CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204251Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 18, 2013
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	204251
Applicant	Alcon Research, Ltd.
Date of Submission	June 19, 2012
PDUFA Goal Date	April 19, 2013
Proprietary Name / Established (USAN) names	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

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%].

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.

2. Background

Clinical studies for this new drug application were conducted under IND 106293.

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.

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.

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
Bausch & Lomb	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 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

Pharmacologic Class/ Applicant	Tradename	Established Name
Alcon	BetopticPilo	betaxolol hydrochloride/ pilocarpine hydrochloride
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

3. 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.

From the original Product Quality Review dated 3/13/2013 and review #2 dated 4/17/13:

DRUG SUBSTANCE:
Alcon's NDA 204-251 provides for Simbrinza (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2%, a fixed dose combination product composed of two individual active ingredients: brinzolamide and brimonidine Tartrate. Brimonidine tartrate is manufactured by two drug substance manufacturers: [redacted] (b) (4) and [redacted] (b) (4) Both are the approved manufacturers for Alcon's Brimonidine Tartrate Ophthalmic Solution (ANDA 76254). The CMC information for brimonidine tartrate produced in [redacted] (b) (4) facility is being referred to the relevant sections of ANDA 76-254 while the CMC information for brimonidine tartrate produced in [redacted] (b) (4) is being referred to DMF [redacted] (b) (4) which is current without any pending CMC issues. Brinzolamide is also manufactured two drug substance manufacturers: [redacted] (b) (4) and [redacted] (b) (4) the same manufacturers of brinzolamide for Alcon's approved Azopt (brinzolamide ophthalmic suspension) 1% in NDA 20-816. The CMC information in the current NDA (NDA 204-251) is being referred to the relevant sections of NDA 20-816.

DRUG PRODUCT:
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) [redacted] (b) (4) of the suspension.

QUANTITATIVE COMPOSITION:

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)

REGULATORY SPECIFICATIONS:

Table 3.2.P.5.1–1 Regulatory Acceptance Specifications for Brinzolamide/Brimonidine Suspension

Test	Specification
Brinzolamide Identity (TLC) [a]	(b) (4)
Brinzolamide Identity (HPLC) [a]	
Brinzolamide Assay	
Brimonidine Tartrate Identity (TLC) [a]	
Brimonidine Tartrate Identity (HPLC) [a]	
Brimonidine Tartrate Assay	
Brinzolamide Impurities [b] (b) (4)	
Brimonidine Impurities [c] (b) (4) Any Single Unspecified Impurity Total Impurities	
Benzalkonium Chloride Identity [a]	
Benzalkonium Chloride Assay	
Boric Acid Identity [a]	
Boric Acid Assay	
pH	
Osmolality	
Viscosity (b) (4)	
Appearance, Suspension Color Uniformity	White to off-white Uniform Suspension
Redispersibility	(b) (4)
Particle Size, (b) (4)	
Bacterial Endotoxins Test [a]	
Sterility Test [d]	

[a] Release test only

(b) (4)

[d] If tested, will pass

INSPECTIONS:

On April 17, 2013, the Office of Compliance made an overall recommendation of "Acceptable" for the facilities related to the NDA (see the attached establishment evaluation report).

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204251/000	**Sponsor:**	ALCON RES LTD
Org. Code:	590		6201 SOUTH FREEWAY
Priority:	4		FORT WORTH, TX 761342099
Stamp Date:	19-JUN-2012	**Brand Name:**	Brinzolamide 1% / Brimonidine Tartrate 0
PDUFA Date:	19-APR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	Brinzolamide 1% / Brimonidine Tartrate 0
District Goal:	18-FEB-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; SUSPENSION; BRINZOLAMIDE; 1% 001; SUSPENSION; BRIMONIDINE TARTRATE; .2%

FDA Contacts:	M. ZHOU	Prod Qual Reviewer		3017962163
	V. PAWAR	Micro Reviewer	(HFD-805)	3017961587
	A. CUFF	Product Quality PM	(HF-01)	3017964061
	J. MILSTEIN	Regulatory Project Mgr	(HFD-590)	3017960763
	D. MATECKA	Team Leader		3017961415

Overall Recommendation:	ACCEPTABLE	on 17-APR-2013	by T. SHARP	()	3017963208
	PENDING	on 28-DEC-2012	by EES_PROD		
	ACCEPTABLE	on 11-OCT-2012	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 20-JUL-2012	by EES_PROD		
	PENDING	on 20-JUL-2012	by EES_PROD		
	PENDING	on 20-JUL-2012	by EES_PROD		
	PENDING	on 20-JUL-2012	by EES_PROD		

Establishment:	**CFN:** 1610287 **FEI:** 1610287		
	ALCON LABORATORIES INC		
	FORT WORTH, , UNITED STATES 761342001		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	STERILE LIQUID (EXCLUDE SUSPENSIONS & EMULSIONS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-APR-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

4. Nonclinical Pharmacology/Toxicology

From the original Clinical Pharmacology Review dated 3/15/2013:

Pharmacology Toxicology did not identify substantial new safety issues. Pending resolution of the question regarding the brinzolamide carcinogenicity studies and agreement on the label, P/T has no objection to approval.

