CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-257

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-257 **Submission date:** 7/7/2000
Product: Travatan™ (travoprost ophthalmic solution) 0.0015% and 0.004%
Sponsor: AlconUniversal
P.O. Box 62, Bosch 69, CH-6331
Hunenberg, Switzerland
Type of submission: Original, 1P **Reviewer:** Abimbola Adebowale Ph.D.

Review of an NDA

I. Background

Travoprost (AL-6221), the drug substance in Travatan™ is a $PGF_{2\alpha}$ prostaglandin analogue. Hydrolysis by esterases in the cornea yields the biologically active free acid AL-5848. It is intended for topical use in the eye for the purpose of reducing intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Travoprost is not the first in its class; Latanoprost, another $PGF_{2\alpha}$ analog, was approved for the same indication by the Agency in 1996 as Xalatan™ Ophthalmic Solution (0.005%). However, the sponsor claims that travoprost (0.0015% and 0.004%) produces an earlier onset of IOP reduction and better IOP control throughout the day compared to Xalatan™. Travatan™ (travoprost ophthalmic solution 0.0015% and 0.004%) has not been marketed in any country at this time.

II. Summary of the Human Pharmacokinetics and Bioavailability Studies

To support the human pharmacokinetics and bioavailability section of this NDA, the sponsor provided results of a multiple dose PK study (#C-99-08). Following application of one drop of either 0.0015% or 0.004% travoprost ophthalmic solution once daily to each eye for one week, peak AL5848 plasma concentrations ranged from BLQ (<10 pg/ml) to 25 pg/ml and, were achieved 30 minutes after dosing. No quantifiable plasma concentrations were observed 1 hour post-dose and beyond. Similarity of plasma concentrations on days 1 and 7 indicated that there was no accumulation. Determination of the ester prodrug by difference (assay plasma samples with and without esterase incubation) indicated that low levels of the ester pro-drug may have been present in the plasma of some subjects. There was a higher incidence of quantifiable data from the 0.004% treatment group relative to the 0.0015% group, indicating a trend of increasing exposure with increasing dose. The results of this study demonstrated that the systemic exposure to travoprost (AL-621) and its acid metabolite AL-5848 are very low following topical ocular application of either 0.0015% or 0.004% travoprost ophthalmic solution once daily to each eye for one week.

Currently, the applicant has ongoing in vivo studies to characterize the steady-state pharmacokinetics of AL-6221 and Al-5848 (acid metabolite) in patients with renal impairment, hepatic impairment and, Japanese volunteers.

III. Recommendation

Based on the data submitted, the applicant has met the requirements outlined in 21CFR 320 and their application is acceptable from a clinical pharmacology and biopharmaceutics perspective. However, the applicant should adequately address the comments on page 8.

Question Based Review of Travoprost Ophthalmic Solution 0.0015% & 0.004%

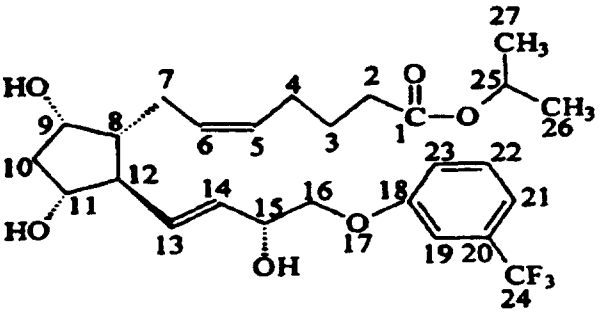
Table of Contents

IV. Physicochemical Properties and Formulation

What is Travoprost Ophthalmic Solution and how does it work?

Physicochemical Properties and Mechanism of Action of the Drug Substance:

Travoprost (AL-6221) is an isopropyl ester of the (+)-enantiomer of fluprostenol (AL-5848). Chemically Travoprost has the 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-methylethyl ester and, an empirical formula of $C_{26}H_{35}F_3O_6$. The chemical structure is:



Travpoprost

The molecular weight is 500.56. It is a clear to slightly opalescent, colorless to yellow viscous oil, which is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

The applicant stated that preclinical pharmacokinetic studies of topical ocular administration of AL-6221 have shown that it undergoes rapid hydrolyses by ester hydrolase enzymes located in the cornea to the biologically active acid metabolite, AL-5848. AL-5848 is a highly selective and potent agonist at the FP prostanoid receptor. The mechanism of action by which it reduces IOP is believed to be primarily through an increase in uveoscleral outflow (i.e. outflow of aqueous humor).

