CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204822Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-822	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DTOP		
Applicant:	Alcon Research, Ltd.	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	IZBA™ (proposed)	**Acting Supervisor:** Richard T. Lostritto, Ph.D.	
Generic Name:	Travoprost	**Date Assigned:**	7/23/2013
Indication:	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	**Date of Review:**	4/9/2014
Formulation/strength	Ophthalmic Solution 0.003%		
Route of Administration	Topical		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Date:	GRMP Date	PDUFA Date
July 15, 2013	April 10, 2014	5/15/2014
Type of Submission	505 (b) (1)	
Key review point	Evaluation of the Biowaiver request	

TABLE OF CONTENTS

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Background:

The Applicant received FDA approval (NDA 021257) and EU marketing authorization (EU/1/01/199/001-002) in 2001 for Travoprost 40 µg/mL eye drops, solution preserved with benzalkonium chloride (Travoprost 0.004% BAK).

The Applicant introduced two additional products. The first product is Travoprost 40 µg/mL eye drops, solution preserved with sofZia (Travoprost 0.004% sofZia) which was approved in the USA in September 2006 (NDA 21-994), and is marketed in Canada and Japan. The second product is Travoprost 40 µg/mL eye drops (Travoprost 0.004% PQ), solution preserved with polyquaternium-1 (POLYQUAD) which was approved by EMA in November 2010 and is marketed in different countries worldwide.

The Applicant stated that both formulations (Travoprost 0.004% sofZia and Travoprost 0.004% PQ) confer benefit relative to the Travoprost 0.004% BAK formulation by providing an alternative to benzalkonium chloride, a preservative associated with conjunctival inflammation, tear film disruption, and symptoms of ocular surface health disease following chronic exposure.

Also, the Applicant pointed out that evaluations of bioavailability data and dose-response relationships for various travoprost formulations suggested that maximization of the benefit risk ratio may be achieved by reducing the active drug concentration while achieving equivalent IOP-lowering efficacy to the previously approved benzalkonium chloride preserved Travoprost 0.004% BAK and maintaining similar safety profile. Therefore, the Applicant developed the proposed product Travoprost Ophthalmic Solution, 0.003% (Travoprost Eye Drops Solution, 0.003%). This product is a sterile, preserved, multi-dose topical ophthalmic formulation containing 30 µg/ml travoprost. The proposed product has a lower concentration (0.003%) and a different preservative (POLYQUAD) than the previously US approved benzalkonium chloride preserved Travoprost 0.004% BAK. However, with the exception of the active drug concentration, the proposed formulation of Travoprost 0.003% Solution is (b) (4) the EU approved formulation of Travoprost 0.004% PQ.

Submission:

NDA 204822 was submitted in accordance with Section 505(b) (1) of the FDC Act and 21 CFR 314.50 for use of Travoprost Opththalmic Solution 0.003% for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The proposed drug product, Travoprost 0.003% Solution (b) (4) the currently EU approved POLYQUAD-preserved TRAVATAN (Travoprost 0.004% PQ) with the exception of a lower travoprost concentration of 0.003% compared with 0.004%.

To support the approval of this formulation, the Applicant is relying on the body of work

that had been compiled for the approval of the US approved Travoprost 0.004% BAK formulation (3 Phase 3 clinical trials and 2 dose-response clinical trials), and the clinical development conducted to support the approval of Travoprost 0.003% Solution (the subject of this NDA), which included one Phase 3 safety and efficacy study (C-11-034, Module 5351). This safety and efficacy study was designed to demonstrate the equivalence of Travoprost 0.003% Solution to Travoprost 0.004% BAK (US approved formulation), with both dosed once daily in the evening in patients with open-angle glaucoma or ocular hypertension.

Proposed Product:

According to the Applicant, evaluation of bioavailability data and dose-response relationships suggested that reducing the active drug concentration would provide a better benefit risk ratio. Hence, the active drug concentration is (b) (4) the formulations Travoprost 0.004% PQ approved in Europe and the proposed Travoprost 0.003% solution.

