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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 204822
Supporting document/s:	SD 1 (eCTD sequence # 0) submitted 7/15/2013
Applicant's letter date:	July 12, 2013
CDER stamp date:	July 15, 2013
Product:	Travoprost ophthalmic solution 0.003% (Izba®)
Indication:	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Applicant:	Alcon Laboratories Inc.
Review Division:	Division of Transplant and Ophthalmology Products (DTOP), Office of Antimicrobial Products (OAP), CDER, HFD-590
Reviewer:	Andrew J. McDougal, Ph.D., D.A.B.T., DTOP
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1 Executive Summary

1.1 Introduction

- Travoprost Ophthalmic Solution 0.003% (Izba™) is a sterile, preserved, multi-dose topical ophthalmic formulation containing 30 µl/ml travoprost.
- Izba™ is preserved with 0.001% w/v (0.01 mg/ml) of polyquaternium-1 (POLYQUAD; PQ).
    - Travatan APS (Travatan 0.004% PQ-preserved) was approved by the EMA in 2010, (b) (4) Travatan APS and Izba™ have the same amount of PQ.

Table 1: Alcon's products for travoprost ophthalmic solutions

Trade name	% of travoprost	Preservative	NDA information
Travatan®	0.004%	Benzalkonium chloride (BAK)	NDA 21-257 received initial approval on 3/16/2001
Travatan Z ®	0.004%	sofZia	NDA 21-994 received initial approval on 9/21/2006
Travatan APS ®	0.004%	PQ	Not approved in the US (b) (4)

- Internally, the electronic document room (EDR) is accessible via: \\CDSESUB1\evsprod\NDA204822\204822.enx

1.2 Brief Discussion of Nonclinical Findings

- To support Travoprost 0.004% PQ, the Applicant conducted one toxicology study: a 3-month topical ocular toxicity and irritation study in New Zealand White (NZW) rabbits (report # TDOC-007787), reviewed below.
    - The doses were vehicle three times daily (TID), 0.002% TID, 0.004% twice daily (BID), and 0.012% BID.
- No additional nonclinical studies were conducted with travoprost 0.003% PQ specifically (NDA Module 2.6.6 Toxicology Written Summary, page 2).
- The Applicant notes that PQ is qualified at higher exposures (10 µg/ml, 1.5 mg/ml, 1 g/ml) in other FDA-approved ophthalmic products. The Applicant re-submitted the nonclinical study reports for PQ (general toxicity, genotoxicity) to this NDA 204822. These study reports were not re-reviewed; this reviewer references the previous P/T reviews of the PQ study reports (see section 2.2 of this review).

- For NDA 21-257, Alcon submitted studies to assess developmental and reproductive toxicity (DART), fertility, genotoxicity, and carcinogenicity. These same studies were submitted to NDA 21-994 for Travatan Z, but no additional studies were conducted for these endpoints for the Travatan Z NDA (Chen, 3/02/2006, NDA 21994).

1.3 Recommendations

1.3.1 Approvability

Presuming that agreement is reached on labeling, P/T recommends approval. From a P/T perspective, no safety issues were identified.

1.3.3 Labeling

The Izba™ label parallels the label for Travatan Z®[1].

- The administration, "one drop in the affected eye(s) once daily in the evening" is the same for both labels
- The dose is less: The 0.004% solution is 0.04 mg/ml, and delivers [redacted] drop. The 0.003% solution is 0.03 mg/ml, and therefore delivers [redacted] drop.

Sponsor's version	**8.1 Pregnancy** Pregnancy Category C [redacted] Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day ([redacted] times the [redacted] (MRHOD)), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost [redacted] in rats at IV doses up to 3 mcg/kg/day ([redacted] times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day ([redacted] times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses [redacted] mcg/kg/day ([redacted] times the MRHOD) and in

[1] For NDA 21-994/S-006, the 9/07/2011 label was accessed via: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021994s006lbl.pdf

	mice at subcutaneous doses [redacted] mcg/kg/day ([redacted] times the MRHOD). In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of 0.12 mcg/kg/day ([redacted] times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity. There are no adequate and well-controlled studies of IZBA (travoprost ophthalmic solution) 0.003% administration in pregnant women. [redacted] IZBA should be [redacted] during pregnancy only if the potential benefit justifies the potential risk to the fetus.
P/T draft version	**8.1 Pregnancy** Pregnancy Category C [redacted] **There are no adequate and well-controlled studies of IZBA (travoprost ophthalmic solution) 0.003% administration in pregnant women. Malformations were observed in rats at doses that were 1500 times higher the maximum recommended human ocular dose (MRHOD) based on estimated C_{max} values for the active free acid. Embryolethality and decreased fetal/neonate viability were observed in mice at subcutaneous doses 9-fold higher than the MRHOD based on estimated C_{max} for the active free acid. IZBA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.** [redacted] -Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day ([redacted] **1500** times the [redacted] ~~(~~MRHOD~~)~~), evidenced by an increase in

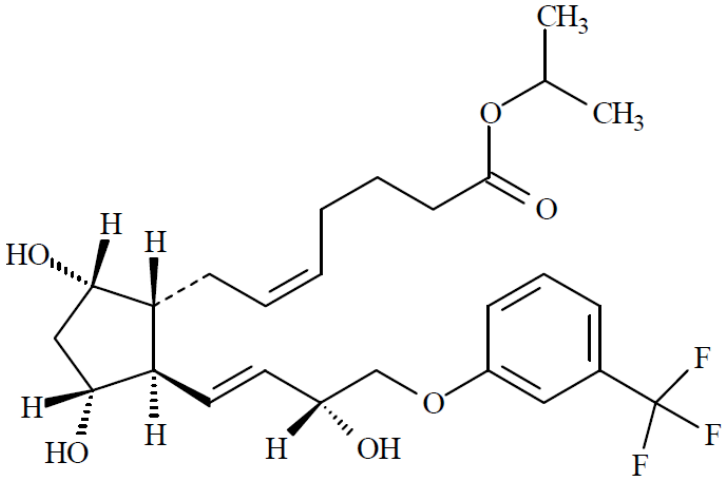
	the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost (b) (4) **did not produce malformations in** rats at IV doses up to 3 mcg/kg/day ((b) (4) **470** times the MRHOD), or in mice at subcutaneous doses up to 1**.0** mcg/kg/day ((b) (4) **9** times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses (b) (4) **of 10** mcg/kg/day ((b) (4) **1500** times the MRHOD) and in mice at subcutaneous doses (b) (4) **of 1.0** mcg/kg/day ((b) (4) **9** times the MRHOD). In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of (b) (4) mcg/kg/day (b) (4) **3.2** times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity. (b) (4)

Sponsor's original version	P/T changes
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study.	No change
The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of (b) (4) mcg/kg, based on (b) (4).	The high dose (100 mcg/kg) corresponds to exposure levels over 400 times **(for the mouse) and 700 times (for the rat)** of the human exposure at the maximum recommended human ocular dose (MRHOD) of (b) (4) **0.03** mcg/kg, based **on estimated plasma C_{max} for active free acid**. (b) (4)
Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.	No change

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day (b) (4) [redacted]. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day ((b) (4) times the MRHOD).	Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [(b) (4) **40** times the (b) (4) [redacted] **MHROD based on estimated plasma C_{max} for active free acid.** At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day ((b) (4) **12** times the MRHOD).

2 Drug Information

2.1 Drug

CAS Registry Number	157283-68-6
Generic name	Travoprost
Code names	AL-6221 AL06221 (b) (4)
Chemical name	[1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester
Molecular formula	$C_{26}H_{35}F_3O_6$
Molecular weight	500.55
Structure	**Figure 1: Chemical structure of travoprost** 
Pharmacologic Class	prostaglandin analog

2.2 Relevant INDs, NDAs, DMFs, and Regulatory Background

- Alcon submitted NDA 21527 for Travatan® (travoprost ophthalmic solution/drops 0.004%), original approval was granted March 16, 2001 and the marketing status is now discontinued. Labeling was most recently updated September 7, 2011.[2]

[2] Accessed from Drugs@FDA via: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021257s025lbl.pdf

- Alcon submitted NDA 21944 for Travatan Z® (travoprost ophthalmic solution/drops 0.004%); original approval was granted September 21, 2006 and the product is still marketed. The CDER Document Archiving, Reporting & Regulatory Tracking System (DARRTS) has an unredacted version of the P/T review, and a published redacted version of the P/T review is also available.[3]

- Alcon has active IND 051000 (AL-6221 ophthalmic solution)

- This NDA references six drug master files (in module 1.4.4 Cross Reference to Other Applications): DMF # (b) (4) DMF # (b) (4) DMF # (b) (4) DMF # (b) (4) DMF # (b) (4) and DMF # (b) (4)

For PQ, this reviewer references the P/T reviews for Alcon's:

- NDA 21764 (Brimonidine tartrate ophthalmic solution 0.15%; Qoliana®) by Dr. Asoke Mukherjee (1/26/2005)[4]
- NDA 20890 (diclofenac sodium ophthalmic solution 0.1%) by Dr. A.W. Coulter (2/28/1997)[5].

Note: Par Pharma has one approved NDA for travoprost ophthalmic solution 0.004% (NDA 91340) and one ANDA for travoprost ophthalmic solution 0.004% with tentative approval (ANDA 09134).

