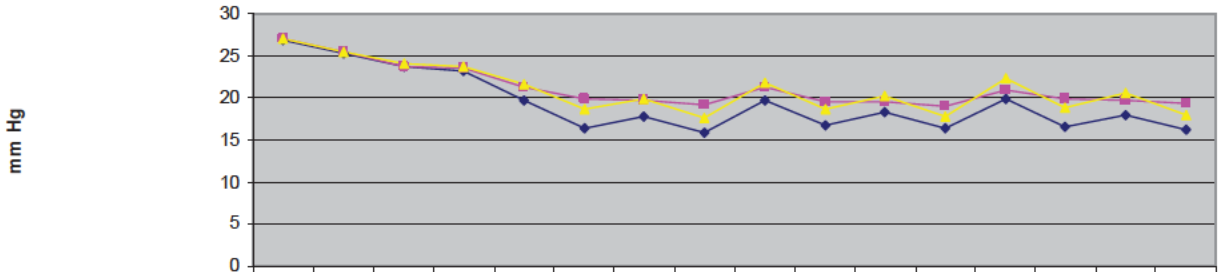


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Lower CI	-1.5	-0.8	-0.9	-1.2	-3.4	-3	-3.4	-2.9	-3.1	-4.2	-3.5	-2.3
Upper CI	1.3	2	1.9	1.6	-0.1	0.3	-0.1	0.5	0.2	-0.9	-0.2	1.1
■ Mean Difference	-0.1	0.6	0.5	0.2	-1.7	-1.4	-1.8	-1.2	-1.5	-2.5	-1.9	-0.6

The mean IOP at baseline for the two treatment groups is comparable. The mean difference between the fixed combination and brimonidine 0.2% is not statistically significant at all time points. The 95% confidence intervals cross zero at Week 2 (10AM, 5PM) and Week 6 (8AM, 5PM). The mean difference ranges from -0.6 to -2.5 mm Hg.

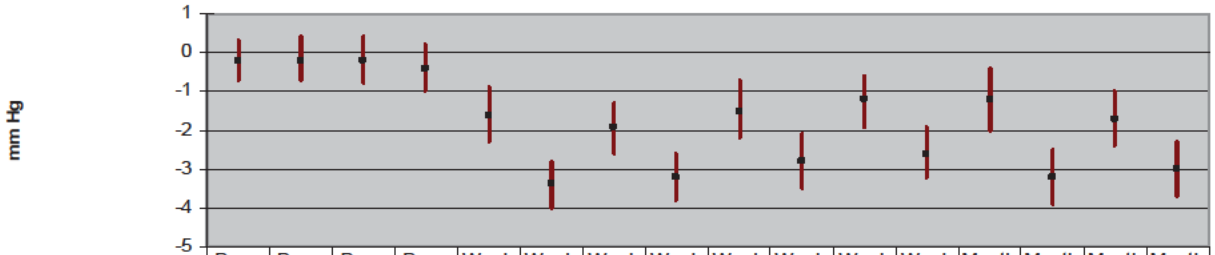
Study C-10-033 ITT Population, LOCF

Mean IOP per Visit and Time



	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Brinz 1%/Brim 0.2%	26.9	25.3	23.7	23.2	19.7	16.4	17.8	15.9	19.7	16.8	18.3	16.4	19.8	16.6	18	16.3
Brinz 1%	27.1	25.4	23.8	23.6	21.3	19.9	19.7	19.1	21.2	19.6	19.5	19	21	19.8	19.7	19.3
Brim 0.2%	27	25.4	24	23.7	21.6	18.6	19.8	17.6	21.8	18.6	20.3	17.8	22.4	18.8	20.5	18

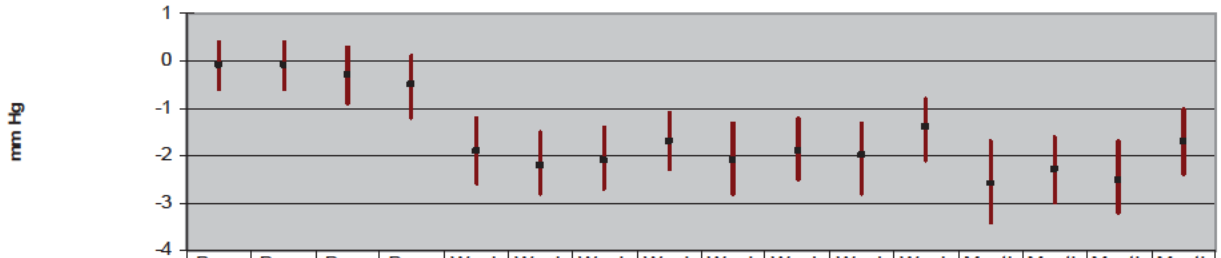
Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1%) with 95% Confidence Intervals



	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.7	-0.7	-0.8	-1	-2.3	-4	-2.6	-3.8	-2.2	-3.5	-1.9	-3.2	-2	-3.9	-2.4	-3.7
Upper CI	0.3	0.4	0.4	0.2	-0.9	-2.8	-1.3	-2.6	-0.7	-2.1	-0.6	-1.9	-0.4	-2.5	-1	-2.3
Mean Difference	-0.2	-0.2	-0.2	-0.4	-1.6	-3.4	-1.9	-3.2	-1.5	-2.8	-1.2	-2.6	-1.2	-3.2	-1.7	-3

The mean differences are statistically significant at all time points ranging from -1.2 to -3.4 mmHg.

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals

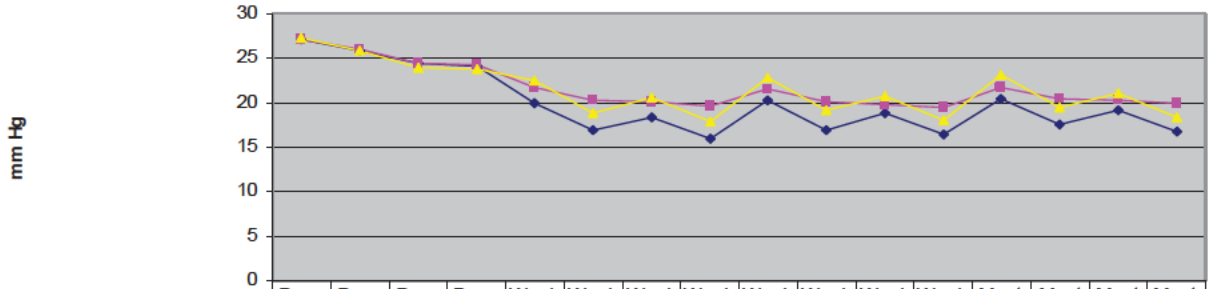


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.6	-0.6	-0.9	-1.2	-2.6	-2.8	-2.7	-2.3	-2.8	-2.5	-2.8	-2.1	-3.4	-3	-3.2	-2.4
Upper CI	0.4	0.4	0.3	0.1	-1.2	-1.5	-1.4	-1.1	-1.3	-1.2	-1.3	-0.8	-1.7	-1.6	-1.7	-1
Mean Difference	-0.1	-0.1	-0.3	-0.5	-1.9	-2.2	-2.1	-1.7	-2.1	-1.9	-2	-1.4	-2.6	-2.3	-2.5	-1.7

The mean differences are statistically significant at all time points ranging from -1.4 to -2.6 mmHg.

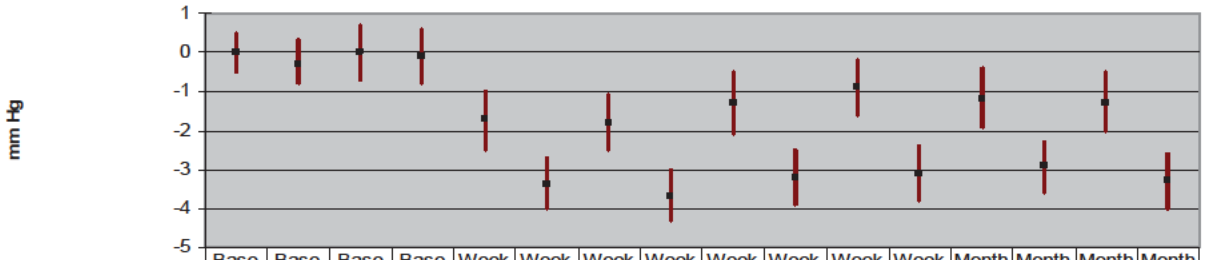
Study C-10-039 ITT Population, LOCF

Mean IOP per Visit and Time



	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Brinz 1%/Brim 0.2%	27.2	25.8	24.4	24.1	20	16.9	18.3	16	20.2	16.9	18.8	16.4	20.5	17.5	19.1	16.7
Brinz 1%	27.2	26	24.4	24.2	21.7	20.3	20.1	19.7	21.5	20.1	19.8	19.5	21.7	20.4	20.3	20
Brim 0.2%	27.3	25.8	24	23.7	22.5	18.8	20.6	17.8	22.8	19.2	20.7	18	23.1	19.5	21.1	18.4

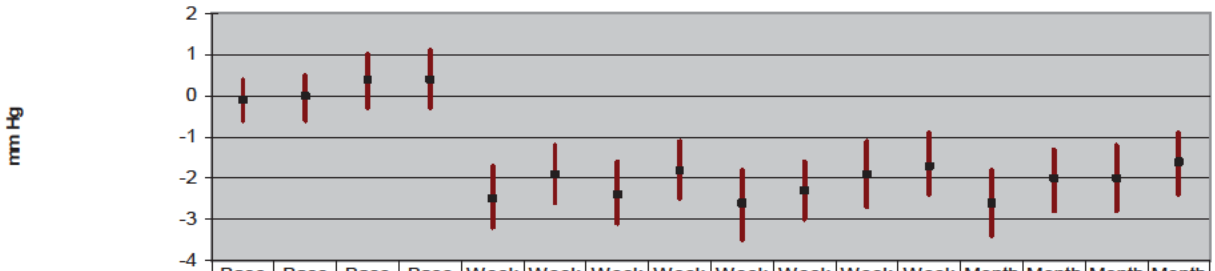
Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1%) with 95% Confidence Intervals



	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.5	-0.8	-0.7	-0.8	-2.5	-4	-2.5	-4.3	-2.1	-3.9	-1.6	-3.8	-1.9	-3.6	-2	-4
Upper CI	0.5	0.3	0.7	0.6	-1	-2.7	-1.1	-3	-0.5	-2.5	-0.2	-2.4	-0.4	-2.3	-0.5	-2.6
Mean Difference	0	-0.3	0	-0.1	-1.7	-3.4	-1.8	-3.7	-1.3	-3.2	-0.9	-3.1	-1.2	-2.9	-1.3	-3.3

The mean differences are statistically significant at all time points ranging from -0.9 to -3.7 mmHg.

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals



	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.6	-0.6	-0.3	-0.3	-3.2	-2.6	-3.1	-2.5	-3.5	-3	-2.7	-2.4	-3.4	-2.8	-2.8	-2.4
Upper CI	0.4	0.5	1	1.1	-1.7	-1.2	-1.6	-1.1	-1.8	-1.6	-1.1	-0.9	-1.8	-1.3	-1.2	-0.9
Mean Difference	-0.1	0	0.4	0.4	-2.5	-1.9	-2.4	-1.8	-2.6	-2.3	-1.9	-1.7	-2.6	-2	-2	-1.6

The mean differences are statistically significant at all time points ranging from -1.6 to -2.6 mmHg.

Summary Efficacy Statement

Considering the observed and projected adverse events associated with the use of the combination product, there are adequate and well controlled studies support the efficacy of Simbrinza (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2% for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Studies C-10-033 and C-10-039 demonstrate superiority of the combination product, brinzolamide/brimonidine over each of the individual components by a statistically significant amount. The contribution of brinzolamide to the combination product ranges from 1.4 to 2.6 mmHg in study C-10-033 and from 1.6 to 2.6 mmHg in study C-10-039. The contribution of brimonidine to the combination product ranges from 1.2 to 3.4 mmHg in study C-10-033 and from 0.9 to 3.7 mmHg in study C-10-039. Unlike many of the other combination products, the fixed combination was not inferior to the concomitant use of the individual components when taken as labeled.

7. Safety

The safety of this combination drug product is based primarily on the safety history of the individual ingredients and the safety data from studies C-10-33 and C-10-039, C-10-010, C-11-002, and C-09-038 comprising 555 subjects were exposed to the fixed combination, brinzolamide/brimonidine.

Common Adverse Events Number (%) of Patients with Adverse Events Reported by ≥1 % of Patients Studies C-10-033, C-10-039, C-09-038

Adverse Event	Brinz/Brim C-10-033 N=214 N (%)	Brinz/Brim C-10-039 N=221 N (%)	Brinz/Brim C-09-038 N=44 N (%)	Brinz N=504 033 & 039 Combined N (%)	Brim N=496 033 & 039 Combined N (%)
OCULAR					
Eye Disorders					
Vision blurred	13 (6%)	10 (5%)	7 (17%)	37 (7%)	7 (1%)
Eye irritation	6 (3%)	14 (6%)	2 (5%)	7 (1%)	14 (3%)
Eye allergy	1 (0.5%)	14 (6%)		1 (0.2%)	8 (2%)
Conjunctivitis allergic	4 (2%)	8 (4%)		2 (0.4%)	11 (2%)
Conjunctivitis		11 (5%)	1 (2%)		15 (3%)
Ocular Hyperaemia	3 (1%)	6 (3%)	3 (7%)	7 (1%)	6 (1%)
Eye pain	3(1%)	6 (3%)		8 (2%)	5 (1%)
Eye pruritus	2 (1%)	7 (3%)	2 (5%)	5 (1%)	6 (1%)
Conjunctival hyperaemia	3 (1%)	5 (2%)		5 (1%)	6 (1%)
Dry eye	2 (1%)	4 (2%)		4 (1%)	8 (2%)
NON-OCULAR					
Gastrointestinal Disorders					
Dry mouth	7 (3%)	7 (3%)			11 (2%)
Nervous System Disorders					
Dysgeusia	8 (4%)	9 (4%)		38 (8%)	1 (0.2%)

The most common ocular adverse events (Phase 3 studies C-10-033 and C-10-039 pooled) were vision blurred (5%), eye irritation (5%), and eye allergy (3%). The most common nonocular adverse events were dysgeusia (4%) and dry mouth (3%).

Safety Summary Statement

The adequate and well controlled studies as well as the prior marketing of the individual component products supports the safety of Simbrinza (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2% for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

8. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

9. Pediatrics

As described in the labeling for brimonidine, brimonidine is contraindicated in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse reactions with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

Brinzolamide when used alone did not have sufficient efficacy to warrant its use in the pediatric population. In combination, it may have an acceptable profile in patients 2 years of age and older. This application was presented at PeRC on March 20, 2013. PeRC agreed with a partial waiver for pediatric patients 0 year - 2 years because of the toxicity seen in this age group with brimonidine monotherapy. PeRC agreed that Simbrinza was appropriately labeled for pediatric patients age 2 years and above based on the referenced brimonidine and brinzolamide monotherapy package inserts. PeRC agreed that extrapolation from other adult and/or Pediatric studies was appropriate for pediatric patients 7 years to 16 years.

10. Other Relevant Regulatory Issues

FINANCIAL DISCLOSURE

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

OSI

A routine Office of Scientific Investigations (OSI) audit was requested. One site from each study was chosen for inspection based on enrollment, number of INDs in the OSI database, and previous inspectional history.

Name of CI	Protocol # /Site #/ # of Subjects Enrolled:	Inspection Date	Classification
George C. Thorne, M.D. Eye Physicians of Austin 5011 Burnet Road Austin, TX 78756	Study C-10-039/2353/ n=27	December 4 to 7 , 2012	NAI
Eugene B. McLaurin, M.D. Total Eye Care, PA 6060 Primacy Parkway Suite 200 Memphis, TN 38119	Study C-10-033/4011/ n=52	November 26 to 29, 2012,	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

The data derived from both inspected sites are considered reliable. The classification of the Clinical Investigator inspection of Dr. Thorne and Dr McLaurin is No Official Action Indicated (NAI).

11. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 204251, Simbrinza (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2%, is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The submitted package insert contains tables and figures in Section 14 Clinical Studies which, in my opinion, detract from the relevant information for the prescribing physician. The clinically relevant information from Study C-10-039 and Study C-10-033 for the prescribing physician is that the IOP-lowering effect of Simbrinza was greater (1-3 mmHg) than monotherapy with either 1% brinzolamide or 0.2% brimonidine tartrate throughout the duration of the trial (i.e. Week 2, Week 6, Month 3). This information is de-emphasized in the tables and figures Alcon has proposed.

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology Products

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/s/

WILEY A CHAMBERS
04/19/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204251
Priority or Standard	Standard
Submit Date(s)	June 19, 2012
Received Date(s)	June 19, 2012
PDUFA Goal Date	April 19, 2013
Division / Office	DAIOP/OAP
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	February 26, 2013
Established Name	brinzolamide/brimonidine ophthalmic suspension 1%/0.2%
(Proposed) Trade Name	Simbrinza
Therapeutic Class	carbonic anhydrase inhibitor/alpha-agonist
Applicant	Alcon Research, Ltd.
Formulation(s)	Ophthalmic suspension
Dosing Regimen	One (1) drop in the affected eye(s) three times daily
Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Intended Population(s)	Patients ages 18 years and older with open-angle glaucoma or ocular hypertension

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 204251 is recommended for approval with the labeling revisions found in this review.