The drug substance Travoprost is a synthetic prostaglandin $F_{2\ (alpha)}$ analogue. Travoprost is insoluble in water but very soluble in acetonitrile, methanol, octanol, and chloroform.

The proposed product, Travoporst Ophthalmic Solution, 0.003%, is a sterile, preserved, multi-dose topical ophthalmic formulation containing 30 µg/mL travoprost.

The following two marketed travoprost formulations are approved in the United States:

- Travoprost 40 µg/mL eye drops, solution preserved with benzalkonium chloride (referred to as Travoprost 0.004% BAK) which was approved in 2001 (NDA 21-257).
- Travoprost 40 µg/mL eye drops, solution preserved with sofZia (referred to as Travoprost 0.004% sofZia) which was approved in 2006 (NDA 21-994).

And, the following one marketed travoprost formulation is approved in Europe:

- Travoprost 40 µg/mL eye drops, solution preserved with polyquaternium-1 (POLYQUAD) (referred to as Travoprost 0.004% PQ) which was approved in 2010.

In the current submission, the Applicant developed 30 µg/mL eye drops, solution (referred to as Travoprost 0.003% Solution) preserved with polyquaternium-1 (POLYQUAD) which is the same preservative used in the Travoprost 40 µg/mL eye drops, solution (referred to as Travoprost 0.004% PQ) approved in Europe.

Travoprost 0.003% Solution will be packaged in a natural (b) (4) polypropylene (b) (4) oval bottle with a natural polypropylene (PP) dispensing plug and a turquoise polypropylene closure.

Review:

In this submission, pursuant to 21 CFR §320.22(b) (1), the Applicant is requesting a waiver from the requirements for submission of in-vivo bioavailability or bioequivalence data. The proposed drug product is an ophthalmic product applied topically to the eye and is intended only for local therapeutic effect. This Biopharmaceutics review is focused on the evaluation of the acceptability of the biowaiver request.

The Applicant provided the following justifications in support of the biowaiver request:

- The clinical pharmacokinetic studies demonstrated very low systemic plasma levels following topical administration of Travoprost 0.004% BAK with concentrations in most all samples from 5 multiple-dose studies being less than a sensitive assay's quantitation limit of 10 pg/mL. Therefore, the proposed product Travoprost 0.003% is expected to have even lower systemic plasma levels than Travoprost 0.004% BAK.

- The concentration of POLYQUAD (0.01 mg/mL) in Travoprost Eye Drops Solution, 0.003% is essentially the same as that approved for some artificial tears products and in the marketed IOP-lowering eye drops Brimonidine Tartrate Ophthalmic Solution, 0.15% (US), TRAVATAN® PQ (EU), and DUOTRAV® PQ (b) (4).

- Compared to TRAVATAN® BAK (containing 0.15 mg/ml BAK) and other approved IOP-lowering products on the market such as XALATAN and LUMIGAN (both containing 0.2 mg/ml BAK), the concentration of preservative in Travoprost Eye Drops Solution, 0.003% at 0.01mg/ml has been reduced by 15- to 20-fold.

- The excipients mannitol, propylene glycol, and sodium chloride concentrations in Travoprost 0.003% solution are (b) (4) in Travoporst 0.004% PQ. And, propylene glycol is used in TRAVATAN Z (Travoprost 0.004% sofZia) in the US and Japan (b) (4).

- The concentration of boric acid in Travoprost 0.003% Solution is (b) (4) in Travoprost 0.004% BAK. And, the concentration of mannitol in Travoprost 0.003% Solution is (b) (4) in Travoprost 0.004% BAK.

- The Polyoxyl 40 Hydrogenated Castor Oil (HCO-40) is utilized in Travoprost Eye Drops Solution, 0.003% to (b) (4) travoprost. Its concentration in Travoprost 0.003% is (b) (4) TRAVATAN® PQ.

- The proposed acceptance criteria for pH and osmolality are (b) (4) mOsm/kg, respectively. The Applicant stated that the proposed pH is (b) (4) the pH used for Travoporst 0.004% PQ (approved in Europe).