Proposed Dosage and Administration:

One drop to be instilled in the affected eye(s) once daily in the evening.

Formulation:

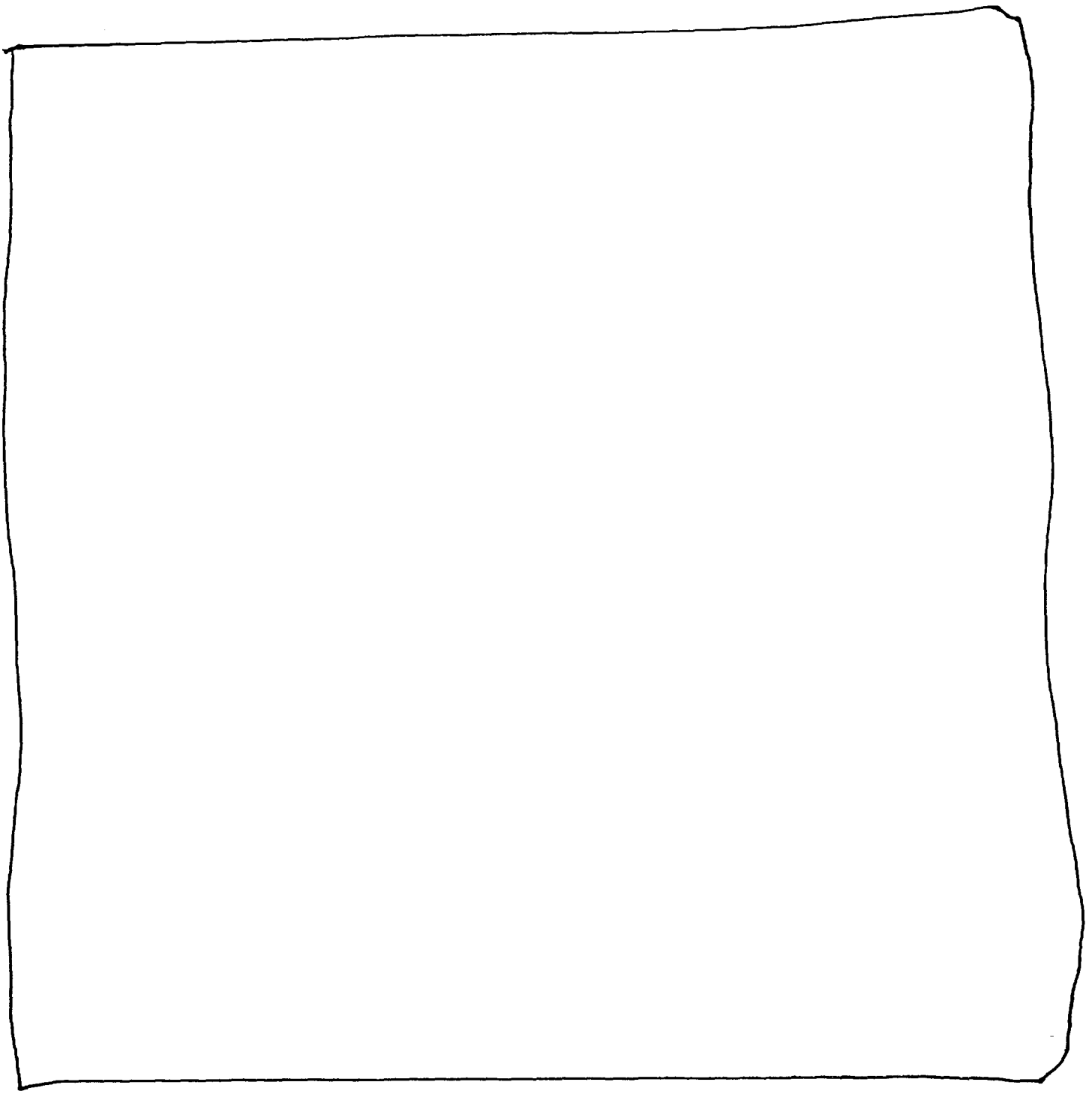
The applicant stated that Travatan™ ophthalmic solutions 0.0015% and 0.004% are to be supplied as sterile, buffered aqueous solutions of travoprost with a pH of ~ 6.0 and an osmolality of ~ 290mOsmol/kg. Reproduced below is a copy of the proposed quantitative composition of the finished drug product.

