CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204822Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	5
Application Number(s)	NDA 204-822
Priority or Standard	Standard
Submit Date(s)	07/15/2013
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PDUFA Goal Date	05/15/2014
Division / Office	DTOP/OAP
Reviewer Name(s)	Jennifer D. Harris M.D.
Review Completion Date	01/22/2014
Established Name	travoprost ophthalmic solution 0.003%
(Proposed) Trade Name	Izba
Therapeutic Class	prostaglandin
Applicant	Alcon Laboratories, Inc.
Formulation(s)	Solution
Dosing Regimen	One drop in the affected eye(s) once daily in the evening
Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Intended Population(s)	patients with open-angle glaucoma or ocular hypertension

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Travoprost 0.003% is recommended for approval for the (b) (4) *of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.*

1.2 Risk Benefit Assessment

The purpose of this development program was to create a new formulation of travoprost that would maintain the IOP-lowering efficacy achieved with Travatan with lower drug exposure and potentially improving the safety profile. The new formulation with a 0.003% concentration trvoprost represents a 25% reduction from the currently approved travoprost 0.004%.

Results from the phase 3 study C-11-034 submitted in this NDA demonstrated that travoprost 0.003% lowered IOP by approximately 7-8 mmHg and was equivalent to Travatan in IOP-lowering efficacy as measured by mean IOP. The difference in mean IOP between travoprost 0.003% and Travatan was within 1.0mmHg at all post-baseline timepoints.

Overall, travoprost 0.003% was safe and well tolerated. The rate of adverse events were similar between travoprost 0.003% and Travatan with exception of conjunctival hemorrhage which was seven (7) fold higher in the Travatan group. There was no significant difference between groups in the number of dropouts/discontinuations.

Based on the single trial submitted in this NDA, the risk/benefit profile of travoprost 0.003% is considered equivalent to Travatan and is therefore recommended for approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.4 Recommendations for Postmarket Requirements and Commitments

There are no postmarket requirements or phase 4 commitments recommended for this product.

2 Introduction and Regulatory Background

2.1 Product Information

Travoprost is the isopropyl ester prodrug of a FP prostaglandin receptor agonist. It belongs to the pharmacological class of PGF2α agonists. Prostaglandin analogues are believed to lower intraocular pressure by increasing the outflow of aqueous humor via trabecular meshwork and uveoscleral pathways.

Comparison of Travoprost Eye Drop Formulation (W/V%)

Component	**Travoprost 0.004% BAK**	**Travoprost 0.003% Solution**
Travoprost	0.004% (40 µg/ml)	0.003% (30 µg/ml)
Polyquaternium-1		0.001
Benzalkonium Chloride	0.015	-
(b) (4)	-	-
Polyoxyethylene Hydrogenated Castor Oil 40	(b) (4)	
Tromethamine		
(b) (4)		
Propylene Glycol		
Sodium chloride		
Boric Acid		
Edetate disodium		
Mannitol		
Hydrochloric Acid and/or Sodium Hydroxide	Adjust pH 6.0	Adjust pH 6.8
Purified Water	(b) (4)	

2.2 Tables of Currently Available Treatments for Proposed Indications

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

Drug Products with Approved NDAs

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

Pharmacologic Class/ Applicant	**Tradename**	**Established Name**
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride
Alcon	Simbrinza	Carbonic anhydrase inhibitor/alpha-agonist
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is currently available in the following marketed products:

Travoporst 0.004% with BAK
Travoprost 0.004% BAK-free

2.4 Important Safety Issues with Consideration to Related Drugs

There are several known ocular complications associated with the use of prostaglandins. These include but are not limited to increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, and growth of eyelashes. Class labeling addressing this issue has been added to all existing topical prostaglandin labels and will be included in the label for this product.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The first travoprost-containing product to be developed was Travoprost 40 µg/mL solution preserved with benzalkonium chloride (BAK). This product, marketed as Travatan, received FDA approval in March 2001 and EU marketing authorization in November 2001. The original indication was for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who were intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication. The product indication was expanded to include approval for first-line therapy in the EU in April 2003 and in the USA in August 2010.

Travoprost 40 µg/mL solution preserved with sofZia (also known as SofZia-preserved Travoprost Ophthalmic Solution, 0.004%, Travatan BAK-free and Travatan Z) was approved in the USA in September 2006 and is also marketed in Canada and Japan. Travoprost 40 µg/mL solution preserved with polyquaternium-1 (also known as PQ-preserved travoprost 0.004% ophthalmic solution and Travatan APS) was approved by EMA in November 2010 and is marketed in approximately 60 countries worldwide.

The clinical development plan for Travoprost 0.003% Solution includes one phase 3 safety and efficacy study (C-11-034). 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.

2.6 Other Relevant Background Information

Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. For equivalence trials, efficacy is attained if the difference in mean IOP between treatment groups is within ±1.50 mm Hg at all post-baseline timepoints; and within ±1.00 mm Hg at the majority of post-baseline timepoints. This requirement for equivalence has been used for the approval of several IOP lowering products.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review. No additional clinical information was required from the sponsor.

3.2 Compliance with Good Clinical Practices

Study C-11-034 was conducted in accordance with the principles of Good Clinical Practice (ICH E6) and the Declaration of Helsinki and with the local laws and regulations relevant to the use of investigational therapeutic agents. Institutional Review Boards/Independent Ethics Committees approved the protocol prior to its initiation. Alcon personnel conducted monitoring of the study.

3.3 Financial Disclosures

Alcon has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for travoprost 0.003%. There were 5 out of 60 investigators who disclosed financial ties to the sponsor.

Investigator	Amount	Source	Patients Randomized
(b) (6)	$107k	Equity Grant and Expenses	(b) (6)
	$152k	Grant	
	$61k	Grant and Expenses	
	$85	Grant and Consulting	

*subinvestigator

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Travoprost Ophthalmic Solution, 0.003% is a sterile, preserved, multi-dose topical ophthalmic formulation containing 30 µg/ml travoprost.