II) RECOMMENDATION

The ONDQA-Biopharmaceutics team reviewed NDA 204-822 for Travoporst Ophthalmic Solution, 0.003% and found the biowaiver request acceptable. Therefore, the biowaiver is granted.

From the Biopharmaceutics perspective, NDA 204-822 is recommended for approval.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: DARRTS/Lostritto

III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW APPROACH

A) GENERAL ATTRIBUTES

a. What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility)?

Travoprost is a synthetic prostaglandin $F_{2(alpha)}$ analogue. It is a colorless to light yellow oil that is insoluble in water but soluble in acetonitrile, methanol, octanol, and chloroform. The partition coefficient between n-octanol and water for travoprost was determined by the shake flask method at 25 ±1 ºC to be 5.03.

b. What is the route of administration? How is the product being administered?

The proposed product is an ophthalmic solution to be administered topically. The product is formulated in a multi-dose, sterile, and preserved formulation.

c. Does the drug product include a delivery device?

No.

B) DRUG PRODUCT FORMULATION

d. What is the formulation?

Travoprost 0.003% Solution is a clear, colorless to pale yellow aqueous solution formulated at a pH of approximately 6.8 and is isotonic.

The selection of excipients for Travoprost Eye Drops Solution, 0.003% was based on the EU approved TRAVATAN® PQ formulation. The product is a polyquaternium-1 (POLYQUAD) preserved formulation containing a lower concentration of travoprost with the primary objective of achieving equivalent IOP-lowering efficacy to the currently US approved benzalkonium chloride (BAK) preserved TRAVATAN® while maintaining similar safety profile.

The components and composition of Travoprost 0.003% solution are shown in Table 1.

Table 1: Components and Composition of Travoprost 0.003 Solution

Component	% w/v	mg/ml	Function	Quality Reference
Travoprost (AL-6221)	0.003 [a]	0.03 [a]	Active	In-House [b]
Polyoxyethylene Hydrogenated Castor Oil 40 (HCO-40)	(b) (4)			JPE [c]
Propylene Glycol				USP
Boric Acid				NF
Mannitol				USP
Sodium Chloride				USP
Polyquaternium-1 Solution [d] (eq. to Polyquaternium-1)	0.001	0.01	Preservative	In-House
Hydrochloric Acid and /or Sodium Hydroxide	Adjust pH to 6.8	Adjust pH to 6.8	pH Adjustment pH Adjustment	NF NF
Purified Water	(b) (4)			USP

(b) (4)

[b] Travoprost will be tested to the approved specifications for TRAVATAN.

[c] JPE = Japanese Pharmaceutical Excipients. The Ph. Eur. (Macrogolglycerol Hydroxystearate) tests for heavy metal, alkalinity and appearance of solution will be substituted for the corresponding JPE tests. In addition, the following (supplemental) tests from the Ph. Eur. Monograph will be applied: free ethylene oxide, dioxan and iodine value. This is the same compendial designation and specification as approved for TRAVATAN).

[d] Polyquaternium-1 = POLYQUAD = polyquat = polidronium chloride. (b) (4)

(b) (4)

e. What are the highlights of the drug product formulation development?

The US and EU approved Travoprost 0.004% eye drops, solution is preserved with benzalkonium chloride (Travoprost 0.004% BAK). Whereas, the EU approved Travoprost 0.004% PQ is preserved with POLYQUAD.

Travoprost 0.003% Solution (b) (4) the currently EU approved POLYQUAD-preserved TRAVATAN (Travoprost 0.004% PQ) with the exception of a lower travoprost concentration of 0.003%.

A comparison of the Travoprost 0.003% Solution, Travoprost 0.004% PQ and the Travoprost 0.004% BAK formulations is shown in Table 2.

