CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204251Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	204-251
Submission Date(s):	June 19, 2012
PDUFA Date:	April 19, 2013
Proposed Brand Name	SIMBRINZA™
Generic Name	Brinzolamide/Brimonidine tartrate
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	Alcon Laboratories, Inc.
Relevant IND(s)	106293
Submission Type; Code	New combination; 4S
Formulation; Strength(s)	Brinzolamide/brimonidine tartrate ophthalmic suspension; 1%/0.2%
Indication	For the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

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1. EXECUTIVE SUMMARY

The active components in this combination of Brinzolamide 1%/Brimonidine 0.2% tartrate ophthalmic suspension (brinzolamide and brimonidine) were approved as monotherapeutic agents for the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension. 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.

The currently proposed product for this NDA has been developed as a combination product that does not contain the beta-blocker, timolol, which is included in all currently approved and marketed ophthalmic combination products for the same indication.

In support of the NDA, the Applicant submitted the following clinical studies:

- Phase 1 study C-10-010 to describe the steady-state PK of brimonidine in plasma and red blood cell (RBC) saturation of brinzolamide and N-desethyl brinzolamide following topical ocular administration of the fixed dose combination product compared to the individual active components alone in healthy subjects.

- Two Phase 2 (C-09-038, C-11-002) and two Phase 3 studies (C-10-033, C-10-039) to demonstrate the safety and efficacy of the combination product and the efficacy of the combination product versus that of the individual components.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable.

The reviewer's proposed label changes in *Appendix 4.1* should be forwarded to the sponsor.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

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).

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cc:
Division File: NDA 204-251/HFD-520 (CSO/Germain)/HFD-520 (MO/Boyd)/HFD-520 (Chambers)/HFD-880 (Lazor)

2. QUESTION BASED REVIEW

The active components in this combination of Brinzolamide 1%/Brimonidine 0.2% tartrate ophthalmic suspension (brinzolamide and brimonidine) were approved as monotherapeutic agents for the same indication following the same route of administration. Only relevant questions are answered as follows.

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

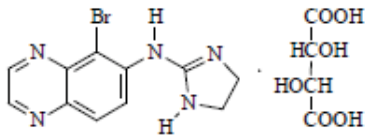
Brimonidine
Brimonidine tartrate is an alpha adrenergic receptor agonist provided as a white to off-white, pale yellow to yellow powder or crystals.

Structural Formula: $C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$

Molecular Weight: 442.23 Dalton

CAS Index Name:
- 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine
- 5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline L-tartrate
- 5-Bromo-6-(imidazolin-2-ylamino)quinoxaline L-tartrate

Chemical Structure:



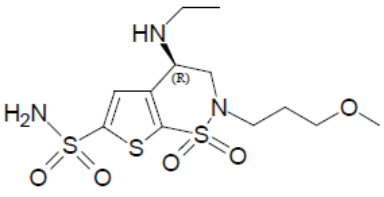
Brinzolamide
Brinzolamide is a topically active sulfonamide carbonic anhydrase inhibitor (CAI) provided as a white to off-white powder or crystals.

Structural Formula: $C_{12}H_{21}N_3O_5S_3$

Molecular Weight: 383.51 Dalton

CAS Index Name:
(R)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

Chemical Structure:



Drug Product:
The Brinzolamide 1% and Brimonidine Tartrate 0.2% Ophthalmic Suspension is a sterile, preserved, multi-dose ophthalmic suspension formulation containing 1% brinzolamide and 0.2% brimonidine tartrate. **(Table 2.1.1-1)**

Table 2.1.1-1: Composition of the drug product (FID115576)

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)		
Sodium Chloride			
Mannitol			
Propylene Glycol			
Tyloxapol			
Boric Acid			
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)

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Brinzolamide is a topically active sulfonamide carbonic anhydrase inhibitor (CAI). Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Brimonidine tartrate is an alpha adrenergic receptor agonist. Brimonidine tartrate has a peak ocular hypotensive effect occurring at two hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow. The result is a reduction in IOP.

The proposed fixed dose combination ophthalmic product is indicated for the reduction of elevated IOP in open-angle glaucoma or ocular hypertension.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The recommended dose is one drop in the affected eye(s) three times daily. If more than one topical ophthalmic drug is being used, the drugs should be administered at least (b) (4) minutes apart.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In support of the NDA, the Applicant submitted clinical studies including:

- Phase 1 study C-10-010 to describe the steady-state PK of brimonidine in plasma and red blood cell (RBC) saturation of brinzolamide and N-desethyl brinzolamide following topical ocular administration of the fixed dose combination product compared to the individual active components alone in healthy subjects.