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)
(b) (4)
(b) (4)

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical assessment for Travoprost 30 µg/mL solution is based upon the established nonclinical profiles of the active drug substance reviewed as part of the original NDA submission for Travatan.

4.4 Clinical Pharmacology

No studies were conducted to evaluate the pharmacokinetics of Travoprost 0.003% Solution in humans. The absorption, distribution, metabolism, excretion and toxicokinetics of AL-6221 have been studied. Topical ocular administration results in extremely low plasma concentrations. Data from four studies with 107 subjects have shown that plasma concentrations of the free acid are below 0.01ng/ml in two-thirds of the subjects.

4.4.1 Mechanism of Action

Travoprost free acid, a prostaglandin analog is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

4.4.2 Pharmacodynamics

N/A - Pharmacodynamic studies were not conducted.

4.4.3 Pharmacokinetics

N/A - Pharmacokinetic studies were not conducted.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol Type/No.	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing Duration	Total No. Randomised: Total No. Exposed to Travoprost 0.003% Solution
Safety/Efficacy Phase 3 C-11-034 (TDOC 0015855, 5351)	Multicenter, double-masked, randomized, active-controlled, 2-arm, parallel-group, equivalence study	Males and females of any race/ethnicity, who were 18 years of age and older, and who were diagnosed with open-angle glaucoma or ocular hypertension	Travoprost 0.003% Solution Travoprost 0.004% BAK	1 drop in the treated eye(s) once daily at 8 PM 1 drop in the treated eye(s) once daily at 8 PM	3 months	864 total: 442 exposed to Travoprost 0.003% Solution

5.2 Review Strategy

This application contains a single bioequivalence study to support the approval travoprost 0.003% for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The study was randomized, multicenter center, double-masked, active-controlled in design. The submitted clinical study report and clinical protocol related to Study C-11-034 were reviewed in depth.

5.3 Discussion of Individual Studies/Clinical Trials

Clinical Protocol – Study C-11-034

Title
A Multicenter, Double-Masked Study of the Safety and Efficacy of Travoprost Ophthalmic Solution, 0.003% Compared to Travatan in Patients with Open-Angle Glaucoma or Ocular Hypertension

Study Centers
This study was conducted at 60 investigational centers, including 52 in the US, 2 each in Sweden, Germany, and Austria, and 1 each in Spain and Finland. Fifty-nine of the 60 Investigators randomized at least 1 patient.

Objectives

To demonstrate that the intraocular pressure (IOP)-lowering efficacy of Travoprost 30 µg/mL Eye Drops, Solution (Travoprost 0.003% Solution) is equivalent to Travoprost 40 µg/mL Eye Drops, Solution (Travatan) in patients with open-angle glaucoma or ocular hypertension

Methodology

This was a multicenter, double-masked, randomized, active-controlled, two-arm, parallel group, equivalence study designed to evaluate the safety and efficacy of Travoprost 0.003% Solution relative to Travatan in adult patients with open-angle glaucoma or ocular hypertension. This study consisted of 6 visits conducted during two sequential phases: the Screening/Eligibility phase, which included a Screening Visit and 2 Eligibility Visits, and the treatment phase, which included 3 on therapy visits (conducted at Week 2, Week 6, and Month 3). Enrolled patients were randomized (1:1) at the second Eligibility Visit to 1 of the 2 study drugs and instructed to instill 1 drop of the assigned study drug in both eyes, once daily for 3 months. Evaluations of safety and efficacy were performed at selected time points (8 AM, 10 AM, and 4 PM) during study visits conducted at Week 2, Week 6, and Month 3.

Study Schedule

Activity	Screen	Eligibility 1 (scheduled based on washout)			Eligibility 2 (3–8 days from Eligibility 1)			Week 2 ± 1 day			Week 6 ± 3 days			Month 3 ± 3 days (Exit) or Early Exit		
		8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM
Informed consent [a]	X															
Demographics	X															
Inclusion/exclusion	X															
General health, medical history / concomitant medications	X	X			X			X			X			X		
Urine pregnancy test [b]	X													X		
Hyperemia [c]					X	X	X	X	X	X	X	X	X	X	X	X
Best-corrected visual acuity [c]	X	X			X			X			X			X		
Ocular signs [c]	X	X			X			X			X			X		
Flare/cells [c]					X			X			X			X		
IOP [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundus [c]	X															X
Gonioscopy [c]	X															
Automated perimetry [e]	X													X		
Pachymetry [c]	X															X
Discontinue current IOP-lowering medications	X															
Dispense study medication [f]							X			X			X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect study medication																X
Exit patient																X

Abbreviation: IOP = intraocular pressure

[a] Must have been signed/dated before any study procedures were performed.
[b] Pregnancy test was required for all female patients of childbearing potential.
[c] Must have been scored according to the grading criteria outlined in the Manual of Procedures.
[d] All IOP measurements should have been performed ± 30 minutes of the required time.
[e] If not performed at Screening, may have been performed between Screening and Eligibility 2 Visit. Visual fields must have been reliable prior to dispensation of medications.
[f] Study Medication was dispensed through an IWRS at the Eligibility 2 Visit once the patient met the inclusion criteria. Should the patient require additional study medication during the study (or not all kits were dispensed at the Eligibility 2 Visit), additional kits were dispensed at either the Week 2 or Week 6 Visits or as needed.

Number of Patients

860 subjects

Diagnosis and Main Criteria for Inclusion
The study population included males and females of any race/ethnicity, who were 18 years of age and older, and who were diagnosed with open-angle glaucoma or ocular hypertension. Patients must have had a mean IOP (after washout) at both the Eligibility 1 and 2 Visits in at least 1 eye (the same eye) that was ≥ 24 mmHg at the 8 AM (± 30 minutes) time point, and ≥ 21 mmHg at both the 10 AM (± 30 minutes) and 4 PM (± 30 minutes) time points. The patients must also have had a mean IOP ≤ 36 mmHg at all timepoints in both eyes.