Table 2: Comparison of Travoprost 0.003% Solution, Travoprost 0.004% PQ and Travoprost 0.004% BAK formulations

Component	Travoprost 0.003% Solution % w/v	Travoprost 0.004% PQ % w/v	Travoprost 0.004% BAK % w/v
Travoprost (AL-6221)	0.003	0.004	0.004
Polyquaternium-1 (POLYQUAD)	0.001	0.001	-
Benzalkonium Chloride (BAK)	-	-	0.015
Polyoxyethylene Hydrogenated Castor Oil 40 (HCO-40)	(b) (4)		
Propylene Glycol			
Sodium Chloride			
Boric Acid			
Mannitol			
Disodium Edetate			
(b) (4)			
Hydrochloric Acid and/or Sodium Hydroxide	Adjust to pH 6.8	(b) (4)	Adjust to pH 6.0
Purified Water	(b) (4)		

"-" = Not present.

The Applicant stated that POLYQUAD, the preservative used in the formulation, is a preservative currently used worldwide in ophthalmic and lens care products. The Applicant selected the 0.01mg/mL concentration of POLYQUAD based on the concentration established for Travoprost 0.004% PQ as well as other ophthalmic formulations (e.g., Brimonidine Tartrate Ophthalmic Solution, 0.15% and DUOTRAV [Travoprost 0.004%/Timolol 0.5%] PQ). Also, the concentration of the preservative in Travoprost Eye Drops Solution, 0.003% (0.01 mg/mL POLYQUAD) is reduced by 15 to 20 fold as compared to the concentration of the preservative in Travoprost 0.004% BAK (0.15 mg/mL BAK).

In Support of the inclusion of the other excipients, the Applicant stated that Boric acid is a (b) (4). Its concentration is (b) (4) in Travoprost 0.004% BAK and Travoprost 0.004% PQ. The (b) (4) (Polyoxyl 40 Hydrogenated Castor Oil, (HCO-40)) concentration in Travoprost 0.003% Solution is (b) (4) Travoprost 0.004% PQ.

The Applicant performed a rabbit pharmacokinetic study to determine the effect of travoprost concentration on topical ocular bioavailability and a second rabbit pharmacokinetic study was conducted to determine the effect of surfactant concentration on topical ocular bioavailability. Also, Preservative Effectiveness Testing (PET) was conducted on formulations containing 40 ppm travoprost to determine the effects of different excipients on preservation effectiveness. These studies will be reviewed by Pharm Tox and Microbiology Reviewers.

C) SUPPORTIVE INFORMATION

f. What data are available to support the approval of the proposed product?

To support the approval of the proposed product, the Applicant is relying on the body of work that had been compiled for the approval of the US approved Travoprost 0.004% BAK formulation (3 Phase 3 clinical trials and 2 dose-response clinical trials), and the clinical development for Travoprost 0.003% Solution which included 1 Phase 3 safety and efficacy study (C-11-034, Module 5351). This safety and efficacy study was designed to demonstrate the equivalence of Travoprost 0.003% Solution to Travoprost 0.004% BAK, with both dosed once daily in the evening in patients with open-angle glaucoma or ocular hypertension.

g. Does the Applicant rely on the safety and/or efficacy of a reference product?

No. (See the answer to *f* above).

h. Was a bioequivalence study conducted? If yes, is a Biopharmaceutics Review needed for the submission?

No, the safety and efficacy study (C-11-034, Module 5351) was designed to demonstrate the equivalence of Travoprost 0.003% Solution to Travoprost 0.004% BAK.

Also, the formulation used in the pivotal clinical study C-11-034 (Lot 11-700064-1) has the same composition as the proposed formula for marketing.

D) BIOWAIVER

i. Is there a waiver request for the submission of in vivo BA/BE data (biowaiver)?

Yes, the Applicant is requesting a biowaiver from the requirements for submission of in vivo bioavailability or bioequivalence data.

j. What is the purpose of the biowaiver request?

Pursuant to 21 CFR § 320.22(b) (1), the applicant requests a waiver from the requirements for submission of *in vivo* bioavailability or bioequivalence data. The drug product is an ophthalmic product applied topically to the eye and is intended only for local therapeutic effect.

k. What information supports the biowaiver request?