Note: DARRTS lists (b) (4) as "pre-assignment", dating to (b) (4) No supporting documents or discipline reviews are in DARRTS. No parent IND was identified in DARRTS, and this reviewer is unclear what this file represents.

2.3 Drug Formulation

Travoprost ophthalmic solution 0.003% will be packaged in Alcon's "Drop Tainer" packaging system, a 4 ml bottle containing 2.5 ml of solution and a (b) (4) ml bottle containing 5 ml of solution.

[3] Accessed from Drugs@FDA via: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021994s000_PharmR.pdf
[4] A published, redacted version of the P/T review for NDA 21764 was accessed via: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021764s000_PharmR.pdf
[5] A published, redacted version of the P/T review for NDA 20809 was accessed via: http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20809A_Diclofenac_phrmr.pdf

Table 2: Specifications for Travoprost 0.003% compared to other Alcon products

Component	Travoprost 0.004% BAK	Travoprost 0.004% sofZia	Travoprost 0.004% PQ	Travoprost 0.003% Soln
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 (BAC)	0.015	-	-	-
Zinc Chloride	(b) (4)			
Polyoxyethylene Hydrogenated Castor Oil 40 (HCO-40)				
Tromethamine				
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)			

Travoprost 0.004% BAK – travoprost 40 µg/mL eye drops, solution (preserved with benzalkonium chloride)
Travoprost 0.004% sofZia – travoprost 40 µg/mL eye drops, solution (preserved with sofZia)
Travoprost 0.004% PQ – travoprost 40 µg/mL eye drops, solution (preserved with POLYQUAD)

2.5 Comments on Impurities/Degradants of Concern

P/T discussed several impurities with CMC (Liu/McDougal, personal communications, January 2014), and P/T concludes that the proposed changes in impurity specifications are not safety concerns. Briefly:

- The Applicant provided specifications for Travoprost 0.003% solution in the NDA, module 3.2.P.5.1
- The Applicant is proposing to (b) (4) the specification for (b) (4) from (b) (4) % to (b) (4) %; this is not a safety concern. (b) (4) P/T discussed this theoretical point with Clinical (McDougal/Harris and Boyd,

personal communication), and the Review Team concludes that a (b) (4)% change in the amount of travoprost would not be expected to affect efficacy.

- The Applicant is proposing to (b) (4) the specification of total degradants from (b) (4)% (for NDA 21-994) to (b) (4)%. This is not a safety concern. The (b) (4) (b) (4) degradants are .
- The Applicant is proposing specifications of not more than (NMT) (b) (4) ppm for (b) (4) and NMT (b) (4) ppm for (b) (4). These specifications are not a safety concern.
  - A search of ChemIDplus (via the U.S. National Library of Medicine) did not find a CAS # or toxicology data for either (b) (4)
  - (b) (4)
  - These specifications would result in daily exposures of (b) (4) ng/day (assuming a 50 µl drop size). Based on the draft ICH M7 Step 2 guidance, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, these exposure levels would not require additional testing.

(b) (4)

3 Studies Submitted

- The Applicant submitted one study not previously submitted to an NDA: "3-Month Topical Ocular Toxicity and Irritation Evaluation of Travoprost Ophthalmic Solution Alternative Preservative System (APS) in New Zealand White Rabbits", report # TDOC-007787.

- No previous FDA P/T reviews were identified for the bioassay TK reports; they are reviewed below:
    - "AL-5848 plasma concentrations from Toxicology Study N-97-412 [# 18030100]: a 2-year subcutaneous oncogenicity study of AL-6221 in mice", report # 003:33:0100
    - "Study title: AL-5848 plasma concentrations from Toxicology Study N-97-413: a 2-year subcutaneous oncogenicity study of AL-6221 in rats", report # 004:33:0100

Additionally, the Applicant re-submitted study reports to NDA 204822:

- 6 for primary pharmacology
- 2 for secondary pharmacology
- 15 for safety pharmacology
- 3 for analytical methods and validation
- 5 for absorption
- 8 for distribution
- 4 for metabolism
- 3 for excretion
- 4 single-dose toxicity
- 12 for repeat-dose toxicity
- 6 for genotoxicity
- 2 for carcinogenicity
- 7 for DART
- 1 for antigenicity/sensitization
- 1 for phototoxicity
- 2 for impurity qualification
- 4 for biocompatibility

The list of study reports is appended to this review (see section 12 below).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 Pharmacokinetics

(If not included in toxicity studies)

Collated from the Pharmacokinetics Tabulated Summary (module 2.6.5):

Table 3: Summary of C_{max} values reported for AL-5848 in single-dose PK studies (iv or sc)

Report # (TDOC-…)	Species	Route	Dose	# doses	C_{max} or C_0 (ng/ml)
0005827	Male rat	iv	1.0 mg/kg	Single	839 (5 minutes) [a]
		sc	1.0 mg/kg	Single	214 (20 minutes) [a]
0005846	Male rat	iv	0.1 mg/kg	Single	140 [b]
		sc	0.1 mg/kg		17.9 [b]
0005892	Male rat	iv	0.1 mg/kg	Single	282 [a]
		sc	0.1 mg/kg		35.5 [a]
0005893	Male rabbit	Iv	0.1 mg/kg	Single	251 [a]
0005848	Male monkey	Iv	0.1 mg/kg	Single	• 35.8 [b] (C_{max}) • 193 (C_0) [b]
0005829	Male rat	Sc	0.1 mg/kg	Single	• 204 [a] (blood) • 55 (plasma) [a]
0005899	Lactating rat (PPD 12)	Sc	0.1 mg/kg	Repeat	• 36.4 [a] (plasma) • 9.0 (milk) [a]

[a] – based on radioactivity
[b] – based on analyzing for AL-5848

5.2 Toxicokinetics

From the Toxicology Tabulated Summary (Module 2.6.7):

Test Article: Travoprost (AL-6221)

Description	Species (Strain)	Daily Dose (µg/kg)*	AL-5848 maximum steady-state plasma conc. (ng/ml)	Sampling time of maximum plasma conc.	Report Number (Location)
3 month topical ocular	Rabbit (New Zealand White)	2.6	0.038 +/- 0.009	1 hour	TR:060:38570:1099 (Mod. 4, Section 4.2.3.2)
6 month topical ocular	Rabbit (New Zealand White)	4.0	0.164 +/- 0.075	30 minutes	TR:026:38570:1297 (Mod. 4, Section 4.2.3.2)
12 month topical ocular	Monkey (Cynomolgus)	1.8	0.096 +/- 0.047	30 minutes	TR:001:33:0100 (Mod. 4, Section 4.2.3.2)
2 year carc. (6 months TK), subcutaneous	Mouse (Crl:CD-1 (ICR) BR)	100	4.18 +/- 2.74	1 hour	TR:003:33:0100 (Mod. 4, Section 4.2.3.4.1)
2 year carc. (6 months TK), subcutaneous	Rat (Crl:CD BR)	100	9.90 +/- 3.04	1 hour	TR:004:33:0100 (Mod. 4, Section 4.2.3.4.1)
Pregnant mouse, subcutaneous	Mouse (Crl:CD-1 (ICR) BR)	10	Range: 0.104-0.126 (4 of 8 animals, rest were below 0.10 ng/mL quantitation limit)	30 minutes	TR:005:33:0100 (Mod. 4, Section 4.2.3.5.2)

*Based on 3.5 and 4 kg average body weights for rabbits and monkeys, respectively.

Test Article: Travoprost (AL-6221)

Description	Species	Daily Dose* (µg/kg)	AL-5848 maximum steady-state plasma conc. (ng/ml)	Sampling time of maximum plasma conc.	Report Number (Location)
1 week topical ocular, normal volunteers (C-99-08)	Human	0.048	0.015 +/- 0.005	10-30 minutes	TR:012:33:0200 (Mod. 4, Section 4.2.3.7.7)
1 week topical ocular, hepatic impaired (C-00-05)	Human	0.048	0.021 +/- 0.008	5-30 minutes	TR:048:33:1100 (Mod. 4, Section 4.2.3.7.7)
1 week topical ocular, renal impaired (C-99-97)	Human	0.048	0.014 +/- 0.003	10-15 minutes	TR:035:33:0900 (Mod. 4, Section 4.2.3.7.7)
1 week topical ocular, Japanese males (C-00-15)	Human	0.048	0.018 +/- 0.007	5-15 minutes	TR:034:33:0900 (Mod. 4, Section 4.2.3.7.7)
3-Day topical ocular, normal volunteers (C-02-35)	Human	0.048	0.020	30 min	TDOC-0000307 (Mod. 4, Section 4.2.3.7.7)

*Based on 50 kg average body weight.

5.2.1 Mouse TK data

The Applicant provided two reports with mouse TK data, both following sc dosing:

- A sc study in pregnant mice (report # TR:005:33:0100)
- The sc bioassay (TK data in report # 003:33:0100)

5.2.1.1 Pregnant mouse study

Two mouse developmental toxicity studies were submitted to the NDA for which no P/T review was identified (i.e. not in Chen, 10/31/2000, NDA 21-257). The latter (report # 161:30:091) has TK results (submitted to the NDA as a separate report, # 005:33:0100). Although summarizing these reports in the label is not warranted (i.e. the studies in the

label already cover these doses), the TK information is useful for estimating human equivalent doses (HEDs).