Ingredient	%w/v
Travoprost	*0.0015 or 0.004*
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)	
Tromethamine	
Boric Acid	
Mannitol	
Edetate Disodium	
Benzalkonium Chloride	
[a]Sodium Hydroxide and/or Hydrochloric Acid	
Purified Water	

[a]Adjusted based on purity of the raw material

The quantitative composition in the above table demonstrates that the only difference between the formulae of the two strengths is the concentration of the active ingredient. Also the formulation (Lot 98-500009-2 (0.004%) and Lot # 98-500007-2 (0.0015%)) used in the clinical pharmacology study (#C-99-08) and, the pivotal clinical trials was the same as the to-be-marketed-formulation (TBMF) (confirmed with the chemistry reviewer Dr. A. Fenselau).

V. Analytical Methods



VI. Summary of Bio/PK/PD Characteristics

What are the systemic exposures to travoprost (AL-6221) and its acid metabolite (AL-5848) after topical ocular administration?

The results of Alcon study C-99-08 demonstrated that the systemic exposure to AL-5848 and so indirectly to AL6221 was minimal as evidenced by the limited number of quantifiable plasma concentrations of Al-5848. Alcon study C-99-08 evaluated the pharmacokinetics of travoprost (AL-6221) and AL-5848, its free acid hydrolysis product, in normal volunteers following topical ocular administration. Subjects were administered either 0.004% or 0.0015% AL-6221 (one drop to each eye) each morning (~ 8:00 a.m.) for seven consecutive days. On days 1 and 7, plasma samples were collected immediately prior to dosing and at 5, 10, 15, 30 minutes and 1, 2, 4 and 8 hours post-dose. Twenty-two subjects were enrolled with twenty-one completing the 7 days of treatment. Details of the study design and methods are attached as the study abstract sheet in the Appendix, pages 1-3. At one hour and later time points, plasma concentrations of AL-5848 were all below the limit of quantitation (BLQ, 10 pg/ml) for all subjects administered either 0.0015% or 0.004% concentrations of AL-6221. The majority of samples (~80%) at the earlier time points (30 minutes or less) assayed BLQ. The distribution of the quantifiable plasma concentrations at the earlier time points (30 minutes or less) are reproduced in the table below (Copies are attached in the Appendix pages 4-7):

Table 1: Plasma concentration distribution of **AL-5848** following administration of AL-6221 (0.0015% & 0.0040%) on Day 1 and Day 7

Product	**AL-6221 (0.0015%)**		**AL 6221 (0.004%)**	
Day #	Day 1	Day 7	Day 1	Day 7
No of subjects with measurable plasma concentrations (% of total)	2/12 (16.7 %)	2/11 (18.2%)	6/10 (60 %)	6/10 (60 %)
No of samples with measurable plasma concentrations (% of total)	2/108 (1.9 %)	4/99 (4.0 %)	15/90 (16.7 %)	17/90 (18.9 %)
Concentration Range (pg/ml)				
Time interval (min)	10-15	10-30	5-30	5-30

The data in the table above demonstrate that the highest plasma concentration of AL-5848 on Day 1 was 25 pg/ml (@ 15 minutes) and, on Day 7 was 19 pg/ml (@ 30 minutes), both following administration of AL-6221 (0.004%). The similarity of quantifiable plasma AL-5848 concentration range of values on both sampling days indicates negligible accumulation during the course of treatment. Due to the limited number of quantifiable plasma concentration values, calculation of other pharmacokinetic parameters for AL-5848 (e.g., AUC and elimination half-life) was not feasible.

Samples from the high dose group (except for pre-dose samples) were reanalyzed by the applicant following esterase incubation to screen for detectable AL-6221 concentrations. Comparison of the results obtained with and without esterase incubation showed a higher incidence of incubated samples having greater AL-5848 concentrations than the corresponding non-incubated samples. Twenty-nine of the samples (~16%) showed either quantifiable AL-5848 concentrations after incubation (having been BLQ without incubation) or showed a higher quantifiable AL-5848 concentration upon re-assay relative to that found initially. Fifteen of the samples (~8%) gave lower AL-5848 concentrations following incubation versus initial assay and