- Two Phase 2 (C-09-038, C-11-002) and two Phase 3 studies (C-10-033, C-10-039) to demonstrate the safety and efficacy of the combination product and the efficacy of the combination product versus that of the individual components.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

IOP is accepted as a surrogate endpoint for assessing the efficacy of treatments for open-angle glaucoma and ocular hypertension. The IOP endpoint has served as the basis for approval for all IOP-lowering agents for open-angle glaucoma or ocular hypertension.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Plasma concentrations of brinzolamide and brimonidine and whole blood concentration of brinzolamide were determined using a fully validated HPLC/MS/MS assay for brinzolamide and a GC/MS/MS method for brimonidine. (*Refer to Section 2.6*).

2.2.4. Exposure-response

2.2.4.1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Not Applicable (N.A.)

2.2.4.2. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.*

N.A.

2.2.4.3. Does this drug prolong the QT or QTc interval? (You must answer this question, unless this is addressed in the question above.)

No, the Brinzolamide 1% and Brimonidine Tartrate 0.2% Ophthalmic Suspension following topical ocular administration did not prolong the QT or QTc interval in the clinical trial population.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and dosing regimen of the combination product are consistent with those of monotherapeutic agents. There is no unresolved dosing or administration issues.

2.2.5. What are the PK characteristics of the drug?

Brinzolamide
Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its affinity for carbonic anhydrase CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (approximately 111 days). In humans, the metabolite N-desethyl brinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds mainly to CA-I in the presence of brinzolamide. In plasma, both parent brinzolamide and N-desethyl brinzolamide concentrations are <10 ng/mL. Binding to plasma proteins is approximately 60%. Brinzolamide is eliminated predominantly in the urine as unchanged drug. N-Desethyl brinzolamide is also found in the urine along with lower concentrations of the N-desmethoxypropyl and O-desmethyl metabolites.

Brimonidine
After ocular administration of a 0.2% solution of brimonidine tartrate, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

Brimonidine / Brinzolamide
In humans, Study C-10-010 was conducted to evaluate the pharmacokinetics of the fixed dose combination of brinzolamide / brimonidine tartrate 1%/ 0.2% ophthalmic suspension. Healthy volunteers were randomly assigned to receive BID or TID doses of either the fixed combination, or either of its individual components, brinzolamide or brimonidine. Subjects who were assigned to the brinzolamide alone or combination arms were administered one mg of oral brinzolamide capsules for two weeks prior to beginning dosing with the topical ocular suspension to allow a determination of whether brinzolamide would interact with brimonidine in the plasma after brinzolamide being saturated in red blood cells. The results showed that the steady-state systemic exposure of brinzolamide (**Tables 2.2.5-1** & **2, whole blood; Table 2.2.5-3, plasma**), N-desethyl brinzolamide (**Tables 2.2.5-1** & **2.2.5-2, whole blood**), and brimonidine (**Tables 2.2.5-4 & 2.2.5-5, plasma Cmax and AUC**) following topical ocular administration of fixed combination Brinzolamide/Brimonidine dosed three times daily (TID) or two times daily (BID) was not

meaningfully different compared to that observed following topical ocular administration of the individual active components, Brinzolamide or Brimonidine alone.

Results also showed that brimonidine achieved steady-state on Day 21 and remained at steady-state on Day 107 following topical ocular administration of fixed combination Brinzolamide/Brimonidine dosed TID or BID (**Tables 2.2.5-6 & 2.2.5-7**).

Table 2.2.5-1: Least Squares Mean Ratio of Brinzolamide and N-Desethyl Brinzolamide RBC Concentrations (μM) for Combination TID (Arm 1) and Brinzolamide 1% TID (Arm 2) on Day 107 (Whole Blood)[a]

	Least Squares Means		Least Squares	Lower	Upper
Analyte	Brinz/Brim TID	Brinzolamide TID	Mean Ratio	90% CI	90% CI
Brinzolamide	12.1	15.3	0.789	0.597	1.04
N-Desethyl Brinzolamide	1.32	1.30	1.02	0.753	1.38

Brinz/Brim TID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, 3 times a day dosing
Brinzolamide TID = Brinzolamide Ophthalmic Suspension, 1%, three times a day dosing
ANOVA performed on ln-tranformed data to calculate least squares means
[a]RBC concentration (μM) derived from whole blood concentration data

Table 2.2.5-2: Least Squares Mean Ratio of Brinzolamide and N-Desethyl Brinzolamide RBC Concentrations (μM) for Combination BID (Arm 4) and Brinzolamide 1% BID (Arm 5) on Day 107 (Whole Blood) [a]

	Least Squares Means		Least Squares	Lower	Upper
Analyte	Brinz/Brim BID	Brinzolamide BID	Mean Ratio	90% CI	90% CI
Brinzolamide	14.2	11.5	1.24	0.996	1.54
N-Desethyl Brinzolamide	1.56	1.44	1.08	0.772	1.51

Brinz/Brim BID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, 2 times a day dosing
Brinzolamide BID = Brinzolamide Ophthalmic Suspension, 1%, two times a day dosing
ANOVA performed on ln-tranformed data to calculate least squares means
[a]RBC concentration (μM) derived from whole blood concentration data

Table 2.2.5-3: Least Squares Mean Ratio of Brinzolamide Plasma Concentrations (ng/mL) for Combination and Brinzolamide alone for TID and BID Administration on Day 107 (Plasma)

