CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-257

MEDICAL REVIEW

Medical Officer's Review of NDA 21-257
Original

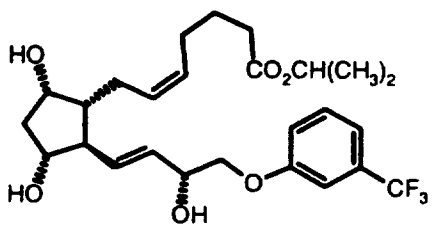
NDA 21-257
Medical Officer's Review

Submission Date: 07/07/00
Review Completed: 10/30/00

Proposed Trademark: Travatan 0.0015% and 0.004% ophthalmic solutions

Generic Name: Travoprost 0.0015% and 0.004% ophthalmic solutions

Chemical Name:



MW 500.56
Travoprost $C_{26}H_{35}F_3O_6$.

[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-mrthylethyl ester

Sponsor:
Alcon Universal, Ltd
P.O. Box 62
Bosch 69
CH-633 Hunnenberg, Switzerland

Authorized U.S. Agent
Alcon Research, Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 568-6116

Pharmacologic Category: Prostaglandin analogue

Proposed Indication: Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Dosage Form and Route of Administration: Ophthalmic solution for topical ocular administration

NDA Drug Classification: 1P

Related IND: [redacted]

2 Table of Contents

3 Material Reviewed

NDA 21-257 Volumes 2.1-2.3, Volumes 2.49- 2.112, and Volume 2.165

4 Chemistry/Manufacturing Controls

Table 1 – Drug Product Formulation

Quantitative Composition of Travoprost Ophthalmic Solution 0.0015% and 0.004%

Ingredient	mg/mL
Travoprost [a]	0.015 or 0.04
Polyoxyl 40 Hydrogenated Castor Oil	[redacted]
Tromethamine	[redacted]
Boric Acid,	[redacted]
Mannitol,	[redacted]
Edetate disodium,	[redacted]
Benzalkonium chloride	0.15
Sodium hydroxide [redacted] and/or Hydrochloric acid	[redacted]
Purified Water	[redacted]

a = Adjusted based on purity of the raw material

Table 2 –Acceptance Specifications
Travoprost Ophthalmic Solution 0.0015% and 0.004%

Test	Specification

Reviewer's Comments:

Any unspecified degradation product ≥ 0.1% should be reported. The minimum and maximum pH are acceptable but the range should be narrowed.

5 Animal Pharmacology/Toxicology – See Pharmacology Review

6 Clinical Background

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factor is elevated intraocular pressure (IOP). The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

Travoprost is a topical ocular $PGF_{2\alpha}$ prostaglandin analogue that is believed to reduce IOP largely due to increased uveoscleral outflow of aqueous humor. The IOP lowering activity of Travoprost ophthalmic solution (Travatan) was evaluated in laser-induced ocular hypertensive monkey model, which showed a dose-related IOP reduction.

Two dose-response studies, Protocol C-96-52 and Protocol C-97-02, were conducted in subjects with primary open-angle glaucoma and ocular hypertension to establish the dose and dosing regimen. Protocol C-97-01 was a randomized triple-masked, vehicle-controlled, parallel group study that compared three concentrations (0.0001%, 0.001%, and 0.002%) of Travoprost ophthalmic solution, to vehicle, dosed once daily in the morning. Results demonstrated a dose-dependent IOP reduction with increasing concentrations of Travoprost that was effective for 24 hours. The results also indicated that the maximum effective dose had not been established.

Protocol C-97-02 is reviewed in detail in Section 8.1.1.

6.1 Relevant Human Experience

Since their introduction in the late 1970s and 1980s, topical beta-adrenergic antagonists are frequently the standard treatment used in glaucoma therapy. The potential systemic beta-adrenergic blockade effects are well known.

In the past two decades, several other topical ocular therapies have been developed including alpha-adrenoceptor agonists and carbonic anhydrase inhibitors. Prostaglandin analogues represent another new class of topical ocular hypotensive agents. However, each of these agents has its advantages and disadvantages with regard to ocular hypotensive efficacy and ocular and systemic safety.

6.2 Foreign Experience

Travatan (travoprost ophthalmic solution) 0.0015% and 0.004% have not been marketed in any country.

6.3 Human Pharmacology, Pharmacokinetics, & Pharmacodynamics

– See Biopharmacology Review

7 Description of Clinical Data Sources

Included in this medical officer's review are five clinical trials conducted in the United States under [redacted] or in Australia, Canada, or Europe. See Table 3 for a descriptive summary of the clinical data sources.

Also included in this review is a synopsis of Protocol C-99-18 which compared Alphagan (Brimonidine) 0.2% BID + AL-6221 0015% BID versus AL-6221 0.0015% BID versus AL-6221 Vehicle BID in subjects with open-angle glaucoma or ocular hypertension.

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Table 3 – Description of Clinical Data Sources

Protocol Number	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Sites	No. Subjects Randomized	Status
Phase II Studies								
Dose-Response C-97-02 US	Triple-masked, randomized, placebo-controlled	28 days	Open-angle glaucoma & ocular hypertension	AL-6221 0.001% AL-6221 0.002% AL-6221 0.004% AL-6221 0.006% AL-6221 Vehicle	1 drop p.m. OU 1 drop p.m. OU 1 drop p.m. OU 1 drop p.m. OU 1 drop p.m. OU	9	227 (1:1:1:1)	Completed
Phase III Studies								
Efficacy/Safety C-97-71 US	Triple-masked, randomized, active-controlled	12 months	Open-angle glaucoma & ocular hypertension	AL-6221 0.0015% AL-6221 0.004% Timoptic 0.5% Xalatan 0.005%	1 drop p.m. OU 1 drop p.m. OU 1 drop BID OU 1 drop p.m. OU	44	801 (1:1:1:1)	Completed
Efficacy/Safety C-97-72 US	Triple-masked, randomized, active-controlled	6 months	Open-angle glaucoma & ocular hypertension	AL-6221 0.0015% AL-6221 0.004% Timoptic 0.5%	1 drop p.m. OU 1 drop p.m. OU 1 drop BID OU	44	605 (1:1:1)	Completed
Efficacy/Safety C-97-73 US & Canada	Triple-masked, randomized, placebo-controlled	6 months	Open-angle glaucoma & ocular hypertension	AL-6221 0.0015% AL-6221 0.004% AL-6221 Vehicle (all dosing adjunctive to Timoptic 0.5%)	1 drop p.m. OU 1 drop p.m. OU 1 drop p.m. OU 1 drop BID OU	46	427 (1:1:1)	Completed
Efficacy/Safety C-97-79 EU & Australia	Triple-masked, randomized, placebo-controlled	6 months	Open-angle glaucoma & ocular hypertension	AL-6221 0.0015% AL-6221 0.004% Timoptic 0.5%	1 drop p.m. OU 1 drop p.m. OU 1 drop BID OU	64	573 (1:1:1)	Completed

8.1.1 Study #1 Protocol C-97-02

Title: A Four-Week, Multicenter, Triple-Masked, Placebo-Controlled, Dose-Response Study of the Safety and Efficacy of AL-6221 Ophthalmic Solution in the Treatment of Patients with Primary Open-Angle Glaucoma or Ocular Hypertension

Study Design: A randomized, multicenter, triple-masked, placebo-controlled, parallel group, dose-range study

Test Drug Schedule: Patients instilled one drop of masked medication into each eye at 8 PM each evening for 28 days.

Investigator Number	Investigator	Number Randomized
271	**Robert H. Stewart, M.D.** Houston, TX 77025	12
553	**Richard M. Evans, M.D.** San Antonio, TX 78240	50
944	**Robert A. Laibovitz, M.D.** Austin, TX 78731	66
1007	**Thomas R. Walters, M.D.** Austin, TX 78746	33
1208	**Robert A. Caine, M.D.** Fredericksburg, VA 22405	02
1403	**Jeffrey B. Morris, M.D.** Encinitas, CA 92024	09
1472	**Thomas K. Mundorf, M.D.** Charlotte, NC 28204	09
1806	**Kenneth Sall, M.D.** Bellflower, CA 90706	31
2128	**Robert D. Williams, M.D.** Louisville, KY 40217	15

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

8.1.1 Study Design

This was a randomized, multicenter, triple-masked, vehicle-controlled, parallel group, dose-response study designed to evaluate the efficacy and safety of 4 concentrations of AL-6221 as compared to AL-6221 Vehicle. The five treatment groups were: 1) AL-6221 0.001%, 2) AL-6221 0.002%, 3) AL-6221 0.004%, 4) AL-6221 0.006%, and 5) AL-6221 Vehicle.

The study consisted of two phases. Phase 1 consisted of a Screening Visit, Washout Period, and Eligibility 1 & Eligibility 2 Visits. Phase 2 consisted of the treatment phase where eligible patients who met all the inclusion criteria at both Eligibility Visits 1 and 2, including entry IOP requirements, were randomized equally into one of five treatment groups and dosed once daily at 8 PM for a treatment period of 28 days.

During the treatment period, IOP was measured on Days 7, 14, and 28 at 8AM, 10AM, 12N, 4PM, and 8PM.