The application supports the safety and effectiveness of the fixed combination brinzolamide/ brimonidine tartrate ophthalmic suspension 1%/0.2% for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

1.2 Risk Benefit Assessment

The data contained in this submission establishes the efficacy of the fixed combination brinzolamide/brimonidine tartrate ophthalmic suspension 1%/0.2% (brinzolamide/brimonidine) dosed three times daily for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

Studies C-10-033 and C-10-039 demonstrate superiority of the combination product, brinzolamide/brimonidine over each of the individual components by a statistically and clinically significant amount. The contribution of brinzolamide to the combination product ranges from1.4 to 2.6 mmHg in study C-10-033 and from 1.6 to 2.6 mmHg in study C-10-039. The contribution of brimonidine to the combination product ranges from 1.2 to 3.4 mmHg in study C-10-033 and from 0.9 to 3.7 mmHg in study C-10-039. The contribution of brinzolamide and brimonidine in the combination product has been demonstrated.

The safety profile of brinzolamide/brimonidine is similar to the marketed individual components, brinzolamide and brimonidine. The most common ocular adverse events were blurred vision (5%) and eye irritation (5%). The most common non-ocular adverse events were dysgeusia (4%) and dry mouth (3%).

The benefit of brinzolamide/brimonidine for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension has been demonstrated in this NDA application. The risk for using this drug is consistent with the currently marketed individual components, brinzolamide and brimonidine.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk evaluations and mitigation strategies beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarket Requirements or Phase 4 Commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name:	brinzolamide/brimonidine ophthalmic suspension 1%/0.2%
Proposed Trade Name:	Simbrinza
Chemical Class:	new formulation
Pharmacological Class:	carbonic anhydrase inhibitor/alpha 2-adrenergic agonist
Proposed Indication:	reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
Dosing Regimen:	one drop in the affected eye(s) three times daily
Age Groups:	patients 18 years or older

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently numerous topical treatments for lowering intraocular pressure in patients with open angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Drug Products with Approved NDAs

Pharmacologic Class/ Applicant	Tradename	Established Name
Alpha-2 agonists		
Alcon	Iopidine	apraclonidine
Allergan, Inc.	Alphagan/ Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/ Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharamaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase		

Pharmacologic Class/ Applicant	Tradename	Established Name
Inhibitors		
Alcon	Azopt	brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan	travoprost
Merck	Zioptan	tafluprost
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/ pilocarpine hydrochloride
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

2.3 Availability of Proposed Active Ingredient in the United States

Brimonidine tartrate at a concentration of 0.2% was approved by the United States FDA on September 6, 1996, and brinzolamide was approved in the United States on April 1, 1998, for the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2.4 Important Safety Issues with Consideration to Related Drugs

As with other drugs in this class (alpha -2 adrenergic agonists), brimonidine tartrate may cause fatigue and/or drowsiness in some patients. In particular, brimonidine tartrate is significantly associated with somnolence and decreased alertness when used in the pediatric population (ages 2 to 7 years). In pediatric patients 7 years or older, somnolence occurs less frequently.

There are no specific issues associated with topical carbonic anhydrase inhibitors that need to be addressed.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An End-of-Phase 2 meeting was held on November 15, 2010, to obtain guidance from all disciplines on the development plan for brinzolamide/brimonidine tartrate ophthalmic suspension.

2.6 Other Relevant Background Information

Brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension has not been marketed in any country. However, the active ingredient brinzolamide is marketed by Alcon as Azopt. The other active ingredient, brimonidine tartrate, is marketed by Allergan as Alphagan and Alphagan P.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

3.2 Compliance with Good Clinical Practices

The clinical studies included in this application conformed with Good Clinical Practices.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Brinzolamide/brimonidine tartrate 1%/ 0.2% ophthalmic suspension is a sterile, preserved, multi-dose ophthalmic suspension formulation containing 1% brinzolamide and 0.2% brimonidine tartrate.

Composition of Brinzolamide/Brimonidine Suspension

Component	% w/v	Function	Compendial Status
Brinzolamide	1.0 [b,c]	Active ingredient	USP [d]
Brimonidine Tartrate	0.2 [b]	Active ingredient	NOC [e]

Carbomer 974P [f]	(b) (4)		NF
Sodium Chloride			USP
Mannitol			USP
Propylene Glycol			USP
Tyloxapol			USP
Boric Acid			NF
Benzalkonium Chloride	0.003 [g]	Preservative	NF
Sodium Hydroxide and/or Hydrochloric Acid	Adjust pH to approximately 6.5	pH Adjustment	NF
Purified Water	(b) (4)		USP

[a] FID = Formulation Identification Number
[b] Amount added based on purity of the raw material.
(b) (4)
[d] Although brinzolamide is a compendial (USP) material, the drug substance will be tested according to the currently approved AZOPT (NDA 20-816) specifications.
[e] NOC = Non-official Compendia.
(b) (4)
(b) (4)

4.2 Clinical Microbiology

There are no clinical microbiology issues. The drug product is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology, pharmacokinetic and toxicology profiles of the individual components have been well characterized in preclinical studies previously submitted to the FDA as part of the NDAs for Azopt, Alphagan, Alphagan P, and brimonidine tartrate ophthalmic solution 0.15%.

Reference is made to the Non-Clinical Pharmacology and Toxicology Documentation of the following NDAs previously approved by the FDA:

- NDA 20-816, Azopt (brinzolamide ophthalmic suspension) 1%, Approval date: April 1, 1998.
- NDA 20-613, Alphagan (brimonidine tartrate ophthalmic solution) 0.2%, Approval date: September 6, 1996.

- NDA 21-262, Alphagan P (brimonidine tartrate ophthalmic solution) 0.15% Approval date: March 16, 2001.

See original Pharm/Tox review for additional findings.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Although both brinzolamide and brimonidine lower IOP by suppressing aqueous humor formation, their mechanisms of action are different. Brinzolamide, a topical CAI, acts by inhibiting the enzyme carbonic anhydrase (CA-II) in the ciliary epithelium that reduces the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport across the ciliary epithelium, resulting in decreased aqueous humor formation. Brimonidine, an alpha-2 adrenergic agonist, inhibits the enzyme adenyl cyclase and suppresses the cAMPdependent formation of aqueous humor. Additionally, administration of brimonidine results in an increase in uveoscleral outflow

4.4.2 Pharmacodynamics

See Biopharmaceutics review.

4.4.3 Pharmacokinetics

See l Biopharmaceutics review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
C-09-038 Phase 2	Parallel-group, multi-center, randomized, observer-masked, active-controlled, proof of concept study	Patients 18 years or more with open-angle glaucoma or ocular hypertension	Brinzolamide/ brimonidine Brinzolamide plus brimonidine Brinzolamide Brimonidine	1 drop TID OU	6 weeks	170 subjects in a ratio of 1:1:1:1 (41:44:44:41)

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
C-11-002 Phase 2	Parallel-group, multi-center, randomized, double-masked, active-controlled ocular comfort descriptive study	Patients 18 years or more with open-angle glaucoma or ocular hypertension	Brinzolamide/ brimonidine Brinzolamide Brimonidine	1 drop TID OU	1 week	101 subjects in a ratio of 1:1:1 (33:34:34)
C-10-033 Phase 3	Parallel-group, multi-center, randomized, double-masked, active-controlled, safety and efficacy study	Patients 18 years or more with open-angle glaucoma or ocular hypertension	Brinzolamide/ brimonidine Brinzolamide Brimonidine	1 drop TID OU	3 months	660 subjects in a ratio of 1:1:1 (216:225:219)
C-10-039 Phase 3	Parallel-group, multi-center, randomized, double-masked active-controlled, safety and efficacy study	Patients 18 years or more with open-angle glaucoma or ocular hypertension	Brinzolamide/ brimonidine Brinzolamide Brimonidine	1 drop TID OU	3 months plus 3 additional months for safety	690 subjects in a ratio of 1:1:1 (221:233:236)

5.2 Review Strategy

The submitted clinical study report and protocol for the studies identified in section 5.1 above were reviewed and formed the primary basis of safety and efficacy for this application. The entire application was submitted in electronic format.

5.3 Discussion of Individual Studies/Clinical Trials

Study C-09-038 - Proof of Concept Study

Title: Safety and IOP-Lowering Efficacy of Brinzolamide/Brimonidine Fixed Combination Ophthalmic Suspension in Patients with Open-Angle Glaucoma and/or Ocular Hypertension

Study Design

This study was a multi-center (9 sites), randomized, observer-masked, parallel group, active-controlled, proof of concept study designed to evaluate the safety and efficacy of brinzolamide/ brimonidine in lowering IOP relative to each of its individual active constituents instilled either individually or concomitantly in patients with open-angle glaucoma and/or ocular hypertension. A total of 170 patients were enrolled. Patients received masked study medication dosed 3 times daily for 28 days. In addition to the baseline visits E1 and E2, there were study visits at Week 2

and Week 6. IOP measurements were taken at 8 AM, +2 hrs, +7 hrs, and +9 hrs at Eligibility 1 Visit (E1), Eligibility 2 Visit (E2), Week 2, and Week 6.

Schedule of Visits and Assessments

	Screen	Eligibility 1[a] Visit (E1)				Eligibility 2[a] Visit (E2) (3-8 days from E1)				Week 2[a] Visit (14 ± 1 days from E2)				Week 6[a] Visit (42 ± 3 days from E2)				Early Exit[b] Visit
		8 AM	10 AM	3 PM	5 PM	8 AM	10 AM	3 PM	5 PM	8 AM	+2 h	+7 h	+9 h	8 AM	+2 h	+7 h	+9 h	
Informed Consent[c]	X																	
Demographics	X																	
Medical history and concomitant medications	X																	
Change in medical history and concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X																	
Urine pregnancy test[d]	X													X				X
Pulse and blood pressure	X	X	X			X	X			X	X			X	X			X
Visual acuity	X	X				X				X				X				X
Slit-lamp exam	X	X				X				X				X				X
Gonioscopy	X																	
Automated perimetry	X																	
Dilated fundus exam[e]	X																X	X
Intraocular pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drugs									X									
Instill study drugs in office										X		X		X		X		
Adverse events										X	X	X	X	X	X	X	X	X
Collect study drugs																	X	X
Exit patient and complete exit form																	X	X

[a] Eligibility 1 visit was conducted a minimum of 3 (± 1) days to 42 (± 1) days following the screening visit, according to the washout schedule. All assessment time points (8 AM, 10 AM, 3 PM, and 5 PM) were to have been conducted within a window of ± 30 minutes.
[b] These assessments were performed on all patients who discontinued study participation prior to the Week 6 visit.
[c] Informed consent was signed/dated before study procedures were performed.
[d] Required for all female patients of childbearing potential.
[e] A dilated fundus examination was performed for all patients at the Screening visit and served as the baseline measurement. At the exit visit, Investigators had the option of performing a dilated or undilated fundus examination based upon their clinical judgment, with the exception of patients who demonstrated any pathology (other than that associated with glaucoma) at the baseline fundus examination or who developed any other pathology during participation in the study. For these patients, a dilated examination was performed.

Study C-11-002 – Descriptive Comfort Study

Title: A Descriptive Comfort Study of Brinzolamide 1%/Brimonidine Tartrate 0.2% Fixed Combination Ophthalmic Suspension, Brinzolammide 1% Ophthalmic Suspension and Brimonidine Tartrate 0.2% Ophthalmic Solution in Patients with Open-Angle Glaucoma or Ocular Hypertension

Study Design

This study was a multi-center (5 sites), randomized, double-masked, parallel group, active-controlled descriptive study designed to describe the ocular comfort of the fixed combination of brinzolamide 1%/brimonidine tartrate 0.2% (brinzolamide/brimonidine), brinzolamide 1% (brinzolamide), and brimonidine tartrate 0.2% (brimonidine), using an ocular discomfort scale.

Study C-10-033

Title: Three Month Efficacy and Safety Study of a Fixed Combination of Brinzolamide 1%/Brimonidine 0.2% Compared to Brinzolamide 1% and Brimonidine 0.2% All Dosed Three Times Daily in Patients with Open-Angle Glaucoma and/or Ocular Hypertension

Study Design

This study was a prospective, multi-center (68 sites), double-masked, parallel group, randomized, active-controlled trial designed to evaluate the efficacy and safety of the fixed combination of brinzolamide/brimonidine in lowering IOP relative to each of its individual active components in patients with open-angle glaucoma and/or ocular hypertension. Approximately 750 patients were planned for enrollment in a ratio of 1:1:1 (brinzolamide/brimonidine:brinzolamide:brimonidine). The patients received 1 drop of assigned study medication in both eyes 3 times daily for 3 months. Evaluations of safety and efficacy were performed at fixed times (8AM, + 2 hrs, + 7 hrs, and + 9 hrs) during the study visits conducted at Week 2, Week 6, and Month 3.

Schedule of Visits and Assessments

Activity	Screen	Eligibility 1 (E1) Visit [a]				Eligibility 2 (E2) Visit (3-8 days from E1)				Week 2 Visit (14 ± 3 days from E2)				Week 6 Visit (42 ± 3 days from E2)				Month 3 Visit (90 ± 4 days from E2)				Early Exit [b]
		8 AM	10 AM	3 PM	5 PM	8 AM	10 AM	3 PM	5 PM	8 AM	+2 h	+7 h	+9 h	8 AM	+2 h	+7 h	+9 h	8 AM	+2 h	+7 h	+9 h	
Informed Consent[c]	X																					
Demographics	X																					
Medical history and concomitant medications	X	X	X	X	X	X	X	X	X													
Change in medical health and concomitant medications										X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X																					
Urine pregnancy test[d]	X																				X	X
Pulse and blood pressure	X	X	X			X	X			X	X			X	X			X	X			X
Best-corrected visual acuity	X	X				X				X				X				X				X
Slit-lamp exam	X	X				X				X				X				X				X
Gonioscopy	X																					
Automated perimetry	X																	X				X
Dilated fundus exam	X																				X	X
Pachymetry	X																				X	X
Intraocular pressure (Goldmann)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medications									X				X				X					
Instill study medications in office										X		X		X		X		X		X		
Adverse events										X	X	X	X	X	X	X	X	X	X	X	X	X
Collect study medications																		X				X
Exit patient, complete exit form																					X	X

[a] The Eligibility 1 Visit was conducted between 3 (± 1) days and 28 (± 1) days following the Screening Visit, in accordance with the washout schedule.
[b] These assessments were performed on all patients who discontinued study participation prior to the Month 3 visit.
[c] The informed consent document was signed/dated before any study procedures were performed.
[d] Required for all female patients of childbearing potential.

Inclusion Criteria

1. Patients 18 years of age or older, of either sex, and any race/ethnicity, diagnosed with open-angle glaucoma or ocular hypertension
2. Mean IOP measurements in at least 1 eye, the same eye(s), must have been:
    - Greater than or equal to 24 mmHg and less than or equal to 36 mmHg at the 8 AM time point at both Eligibility Visit 1 and Eligibility Visit 2
    - Greater than or equal to 21 mmHg and less than or equal to 36 mmHg at the 10AM time point at at both Eligibility Visit 1 and Eligibility Visit 2

The mean IOP in either eye must not have been greater than 36 mmHg at any time point.

Exclusion Criteria

1. Patients unable to understand and unable or unwilling to sign an IRB-approved informed consent
2. Females of childbearing potential (those who were not surgically sterilized or not at least 2 years postmenopausal) were excluded from participation in the study if they met any one of the following conditions:
    - They were pregnant at the time
    - They had a positive result on the urine pregnancy test at the Screening Visit
    - They intended to become pregnant during the study period
    - They were breast-feeding
    - They were not using highly effective birth control measures, such as:
        Hormonal – oral, implanted, transdermal, or injected contraceptives
        Mechanical – spermicide in conjunction with a barrier such as a condom, diaphragm, or intrauterine device

Important Notes:

All females of childbearing potential must have consented to a urine pregnancy test upon exiting the study.

Females of childbearing potential were instructed to immediately inform the Investigator if they became pregnant during the study. Should this have occurred, the Investigator immediately contacted Alcon.

For females who were not sexually active, abstinence may have been regarded as an adequate method of birth control; however if the patient became sexually active during the study, she must have agreed to use adequate birth control method as defined above for the remainder of the study.