Efficacy

Primary Efficacy

- IOP at Week 2, Week 6, and Month 3 for each assessment time point (8 AM, 10 AM, and 4 PM)

Supportive Efficacy

- Change from baseline in IOP and percent change from baseline in IOP at each visit (Week 2, Week 6, and Month 3) and assessment time point (8 AM, 10 AM, and 4 PM)
- Percentage of patients who achieved a target IOP level < 18 mmHg at each visit (Week 2, Week 6, and Month 3) and assessment time point (8 AM, 10 AM, and 4 PM)
- Percentage of patients who achieved IOP-lowering of at least 30% from baseline at each visit (Week 2, Week 6, and Month 3) and assessment time point (8 AM, 10 AM, and 4 PM)

Safety

A safety evaluation was conducted on all subjects who were enrolled into this study and received study drug. Safety-related parameters that included:

- Extent of exposure
- Adverse events (AEs)
- Best corrected visual acuity (BCVA)
- Ocular signs (eyelids/conjunctiva, cornea, lens, and iris/anterior chamber including aqueous flare and inflammatory cells)
- Visual field function tests (standard automated perimetry)
- Central corneal thickness (CCT)
- Ocular hyperemia
- Dilated fundus exam (vitreous, retina, macula, choroid, optic nerve, and cup to disc ratio)

Efficacy Analysis
The ITT analysis set was used to conduct the primary efficacy analysis. All supportive analyses were also based on the ITT analysis set. The PP analysis set was considered supportive and was

used only for the primary efficacy endpoint. The primary and supportive efficacy analyses were based on observed cases; missing data were not imputed.

Descriptive statistics were summarized for IOP at each on-therapy visit (Week 2, Week 6, and Month 3) and assessment time point (8 AM, 10 AM and 4 PM). In order to conclude equivalence, the 2-sided 95% CI for the difference in IOP between treatment groups (ie, the mean IOP in the Travoprost 0.003% Solution group minus the mean IOP in the Travatan group) must have been within ± 1.5 mmHg at each of the 3 assessment time points (8 AM, 10 AM, and 4 PM) for each on-therapy visit (Week 2, Week 6, and Month 3). In addition the majority of the CIs must also lie entirely within ± 1.0 mmHg.

Analysis Populations:

Safety – All randomized patients who received exposure to study drug

ITT – all patients who received exposure to study medication and had at least 1 scheduled on-therapy study visit.

PP– all patients who received study medication, had at least 1 scheduled on-therapy study visit and satisfied inclusion/exclusion criteria

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

6.1.1 Methods

The description of the clinical trial design is contained in section 5.3.

6.1.2 Demographics

Baseline Demographics Study – Study C-11-034

	Total (N = 860)		Trav 0.003% (N = 442)		Travatan (N = 418)	
	N	(%)	N	(%)	N	(%)
Age (Years)						
<65	380	(44.2)	189	(42.8)	191	(45.7)
≥65	480	(55.8)	253	(57.2)	227	(54.3)
Age (≥65 Years)						
≥65 to <75	307	(35.7)	167	(37.8)	140	(33.5)
≥75 to <85	157	(18.3)	79	(17.9)	78	(18.7)
≥85 to <95	16	(1.9)	7	(1.6)	9	(2.2)
Sex						
Male	347	(40.3)	173	(39.1)	174	(41.6)
Female	513	(59.7)	269	(60.9)	244	(58.4)
Ethnicity						
Hispanic, Latino, or Spanish	105	(12.2)	47	(10.6)	58	(13.9)
Not Hispanic, Latino, or Spanish	755	(87.8)	395	(89.4)	360	(86.1)
Race						
American Indian or Alaska Native	2	(0.2)	2	(0.5)	0	(0.0)
Asian	15	(1.7)	11	(2.5)	4	(1.0)
Black or African American	218	(25.3)	112	(25.3)	106	(25.4)
Native Hawaiian or Other Pacific Islander	2	(0.2)	1	(0.2)	1	(0.2)
White	623	(72.4)	316	(71.5)	307	(73.4)

	Total (N = 860) N	(%)	Trav 0.003% (N = 442) N	(%)	Travatan (N = 418) N	(%)
Iris Color						
Blue	201	(23.4)	94	(21.3)	107	(25.6)
Brown	519	(60.3)	276	(62.4)	243	(58.1)
Green	48	(5.6)	22	(5.0)	26	(6.2)
Grey	7	(0.8)	4	(0.9)	3	(0.7)
Hazel	84	(9.8)	45	(10.2)	39	(9.3)
Other	1	(0.1)	1	(0.2)	0	(0.0)
Diagnosis						
Ocular Hypertension	251	(29.2)	130	(29.4)	121	(28.9)
Open-Angle Glaucoma	594	(69.1)	304	(68.8)	290	(69.4)
Open-Angle Glaucoma with Pigment Dispersion	14	(1.6)	7	(1.6)	7	(1.7)
Open-Angle Glaucoma with Pseudoexfoliation	1	(0.1)	1	(0.2)	0	(0.0)
Actual Baseline IOP Stratum						
24 - 27 mmHg	594	(69.1)	303	(68.6)	291	(69.6)
28 - 36 mmHg	266	(30.9)	139	(31.4)	127	(30.4)
Randomized Baseline IOP Stratum						
24 - 27 mmHg	594	(69.1)	303	(68.6)	291	(69.6)
28 - 36 mmHg	266	(30.9)	139	(31.4)	127	(30.4)

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK
Actual Baseline IOP Stratum are constructed from the IOP data entered into EDC by the site.
Randomized Baseline IOP Stratum is constructed from the data entered in IWRS by the site at the time of randomization.