The Applicant submitted two topical ocular distribution studies for brin/brim in rabbits. The Applicant also submitted two topical ocular toxicology studies in rabbits, a 6-week study testing two doses (brin 1% / brim 0.15%; brin 2% / brim 0.2%) and a 9-month study testing two doses (brin 1% / brim 0.2%; brin 2% / brim 2%). Comparing pharmacokinetic (PK) parameters for the rabbit studies versus the clinical trials (e.g. NDA module 2.7.2 Summary of Clinical Pharmacology Studies), the Applicants concluded that systemic exposure to brimonidine is substantially higher in rabbits compared to patients. This reviewer concurs.

The two topical ocular rabbit studies for the combination product did not identify any new concerns for the local/eye toxicity.

Brimonidine is an alpha-2 adrenergic agonist, and multiple nonclinical toxicology studies with brimonidine have reported increased serum glucose, weight loss/reduced weight gain, and liver weight changes in rats, mice, rabbits, and monkeys; however, changes in liver histopathology have not been noted in previous FDA P/T reviews. Notably, hyperglycemia has not been reported clinically (for brimonidine alone or for brin/brim), suggesting these glucose and hepatic effects are species-specific.

The 6-week rabbit study with brin/brim did not detect increased serum glucose, and no liver histopathology was observed. Urinary glucose was not measured in the 6-week study.In the 9-month rabbit study with Brin/Brim, a dramatic increase in the severity of hepatocellular cytoplasmic vacuolization was observed (standard hematoxylin and eosin staining), and PAS staining found cytoplasmic glycogen accumulation.

The authors and Applicant consider the liver histopathology secondary to the increased serum glucose, and therefore not relevant to patient safety.

Both the 6-week and 9-month rabbit studies observed increased incidence of penile erection in males, and urogenital swelling and discoloration in females.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review dated 3/22/2013:

Brinzolamide, a carbonic anhydrase inhibitor (CAI), was FDA-approved in 1998 as Azopt (1%). Brimonidine, an alpha 2-adrenergic agonist, was FDA approved in 1996 and 1997 as Alphagan at strengths of 0.2% and 0.5%, respectively. Later Brimonidine was approved as Alphagan P in 2001 and 2005 at lower strengths of 0.15% and 0.1%, respectively.

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 Ndesethyl 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).

6. Sterility Assurance

From the original Product Quality Microbiology Review dated 12/21/2012:

Brinzolamide/Brimonidine Suspension will be packaged in Alcon's standard white low density polyethylene (LDPE) DROP-TAINER bottles with fill volumes of (b) (4) 8 mL (in the 10 mL bottle) with natural LDPE dispensing plug and a white polypropylene (PP) closure. (b) (4)

NDA 204251 is recommended for approval from the standpoint of product quality microbiology:

- The applicant's verification of container closure integrity is consistent with regulatory expectations for a pharmaceutical product.
- The applicant's verification of the preservative effectiveness at 39 weeks storage time and the plan to perform this test at stability end point meets the regulatory expectations.
- The applicant met the regulatory expectations for (b) (4)
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- The applicant met regulatory expectations for (b) (4)
- The applicant met regulatory expectations with regard to the Endotoxin and Sterility test methods, acceptance criteria and verification of the suitability of use of these tests.

No product quality microbiology deficiencies were identified based upon the information provided.

7. 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).

From the original Medical Officer Review dated 4/9/2013:

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.