The Applicant stated that pharmacokinetics studies were not conducted with Travoprost 0.003% Solution for the following two reasons:

1. *The results on rabbit ocular tissue distribution and plasma data showed both C_{max} and $AUC_{0\text{-}6h}$ levels were very similar following topical ocular doses of Travoprost 0.004% BAK, and*
2. *Travoprost 0.004% PQ (formulated* [redacted] *as Travoprost 0.003% Solution).*

Therefore, the Applicant concluded that it is reasonable to expect that ocular and systemic exposure levels would be approximately dose proportionally less with Travoprost 0.003% Solution compared to Travoprost 0.004% BAK and Travoprost 0.004% PQ.

- The clinical pharmacokinetic studies demonstrated very low systemic plasma levels following topical administration of Travoprost 0.004% BAK with concentrations in most all samples from 5 multiple-dose studies being less than a sensitive assay's quantitation limit of 10 pg/mL.

- *In vitro* and *in vivo* toxicity studies were conducted comparing the tolerability and toxicity of POLYQUAD versus BAK. Results of the *in vitro* studies show that POLYQUAD and ophthalmic formulations preserved with POLYQUAD demonstrate less toxicity than ophthalmic formulations containing BAK. Results of the *in vivo* study suggest that POLYQUAD and TRAVATAN® PQ are better tolerated than BAK or BAK-preserved formulations.

The Applicant provided the following justifications for using the excipients found in Travoprost Eye Drops Solution, 0.003%:

- At 0.01 mg/mL, the concentration of POLYQUAD in Travoprost Eye Drops Solution, 0.003% is essentially the same as that approved for some artificial tears products and in the marketed IOP-lowering eye drops Brimonidine Tartrate Ophthalmic Solution, 0.15% (US), TRAVATAN® PQ (EU), and DUOTRAV® PQ [redacted].

- Compared to TRAVATAN® BAK (containing 0.15 mg/ml BAK) and other approved IOP-lowering products on the market such as XALATAN and LUMIGAN (both containing 0.2 mg/ml BAK), the concentration of preservative in Travoprost Eye Drops Solution, 0.003% at 0.01mg/ml has been reduced by 15- to 20-fold.

- The concentrations of Boric acid and mannitol acting as [redacted] in Travoprost 0.003% Solution are either [redacted] (boric acid) [redacted] (mannitol) than the concentration of the same two excipients in Travoprost 0.004% BAK.

- The Applicant stated that the development of TRAVATAN® PQ included [redacted] with propylene glycol and sodium chloride [redacted].

- The Applicant stated that the mannitol, propylene glycol, and sodium chloride concentrations in Travoprost 0.003% Solution are [redacted] Travoprost 0.004%

PQ. And, propylene glycol is used in TRAVATAN Z (Travoprost 0.004% sofZia) in the US and Japan [redacted (b) (4)].

- The Polyoxyl 40 Hydrogenated Castor Oil (HCO-40) is utilized in Travoprost Eye Drops Solution, 0.003% to [redacted (b) (4)]. The HCO-40 concentration in Travoprost 0.003% is [redacted (b) (4)] TRAVATAN® PQ.

Reviewer's Overall Assessment: **SATISFACTORY**.

l. Are the CFR requirements for granting a biowaiver met? If not, are the provided justification and supportive data appropriate?

Yes.

m. Is the overall information supporting the biowaiver request acceptable?

Yes.

n. Is the biowaiver granted?

Yes.

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

/s/

HOUDA MAHAYNI
04/20/2014

ANGELICA DORANTES
04/20/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	204,822
Submission Date(s):	July 15, 2013
Proposed Brand Name	IZBA™
Generic Name	Travoprost Ophthalmic Solution
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.
Submission Type; Code	Original Standard
Formulation; Strength(s)	Travoprost Ophthalmic Solution, 0.003%
Indication	For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

SUMMARY

Travoprost is the isopropyl ester prodrug of a potent and selective FP prostaglandin receptor agonist, i.e., travoprost acid. It is in the pharmacological class of PGF2α agonists that includes the IOP-lowering agents latanoprost and bimatoprost, marketed in the United States as XALATAN® and LUMIGAN®, respectively. Prostaglandin analogues are believed to lower intraocular pressure by increasing the outflow of aqueous humor via trabecular meshwork and uveoscleral pathways.