6.1.3 Subject Disposition

	Travoprost 0.003%	Travoprost 0.004%
All Randomized	442	422
Safety Population	442	421
ITT Population	442	418
PP Population	436	415

Patient Disposition (All Randomized Patients)

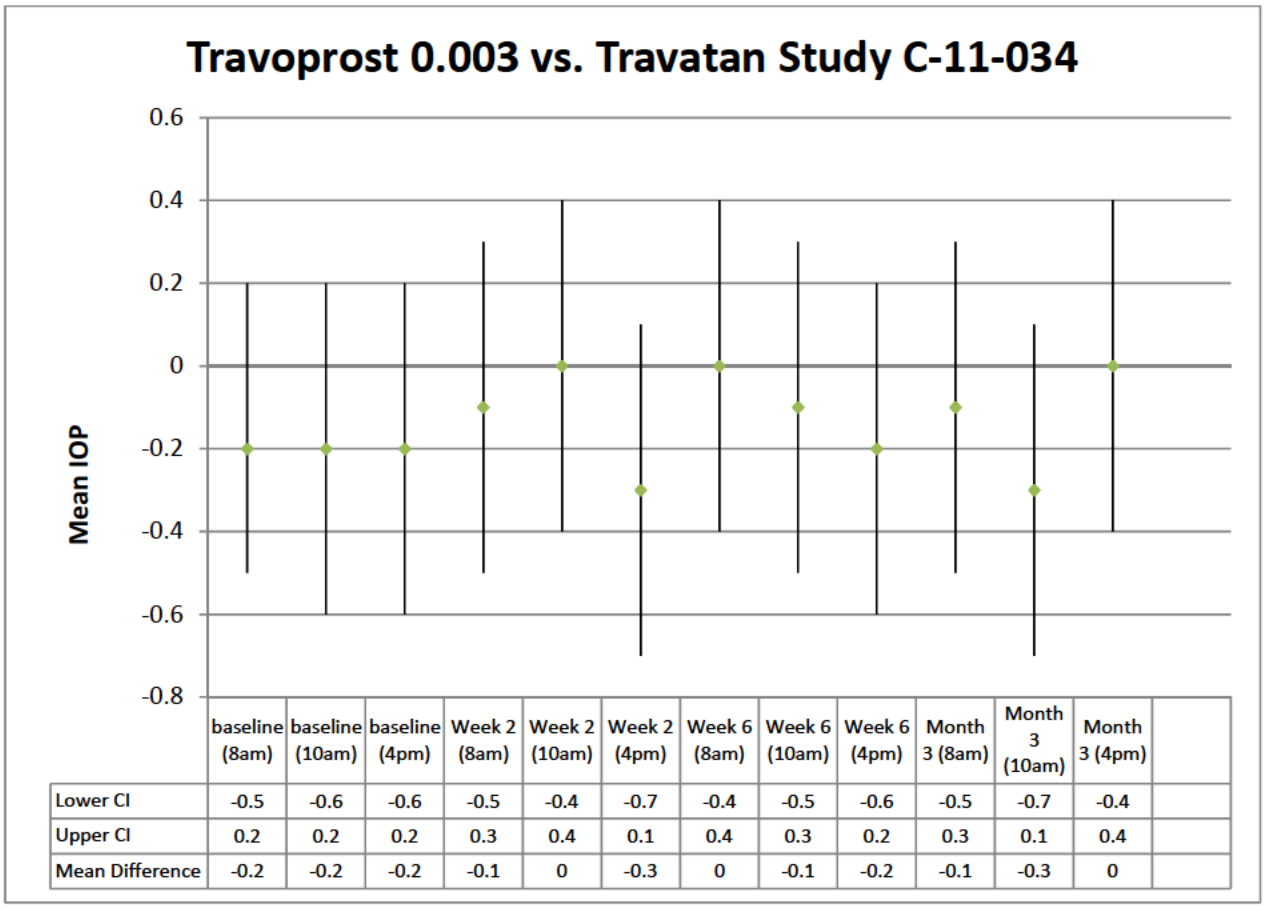
	Travoprost 0.003%	**Travoprost 0.004%**
Patients randomized (N)	442	422
Completed study, n (%)	432	408
Discontinued from study, n (%)	10	14

Adverse event	3	4
Patient decision	3	3
Noncompliance	1	0
Lost to follow-up	2	1
Inadequate IOP control	1	5
Other		1*

*Patient went out of town for 1 month. Patient was exited at sponsor's request.

Reviewer's Comments: *The patient disposition for both treatment groups were similar. Over 97% of patients in each both treatment groups completed the study.*

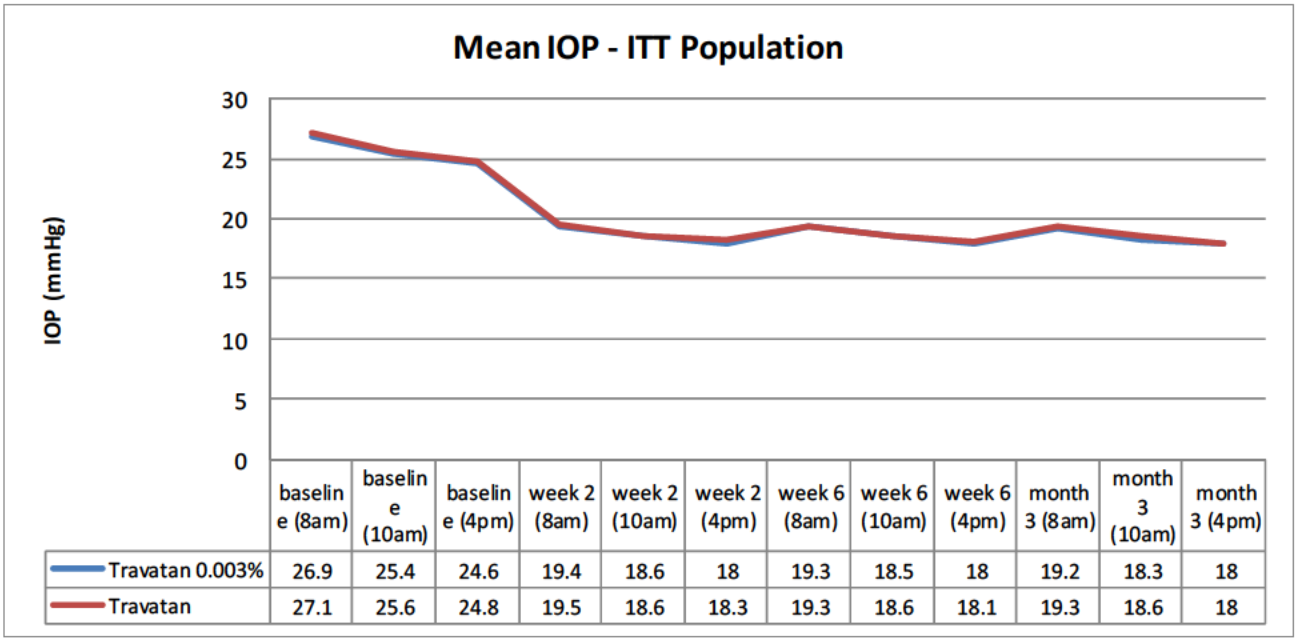
6.1.4 Analysis of Primary Endpoint(s)