- "**Study for the effects of AL-62211 on embryo-fetal development in the mouse, MPI study 299-038**", report # 081:30:0400. GLP & QA
  - The authors note (page 2) that the delivered dose was uncertain, "as low as 30% of target", and this study was repeated.
    - The high-dose (nominally 1.0 µg/kg/day) was reported as the developmental NOAEL.
    - The mid-dose (nominally 0.3 µg/kg/day) was reported as the maternal NOAEL, based on increased incidence of early delivery (GD17 or GD18) for the 1.0 µg/kg/day group.
  - This reviewer speculates this report was not formally reviewed, because of the dose analysis error.
- "**Second pilot teratology study in mice with AL-6221, MPI study 298-037**", report # 161:30:091
  - GLP & QA. Protocol # N-98-98.
  - The authors report this study was a range-finder "to determine dose levels for a subsequent developmental toxicity study in mice" (presumably report # 099:30:0400 reviewed by P/T for NDA 21-257)
  - Total of 18 time-mated female CD-1 mice per dose (10 main-group, 8 TK) received 0, 0.03, 0.1, 0.3 or 1 µg/kg/day by sc injection from GD6 to GD16.
  - Blood was collected from TK animals on D16, at 30 minutes post-dose
  - Litters were delivered by cesarean section on GD18 for main-group animals.
    - Endpoints: maternal survival body weight, and food consumption; gravid uterine weight, total # of corpora lutea, implantation, early and late resorptions, live and dead fetuses
  - Abortion was reported for 5/10 mice in the 1 µg/kg/day group. [abortion defined by the authors as "premature expulsion from the uterus of products of conception – of the embryo or a nonviable fetus"]
  - The authors identified 0.3 µg/kg/day as the NOAEL for maternal and fetal toxicity

Table 4: Authors' reporting of the results for the pilot mouse teratology study (report # 161:30:091)

Summary of Uterine Status for Main Study and Toxicokinetics Animals					
	Dose Level (µg/kg/day)				
Parameter	0	0.03	0.1	0.3	1
No. Animals assigned	18	17*	18	18	18
No. Pregnant	12	11	14	9	13
Pregnancy Rate (%)	67	65	78	50	72
No. Pregnant by stain	3	1	0	2	4
No. Abortions	0	0	0	0	5
No. Early deliveries	0	0	1	1	0

*One animal accidentally killed.

Study title: AL-5848 plasma concentrations from toxicology study N-98-98: "Second pilot study for effects of prostaglandin on embryo-fetal development in the mouse

Study no.:	005:33:0100
Study report location:	NDA 204822 module 4.2.3.5.2 Embryo-fetal development
Report date:	May 5, 2000
Conducting laboratory:	Alcon Pharmacokinetics / Drug Metabolism (PK/DM) Unit
Date of study initiation:	Not specified
GLP compliance:	• No claim of GLP compliance is made • The samples were collected by MPI Research under GLP, as part of the study 161:30:091
QA statement:	Yes, signed

Methods

Doses:	0, 0.03, 0.10, 0.30, and 1.0 µg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Subcutaneous injection
Species/Strain:	CD-1 mice
Number/Sex/Group:	• Time-mated female CD-1 mice were dosed sc once daily from GD6 to GD16 • The size of the TK satellite groups were 8 females/dose • Blood sampling on GD16, approximately 30 minutes post-dose, by cardiac puncture

Results

- No detectable AL-5848 for the 0, 0.03 and 0.1 µg/kg/day groups
- For the 0.3 µg/kg group, all samples were below the LLOQ (0.1 ng/ml in mice)
- For the 1.0 µg/kg group, 4/8 samples were below the LLOQ, and 4/8 were quantified.
    - For those 4 mice in the 1.0 µg/kg group, the mean = 0.116 ng/ml (standard deviation ± 0.011)
- From the report (p 5):

Table 5: AL-5848 plasma concentrations from the pilot mouse sc developmental toxicity study (report # 005330100)

Individual 30-Minute Post-Dose AL-5848 Mouse Plasma Concentrations on Day 16 of Alcon Study N-98-98

Treatment Group	AL-6221 Dose (µg/kg)	Animal Number	AL-5848 Concentration (ng/mL)
2	0.03	2171	BLQ
		2172	BLQ
		2173	BLQ
		2175	BLQ
		2176	BLQ
		2177	BLQ
		2181	BLQ
3	0.10	2187	BLQ
		2188	BLQ
		2190	BLQ
		2192	BLQ
		2193	BLQ
		2195	BLQ
		2201	BLQ
		2202	BLQ
4	0.30	2203	BLQ
		2204	BLQ
		2205	BLQ
		2206	BLQ
		2209	BLQ
		2214	BLQ
		2215	BLQ
		2220	BLQ
5	1.0	2221	**0.111**
		2222	**0.104**
		2223	BLQ
		2224	BLQ
		2225	**0.124**
		2228	**0.126**
		2233	BLQ
		2235	BLQ

BLQ: Below Limit of Quantitation (<0.100 ng/mL

5.2.1.2 Mouse bioassay

The mouse subcutaneous bioassay (report # 180301000) was previously reviewed (Chen, 12/02/2002, NDA 21-257). The report was re-submitted to this NDA. Briefly:

- CD-1 mice were dosed once-daily by subcutaneous injection with 0, 10, 30 or 100 µg/kg/day for 2 years.

- TK groups were included, with plasma collection (terminal, by cardiac puncture) just prior to dosing (i.e. trough) and 1 hour post-dose during week 4, month 12 and month 24.
- No TK data were included in the carcinogenicity report; the authors state (p 34) that "…samples were sent on dry ice to the Sponsor. The Sponsor will analyze the samples and interpret the data. The Sponsor is responsible for the conduct, reporting, and any regulatory requirement for these analyses."
- Note: Although the carcinogenicity report states on multiple pages that **20** mice/sex/dose were used for TK, this appears to be a typographic error. The actual number used was 24 mice/sex/dose (based on the carcinogenicity's tables of "individual toxicokinetic body weights" [pdf pp 509-517 and 568-576] and the separate TK report).

Alcon provided the TK data as a separate report, reviewed below:

Study title: AL-5848 plasma concentrations from toxicology study N-97-412: a 2-year subcutaneous oncogenicity study of AL-6221 in mice

Study no.:	003:33:0100
Study report location:	NDA 204822 module 4.2.3.4 (Carcinogenicity)
Report date:	November 8, 2000
Conducting laboratory:	Alcon Pharmacokinetics / Drug Metabolism (PK/DM) Unit
Date of study initiation:	Not specified
GLP compliance:	• No claim of GLP compliance is made • The samples were collected by MPI Research under GLP, as part of the carcinogenicity study
QA statement:	Yes, signed

Methods

Doses:	0, 10, 30, 100 µg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Subcutaneous injection
Species/Strain:	CD-1 mice
Number/Sex/Group:	• Total of 24/sex for the 10, 30 and 100 µg/kg groups • 4/sex prior to dosing (i.e. trough) and another 4/sex 1 hour after dosing during week 4, month 12 and month 24 • Blood collection by terminal cardiac puncture

Results

- Plasma samples were analyzed for AL-5848 (travoprost free acid).

- The pre-dose plasma levels were below the limit of quantitation (LLOQ) of 0.100 ng/ml for each sample.
- Alcon's previous PK data indicates that the elimination half-life is approximately 30 minutes following iv and sc dosing. Therefore, the true C_{max} is likely much higher than the plasma concentration at 1 hour.
- The authors conclude, and this reviewer concurs, that no sex-difference was apparent.
- The plasma concentrations measured at 24 months were notably lower than the concentrations measured at 1 and 12 months. The authors did not identify a cause. This reviewer speculates an age-related effect.

Table 6: TK for the mouse sc bioassay (report # 003:33:0100)

Sc dose (µg/kg)	Month			Average
	1	12	24	
10	0.54 ± 0.10	0.61 ± 0.29	0.51 ± 0.17	0.55
30	1.98 ± 0.41	1.65 ± 0.44	1.03 ± 0.24	1.55
100	6.96 ± 1.84	6.51 ± 1.77	4.18 ± 2.74	5.88

Note: the values are plasma concentrations (ng/ml) of AL-5848 measured 1-hour post-dose, presented as mean ± standard deviation.