two samples (~1%) gave identical AL-5848 concentrations for both assays. The levels of AL-6221 obtained by difference appear relatively low (ranging from [redacted] pg/ml) with the majority (~75 %) being < BLQ =[redacted] pg/ml (See Appendix page8). Given the low drug concentrations and inter-day assay variability at concentrations so close to the quantitation limit and possibly non-specificity (due to the rabbit esterase) of the assay method, statistical assessment of the significance of these trends, or lack thereof, would be unreliable. However, the overall trend of these results suggests that low levels of AL-6221 may have been present in the plasma of some subjects. Assays for samples collected at one hour and beyond were BLQ in all cases suggesting that levels of parent drug present were probably eliminated rapidly, in a similar manner to AL-5848.

What are the relationships between exposure and response to travoprost (AL-6221) and its acid metabolite (AL-5848) after topical ocular administration?

Efficacy: The primary efficacy variable in the pivotal clinical trials was the mean intraocular (IOP) reduction in the patients' worst eye. The applicant did not quantitatively assess the systemic exposure-response relationship between treatment groups in Study #C-99-08. However, the applicant conducted two dose-ranging Phase II studies (C-96-52 and C-97-02) that are currently under review by the medical officer (Dr. L. Lim). Briefly, the patients in these studies were administered single dose travoprost (0.00009, 0.0008, or 0.0016% at 8:00 am (Study # C-96-52) and (0.001, 0.002, 0.004, 0.006 % at 8:00 PM (Study # C-97-02). Although the 0.0015% concentration was not specifically studied, it is inclusive of the concentrations studied.

The results of both these dose ranging studies indicated that all the travoprost concentrations evaluated demonstrated dose dependent IOP reductions (Copy of the summary table of the results are attached in the Appendix, page 9 and 10). The IOP reductions for the 0.002, 0.004 and 0.006 % concentrations were similar to each other. The applicant stated that these differences were not clinically or statistically significant but that the IOP- lowering was generally greater with the 0.004%.

The applicant stated that the selection of the travoprost doses for the Phase III trials were based primarily on efficacy considerations supported by the data from the two dose ranging studies. The efficacy considerations included the selection of a low concentration (0.0015%) that would provide IOP-lowering non-inferior (equal or superior) to Timoptic 0.5% BID (e.g. 20 to 25% reduction) and a higher concentration (0.004%) that would provide IOP-lowering equal or superior to Xalatan 0.005% (25 to 30%). The confirmation of this rationale for dose selection is yet to be confirmed by the medical reviewer. Discussions with the chemistry reviewer (Dr. A. Fensalau), indicated that the 0.0015% concentration could be problematic in terms of quality control.

Safety: Safety was based on ocular and systemic parameters. A dose–concentration relationship could be qualitatively inferred from study # C-99-08 based on the higher incidence of quantifiable plasma concentration values (~19%) for the 0.004% dose group compared to (~4%) for the 0.0015% dose group, indicating increasing exposure to AL-5848 with increasing travoprost dose. Following discussions with the medical reviewer (Dr. L. Lim), this increase in

exposure to AL-5848 with increasing travoprost dose did not indicate any concern with regards to systemic safety due to the absolute low levels present.

Also in nonclinical studies in rabbits and cynomolgus monkeys dosed by topical ocular administration twice daily, the highest plasma concentration of Al-5848 achieved was up to 360 and 150 pg /ml respectively. This systemic exposure (~14-fold and 6-fold greater than that obtained in humans) did not result in any significant ocular or systemic effects (confirmed with the Pharmacology/Toxicology reviewer Dr. Z.Chen).

Are there any effects of intrinsic factors (such as gender, renal impairment, hepatic impairment and ethnicity) on the PK of travoprost (AL-6221) and, its acid metabolite (AL-5848) after topical ocular administration?

Gender

The results from the PK study C-99-08 suggests that the pattern of systemic exposure as determined by the plasma concentrations is similar in both males and females. The plasma concentrations for males administered AL-6221 0.004% ranged from BLQ to 24 pg/ml on Day 1 and BLQ to 19 pg/ml on Day 7. For females they ranged from BLQ to 25 pg/ml on Day1 and BLQ to 14 pg/ml on Day 7 (copy of the analysis is attached in the Appendix page 8). However, the low absolute levels present make any findings speculative at best.