Minimum Washout Periods by Drug Class

Glaucoma Medication Class	Minimum Washout Period Screening to Eligibility 1 Visit
Beta-antagonists	Three (3) weeks
Alpha and alpha/beta agonists	Two (2) weeks
Miotics	Five (5) days
Oral/topical carbonic anhydrase inhibitor	Five (5) days
No ocular hypotensive medication	Three (3) days

Reviewer's Comments:

The washout period schedule is marginal since beta-antagonists may continue to have an effect for six weeks.

Study Medications

- AL-6221 0.001% (Lot# ARE-2879)
- AL-6221 0.002% (Lot# ARE-2880)
- AL-6221 0.004% (Lot# ARE-2881)
- AL-6221 0.006% (Lot# ARE-2882)
- AL-6221 Vehicle (Lot# ARE-2883)

Study Population

- Adult patients of either sex, 21 years of age or older and any race diagnosed with primary open-angle glaucoma (with or without pigment dispersion or pseudoexfoliation components) or ocular hypertension.

- Entry mean IOP of 24 to 36 mmHg, inclusive, in one eye, the same eye, at the post-washout 8AM IOP measurement at both Eligibility Visits 1 and 2. Additionally, the 10AM, 12N, 4PM, and 8PM mean IOP measurements must be 21 to 36 mmHg, inclusive, in one eye, the same eye that previously qualified. Mean IOP measurements at both Eligibility Visits 1 and 2 must be less than or equal to 36 mmHg at all times.

Primary Efficacy Variable

The primary efficacy variable was the change in IOP from the diurnally corrected baseline IOP and was measured on Days 7, 14, and 28 at 8AM, 10AM, 12N, 4PM, and 8PM.

The IOP measurements from each time point at the Eligibility 1 and 2 visits were averaged to obtain estimates of "baseline IOP" for each time point. The calculation of IOP change from baseline was diurnally adjusted such that the baseline measurement used in the calculation was obtained at the same time of day as the on-therapy measurements. For example, the 8AM baseline IOP measurement was subtracted from the 8AM on-therapy measurements.

Reviewer's Comments:

The primary efficacy variable utilized in the review of this NDA is the assessment of mean IOP and change in mean IOP from baseline at each time point on Days 7, 14, and 28.

Safety Variables

Ocular safety assessments included logMAR visual acuity, slit lamp biomicroscopy, ocular flare, ocular hyperemia, dilated fundus examination, automated perimetry, gonioscopy, and iris pigmentation. Systemic safety assessments included resting pulse and blood pressure. Safety analysis was based on the following: 1) extent of exposure to study drug, 2) adverse events including serious adverse events, and 3) other clinically relevant adverse events as well as observations related to safety.

Protocol C-97-02
Study Plan

Activity	Screen	Eligibility Visit 1					Eligibility Visit 2					Day 7 Exam					Day 14 Exam					Day 28 Exam				
		8 AM	10 AM	12 PM	4 PM	8 PM	8 AM	10 AM	12 N	4 PM	8 PM	8 AM	10 AM	12 N	4 PM	8 PM	8 AM	10 AM	12 PM	4 PM	8 PM	8 AM	10 AM	12 PM	4 PM	8 PM
Screen Patient	X																									
Informed Consent	X																									
Demographics	X																									
Medical History	X																									
Urine Pregnancy Test[1]	X																					X				
Discontinue Glaucoma Rx	X																									
IOP[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hyperemia Assessment							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Flare Assessment							X					X					X					X				
VA (Best Corrected)	X	X					X					X					X					X				
Biomicroscopy	X	X					X					X					X					X				
Resting Pulse	X																									
Resting Blood Pressure	X																									
Dilated Fundus Exam	X																									
Automated Perimetry[3]		X																								
Gonioscopy[4]	X																									
Iris Photography							X															X				
Dispense Study Drug											X															
Adverse Events												X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Study Medication																						X				
Complete Exit Exam																										X
Dismiss Patient																										X

[1] A urine pregnancy test will be performed for all females of childbearing potential. [2] All IOP measurements should be ± 30 minutes of the required time.
[3] Automated Perimetry is to be conducted at the Eligibility Visit 1 or before drug is dispensed at the Eligibility Visit 2 Exam. A visual field evaluation will be performed if one has not been done within the last six months or if visual field does not meet entry criteria. [4] Gonioscopy is to be conducted only if it has not been performed within the last six months.

Subject Disposition and Demographics

All 227 randomized subjects received double-masked study medications and 221 subjects completed the study.

Subject Disposition

	Number of Subjects				
	AL-6221				
	0.001%	0.002%	0.004%	0.006%	Vehicle
Randomized	47	44	48	43	45
Received masked study medication	47	44	48	43	45
Completed study	46	43	47	42	43
Analyzed for efficacy (Intent-to-Treat)	47	44	48	43	45
Analyzed for efficacy (Per Protocol)	47	42	46	42	45
Analyzed for safety	47	44	48	43	45

Discontinued Patients and Reason

Investigator	Patient	Treatment	Reason
271	911	AL-6221 0.001%	Noncompliance to study medication
943	541	AL-6221 0.002%	Inappropriately entered into study
553	239	AL-6221 0.004%	Back injury
1806	617	AL-6221 0.006%	Noncompliance to study medication
553	221	AL-6221 Vehicle	Inadequate control of IOP
1403	305	AL-6221 Vehicle	Inadequate control of IOP

Summary of Demographic Characteristics (Intent-to-Treat)

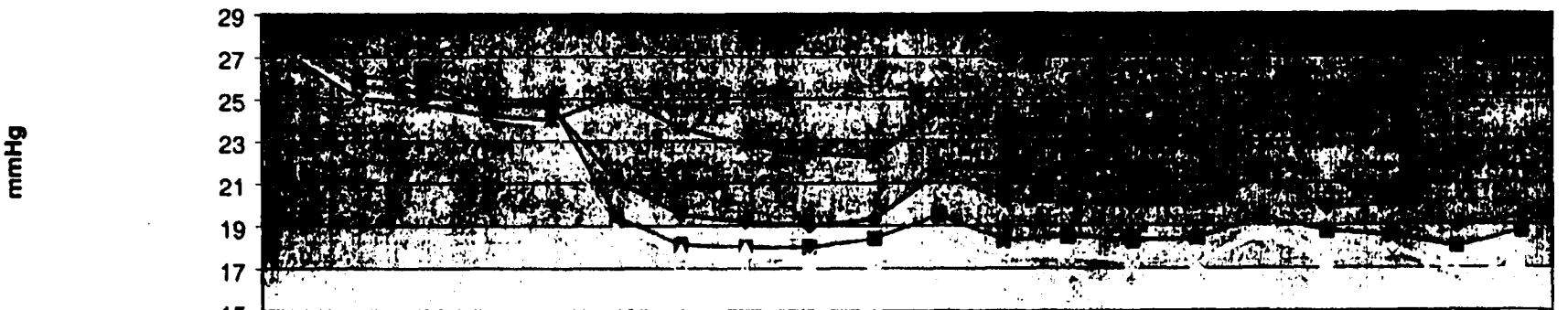
	AL6221 0.001%		AL6221 0.002%		AL6221 0.004%		AL6221 0.006%		AL6221 Vehicle		
	N	%	N	%	N	%	N	%	N	%	p-value
Age											
<65	27	57.4	29	65.9	25	52.1	24	55.8	29	64.4	0.627
>=65	20	42.6	15	34.1	23	47.9	19	44.2	16	35.6	
Sex											
MALE	18	38.3	21	47.7	15	31.3	17	39.5	24	53.3	0.230
FEMALE	29	61.7	23	52.3	33	68.8	26	60.5	21	46.7	
Race											
CAUCASIAN	33	70.2	32	72.7	35	72.9	36	83.7	38	84.4	0.218
BLACK	9	19.1	5	11.4	6	12.5	.	.	4	8.9	
ASIAN	.	.	1	2.3	.	.	.	.	.	.	
OTHER	5	10.6	6	13.6	7	14.6	7	16.3	3	6.7	
Iris											
BROWN	34	72.3	23	52.3	31	64.6	17	39.5	18	40.0	0.013
HAZEL	2	4.3	7	15.9	3	6.3	10	23.3	14	31.1	
GREEN	.	.	2	4.5	1	2.1	3	7.0	3	6.7	
BLUE	11	23.4	11	25.0	13	27.1	13	30.2	10	22.2	
GREY	.	.	1	2.3	.	.	.	.	.	.	
Diagnosis											
OH	28	59.6	25	56.8	25	52.1	29	67.4	25	55.6	0.600
POAG	19	40.4	19	43.2	23	47.9	14	32.6	19	42.2	
POAG/PD	.	.	.	.	.	.	.	.	1	2.2	