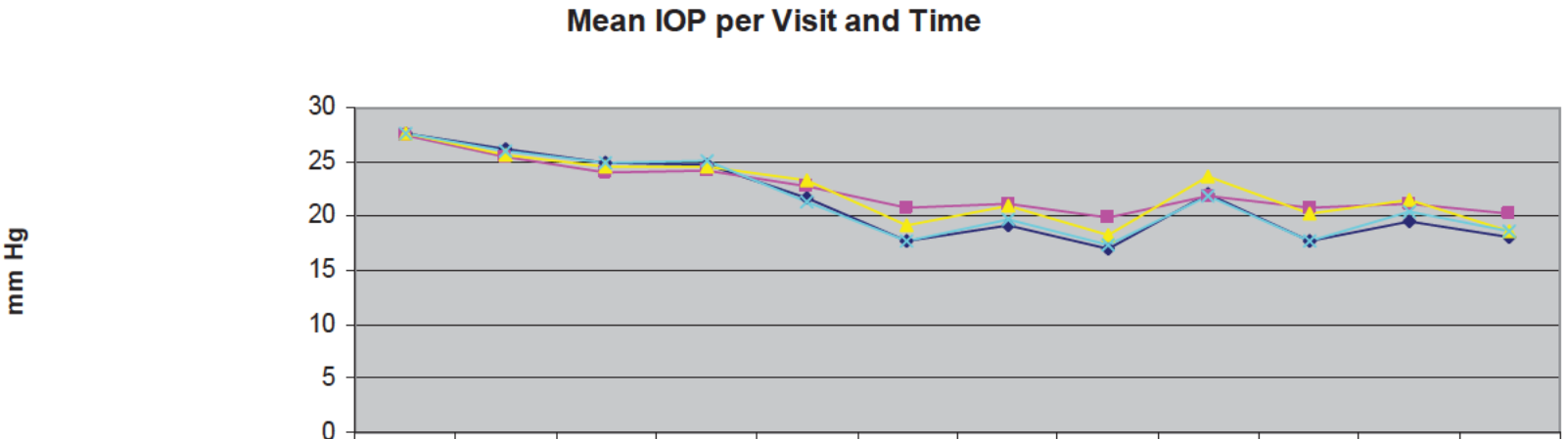
The primary efficacy endpoint for Study C-10-039 was the mean IOP at each of the assessment time points (8 AM, + 2 hrs, + 7 hrs, and + 9 hrs) at Month 3. IOP measurements were done at 8AM, 10AM, 3PM, and 5PM at Eligibility 1 Visit (E1), Eligibility 2 Visit (E2), Week 2 Visit, Week 6 Visit, Month 3 Visit,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

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

Analysis of Primary Endpoint(s)

Study C-09-038 ITT LOCF Population

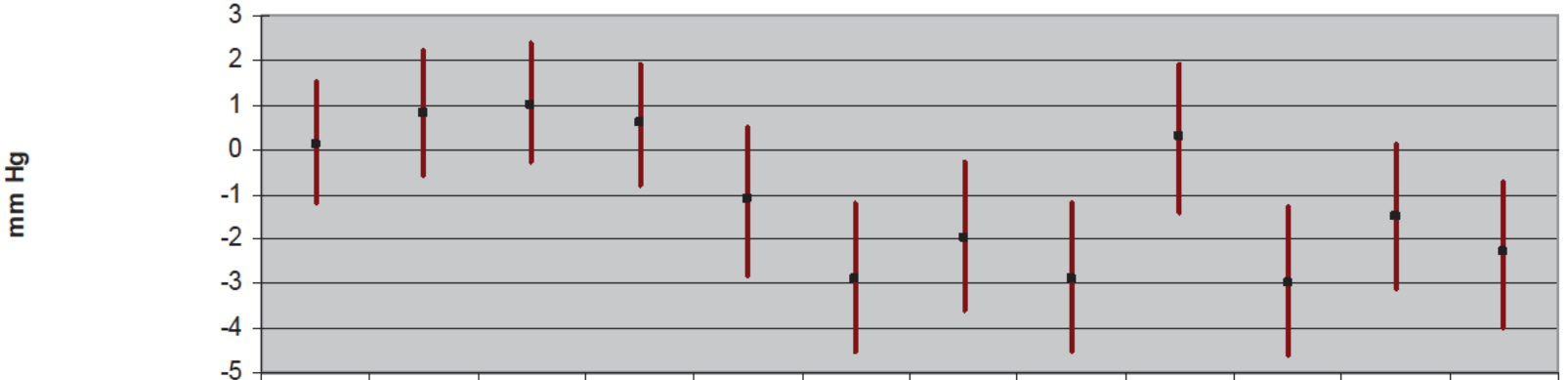


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Brinz 1%/Brim 0.2%	27.6	26.2	25	24.8	21.7	17.8	19.1	17	22.1	17.7	19.6	18
Brinz 1%	27.5	25.4	24	24.2	22.8	20.7	21.1	19.9	21.8	20.7	21.1	20.3
Brim 0.2%	27.7	25.6	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 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 LOCF Population