From the report (page 8):

Figure 3: Mean AL-5848 plasma concentration data for the mouse sc bioassay (report # 003:33:0100)

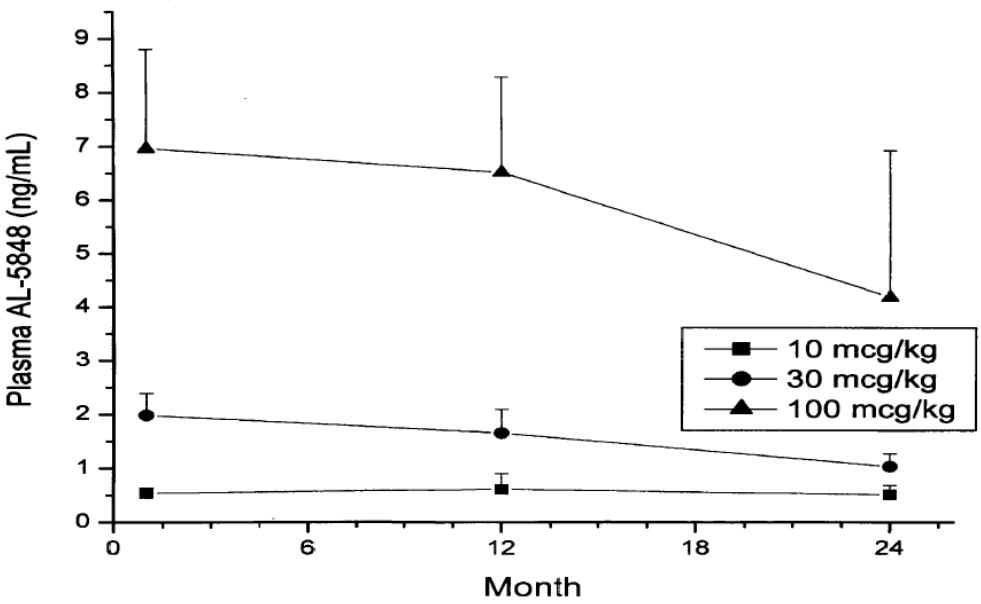


Table 7: Individual animal TK data for the mouse sc bioassay

AL-6221 Dose (µg/kg/day)	AL-5848 Concentration (ng/mL)					
	Animal ID (Sex)	Week 4	Animal ID (Sex)	12 Months	Animal ID (Sex)	24 Months
10	2023 (M)	0.454	2032 (M)	0.698	1662 (M)	0.826
	2024 (M)	0.691	2033 (M)	0.339	1663 (M)	0.486
	2025 (M)	0.525	2034 (M)	0.826	1664 (M)	0.459
	2026 (M)	0.504	2035 (M)	0.784	1667 (M)	0.501
	2043 (F)	0.452	2052 (F)	0.783	1731 (F)	0.299
	2044 (F)	0.441	2053 (F)	BLQ	1732 (F)	0.474
	2045 (F)	0.566	2054 (F)	0.868	1737 (F)	0.645
	2046 (F)	0.667	2055 (F)	0.508	1754 (F)	0.353
30	2064 (M)	2.12	2072 (M)	1.86	1783 (M)	1.32
	2065 (M)	2.45	2073 (M)	1.23	1784 (M)	1.28
	2066 (M)	2.32	2074 (M)	2.20	1785 (M)	0.937
	2067 (M)	1.50	2075 (M)	1.89	1788 (M)	1.13
	2083 (F)	1.90	2092 (F)	1.81	1852 (F)	0.906
	2084 (F)	2.03	2093 (F)	1.87	1853 (F)	0.638
	2085 (F)	1.29	2095 (F)	0.822	1854 (F)	1.22
	2086 (F)	2.26	2096 (F)	1.50	1877 (F)	0.830
100	2103 (M)	9.02	2111 (M)	8.18	1902 (M)	3.28
	2104 (M)	7.02	2112 (M)	8.79	1903 (M)	5.44
	2105 (M)	9.25	2113 (M)	6.64	1904 (M)	3.56
	2106 (M)	5.40	2114 (M)	7.78	1905 (M)	4.13
	2123 (F)	4.04	2133 (F)	5.21	1969 (F)	4.96
	2124 (F)	8.42	2134 (F)	5.05	1972 (F)	2.46
	2125 (F)	6.30	2135 (F)	6.84	1994 (F)	BLQ
	2126 (F)	6.21	2138 (F)	3.62	1990 (F)	9.58

BLQ = Below Limit of Quantitation (<0.100 ng/mL)

5.2.2 Toxicokinetics for the rat sc bioassay

The rat subcutaneous bioassay (report # 170301000) was also previously reviewed (Chen, 12/02/2002, NDA 21-257). The report was re-submitted to this NDA. Briefly:

- The strain of rat used is "Crl:CD BR"
- Rats were dosed once daily by subcutaneous injection with 0, 10, 30 or 100 µg/kg/day for 2 years [i.e. same doses as the mouse bioassay]
- TK satellite groups of 10 rats/sex/dose were included.
- Note: The report (#17930100) notes "Dosing was discontinued at Week 83 in males at 100 µg/kg/day because of reduced survival." (report pdf p 39). The protocol amendment (pdf p 2096) makes clear this discontinuation was only for Group 4 (the main study high-dose group), not for group 7 (the TK high-dose group).

Study title: AL-5848 plasma concentrations from Toxicology Study N-97-413: a 2-year subcutaneous oncogenicity study of AL-6221 in rats

Study no.:	004:33:0100
Study report location:	NDA 204822 module 4.2.3.4 (Carcinogenicity)
Report date:	November 8, 2000
Conducting laboratory:	Alcon Pharmacokinetics / Drug Metabolism (PK/DM) Unit
Date of study initiation:	Not specified
GLP compliance:	• No claim of GLP compliance is made • The samples were collected by MPI Research under GLP, as part of the carcinogenicity study
QA statement:	Yes, signed

Methods

Doses:	0, 10, 30 or 100 µg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Sc injection
Dose volume:	1 ml/kg
Formulation/Vehicle:	Aqueous 0.6% polyoxyl castor oil
Group size:	4/sex/dose
Species/Strain:	Crl:CD BR rats
TK sampling:	• Blood was collected by orbital sinus puncture or by tail vein puncture • Collection immediately prior to dosing (i.e. trough) and approximately 1 hour after dosing • Collections during months 1, 12 and 24
Note:	The individual animal IDs show that some TK animals were replaced at month 12 and 24 (presumably main-group animals were bled)

Results:

- As with the mouse bioassay, plasma samples were analyzed for travoprost free acid (AL-5848) and none was detected in any trough sample at the LLOQ of 0.040 ng/ml.
- The authors concluded that no sex-difference was apparent.

Table 8: TK for the rat sc bioassay (report # 004:33:0100)

Sc dose (µg/kg)	Month			Average
	1	12	24	
10	1.09 ± 0.18	1.89 ± 0.69	0.97 ± 0.29	1.32
30	3.14 ± 1.43	3.94 ± 1.76	3.65 ± 0.60	3.58
100	8.86 ± 2.37	10.8 ± 3.7	9.90 ± 3.04	9.85

Note: the values are plasma concentrations (ng/ml) of AL-5848 measured 1-hour post-dose, presented as mean ± standard deviation.

From the report (page 8):

Figure 4: Mean AL-5848 plasma concentration data for the rat sc bioassay (report # 004:33:0100)