p-values from chi-square test of independence

8.1.1 Efficacy – Protocol C-97-02 Intent-to-Treat Population

Primary Efficacy Variable

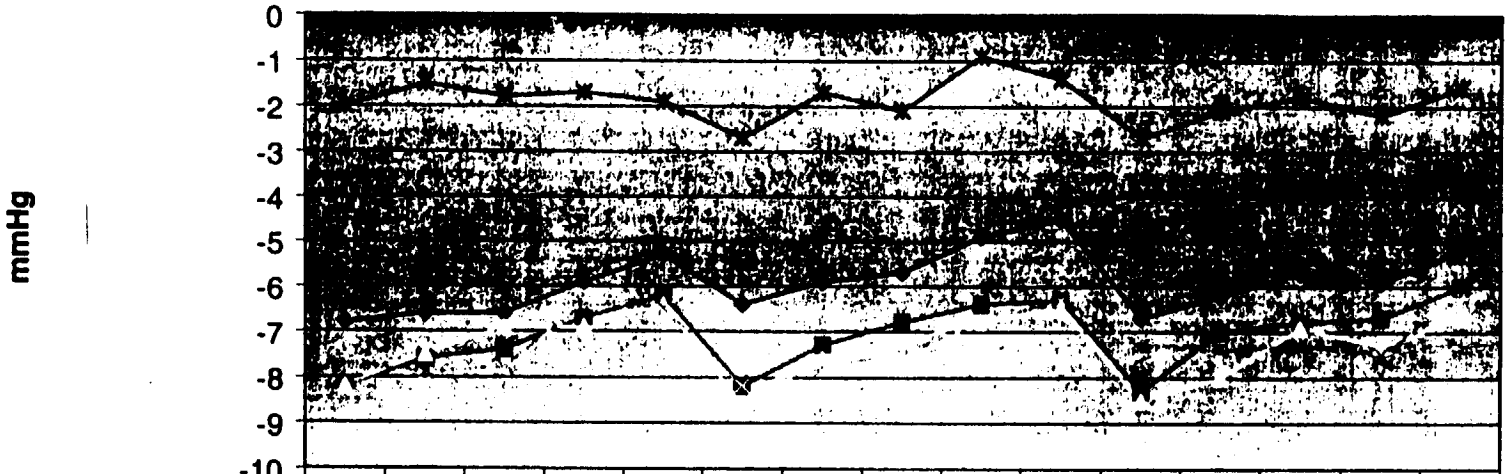
Mean IOP per Visit and Time



	Baseline 8AM	Baseline 10AM	Baseline 12N	Baseline 4PM	Baseline 8PM	Day 7 8AM	Day 7 10AM	Day 7 12N	Day 7 4PM	Day 7 8PM	Day 14 8AM	Day 14 10AM	Day 14 12N	Day 14 4PM	Day 14 8PM	Day 28 8AM	Day 28 10AM	Day 28 12N	Day 28 4PM	Day 28 8PM
AL-6221 0.001%	27.9	26.1	25.8	24.8	24.6	21.1	19.5	19.2	19	19.3	21.5	20.2	20.1	19.9	20	21.2	19.8	20	18.9	19.4
AL-6221 0.002%	27.7	25.6	25.3	24.7	24.8	19.4	18.1	18	18	18.4	19.5	18.3	18.5	18.3	18.4	19.4	18.7	18.5	18	18.7
AL-6221 0.004%	27.1	25.2	24.8	24.1	23.7	18.8	17.8	17.9	17.2	17.3	18.4	17.7	17.6	17.3	17.2	18.6	17.3	17.9	16.8	17
AL-6221 0.006%	26.6	25.1	24.8	24	23.6	19	17.3	17.1	17.6	17.1	18.5	17.4	17.3	17.2	17.3	19.3	17.8	17.6	16.5	17.4
AL-6221 Vehicle	27	25	24.7	24.2	24	25.1	23.6	22.8	22.4	22.2	24.4	23.4	22.5	23.1	22.5	24.4	22.9	22.7	21.8	22.5

Reviewer's Comments: *The mean IOP for all four concentrations of AL-6221 are consistently lower than AL-6221 Vehicle at all time points measured. Of the four concentrations, the mean IOP for AL-6211 0.002%, 0.004%, and 0.006% are similar over visit days and time and are consistently lower than AL-6221 Vehicle.*

Change from Diurnally Adjusted Baseline IOP per Visit and Time



	Day 7 8AM	Day 7 10AM	Day 7 12N	Day 7 4PM	Day 7 8PM	Day 14 8AM	Day 14 10AM	Day 14 12N	Day 14 4PM	Day 14 8PM	Day 28 8AM	Day 28 10AM	Day 28 12N	Day 28 4PM	Day 28 8PM
AL6221 0.001%	-6.8	-6.6	-6.6	-5.9	-5.3	-6.4	-5.9	-5.7	-4.9	-4.5	-6.7	-6.2	-5.7	-5.9	-5.2
AL6221 0.002%	-8.2	-7.6	-7.4	-6.7	-6.2	-8.2	-7.3	-6.8	-6.4	-6.3	-8.3	-7	-6.8	-6.7	-6
AL6221 0.004%	-8.2	-7.5	-6.9	-6.9	-6.4	-8.6	-7.6	-7.2	-6.8	-6.5	-8.5	-8	-6.9	-7.3	-6.7
AL6221 0.006%	-7.7	-7.9	-7.8	-6.4	-6.5	-8.2	-7.8	-7.5	-6.8	-6.3	-7.3	-7.4	-7.3	-7.5	-6.2
AL6221 Vehicle	-2	-1.5	-1.8	-1.7	-1.9	-2.7	-1.7	-2.1	-0.9	-1.4	-2.7	-2.1	-1.8	-2.2	-1.6

Reviewer's Comments: *When corrected for baseline, the IOP lowering ability for all four AL-6221 concentrations are consistently greater than AL-6221 Vehicle at every time points measured. The treatments with the greatest IOP lowering effect are AL-6221 0.002%, 0,004%, and 0.006%. The IOP reducing ability of these three AL-6221 concentrations are consistently similar over visit days and time.*

8.1.1 Safety

Adverse Events

Two serious adverse events were reported in one of the 43 subjects receiving AL-6221 0.006%. No serious adverse events were reported for any of the other treatment groups.

Serious Adverse Events

Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C Pt from Study
813	AL-6221 0.006%	Hemoptysis	Continuing with Treatment	No
		Lung Disorder	Continuing with Treatment	No

D/C Pt = Discontinued Patient

No deaths were reported during the study.

One of the 48 subjects receiving AL-6221 0.004% discontinued from the study due to an adverse event. No subjects discontinued from the study due to an adverse event from the other four treatment groups.

Patients Discontinued from the Study Due to Adverse Events

Patient Number	Treatment	Coded Adverse Event	Outcome of Event	Serious
239	AL-6221 0.004%	Accidental Injury	Continuing with Treatment	No

Frequency and Incidence of Ocular and Non-ocular Adverse Events
Occurring at Rates Greater than 1%

Coded Adverse Event	AL-6221				
	0.001% N=47	0.002% N=44	0.004% N=48	0.006% N=43	Vehicle N=45
	N (%)	N (%)	N (%)	N (%)	N (%)
All Events	12 (25.5)	20 (45.5%)	18 (37.5)	25 (58.1)	8 (17.8)
OCULAR					
Hyperemia Eye	3 (6.4)	8 (18.2)	3 (6.3)	11 (25.6)	
Flare	2 (4.3)			1 (2.3)	
Pruritus Eye	1 (2.1)	5 (11.4)	5 (10.4)	5 (11.6)	1 (2.2)
Cataract	1 (2.1)				
Discomfort Eye	1 (2.1)		1 (2.1)		2 (4.4)
Dry Eye	1 (2.1)	1 (2.3)	1 (2.1)	4 (9.3)	2 (4.4)
Hem Subconjunctival	1 (2.1)				1 (2.2)
Staining Corneal	1 (2.1)		1 (2.1)	4 (9.3)	1 (2.2)
Surgical/Medical Proc	1 (2.1)				
Vision Change	1 (2.1)				
Browache			1 (2.1)		
Conjunctivitis		1 (2.3)		1 (2.3)	
Corneal Abrasion				1 (2.3)	
Discharge Eye Nos				1 (2.3)	
Eye Fatigue		1 (2.3)			
Foreign Body Sensation		1 (2.3)	1 (2.1)	1 (2.3)	1 (2.2)
Keratitis				1 (2.3)	
Pain Eye		2 (4.5)	1 (2.1)	4 (9.3)	
Photophobia		2 (4.5)	1 (2.1)	3 (7.0)	
Spasm Lid				1 (2.3)	
Tearing			2 (4.2)	1 (2.3)	
Vision Blurred				1 (2.3)	
Vision Decreased				1 (2.3)	
NON-OCULAR					
Body As A Whole					
Injury Accidental			1 (2.1)	1 (2.3)	
Surgical/Medical Proc				1 (2.3)	
Cardiovascular System					
Hypertension			1 (2.1)		
Digestive System					
Diarrhea				1 (2.3)	
GI Disease				1 (2.3)	
Nausea				1 (2.3)	
Metabolic & Nutritive					
Edema		1 (2.3)			
Respiratory System					
Hemoptysis				1 (2.3)	
Lung Disease				1 (2.3)	
Pneumonia				1 (2.3)	

8.1.1 Reviewer's Summary of Efficacy and Safety

The IOP lowering ability for all four concentrations of AL-6221 are consistently greater than AL-6221 Vehicle over visit days and time.

The IOP reducing ability of AL-6221 0.002%, 0.004%, and 0.006% are similar and consistently greater than AL-6221 0.001%.

The safety profile is similar for the three concentrations of AL-6221 with the greatest IOP lowering ability.

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8.1.2 Study #2 Protocol C-97-71

Title: A Twelve-Month, Triple-Masked, Parallel Group, Primary Therapy Study of the Safety and Efficacy of AL-6221 0.0015% and AL-6221 0.004% Compared to Timoptic 0.5% and Xalatan 0.005% in Patients With Open-Angle Glaucoma or Ocular Hypertension

Study Design: A randomized, multicenter, triple-masked, active-controlled, parallel group study.