3. Patients with any form of glaucoma other than open-angle glaucoma
4. Patients with a central cornea thickness greater than 620 µm as measured by pachymetry in either either

5. Patients with Schaffer angle Grade less than 2 in either eye, as measured by gonioscopy (extreme narrow angle with complete or partial closure)
6. Patients with a cup/disc ratio greater than 0.80 (horizontal or vertical measurement) in either eye
7. Patients with severe central visual field loss in either eye; severe central visual field loss was defined as a sensitivity of less than or equal to 10 dB in at least 2 of the 4 visual field test points closest to the point of fixation
8. Chronic, recurrent, or severe inflammatory eye disease (e.g., scleritis, uveitis, herpes keratitis)
9. Ocular trauma within the preceding 6 months
10. Ocular infection or ocular inflammation within the preceding 3 months
11. Clinically significant or progressive retinal disease such as retinal degeneration, diabetic retinopathy, or retinal detachment
12. BCVA score worse than 55 letters using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (equivalent to approximately 20/80 Snellen, 0.60 logMAR, or 0.25 decimal)
13. Other ocular pathology (including severe dry eye) that may, in the opinion of the Investigator, have precluded the administration of an alpha-adrenergic agonist and/or a topical CAI
14. Intraocular surgery within the preceding 6 months
15. Ocular laser surgery within the preceding 3 months
16. Any abnormality preventing reliable applanation tonometry
17. Any other conditions, including severe illness, which would have made the patient, in the opinion of the Investigator, unsuitable for the study
18. Patients with recent (within 4 weeks of the Eligibility Visit 1) use of high dose (> 1 g daily) saclicylate therapy
19. History of active, severe, unstable, or uncontrolled cardiovascular (e.g., coronary insufficiency, hypertension, Raynaud's phenomenon, orthostatic hypotension, thromboangiitis obliterans), cerebrovascular (e.g., cerebral insufficiency), hepatic, or renal disease that would have precluded the safe administration of a topical alpha-adrenergic agonist or CAI in the opinion of the Investigator
20. Current or anticipated treatment with any psychotropic drugs that augment adrenergic response (e.g., desipramine, amitriptyline)
21. Concurrent use of a monoamine oxidase inhibitor
22. Therapy with another investigational agent within 30 days prior to the Screening Visit
23. Hypersensitivity to alpha-adrenergic agonist drugs, topical or oral CAIs, sulfonamide derivatives, or to any component of the study medications in the opinion of the Investigator
24. Patients who could not safely discontinue use of all IOP-lowering ocular medication(s) for a minimum period of 3 days ± 1 day to 28 days ± 1 day prior to Eligibility Visit 1
25. Less than 30 days stable dosing regimen before the Screening Visit of any medications or substances administered by any route and used on a chronic basis that may affect IOP, including but not limited to, beta-adrenergic blocking agents
26. Use of any additional systemic or topical ocular hypotensive medication during the study

27. patients who could not safely discontinue all glucocorticoid administered by any route

The Medical Monitor may have declared any patient ineligible for a valid medical reason.

Primary Efficacy Endpoint

The primary efficacy variable was IOP and the primary efficacy endpoint was the mean IOP at each of the assessment time points (8 AM, + 2 h, + 7 h, and + 9 h) at Month 3. IOP measurements were done at 8:00, 10:00, 15:00, and 17:00 at Eligibility 1 Visit (E1), Eligibility 2 Visit (E2), Week 2 Visit, Week 6 Visit, and Month 3 Visit.

Secondary Efficacy Endpoint

The secondary efficacy endpoints included the mean IOP at each of the assessment time points (8 AM, + 2 h, + 7 h, and + 9 h) at Week 2 and Week 6. IOP measurements were done at 8:00, 10:00, 15:00, and 17:00 at Eligibility 1 Visit (E1), Eligibility 2 Visit (E2), Week 2 Visit, Week 6 Visit, and Month 3 Visit.

Reviewer's comments:

Clinical disagrees with using only mean IOP measurements at month 3 to evaluate efficacy. The primary efficacy endpoint utilized by Clinical in the review of this NDA is mean IOP at each time point measured.

Investigators

Investigator	Investigator #	# of Patients Enrolled
Altman, Bruce MD Danbury Eye Physicians & Surgeons, PC Danbury, CT 06810	1160	4
Arzeno, George MD Bayamon, PR 00961	4601	5
Bashford, Kent DO Eye Center of Northern Colorado, PC Fort Collins, CO 80525	4421	7
Bennett, Donald OD, MD Kentuckiana Institute for Eye Research, dba Bennett and Bloom Eye Centers Louisville, KY 40207	5770	1
Bergmann, Mark MD Eye Care Associates of Greater Cincinnati, Inc. Cincinnati, OH 45238.	5476	0
Berke, Stanley MD (replaced during the study	3962	23

Investigator	Investigator #	# of Patients Enrolled
by Richard Sturm, MD as the Principal Investigator) Ophthalmic Consultants of Long Island Lynbrook, NY 11563		
Bluestein, Ettaleah MD Bluestein Custom Vision Charleston, SC 29414	5443	4
Bond, Jeffrey MD Wake Forest University Eye Center Winston-Salem, NC 27157	4570	3
Boyce, James MD Orange County Ophthalmology Medical Group Garden Grove, CA 92843	5239	2
Branch, James MD Winston-Salem, NC 27101	3631	20
Chace, Richard MD Eyesight Ophthalmic Services, PA Portsmouth, NH 03801	3910	6
Dehning, Doug MD Discover Vision Centers Independence, MO 64055	2346	5
Dixon, El-Roy MD Dixon Eye Care Albany, GA 31701	5303	18
DuBiner, Harvey MD Eye Care Centers Management Morrow, GA 30260	1927	29
Engelman, Christopher MD Spectrum Eye Physicians Los Gatos, CA 95030	4032	5
Fong, Raymond MD New York, NY 10013	5758	3
Freeman, Wayne L. MD Complete Eye Care Associates Los Alamitos, CA 90720	5289	5
Gira, Joseph MD Ophthalmology Consultants, Ltd. Des Peres, MO 63131	5459	9
Goldberg, Damien MD Wolstan & Goldberg Eye Associates Torrance, CA 90505	5489	10

Investigator	Investigator #	# of Patients Enrolled
Graul, Thomas MD Eye Surgical Associates Lincoln, NE 68506	5593	11
Greene, Brennan MD The Eye Care Institute Louisville, KY 40206	5582	4
Haynes, William MD Asheville Eye Associates Asheville, NC 28803	5480	8
Henry, John MD Little Rock Eye Clinic Little Rock, AR 72205	983	4
Jacobs, Brian MD North Shore Glaucoma Center Libertyville, IL 60048	5654	0
Jerkins, Gary MD Nashville Vision Associates 4306 Harding Road Suite 202Nashville, TN 37205	1159	23
Kaback, Martin MD Glaucoma Consultants of the Capital Region Slingerlands, NY 12159	962	4
Katz, Gregory MD Huron Ophthalmology, PC Ypsilanti, MI 48197	3731	16
Katzen, Lawrence MD Katzen Eye Care Boynton Beach, FL 33426	6229	3
Kent, Alexander MC Palmetto Research, LLC Charleston, SC 29403	3974	9
Kirby, Charles MD Chattanooga Eye Institute, PC Chattanooga, TN 37411	6102	4
Lozier, Jeffrey MD Arch Health Partners Poway, CA 92064	3678	18
Macy, Jonathan MD Macy Eye Center Los Angeles, CA 90048	2029	7
Mayer, Hylton MD	6228	1

Investigator	Investigator #	# of Patients Enrolled
Eye Doctors of Washington Chevy Chase, MD 20815		
McLaurin, Eugene MD Total Eye Care, PA 6060 Primacy Parkway Suite 200 Memphis, TN 38119	4011	44
Mundorf, Thomas MD Mundorf Eye Center Charlotte, NC 28204	1473	17
Nutaitis, Matthew MD MUSC Storm Eye Institute Charleston, SC 29425	5769	2
Okeke, Constance MD Virginia Eye Consultants Norfolk, VA 23502	5333	3
Olander, Kenneth MD University Eye Surgeons Maryville, TN 37803	750	16
Pantcheva, Mina MD University of Colorado – Department of Ophthalmology Aurora, CO 80045	6039	5
Peace, James MD United Medical Research Institute Inglewood, CA 90301	3627	15
Perez, Bernard MD International Eye Center Tampa, FL 33603	3720	3
Portnoy, Scott MD Siegel and Portnoy Eyecare Associates Pittsburgh, PA 15203	5176	5
Quinones, Richard MD Arbor Centers for EyeCare Homewood, IL 60430	4146	6
Rauchman, Steven MD North Valley Eye Medical Group, Inc. Mission Hills, CA 91345	5180	29
Reinstein, Ned MD Reinstein Eye Associates, PC Tulsa, OK 74136	2448	8
Reiss, George MD	1627	0

Investigator	Investigator #	# of Patients Enrolled
George R. Reiss, MD, PC Glendale, AZ 85306		
Rothman, Robert MD Eye Care Ophthalmology, PC Bethpage, NY 11714	6366	0
Rubin, Jay MD Eye Clinics of South Texas San Antonio, TX 78209	1725	4
Sall, Kenneth MD Sall Research Medical Center Artesia, CA 90701	1806	41
Samples, John MD Glaucoma Consultants of Colorado Parker, CO 80134	4347	3
Sharpe, Elizabeth MD Glaucoma Consultants & Center for Eye Research, PA Mount Pleasant, SC 29464	731	21
Shettle, Philip DO Lee Shettle DOPA Largo, FL 33773	3346	18
Smith, Shannon MD Cataract, Glaucoma & Retina Consultants of East Texas Nacogdoches, TX 75965	1892	24
Smith, Stacy MD Stacy R. Smith, MD, PC Salt Lake City, UT 84117	6160	12
Solish, Alfred MD Southern California Glaucoma Consultants Pasadena, CA 91105	2454	1
Stein, Emil MD Nevada Eye Care Professionals Las Vegas, NV 89119	3851	17
Stewart, Colby W. MD Houston Eye Associates Houston, TX 77025	2631	8
Sutton, James MD Mississippi Eye Associates Ocean Springs, MS 39564	3993	4
Swanic, Matthew MD	6339	3

Investigator	Investigator #	# of Patients Enrolled
AdvanceMed Clinical Research Eye Care Associates of Nevada Las Vegas, NV 89106		
Tayeri, Thomas MD Palo Alto Eye Group Palo Alto, CA 94306	4338	2
Tibbets, Jean MD Eastern Maine Medical Center Focus Eye Care of Maine Bangor, ME 04401	3665	3
Tyson, Farrell II MD Cape Coral Eye Center Cape Coral, FL 33904	5468	12
Vold, Steven MD Boozman Hof Regional Eye Center Rogers, AR 72756	4734	0
Wallshein, Jay MD Altus Research Lake Worth, FL 33461	5397	7
Weiss, Mark MD Mark J. Weiss, MD, Inc. Tulsa, OK 74104	394	25
Williams, Robert MD (replaced during the study by Gregory Sulkowski, MD as the Principal Investigator) The Taustine Eye Center Louisville, KY 40217	2128	9
Wollan, Peter MD Hill Country Eye Center Cedar Park, TX 78613	6239	11
Woodruff, Todd MD The Glaucoma Center Akron, OH 44320	4194	11

See Section 6 for efficacy results and Section 7 for safety.

Study C-10-039

Title: A Three-Month, Randomized, Double-Masked, Parallel-Group Study with a Planned Three-Month Safety Extension of the Efficacy and Safety of a Fixed Combination of Brinzolamide 1%/Brimonidine 0.2% Compared to Brinzolamide 1% and Brimonidine 0.2% All Dosed Three Times Daily in Patients with Open-Angle Glaucoma and/or Ocular Hypertension

Study Design

This study was a prospective, multi-center (64 sites), double-masked, parallel group, randomized, active-controlled trial designed to evaluate the efficacy and safety of the fixed combination of brinzolamide/brimonidine in lowering IOP relative to each of its individual active components in patients with open-angle glaucoma and/or ocular hypertension. Approximately 750 patients were planned for enrollment in a ratio of 1:1:1 (brinzolamide/brimonidine:brinzolamide:brimonidine). The patients received 1 drop of assigned study medication in both eyes 3 times daily for 3 months. Evaluations of safety and efficacy were performed at fixed times (8AM, + 2 hrs, + 7 hrs, and + 9 hrs) during the study visits conducted at Week 2, Week 6, Month 3, and Month 6.

Schedule of Visits and Assessments

Activity	Screen	Eligibility 1 [a] Visit				Eligibility 2 Visit (3-8 days from Eligibility 1)				Week 2 Visit (14 ± 3 days from Eligibility 2)				Week 6 Visit (42 ± 3 days from Eligibility 2)			
		8 AM	10 AM	3 PM	5 PM	8 AM	+2 h	+7 h	+9 h	8 AM	+2 h	+7 h	+9 h	8 AM	+2 h	+7 h	+9 h
Informed consent [b]	X																
Demographics	X																
Medical history and concomitant medications	X	X	X	X	X	X	X	X	X								
Change in medical health and concomitant medications										X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X																
Urine pregnancy test [c]	X																
Pulse and blood pressure	X	X	X			X	X			X	X			X	X		
Best-corrected visual acuity	X	X				X				X				X			
Slit-lamp exam	X	X				X				X				X			
Gonioscopy	X																
Automated perimetry	X																
Dilated fundus exam	X																
Pachymetry	X																
Intraocular pressure (Goldmann)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study medications									X				X				X
Instill study medications in office										X		X		X		X	
Adverse events										X	X	X	X	X	X	X	X

Schedule of Visits and Assessments

Activity	Month 3 Visit (90 ± 4 days from Eligibility 2)				Month 6 Visit (180 ± 7 days from Eligibility 2)				Early Exit[d]
	8 AM	+2 h	+7 h	+9 h	8 AM	+2 h	+7 h	+9 h	
Informed consent [b]									
Demographics									
Medical history and concomitant medications									
Change in medical health and concomitant medications	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria									
Urine pregnancy test [c]								X	X
Pulse and blood pressure	X	X			X	X			X
Best-corrected visual acuity	X				X				X
Slit-lamp exam	X				X				X
Gonioscopy									
Automated perimetry	X				X				X
Dilated fundus exam				X				X	X
Pachymetry				X				X	X
Intraocular pressure (Goldmann)	X	X	X	X	X	X	X	X	X
Dispense study medications				X					
Instill study medications in office	X		X		X		X		
Adverse events	X	X	X	X	X	X	X	X	X
Collect study medications					X				X
Exit patient, complete exit form								X	X

[a] The Eligibility 1 Visit was conducted between 3 (± 1) days and 28 (± 1) days following the Screening Visit, in accordance with the washout schedule.
[b] The informed consent document was signed/dated before any study procedures were performed.
[c] Required for all female patients of childbearing potential.
[d] These assessments were performed on all patients who discontinued study participation prior to the Month 6 visit.

The inclusion/exclusion criteria for study C-10-039 were the same as for study C-10-033.

Primary Efficacy Endpoint

The primary efficacy variable was IOP and the primary efficacy endpoint was the mean IOP at each of the assessment time points (8 AM, + 2 h, + 7 h, and + 9 h) at Month 3. IOP measurements were done at 8:00, 10:00, 15:00, and 17:00 at Eligibility 1 Visit (E1), Eligibility 2 Visit (E2), Week 2 Visit, Week 6 Visit, Month 3 Visit, and Month 6 visit.

Secondary Efficacy Endpoint

The secondary efficacy endpoints included the mean IOP at each of the assessment time points (8 AM, + 2 h, + 7 h, and + 9 h) at Week 2 and Week 6. IOP measurements were done at 8:00, 10:00, 15:00, and 17:00 at Eligibility 1 Visit (E1), Eligibility 2 Visit (E2), Week 2 Visit, Week 6 Visit, Month 3 Visit, and Month 6 visit.

Reviewer's comments:

Clinical disagrees with using only mean IOP measurements at month 3 to evaluate efficacy. The primary efficacy endpoint utilized by Clinical in the review of this NDA is mean IOP at each time point measured.

Investigators

Investigator	**Investigator #**	**# of Patients Enrolled**
Marc A Abrams, MD, PhD. Abrams Eye Center Cleveland, OH 44115	4798	4
Ahmad Amir, MD Pacific Eye San Luis Obispo, CA 93401	6095	13
Guy J. Angella, MD Eye Surgery Associates Pembroke Pines, FL 33028	6100	9
Jason Bacharach, MD North Bay Eye Associates, Inc Petaluma, CA 94954	2434	11
Howard Barnebey, MD Specialty Eyecare Centre Bellevue, Washington 98004 Specialty Eyecare Centre Seattle, WA 98104	2195	17
Janet A Betchkal, MD	4404	2

Investigator	Investigator #	# of Patients Enrolled
Gilbert Cataract Center Jacksonville, FL		
Leonard R. Cacioppo, MD P.A. Dba: Hernando Eye Institute Brooksville, FL 34613	1946	10
Williams C Christie, MD Scott & Christie and Associates, PC Pittsburgh, PA 15238 Scott & Christie and Associates, PC Cranberry Township, PA 16066	4570	3
James P. Cornetet, MD, FAAO Billings Clinic Research Center Billings, Montana 59101 Billings Clinic Billings, Montana 59101	6243	1
Frank Cotter, MD Vistar Eye Center Roanoke, VA 57149 Vistar Eye Center Salem, VA 24153	4455	15
Andrew J Cottingham, Jr., MD Texas Quest Medical Research, LLC San Antonio, TX 78256	3349	14
Charles J Crane, MD Northern New Jersey Eye Institute, PA South Orange, NJ 07079	4189	12
Site Management Organization Coastal Research Associates, LLC Roswell, GA 30076 Douglas Day, MD Omni Eye Services Atlanta, GA 30342 Douglas Day, MD Omni Eye Services College Park, GA 30349	2348	10
Steven Day, MD Spokane Eye Clinical Research, PLLC	6255	4

Investigator	Investigator #	# of Patients Enrolled
Spokane, Washington 99204 Spokane Eye Clinical Research, PLLC Spokane, WA 99208 Spokane Eye Clinical Research, PLLC Spokane Valley, WA 99216		
Donald Digby, MD Digby Eye Associates Greensboro, NC, 27408	4029	0
Monte S Dirks, MD Black Hills Regional Eye Institute Rapid City, SD 57701	1931	11
Efraim Duzman, MD Lakeside Vision Center Irvine, CA 92604	3785	6
Robert Ewing, MD Siskiyou Eye Center Medical Group, Inc Ashland, Oregon 97520 Siskiyou Eye Center Medical Group, Inc Yreka, CA 96097	4221	0
Robert M Feldman, MD Robert Cizik Eye Clinic Houston, TX Robert Cizik Eye Clinic Clinical Trials Unit Houston, TX 77030	2564	2
Mark Feldman, MD Fort Lauderdale Eye Institute Plantation, FL 33324	5636	9
Asra S. Firozvi, MD North Carolina Eye, Ear, Nose & Throat Durham, NC 27704	5465	12
Williams J. Flynn, MD, OD R and R Eye Research, LLC San Antonio, TX 78229	5145	14
Ronald Frenkel, MD East Florida Eye Institute Stuart, FL 34994	2137	12
Robert S. Friedman, MD	1930	7