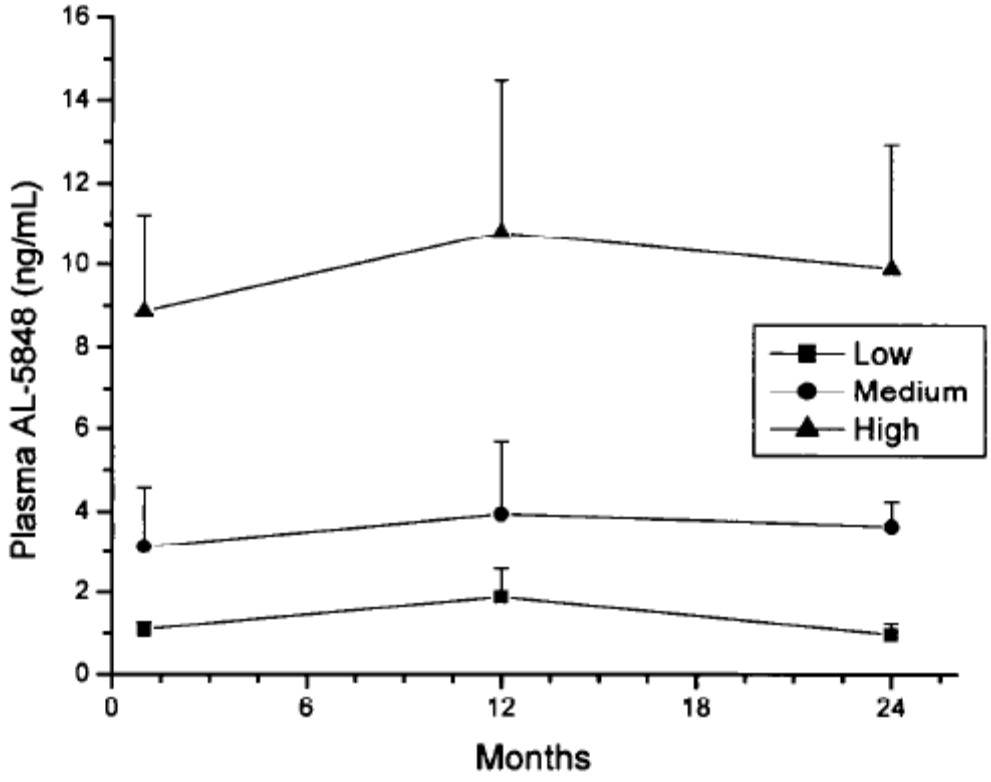


Table 9: Individual animal TK data for the rat sc bioassay

AL-6221 Dose (µg/kg/day)	AL-5848 Concentration (ng/mL)					
	Animal ID (Sex)	Week 4	Animal ID (Sex)	12 Month	Animal ID (Sex)	Week 105
10	3337 (M)	0.970	3338 (M)	1.70	2973 (M)	0.994
	3338 (M)	1.22	3339 (M)	1.51	2980 (M)	0.797
	3339 (M)	1.47	3340 (M)	2.41	3333 (M)	1.41
	3340 (M)	1.01	3342 (M)	1.13	3335 (M)	0.850
	3347 (F)	1.09	3347 (F)	3.23	3041 (F)	0.697
	3348 (F)	0.993	3348 (F)	1.59	3047 (F)	1.28
	3349 (F)	0.948	3349 (F)	1.35	3050 (F)	0.592
	3350 (F)	1.00	3350 (F)	2.18	3349 (F)	1.11
30	3357 (M)	4.12	3358 (M)	5.59	3101 (M)	2.80
	3358 (M)	4.80	3359 (M)	4.13	3094 (M)	3.81
	3359 (M)	2.80	3360 (M)	3.80	3097 (M)	3.18
	3360 (M)	1.59	3361 (M)	1.60	3357 (M)	3.29
	3367 (F)	1.26	3367 (F)	2.96	3194 (F)	4.17
	3368 (F)	3.32	3368 (F)	2.44	3157 (F)	4.11
	3369 (F)	5.02	3369 (F)	7.14	3161 (F)	4.56
	3370 (F)	2.17	3370 (F)	3.87	3210 (F)	3.28
100	3377 (M)	5.58	3378 (M)	11.6	3213 (M)	NS
	3378 (M)	10.3	3379 (M)	15.6	3217 (M)	NS
	3379 (M)	11.3	3380 (M)	9.02	3380 (M)	11.6
	3380 (M)	6.30	3382 (M)	12.2	3382 (M)	6.84
	3387 (F)	9.42	3387 (F)	4.66	3384 (F)	9.74
	3388 (F)	7.33	3388 (F)	9.96	3386 (F)	9.92
	3389 (F)	12.2	3389 (F)	15.4	3387 (F)	14.7
	3390 (F)	8.47	3390 (F)	7.96	3392 (F)	6.62

5.3 Considering nonclinical PK/TK relative to clinical exposure

- The label's Section 12.2 Pharmacokinetics reports for the 0.004% solution, " **the mean plasma C_{max} was 0.018 ± 0.007 ng/mL (range: 0.010 to 0.052 ng/mL) and was reached within 30 minutes**."
- Because the Izba® label is for 0.003% travoprost, rather than 0.004% travoprost, it is appropriate to extrapolate a **mean plasma C_{max} of 0.0135 ng/ml (upper bound of the range = 0.039 ng/ml)**
- Patient daily exposure is 1 drop of ~ 25 µl of 0.003% travoprost (0.3 mg/ml solution) equivalent to 0.045 mg/kg (assuming 60 kg body weight), and equivalent to 1.665 mg/m^2/day.

5.3.1: Reporting the mouse sc bioassay HED for Label Section 13.1

For the mouse bioassay, the high dose was 100 µg/kg. The most protective (lowest) mean C_{max} value is the 24 month time point, 4.18 ng/ml. The averaged mean C_{max} (for months 1, 12 and 24 together) is 5.88 ng/ml.

Table 10: The assumptions used to estimate the mouse sc bioassay HED affect the margin of exposure

Clinical C_{max} value (ng/ml) → C_{max} at 100 µg/kg ↓	Mean = 0.0135 ng/ml	Upper bound of range = 0.039 ng/ml
	Margin of exposure	
Most protective C_{max} value at 100 µg/kg = 4.18 ng/ml	310 x	107 x
Average C_{max} value at 100 µg/kg = 5.88 ng/ml	**436 x**	151 x

This table shows that the margin of exposure can reasonably be calculated to be from 107x to 436x (a 4-fold range). This reviewer considers using the mean clinical value and the mean mouse value to be appropriate. Therefore, the margin of exposure is reported as **436x.**

5.3.2: Reporting the rat sc bioassay HED for Label Section 13.1

Just as for the mouse bioassay calculation (above), the rat bioassay high dose was 100 µg/kg. The most protective (lowest) mean C_{max} value is the 1 month time point, 8.86 ng/ml. The averaged mean Cmax (for months 1, 12 and 24 together) is 9.85 ng/ml.

Table 11: The assumptions used to estimate the rat sc bioassay HED affect the margin of exposure

Clinical C_{max} value (ng/ml) → C_{max} at 100 µg/kg ↓	Mean = 0.0135 ng/ml	Upper bound of range = 0.039 ng/ml
	Margin of exposure	
Most protective C_{max} value at 100 µg/kg = 8.86 ng/ml	656 x	227 x
Average C_{max} value at 100 µg/kg = 9.85 ng/ml	**730 x**	253 x

This table shows that the margin of exposure can reasonably be calculated to be from 227 to 730 x (a 3-fold range). This reviewer considers using the mean clinical value and the mean rat value to be appropriate. Therefore, the margin of exposure is reported as 730x.

5.3.3: Reporting the mouse doses for Label Section 8.1

The label discusses two mouse sc doses: 0.3 and 1 µg/kg. Note that the P/T review (Chen, 10/31,2000, NDA 21-257) has typographical errors on page 42: the doses for this study were 0.1, 0.3 and 1 µg/kg/day [in some places, Chen reports the mid-dose as 3 µg/kg and the high-dose as 10 µg/kg). The study report was submitted to NDA 204822 (report # 99300400).

The Applicant provided two sources of mouse sc TK data; this reviewer considers the pregnancy study to be the appropriate benchmark for the results described in Section 8.1. The 1.0 µg/kg dose was associated with a **C_{max} of 0.116 ng/ml**.

Table 12: Estimating the HED values for the mouse doses in section 8.1 of the label

Species	Route	Dose (µg/kg/day)	Extrapolated C_{max} (ng/ml)	Margin of exposure from the clinical mean C_{max} of 0.0135 ng/ml
mouse	sc	1	0.116	8.6 x
	sc	0.3	0.0348	2.6 x

5.3.4: Reporting the rat doses for Label Section 8.1

The single-dose C_{max} values shown in Table 3 above are higher, relative to the dose, than the C_{max} values for the mouse sc bioassay.

For the iv dose benchmark, one approach is to average the numbers above (140 and 282 ng/ml) to calculate a **C_{max} of 211 ng/ml** for 100 µg/kg/day iv.

Likewise, for the sc dose benchmark, one approach is to average the numbers above (17.9, 35.5, 55, 36.4 ng/ml) to calculate 36.2 ng/ml as the C_{max} for 100 µg/kg/day sc. Alternatively, using the value from the lactating rat study (36.4 ng/ml for 100 µg/kg/day sc) yields the same estimate.

Table 13: Estimating the HED values for the rat doses in section 8.1 of the label

Species	Route	Dose (µg/kg/day)	Extrapolated C_{max} (ng/ml)	Margin of exposure from the clinical mean C_{max} of 0.0135 ng/ml
Rat	iv	10	21.1	1562 x
	iv	3	6.33	469 x
	sc	0.12	0.043	3.2 x

5.3.5: Reporting the rat doses for Label Section 13.1

Because the rat fertility study doses (3 and 10 µg/kg/day) are closer to the rat bioassay low-dose (10 µg/kg/day), it is appropriate to use the mean **C_{max} of 0.54 ng/ml** for the 10 µg/kg dose.

Table 14: Estimating the HED values for the rat doses in section 13.1 of the label

Species	Route	Dose (µg/kg/day)	Extrapolated C_{max} (ng/ml)	Margin of exposure from the clinical mean C_{max} of 0.0135 ng/ml
Rat	sc	10	0.54	40 x
	sc	3	0.163	12 x

6.2 Repeat-Dose Toxicity

Study title: 3-month topical ocular toxicity and irritation evaluation of travoprost ophthalmic solution alternative preservation system (APS) in New Zealand White rabbits

Study no.:	TDOC-007787
Study report location:	NDA 204822 module 4.2.3.2 (Rabbit – topical – medium)
Conducting laboratory and location:	Alcon Research Ltd. Fort Worth, Texas 76134
Report date	March 4, 2009
Date of study initiation:	November 28, 2007
GLP compliance:	Yes
QA statement:	yes
Drug, lot #:	• AL-06221 lot # 00208681 • Polyquad lot # 00200210

Methods

Doses:	Four groups of 5/sex rabbits: • Group 1 received APS vehicle TID OD • Group 2 received 0.002% travoprost APS TID OD • Group 3 received 0.004% travoprost APS BID OD • Group 4 received 0.012% travoprost APS BID OD
Frequency of dosing:	Topical ocular dosing for 92 days
Dose volume:	Each treatment consisted of 2 drops of 25 µl each OD
Species/Strain:	NZW rabbits
Age:	4 to 5 months at start of dosing
Weight:	2.8 to 3.2 kg at start of dosing

Table 15: Composition of the test articles for the 3-month rabbit study (report # TDOC-0007787)

Composition of Test and Control Articles

Control/ Test Articles	AL-06221 Vehicle[a]	AL-06221 Solution APS, 0.002%[a]	AL-06221 Solution APS, 0.004% [a]	AL-06221 Solution APS, 0.012%[a]
Lot Numbers	07-49256-1	07-49257-1	07-49258-1	07-49259-1
FID Numbers	(b) (4)			
AL-06221	-	0.002 %	0.004 %	0.012 %
Polyoxyl 40 Hydrogenated Castor Oil	(b) (4)			
Propylene Glycol				
Boric Acid				
Mannitol				
Sodium Chloride				
Polyquaternium-1	0.001 %	0.001 %	0.001 %	0.001 %
Sodium Hydroxide	(b) (4)			
Hydrochloric Acid				
Purified Water				

[a] % (w/v)

Endpoints:

- Cage-side observations were performed twice-daily
- Detailed physical examinations were performed twice weekly
- Ophthalmology:
  - Slit lamp biomicroscopy was performed pre-dose, on D2, during weeks 1, 2, 5, 8 and prior to necropsy.
  - Binocular indirect ophthalmoscopy, specular microscopy, and photography of the central corneal epithelium were performed pre-dose, during week 5 at prior to necropsy
  - Corneal thickness and intraocular pressure were measured for both eyes pre-dose, during weeks 1 and 5, and prior to necropsy
- Blood was collected for PK on D1 and D92 from 3 rabbits/sex/time point: immediately prior to the last dose of the day, and at 0.5, 1 and 3 hours after the last dose of the day.
- Animals were sacrificed on D93.