	Least Squares Means		Least Squares	Lower	Upper
Dosing Regimen	Brinz/Brim	Brinzolamide	Mean Ratio	90% CI	90% CI
TID	2.50	2.56	0.975	0.769	1.24
BID	2.27	1.63	1.39	1.10	1.76

Brinz/Brim = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension
Brinzolamide = Brinzolamide Ophthalmic Suspension, 1%
TID = three times a day dosing
BID = two times a day dosing
ANOVA performed on ln-transformed data to calculate least squares means

Table 2.2.5-4: Least Squares Mean Ratio of Brimonidine Plasma for Combination TID and Brimonidine TID on Day 21(PK Data)

Parameter	Least Squares Means Brinz/Brim TID	Least Squares Means Brimonidine TID	Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	0.0479	0.0508	0.943	0.724	1.23
AUC_{0-t} (ng*hr/mL)	0.183	0.205	0.893	0.668	1.19

Brinz/Brim TID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, 3 times a day dosing
Brimonidine TID = Brimonidine Tartrate Ophthalmic Solution, 0.2%, three times a day dosing
ANOVA performed on ln-tranformed data to calculate least squares means

Table 2.2.5-5: Least Squares Mean Ratio of Brimonidine Plasma for Combination BID and Brimonidine BID on Day 21(PK Data)

Parameter	Least Squares Means Brinz/Brim BID	Least Squares Means Brimonidine BID	Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	0.0643	0.0602	1.07	0.863	1.32
AUC_{0-t} (ng*hr/mL)	0.174	0.227	0.765	0.614	0.954

Brinz/Brim BID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, 2 times a day dosing
Brimonidine BID = Brimonidine Tartrate Ophthalmic Solution, 0.2%, two times a day dosing
ANOVA performed on ln-tranformed data to calculate least squares means

Table 2.2.5-6: Least Squares Mean Ratio of Brimonidine Plasma Exposure of Days 107 and 21 for Combination TID (PK Data)

Parameter	Least Squares Means 107	Least Squares Means 21	Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	0.0419	0.0479	0.875	0.640	1.20
AUC_{0-t} (ng*hr/mL)	0.145	0.183	0.791	0.562	1.11

Brinz/Brim TID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, three times a day dosing
107 = Visit Day 107
21 = Visit Day 21
ANOVA performed on ln-tranformed data to calculate least squares means

Table 2.2.5-7: Least Squares Mean Ratio of Brimonidine Plasma Exposure of Days 107 and 21 for Combination BID (PK Data)

Parameter	Least Squares Means 107	Least Squares Means 21	Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	0.0592	0.0643	0.921	0.694	1.22
AUC_{0-t} (ng*hr/mL)	0.172	0.174	0.991	0.749	1.31

Brinz/Brim BID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, two times a day dosing
107 = Visit Day 107
21 = Visit Day 21
ANOVA performed on ln-tranformed data to calculate least squares means

2.3. Intrinsic Factors

2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of the commonly known intrinsic factors including race, gender and age on the PK of brinzolamide and brimonidine following topical administration of brinzolamide / brimonidine tartrate 1%/ 0.2% ophthalmic suspension has not been thoroughly studied.

Since brinzolamide and its metabolite are excreted predominantly by the kidney, the combination product is not recommended for patients with severe renal impairment (CLcr <30 mL/min). Similar wording is in the approved AZOPT label (WARNINGS & PRECAUTIONS).

The brimonidine component of SIMBRINZA™ has not been specifically studied in patients with hepatic failure. However, since brimonidine is primarily metabolized by the liver, the proposed labeling for this combination product indicates that caution should be exercised when using this product in patients with severe hepatic impairment.

2.4. Extrinsic Factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?
Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

The impact of the commonly known extrinsic factors on brinzolamide and brimonidine dose-exposure and/or –response has not been evaluated.

2.6 Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma concentrations of brinzolamide and brimonidine and whole blood concentrations of brinzolamide were determined using a fully validated HPLC/MS/MS assay for brinzolamide and a GC/MS/MS method for brimonidine.

2.6.2. Which metabolites have been selected for analysis and why?

N-desethyl brinzolamide is selected for analysis. In humans, the metabolite N-desethyl brinzolamide is formed and binds to carbonic anhydrase (CA) and accumulates in RBCs. This metabolite binds mainly to CA-I in the presence of brinzolamide.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Free plasma concentrations of brinzolamide and brimonidine were determined. The total whole blood concentration of brinzolamide was also determined.

2.6.4. What bioanalytical methods are used to assess concentrations?

Refer to Section 2.6.1. for further information.

2.6.4.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See Table 2.6-1. The ranges of standard curve are adequate for purposes of determining plasma concentrations of brinzolamide and brimonidine in the clinical studies.

2.6.4.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Table 2.6-1.

2.6.4.3. What are the accuracy, precision, and selectivity at these limits?

See Table 2.6-1.