Investigator	Investigator #	# of Patients Enrolled
The Eye Associates of Manatee, LLP Sarasota, FL 34239		
David Godfrey, MD Glaucoma Associates of Texas 10740 N Central Expressway, Suite 300 Dallas, TX 75231	3377	1
Frank J. Grady, MD, PhD Frank J. Grady, MD, Association- Brazosport Eye Clinic Lake Jackson, TX 77566	4364	14
Wade A. Graham, MD Thurmond Eye Associates, PA Weslaco, TX 78596	6180	5
Ronald L Gross, MD Alkek Eye Center of Baylor College of Medicine Houston, TX 77030	961	0
Robert F. Haverly, MD Laser Eye Surgery of Erie Erie, PA 16502	4567	19
Joseph E. Humble, MD Eye Associates of Northeast Louisiana dba Haik Humble Eye Center West Monroe, LA 71291	6232	15
Michael Jacobs, MD Athens Eye Associates Bogart, GA 30622	5404	9
Barry Katzman, MD West Coast Eye Care Associates San Diego, CA 92115	2449	15
Dawnielle Kerner, MD The Glaucoma & Laser Center Norfolk, VA 23505	4247	4
Karen L. Klugo, MD Eye Care Associates of Greater Cincinnati, Inc Cincinnati, OH 45236	5304	15
Alexander Kostick, MD Atlantic Eye Center Palm Coast, FL 32137	3991	7
Bradley Kwapiszeski, MD Heart of America Eye Care, PA Shawnee Mission, KS 66204	3112	12
John M. Lim, MD	5515	7

Investigator	Investigator #	# of Patients Enrolled
Houston Eye Associates Houston, TX 77025 Houston Eye Associates Houston, TX 77024		
Christopher Lin, MD Shasta Eye Medical Group, Inc Redding, CA 96002	3975	11
Jodi Ian Luchs, MD South Shore Eye Care, LLP Wantagh, NY 11793	4780	14
Ranjan P. Malhorta, MD Ophthalmology Associates St. Louis, MO 63131	4824	7
Cynthia Mattox, MD, FACS New England Eye Center at Tufts Medical Center Boston, MA 02111	3830	1
Donald McCormick, MD Boulder Medical Center PC Boulder, CO 80304	5387	11
Ryan McKinnon, MD Saltzer Medical Group, PA Nampa, ID 83686 Saltzer Medical Group, PA Caldwell, ID 83605	5583	11
Matthew G. McMenemy, MD Lone Star Eye Care Sugarland, TX 77479	2421	21
John L. Michaelos, MD St. Michael's Eye & Laser Institute Largo, FL 33770	6099	13
Martin W. Mizener, MD Midwest Eye Care PC Omaha, NE 68131	2576	11
George A. Moninger, MD Botherman & Moninger, LLP Dallas, TX 75234-7840	3722	6
John Narin, MD Associates in Ophthalmology West Mifflin, PA 15122	6233	0
Quang H. Nguyen, MD	6159	11

Investigator	Investigator #	# of Patients Enrolled
Scripps Clinic La Jolla, CA 92037		
Katherine Isabel Ochsner, MD Eye Associates of Wilmington Wilmington, NC 28403	1011	4
Parag Parekh, MD, MPA Ophthalmic Consultants of Boston West Yarmouth, MA 02673	5760	0
Jose Luis Perez-Beccerra, MD Belle Vue Eye Centre San Antonio, TX 78221	5175	0
Scott Petermann, MD South Georgia Eye Partners, PC Valdosta, GA 31602	5220	6
Jody Piltz-Seymour, MD Glaucoma Care Center, PC Ardmore, PA 19003 Glaucoma Care Center, PC Philadelphia, PA 19107	3967	8
Omar Piovanetti, MD Centro Oftalmologico Metropolitano San Juan, PR 00921	6242	3
Eugene E. Protzko Seidenberg Protzko Eye Associates Havre de Grace, MD 21078 Seidenberg Protzko Eye Associates Bel Air, MD 21014	3132	10
Anthony Realini, MD, Ph.D West Virginia University Eye Institute Morgantown, WV 26506	3362	5
Research Center Eastside Westside Research Center Spartenburg, SC 29306 Lawrence Roel, MD, PhD Eastside Eye Center Spartenburg, SC 29302 Lawrence Roel, MD, PhD Westside Eye Center	5541	17

Investigator	Investigator #	# of Patients Enrolled
Spartanburg, SC 29306		
Michael H. Rotberg, MD Charlotte Eye Ear Nose & Throat Associates, PA Charlotte, NC 28210 Charlotte Eye Ear Nose & Throat Associates, PA Belmont, NC 28012 Charlotte Eye Ear Nose & Throat Associates, PA Matthews, NC 28105	1393	17
Howard I. Schenker, MD Rochester Ophthalmological Group, PC Rochester, NY 14618	1939	23
Zachary Kaufman Segal, MD MedEye Associates Miami, FL 33143	5444	0
Steven Marc Silverstein, MD Silverstein Eye Centers Kansas City, MO 64133	3807	3
Inder Paul Singh, MD Eye Center Of Racine & Kenosha, Ltd. St. Mary's Medical Center Racine, WI 53405	5471	3
Stephen E. Smith, MD Eye Associates of Fort Myers Fort Myers, FL 33901	3988	20
Joseph Sokal, MD Connecticut Eye Specialists, LLC Shelton, CT 06484	4305	7
Navin Tekwani, MD Tekwani Vision Center Inc. Saint Louis, MO 63128	4311	18
Michael E. Tepedino, MD Cornerstone Eye Care High Point, NC 27262	3626	18
George C. Thorne, MD Eye Physicians of Austin Austin, TX 78756	2353	25
Robert Treft, MD Mountain View Eye Center Layton, Utah 84041	4424	10
Jess Whitson, MD	1909	5

Investigator	**Investigator #**	**# of Patients Enrolled**
UT Southwestern Medical Center at Dallas Department of Ophthalmology Dallas, TX 75390 UT Southwestern Medical Center at Dallas Department of Ophthalmology Aston Ambulatory Care Center Dallas, TX 75390		
David Wirta, MD Eye Research Foundation Newport Beach, CA 92663	2600	30

See Section 6 for efficacy results and Section 7 for safety.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is for the reduction of intraocular pressure in patients, 18 years old or more, with open angle glaucoma or ocular hypertension.

6.1.1 Methods

Description of the clinical trial design is contained in Section 5.3.

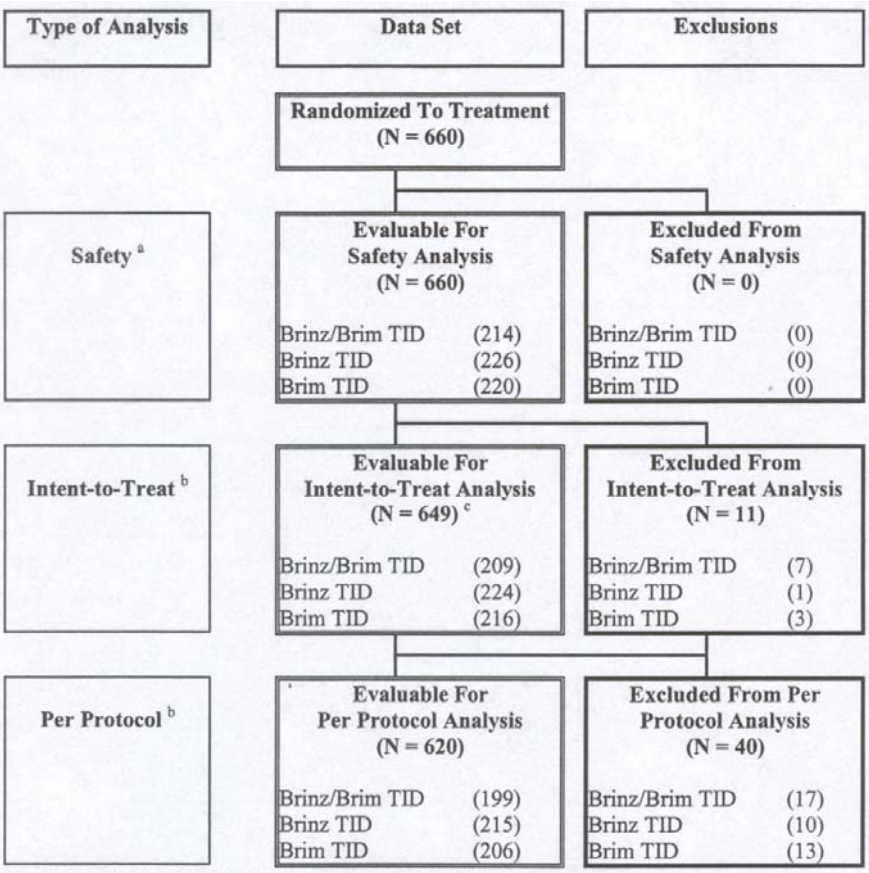
6.1.2 Demographics

		Study		
		C-10-033		
Treatment Group		brinzolamide/ brimonidine	brinzolamide	brimonidine
Total enrollment in study		209 **N (%)**	224 **N (%)**	216 **N (%)**
Race	White	143 (68.4)	141(62.9)	155 (71.8)
	Black or African American	62 (29.7)	75 (33.5)	59(27.3)
	Asian	3 (1.4)	5 (2.2)	0 (0.0)
	American Indian or Alaska Native	1 (0.5)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	3 (1.3)	2 (0.9)
Ethnicity	Hispanic, Latino, or Spanish	24 (11.5)	25 (11.2)	27 (12.5)
	Non Hispanic, Latino, or Spanish	185 (88.5)	199 (88.8%)	189 (87.5)
Age (Years)	< 65	104 (49.8)	99 (44.2)	115 (53.2)
	≥ 65	105 (50.2)	125 (55.8)	101 (46.8)
	≥ 65 to < 75	72 (34.4)	85 (37.9)	64 (29.6)
	≥ 75 to < 85	30 (14.4)	37 (16.5)	30 (13.9)
	≥ 85 to < 95	3 (1.4)	3 (1.3)	7 (3.2)
Gender	Male	73 (34.9)	97 (43.3)	84 (38.9)
	Female	136 (65.1)	127 (56.7)	132 (61.1)
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)

		Study		
		C-10-039		
Treatment Group		brinzolamide/ brimonidine	brinzolamide	brimonidine
Total enrollment in study		218	229	232
		N (%)	**N (%)**	**N (%)**
Race	White	174 (79.8)	179(78.2)	176 (75.9)
	Black or African American	36 (16.5)	42 (18.3)	52(22.4)
	Asian	3 (1.3)	5 (0.4)	1 (0.4)
	Multi-racial	0 (0.0)	1 (0.4)	2 (0.9)
	Other	5 (2.3)	2 (0.9)	1 (0.4)
Ethnicity	Hispanic, Latino, or Spanish	21 (9.6)	15 (6.6)	26 (11.2)
	Non Hispanic, Latino, or Spanish	197 (90.4)	214 (93.4%)	206 (88.8)
Age (Years)	< 65	98 (45.0)	110 (48.0)	115 (49.6)
	≥ 65	120 (55.0)	119 (52.0)	117 (50.4)
	≥ 65 to < 75	80 (36.7)	90 (39.3)	73 (31.5)
	≥ 75 to < 85	34 (15.6)	26 (11.4)	39 (16.8)
	≥ 85 to < 95	5 (2.3)	3 (1.3)	5 (2.2)
	≥ 95	1 (0.5)	0 (0.0)	0 (0.0)
Gender	Male	100 (45.9)	97 (42.4)	101 (43.5)
	Female	118 (54.1)	132 (57.6)	131 (56.5)
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 (0.0)	1 (0.4)	0 (0.0)
	Hazel	35 (16.1)	28 (12.2)	36 (15.5)
	Other	1 (0.5)	1 (0.4)	1 (0.4)

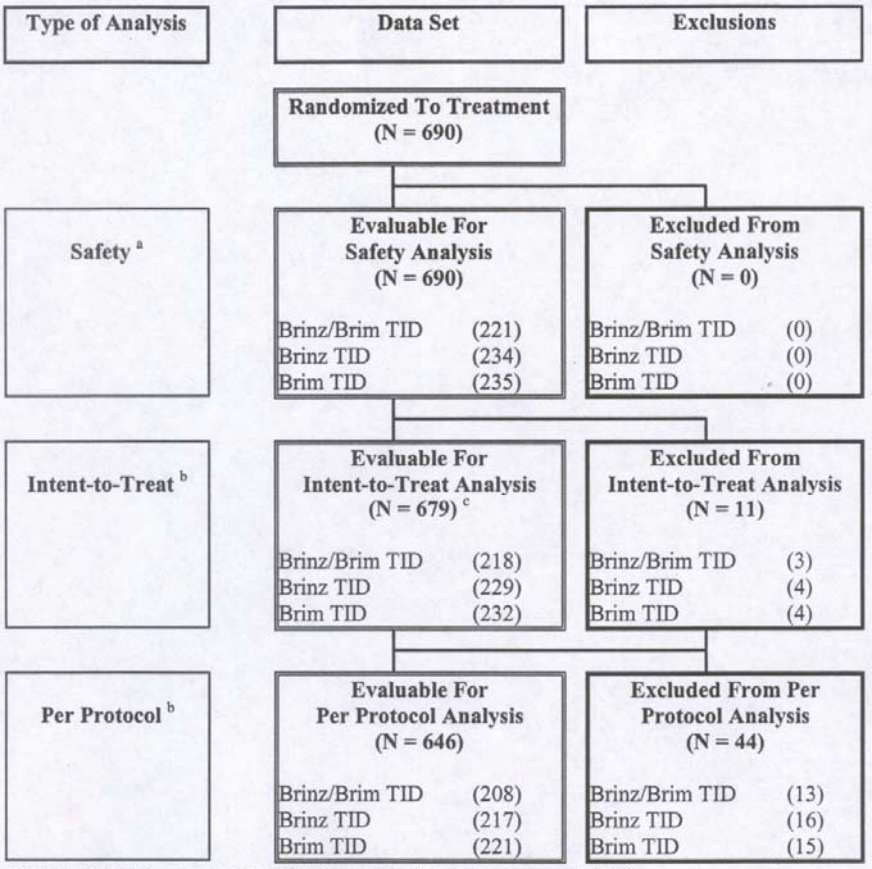
6.1.3 Subject Disposition

Study C-10-033



Brinz/Brim TID = brinzolamide 1% / brimonidine tartrate 0.2% ophthalmic suspension TID
Brinz TID = brinzolamide ophthalmic suspension, 1% TID
Brim TID = brimonidine tartrate ophthalmic solution, 0.2% TID
[a] Patients were analyzed according to the actual treatment received.
[b] Patients were analyzed according to the randomized treatment assignment.
[c] Primary efficacy was based on an observed case analysis of the ITT dataset.

Study C-10-039



Brinz/Brim TID = brinzolamide 1% / brimonidine tartrate 0.2% ophthalmic suspension TID
Brinz TID = brinzolamide ophthalmic suspension, 1% TID
Brim TID = brimonidine tartrate ophthalmic solution, 0.2% TID
[a] Patients were analyzed according to the actual treatment received.
[b] Patients were analyzed according to the randomized treatment assignment.
[c] Primary efficacy was based on an observed case analysis of the ITT dataset.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for Study C-10-033 was the mean IOP at each of the assessment time points (8 AM, + 2 hrs, + 7 hrs, and + 9 hrs) at Month 3. IOP measurements were done at 8AM, 10AM, 3PM, and 5PM at Eligibility 1 Visit (E1), Eligibility 2 Visit (E2), Week 2 Visit, Week 6 Visit, and Month 3 Visit.

The primary efficacy endpoint for Study C-10-039 was the mean IOP at each of the assessment time points (8 AM, + 2 hrs, + 7 hrs, and + 9 hrs) at Month 3. IOP measurements were done at 8AM, 10AM, 3PM, and 5PM at Eligibility 1 Visit (E1), Eligibility 2 Visit (E2), Week 2 Visit, Week 6 Visit, Month 3 Visit, and Month 6.

The primary efficacy endpoint for Study C-09-038 was the mean change in IOP from baseline of the assessment time points (8 AM, + 2 hrs, + 7 hrs, and + 9 hrs) at Week 6. IOP measurements of IOP were taken once at screening and 4 times (at 8 AM, 10AM, 3PM, and 5PM [±30 minutes in all cases]) at all other post-Screening visits.

Reviewer's comments:

The primary efficacy variable utilized in the review of this NDA is mean IOP at each time point measured.