- Gross pathology was limited to the eye, eyelid, optic nerve, Harderian gland, nictitating membrane, and lacrimal gland.
- The eyes and adnexa (including the lacrimal glands) were preserved for histology.

Results:

- The authors concluded that the high dose, 0.012% travoprost APS ophthalmic solution BID in one eye was the no observed adverse effect level (NOAEL)
- The high-dose group exhibited increased incidence of conjunctival congestion and discharge, which the authors concluded "may have been treatment related because … expected pharmacological findings"
- No treatment-related gross or microscopic findings were apparent in the tissues evaluated.
- TK
  - The authors conclude that no sex-effect was apparent
  - The authors conclude that exposure was dose-proportional, with no evidence of accumulation.
  - From the report p 176:

Table 16: TK for the rabbit 3-month topical ocular toxicity study (report # TDOC_0007787)

Group	Study Day		Combined
2 0.002% AL-6221 (0.003 mg/day)	1	Mean	ISD
		Stdev	-
	92	Mean	ISD
		Stdev	-
3 0.004% AL-6221 (0.005 mg/day)	1	Mean	0.0362
		Stdev	0.0128
	92	Mean	0.0325
		Stdev	0.00895
4 0.012% AL-6221 (0.013 mg/day)	1	Mean	0.0995
		Stdev	0.0404
	92	Mean	0.0964
		Stdev	0.0374

ISD: Insufficient data to permit calculation

11 Integrated Summary and Safety Evaluation

The nonclinical studies previously conducted to support travoprost 0.004% also support this NDA for travoprost 0.003%. For this review, the primary focus is accurately presenting the nonclinical data in the label. Travoprost is rapidly metabolized to travoprost free acid. Plasma concentrations of travoprost and travoprost free acid are frequently below the limits of quantitation, in both clinical trials and in nonclinical studies. This review proposes to use plasma concentrations reported for the free acid, to extrapolate HEDs. The HEDs are protective, because (a) data points below the lower limit of quantitation were ignored for the purposes of HED calculation, (b) true nonclinical C_{max} values may be higher, if blood was collected after T_{max}, and (c) distribution from the eye into systemic tissues may be slower than distribution following sc dosing.

As noted above (section 5.5), the label reported a mean plasma C_{max} of 0.018 ng/ml for patients receiving a single dose of 0.004% travoprost. Assuming linearity, this reviewer estimates that the 0.003% travoprost dose will result in a C_{max} of 0.0135 ng/ml. This value was used to extrapolate the HEDs for the label.

Table 17: Summary of the nonclinical doses and HEDs in the label

Section of label	Species	Route	Dose	C_{max} estimate (ng/ml)	MHROD estimate (rounded)	Basis for benchmark
8.1 Pregnancy	Rat	iv	10 µg/kg/day	21.1	1500 x	Averaged C_{max} of 211 ng/kg for 100 µg/kg iv rat doses
	Mouse	sc	1 µg/kg/day	0.116	9 x	Mouse sc data at 1 µg/kg/day (C_{max} = 0.116 ng/ml) from another report
	Rat	iv	10 µg/kg/day	As above		
	Rat	iv	3 µg/kg/day	6.33	470 x	Extrapolated down from the averaged C_{max} for 100 µg/kg iv doses
	Mice	sc	1 µg/kg/day	As above		
	Rat	iv	3 µg/kg/day	As above		
	Mice	sc	0.3	0.0348	2.6 x	Extrapolated from mouse 1 µg/kg C_{ma}
	Rat	sc	0.12 µg/kg/day	0.434	3.2x	Averaged Cmax of 362 ng/ml for 100 µg/kg sc rat doses
13.1 Carcinogenesis	Mice	sc	100 µg/kg/day	5.88	400 x	study TK data
	Rat	sc	100 µg/kg/day	9.85	700 x	study TK data
13.1 Fertility	Rat	sc	10 µg/kg/day	0.52	40 x	rat sc C_{max} of 0.54 ng/ml for the 10 µg/kg dose from another report
	Rat	sc	3 µg/kg/day	0.163	12 x	Extrapolated from rat 10 µg/kg C_{max}

12 Appendix/Attachments

List of P/T reports submitted to the NDA (list copied from Modules 2.6.3, 2.6.5 and 2.6.7):

Test Article: Travoprost (AL-6221), AL-5848

Type of Study	Test System	Method of Administration	Testing Facility	Report Number	Location in CTD
Primary Pharmacodynamics	*In vitro*	N/A	Alcon	TR:011:39730:0496	Mod.4, Section 4.2.1.1
	Laser-induced ocular hypertension	Topical ocular	Alcon	TR:007:39500:0196	
	Laser-induced ocular hypertension	Topical ocular	Alcon	TR:305:39600:0693	
	Laser-induced ocular hypertension	Topical ocular	Alcon	TR:012:39500:0396	
	Laser-induced ocular hypertension	Topical ocular	Alcon	TR:019:39500:0596	
	Laser-induced ocular hypertension	Topical ocular	Alcon	TR:020:39500:0596	
Secondary Pharmacodynamics	Optic nerve head blood flow	Topical ocular	Alcon	TR:126:39500:1098	Mod.4, Section 4.2.1.2
	Flash electroretinogram	Subcutaneous	Alcon	TR:069:41:0900	
Safety Pharmacology	Ocular Hyperemia	Topical Ocular	Alcon	TR:022:39500:0596	Mod. 4, Section 4.2.1.3

Type of Study	Test System	Method of Administration	Testing Facility	Report Number	Location in CTD
Safety Pharmacology (Cont)	Neuropharmacological Profile	Oral	(b) (4)	TR:015:39730:0596	Mod. 4, Section 4.2.1.3
	Neuropharmacological Profile	Subcutaneous		TR:021:39730:0998	
	Barbiturate Sleep Time	Subcutaneous		TR:025:39730:0998	
	Cardiovascular Assay	Intravenous		TR:016:39730:0596	
	Cardiovascular Assay	Subcutaneous		TR:005:39730:0599	
	Cardiovascular Assay	Intravenous		TR:028:39730:0998	
	Cardiovascular Assay	Subcutaneous		TR:007:39730:0599	
	Cardiovascular Assay	Intravenous		TR:006:39730:0599	
	Cardiac Action Potential	*In vitro*		TR:006:41:0500	
	Respiratory Function	Intravenous		TR:017:39730:0596	
	Respiratory Function	Intravenous		TR:018:39730:0596	
	Gastrointestinal Function	Subcutaneous		TR:023:39730:0998	
	Renal Function	Intravenous		TR:022:39730:0998	
	Uterine Effects	*In vitro*		TR:026:39730:0998	

Type of Study	Test System	Method of Administration	Testing Facility	Report or Reference No, Location
Analytical Methods and Validation Reports				
Validation of an HPLC Tandem Mass Spectrometry Method for the Determination of AL-5848 in Rat Plasma	NA	NA	Alcon Laboratories	TDOC-0005849 (4221), Module 4, Section 4.2.2.1
Validation of an HPLC Tandem Mass Spectrometry Method for the Determination of AL-5848 in Rabbit Plasma	NA	NA	Alcon Laboratories	TDOC-0005850 (4221), Module 4, Section 4.2.2.1
Validation of an HPLC/Tandem Mass Spectrometry (HPLC/MS/MS) Method for the Determination of AL-5848 in Cynomolgus Monkey Plasma at Alta Analytical Laboratory	NA	NA	(b) (4)	TDOC-0005851 (4221), Module 4, Section 4.2.2.1