	baseline (8am)	baseline (10am)	baseline (4pm)	Week 2 (8am)	Week 2 (10am)	Week 2 (4pm)	Week 6 (8am)	Week 6 (10am)	Week 6 (4pm)	Month 3 (8am)	Month 3 (10am)	Month 3 (4pm)
Lower CI	-0.5	-0.6	-0.6	-0.5	-0.4	-0.7	-0.4	-0.5	-0.6	-0.5	-0.7	-0.4
Upper CI	0.2	0.2	0.2	0.3	0.4	0.1	0.4	0.3	0.2	0.3	0.1	0.4
Mean Difference	-0.2	-0.2	-0.2	-0.1	0	-0.3	0	-0.1	-0.2	-0.1	-0.3	0

Source:NDA 204-822, Module 5, CSR for protocol C-11-034, Table 11.4.1.1-1..

Reviewer's Comments: *The 95% confidence interval of the mean difference in IOP between Travatan and travoprost 0.003% is within 1.0mmHg for all timepoints measured.*



	baseline (8am)	baseline (10am)	baseline (4pm)	week 2 (8am)	week 2 (10am)	week 2 (4pm)	week 6 (8am)	week 6 (10am)	week 6 (4pm)	month 3 (8am)	month 3 (10am)	month 3 (4pm)
Travatan 0.003%	26.9	25.4	24.6	19.4	18.6	18	19.3	18.5	18	19.2	18.3	18
Travatan	27.1	25.6	24.8	19.5	18.6	18.3	19.3	18.6	18.1	19.3	18.6	18

Source: NDA 204-822, Module 5, CSR for protocol C-11-034, Table 11.4.1.1-1.

Reviewer's Comments: *Travatan and travoprost 0.003% have similar IOP lowering ability throughout the trial. The mean reduction from baseline in IOP ranged from approximately 7 to 8 mmHg for both treatment groups.*

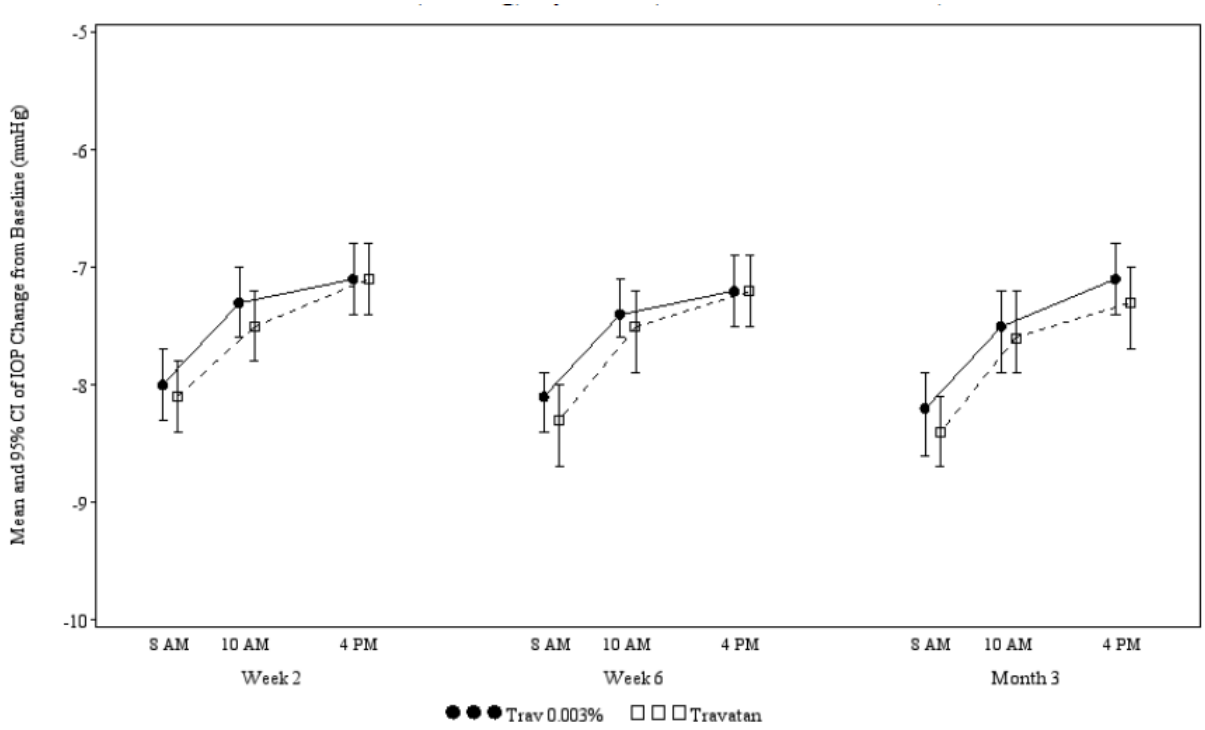
6.1.5 Analysis of Secondary Endpoints(s)

There were no secondary endpoints analyzed in this study.