2.6.4.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

See Table 2.6-1.

Table 2.6-1: Assay Validation Information

Criterion	Brinzolamide (Plasma)	Brinzolamide (Whole blood)	Brimonidine (Plasma)	**Comments**
Conc. range, ng/mL	1.00-120	100-8000	0.00265 -0.993	satisfactory
LLOQ, ng/mL	1.00	100	0.00265	satisfactory
Accuracy, % RE	-3.2 % - 3.0 % [a] -5.3 % - 5.0 % [b] -1.0 % - 5.9 % [c] -4.7 % - 6.2 % [d]	-4.3 % - 6.7 % [a] -1.3 % - 1.0 % [b] -3.3 % -4.7 % [c] -2.3 % - 0 % [d]	-2.01 % - 2.64 % [a] -1.71 % - 1.51 % [b] -0.882 % - 1.01 % [c] -0.630 % - -0.378 % [d]	Satisfactory
Precision, % CV	1.33 % - 10.89 % [a] 2.61 % - 7.30 % [b] 1.80 % - 8.55 % [c] 7.05 % - 11.47 % [d]	0.28 % - 4.87 % [a] 2.17 % - 7.34 % [b] 0.66 % -6.03 % [c] 1.47 % - 3.77 % [d]	≤13.1 % [a] ≤8.87 % [b] ≤10.8 % [c] ≤12.6% [d]	Satisfactory
Selectivity	Control human blood from at least ten individuals	Control human blood from at least ten individuals	Control human blood from at least ten individuals	Satisfactory
Recovery	QC samples mean: 93.7%	QC samples mean: 90.5%	QC samples mean: 48.2%	Satisfactory
Stability	Stable through at lease six freeze/thaw cycles, at room temperature (RM) for at least 6.75 hours, in dried extract residues for at least 2 hours at RM, in reconstituted samples after autosampler storage for 115 hours at RM., and stable in human	Stable through at lease five freeze/thaw cycles, at room RM for at least 6 hours, in dried extract residues for at least 2 hours at RM, for at least 120 hours in reconstituted extracts at RM, and stable in human whole blood for 433 days at -20 & -80 °C	Stable through at lease six freeze/thaw cycles, at RM for at least 27 hours, as extract in autosampler at RM for 95 hours., and in storage container for 31 days at -70 °C	satisfactory

	whole blood for 433 days at -20 & -80 °C			

[a], Intra-day for standards; [b], Inter-day for standards; [c], Intra-assay for QCs; [d], Inter-assay for QCs
From Reports TDOC-0015018 (Brinzolamide/plasma), TDOC-0013325 (Brimonidine/plasma), and TDOC-0013332 (Brinzolamide/whole blood).

3. LABELING RECOMMENDATIONS

See Appendix 4.1. for detail.

4. APPENDICES

4.1. Proposed Package Insert (Original and Annotated)

~~Strikethrough~~ reflects the reviewer's deletion. Underline reflects the reviewer's addition.

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

4.2. Individual Study Review

4.2.1. Pharmacokinetic study in healthy subjects: Study C-10-010

Study Number: C-10-010
Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension Pharmacokinetic Study in Healthy Subjects (Phase 1)

Dates: 11 January 2011 to 9 August 2011
Study Director: (b) (4)
Analytical site: Alcon Research Ltd. 6201 S. Freeway, Fort Worth, Texas 76134;
(b) (4)

OBJECTIVES:
The primary objective of this study was to compare the steady-state PK of brimonidine in plasma and red blood cell (RBC) saturation of brinzolamide and N-desethyl brinzolamide following topical ocular administration of Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension dosed TID or BID to the individual components (ie, Brinzolamide or Brimonidine Tartrate) in healthy subjects.

FORMULATION
- Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension (*Batch Number: Lots 10-501205-1 and 11-501250-1, FID 115576*)
- Brinzolamide Ophthalmic Suspension, 1% (*Batch Number: Lot 10-501226-1, FID 89984*)
- Brimonidine Tartrate Ophthalmic Solution, 0.2% (*Batch Number: Lot 10-501227-1, FID 101461*)
- Brinzolamide, 1 mg capsule (*Batch Number: Lot 10-600283-1, FID 91207*)

STUDY DESIGN:
This is a multicenter, randomized, parallel-group, open-label, 13 week PK study; N=144 adult healthy subjects; randomized into 6 treatment arms. Demographic characteristics are summarized in **Table 1**. The study was conducted in 2 phases, an oral treatment phase and a topical ocular treatment phase (**Table 2**). Arms 1&4 or Arms 2&5 contain an oral Brinzolamide phase. One mg Brinzolamide capsule was given orally BID for 14 days prior to the topical ocular administration phase to allow a determination of whether Brinzolamide would interact with Brimonidine in the plasma after Brinzolamide being saturated in red blood cells.

Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension was administered topically one drop into both eyes TID (Arm 1) or BID (Arm 4) from Day 15-107.