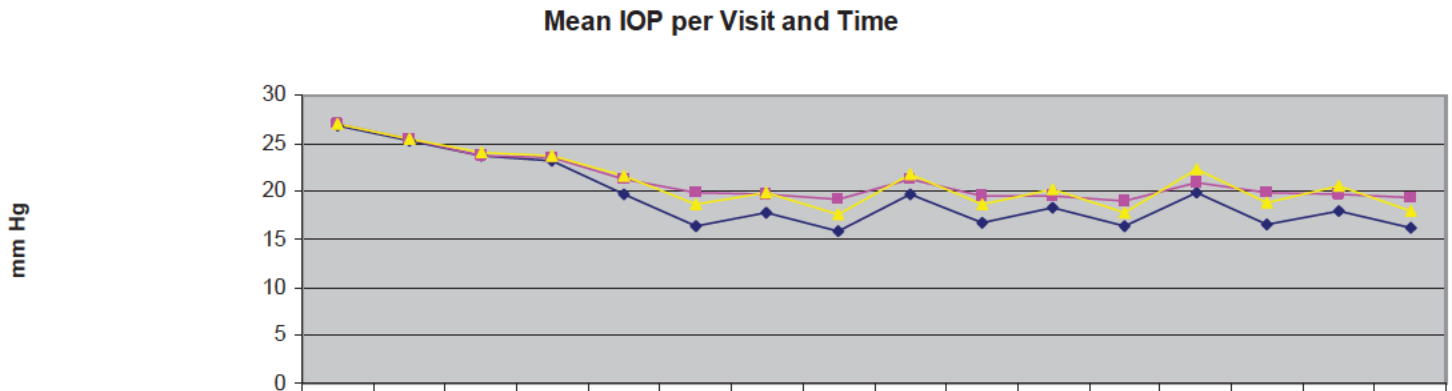
Analysis Populations:

Safety: All patients who received study drug.

Intent-to-Treat (ITT): All patients who received study drug and completed at least one scheduled on-therapy study visit.

Per-Protocol (PP): All patients who satisfied pre-randomization inclusion/exclusion criteria, received study drug, and completed at least 1 scheduled on-therapy study visit. In addition, individual patient visits and data points that did not satisfy the protocol criteria may have been excluded from the PP analysis set.

Study C-10-033 ITT Population

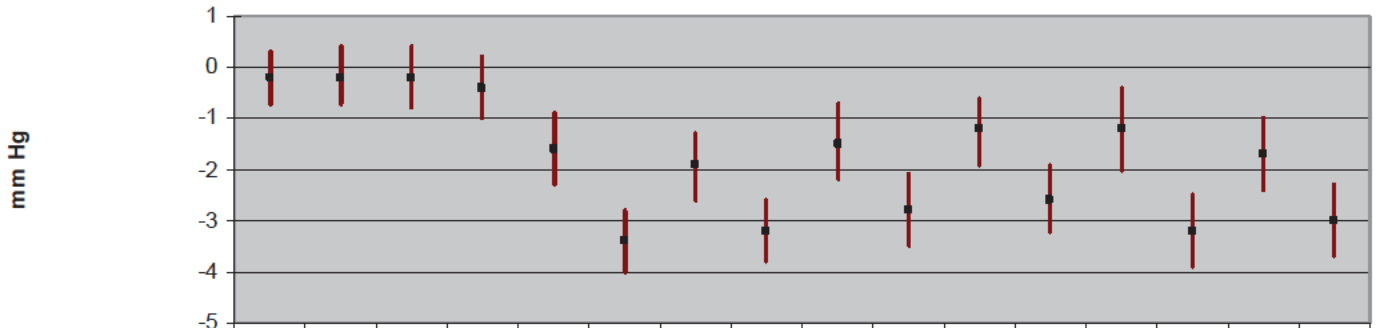


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Brinz 1%/Brim 0.2%	26.9	25.3	23.7	23.2	19.7	16.4	17.8	15.9	19.7	16.8	18.3	16.4	19.8	16.6	18	16.3
Brinz 1%	27.1	25.4	23.8	23.6	21.3	19.9	19.7	19.1	21.2	19.6	19.5	19	21	19.8	19.7	19.3
Brim 0.2%	27	25.4	24	23.7	21.6	18.6	19.8	17.6	21.8	18.6	20.3	17.8	22.4	18.8	20.5	18

Reviewer's Comments: *Baseline mean IOP of the three treatment groups is similar. The mean IOP of the fixed combination is numerically lower than the individual components at all time points measured. Among the individual components, the mean IOP of each component is similar.*

Study C-10-033 ITT Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1%) with 95% Confidence Intervals

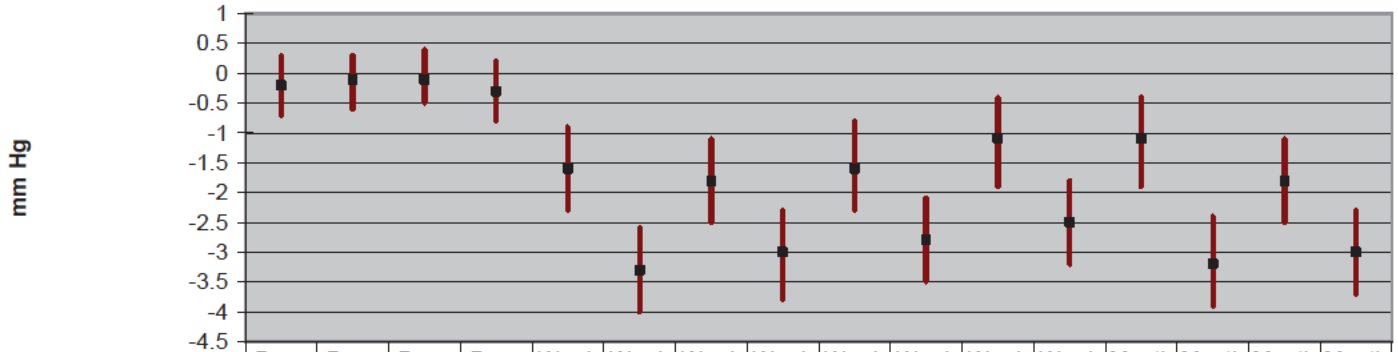


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.7	-0.7	-0.8	-1	-2.3	-4	-2.6	-3.8	-2.2	-3.5	-1.9	-3.2	-2	-3.9	-2.4	-3.7
Upper CI	0.3	0.4	0.4	0.2	-0.9	-2.8	-1.3	-2.6	-0.7	-2.1	-0.6	-1.9	-0.4	-2.5	-1	-2.3
▪ Mean Difference	-0.2	-0.2	-0.2	-0.4	-1.6	-3.4	-1.9	-3.2	-1.5	-2.8	-1.2	-2.6	-1.2	-3.2	-1.7	-3

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brinzolamide 1% is statistically significant at all time points. The mean difference ranges from -1.2 to -3.4 mm Hg.*

Study C-10-033 PP Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1%) with 95% Confidence Intervals

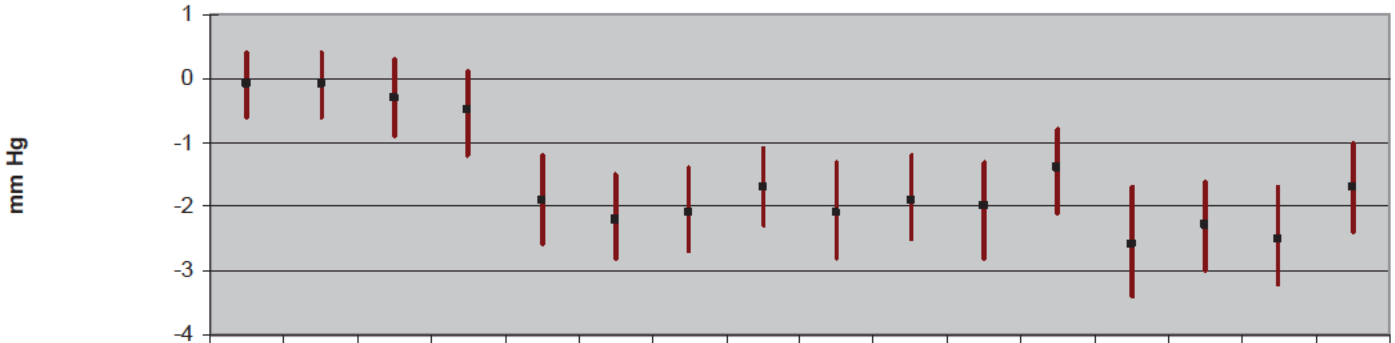


	Baseline 8AM	Baseline 10AM	Baseline 5PM	Baseline 7PM	Week 2 8AM	Week 2 10AM	Week 2 5PM	Week 2 7PM	Week 6 8AM	Week 6 10AM	Week 6 5PM	Week 6 7PM	Month 3 8AM	Month 3 10AM	Month 3 5PM	Month 3 7PM
Lower CI	-0.7	-0.6	-0.5	-0.8	-2.3	-4	-2.5	-3.8	-2.3	-3.5	-1.9	-3.2	-1.9	-3.9	-2.5	-3.7
Upper CI	0.3	0.3	0.4	0.2	-0.9	-2.6	-1.1	-2.3	-0.8	-2.1	-0.4	-1.8	-0.4	-2.4	-1.1	-2.3
■ Mean Difference	-0.2	-0.1	-0.1	-0.3	-1.6	-3.3	-1.8	-3	-1.6	-2.8	-1.1	-2.5	-1.1	-3.2	-1.8	-3

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brinzolamide 1% is statistically significant at all time points. The mean difference ranges from -1.1 to -3.3 mm Hg.*

Study C-10-033 ITT Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals

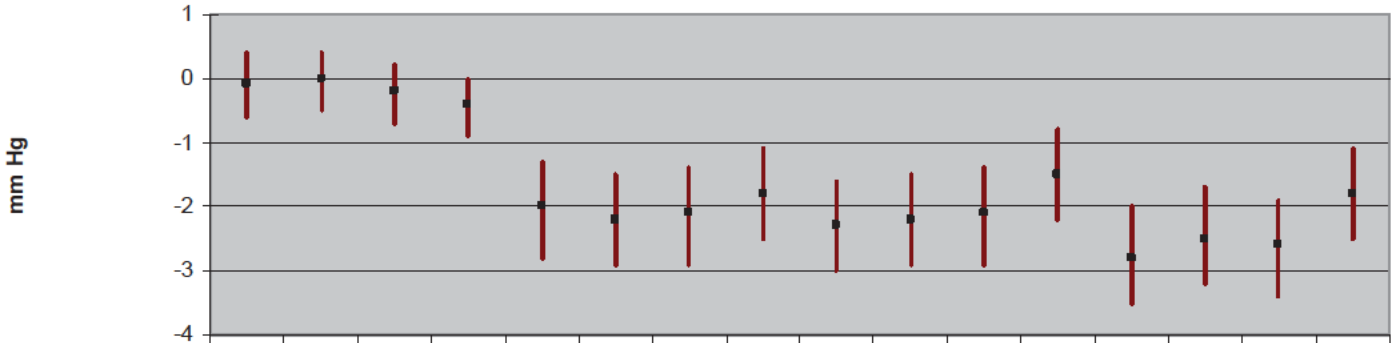


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.6	-0.6	-0.9	-1.2	-2.6	-2.8	-2.7	-2.3	-2.8	-2.5	-2.8	-2.1	-3.4	-3	-3.2	-2.4
Upper CI	0.4	0.4	0.3	0.1	-1.2	-1.5	-1.4	-1.1	-1.3	-1.2	-1.3	-0.8	-1.7	-1.6	-1.7	-1
Mean Difference	-0.1	-0.1	-0.3	-0.5	-1.9	-2.2	-2.1	-1.7	-2.1	-1.9	-2	-1.4	-2.6	-2.3	-2.5	-1.7

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brimonidine 0.2% is statistically significant at all time points. The 95% confidence intervals do not cross zero. The mean difference ranges from -1.4 to -2.6 mm Hg.*

Study C-10-033 PP Population

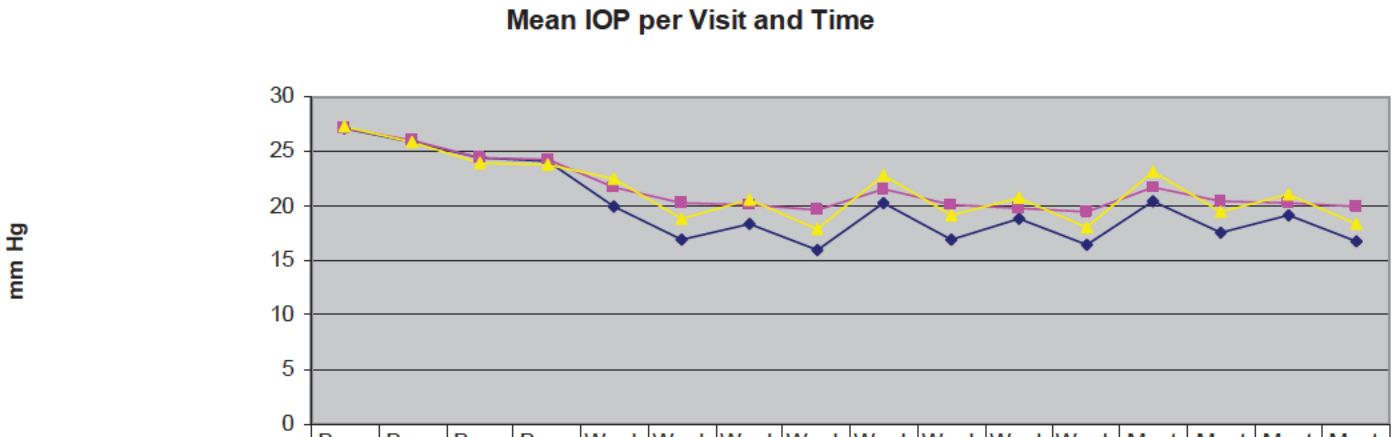
Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals



	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.6	-0.5	-0.7	-0.9	-2.8	-2.9	-2.9	-2.5	-3	-2.9	-2.9	-2.2	-3.5	-3.2	-3.4	-2.5
Upper CI	0.4	0.4	0.2	0	-1.3	-1.5	-1.4	-1.1	-1.6	-1.5	-1.4	-0.8	-2	-1.7	-1.9	-1.1
Mean Difference	-0.1	0	-0.2	-0.4	-2	-2.2	-2.1	-1.8	-2.3	-2.2	-2.1	-1.5	-2.8	-2.5	-2.6	-1.8

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brimonidine 0.2% is statistically significant at all time points. The 95% confidence intervals do not cross zero. The mean difference ranges from -1.5 to -2.6 mm Hg.*

Study C-10-039 ITT Population

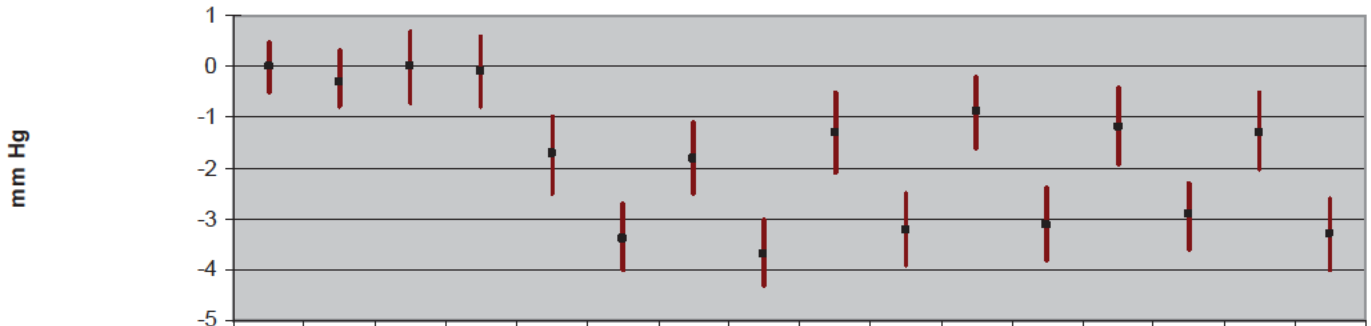


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Brinz 1%/Brim 0.2%	27.2	25.8	24.4	24.1	20	16.9	18.3	16	20.2	16.9	18.8	16.4	20.5	17.5	19.1	16.7
Brinz 1%	27.2	26	24.4	24.2	21.7	20.3	20.1	19.7	21.5	20.1	19.8	19.5	21.7	20.4	20.3	20
Brim 0.2%	27.3	25.8	24	23.7	22.5	18.8	20.6	17.8	22.8	19.2	20.7	18	23.1	19.5	21.1	18.4

Reviewer's Comments: *Baseline mean IOP of the three treatment groups is similar. The mean IOP of the fixed combination is numerically lower than the individual components at all time points measured. Among the individual components, the mean IOP of each component is similar.*

Study C-10-039 ITT Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1%) with 95% Confidence Intervals

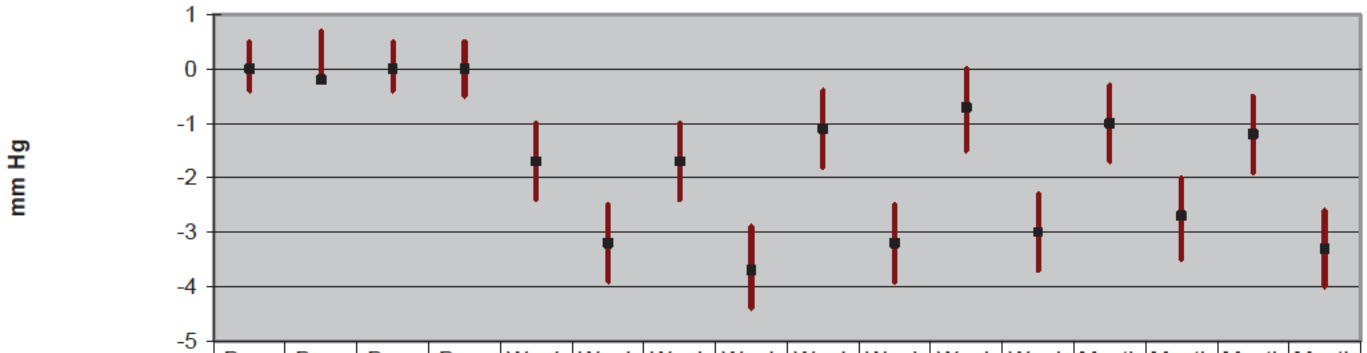


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.5	-0.8	-0.7	-0.8	-2.5	-4	-2.5	-4.3	-2.1	-3.9	-1.6	-3.8	-1.9	-3.6	-2	-4
Upper CI	0.5	0.3	0.7	0.6	-1	-2.7	-1.1	-3	-0.5	-2.5	-0.2	-2.4	-0.4	-2.3	-0.5	-2.6
▪ Mean Difference	0	-0.3	0	-0.1	-1.7	-3.4	-1.8	-3.7	-1.3	-3.2	-0.9	-3.1	-1.2	-2.9	-1.3	-3.3