6.1.6 Other Endpoints

Supportive Efficacy

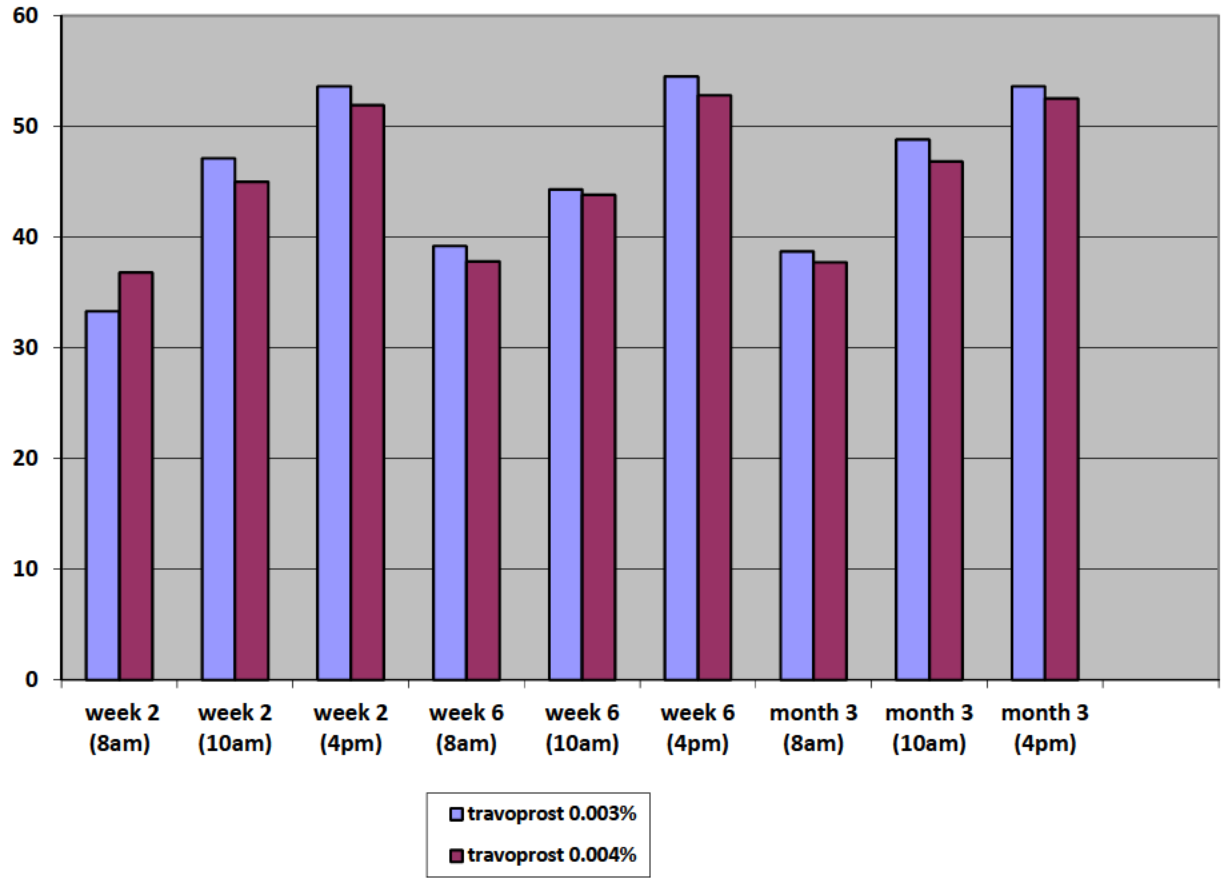
- **Change From Baseline in IOP at Each Visit**



Source: NDA 204-822, Section 2.5, Figure 2.5.4-1, page 29

Reviewer's Comments: *The percent reductions in IOP from baseline to each study visit and assessment time point ranged from approximately 28% to 30%.*

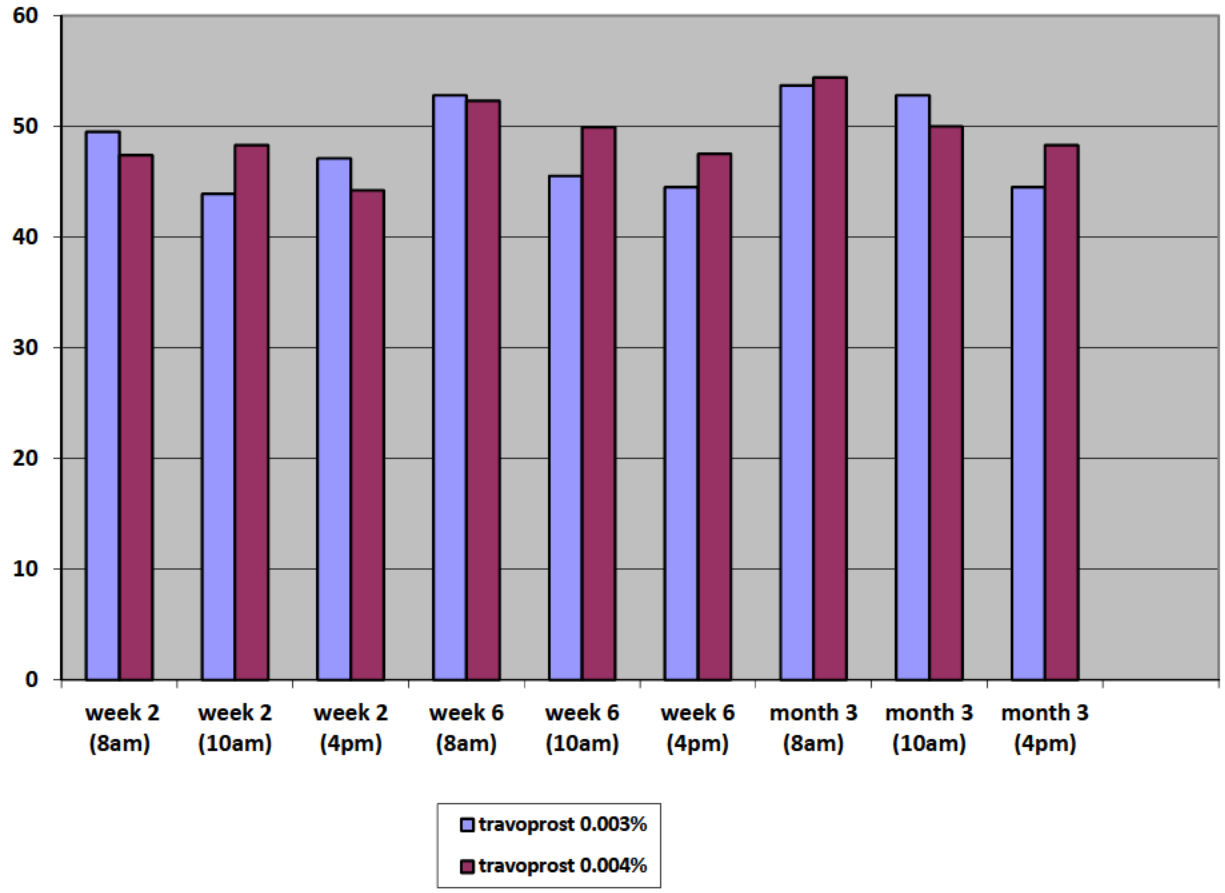
- **Percentage of Patients Who Achieved a Target IOP Level < 18**