Test Drug Schedule: Patient instilled one drop of masked medication into each eye, twice daily at 8AM and 8PM for 12 months.

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
236	**Robert L. Stamper, M.D.** San Francisco, CA 94115	02	02	02
271	**Robert H. Stewart, M.D.** Houston, TX 77025	37	36	35
331	**Alan I. Mandell, M.D.** Memphis, TN 38119	19	19	18
355	**Michael S. Kottler, M.D.** Salt Lake City, UT 84107	18	18	18
362	**Delmar R. Caldwell, M.D.** New Orleans, LA 70112	25	22	21
386	**Wayne F. March, M.D.** Galveston, TX 77550	14	14	14
394	**Mark J. Weiss, M.D.** Tulsa, OK 74101	17	16	16
553	**Richard M. Evans, M.D.** San Antonio, TX 78240	31	31	31
649	**Richard A. Lewis, M.D.** Sacramento, CA 95819	22	22	20
731	**Elizabeth D. Sharpe, M.D.** Mt. Pleasant, SC 29464	16	16	16
750	**Kenneth W. Olander, M.D.** Maryville, TN 37803	11	11	11
821	**David E. Silverstone, M.D.** New Haven, CT 06510	07	07	06
983	**Charles J. Henry, M.D.** Little Rock, AK 72205	22	21	21

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
989	**William C. Stewart, M.D.** Charleston, SC 29412	16	15	15
1208	**Robert Caine, M.D.** Fredericksburg, VA 22405	19	19	19
1212	**Michael C. Stiles, M.D.** Kansas City, MO 64111	18	17	17
1340	**Joseph W. Spadafora, O. D.** Port Charlotte, FL 33952	08	08	08
1393	**Michael H. Rotberg, M.D.** Charlotte, NC 28204	20	20	20
1409	**Dong H. Shin, M.D.** Detroit, MI 48201	13	11	11
1473	**Thomas K. Mundorf, M.D.** Charlotte, NC 28204	16	16	15
1552	**Carl Camras, M.D.** Omaha, NE 68198	14	14	14
1565	**Louis B. Cantor, M.D.** Indianapolis, IN 46202	06	06	06
1782	**Miles A. Galin, M.D.** New York, NY 10016	11	11	11
1806	**Kenneth N. Sall, M.D.** Bellflower, CA 90706	40	38	39
1892	**Shannon L. Smith, M.D.** Nacogdoches, TX 75961	16	15	15
1913	**Jeffrey P. Wasserstrom, M.D.** La Mesa, CA 91942	25	23	23
1927	**Harvey B. DuBiner, M.D.** Morrow, GA 30260	32	32	31
1939	**Howard I. Schenker, M.D.** Rochester, NY 14618	29	29	29
1960	**Peter A. Netland, M.D.** Memphis, TN 38163	05	05	05
1972	**Onex D. Stevenson, M.D.** New Orleans, LA 70119	17	17	17
1973	**Cecil Beehler, M.D.** Ft. Meyer, FL 33901	45	44	41
2128	**Robert D. Williams, M.D.** Louisville, KY 40217	21	21	20

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
2133	**Silvia Orengo-Nania, M.D.** Houston, TX 77030	31	31	30
2153	**Frank J. Mares, M.D.** Albuquerque, NM 87109	15	15	15
2247	**Richard Sturm, M.D.** Lynbrook, NY 11563	28	27	27
2346	**Doug O. Dehning, M.D.** Blue Springs, MO 64014	28	28	27
2347	**Paul A. Sidoti, M.D.** New York, NY 10003	04	03	03
2348	**Douglas G. Day, M.D.** Atlanta, GA 30342	16	16	16
2353	**George C. Thorne, M.D.** Austin, TX 78756	34	33	28
2418	**Rudolf Churner, M.D.** McKinney, TX 75069	09	09	08
2479	**John E. Bokosky, M.D.** San Diego, CA 92103	08	08	05
2482	**Douglas Ripkin, M.D.** Kent, OH 44240	05	05	03
2558	**Todd D. Severin, M.D.** Albany, CA 94706	09	09	08
2564	**Richard M. Feldman, M.D.** Houston, TX 77030	02	02	01

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

8.1.2 Study Design

This was a randomized, multicenter, triple-masked, active-controlled, parallel group comparison of two concentrations of AL-6221 (0.0015% and 0.004%) to Timoptic 0.5% and Xalatan 0.005% (1:1:1:1 randomization) to evaluate their efficacy and safety in patients diagnosed with open-angle glaucoma (with or without pigment dispersion or pseudoexfoliation component) or ocular hypertension. The four treatment groups were 1) AL-6221 0.0015%, 2) AL-6221 0.004%, 3) Timoptic 0.5%, and 4) Xalatan 0.005%.

The study consisted of two phases. Phase 1 consisted of a Screening Visit, Washout Period, and Eligibility 1 and Eligibility 2 Visits. Phase 2 consisted of the treatment phase where eligible patients who met all the inclusion criteria at both Eligibility Visits 1 and 2, including entry IOP requirements, were randomized equally into one of four treatment groups and dosed once-daily (at 8PM) with either AL-6221 or Xalatan 0.005%, or twice-daily with Timoptic 0.5% (at 8AM and 8PM) for a treatment period of 12 months.

The study utilized the washout period schedule outlined in Study Protocol C-97-02.

For masking purposes, AL-6221 Vehicle was dosed QD at 8AM for the AL-6221 0.0015%, AL-6221 0.004%, and Xalatan 0.005% groups

All eligible patients were required to have post-washout IOP measurements at 8AM of 24 mmHg to 36 mmHg in at least one eye (the same eye) at both Eligibility 1 and 2 Visits. Ten (10)AM and 4PM IOP measurements were required to be 21 mmHg to 36 mmHg in at least one eye (the same eye) at both Eligibility 1 and 2 Visits.

Patients meeting all qualifying criteria entered the triple-masked treatment phase and were randomized to receive one of the following four treatments: 1) AL-6221 0.0015%, 2) AL-6221 0.004%, 3) Timoptic 0.5%, or 4) Xalatan 0.005%. Patients were instructed to instill one drop of masked medication in each eye at 8AM each morning with the bottle labeled "morning," and 8PM each evening with the bottle labeled "evening."

Follow-up study visits were scheduled at Week 2, Month 1.5, Month 3, Month 4.5, Month 6, Month 9, Month 12. Patients' IOP was measured at 8AM, 10AM, and 4PM, on Week 2, Month 3, Month 6, Month 12 and at 8AM and 10AM on Month 1.5, Month 4.5, and Month 9.

Study Medications

• AL-6221 0.0015%	Lot # ARE-2948B; ASE-2970A; ASE-2870B; ASE-2999A; 98-500007-2; and 99-500042-3
• AL-6221 0.004%	Lot # ARE-2946A; ASE-2971B; ASE-2998A; ASE-2998B; 98-500009-2; and 99-500044-3
• AL-6221 Vehicle	Lot # ARE-2947A; ASE-2972A; ASE-2972B; ASE-2989; ASE-2996B; 98-500002-1; 99-500022-2; and 99-500050-1
• Timoptic 0.5%	Lot # ARE-2949; ASE-2969; ASE-2977; ASE-2995; ASE-3003B; 98-500013-1; 99-500023-1; and 99-500031-1
• Xalatan 0.005%	Lot # ARE-2950; ASE-2976A; ASE-2976B; ASE-3004; and 99-500025-1

All masked test medications used during the treatment phase were supplied in a masked 5ml Drop-Tainer labeled with the appropriate patient number.

Study Population

Inclusion Criteria

1) Patients of either sex, of any race, diagnosed with open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension.
2) Patients who meet the following IOP entry criteria:
    - Each qualifying eye(s) must have:
        - 24 to 36 mmHg mean IOP at 8AM on both Eligibility Visit days.
        - 21 to 36 mmHg mean IOP at 10AM and 4PM on both Eligibility Visit days.
          (The mean IOP is the average of two (2) IOP measurements in the same eye.)
    - The same eye(s) must qualify at both Eligibility visits.
    - The mean IOP in either eye at any Eligibility exam visit must not be greater than 36 mmHg.
3) Informed consent read, signed, and dated by the patient or legally authorized representative, before conducting the Screening exam. If the patient is less than 18 years of age, the informed consent MUST also be signed and dated by a parent or legal guardian.
4) Nonprescription and prescription topical ophthalmic products and systemic medications other than those mentioned in the exclusion criteria will be allowed during the study.

Exclusion Criteria

1) Women who are of childbearing potential.
   Note: All women entered into the study must have been surgically sterilized at least 3 months prior to study start, or be one year postmenopausal.
2) Best corrected visual acuity worse than 0.6 logMAR in either eye.
3) History of chronic or recurrent severe inflammatory eye disease (i.e., scleritis, uveitis).
4) History of ocular trauma within the past six (6) months.
5) History of ocular infection or ocular inflammation within the past three (3) months.
6) History of clinically significant or progressive retinal disease such as retinal degeneration, diabetic retinopathy or retinal detachment.
7) Any abnormality preventing reliable applanation tonometry of either eye.
8) History of any severe ocular pathology (including severe dry eye) in either eye, that would preclude the administration of a topical beta-blocker or prostaglandin.
9) Patients who cannot be safely discontinued from use of all ocular hypotensive medication(s) for a minimum period of twelve (12) days to a maximum period of four (4) weeks.
10) Patient with cup-disc ratio greater than 0.80 in either eye.