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

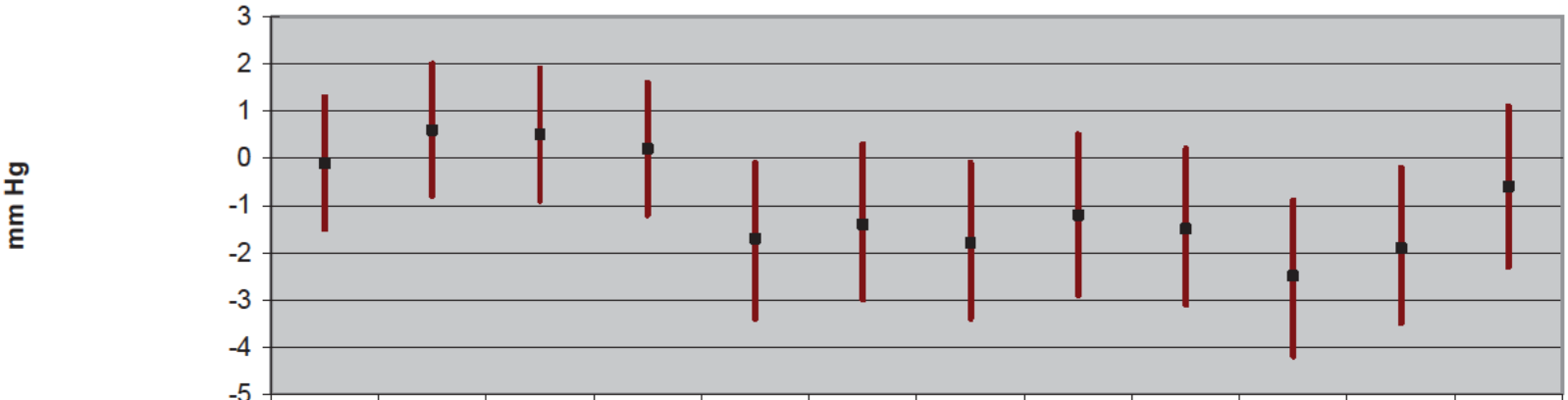


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM
Lower CI	-1.2	-0.6	-0.3	-0.8	-2.8	-4.5	-3.6	-4.5	-1.4	-4.6	-3.1	-4
Upper CI	1.5	2.2	2.4	1.9	0.5	-1.2	-0.3	-1.2	1.9	-1.3	0.1	-0.7
• Mean Difference	0.1	0.8	1	0.6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

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 ITT LOCF Population

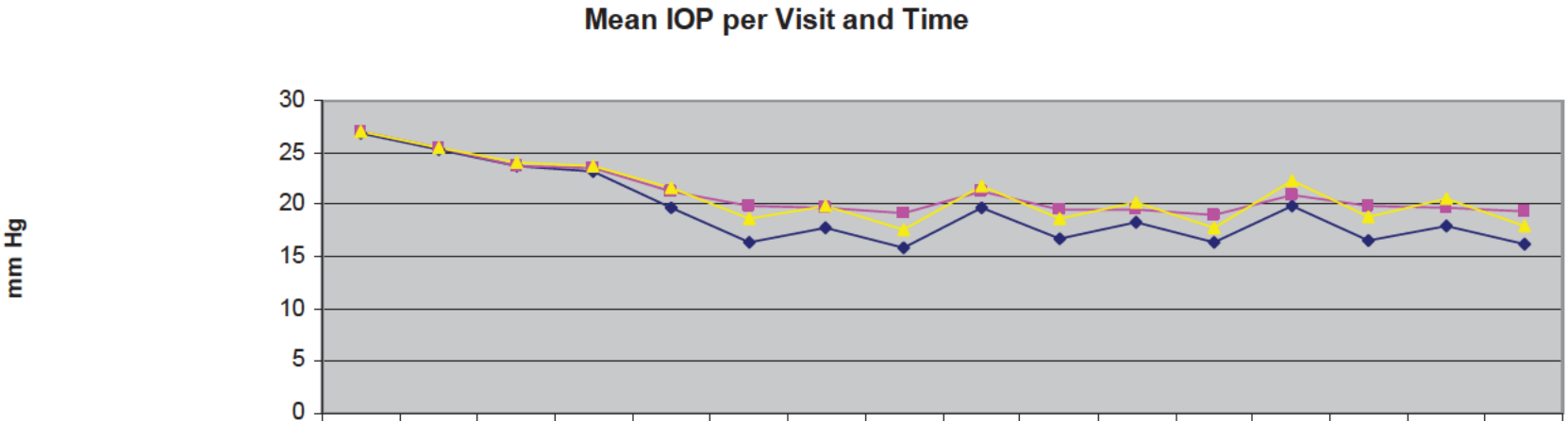
Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals



	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

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-10-033 ITT LOCF Population

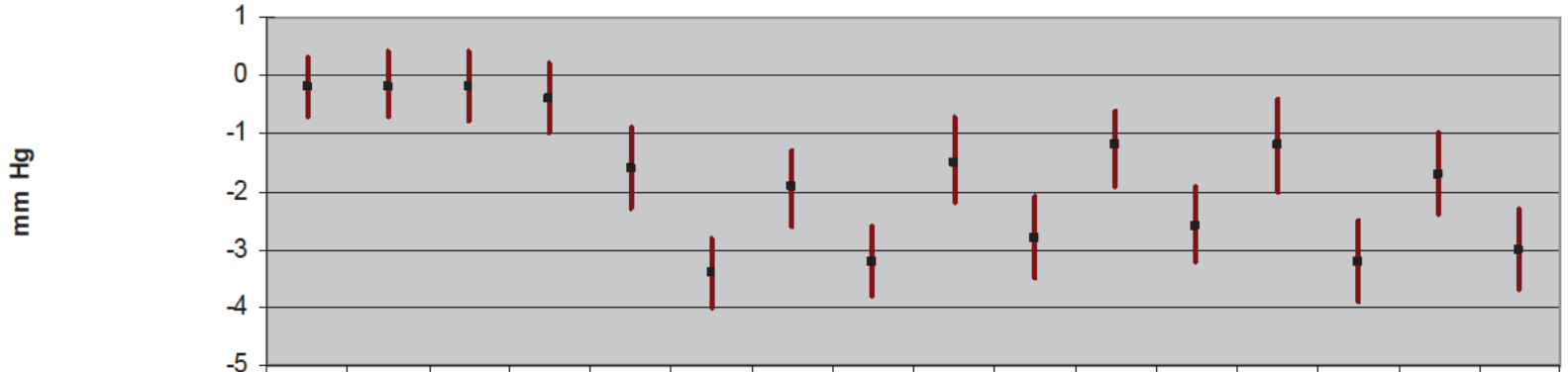


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Brinz 1%/Brim 0.2%	26.9	25.3	23.7	23.2	19.7	16.4	17.8	15.9	19.7	16.8	18.3	16.4	19.8	16.6	18	16.3
Brinz 1%	27.1	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

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 LOCF Population

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

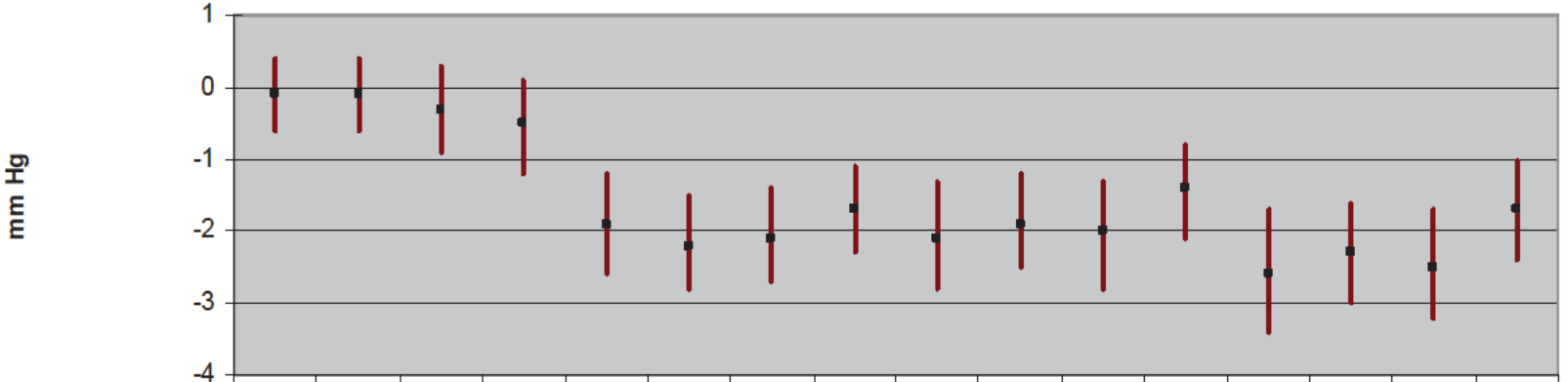


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.7	-0.7	-0.8	-1	-2.3	-4	-2.6	-3.8	-2.2	-3.5	-1.9	-3.2	-2	-3.9	-2.4	-3.7
Upper CI	0.3	0.4	0.4	0.2	-0.9	-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