The first travoprost-containing product was approved as TRAVATAN in 2001 under NDA 21257, 0.004% preserved with benzalkonium chloride (BAK). The marketing status for this product is "discontinued". The submitted clinical pharmacokinetic studies have demonstrated low systemic plasma concentrations following topical administration of Travoprost 0.004% BAK.

In 2006, a new travoprost-containing product was approved as TRAVATAN Z under NDA 21994. It has the same strength of 0.004% but without BAK. The Clinical Pharmacology reviewer accepted the sponsor's request for the *in vivo* BA waiver, based on the considerations that " *the difference between TRAVATAN and TRAVATAN Z are not expected to influence the limited systemic bioavailability of travoprost, and the therapeutic bioequivalence established in Study C-04-17 (TRAVATAN versus TRAVATAN Z, N=690 patients)".* Please refer to the Clinical Pharmacology Review in DARRTS dated 06/28/2006.

In 2010, another travoprost-containing product was approved as TRAVATAN APS by EMA. The strength is still 0.004% but polyquaternium-1 was used as the preservative.

For the current NDA, the proposed product is similar to the one approved by EMA (*0.004% with polyquarternium-1*), except that the strength is lowered to 0.003%. The proposed dosage and indication for the new product is the same as that FDA-approved for TRAVATAN and

TRAVATAN Z: once-daily topical ocular therapy for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The sponsor has not conducted any additional clinical pharmacology studies and requested a waiver from the requirements for submission of *in vivo* bioavailability or bioequivalence data. To support the NDA, the sponsor conducted a therapeutic equivalence Phase 3 Study C-11-034 (*Travoprost 0.003% vs. Travoprost 0.004% BAK, i.e., TRAVATAN, N=864 patients*).

The Sponsor's request for a waiver from the requirements for submission of *in vivo* bioavailability/ bioequivalence data is acceptable based on the consideration that the differences in formulation between TRAVATAN and Travoprost ophthalmic solution 0.003% (*Polyquarternium-1 as the preservative*) are not expected to influence the limited systemic availability of travoprost, and the therapeutic bioequivalence established by Alcon Study C-11-034 (*Travoprost 0.003% vs. Travoprost 0.004% BAK, i.e., TRAVATAN, N=864 patients)*.

In conclusion, no substantial review and labeling update (*with respect to Section 12.3 Pharmacokinetics*) are needed for this NDA from a clinical pharmacology perspective. The submission is approvable from a clinical pharmacology perspective.

_____
Yongheng Zhang, Ph.D.
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

Concurrence:

_____
Philip Colangelo, Pharm.D., Ph. D.
Team Leader
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

cc: Division File: NDA 204822; HFD-520 (CSO/ Milstein); HFD-520 (MO/Boyd); HFD-520 (Chambers); HFD-880 (Lazor)

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

/s/

YONGHENG ZHANG
12/13/2013

PHILIP M COLANGELO
12/13/2013

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA:	204,822
Drug Name:	Travoprost Ophthalmic Solution, 0.003%
Indication:	For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Applicant:	Alcon Laboratories Inc.
Submission Date:	July 15, 2013
Filing Date:	September 13, 2013
PDUFA Date:	May 15, 2014
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***			A waiver of the requirement for submission of in vivo bioavailability data was requested by the sponsor
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?	☐	☐	☒	No new clinical pharmacology studies conducted
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)?	☐	☐	☒	
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?	☐	☐	☒	

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

/s/

YONGHENG ZHANG
08/27/2013

PHILIP M COLANGELO
08/27/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204-822
Submission Date	July 15, 2013
Product name, generic name of the active	Travoprost
Dosage form and strength	Ophthalmic Solution 0.003%
Indication	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Applicant	Alcon Research, Ltd.
Clinical Division	DTOP
Type of Submission	Original New Drug Application
Biopharmaceutics Reviewer	Houda Mahayni, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

I. SUBMISSION OVERVIEW

NDA 204822 was submitted in accordance with Section 505(b) (1) of the FDC Act and 21 CFR 314.50 for use of Travoprost Opththalmic Solution 0.003% for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The product is to be used topically, once-daily.