Source: NDA 204-822, Module 5, CSR for protocol C-11-034, Table 2-2

Reviewer's Comments: *Approximately 35- 53% of patients were able to attain an IOP less than 18 mmHg during this study in both treatment groups. There appears to be a trend in that the largest number of patients achieving IOP < 18 is at the 4 pm measurement. There is a gradual increase in the number of patients achieving < 18 trend throughout the day.*

- **Percentage of Patients Who Achieved IOP-Lowering of at Least 30% From Baseline**



Source: NDA 204-822, Module 5, CSR for protocol C-11-034, Table 2-3

Reviewer's Comments: The number of patients who achieved and 30% reduction in IOP from baseline is similar in both the *Travatan and travoprost 0.003% groups.*

6.1.7 Subpopulations

Effects of the following subgroups were examined:

- age category (< 65 years, ≥ 65 years, and then further by ≥ 65 years to < 75 years, ≥ 75 years to < 85 years, and ≥ 85 years to < 95 years),
- sex,
- race,
- ethnicity,
- iris color,

- diagnosis
- IOP

Overall, there were no substantial differences observed between groups with respect to IOP at each study visit.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There are no additional dosing recommendations. Once daily administration in the evening has been shown to be optimal for this class of drugs.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The IOP lowering effect with travoprost 0.003% was consistent over the duration of the 3 month treatment phase. Travatan which has been marketed since 2001 has not demonstrated any tolerance effects.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocol Type/No.	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen	Dosing Duration	Total No. Randomised: Total No. Exposed to Travoprost 0.003% Solution
Safety/Efficacy Phase 3 C-11-034 (TDOC 0015855, 5351)	Multicenter, double-masked, randomized, active-controlled, 2-arm, parallel-group, equivalence study	Males and females of any race/ethnicity, who were 18 years of age and older, and who were diagnosed with open-angle glaucoma or ocular hypertension	Travoprost 0.003% Solution Travoprost 0.004% BAK	1 drop in the treated eye(s) once daily at 8 PM 1 drop in the treated eye(s) once daily at 8 PM	3 months	864 total: 442 exposed to Travoprost 0.003% Solution

Source: NDA 204-822, Section 2.5, Table 2.5.1-2, page 9

7.1.2 Categorization of Adverse Events

MedDRA nomenclature was used to code adverse events.

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

Data pooling is not applicable to this application. The safety of this product is based on the 12 month results of a single phase 3 study: 192024-031 in conjunction with what is known about the adverse effects associated with the use of this class of drugs.

7.2 Adequacy of Safety Assessments

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

A total of 863 patients (21 to 92 years of age) were exposed to one of the following treatments once daily for 3 months:

- Travoprost 0.003% Solution
- Travatan

Descriptive Statistics for Duration of Exposure to Study Drug (Days) (Safety Population)

	Trav 0.003% (N = 442)	Travatan (N = 421)
Mean	88.2	87.6
SD	8.27	10.76
Median	91	90
(Min, Max)	(19, 100)	(3, 98)

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK
SD = Standard Deviation

Source: NDA 204-822, Module 5, CSR for protocol C-11-034, Table 12.1-1.

Number and Percentage of Patients Exposed to Study Drug (Safety Population)

	Trav 0.003% (N = 442)		Travatan (N = 421)	
	N	(%)	N	(%)
1-15 Days	0	(0.0)	5	(1.2)
16-45 Days	7	(1.6)	4	(1.0)
46-87 Days	113	(25.6)	111	(26.4)
>87 Days	322	(72.9)	301	(71.5)

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK

Source: NDA 204-822, Module 5, CSR for protocol C-11-034, Table 12.1-2.

7.2.2 Explorations for Dose Response

Dose ranging was not conducted during development. Travaprost 0.003% is a 25% reduction in dose from the currently approved travoprost 0.004% formulation.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal/in vitro testing done for travoprost 0.003%.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of topical drops (i.e., biomicroscopy, visual acuity, fundoscopy, etc) were adequately addressed in the design and conduct of the clinical trial. There were no meaningful differences in visual acuity, visual fields, corneal thickness, and fundus parameters.

7.2.5 Metabolic, Clearance, and Interaction Workup

Clinical pharmacology studies have not been conducted with travoprost 0.003% solution. Travoprost 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

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

There are several known ocular complications associated with the use of prostaglandins. These include but are not limited to increased pigmentation of the iris, periorbital tissue (eyelid) and

eyelashes, and growth of eyelashes. The applicant's trial design adequately assessed these known adverse events. There were no additional assessments required.

7.3 Major Safety Results

7.3.1 Deaths

No patient deaths were reported during the clinical trial.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal Serious Adverse Events-Study C-11-034

Treatment	Age/Sex	Adverse Event
Travoprost 0.003%	66/M	chest pain
Travoprost 0.003%	57/F	gastroenteritis viral
Travoprost 0.003%	85/F	pneumothorax
Travoprost 0.003%	71/F	chest pain
Travoprost 0.003%	75/M	abdominal pain, collapse of lung, injury
Travoprost 0.004%	80/M	nephrolithiasis
Travoprost 0.004%v	68/M	myocardial infarction
Travoprost 0.004%	83/M	cellulitis
Travoprost 0.004%	75/M	diabetes mellitus
Travoprost 0.004%	51/F	diabetic ketoacidosis
Travoprost 0.004%	66/M	erysipelas
Travoprost 0.004%	69/F	drug hypersensitivity

Reviewer's Comments:
There are no significant differences in the rate of serious non-fatal adverse events between the two treatment groups.