Renal Impairment, Hepatic impairment and Ethnicity

Following a discussion with the medical reviewer (Dr. B. Boyd), it was inferred that although these studies are important, there were currently no known toxicity concerns with regards to these populations being studied, so the applicant was probably conducting them for labeling purposes.

VII. Overall Conclusions

Systemic plasma exposure to AL-5848 (the acid metabolite of Al-6221), following QD dosing of AL-6221 (0.0015% & 0.004%) for 7 days was very low (25 pg/mL or less) and occurred within 30 minutes following topical administration. Plasma concentrations being below the limit of quantitation after one hour suggested that elimination from plasma was rapid. The similarity of AL-5848 plasma concentrations on Day 1 and Day 7 indicated negligible AL-5848 accumulation in plasma. In some subjects, the re-determination of AL-5848 following esterase hydrolysis suggested low levels of unchanged AL-6221 may be present (< 27 pg/ml). The limited quantifiable plasma data did not provide a definitive assessment of dose-related increases in plasma concentrations at the two concentrations studied. The plasma concentration patterns for

males and females appear to be similar, but such comparisons are necessarily suspect due to the absolutely low levels seen.

VIII. Comments

1. The label section entitled "Clinical Pharmacology" and subtitled "Pharmacokinetics and Pharmacodynamics" includes data from the animal and the human studies mixed together (Copy in Appendix page 3). The applicant should revise the label as follows:

   CLINICAL PHARMACOLOGY (revised labeling)

   Mechanism of Action

   Travoprost free acid is a highly selective, potent agonist for the FP prostanoid receptor that is absorbed through the cornea. FP receptor agonists are reported to reduce intraocular pressure by increasing uveoscleral outflow. Studies in rabbits have shown peak concentrations in aqueous humor were reached one to two hours following topical administration. In rats, 95% of a subcutaneous radiolabeled dose was eliminated within 24 hours. The major route of elimination was via the bile (61%) with the remainder excreted by the kidneys.

   Pharmacokinetics/Pharmacodynamics

   Absorption: In humans, peak plasma concentrations of travoprost free acid were 25 pg/mL or less and, occurred within 30 minutes following topical administration of a single drop to each eye once daily.

   Metabolism: Travoprost, an isopropyl ester prodrug, is rapidly hydrolyzed by esterases in the cornea to the biologically active free acid. In animals, travoprost free acid is rapidly and extensively oxidized to inactive metabolites. Biotransformations include beta-oxidation of the α (carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, oxidation of the 15-hydroxyl moiety, as well as reduction of the 13,14 double bond. In vivo studies of the metabolism of travoprost in humans are still ongoing.

   Elimination: The disappearance of travoprost from human plasma was rapid resulting in concentrations below the limit of quantitation (< 10 pg/mL) by one hour.

2. The mention of the ongoing studies in patients with renal impairment, hepatic impairment and Japanese volunteers is acknowledged. When the studies are completed the applicant should submit them as a supplement for labeling changes.

Abimbola O. Adebowale Ph.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Dennis Bashaw, Pharm. D.

CC:
NDA 21-257
HFD-550 (Div.File)
HFD-550 (CSO/Puglisi)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Adebowale)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

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APPENDIX

Page 1

Study Summary Sheet

NDA/IND#	21-257	**Suppl/Amend #**	Original	**Submission Date:**	07/07/00
Study Type	Phase 1	**Study #**	C-99-08	**Volume #**	2.47
Study Title	An Open-Label, Parallel, Multi-Dose Pharmacokinetic Study of AL-6221 0.004% Ophthalmic Solution and AL-6221 0.0015% Ophthalmic Solution Following Topical Ocular Administration in Normal Volunteers				

Clinical Investigator	Aziz L.laurent, M.D.	**Analytical Investigator**	Bette A. McCue and Michael A. Curtis
Study Site	[redacted]	**Study Site:**	Alcon Research Limited, 6201 South Freeway Fort Worth, Texas 76134
	4/5/99 – 4/26/99		

Single Dose		**Multiple Dose**	X	**Washout Period**	None
Cross-Over		**Parallel**	X	**Other Design:**	NA
Fasted		**Food Study**		**FDA Breakfast?**	NA

If Fasted, how long, (hrs) NA

Subject Breakdown

Normal [X] **Patients** [ ] **Young** [X] **Elderly** [ ] **Renal** [ ] **Hepatic** [ ]