Pursuant to 21 CFR §320.22(b) (1), the Applicant requests a waiver from the requirements for submission of in-vivo bioavailability or bioequivalence data. The proposed drug product is an ophthalmic product applied topically to the eye and is intended only for local therapeutic effect.

II. BIOPHARMACEUTICS SUMMARY INFORMATION

The drug substance Travoprost is a synthetic prostaglandin $F_{2\ (alpha)}$ analogue. Travoprost is insoluble in water but very soluble in acetonitrile, methanol, octanol, and chloroform.

The following two marketed travoprost formulations are approved in the United States:

- Travoprost 40 µg/mL eye drops, solution preserved with benzalkonium chloride (referred to as Travoprost 0.004% BAK) which was approved in 2001 (NDA 21-257).
- Travoprost 40 µg/mL eye drops, solution preserved with sofZia (referred to as Travoprost 0.004% sofZia) which was approved in 2006 (NDA 21-994).

And, the following one marketed travoprost formulation is approved in Europe:

- Travoprost 40 µg/mL eye drops, solution preserved with polyquaternium-1 (POLYQUAD) (referred to as Travoprost 0.004% PQ) which was approved in Europe in 2010.

In the current submission, the Applicant developed 30 µg/mL eye drops, solution (referred to as Travoprost 0.003% Solution) preserved with polyquaternium-1 (POLYQUAD) which is the same preservative used in the Travoprost 40 µg/mL eye drops, solution (referred to as Travoprost 0.004% PQ) approved in Europe.

A comparison of Travoprost Eye Drop Formulations (w/v %) is shown in Table 1.

Table 1: Comparison of Travoprost Eye Drop Formulations (W/V %)

Component	Travoprost 0.004% BAK	Travoprost 0.004% sofZia	Travoprost 0.004% PQ	Travoprost 0.003% Solution
Travoprost (AL-6221)	0.004% (40 µg/mL)	0.004% (40 µg/mL)	0.004% (40 µg/mL)	0.003% (30 µg/mL)
Polyquaternium-1 (POLYQUAD)	-	-	0.001	0.001
Benzalkonium Chloride (BAK)	0.015	-	-	-
Zinc Chloride	(b) (4)			
Polyoxyethylene Hydrogenated Castor Oil 40 (HCO-40)				
Tromethamine (b) (4)				
Sorbitol				
Propylene Glycol				
Sodium Chloride				
Boric Acid				
Edetate disodium				
Mannitol				
Hydrochloric Acid and/or Sodium Hydroxide	Adjust pH 6.0	Adjust pH (b) (4)	Adjust pH (b) (4)	Adjust pH 6.8
Purified Water	(b) (4)			

To support the approval of this formulation, the Applicant is relying on the body of work that had been compiled for the approval of the U.S. approved Travoprost 0.004% BAK formulation (3 Phase 3 clinical trials and 2 dose-response clinical trials, and clinical development conducted to support the approval of Travoprost 0.003% Solution (the subject of this NDA) which included one Phase 3 safety and efficacy study (C-11-034, Module 5351). This safety and efficacy study was designed to demonstrate the equivalence of Travoprost 0.003% Solution to Travoprost 0.004% BAK (US approved formulation), with both dosed once daily in the evening in patients with open-angle glaucoma or ocular hypertension.

According to the Applicant, evaluation of bioavailability data and dose-response relationships suggested that reducing the active drug concentration would provide a better benefit risk ratio. Hence, the active drug concentration is (b) (4) the Travoprost 0.004% PQ formulation approved in Europe and the proposed formulation of Travoprost 0.003% solution.

Travoporst Ophthalmic Solution, 0.003% is a sterile, preserved, multi-dose topical ophthalmic

formulation containing 30 µg/mL travoprost.

The components of Travoprost 0.003% Solution, their concentration, function and quality reference are given in Table 2.