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brinzolamide 1% is statistically significant at all time points. The 95% confidence intervals do not cross zero. The mean difference ranges from -0.9 to -3.7 mm Hg.*

Study C-10-039 PP Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1%) with 95% Confidence Intervals

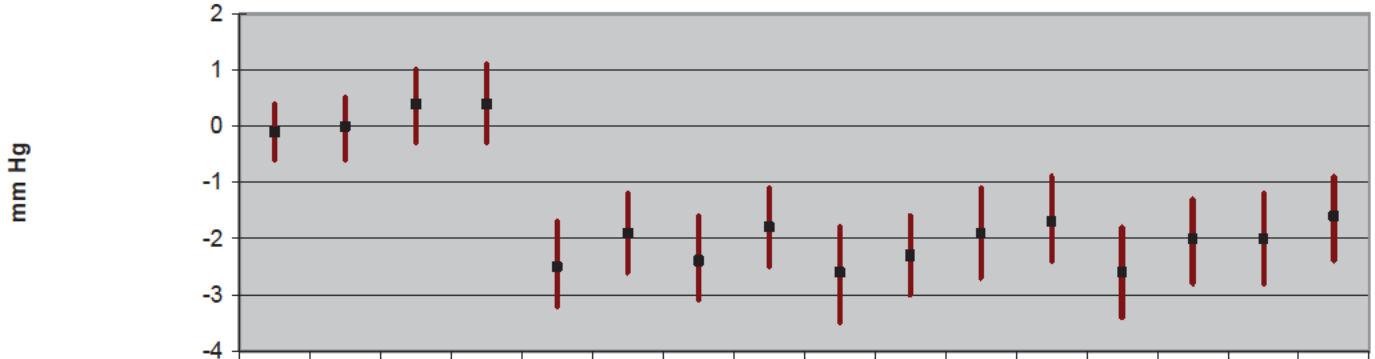


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.4	0.7	-0.4	-0.5	-2.4	-3.9	-2.4	-4.4	-1.8	-3.9	-1.5	-3.7	-1.7	-3.5	-1.9	-4
Upper CI	0.5	0.2	0.5	0.5	-1	-2.5	-1	-2.9	-0.4	-2.5	0	-2.3	-0.3	-2	-0.5	-2.6
Mean Difference	0	-0.2	0	0	-1.7	-3.2	-1.7	-3.7	-1.1	-3.2	-0.7	-3	-1	-2.7	-1.2	-3.3

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brinzolamide 1% is statistically significant at all time points except at Week 6 (3PM). The 95% confidence intervals cross zero at Week 6 (3PM). The mean difference ranges from -0.7 to -3.7 mm Hg.*

Study C-10-039 ITT Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals

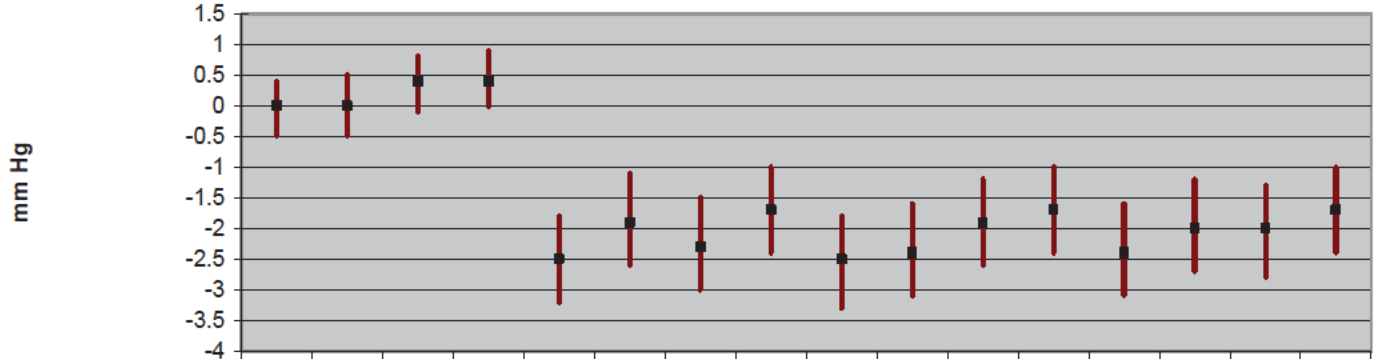


	Base line 8AM	Base line 10AM	Base line 3PM	Base line 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.6	-0.6	-0.3	-0.3	-3.2	-2.6	-3.1	-2.5	-3.5	-3	-2.7	-2.4	-3.4	-2.8	-2.8	-2.4
Upper CI	0.4	0.5	1	1.1	-1.7	-1.2	-1.6	-1.1	-1.8	-1.6	-1.1	-0.9	-1.8	-1.3	-1.2	-0.9
■ Mean Difference	-0.1	0	0.4	0.4	-2.5	-1.9	-2.4	-1.8	-2.6	-2.3	-1.9	-1.7	-2.6	-2	-2	-1.6

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brimonidine 0.2% is statistically significant at all time points. The 95% confidence intervals do not cross zero. The mean difference ranges from -1.6 to -2.6 mm Hg.*

Study C-10-039 PP Population

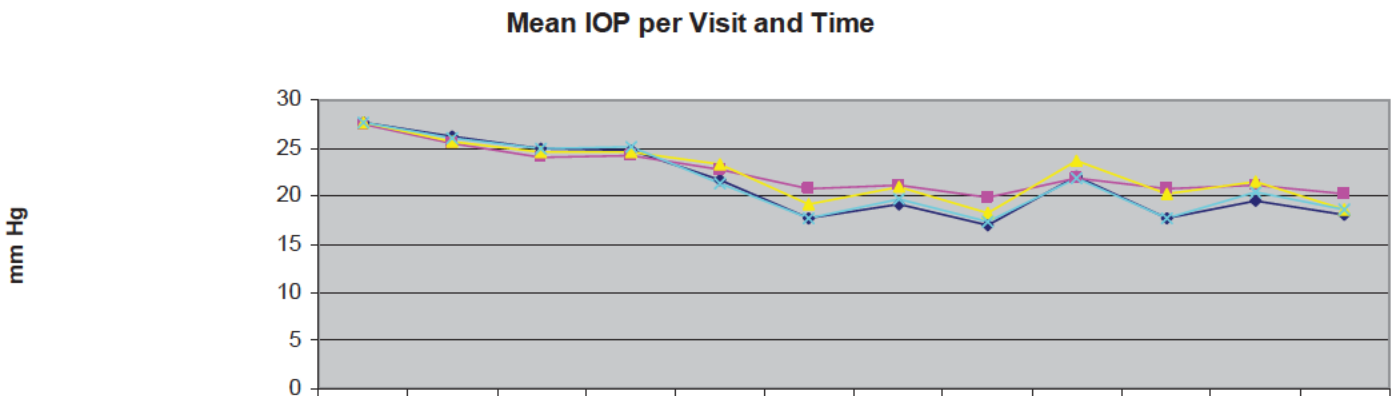
Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals



	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.5	-0.5	-0.1	0	-3.2	-2.6	-3	-2.4	-3.3	-3.1	-2.6	-2.4	-3.1	-2.7	-2.8	-2.4
Upper CI	0.4	0.5	0.8	0.9	-1.8	-1.1	-1.5	-1	-1.8	-1.6	-1.2	-1	-1.6	-1.2	-1.3	-1
■ Mean Difference	0	0	0.4	0.4	-2.5	-1.9	-2.3	-1.7	-2.5	-2.4	-1.9	-1.7	-2.4	-2	-2	-1.7

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brimonidine 0.2% is statistically significant at all time points. The 95% confidence intervals do not cross zero. The mean difference ranges from -1.7 to -2.5 mm Hg.*

Study C-09-038 ITT Population

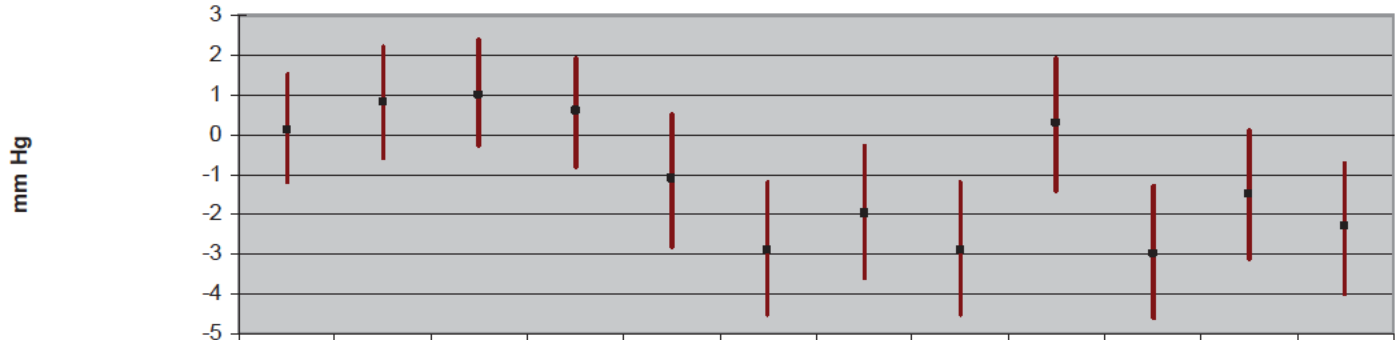


	Base line 8AM	Base line 10AM	Base line 3PM	Base line 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Brinz 1%/Brim 0.2%	27.6	26.2	25	24.8	21.7	17.8	19.1	17	22.1	17.7	19.6	18
Brinz 1%	27.5	25.4	24	24.2	22.8	20.7	21.1	19.9	21.8	20.7	21.1	20.3
Brim 0.2%	27.7	25.6	24.5	24.6	23.4	19.2	20.9	18.2	23.6	20.3	21.5	18.6
Brinz 1%+Brim 0.2%	27.7	26.1	25	25.2	21.3	17.8	19.7	17.3	21.8	17.7	20.4	18.7

Reviewer's Comments: *Baseline mean IOP of the four treatment groups is similar. The mean IOP of the fixed combination and brinzolamide 1% and brimonidine 0.2% given concomitantly is numerically lower than brinzolamide 1% at all time points measured except Week 6 (8AM). The mean IOP of the fixed combination is numerically lower than brimonidine 0.2% at all time points measured. The mean IOP of brinzolamide 1% and brimonidine 0.2% given concomitantly is lower than brimonidine 0.2% at all time points except at Week 6 (5PM). Among the individual components, the mean IOP of each component is similar.*

Study C-09-038 ITT Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1%) with 95% Confidence Intervals

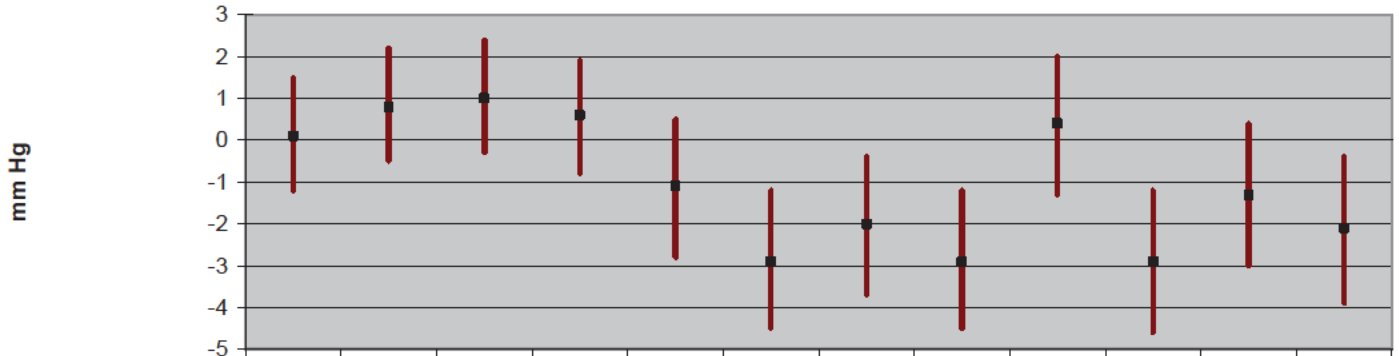


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Lower CI	-1.2	-0.6	-0.3	-0.8	-2.8	-4.5	-3.6	-4.5	-1.4	-4.6	-3.1	-4
Upper CI	1.5	2.2	2.4	1.9	0.5	-1.2	-0.3	-1.2	1.9	-1.3	0.1	-0.7
■ Mean Difference	0.1	0.8	1	0.6	-1.1	-2.9	-2	-2.9	0.3	-3	-1.5	-2.3

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brinzolamide 1% is not statistically significant at all time points. The 95% confidence intervals cross zero at Week 2 (8AM) and Week 6 (8AM, 3PM). The mean difference ranges from 0.3 to -3.0 mm Hg.*

Study C-09-038 PP Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1%) with 95% Confidence Intervals

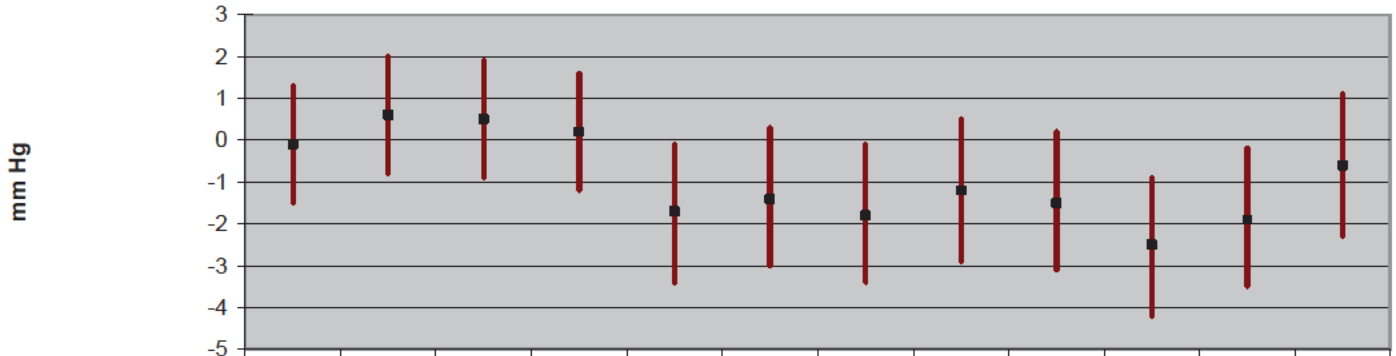


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Lower CI	-1.2	-0.5	-0.3	-0.8	-2.8	-4.5	-3.7	-4.5	-1.3	-4.6	-3	-3.9
Upper CI	1.5	2.2	2.4	1.9	0.5	-1.2	-0.4	-1.2	2	-1.2	0.4	-0.4
■ Mean Difference	0.1	0.8	1	0.6	-1.1	-2.9	-2	-2.9	0.4	-2.9	-1.3	-2.1

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brinzolamide 1% is not statistically significant at all time points. The 95% confidence intervals cross zero at Week 2 (8AM) and Week 6 (8AM, 3PM). The mean difference ranges from 0.4 to -2.9 mm Hg.*

Study C-09-038 ITT Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals

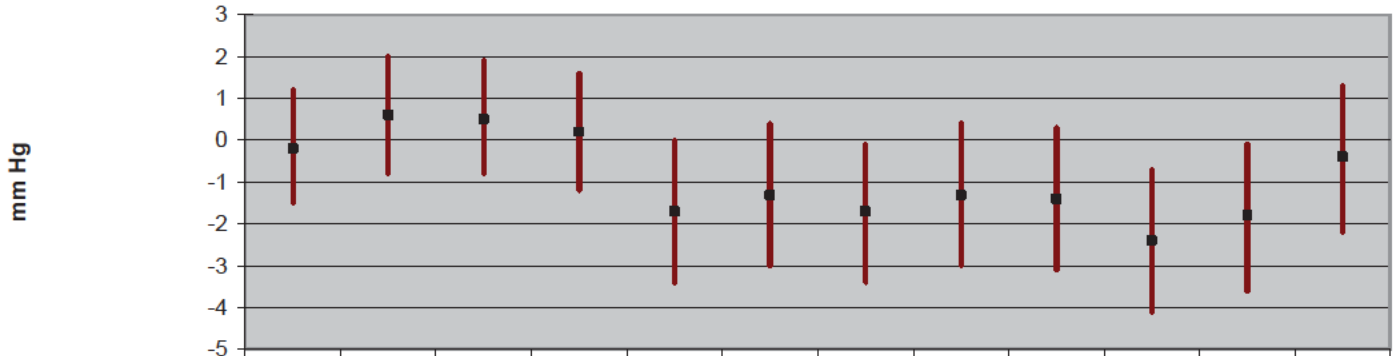


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Lower CI	-1.5	-0.8	-0.9	-1.2	-3.4	-3	-3.4	-2.9	-3.1	-4.2	-3.5	-2.3
Upper CI	1.3	2	1.9	1.6	-0.1	0.3	-0.1	0.5	0.2	-0.9	-0.2	1.1
■ Mean Difference	-0.1	0.6	0.5	0.2	-1.7	-1.4	-1.8	-1.2	-1.5	-2.5	-1.9	-0.6