11) Patients with severe central field loss in either eye defined as a sensitivity ≤ 10dB in at least two (2) of the four (4) visual field test points closest to the point of fixation.
12) Intraocular surgery within the past six (6) months as determined by patient history and/or examination.
13) Ocular laser surgery within the past three (3) months as determined by patient history and/or examination.
14) History of severe or serious hypersensitivity to prostaglandins, prostaglandin analogs, topical or systemic beta-blockers or to any components of the study medications.
15) History of severe, unstable or uncontrolled cardiovascular, hepatic or renal disease (e.g., sinus bradycardia, overt cardiac failure, greater than first degree atrioventricular block, cardiogenic shock, clinically relevant angina or uncontrolled hypertension) that would preclude the safe administration of a topical beta-blocker.
16) History of bronchial asthma, or severe chronic obstructive pulmonary disease that would preclude the safe administration of a topical beta-blocker.
17) Less than one month stable dosing regimen of any medication used on a chronic basis that may affect IOP (i.e., sympathomimetic agents, beta-adrenergic blocking agents, alpha agonists, alpha adrenergic blocking agents, calcium channel blockers, angiotensin converting enzyme inhibitors, etc.). Patients must be on a stable dosing regimen of these medications for at least thirty (30) days prior to the Screening Visit and must not change the dosing regimen during the eligibility period. Any change in dosage or addition of such medication(s) following randomization must be documented in the patient's chart.
18) Use of ANY glucocorticoid during eligibility phase. Patient must have washed out of any chronic glucocorticoid therapy for at least 4 weeks, or intermittent glucocorticoid use for at least 2 weeks prior to Eligibility 1 Visit.
19) Current use of topical, ocular nonsteroidal anti-inflammatory agents which inhibit cyclooxygenase and prostaglandin synthesis.
20) Any form of glaucoma other than open-angle glaucoma (with or without a pigment dispersion or pseudoexfoliation component) or ocular hypertension.
21) Angle grade less than 2 (extreme narrow angle with complete or partial closure-see manual for definitions) as measured by gonioscopy.
22) Therapy with another investigational agent within the past 30 days.
23) Patients with clinically significant hematologic, electrolyte, renal or hepatic abnormalities, based upon laboratory testing performed during the Eligibility Phase or by patient history, who would be at risk from treatment with a topical prostaglandin, prostaglandin analog or beta-blocker, or would be at risk from participation in the study.
24) Patients who cannot be dosed in both eyes.
25) Patients who cannot discontinue contact lens wear at the Screening Visit for the duration of the study. (Contact lens wear will not be allowed during the study.)
26) Use of any adjunctive therapy, either topical or systemic, for lowering IOP.

Additionally, the Alcon Medical Monitor may declare any patient ineligible for a valid medical reason. Any exceptions to the above eligibility requirements must be approved by the Alcon Medical Monitor.

Efficacy Variable

The primary efficacy parameter of the study was mean IOP at the 8AM, 10AM, and 4 PM time points for the patient's worse eye. The measurement times assessed trough (4PM) IOP response and peak activity (8AM and 10AM) for AL-6221.

The IOP lowering effect of AL-6221 0.0015% and 0.004% was compared to that of Timoptic 0.5% and Xalatan 0.005%. IOP measurements were assessed at Eligibility 1 and 2 Visits prior to randomization in order to establish a baseline. The IOP measurement for each time point from the Eligibility 1 and 2 Visits were averaged to obtain estimates of "baseline IOP" for each time point.

Reviewer's Comments:

The primary efficacy variable utilized in the review of this NDA is mean IOP and change in mean IOP from baseline at each time point at Week 2, Month 1.5, Month 3, Month 4.5, Month 6, Month 9, and Month 12.

Safety Variables

The following safety variables were assessed:
1) ocular hyperemia
2) ocular flare/cells
3) best corrected visual acuity (logMAR scale)
4) slit lamp biomicroscopy
5) resting pulse and blood pressure
6) dilated fundus examination
7) automated perimetry [redacted]
8) gonioscopy
9) iris pigmentation
10) eyelash appearance (eyelash length, color, density, and thickness)
11) corneal endothelial cell density
12) corneal thickness
13) laboratory analysis (blood chemistry, hematology, and urinalysis)

Adverse events were obtained as volunteered and solicited events. Any clinically relevant changes from baseline levels of all safety parameters were considered adverse events.

Protocol C-97-71
Study Plan

Activity	Screen	Eligibility Visit 1			Eligibility Visit 2			Week 2 ± 1 day			Month 1.5 ± 3 days		Month 3 ± 3 days			Month 4.5 ± 3 days		Month 6 ± 3 days			Month 9 ± 3 days		Month 12 ± 3 days		
		8 am	10 am	4 pm	8 am	10 am	4 pm	8 am	10 am	4 pm	8 am	10 am	8 am	10 am	4 pm	8 am	10 am	8 am	10 am	4 pm	8 am	10 am	8 am	10 am	4 pm
Screen Patients	X																								
Informed Consent	X																								
Demographics	X																								
Medical History	X																								
Discontinue All Glaucoma Rx	X																								
IOP[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hyperemia Assessment					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Flare/Cells Assessment[2]					X			X			X		X			X		X			X		X		
Visual Acuity (Best corrected) (logMAR scale)	X	X			X			X			X		X			X		X			X		X		
Biomicroscopy	X	X			X			X			X		X			X		X			X		X		
Resting Pulse/Blood Pressure	X				X	X		X	X		X	X	X	X		X	X	X	X		X	X	X	X	
Dilated Fundus	X																							X	
Automated Perimetry	X[1]																							X[6]	
Gonioscopy[4]	X																								
Iris/eyelash photographs					X						X		X			X		X			X		X		
Endothelial cell photography					X													X					X		
Pachymetry					X													X					X		
Hematology/blood chemistry		X																X					X		
Urinalysis		X																X					X		
Dispense study meds[5]							X			X		X			X		X			X		X			
Adverse Events								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Rx																								X		
Exit Patient																										X

[1]All IOP measurements should be ± 30 minutes of the required time.
[2]Flare/cells will be assessed at all sites according to the grading provided in the Manual of Definitions. At selected sites only, flare/cells assessment will be conducted using an automated flare/cells meter.
[3]Automated Perimetry , if not performed at Screening, may be performed between Screening and Eligibility 1 Visit. Visual fields must be faxed to Alcon and approved prior to drug dispensation.
[4]Gonioscopy is to be conducted only if this procedure has not been performed and documented within the last six (6) months.
[5]Dispense meds as needed.
[6] Exit automated perimetry may be performed after the 8 AM exam and before the 4 PM exam.

Subject Disposition and Demographics

All 801 randomized subjects received treatment and 688 subjects completed the study.

Subject Disposition

	Number of Subjects				
	AL-6221 0.0015%	AL-6221 0.004%	Timoptic 0.5%	Xalatan 0.005%	Total
Randomized	205	200	200	196	801
Discontinued prematurely	28	27	33	25	113
Included in safety evaluations	205	200	200	196	801
Included in intent-to-treat efficacy analysis	202	197	195	193	787
Included in per protocol efficacy analysis	198	187	187	188	760

Reviewer's Comments:

The intent-to-treat population excluded 14 subjects who received medication but had no on-treatment visit data.

Summary of Reasons for Premature Discontinuation from Study

	Number (%) of Subjects			
Reason for Discontinuation	AL-6221 0.0015% (N=205)	AL-6221 0.004% (N=200)	Timoptic 0.5% (N=200)	Xalatan 0.005% (N=196)
Adverse events	15(7.3)	15(7.5)	11(5.5)	6(3.1)
Inadequate control of IOP	1(0.5)	3(1.5)	7(3.5)	3(1.5)
Non-qualifying IOP	1(0.5)	6(3.0)	5(2.5)	4(2.0)
Noncompliance	2(1.0)	2(1.0)	0(0)	1(0.5)
Patient decision	1(0.5)	1(0.5)	1(0.5)	2(1.0)
Site closed	4(2.0)	3(1.5)	4(2.0)	2(1.0)
Use of contraindicated medications	1(0.5)	1(0.5)	3(1.5)	1(0.5)
Lost to follow-up	2(1.0)	4(2.0)	0(0)	4(2.0)
Other	1(0.5)	2(1.0)	2(1.0)	2(1.0)
Total	28(13.7)	37(18.5)	33(16.5)	25(12.8)