Table 2: Composition of Travoprost 0.003% Solution (Formulation Identification Number 119592)

Component	% w/v	mg/ml	Function	Quality Reference
Travoprost (AL-6221)	0.003 [a]	0.03 [a]	Active	In-House [b]
Polyoxyethylene Hydrogenated Castor Oil 40 (HCO-40)	(b) (4)			JPE [c]
Propylene Glycol				USP
Boric Acid				NF
Mannitol				USP
Sodium Chloride				USP
Polyquaternium-1 Solution [d] (eq. to Polyquaternium-1)	0.001	0.01	Preservative	In-House
Hydrochloric Acid and /or Sodium Hydroxide	Adjust pH to 6.8	Adjust pH to 6.8	pH Adjustment pH Adjustment	NF NF
Purified Water	(b) (4)			USP

[a] (b) (4)

[b] Travoprost will be tested to the approved specifications for TRAVATAN.

[c] JPE = Japanese Pharmaceutical Excipients. The Ph. Eur. (Macrogolglycerol Hydroxystearate) tests for heavy metal, alkalinity and appearance of solution will be substituted for the corresponding JPE tests. In addition, the following (supplemental) tests from the Ph. Eur. Monograph will be applied: free ethylene oxide, dioxan and iodine value. This is the same compendial designation and specification as approved for TRAVATAN).

[d] Polyquaternium-1 = POLYQUAD = polyquat = polidronium chloride. (b) (4)
(b) (4)

Travoprost 0.003% Solution will be packaged in a natural (b) (4) polypropylene (b) (4) oval bottle with a natural polypropylene (PP) dispensing plug and a turquoise polypropylene closure.

The proposed acceptance criteria are: pH (b) (4) and osmolality ((b) (4) mOsm/kg). The Applicant stated that the proposed pH is similar to the pH used for Travoporst 0.004% PQ. Also, the mannitol, propylene glycol, and sodium chloride concentrations in Travoprost 0.003%

solution are (b) (4) in Travoporst 0.004% PQ.

The Biopharmaceutics review will evaluate the data provided in support of the biowaiver request.

III. POTENTIAL REVIEW ISSUES – DAY 74 LETTER COMMENTS

The following parameters for the ONDQA's Product Quality - Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?		x	Solution product – Not Applicable.
2.	Is the dissolution test part of the DP specifications?		x	Solution product – Not Applicable.
3.	Does the application contain the dissolution method development report?		x	Solution product – Not Applicable.
4.	Is there a validation package for the analytical method and dissolution methodology?		x	Solution product – Not Applicable.
5.	Does the application include a biowaiver request?	x		Pursuant to 21 CFR §320.22 (b) (1), the Applicant requests a waiver from the requirements for submission of in vivo bioavailability or bioequivalence data. The drug product is an ophthalmic product applied topically to the eye and is intended only for local therapeutic effect.
6.	Does the application include an IVIVC model?		x	Not applicable.
7.	Is there a modified-release claim? If yes, address the following: a) Is there information submitted to support the claim in accordance with 320.25 (f)? b) Is there information on the potential for alcohol-induced dose dumping?		x	Not applicable.
8.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not applicable.

9.	Is information on mixing the product with foods or liquids included?		x	Not applicable.
10.	Is there any in *vivo* BA or BE information in the submission?		x	Pharmacokinetic studies demonstrated very low systemic plasma levels following topical administration of Travoprost 0.004% BAK with concentrations in most samples from 5 multiple-dose studies being less than a sensitive assay's quantitation limit of 10 pg/mL. Therefore, pharmacokinetic studies with Travoprost 0.003% Solution were not conducted.
11.	Is there any design space proposed using in vitro release as a response variable?		X	Not applicable. This NDA does not contain QbD elements.
12.	Is the control strategy related to in vitro drug release?		X	Not applicable.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
13.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		• The NDA is fileable from Biopharmaceutics Perspective. • The acceptability of the biowaiver request is a review issue.
14.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not Applicable.
15.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}
Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

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

/s/

HOUDA MAHAYNI
08/21/2013

ANGELICA DORANTES
08/21/2013