Brinzolamide Ophthalmic Suspension, 1% was administered topically one drop into both eye TID (Arm 2) or BID (Arm 5) from Day 15-107.

Arms 3& 6 contain no oral Brinzolamide phase therefore no dosing for Days 1-14. Brimonidine Tartrate Ophthalmic Solution, 0.2% was administered topically TID (Arm 3) or BID (Arm 6) from Day 15-21.

Table 1: Demographic statistics by treatment group

	Total (N = 144)		Brinz/Brim TID (N=24)		Brinzolamide TID (N=24)		Brimonidine TID (N=24)		Brinz/Brim BID (N=24)		Brinzolamide BID (N=24)		Brimonidine BID (N=24)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total	**144**		**24**		**24**		**24**		**24**		**24**		**24**	
Age (Years)														
Adults (18-64 yrs)	134	(93.1)	23	(95.8)	19	(79.2)	24	(100.0)	21	(87.5)	23	(95.8)	24	(100.0)
Elderly (≥65 yrs)	10	(6.9)	1	(4.2)	5	(20.8)	0	(0.0)	3	(12.5)	1	(4.2)	0	(0.0)
Sex														
Male	78	(54.2)	15	(62.5)	10	(41.7)	17	(70.8)	16	(66.7)	11	(45.8)	9	(37.5)
Female	66	(45.8)	9	(37.5)	14	(58.3)	7	(29.2)	8	(33.3)	13	(54.2)	15	(62.5)
Ethnicity														
Hispanic, Latino, or Spanish	44	(30.6)	13	(54.2)	13	(54.2)	10	(41.7)	1	(4.2)	2	(8.3)	5	(20.8)
Not Hispanic, Latino, or Spanish	100	(69.4)	11	(45.8)	11	(45.8)	14	(58.3)	23	(95.8)	22	(91.7)	19	(79.2)
Race														
American Indian or Alaska Native	5	(3.5)	0	(0.0)	3	(12.5)	1	(4.2)	0	(0.0)	0	(0.0)	1	(4.2)
Asian	2	(1.4)	1	(4.2)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)	0	(0.0)
Black or African American	31	(21.5)	4	(16.7)	3	(12.5)	7	(29.2)	8	(33.3)	3	(12.5)	6	(25.0)
Native Hawaiian or Other Pacific Islander	1	(0.7)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
White	105	(72.9)	19	(79.2)	18	(75.0)	15	(62.5)	15	(62.5)	21	(87.5)	17	(70.8)
Ethnicity and Race														
Hispanic, Latino, or Spanish														
American Indian or Alaska Native	3	(2.1)	0	(0.0)	2	(8.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
Asian	1	(0.7)	1	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Black or African American	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)
White	39	(27.1)	12	(50.0)	11	(45.8)	10	(41.7)	1	(4.2)	2	(8.3)	3	(12.5)
Not Hispanic, Latino, or Spanish														
American Indian or Alaska Native	2	(1.4)	0	(0.0)	1	(4.2)	1	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
Asian	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)	0	(0.0)
Black or African American	30	(20.8)	4	(16.7)	3	(12.5)	7	(29.2)	8	(33.3)	3	(12.5)	5	(20.8)
Native Hawaiian or Other Pacific Islander	1	(0.7)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)	0	(0.0)	0	(0.0)
White	66	(45.8)	7	(29.2)	7	(29.2)	5	(20.8)	14	(58.3)	19	(79.2)	14	(58.3)
Iris Color														
Blue	17	(11.8)	4	(16.7)	0	(0.0)	1	(4.2)	4	(16.7)	5	(20.8)	3	(12.5)
Brown	99	(68.8)	17	(70.8)	20	(83.3)	21	(87.5)	15	(62.5)	12	(50.0)	14	(58.3)
Green	10	(6.9)	1	(4.2)	2	(8.3)	1	(4.2)	2	(8.3)	2	(8.3)	2	(8.3)
Grey	2	(1.4)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)	1	(4.2)	0	(0.0)
Hazel	16	(11.1)	2	(8.3)	2	(8.3)	0	(0.0)	3	(12.5)	4	(16.7)	5	(20.8)

Brinz/Brim = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension
Brinzolamide = Brinzolamide Ophthalmic Suspension, 1%
Brimonidine = Brimonidine Tartrate Ophthalmic Solution, 0.2%
TID = three times a day dosing
BID = two times a day dosing

Table 2: Study Outline

Treatment Arm	Oral Treatment Phase	Topical Ocular Treatment Phase		
	Day 1 to Day 14	Test Article	Dosing Schedule	Length of Treatment
1	Brinzolamide, 1 mg capsule, PO, BID	Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension	TID, OU	Day 15 to Day 107
2	Brinzolamide, 1 mg capsule, PO, BID	Brinzolamide Ophthalmic Suspension, 1%	TID, OU	Day 15 to Day 107
3	None	Brimonidine Tartrate Ophthalmic Solution, 0.2%	TID, OU	Day 15 to Day 21
4	Brinzolamide, 1 mg capsule, PO, BID	Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension	BID, OU	Day 15 to Day 107
5	Brinzolamide, 1 mg capsule, PO, BID	Brinzolamide Ophthalmic Suspension, 1%	BID, OU	Day 15 to Day 107
6	None	Brimonidine Tartrate Ophthalmic Solution, 0.2%	BID, OU	Day 15 to Day 21