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 ITT LOCF Population

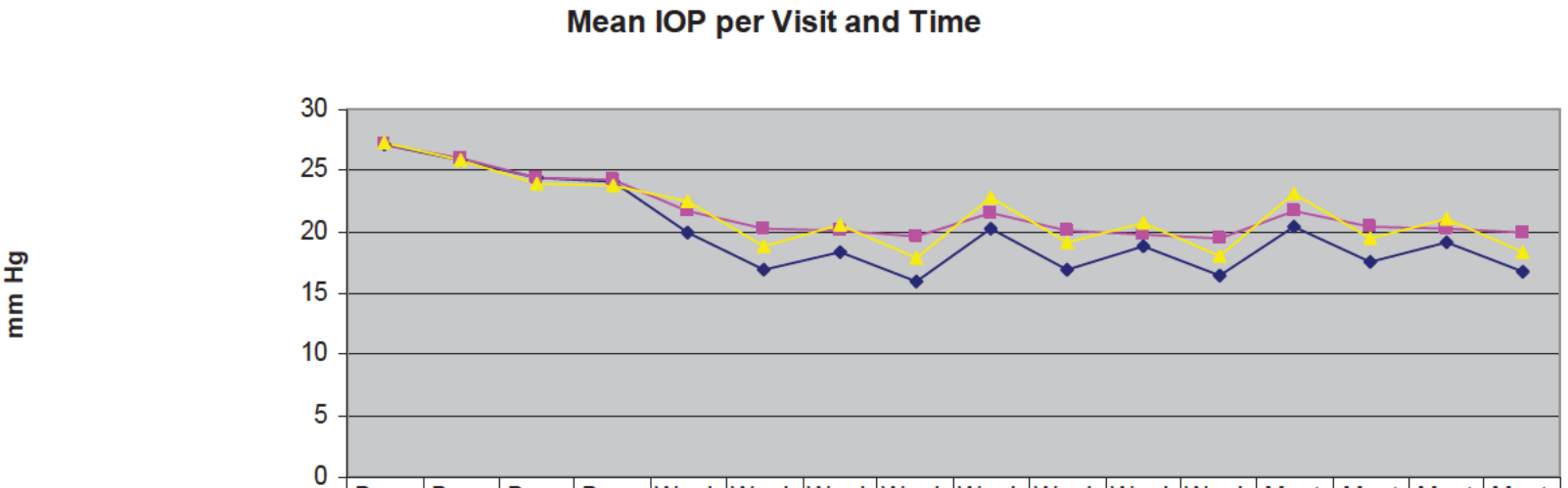
Mean Difference (Brinzolamide 1%/Brimonidine 0.2% - Brimonidine 0.2%) with 95% Confidence Intervals



	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

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-10-039 ITT LOCF Population

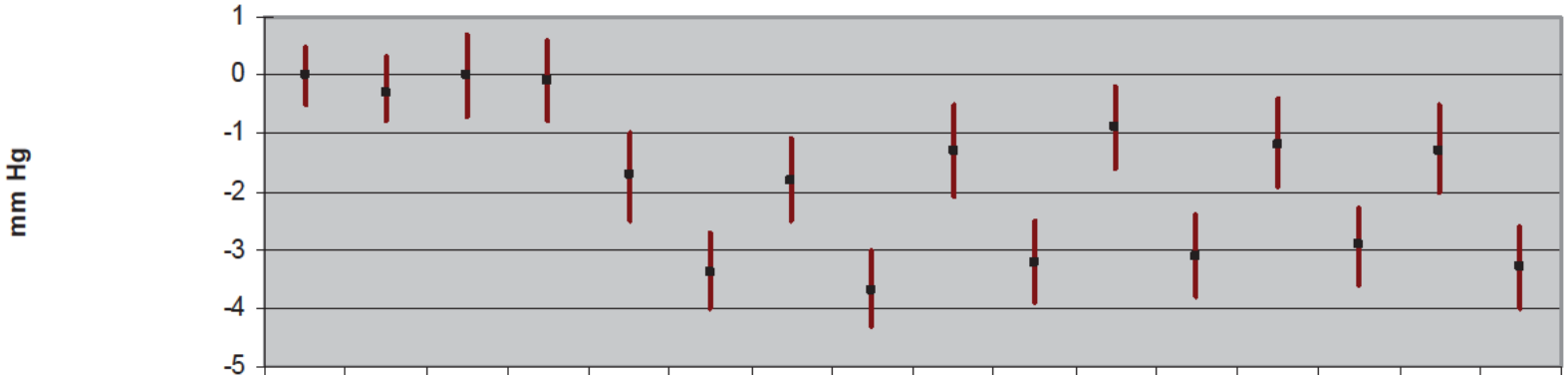


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Brinz 1%/Brim 0.2%	27.2	25.8	24.4	24.1	20	16.9	18.3	16	20.2	16.9	18.8	16.4	20.5	17.5	19.1	16.7
Brinz 1%	27.2	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