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Duration (Days)	Reason
236	5301	Timoptic 0.5%	77	Site closed
	5302	AL-6221 0.0015%	56	Site closed
271	8014	AL-6221 0.004%	196	Lost to follow-up
	8020	AL-6221 0.004%	62	Failed Eligibility 2 requirements
	8025	AL-6221 0.004%	84	Adverse event-hyperemia eye, discomfort eye
	8036	AL-6221 0.0015%	9	Adverse event-hyperemia eye, pain eye
331	4002	Timoptic 0.5%	238	Adverse event-discomfort eye
	4007	Timoptic 0.5%	14	Failed Eligibility 1 & 2 IOP requirements
	4019	AL-6221 0.004%	297	Noncompliance
355	5305	AL-6221 0.0015%	56	On glucocorticoid
	5212	Xalatan 0.005%	300	Inadequate control of IOP
	5214	Xalatan 0.005%	196	Moved to California
362	2101	AL-6221 0.004%	25	Failed Eligibility 2 requirements
	2103	Timoptic 0.5%	15	Failed Eligibility 2 IOP requirements
	2104	Xalatan 0.005%	14	Failed Eligibility 1 requirements
	2105	Xalatan 0.005%	13	Failed Eligibility 1 requirements
	2114	Timoptic 0.5%	205	Adverse event-heart block, surgical/medical proc
	2119	AL-6221 0.0015%	72	Adverse event-cardiomegaly
386	3001	AL-6221 0.0015%	70	Adverse event-cells
	3002	Xalatan 0.005%	155	Lost to follow-up
	3006	AL-6221 0.004%	361	Subject decision unrelated to adverse event
	3008	Timoptic 0.5%	220	Inadequate control of IOP
	3013	AL-6221 0.0015%	203	Adverse event-hyperemia eye, pain eye, libido decrease
394	3607	AL-6221 0.0015%	112	History of emphysema
	3609	AL-6221 0.0015%	176	Adverse event-asthenia
553	1701	AL-6221 0.004%	279	Inadequate control of IOP
649	1504	AL-6221 0.004%	135	Adverse event-hyperemia eye, dry eye, foreign body sensation
	1517	Timoptic 0.5%	44	Inadequate control of IOP
731	2301	Timoptic 0.5%	266	Inadequate control of IOP
	2304	AL-6221 0.0015%	240	Inadequate control of IOP
	2305	Xalatan 0.005%	226	Noncompliance
750	1806	AL-6221 0.004%	206	Lost to follow-up
	1810	AL-6221 0.004%	329	Lost to follow-up
983	1402	AL-6221 0.0015%	301	Adverse event-cardiovascular disease(patient died)
	1407	AL-6221 0.004%	35	Adverse event-Injury accidental(patient died)
	1410	AL-6221 0.004%	13	Non-qualifying IOP
	1420	Xalatan 0.005%	173	Adverse event-cardiovascular disease(patient died)
989	2503	Timoptic 0.5%	21	Improper entry into study
	2515	AL-6221 0.0015%	28	Adverse event-eye disease, rhinitis, cells, iritis
1208	2004	Timoptic 0.5%	182	Inadequate control of IOP
	2010	AL-6221 0.004%	52	Adverse event-hypertension
	2013	Timoptic 0.5%	62	Adverse event-alopecia
1212	1604	Timoptic 0.5%	49	Subject decision unrelated to adverse event
	1613	AL-6221 0.004%	56	Inadequate control of IOP
	1616	Xalatan 0.005%	21	Subject decision unrelated to adverse event
1393	5001	AL-6221 0.0015%	302	Adverse event-infarct myocardial, heart fail(patient died)
	5010	Xalatan 0.005%	21	Inadequate control of IOP
	5011	Timoptic 0.5%	352	Adverse event-infarct myocardial(patient died)
	5015	Timoptic 0.5%	135	Inadequate control of IOP
1409	2403	AL-6221 0.004%	146	Adverse event-dermatitis contact
	2413	Xalatan 0.005%	17	Lost to follow-up
1473	2708	AL-6221 0.004%	146	Adverse event-hyperemia eye

Investigator	Patient	Treatment	Duration (Days)	Reason
1473	2712	Timoptic 0.5%	15	Protocol violation-steroid use
1552	1306	Xalatan 0.005%	131	Adverse event-heart arrest(patient died)
	1310	Xalatan 0.005%	42	Lost to follow-up
1782	4301	Timoptic 0.5%	286	Site discontinued
	4302	AL-6221 0.004%	237	Site discontinued
	4303	AL-6221 0.0015%	217	Site discontinued
	4304	Xalatan 0.005%	236	Site discontinued
	4305	AL-6221 0.004%	181	Site discontinued
	4306	Xalatan 0.005%	162	Site discontinued
	4307	Timoptic 0.5%	179	Site discontinued
	4308	AL-6221 0.0015%	188	Site discontinued
	4309	Timoptic 0.5%	186	Site discontinued
	4310	AL-6221 0.0015%	175	Site discontinued
	4311	AL-6221 0.004%	119	Site discontinued
1806	1205	AL-6221 0.0015%	216	Adverse event-angina pectoris, infarct myocardial
	1223	AL-6221 0.0015%	62	Noncompliance
	1225	Xalatan 0.005%	56	Subject decision unrelated to adverse event
1892	4403	AL-6221 0.004%	255	Noncompliance
	4404	Timoptic 0.5%	14	Did not pass eligibility
	4405	AL-6221 0.004%	234	Adverse events-cells, flare
	4406	Timoptic 0.5%	46	Adverse events-cells, flare
	4414	AL-6221 0.004%	17	Lost to follow-up
1927	3902	AL-6221 0.004%	28	Adverse event-discomfort eye, pruritus eye, pain eye
	3925	Timoptic 0.5%	264	Adverse event-cardiovascular disease(patient died)
	3929	AL-6221 0.004%	186	Adverse event-discomfort eye, pain eye
1939	6007	AL-6221 0.004%	181	Adverse event-retinal detachment
	6008	Timoptic 0.5%	15	Adverse event-dyspnea
1973	1002	Xalatan 0.005%	383	Adverse event-surgical/medical proc, pneumonia(patient died)
	1005	Xalatan 0.005%	105	Protocol violation
	1007	AL-6221 0.0015%	91	Subject decision unrelated to adverse event
	1013	AL-6221 0.0015%	89	Adverse event-arrhythmia, coronary artery dis(patient died)
	1019	AL-6221 0.004%	71	Protocol violation
	1037	Xalatan 0.005%	168	Moved to Beverly Hills Florida
	1042	AL-6221 0.0015%	287	Adverse event-leukemia(patient died)
	1043	AL-6221 0.004%	12	Adverse event-hyperemia eye, pain eye
2128	1104	Timoptic 0.5%	21	Adverse event-angina pectoris
	1105	Timoptic 0.5%	63	Inadequate control of IOP
	1106	Xalatan 0.005%	168	Lost to follow-up
2133	1901	AL-6221 0.004%	58	Adverse event-asthenia, bradycardia
	1904	Timoptic 0.5%	287	Adverse event-edema lung, infarct myocardial, shock(patient died)
	1905	AL-6221 0.0015%	130	Lost to follow-up
	1909	Xalatan 0.005%	143	Protocol violation at entry
	1913	AL-6221 0.004%	145	Protocol violation on entry
	1925	Xalatan 0.005%	149	Adverse event-tachycardia ventricular(patient died)
	1930	AL-6221 0.0015%	42	Lost to follow-up
2247	3412	AL-6221 0.004%	14	Adverse event-discomfort eye, dry eye, foreign body sensation
	3417	AL-6221 0.004%	18	Adverse event-hyperemia eye
	3420	AL-6221 0.0015%	42	Adverse event-pain, carcinoma lung
2346	2805	AL-6221 0.004%	90	Failed eligibility IOP requirements
	2818	AL-6221 0.0015%	240	Noncompliance
	2819	Timoptic 0.5%	56	Inadequate control of IOP
	2822	Timoptic 0.5%	308	Adverse event-cardiovascular disease
	2823	AL-6221 0.0015%	357	Adverse event-retinal detachment
	2827	Xalatan 0.005%	182	Inadequate control of IOP

Investigator	Patient	Treatment	Duration (Days)	Reason
2347	3302	Xalatan 0.005%	371	Adverse event-eye disease. surgical/medical proc
	3304	Timoptic 0.5%	8	Patient is of child bearing potential
2348	2902	AL-6221 0.004%	12	Adverse event-hyperemia eye. pruritus eye
	2907	AL-6221 0.0015%	46	Adverse event-malaise. insomnia
2353	3103	Timoptic 0.5%	250	Protocol violation-steroid use
	3107	Timoptic 0.5%	17	Adverse event-retinal detachment
	3108	AL-6221 0.0015%	84	Protocol violation-high IOPs
	3109	Xalatan 0.005%	105	Protocol violation-high IOPs at eligibility 2 visit
	3114	Timoptic 0.5%	84	Protocol violation-high IOPs
	3116	AL-6221 0.004%	99	Protocol violation-steroid use
	3122	AL-6221 0.004%	168	Protocol violation-D/C heart med during eligibility
	3131	AL-6221 0.004%	221	Inadequate control of IOP
2418	3802	Timoptic 0.5%	55	Protocol violation-steroid use
2558	5601	Xalatan 0.005%	355	Adverse event-embolism
	5604	AL-6221 0.004%	14	Laser 7/98
	5605	AL-6221 0.0015%	357	Adverse event-pain back. surgical/medical proc
2564	5701	Timoptic 0.5%	42	Protocol violation

The study site of investigator #236 was closed prematurely. The two subjects enrolled at the site were discontinued from the study prematurely.