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brimonidine 0.2% is not statistically significant at all time points. The 95% confidence intervals cross zero at Week 2 (10AM, 5PM) and Week 6 (8AM, 5PM). The mean difference ranges from -0.6 to -2.5 mm Hg.*

Study C-09-038 PP Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals

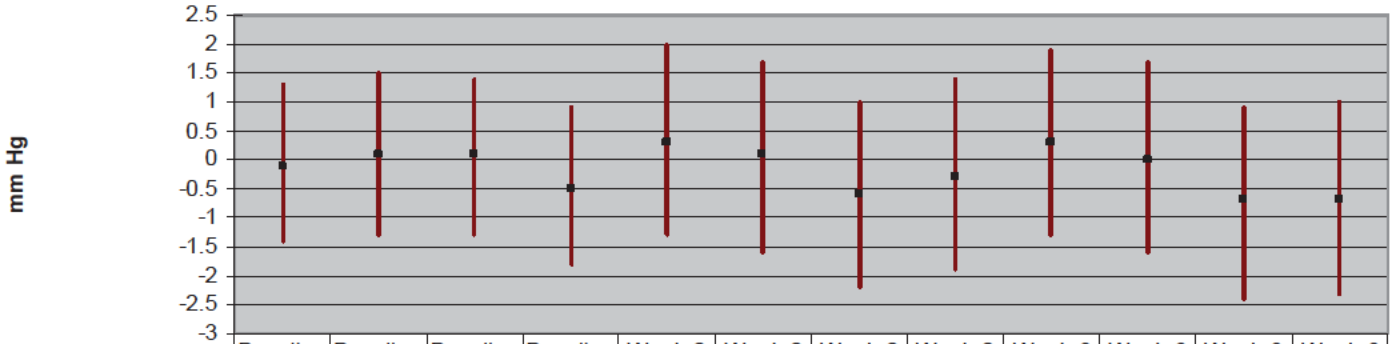


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Lower CI	-1.5	-0.8	-0.8	-1.2	-3.4	-3	-3.4	-3	-3.1	-4.1	-3.6	-2.2
Upper CI	1.2	2	1.9	1.6	0	0.4	-0.1	0.4	0.3	-0.7	-0.1	1.3
■ Mean Difference	-0.2	0.6	0.5	0.2	-1.7	-1.3	-1.7	-1.3	-1.4	-2.4	-1.8	-0.4

Reviewer's Comments: *The mean IOP at baseline for the two treatment groups is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference between the fixed combination and brimonidine 0.2% is not statistically significant at all time points. The 95% confidence intervals cross zero at Week 2 (8AM, 10AM, 5PM) and Week 6 (8AM, 5PM). The mean difference ranges from -0.4 to -2.4 mm Hg.*

Study C-09-038 ITT Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1% plus Brimonidine 0.2%) with 95% Confidence Intervals

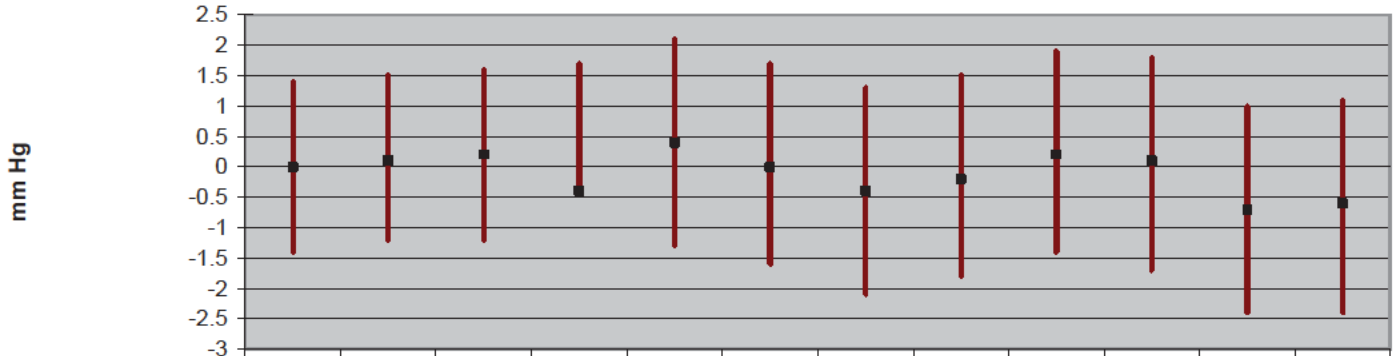


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Lower CI	-1.4	-1.3	-1.3	-1.8	-1.3	-1.6	-2.2	-1.9	-1.3	-1.6	-2.4	-2.3
Upper CI	1.3	1.5	1.4	0.9	2	1.7	1	1.4	1.9	1.7	0.9	1
▪ Mean Difference	-0.1	0.1	0.1	-0.5	0.3	0.1	-0.6	-0.3	0.3	0	-0.7	-0.7

Reviewer's Comments: *The mean IOP of the two treatment groups at baseline is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference in IOP between the fixed combination and brinzolamide 1% and brimonidine 0.2% given concomitantly is not statistically significant at all time points measured and ranges from 0.3 to -0.7 mmHg. The 95% confidence intervals cross zero at all time points measured. The IOP lowering ability of the fixed combination and brinzolamide 1% and brimonidine 0.2% given concomitantly is not equivalent. The 95% confidence intervals of the mean difference is greater than 1.5 mmHg at Week 2 (8AM, 10AM) and Week 6 (8AM, 10AM).*

Study C-09-038 ITT Population

Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brinzolamide 1% plus Brimonidine 0.2%) with 95% Confidence Intervals



	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Lower CI	-1.4	-1.2	-1.2	1.7	-1.3	-1.6	-2.1	-1.8	-1.4	-1.7	-2.4	-2.4
Upper CI	1.4	1.5	1.6	1	2.1	1.7	1.3	1.5	1.9	1.8	1	1.1
■ Mean Difference	0	0.1	0.2	-0.4	0.4	0	-0.4	-0.2	0.2	0.1	-0.7	-0.6

Reviewer's Comments: *The mean IOP of the two treatment groups at baseline is comparable. The 95% confidence intervals cross zero at all time points measured at baseline. The mean difference in IOP between the fixed combination and brinzolamide 1% and brimonidine 0.2% given concomitantly is not statistically significant at all time points measured and ranges from 0.4 to -0.7 mmHg. The 95% confidence intervals cross zero at all time points measured. The IOP lowering ability of the fixed combination and brinzolamide 1% and brimonidine 0.2% given concomitantly is not equivalent. The 95% confidence intervals of the mean difference is greater than 1.5 mmHg at Week 2 (8AM, 10AM) and Week 6 (8AM, 10AM).*

6.1.5 Subpopulations

For studies C-09-038, C-10-033 and C-10-039, the effects of age, gender, race, ethnicity, iris color, and diagnosis on the IOP-reducing effect of the fixed combination were investigated.

Reviewer's Comments:

No clinically significant effects were identified.

6.1.6 Analysis of Clinical Information Relevant to Dosing Recommendations

The optimal dosing regimen for the individual components (brinzolamide ophthalmic suspension and brimonidine tartrate ophthalmic solution) of the fixed combination (brinzolamide/ brimonidine) has been previously investigated. The recommended dosing regimen for both drug products is three times daily administration.

6.1.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

In study C-09-038 subjects received treatment for 6 weeks. In studies C-10-033 and C-10-039 subjects received treatment for 3and 6 months respectively. No evidence of tolerance was detected.

6.1.8 Additional Efficacy Issues/Analyses

There are no additional efficacy issues.

7 Review of Safety

7.1 Methods

Primary Data Used to Evaluate Safety

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
C-10-010 Phase1	Parallel-group, multi-center, randomized, open-label PK study Oral	Healthy volunteers 18 years or more	Oral brinzolamide + brinzolamide/ brimonidine Oral brinzolamide + brinzolamide/ brimonidine	1 drop TID OU 1 drop BID OU 1 drop	13 weeks 13 weeks 13 weeks	144 subjects in a ratio of 1:1:1:1:1:1 (24:24:24:24:24:24)

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
			Oral brinzolamide + brinzolamide Oral brinzolamide + brinzolamide Brimonidine Brimonidine	TID OU 1 drop BID OU 1 drop TID OU 1 drop BID OU	13 weeks 1 week 1 week	
C-09-038 Phase 2	Parallel-group, multi-center, randomized, observer-masked, active-controlled, proof of concept study	Patients 18 years or more with open-angle glaucoma or ocular hypertension	Brinzolamide/ brimonidine Brinzolamide plus brimonidine Brinzolamide Brimonidine	1 drop TID OU	6 weeks	170 subjects in a ratio of 1:1:1:1 (41:44:44:41)
C-11-002 Phase 2	Parallel-group, multi-center, randomized, double-masked, active-controlled ocular comfort descriptive study	Patients 18 years or more with open-angle glaucoma or ocular hypertension	Brinzolamide/ brimonidine Brinzolamide Brimonidine	1 drop TID OU	1 week	101 subjects in a ratio of 1:1:1 (33:34:34)
C-10-033 Phase 3	Parallel-group, multi-center, randomized, double-masked, active-controlled, safety and efficacy study	Patients 18 years or more with open-angle glaucoma or ocular hypertension	Brinzolamide/ brimonidine Brinzolamide Brimonidine	1 drop TID OU	3 months	660 subjects in a ratio of 1:1:1 (214:226:220)
C-10-039 Phase 3	Parallel-group, multi-center, randomized, double-masked active-controlled,	Patients 18 years or more with open-angle glaucoma or ocular	Brinzolamide/ brimonidine Brinzolamide	1 drop TID OU	3 months plus 3 additional months for safety	690 subjects in a ratio of 1:1:1 (221:234:235)

Protocol	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing duration	Total No. Subjects/Patients Enrolled
	safety and efficacy study	hypertension	Brimonidine			

7.1.2 Categorization of Adverse Events

Routine clinical testing was used to establish the safety of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.). This was adequately addressed in the design and conduct of the clinical trials. All adverse events were coded using a MedDRA dictionary.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The adverse events for studies C-10-33 and C-10-039 were pooled. The adverse events for studies C-10-010, C-11-002, and C-09-038 were evaluated individually.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 555 subjects were exposed to brinzolamide/brimonidine.

Overview of Exposure to Study Drug by Protocol

Protocol #	Safety N	Brinzolamide/ Brimonidine	Brinzolamide + Brimonidine	Brinzolamide	Brimonidine
C-10-010	142	47		47	48
C-09-038	170	40	44	44	41
C-11-002	101	33		34	34
C-10-033	660	214		226	220
C-10-039	690	221		234	235
Total	**1763**	**555**	**44**	**585**	**578**

Distribution of Subjects by Study and Duration of Treatment for brinzolamide/brimonidine

Duration of Treatment (days)	Study Number: Number of Subjects
1 to ≤ 17	C-11-002: 33 C-09-038: 01 C-10-033: 15 C-10-039: 10

Duration of Treatment (days)	Study Number: Number of Subjects
	Total: 59
18 to ≤ 45	C-09-038: 39 C-10-033: 05 C-10-039: 11 **Total: 55**
46 to ≤ 94	C-10-010: 47 C-10-033: 183 C-10-039: 14 **Total: 244**
95 to ≤ 187	C-10-033: 11 C-10-039: 174 **Total: 185**
> 187	C-10-039: 12 **Total: 12**
	TOTAL: 555

7.2.2 Explorations for Dose Response

Dose-response of the individual components (brinzolamide ophthalmic suspension and brimonidine tartrate ophthalmic solution) of the fixed combination (brinzolamide/ brimonidine) has been previously investigated in NDA 20-816 and NDA 20-613, respectively.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with brinzolamide/brimonidine.

7.2.4 Routine Clinical Testing

The routine clinical testing used to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the submitted clinical studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

No drug interactions were reported in any of the clinical trials.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events reported during the development of brinzolamide/brimonidine are consistent with those reported with the individual components. The assessments of these adverse events in the clinical trials were adequate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the clinical development of brinzolamide/brimonidine.

7.3.2 Other Serious Adverse Events

No serious adverse events were reported in studies C-10-010 and C-11-002.

There were a total of 40 serious adverse events across all treatment groups in all masked phase 2 and phase 3 studies (Studies C-09-038, C-10-033 and C-10-039) during the clinical development of brinzolamide/brimonidine.

Listing of Patients with Serious Adverse Events – Studies C-09-038, C-10-033 and C-10-039

Protocol	Subject	Age (yrs)	Sex	Treatment	Onset Day	Adverse event	DC'D Due AE
C-10-033	4910	67	F	Brinz/Brim TID	31	Cardiac pacemaker insertion	No
C-10-033	3253	81	F	Brinz/Brim TID	6	Vertigo	No
C-10-039	1203	64	M	Brinz/Brim TID	29	Bronchitis	No
C-10-039	1205	49	F	Brinz/Brim TID	25	Retinal detachment	Yes
C-10-039	1205	49	F	Brinz/Brim TID	61	Retinal tear	No
C-10-039	1205	49	F	Brinz/Brim TID	76	Retinal tear	No
C-10-039	3853	95	M	Brinz/Brim TID	87	Injury	Yes
C-10-039	2766	54	M	Brinz/Brim TID	17	Nephrectomy	No
C-10-039	2108	39	M	Brinz/Brim TID	141	Appendicitis	No
C-10-039	3406	60	F	Brinz/Brim TID	102	Chest pain	No
C-10-039	2953	80	M	Brinz/Brim TID	126	Pneumonia	No
C-09-038	1122	71	M	Brinz/Brim TID	40	Abdominal pain	Yes
C-09-038	1122	71	M	Brinz/Brim TID	40	Cholecystitis	Yes
C-09-038	1818	71	F	Brinz + Brim TID	8	Chest pain	No
C-09-038	1818	71	F	Brinz + Brim TID	8	Dyspnoea	No
C-10-033	3609	54	F	Brinz TID	32	Amnesia	Yes
C-10-033	4414	61	F	Brinz TID	29	Vulval neoplasm	No
C-10-033	4704	79	F	Brinz TID	71	Anaemia	No
C-10-033	4704	79	F	Brinz TID	71	Angina pectoris	No
C-10-033	4907	75	M	Brinz TID	10	Vertebroplasty	No
C-10-033	2901	61	M	Brinz TID	63	Collapse of lung	No
C-10-033	1801	68	M	Brinz TID	8	Chest pain	Yes
C-10-039	1805	85	F	Brinz TID	3	Amnesia	No
C-10-039	6751	82	M	Brinz TID	163	Cholecystitis	No
C-10-039	1001	80	M	Brinz TID	111	Delirium	No
C-10-039	3310	58	F	Brinz TID	129	Endometrial hyperplasia	No
C-10-039	3410	52	F	Brinz TID	149	Intervertebral disc operation	No

Protocol	Subject	Age (yrs)	Sex	Treatment	Onset Day	Adverse event	DC'D Due AE
C-10-039	4910	65	M	Brinz TID	102	Pancreatic carcinoma	Yes
C-10-039	1201	69	M	Brinz TID	147	Vertigo	No
C-10-033	4916	55	F	Brim TID	66	Chest pain	No
C-10-033	4916	55	F	Brim TID	77	Chest pain	No
C-10-033	1209	63	F	Brim TID	91	Injury	Yes
C-10-039	4813	68	F	Brim TID	37	Asthenia	No
C-10-039	9104	81	M	Brim TID	50	Atrial fibrillation	No
C-10-039	1405	71	M	Brim TID	7	Benign prostatic hyperplasia	No
C-10-039	1405	71	M	Brim TID	7	Prostatitis	No
C-10-039	3220	76	M	Brim TID	86	Otitis media chronic	No
C-10-039	2302	74	F	Brim TID	69	Osteoarthritis	No
C-10-039	3411	76	F	Brim TID	160	Knee arthroplasty	No
C-10-039	2608	87	F	Brim TID	91	Pulmonary embolism	No

7.3.3 Dropouts and/or Discontinuations

All of the subjects in study C-11-002 completed the study.