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 LOCF Population

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

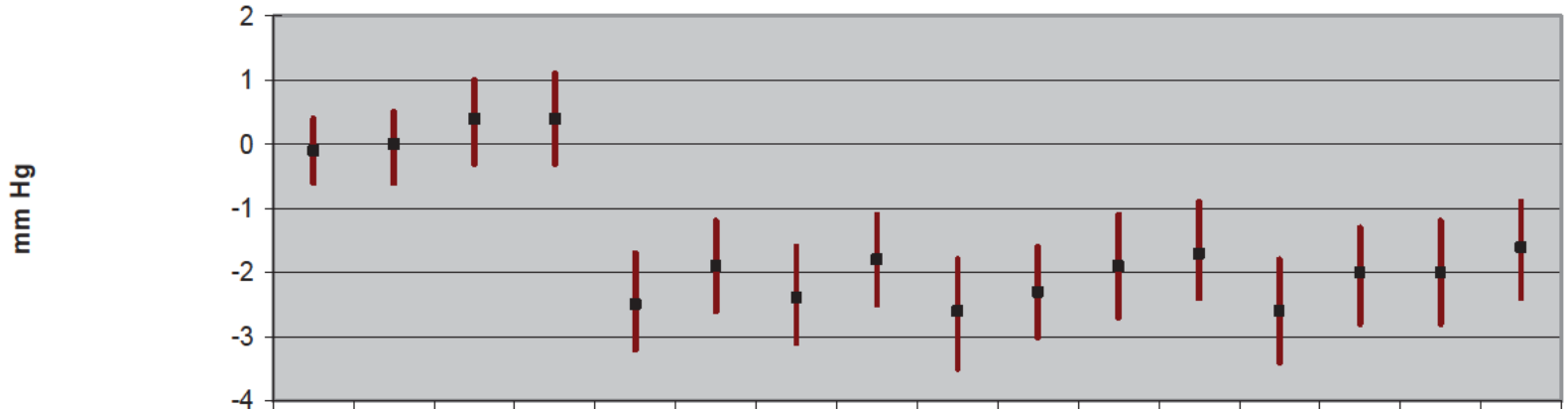


	Baseline 8AM	Baseline 10AM	Baseline 3PM	Baseline 5PM	Week 2 8AM	Week 2 10AM	Week 2 3PM	Week 2 5PM	Week 6 8AM	Week 6 10AM	Week 6 3PM	Week 6 5PM	Month 3 8AM	Month 3 10AM	Month 3 3PM	Month 3 5PM
Lower CI	-0.5	-0.8	-0.7	-0.8	-2.5	-4	-2.5	-4.3	-2.1	-3.9	-1.6	-3.8	-1.9	-3.6	-2	-4
Upper CI	0.5	0.3	0.7	0.6	-1	-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

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 ITT LOCF 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	-0.3	-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 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.

Summary Efficacy Statement

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 and clinically 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. The contribution of brinzolamide and brimonidine in the combination product has been demonstrated.

8. Safety

The primary sources for safety data for this application came from studies C-10-33 and C-10-039, C-10-010, C-11-002, and C-09-038.

From the original Medical Officer Review dated 4/9/2013:

Exposure

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
	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	

Disposition of Subjects

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)
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)

Deaths

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

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)
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)	

Adverse Event	Brinz/Brim TID N=33 N (%)	Brinz TID N=34 N (%)	Brim TID N=34 N (%)
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							
Ear and Labyrinth Disorders							
Tinnitus		1 (4.3)					
Gastrointestinal Disorders							
Diarrhoea	**4 (4.2)**				1 (4.2)		**1 (4.2)**

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 (%)
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)						

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

Adequate and well controlled studies (C-10-033 nad C-10-039) support 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.

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. No new safety issues relating to Simbrinza (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2% have been found.

9. 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.

10. Pediatrics

For this 505(b)(2) application which references brimonidine, the brimonidine labeling states:

> 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.