	Subject Type			**All**	1&2		22				
Age	**Mean**	45.2± 16.8	**Range**	18-64	**Group** AL-6221 0.0015%	1	**N =**	12	**M =**	5	**F=**	7
	Subject Type											
Age	**Mean**	44.9± 17.7	**Range**	20-64	**Group** AL-6221 0.004%	2		10		6		4

Race

Black [1] **Caucasian** [19] **Asian** [ ] **Hispanic** [ ] **Other** [1]

Iris color

Brown [10] **Hazel** [2] **Green** [4] **Blue** [5] **Grey** [1]

Treatment (s)

Treatment Group	Dose	Dosage Form	Strength	Formulation ID and Lot #
AL-6221 0.004%	Study personnel applied one drop once daily in the morning to both eyes for 7 days.	Ophthalmic solution	0.004%	[redacted] 98-500009-2
AL-6221 0.0015%	Study personnel applied one drop once daily in the morning to both eyes for 7 days.	Ophthalmic solution	0.0015%	[redacted] 98-500007-2

Sampling Times

Plasma	Pre-dose (hour 0), 5, 10, 15, 30 minutes and, 1, 2 4 and 8 hours post administration on Days 1 and 7

[redacted]

Table 2: **Plasma concentration distribution of AL-5848 following administration of AL-621 (0.0040%) on Day 1 and Day 7 and incubation with esterase**

Product	AL 6221 (0.004%)		AL 6221 (0.004%) Esterase Treated samples	
Day #	Day 1	Day 7	Day 1	Day 7
No of subjects with measurable plasma concentrations (% of total)	6/10 (60 %)	6/10 (60 %)	8/10 (80 %)	6/10 (60 %)
No of samples with measurable plasma concentrations (% of total)	15/90 (16.7 %)	17/90 (18.9 %)	25/90 (27.8 %)	21/90 (23.3 %)
Concentration Range (pg./ml)	[redacted]			
Time interval (min)	5-30	5-30	5-30	5-30

Page 3

Preliminary Safety Evaluation: Based on a preliminary evaluation of the analysis of the adverse events (Study C-99-08) indicated that the incidence of adverse events was higher in the AL-621 0.0015% dose group than in the AL-621 0.004% dose group. Eight (8) of 12 subjects (66.7%) receiving AL-6221 0.0015%, and four (4) of ten subjects (40.0%) receiving AL-6221 0.004% experienced adverse events. A brief summary of the results of the breakdown of the adverse event analysis is as follows:

1. *Ocular events related to therapy*: Six (6) of twelve (12) subjects (50.0%) experienced six ocular adverse events related to AL-6221 0.0015%. Dry eye, ocular hyperemia, and ocular irritation occurred two times each. Three (3) of ten (10) subjects (30.0%) experienced three ocular adverse events related to AL-6221 0.004%. Ocular hyperemia occurred twice and ocular pruritus occurred once. No subject receiving AL-6221 (0.0015%, 0.004%) experienced an ocular adverse event unrelated to therapy.
2. *Nonocular events related to therapy*: Two (2) of twelve (12) subjects (16.7%) experienced two nonocular adverse events related to AL-6221 0.0015%. Headache and photosensitivity occurred one time each. No subject receiving AL-6221 0.004% experienced a nonocular adverse event related to therapy.
3. *Nonocular events not related to therapy*: Three (3) of twelve (12) subjects (25.0%) experienced three nonocular adverse events unrelated to AL-6221 0.0015% (headache, pain, rhinitis) attributed to intercurrent illness, accidental injury, and seasonal allergy therapy. One (1) of ten (10) subjects (10.0%) experienced rhinitis unrelated to AL-6221 0.004% attributed to seasonal allergy.

Conclusions: adverse events

Systemic exposure to Al-621 following ocular topical administration is very low and does do not appear to be dose related or pose any safety concern. – To be confirmed (MO)

Labeling Claims from Study: Shaded part in labeling section below

CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost free acid is a highly selective, potent agonist for the FP prostanoid receptor. FP receptor agonists are reported to reduce intraocular pressure by increasing uveoscleral outflow.

Pharmacokinetics/Pharmacodynamics

Absorption: Travoprost is absorbed through the cornea. Studies in rabbits have shown peak concentrations in aqueous humor were reached one to two hours following topical administration. [redacted]

Metabolism: Travoprost, an isopropyl ester prodrug, is rapidly hydrolyzed by esterases in the cornea to the biologically active free acid. Systemically, travoprost free acid is rapidly and extensively oxidized to inactive metabolites. Biotransformations include beta-oxidation of the a (carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, oxidation of the 15-hydroxyl moiety, as well as reduction of the 13,14 double bond.