Pharmacokinetic Sampling:
Brimonidine

- Plasma Samples for Treatment Arms 1&4 (Combination):
  Day 15 ± 2 Days: 0 hr (trough)
  Day 21 ± 2 Days:
  TID (Arms 1&3): 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, & 8 hrs post morning dose
  BID (Arms 4&6): 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 8, & 12 hrs post morning dose
  Day 107 ± 2 Days:
  TID (Arm 1): 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, & 8 hrs post morning dose
  BID (Arm 4): 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 8, & 12 hrs post morning dose

- Plasma Samples for Arms 3&6 (Brimonidine alone)
  Day 15 ± 2 Days: 0 hr (trough)
  Day 21 ± 2 Days:
  TID (Arms 1&3): 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, & 8 hrs post morning dose
  BID (Arms 4&6): 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 8, & 12 hrs post morning dose

Brinzolamide and N-desethyl brinzolamide

- Whole Blood and Plasma Samples for Arms 1&4 or Arms 2&5(Brinzolamide alone):
  Day 1: Prior to oral administration (0 hr, pre-dose)
  Day 15 ± 2 Days: Prior to instillation (0 hr, trough)
  Day 21 ± 2 Days: Prior to instillation (0 hr, trough)
  Day 107 ± 2 Days: Prior to final instillation (0 hr, trough)

ASSAY METHODOLOGY:

Plasma concentrations of brinzolamide and brimonidine and whole blood concentration of brinzolamide were determined at (b) (4) using fully validated HPLC/MS/MS assay for brinzolamide and a GC/MS/MS method for brimonidine. For N-desethyl brinzolamide, during development of the plasma method, no set of conditions could be found which gave sufficient precision and ruggedness for N-desethyl brinzolamide to meet validation criteria for this analyte. Therefore, only assay data for the parent drug (i.e., brinzolamide) in plasma were reported.

The analysis consisted of estimating red blood cell (RBC) concentrations of brinzolamide and N-desethyl brinzolamide by dividing the ng/mL whole blood trough concentrations by the sample hematocrit and expressing the result on a micromolar basis. Following the calculation of the micromolar equivalents, least squares mean (LSM) ratio post-hoc analysis along with 90% confidence intervals (CI) were performed on the following PK data:

1. Trough RBC concentration of brinzolamide and N-desethyl brinzolamide on Day 107 between combination product (Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension) three times daily (TID) to Brinzolamide Ophthalmic Suspension, 1%, TID regimen. Similar comparison was performed for twice daily (BID) regimen.
2. Trough plasma concentration of brinzolamide on Day 107 between combination product TID versus brinzolamide 1% TID regimen. Similar comparison was performed for twice daily (BID) regimen.

3. Brimonidine plasma PK parameters (AUC0-t and Cmax) comparison between combination products TID versus brimonidine TID regimen. Similar comparison was performed for twice daily (BID) regimen.

Criterion	Brinzolamide (Plasma)	Brinzolamide (Whole blood)	Brimonidine (Plasma)	**Comments**
Conc. range, ng/mL	1.00-120	100-8000	0.00265 -0.993	satisfactory
LLOQ, ng/mL	1.00	100	0.00265	satisfactory
Accuracy, % RE	-3.2 % - 3.0 % [a] -5.3 % - 5.0 % [b] -1.0 % - 5.9 % [c] -4.7 % - 6.2 % [d]	-4.3 % - 6.7 % [a] -1.3 % - 1.0 % [b] -3.3 % -4.7 % [c] -2.3 % - 0 % [d]	-2.01 % - 2.64 % [a] -1.71 % - 1.51 % [b] -0.882 % - 1.01 % [c] -0.630 % - -0.378 % [d]	Satisfactory
Precision, % CV	1.33 % - 10.89 % [a] 2.61 % - 7.30 % [b] 1.80 % - 8.55 % [c] 7.05 % - 11.47 % [d]	0.28 % - 4.87 % [a] 2.17 % - 7.34 % [b] 0.66 % -6.03 % [c] 1.47 % - 3.77 % [d]	≤13.1 % [a] ≤8.87 % [b] ≤10.8 % [c] ≤12.6% [d]	Satisfactory
Selectivity	Control human blood from at least ten individuals	Control human blood from at least ten individuals	Control human blood from at least ten individuals	Satisfactory
Recovery	QC samples mean: 93.7%	QC samples mean: 90.5%	QC samples mean: 48.2%	Satisfactory
Stability	Stable through at lease six freeze/thaw cycles, at room temperature (RM) for at least 6.75 hours, in dried extract residues for at least 2 hours at RM, in reconstituted samples after autosampler storage for 115 hours at RM., and stable in human whole blood for 433 days at -20 & -80 °C	Stable through at lease five freeze/thaw cycles, at room RM for at least 6 hours, in dried extract residues for at least 2 hours at RM, for at least 120 hours in reconstituted extracts at RM, and stable in human whole blood for 433 days at -20 & -80 °C	Stable through at lease six freeze/thaw cycles, at RM for at least 27 hours, as extract in autosampler at RM for 95 hours., and in storage container for 31 days at -70 °C	satisfactory