For this 505(b)(2) application which references brinzolamide, the brinzolamide labeling states:

> A three-month controlled clinical study was conducted in which brinzolamide ophthalmic suspension 1% was dosed only twice a day in pediatric patients 4 weeks to 5 years of age. Patients were not required to discontinue their IOP-lowering medication(s) until initiation of monotherapy with brinzolamide ophthalmic suspension 1%. IOP-lowering efficacy was not demonstrated in this study in which the mean decrease in elevated IOP was between 0 and 2 mmHg. Five out of 32 patients demonstrated an increase in corneal diameter of one millimeter.

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 2 years - 7 years 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.

In summary:

1) Simbrinza is contraindicated in children under the age of 2 years.
2) Simbrinza is effective but should be used with caution in children 2-7 years of age because of somnolence and deceased alertness.
3) Simbrinza is safe and effective in children 7 – 16 years of age and in adults.

11. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the original Biostatistics review dated 3/15/2013:

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

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

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

Furthermore, the differences in mean IOP between brinzolamide/brimonidine and brinzolamide alone were at least 1.5 mmHg for 8 of 12 assessment time points and differences in mean IOP between brinzolamide/brimonidine and brimonidine alone were at least 1.5 mmHg for all 12 of 12 assessment time points.

Note: The Biostatistics review suggests including as table for the mean IOPS in each group at Month three in the two phase three trials. Clinical does not agree with including the table; as stated previously, comparison of IOP at all visits and assessment time points would be considered primary efficacy comparisons. Listing Month 3 data alone implies the Agency is only concerned with the resultant IOP at Month 3; any table would also need to list IOPs at 8AM, 10AM, 3PM, and 5PM at baseline, Week 2, Week 6, and Month 3 for both trials; this would be voluminous for the package insert and is not recommended.

OPDP
Office of Prescription Drug Promotion (OPDP) completed a formal review of the package insert based on the substantially complete labeling from 4/8/13.

OPDP's suggestion to revise Section 5.1 and remove (b) (4) is not recommended. This section of the labeling contains standard language for sulfonamide-containing products.

OPDP's suggestion to revise Section 5.6 and remove (b) (4) is not recommended. This section of the labeling contains language from brimonidine tartrate monotherapy products; this is a 505(b)(2) application.

OPDP's suggestion to revise Section 6.1 and include discontinuation rates is not recommended. Discontinuation rates were very low (consistent with the monotherapy) and not attributable to specific adverse events.

OPDP's suggestion to revise Section 6.1 and include the exact adverse event percentage is not recommended. For the common adverse events in the pooled Phase 3 trials, the rates were essentially either 3% or 5% for each (i.e. vision blurred (5%), eye irritation (5%), and eye allergy (3%)).

OPDP's suggestion to revise Section 12.1 is not recommended. The mechanism of action of these class of products is well-documented and contains language from referenced monotherapy products; this is a 505(b)(2) application.

OPDP's suggestion to revise Section 14 is not recommended. Listing Month 3 data alone implies the Agency is only concerned with the resultant IOP at Month 3. Any table would also need to list IOPs at 8AM, 10AM, 3PM, and 5PM at baseline, Week 2, Week 6, and Month 3 for both trials; this would take several pages.

OPDP's suggestion to revise Section 17 is not recommended. The specific sulfonamide reactions of concern (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant

hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias) are not amenable to simplified language for patients. The most useful terminology is already proposed: serious or unusual ocular or systemic reactions or signs of hypersensitivity.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Simbrinza, and granted conditional acceptance 8/27/2012. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

DMEPA finalized their review of the Simbrinza carton and container labeling on 3/14/2013. Comments regarding suggested changes to the carton and container that were not supported by regulation were not transmitted to the applicant.

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.

Per the OSI review dated 2/22/2013:

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).

12. Labeling

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.

Carton and container labeling submitted on 4/16/13 and found in the Appendix of this review is acceptable.

The package insert submitted on 4/18/13 is also found in the Appendix of this review. It contains tables and figures in Section 14 Clinical Studies which, in this reviewer's opinion, detract from the relevant information for the prescribing physician. The clinically relevant information from Study 1 and Study 2 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 de-emphasized in the six pages of tables and figures Alcon has proposed.

13. 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.

RISK BENEFIT ASSESSMENT:
There is substantial evidence of effectiveness consisting of adequate and well controlled studies which support the efficacy and 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.

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%).

The benefits of using this drug product outweigh the risks for the above indication(s).

Clinical, Pharmacology/Toxicology, Clinical Pharmacology, Product Quality Microbiology, Product Quality, and Biostatistics have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

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/

WILEY A CHAMBERS
04/19/2013
for William Boyd, MD