NA: Not applicable

Type of Study	Test System	Method of Administration	Testing Facility	Report or Reference No, Location
Absorption				
Absorption of Radioactivity and Bioavailability of AL-6221 in Male Sprague Dawley Rats Following Intravenous, Oral, and Subcutaneous Dosing	Rat	IV, PO, SQ	Alcon Laboratories	TDOC-0005827 (4222), Module 4, Section 4.2.2.2
Pharmacokinetics of AL-6221 and AL-5848 in Male Sprague Dawley Rats Following a Single 0.1 mg/kg Intravenous or Subcutaneous Doses in Male Sprague Dawley Rats	Rat	IV, SQ	Alcon Laboratories	TDOC-0005846 (4222), Module 4, Section 4.2.2.2
Pharmacokinetics of Radioactivity in Male Sprague Dawley Rats Following a Single 0.1 mg/kg Intravenous or Subcutaneous Doses of ^{3}H-AL-6221	Rat	IV, SQ	Alcon Laboratories	TDOC-0005892 (4222), Module 4, Section 4.2.2.2
Plasma Pharmacokinetics of Radioactivity in Male New Zealand White Rabbits Following a Single 0.1 mg/kg Intravenous Dose of ^{3}H-AL-6221	Rabbit	IV	Alcon Laboratories	TDOC-0005893 (4222), Module 4, Section 4.2.2.2
Pharmacokinetics of Travoprost (AL-6221) and AL-5848 in Cynomolgus Monkeys Following Single 0.1 mg/kg Intravenous Doses of Travoprost and its Carboxylic Acid Analogue, AL-5848	Monkey	IV	Alcon Research Ltd.	TDOC-0005848 (4222), Module 4, Section 4.2.2.2

Type of Study	Test System	Method of Administration	Testing Facility	Report or Reference No, Location
Distribution				
Distribution of AL-5848 Following Topical Ocular Administration of TRAVATAN and Travatan APS to New Zealand White Rabbits	Rabbit	TO	Alcon Research Ltd.	TDOC-0010241 (4223), Module 4, Section 4.2.2.3
Distribution of Travoprost (AL-6221) and AL-5848 in Ocular Tissues Following a Single Bilateral Topical Ocular Dose of 0.004% Travoprost Ophthalmic Solution to Male White New Zealand Rabbits	Rabbit	TO	Alcon Research Ltd	TDOC-0005896 (4223), Module 4, Section 4.2.2.3
Distribution of AL-6221 and AL-5848 in Ocular Tissues of the Non-Pigmented New Zealand White Rabbit and the Pigmented New Zealand White x New Zealand Red F1 Rabbit Following a Single Bilateral Topical Ocular Dose of 0.004% Travoprost Ophthalmic Solution	Rabbit	TO	Alcon Research Ltd.	TDOC-0005895 (4223), Module 4, Section 4.2.2.3
Distributionof AL-5848 in Ocular Tissues Following a Single Bilateral Topical Ocular Dose of Travatan PQ or Travatan Ophthalmic Solutions to Male New Zealand White Rabbits	Rabbit	TO	Alcon Research Ltd.	TDOC-0014114 (4223), Module 4, Section 4.2.2.3
Distribution of Radioactivity in Ocular Tissues Following a Single Topical Ocular Dose of 0.004% ^{3}H-AL-6221 to Male New Zealand Rabbits	Rabbit	TO	Alcon Laboratories	TDOC-0005900 (4223), Module 4, Section 4.2.2.3
Distribution of Radioactivity in the Tissues, Blood and Plasma of Male Sprague-Dawley Rats Following Single and Multiple 0.1 mg/kg Subcutaneous Doses of ^{3}H-AL-6221	Rat	SQ	(b) (4)	TDOC-0005829 (4223), Module 4, Section 4.2.2.3

Type of Study	Test System	Method of Administration	Testing Facility	Report or Reference No, Location
Distribution				
Distribution of Radioactivity in Pregnant and Fetal Rat Tissues Following a Single 0.1 mg/kg Subcutaneous Dose of ^{3}H-AL-6221 to Pregnant Female Sprague Dawley Rats	Rat	SQ	(b) (4)	TDOC-0005894 (4223), Module 4, Section 4.2.2.3
In Vitro Binding of [^{3}H-Ph]-AL-5848 to Human, Monkey and Rat Plasma Proteins.	In Vitro	Not Applicable	Alcon Research Ltd.	TDOC-0005914 (4223), Module 4, Section 4.2.2.3
Metabolism				
In Vitro Metabolism Studies of [^{3}H-Ph]-AL-5848 in Rat Hepatic Microsomes	In Vitro	Not Applicable	Alcon Research Ltd.	TDOC-0001846 (4224), Module 4, Section 4.2.2.4
Metabolite Profiles in Urine, Feces, Plasma and Bile Following a Single 0.1 mg/kg Subcutaneous Dose of [^{3}H-Ph]-AL-6221 to Male Sprague-Dawley Rats	Rat	SQ	Alcon Research Ltd.	020:38570:1097 (4224), Module 4, Section 4.2.2.4
Metabolite Profiles in Urine and Plasma Following a Single 0.1 mg/kg Intravenous Dose of [^{3}H-Ph]-AL-6221 to Cynomolgus Monkey	Monkey	IV	Alcon Research Ltd.	TDOC-0005913 (4224), Module 4, Section 4.2.2.4
Identification of the Principal Metabolites of AL-6221 in Rat and Monkey Plasma and Urine by LC-MS/MS	Rat Monkey	Not Applicable	Alcon Research Ltd.	TDOC-0005830 (4224), Module 4, Section 4.2.2.4

Type of Study	Test System	Method of Administration	Testing Facility	Report or Reference No, Location
Excretion				
Excretion and Mass Balance of Radioactivity in Male Sprague Dawley Rats Following a Single 0.1 mg/kg Subcutaneous Dose of ^{3}H-AL-6221	Rat	SQ	(b) (4)	TDOC-0005898 (4225), Module 4, Section 4.2.2.5
Excretion of Radioactivity in Milk From Lactating Female Sprague Dawley Rats Following a Single 0.1 mg/kg Subcutaneous Dose of ^{3}H-AL-6221	Rat	SQ		TDOC-0005899 (4225), Module 4, Section 4.2.2.5
Biliary Excretion of Radioactivity Following a Single Subcutaneous Dose of ^{3}H-AL-6221 in Bile Duct Cannulated Sprague Dawley Rats	Rat	SQ		TDOC-0005901 (4225), Module 4, Section 4.2.2.5

Type of Study	Species (Strain)	Method of Admin.	Duration of Dosing	Doses[a]	GLP Comp.	Testing Facility	Report Number (Location)
Travoprost (AL-6221)							
Single-Dose Toxicity	Rabbit (New Zealand White)	Topical Ocular	1 Day 10 doses	0 (Vehicle), 0.004%	Yes	Alcon	TDOC-0003457 (Mod. 4, Section 4.2.3.1)
	Rabbit (New Zealand White)	Topical Ocular	1 Day 10 doses	Untreated, 0 (Vehicle), 0.004%	Yes	Alcon	TDOC-0003351 (Mod. 4, Section 4.2.3.1)
	Rats (Crl:CD BR VAF/Plus)	Intravenous	Single Dose	10 mg/kg	Yes	(b) (4)	TR:061:30:0300 (Mod. 4, Section 4.2.3.1)
	Rats (Sprague-Dawley)	Intravenous	Single Dose	100 mg/kg	Yes	Alcon	TR:014:30:0203 (Mod. 4, Section 4.2.3.1)
Repeat-Dose Toxicity	Rabbit (New Zealand White)	Topical Ocular, TID or BID, OU	3 Months	0, 0, 20, 40, 120 µg/mL TRAVATAN PQ	Yes	Alcon	TDOC-0007787 (Mod. 4, Section 4.2.3.2)

a - For repeat-dose toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined

Type of Study	Species (Strain)	Method of Admin.	Duration of Dosing	Doses[a]	GLP Comp.	Testing Facility	Report Number (Location)
Repeat-Dose Toxicity	Rabbit (New Zealand White)	Topical Ocular	4 Weeks	0%, 0.001%, 0.01%, BID or TID, OD	Yes	Alcon	TR:057:38520:0496 (Mod. 4, Section 4.2.3.2)
	Rabbit (New Zealand White)	Topical Ocular	3 Months	TRAVATAN Vehicle (0%), TRAVATAN BAC-free Vehicle (0%), TRAVATAN 0.004%, TRAVATAN BAC free 0.004%, TRAVATAN BAC free Vehicle + 5x $ZnCl_2$, 2 drops OD, TID	Yes	Alcon	TDOC-0003456 (Mod. 4, Section 4.2.3.2)
	Rabbit (New Zealand White)	Topical Ocular	3 Months	0%, 0.001%, 0.003%, 0.01% TID, OD	Yes	Alcon	TR:119:38520:0896 (Mod. 4, Section 4.2.3.2)
	Rabbit (New Zealand White)	Topical Ocular	6 Months	0%, 0.001%, 0.003%, 0.01% BID, OU	Yes	Alcon	TR:029:38520:0497 (Mod. 4, Section 4.2.3.2)
	Monkey-Cynomolgus	Topical Ocular	1 year	0%, 0.0015%, 0.004%, 0.012%, BID, OD	Yes	(b) (4)	TR:080:30:0400 (Mod. 4, Section 4.2.3.2)