[a], Intra-day for standards; [b], Inter-day for standards; [c], Intra-assay for QCs; [d], Inter-assay for QCs
From Reports TDOC-0015018 (Brinzolamide/plasma), TDOC-0013325 (Brimonidine/plasma), and TDOC-0013332 (Brinzolamide/whole blood).

DATA ANALYSIS

Descriptive statistics were used to summarize the steady-state PK of brimonidine in plasma and red blood cell (RBC) saturation of brinzolamide and N-desethyl brinzolamide following topical ocular administration of Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension fixed combination dosed TID or BID compared to the individual Components in healthy subjects.

Safety: physical examination, vital signs (pulse, blood pressure, oral temperature), 12-lead ECG, clinical laboratory tests (hematology, serum chemistry, urinalysis), adverse events

(AE), slit-lamp examination (eyelids and conjunctiva, cornea, iris/anterior chamber, lens), IOP, best-corrected visual acuity (BCVA) by ETDRS, dilated fundus examination (vitreous, retina/macula/choroid, optic nerve).

RESULTS & SPONSOR'S CONCLUSIONS:

Pharmacokinetics

The results showed the steady-state systemic exposure of brinzolamide (**Tables 3** & **4, whole blood; Table 5, plasma**), N-desethyl brinzolamide (**Tables 3** & **4, whole blood**), and brimonidine (**Tables 6&7, plasma Cmax and AUC**) following topical ocular administration of fixed combination Brinzolamide/Brimonidine dosed three times daily (TID) or two times daily (BID) was not meaningfully different compared to that observed following topical ocular administration of the individual active components, Brinzolamide or Brimonidine alone.

Results also showed that brimonidine achieved steady-state on Day 21 and remained at steady-state on Day 107 following topical ocular administration of fixed combination Brinzolamide/Brimonidine dosed TID or BID (**Tables 8 & 9**).

Table 3: Least Squares Mean Ratio of Brinzolamide and N-Desethyl Brinzolamide RBC Concentrations (μM) for Combination TID (Arm 1) and Brinzolamide 1% TID (Arm 2) on Day 107 (Whole Blood)[a]

	Least Squares Means		Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
Analyte	Brinz/Brim TID	Brinzolamide TID			
Brinzolamide	12.1	15.3	0.789	0.597	1.04
N-Desethyl Brinzolamide	1.32	1.30	1.02	0.753	1.38

Brinz/Brim TID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, 3 times a day dosing
Brinzolamide TID = Brinzolamide Ophthalmic Suspension, 1%, three times a day dosing
ANOVA performed on ln-tranformed data to calculate least squares means
[a]RBC concentration (μM) derived from whole blood concentration data

From Section 2.7.2 Summary of clinical pharmacology studies; Table 2.7.2-2

Table 4: Least Squares Mean Ratio of Brinzolamide and N-Desethyl Brinzolamide RBC Concentrations (μM) for Combination BID (Arm 4) and Brinzolamide 1% BID (Arm 5) on Day 107 (Whole Blood) [a]

	Least Squares Means		Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
Analyte	Brinz/Brim BID	Brinzolamide BID			
Brinzolamide	14.2	11.5	1.24	0.996	1.54
N-Desethyl Brinzolamide	1.56	1.44	1.08	0.772	1.51

Brinz/Brim BID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, 2 times a day dosing
Brinzolamide BID = Brinzolamide Ophthalmic Suspension, 1%, two times a day dosing
ANOVA performed on ln-tranformed data to calculate least squares means
[a]RBC concentration (μM) derived from whole blood concentration data
From Section 2.7.2 Summary of clinical pharmacology studies; Table 2.7.2-3

Table 5: Least Squares Mean Ratio of Brinzolamide Plasma Concentrations (ng/mL) for Combination and Brinzolamide alone for TID and BID Administration on Day 107 (Plasma)

Dosing Regimen	Least Squares Means Brinz/Brim	Brinzolamide	Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
TID	2.50	2.56	0.975	0.769	1.24
BID	2.27	1.63	1.39	1.10	1.76

Brinz/Brim = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension
Brinzolamide = Brinzolamide Ophthalmic Suspension, 1%
TID = three times a day dosing
BID = two times a day dosing
ANOVA performed on ln-transformed data to calculate least squares means

From Section 2.7.2 Summary of clinical pharmacology studies; Table 2.7.2-4

Table 6: Least Squares Mean Ratio of Brimonidine Plasma for Combination TID and Brimonidine TID on Day 21(PK Data)