The study site of investigator #1782 was closed prematurely. All 11 patients enrolled at the site were discontinued from the study. Site monitoring visits and monitoring records failed to reveal any data validity or protocol compliance issues. To evaluate the effect of these patients on the results, the primary analysis was performed with and without these patients. No substantive differences between these analyses were observed, therefore the patients were retained in all analysis.

p-Values from Primary Analysis With and Without Investigator 1782 Data (Intent-to-Treat Data)

Source	p-value Including Inv. 1782 Data	Excluding Inv. 1782 Data
Treatment	0.0001	0.0001
Day	0.0001	0.0001
Treatment by Day	0.0082	0.0063
Time	0.0001	0.0001
Treatment by Time	0.0015	0.0004
Day by Time	0.6109	0.6438
Treatment by Day by Time	0.9903	0.9818

Reviewer's Comments:

Agree.

Summary of Demographic Characteristics (Intent-to-Treat)

Treatment	Age Mean*	Std	N	Min	Max
AL-6221 0.0015%	63.7	11.0	202	35	88
AL-6221 0.004%	64.0	13.3	197	22	94
TIMOPTIC 0.5%	64.8	11.6	195	25	87
XALATAN 0.005%	64.5	11.6	193	28	86

*p=0.7855 for test of mean age differences among groups.

	Treatment 0.0015% N	%	0.004% N	%	TIMOPTIC 0.5% N	%	XALATAN.005% N	%	p-value
Age									
<65	103	51.0	86	43.7	75	38.5	86	44.6	0.094
>=65	99	49.0	111	56.3	120	61.5	107	55.4	
Age (>=65)									
>=65 - <75	63	63.6	72	64.9	84	70.0	62	57.9	0.460
>=75 - <85	33	33.3	36	32.4	33	27.5	44	41.1	
>=85 - <95	3	3.0	3	2.7	3	2.5	1	0.9	
Sex									
MALE	96	47.5	100	50.8	107	54.9	89	46.1	0.315
FEMALE	106	52.5	97	49.2	88	45.1	104	53.9	
RACE									
CAUCASIAN	147	72.8	138	70.1	146	74.9	135	69.9	0.807
BLACK	45	22.3	49	24.9	40	20.5	43	22.3	
ASIAN	2	1.0	2	1.0	--	--	2	1.0	
OTHER	8	4.0	8	4.1	9	4.6	13	6.7	
Iris Color*									
.	--	--	1	0.5	--	--	--	--	0.395
BROWN	108	53.5	106	53.8	90	46.2	114	59.1	
HAZEL	27	13.4	23	11.7	28	14.4	24	12.4	
GREEN	8	4.0	10	5.1	11	5.6	8	4.1	
BLUE	56	27.7	52	26.4	59	30.3	38	19.7	
GREY	3	1.5	5	2.5	7	3.6	9	4.7	
Diagnosis (ICD9)									
OCULAR HYPERTEN.	66	32.7	67	34.0	55	28.2	59	30.6	0.632
OPEN-ANGLE GL.	134	66.3	127	64.5	137	70.3	132	68.4	
PIGMENTARY GL.	--	--	3	1.5	2	1.0	1	0.5	
PSEUDOEXFOLIAT GL.	2	1.0	--	--	1	0.5	1	0.5	

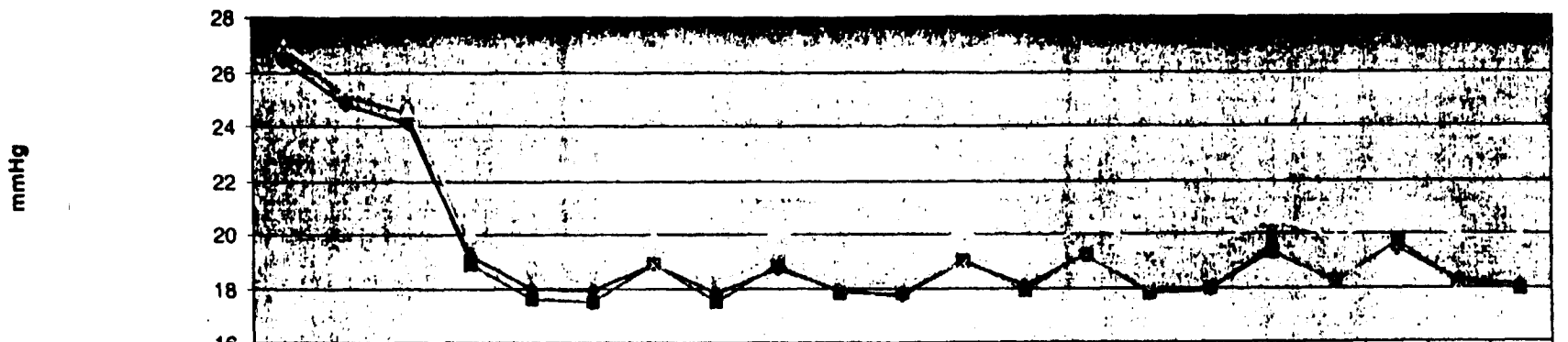
*One patient (2014) did not have iris color recorded.

APPEARS THIS WAY
ON ORIGINAL

8.1.2 Efficacy – Protocol C-97-71 Intent-to-Treat Population

Primary Efficacy Variable

Mean IOP per Visit and Time

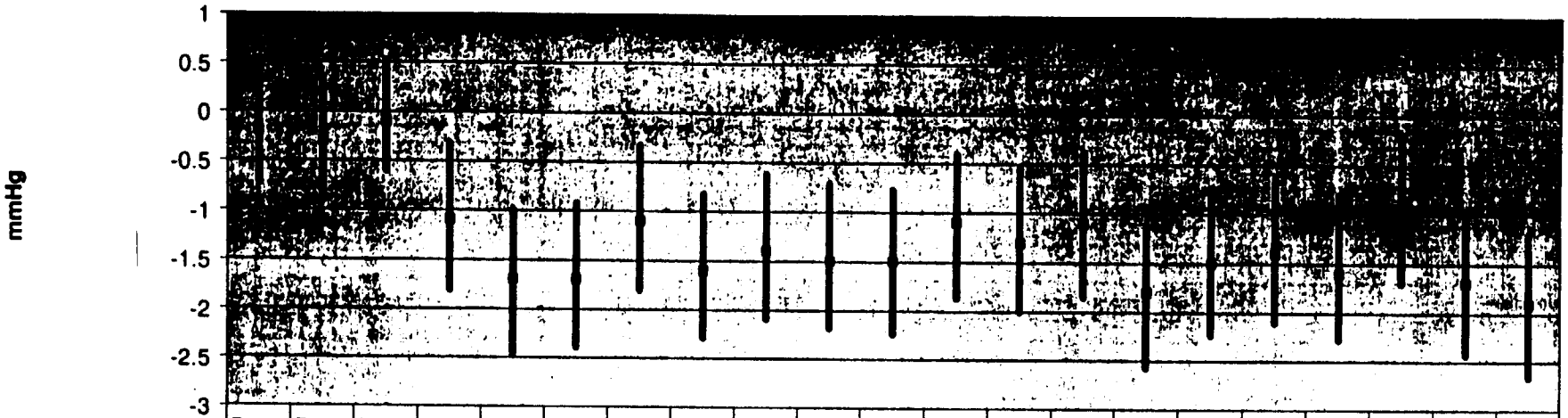


	Baseline 8AM	Baseline 10AM	Baseline 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
AL-6221 0.0015%	26.4	24.8	24.1	19.2	18	17.9	18.9	17.8	18.7	17.9	17.7	19	18.1	19.2	17.8	17.9	19.5	18.3	19.4	18.3	18.1
AL-6221 0.004%	26.8	25.1	24.5	18.9	17.6	17.5	18.9	17.5	18.8	17.8	17.8	19	17.9	19.2	17.8	18	19.3	18.2	19.7	18.2	17.9
Timoptic 0.5%	27	25.4	24.6	20	19.3	19.2	19.9	19.1	20.1	19.3	19.3	20.1	19.2	20.3	19.6	19.5	20.6	19.8	20.7	19.9	19.9
Xalatan 0.005%	26.9	25.2	24.9	19.5	18.5	18.7	18.8	18.2	19.1	18.1	18.2	18.9	18	19.2	17.9	18.4	19.5	18.3	19.4	18.1	18.6

Reviewer's Comments: *Baseline mean IOP of the four treatment arms is similar. The mean IOP for both concentrations of AL-6221 (0.0015% and 0.004%) and Xalatan 0.005% is consistently lower than Timoptic 0.5% at all time points measured. AL-6221 0.0015%, AL-6221 0.004%, and Xalatan 0.005% demonstrate similar ability to lower IOP over visit days and time.*