Type of Study	Species (Strain)	Method of Admin.	Duration of Dosing	Doses[a]	GLP Comp.	Testing Facility	Report Number (Location)
Repeat-Dose Toxicity	Mouse (ICR)	Oral	2 Weeks	0, 1, 3, 10 mg/kg	Yes	Alcon	TR:092:38520:0696 (Mod. 4, Section 4.2.3.2)
	Mouse (CD-1 ICR BR)	Intravenous	4 Weeks	0, 100, 300, 1000 µg/kg	Yes	(b) (4)	TR:093:38520:0797 (Mod. 4, Section 4.2.3.2)
	Rat (Crl:CD BR VAF/ Plus)	Intravenous	4 Weeks	0, 100, 300, 1000 µg/kg	Yes		TR:092:38520:0797 (Mod. 4, Section 4.2.3.2)
	Mouse (CD-1 ICR BR)	Intravenous / intraperitoneal	13 Weeks	0, 100, 300, 1000 µg/kg	Yes		TR:047:30:0300 (Mod. 4, Section 4.2.3.2)
	Rat (Crl:CD BR VAF/Plus)	Intravenous	13 weeks	0, 100, 300, 1000 µg/kg	Yes		TR:048:30:0300 (Mod. 4, Section 4.2.3.2)
	Rat (Crl:CD BR VAF/Plus)	Subcutaneous	6 Months	0, 10, 30, 100 µg/kg	Yes		TR:052:30:0300 (Mod. 4, Section 4.2.3.2)

Type of Study	Species (Strain)	Method of Admin.	Duration of Dosing	Doses	GLP Comp.	Testing Facility	Report Number (Location)
Genotoxicity	*S. Typhimurium* & *E. coli*	*In Vitro*	-	Up to 5000 µg/plate	Yes	(b) (4)	TR:056:30:0300 (Mod. 4, Section 4.2.3.3.1)
	L5178Y TK± Mouse Lymphoma Cells	*In Vitro*	-	30-500 µg/ml	Yes		TR:058:30:0300 (Mod. 4, Section 4.2.3.3.1)
	L5178Y TK± Mouse Lymphoma Cells	*In Vitro*	-	10 –140 µg/ml	Yes		TR:062:30:0300 (Mod. 4, Section 4.2.3.3.1.)
	Syrian Hamster Embryo Cells	*In Vitro*	-	5.0 –37.5 µg/ml	Yes		TR:123:30:0500 (Mod. 4, Section 4.2.3.3.1)
	Mouse (ICR)	Intravenous	Single dose	25-100 mg/kg	Yes		TR:055:30:0300 (Mod. 4, Section 4.2.3.3.2)
	Rat (Crl:CD [SD] IGS BR)	Intravenous	Single dose	18.8-75 mg/kg	Yes		TR:060:30:0300 (Mod. 4, Section 4.2.3.3.2)
Carcinogenicity	Mouse (CD-1 ICR BR)	Subcutaneous	2 years	0, 0.01, 0.03, 0.1 mg/kg	Yes		TR:180:30:1000 (Mod. 4, Section 4.2.3.4.1)
	Rat (Crl:CD BR)	Subcutaneous	2 years	0, 0.01, 0.03, 0.1 mg/kg	Yes		TR:179:30:1000 (Mod. 4, Section 4.2.3.4.1.)

Type of Study	Species (Strain)	Method of Admin.	Duration of Dosing	Doses[a]	GLP Comp.	Testing Facility	Report Number (Location)
Reproductive and Developmental Toxicity	Rat (Crl:CD VAF/Plus)	Subcutaneous	F: -14- G7 M: Day -28 to Day 37[a]	0, 1, 3, 10 µg/kg	Yes	(b) (4)	TR:082:30:0400 (Mod. 4, Section 4.2.3.5.1)
	Mouse (CD-1 ICR BR)	Subcutaneous	F: G6-G16[b]	0, 0.1, 0/3, 1 µg/kg	Yes		TR:081:30:0400 (Mod. 4, Section 4.2.3.5.2)
	Mouse (Crl:CD ICR BR)	Subcutaneous	F: G6-G16[b] (Pilot)	0, 0.03, 0.1, 0.3, 1.0 µg/kg	Yes		TR:161:30:0901 (Mod. 4, Section 4.2.3.5.2)
	Mouse (CD-1 ICR BR)	Subcutaneous	F: G6-G16[b]	0, 0.1, 0.3, 1 µg/kg	Yes		TR:099:30:0400 (Mod. 4, Section 4.2.3.5.2)

a- For repeat-dose toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined

Type of Study	Species (Strain)	Method of Admin.	Duration of Dosing	Doses[a]	GLP Comp.	Testing Facility	Report Number (Location)
Reproductive and Developmental Toxicity (continued)	Rat (Crl:CD VAF/Plus)	Intravenous	F: G6-G17[b]	0, 1, 3, 10 µg/kg	Yes	(b) (4)	TR:079:30:0400 (Mod. 4, Section 4.2.3.5.2)
	Rat (Crl:CD VAF/Plus	Sub-cutaneous	F: G6-L21[b]	0, 0.12, 0.36, 0.72 µg/kg (NOAEL not established)	Yes		TR:085:30:0400 (Mod. 4, Section 4.2.3.5.3)
	Rat (Crl:CD VAF/Plus	Sub-cutaneous	F: G6-L21[b]	0, 0.01, 0.03, and 3 µg/kg	Yes		TR:083:30:0400 (Mod. 4, Section 4.2.3.5.3)
Other Toxicity Studies							
1. Antigenicity/ Sensitization	Guinea Pig (Hartley)	Intradermal; Dermal	-	0, 0.01%, 0.05%, 0.1%	Yes		TR:057:30:0300 (Mod. 4, Section 4.2.3.7.1)
2. Phototoxicity	BALB/c 3T3 Mouse Fibroblasts	*In vitro*	1 hour	1.770100 µg/mL	Yes		TR:003:30:0102 Mod. 4, Section 4.2.3.7.7
3. Impurity Qualification	Rabbit (New Zealand White)	Topical Ocular	2-Weeks	(b) (4) (b) (4) AL-6221 w/ (b) (4)	Yes	Alcon	TR:012:30:0101 (Mod.4, Section 4.2.3.7.6)

M-Males: 4 weeks prior to mating. F-Females: 2 weeks prior to mating through Gestation Day 7.

[b] G - Gestation Day; L - Lactation Day, a- For repeat-dose toxicity, the highest NOAEL (No Observed Adverse-Effect Level) is underlined

Type of Study	Species (Strain)	Method of Admin.	Duration of Dosing	Doses	GLP Comp.	Testing Facility	Report Number (Location)
Impurity Qualification (Continued)	Rabbit (New Zealand F1 Cross)	Topical Ocular	1-Month	0%, 0.004%, 0.012% w/ Epoxide, AL (b) (4) and AL	Yes	Alcon	TR:051:30:0601 (Mod.4, Section 4.2.3.7.6)
4. Biocompatibility	L-929 Mouse fibroblast cells	*In vitro*	24 hours	0.1 mL Vehicle, 0.1 mL Package Extract, Negative Control, Positive Control	Yes	(b) (4)	TDOC-0001369 (Mod.4, Section 4.2.3.7.7)
	Rabbits / NZW	Intracutaneous	Single Dose	0.2 mL Vehicle, 0.2 mL Package Extract	Yes		TDOC-0001370 (Mod.4, Section 4.2.3.7.7)
	Rabbits / NZW	Topical Ocular	Single Dose	0.2 mL Vehicle, 0.2 mL Package Extract	Yes		TDOC-0001371 (Mod.4, Section 4.2.3.7.7)
	Mouse / Crl:CF1 BR	I.V.	Single Dose	50 mL/kg Vehicle, 50 mL/kg Package Extract	Yes		TDOC-0001372 (Mod.4, Section 4.2.3.7.7)

In the EDR, each of the nonclinical studies is tagged with the descriptor legacy, except for 7. Based on the report dates, this reviewer concludes that these 7 were available for submission to a previous Alcon travoprost NDA.

Report #	Title	Date
026397300998	The effect of AL-5848 on the isolated rat uterus	1998
014330300	*In vitro* binding of [3H-Ph]Al-5848 to human, monkey and rat plasma proteins	5/10/2000
014300203	Single dose toxicity evaluation of AL-6221-08 and AL-6221-21 in rats following intravenous administration	2003
048300300	13-week intravenous toxicity study in rats with AL-6221, MPI 298-021	4/14/2000
0923850079	28-day intravenous toxicity study in rats with AL-6211	2/27/1998
04933201083	Sister chromatid exchange assay with 0.003% solution	1983

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/s/

ANDREW J MCDOUGAL
04/03/2014

LORI E KOTCH
04/03/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 204822 **Applicant: Alcon Research, Ltd.** **Stamp Date: July 15, 2013**

Drug Name:
- **Travoprost ophthalmic solution 0.003%**
- **Izba (proposed)**

NDA Type: 505(b)1

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	**X**		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		Only a partial audit was performed for filing: all pages were legible
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations?	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		Yes, in NDA module 2.6.3 (Pharmacology Tabulated Summary) and module 2.6.7 (Toxicology Tabulated Summary)
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Not applicable from a P/T perspective		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	P/T doses are presented relative to the maximum recommended human ocular dose (MRHOD). Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Travoprost and travoprost free acid are eliminated relatively rapidly. The feasibility of calculating P/T doses based on comparative plasma levels will be a review issue.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		This is a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?	Not applicable, from a P/T perspective		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	Not applicable		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

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

NONE

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/s/

ANDREW J MCDOUGAL
08/27/2013

LORI E KOTCH
08/27/2013