Parameter	Least Squares Means Brinz/Brim TID	Brimonidine TID	Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	0.0479	0.0508	0.943	0.724	1.23
AUC_{0-t} (ng*hr/mL)	0.183	0.205	0.893	0.668	1.19

Brinz/Brim TID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, 3 times a day dosing
Brimonidine TID = Brimonidine Tartrate Ophthalmic Solution, 0.2%, three times a day dosing
ANOVA performed on ln-tranformed data to calculate least squares means

From Section 2.7.2 Summary of clinical pharmacology studies; Table 2.7.2-5

Table 7: Least Squares Mean Ratio of Brimonidine Plasma for Combination BID and Brimonidine BID on Day 21(PK Data)

Parameter	Least Squares Means Brinz/Brim BID	Brimonidine BID	Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	0.0643	0.0602	1.07	0.863	1.32
AUC_{0-t} (ng*hr/mL)	0.174	0.227	0.765	0.614	0.954

Brinz/Brim BID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, 2 times a day dosing
Brimonidine BID = Brimonidine Tartrate Ophthalmic Solution, 0.2%, two times a day dosing
ANOVA performed on ln-tranformed data to calculate least squares means

From Section 2.7.2 Summary of clinical pharmacology studies; Table 2.7.2-6

Table 8: Least Squares Mean Ratio of Brimonidine Plasma Exposure of Days 107 and 21 for Combination TID (PK Data)

Parameter	Least Squares Means 107	21	Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	0.0419	0.0479	0.875	0.640	1.20
AUC_{0-t} (ng*hr/mL)	0.145	0.183	0.791	0.562	1.11

Brinz/Brim TID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, three times a day dosing
107 = Visit Day 107
21 = Visit Day 21
ANOVA performed on ln-tranformed data to calculate least squares means

From Section 2.7.2 Summary of clinical pharmacology studies; Table 2.7.2-7

Table 9: Least Squares Mean Ratio of Brimonidine Plasma Exposure of Days 107 and 21 for Combination BID (PK Data)

Parameter	Least Squares Means 107	Least Squares Means 21	Least Squares Mean Ratio	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	0.0592	0.0643	0.921	0.694	1.22
AUC_{0-t} (ng*hr/mL)	0.172	0.174	0.991	0.749	1.31

Brinz/Brim BID = Brinzolamide 1%/Brimonidine Tartrate 0.2% Ophthalmic Suspension, two times a day dosing
107 = Visit Day 107
21 = Visit Day 21
ANOVA performed on ln-tranformed data to calculate least squares means

From Section 2.7.2 Summary of clinical pharmacology studies; Table 2.7.2-8

SAFETY RESULTS:

The safety population included a total of 144 healthy male and female subjects ranging from 18 to 77 years of age who were exposed to study medication. No subject experienced a serious adverse event. No subject discontinued study participation due to an adverse event.

A similar safety profile was observed comparing Brinzolamide/Brimonidine to the individual components. No additional risks were identified in a population of healthy subjects dosed with Brinzolamide/Brimonidine TID or BID for 13 weeks, based upon a review of adverse events, an assessment of ocular, cardiovascular, physical examination, and clinical laboratory parameters, and the known risks of the individual components.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from Study C-10-010 adequately assessed the steady-state PK of brimonidine in plasma and RBC saturation of brinzolamide and N-desethyl brinzolamide following topical ocular administration of Brinzolamide 1% / Brimonidine Tartrate 0.2% Ophthalmic Suspension dosed 3 TID or BID to the individual components (i.e.,Brinzolamide or Brimonidine Tartrate, respectively) in healthy subjects. The sponsor's conclusions are valid.

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/s/

YONGHENG ZHANG
03/22/2013

PHILIP M COLANGELO
03/22/2013

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA:	204251
Drug Name:	Brinzolamide/Brimonidine Tartrate 1%/0.2%
Indication:	For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Applicant:	Alcon Research, Ltd.
Submission Date:	June 19, 2012
Filing Date:	August 18, 2012
PDUFA Date:	April 19, 2013
OCP Primary Reviewer:	Yongheng Zhang Ph. D.
OCP Team Leader:	Philip Colangelo Pharm. D., Ph.D.

QUESTION	***YES***	***NO***	***NA***	***COMMENTS***
Fileability: ***Is the Clinical Pharmacology section of the application fileable?*** ***(if 'NO', please comment as to why it is not fileable)***	***YES***			
Fileability Review Components				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	☒	☐	☐	
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	☒	☐	☐	Phase 1 multi-dose PK study (C-10-010) submitted
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	☐	☐	☒	The formulation used in Study C-10-010 is the same as the to-be-marketed formulation
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	☐	☐	☒	
5. Are complete and relevant bioanalytical reports included in the NDA submission?	☒	☐	☐	
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	☐	☐	☒	
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	☒	☐	☐	

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/s/

YONGHENG ZHANG
08/24/2012

PHILIP M COLANGELO
08/24/2012