7.3.3 Dropouts and/or Discontinuations

Discontinuations – Safety Population

	Travoprost 0.003%	**Travoprost 0.004%**
Total	10	14
Adverse event	3	4
Patient decision	3	3
Noncompliance	1	0
Lost to follow-up	2	1
Inadequate IOP control	1	5
Other		1

Patients with Adverse Events Leading to Patient Discontinuation (Safety Set)

Treatment	**Age/Sex**	**Adverse Event**	**Onset day**
Travoprost 0.003%	66/F	eye irritation, eye pruritus	16
Travoprost 0.003%	44/F	myalgia	2
Travoprost 0.003%	67/F	conjunctival hyperemia, photophobia vision blurred	40 64
Travoprost 0.004%	62/F	dizziness, somnolence	4
Travoprost 0.004%	51/F	ulcerative keratitis	82
Travoprost 0.004%	72/F	eyelid edema headache ocular hyperemia	9 3 3
Travoprost 0.004%	61/F	conjunctivitis allergic, ocular hyperemia	1

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuations are presented in section 7.3.3. There were no other significant adverse events identified.

7.3.5 Submission Specific Primary Safety Concerns

N/A-There are no submission specific safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse Events Reported at a Rate of ≥ 1% (Safety Set) – Study C-11-034

	Travoprost 0.003% N=442	**Travoprost 0.004% N=421**
Coded Adverse Event	N(%)	N(%)
Eye disorders		
Ocular hyperemia	31 (7)	34 (8.1)
Conjunctival hyperemia	25 (5.7)	30 (7.1)
Eye pruritus	15 (3.4)	10 (2.4)
Eye irritation	10 (2.3)	6 (1.4)
Dry eye	7 (1.6)	7 (1.7)
Photophobia	4 (0.9)	5 (1.2)
Punctate keratitis	6 (1.4)	3 (0.7)
Conjunctival hemorrhage	1 (0.2)	6 (1.4)
Eye pain	3 (0.7)	4 (1.0)
Vision blurred	2 (0.5)	4 (1.0)
Vitreous floaters	2 (0.5)	4 (1.0)
Conjunctivitis allergic	-	4 (1.0)
Infections and infestations		
Upper respiratory tract infection	5 (1.1)	1 (0.2)
Musculoskeletal and connective tissue disorders		
Osteoarthritis	1 (0.2)	4 (1.0)

NDA 204-822, Module 5, CSR for protocol C-11-034, Table 14.3.1.5-1

Reviewer's Comments: *The rate of adverse events were similar between travoprost 0.003% and Travatan with exception of conjunctival hemorrhage which was seven (7) fold higher in the Travatan group.*

7.4.2 Laboratory Findings

Clinical laboratory data were not collected in this study.

7.4.3 Vital Signs

Vital signs were not assessed in this study.

7.4.4 Electrocardiograms (ECGs)

ECG's were no performed in this study.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies conducted for this submission.

7.4.6 Immunogenicity

Immunogenicity testing was not conducted for travoprost 0.003%.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A-only one dose for each formulation was evaluated for this submission.

7.5.2 Time Dependency for Adverse Events

There was no trend noted in the time to onset of adverse events.

7.5.3 Drug-Demographic Interactions

Overall, no clinically meaningful differences were observed in any treatment group based upon a review of demographic characteristics for patients with and without AEs. This class of drugs is known to increase iris pigmentations which is more noticeable in patients with light color iridies.

7.5.4 Drug-Disease Interactions

Drug-Disease interactions were not studied for this submission. However, based on the information available regarding specific patient populations for Travatan, the following interactions are likely with the use of travoprost 0.003%.

Macular edema, including cystoid macular edema, has been reported during treatment with Travatan therefore travoprost 0.003% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

7.5.5 Drug-Drug Interactions

N/A- this study did not evaluate drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Two-year carcinogenicity studies in mice and ratsat subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of travoprost 0.003% or 0.004% administration in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

A full waiver request for pediatric studies has been submitted. Pediatric studies using travoprost 0.004% are in progress and data from this trial may be applicable to the current application.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose of Travoprost 0.003% were reported during the clinical trial. No evidence of drug abuse has been identified with the use of travoprost in clinical trials. No reports of withdrawal or rebound phenomena have been identified with the use of travoprost in clinical trials.

7.7 Additional Submissions / Safety Issues

The 120-day safety update was submitted to the Agency on November 5, 2013. There are no ongoing clinical studies evaluating Travoprost Ophthalmic Solution, 0.003% and there are no trials that have been initiated or completed since the NDA was submitted in July 2013. Travoprost Ophthalmic Solution, 0.003% is not marketed in any country. There is no new safety information available for Travoprost Ophthalmic Solution, 0.003%.

8 Postmarket Experience

Travoprost 0.003% has not been marketed. No new significant safety concerns regarding the use of Travoprost 0.004% have been identified in clinical trials since the original NDA submission in 2001.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

(b) (4)

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

9.3 Advisory Committee Meeting

N/A

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

/s/

JENNIFER D HARRIS
02/03/2014

WILLIAM M BOYD
02/03/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204822 **Applicant**: Alcon Research **Stamp Date:** 07/15/2013

Drug Name: Travoprost Ophthalmic Solution, 0.003% **NDA/BLA Type**: 5

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	√			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			√	
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			√	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 C-11-034 Indication:	√			

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

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

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

None

Jennifer Harris, M.D.	7/31/2013
Reviewing Medical Officer	Date
Clinical Team Leader	Date

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

/s/

JENNIFER D HARRIS
08/26/2013

WILLIAM M BOYD
08/26/2013