Excretion: In rats, 95% of a subcutaneous radiolabeled dose was eliminated within 24 hours. The major route of elimination was via the bile (61%) with the remainder excreted by the kidneys.

5 *pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.*

Table 8.F.B-1

IOP Change from Baseline at Each Visit Time[a]
(Intent-To-Treat Data)

Treatment	Time of Visit				
	8 AM	10 AM	12 N	4 PM	8 PM
Study C-96-52					
AL-2221 0.0001% (N=35)	-3.2[b]	-2.0[b]	NAP	-2.9[b]	-3.6[b]
AL-6221 0.001% (N=35)	-5.0[b,c]	-3.9[b,c]	NAP	-5.5[b,c]	-6.1[b,c]
AL-6221 0.002% (N=34)	-7.4[b,c,d]	-5.6[b,c,d]	NAP	-6.0[b,c]	-6.6[b,c]
Vehicle (N=34)	-1.1	-0.5	NAP	-0.8	-0.8
Study C-97-02					
AL-6221 0.001% (N=47)	-6.6[e]	-6.2[e]	-6.0[e]	-5.5[e]	-5.0[e]
AL-6221 0.002% (N=44)	-8.2[e,f]	-7.3[e,f]	-7.0[e]	-6.6[e]	-6.2[e,f]
AL-6221 0.004% (N=48)	-8.5[e,f]	-7.7[e,f]	-7.0[e,f]	-7.0[e,f]	-6.6[e,f]
AL-6221 0.006% (N=43)	-7.7[e,f]	-7.7[e,f]	-7.5[e,f]	-6.9[e,f]	-6.3[e,f]
Vehicle (N=45)	-2.4	-1.7	-1.9	-1.6	-1.6

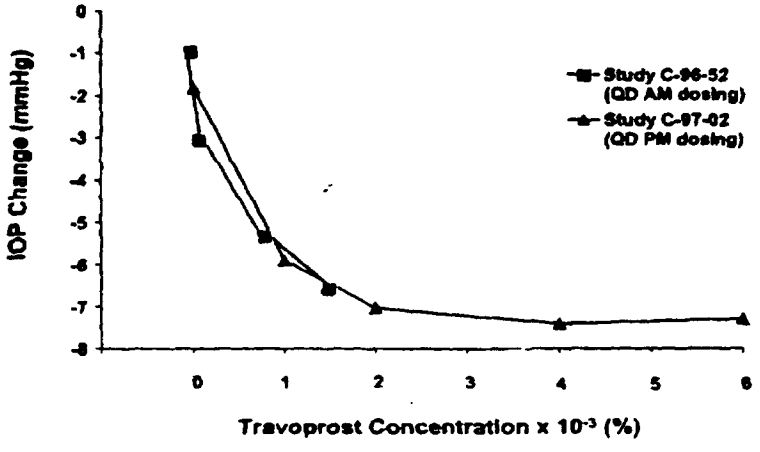
Abbreviations used include the following: AL-6221 (Travoprost); NAP (not applicable).

[a]Least square means (in mmHg) from analysis of variance, collapsed over visit days.
[b]Significant reduction relative to Vehicle ($p<0.02$) and baseline ($p\leq0.0001$).
[c]Significant reduction relative to 0.0001% concentration ($p\leq0.0004$)
[d]Significant reduction relative to 0.001% concentration ($p\leq0.007$)
[e]Significant reduction relative to Vehicle and baseline ($p\leq0.0001$).
[f]Significant reduction relative to 0.001% concentration ($p<0.05$).

These data are from Table 8.C.B-2 and Table 8.C.C-2 contained in Part 8.C. (Controlled Clinical Studies) of this NDA.

Figure 8.F.B-3

Mean IOP Changes from Baseline



Results (mean IOP change) from both dose-response studies (intent-to-treat data) are presented. Data is pooled over visit (Days 7, 14 and 28) and time of day (8 AM, 10 AM, 12 N, 4 PM and 8 PM). All IOP changes are from least squares means and values are provided in Clinical Study Reports C-96-52 and C-97-02 contained in Parts 8.C.J.1. and 8.C.J.2. of this NDA, respectively.

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