Patient Discontinuation – Study 10-010

Patients	Total N (%)	Brinz/Brim TID N (%)	Brinz TID N (%)	Brim TID N (%)	Brinz/Brim TID N (%)	Brinz BID N (%)	Brim BID N (%)
Total randomized	144 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)
Completed Study	136 (94.4)	19 (79.2)	21 (87.5)	24 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)
Discontinued	8 (5.6)	5 (20.8)	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to F/U	1 (0.7)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Noncompliance	4 (2.8)	4 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient decision	3 (2.1)	1 (4.2)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Patient Discontinuation – Study 09-038

Patients	Total N (%)	Brinz/Brim TID N (%)	Brinz + Brim TID N (%)	Brinz TID N (%)	Brim TID N (%)
Total randomized	170 (100.0)	41 (100.0)	44 (100.0)	44 (100.0)	41 (100.0)
Completed Study	148 (87.1)	32 (78.0)	40 (90.9)	39 (88.6)	37 (90.2)

Patients	Total N (%)	Brinz/Brim TID N (%)	Brinz + Brim TID N (%)	Brinz TID N (%)	Brim TID N (%)
Discontinued	22 (12.9)	9 (22.0)	4 (9.1)	5 (11.4)	4 (9.8)
Adverse event	1 (0.6)	4 (9.8)	0 (0.0)	0 (0.0)	2 (4.9)
Inadequate control of IOP	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Patient has travel plans	1 (0.6)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Family emergency	1 (0.6)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Terminated by Sponsor	13 (7.6)	4 (9.8)	4 (9.1)	4 (9.1)	1 (2.4)

Patient Discontinuation – Study 10-033

Patients	Total N (%)	Brinz/Brim TID N (%)	Brinz TID N (%)	Brim TID N (%)
Total randomized	660 (100.0)	216 (100.0)	225 (100.0)	219 (100.0)
Completed Study	594 (90.0)	189 (87.5)	213 (94.7)	192 (87.7)
Discontinued Study:	66 (10.0)	27 (12.5)	12 (5.3)	27 (12.3)
Adverse event	44 (6.7)	21 (9.7)	7 (3.1)	16 (7.3)
Lost to follow-up	2 (0.3)	1 (0.5)	0 (0.0)	1 (0.5)
Patient's decision	12 (1.8)	2 (0.9)	3 (1.3)	7 (3.2)
Noncompliance	1 (0.2)	1 (0.5)	0 (0.0)	0 (0.0)
Protocol violation	3 (0.5)	1 (0.5)	1 (0.4)	1 (0.5)
Inadequate control of IOP	4 (0.6)	1 (0.5)	1 (0.4)	2 (0.9)

Patient Discontinuation through Month 3 – Study 10-039

Patients	Total N (%)	Brinz/Brim TID N (%)	Brinz TID N (%)	Brim TID N (%)
Total randomized	690 (100.0)	221 (100.0)	233 (100.0)	236 (100.0)
Completed Study	615 (89.1)	196 (88.7)	216 (92.7)	203 (86.0)
Discontinued Study:	75 (10.9)	25 (11.3)	17 (7.3)	33 (14.0)
Adverse event	46 (6.7)	19 (8.6)	8 (3.4)	19 (8.1)
Patient's decision	3 (0.4)	2 (0.9)	0 (0.0)	1 (0.4)
Noncompliance	1 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)
Protocol violation	3 (0.4)	1 (0.5)	2 (0.9)	0 (0.0)
Inadequate control of IOP	21 (3.0)	1 (0.5)	7 (3.0)	13 (5.5)
Patient did not meet entrance criteria	1 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)

Patient Discontinuation through Month 6 – Study 10-039

Patients	Total N (%)	Brinz/Brim TID N (%)	Brinz TID N (%)	Brim TID N (%)
Total randomized	690 (100.0)	221 (100.0)	233 (100.0)	236 (100.0)
Completed Study	548 (79.4)	163 (73.8)	206 (88.4)	179 (75.8)
Discontinued Study:	142 (20.6)	58 (26.2)	27 (11.6)	57 (24.2)
Adverse event	90 (13.0)	42 (19.0)	10 (4.3)	38 (16.1)
Patient's decision	13 (1.9)	6 (2.7)	5 (2.1)	2 (0.8)
Noncompliance	1 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)
Protocol violation	4 (0.6)	1 (0.5)	3 (1.3)	0 (0.0)
Inadequate control of IOP	33 (4.8)	7 (3.2)	9 (3.9)	17 (7.2)
Patient did not meet entrance criteria	1 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuation are presented in section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable. No specific safety issues were identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Number (%) of Patients with Adverse Events Reported by ≥ 1 % of Patients
Studies C-10-033 and C-10-039 Pooled

Adverse Event	Brinz/Brim TID N=435 N (%)	Brinz TID N=460 N (%)	Brim TID N=455 N (%)
OCULAR			
Eye Disorders			
Vision blurred	23 (5.3)	30 (6.5)	1 (0.2)
Eye irritation	20 (4.6)	5 (1.1)	12 (2.6)
Eye allergy	15 (3.4)	1 (0.2)	8 (1.8)
Conjunctivitis allergic	12 (2.8)	2 (0.4)	11 (2.4)
Conjunctivitis	11 (2.5)		14 (3.1)
Ocular Hyperaemia	9 (2.1)	5 (1.1)	6 (1.3)
Eye pain	9 (2.1)	8 (1.7)	5 (1.1)
Eye pruritus	9 (2.1)	4 (0.9)	6 (1.3)
Conjunctival hyperaemia	8 (1.8)	5 (1.1)	6 (1.3)
Dry eye	6 (1.4)	4 (0.9)	8 (1.8)
NON-OCULAR			
Gastrointestinal Disorders			
Dry mouth	14 (3.2)		11 (2.4)

Adverse Event	Brinz/Brim TID N=435 N (%)	Brinz TID N=460 N (%)	Brim TID N=455 N (%)
Nervous System Disorders			
Dysgeusia	17 (3.9)	38 (8.3)	1 (0.2)

Number (%) of Patients with Adverse Events Reported by ≥ 1 % of Patients
Study C-09-038

Adverse Event	Brinz/Brim TID N=41 N (%)	Brinz + Brim TID N=44 N (%)	Brinz TID N=44 N (%)	Brim TID N-41 N (%)
OCULAR				
Eye Disorders				
Vision blurred	7 (17.1)	6 (13.6)	7 (15.9)	6 (14.6)
Eye irritation	2 (4.9)	2 (4.5)	2 (4.5)	2 (4.5)
Ocular Hyperaemia	3 (7.3)		2 (4.5)	
Eye pruritis	2 (4.9)		1 (2.3)	
Foreign body sensation in eyes	1 (2.4)		1 (2.3)	1 (2.4)
Conjunctivitis	1 (2.4)			1 (2.4)
Eyelid margin crusting	1 (2.4)		1 (2.3)	
Lacrimation increased	1 (2.4)			1 (2.4)
Conjunctival oedema	1 (2.4)			
Erythema of eyelid	1 (2.4)			
Photophobia	1 (2.4)			
Punctate keratitis	1 (2.4)			
Eye pain		3 (6.8)	1 (2.3)	
Abnormal sensation in eye		1 (2.3)	2 (4.5)	
Dry eye				
Eye discharge			1 (2.3)	
NON-OCULAR				
Gastrointestinal Disorders				
Dry mouth	**2 (4.9)**			
Dyspepsia	1 (2.4)			
Immune System Disorders				
Hypersensitivity				1 (2.4)
Investigations				
Corneal staining			**1 (2.3)**	1 (2.4)
Nervous System Disorders				
Dysgeusia	2 (4.9)		2 (4.5)	
Somnolence	1 (2.4)			

Number (%) of Patients with Adverse Events Reported by ≥ 1 % of Patients
Study C-11-002

Adverse Event	Brinz/Brim TID N=33 N (%)	Brinz TID N=34 N (%)	Brim TID N=34 N (%)
OCULAR			
Eye Disorders			
Vision blurred	2 (6.1)	4 (11.8)	
Eye irritation	2 (6.1)	3 (8.8)	
Eye pain	1 (3.0)	1 (2.9)	
Foreign body sensation in eyes	1 (3.0)		1 (2.9)
Conjunctivitis allergic			1 (2.9)
Eye pruritis			1 (2.9)
NON-OCULAR			
General Disorders and Administration Site Conditions			
Medication residue	**1 (3.0)**		
Nervous System Disorders			
Dysgeusia	2 (6.1)	1 (2.9)	
Dizziness			1 (2.9)
Skin and Subcutaneous Tissue Disorders			
Dermatitus			1 (2.9)

Number (%) of Patients with Adverse Events Reported by ≥ 1 % of Patients
Study C-10-010

Adverse Event	Oral Brinz N=96 N (%)	Brinz/ Brim TID N=23 N (%)	Brinz TID N=23 N (%)	Brim TID N-24 N (%)	Brinz/ Brim BID N=24 N (%)	Brinz BID N=24 N (%)	Brim BID N-24 N (%)
OCULAR							
Eye Disorders							
Eye irritation			1 (4.3)	1 (4.2)	5 (20.8)	7 (29.2)	2 (8.3)
Dry eye	2 (2.1)	1 (4.3)	1 (4.3)	2 (8.3)		1 (4.2)	
Conjunctivitis hyperaemia	1 (1.0)	1 (4.3)	1 (4.3)	2 (8.3)	1 (4.2)		
Lacrimation increased	2 (2.1)			1 (4.2)		1 (4.2)	
Vision blurred	1 (1.0)		1 (4.3)		2 (8.3)		
Photophobia	1 (1.0)			1 (4.2)			1 (4.2)
Eye pain			1 (4.3)		1 (4.2)		
Eye pruritus	1 (1.0)				1 (4.2)		
Ocular discomfort					1 (4.2)	1 (4.2)	
Ocular Hyperaemia			2 (8.7)				
Conjunctivitis	1 (1.0)						
Eye discharge	1 (1.0)						
Foreigh body sensation in eyes						1 (4.2)	
Hypoaesthesia eye		1 (4.3)					
NON-OCULAR							
Cardiac Disorders							
Nodal arrhythmia							

Adverse Event	Oral Brinz N=96 N (%)	Brinz/ Brim TID N=23 N (%)	Brinz TID N=23 N (%)	Brim TID N-24 N (%)	Brinz/ Brim BID N=24 N (%)	Brinz BID N=24 N (%)	Brim BID N-24 N (%)
Ear and Labyrinth Disorders							
Tinnitus		1 (4.3)					
Gastrointestinal Disorders							
Diarrhoea	**4 (4.2)**				1 (4.2)		**1 (4.2)**
Nausea	**2 (2.1)**		**1 (4.3)**			1 (4.2)	
Vomiting	1 (1.0)				1 (4.2)		
Dry mouth	1 (1.0)						
Dyspepsia	1 (1.0)						
Paraesthesia oral	1 (1.0)						
Sensitivity of teeth					1 (4.2)		
Infections and Infestations							
Sinusitis					1 (4.2)		
Metabolism and Nutrition Disorders							
Decreased appetite	1 (1.0)						
Nervous System Disorders							
Dysgeusia	3 (3.1)	2 (8.7)	1 (4.3)		5 (20.8)	8 (33.3)	
Headache	7 (7.3)	1 (4.3)		1 (4.2)	2 (8.3)	2 (8.3)	5 (20.8)
Paraesthesia	4 (4.2)				1 (4.2)		
Somnolence	1 (1.0)			1 (4.2)			
Dizziness					1 (4.2)		
Parosmia					1 (4.2)		
Psychiatric Disorders							
Dysphoria						1 (4.2)	
Respiratory, Thoracic and Mediastinal Disorders							
Postnasal drip					1 (4.2)		1 (4.2)
Nasal congestion							1 (4.2)
Nasal discomfort							1 (4.2)
Nasal dryness							1 (4.2)
Rhinorrhoea	1 (1.0)						

Reviewer's Comments:
The most common ocular adverse events (studies C-10-033 and C-10-039 pooled) were vision blurred (5%), eye irritation (5%), and eye allergy (3%). The most common nonocular adverse events were dysgeusia (4%) and dry mouth (3%).

7.4.2 Laboratory Findings

No clinical laboratory evaluations were conducted in studies C-09-038, C-11-002, C-10-033, and C-10-039. Clinical laboratory evaluations (hematology, blood chemistry and urinalysis) were performed in the clinical PK study C-10-010. No clinically significant observations were seen in patients treated with brinzolamide./brimonidine as compared to the individual components.

7.4.3 Vital Signs

Cardiovascular parameters (systolic blood pressure, diastolic blood pressure and heart rate) were measured in studies C-10-010, C-09-038, C-11-002, C-10-033, 1nd C-10-039. No clinically significant observations in cardiovascular parameters were seen in patients treated with brinzolamide/brimonidine as compared to the individual components.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed in study C-10-010. No clinically significant observations in ECGs were seen in patients treated with brinzolamide/brimonidine as compared to the individual components.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable. No special safety studies were conducted for this product.

7.4.6 Immunogenicity

Not applicable. The drug product is not expected to induce immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No dose-response or dose-ranging studies were performed for brinzolamide/brimonidine.

7.5.2 Time Dependency for Adverse Events

Not applicable. Brinzolamide/brimonidine does not have a delayed onset of action.

7.5.3 Drug-Demographic Interactions

Based on a review of adverse events sorted by age, gender and race, the events are consistent with the overall safety population.

7.5.4 Drug-Disease Interactions

A review of adverse events revealed no untoward safety issues in each of the subpopulations categorized by concomitant diseases in patients treated with brinzolamide/brimonidine as compared to the individual components.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were reported in any of the clinical trials.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been performed with the combination of brinzolamide and brimonidine. Studies were performed using the individual components in the previously approved applications for brinzolamide and brimonidine.

7.6.2 Human Reproduction and Pregnancy Data

Reproductive toxicity studies have not been performed with the combination of brinzolamide and brimonidine. Studies were performed using the individual components in the previously approved applications for brinzolamide and brimonidine.

There have been no adequate and well-controlled studies in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

A waiver of pediatric studies has been requested for the fixed combination. The individual component, brinzoalmide has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine has been studied in pediatric patients ages 2 to 7 years. Somnolence and decreased alertness was seen in 50-83% of patients ages 2 to 6 years. Brimonidine is contraindicated in children under the age of 2 years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Although there are no information is available on overdosage in humans, symptoms of overdose in humans may occur following an oral overdose of brinzolamide. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. No evidence of drug abuse was reported in the clinical trials.

There are no data to suggest that there is a withdrawal or rebound effect after cessation of brinzolamide/brimonidine.

7.7 Additional Submissions / Safety Issues

The four-month safety update was received on October 4, 2012. The safety update contains the through month 6 safety data for study C-10-039. This data is included in the evaluation of safety in the “Review of Safety” section of this review. See Section 7 above.

8 Postmarket Experience

The fixed combination brinzolamide/brimonidine is not marketed in any country. The individual components are marketed worldwide.

In the time period between the product launch of brinzolamide (April 2008) to 31 March 2012, (b) (4) units of the drug product has been sold worldwide. For brimonidine, (b) (4) units have been sold worldwide since the product launch (June 2002) to 31 March 2012.

Summary of Worldwide Postmarketing Reports by System Organ Class Received from Product Launch to 31 March 2012: Brinzolamide 1% Ophthalmic Suspension

System Organ Class	Total Number of Reports	% of Total Reports
Blood and lymphatic system disorders	12	0.2
Cardiac disorders	102	2.0
Congenital, familial, and genetic disorders	2	0.0
Ear and labyrinth disorders	66	1.3
Endocrine disorders	3	0.0
Eye disorders	1,821	36.5
Gastrointestinal disorders	355	7.1
General disorders and administration site conditions	505	10.1
Hepatobiliary disorders	11	0.2
Immune system disorders	50	1.0
Infections and infestations	80	1.6
Injury, poisoning and procedural complications	86	1.7
Investigations	202	4.0
Metabolism and nutrition disorders	23	0.4
Musculoskeletal and connective tissue disorders	125	2.5
Neoplasm benign, malignant and unspecified (including cysts and polyps)	3	0.0
Nervous system disorders	593	11.9
Pregnancy, puerperium and perinatal conditions	1	0.0
Psychiatric disorders	133	2.7
Renal and urinary disorders	45	0.9
Reproductive system and breast disorders	17	0.3
Respiratory, thoracic and mediastinal disorders	375	7.5
Skin and subcutaneous tissue disorders	343	6.9
Surgical and medical procedures	3	00
Vascular disorders	37	0.7
TOTAL	**4,993**	

Summary of Worldwide Postmarketing Reports by System Organ Class Received from Product Launch to 31 March 2012: Brimonidine 0.2% Ophthalmic Solution

System Organ Class	Total Number of Reports	% of Total Reports
Cardiac disorders	5	2.0
Eye disorders	107	43.1

System Organ Class	Total Number of Reports	% of Total Reports
Gastrointestinal disorders	23	9.3
General disorders and administration site conditions	28	11.3
Immune system disorders	1	0.4
Infections and infestations	2	0.8
Injury, poisoning and procedural complications	7	2.8
Investigations	9	3.6
Metabolism and nutrition disorders	1	0.4
Musculoskeletal and connective tissue disorders	1	0.4
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	2	0.8
Nervous system disorders	33	13.3
Psychiatric disorders	4	1.6
Respiratory, thoracic and mediastinal disorders	15	6.0
Skin and subcutaneous tissue disorders	9	3.6
Vascular disorders	1	0.4
TOTAL	**248**	

9 Appendices

9.1 Literature Review/References

N/A – An independent literature review was not conducted for this application.

9.2 Advisory Committee Meeting

No advisory committee meeting was required or convened for this drug product. The individual components of the fixed combination are approved and marketed in the United States.

9.3 Labeling Recommendations

See labeling recommendations below.

APPEARS THIS WAY ON ORIGINAL

16 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUCIOUS LIM
04/09/2013

WILLIAM M BOYD
04/09/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204251

Applicant: Alcon Research, Ltd.

Stamp Date: June 19, 2012

Drug Name: Simbrinza (brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension)

NDA/BLA Type: NDA 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	The individual active components of the combination product are approved products in the US.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 C-10-033 Pivotal Study #2 C-10-039 Indication: reduction of IOP in patients with open angle glaucoma or ocular hypertension				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____YES___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUCIOUS LIM
08/22/2012

WILLIAM M BOYD
08/27/2012