APPEARS THIS WAY
ON ORIGINAL

Mean Difference (AL-6221 0.004% - Timoptic 0.5%) with 95% Confidence Intervals

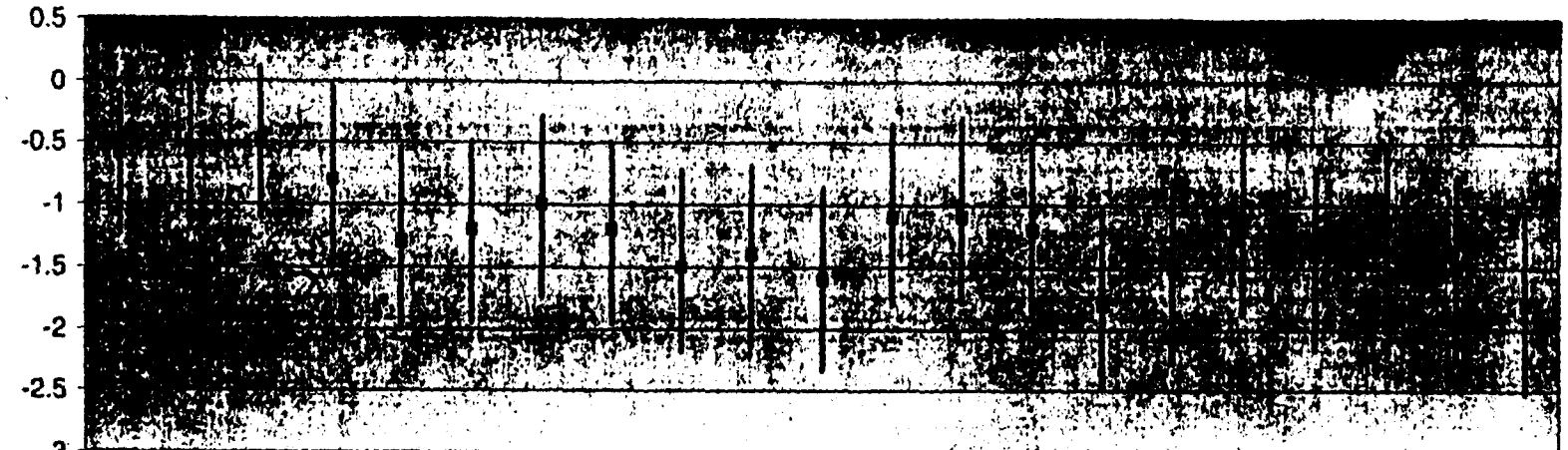


	Base-line 8AM	Base-line 10AM	Base-line 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
Lower CI	-0.7	-0.9	-0.6	-1.81	-2.46	-2.39	-1.8	-2.29	-2.09	-2.18	-2.24	-1.87	-2	-1.85	-2.57	-2.23	-2.1	-2.28	-1.7	-2.43	-2.66
Upper CI	0.4	0.3	0.5	-0.35	-1	-0.93	-0.34	-0.83	-0.63	-0.72	-0.78	-0.41	-0.54	-0.39	-1.11	-0.77	-0.64	-0.82	-0.24	-0.97	-1.2
■ Mean Difference	-0.2	-0.3	-0.1	-1.1	-1.7	-1.7	-1.1	-1.6	-1.4	-1.5	-1.5	-1.1	-1.3	-1.1	-1.8	-1.5	-1.4	-1.6	-1	-1.7	-1.9

Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean difference between the mean IOP of AL-6221 0.004% and Timoptic 0.5% is statistically significant at all time points and ranges from* [redacted] *The IOP lowering ability of AL-6221 0.004% is not superior to Timoptic 0.5% by a clinically significant amount.*

APPEARS THIS WAY
ON ORIGINAL

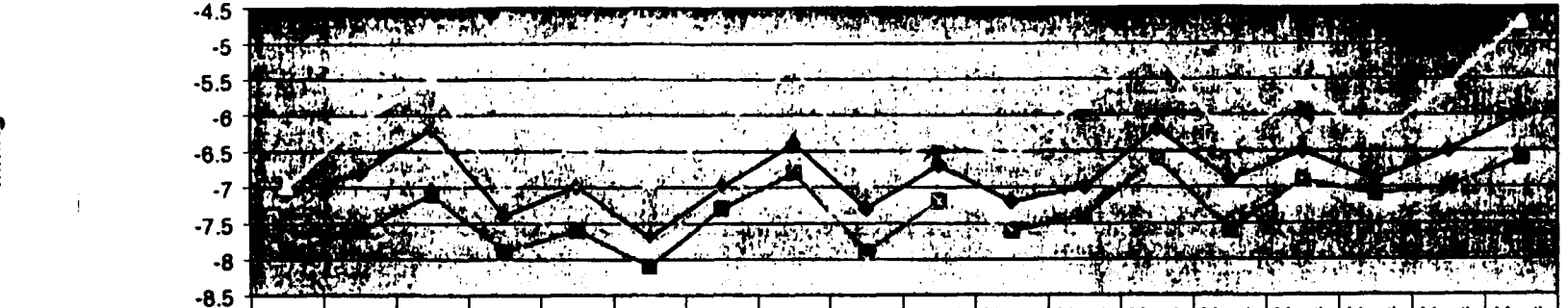
Mean Difference (AL-6221 0.0015% - Timoptic 0.5%) with 95% Confidence Intervals



	Base-line 8AM	Base-line 10AM	Base-line 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
Lower CI	-1.2	-1.2	-1.1	-1.5	-2	-1.94	-1.74	-1.96	-2.18	-2.15	-2.33	-1.81	-1.78	-1.92	-2.49	-2.27	-1.88	-2.16	-1.97	-2.25	-2.52
Upper CI	-0.1	0	0.1	-0.05	-0.55	-0.49	-0.29	-0.51	-0.73	-0.7	-0.88	-0.36	-0.33	-0.47	-1.04	-0.82	-0.43	-0.71	-0.52	-0.79	-1.07
■ Mean Difference	-0.6	-0.6	-0.5	-0.8	-1.3	-1.2	-1	-1.2	-1.5	-1.4	-1.6	-1.1	-1.1	-1.2	-1.8	-1.5	-1.2	-1.4	-1.2	-1.5	-1.8

Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is not comparable. The mean IOP of the two groups at Baseline 8AM is statistically significant. The 95% confidence interval does not cross zero at Baseline 8AM time point. Any analysis comparing the IOP lowering ability of these two treatment groups is questionable.*

Change in Mean IOP from Baseline per Visit and Time

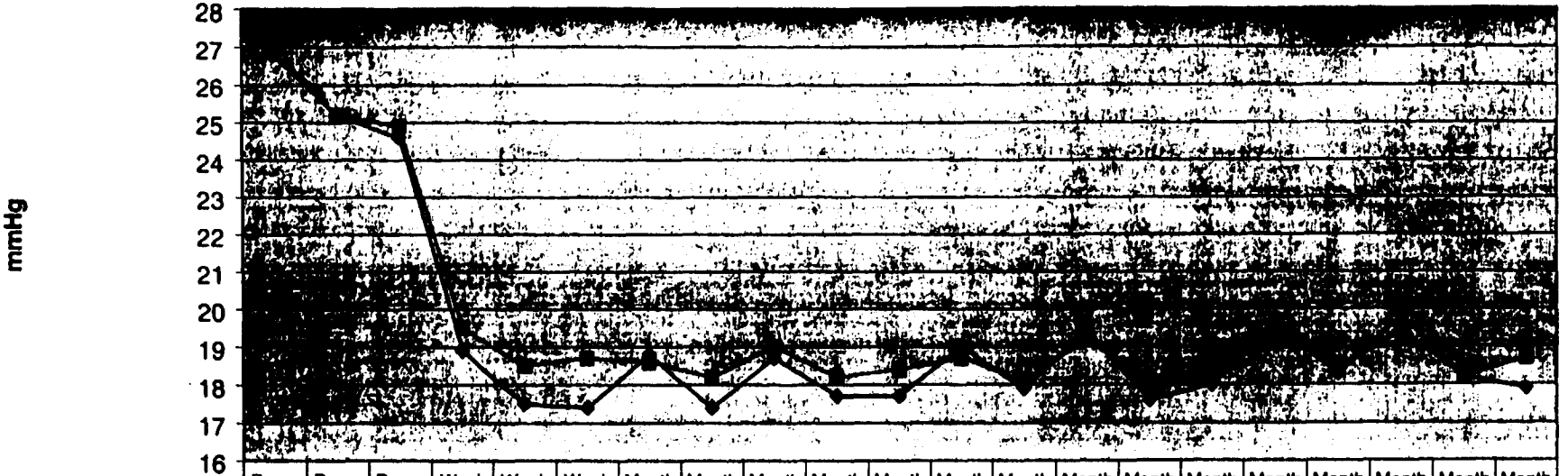


	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
AL-6221 0.0015%	-7.1	-6.8	-6.2	-7.4	-7	-7.7	-7	-6.4	-7.3	-6.7	-7.2	-7	-6.2	-6.9	-6.5	-6.9	-6.5	-6
AL-6221 0.004%	-7.9	-7.6	-7.1	-7.9	-7.6	-8.1	-7.3	-6.8	-7.9	-7.2	-7.6	-7.4	-6.6	-7.6	-6.9	-7.1	-7	-6.6
Timoptic 0.5%	-7	-6.1	-5.5	-7.1	-6.4	-6.9	-6.2	-5.3	-6.9	-6.3	-6.6	-5.8	-5.1	-6.4	-5.7	-6.3	-5.6	-4.7
Xalatan 0.005%	-7.4	-6.7	-6.2	-8.1	-7	-7.8	-7.1	-6.7	-8	-7.2	-7.6	-7.3	-6.6	-7.4	-6.9	-7.5	-7.1	-6.4

Reviewer's Comments: *When corrected for baseline, AL-6221 0.0015%, AL-6221 0.004%, and Xalatan 0.005% consistently lower IOP more than Timoptic 0.5% over visit days and time. The IOP lowering ability of AL-6221 0.0015%, AL-6221 0.004%, and Xalatan 0.005% is similar. The change in mean IOP from baseline ranges from –6.0 to –7.7 mmHg for AL-6221 0.0015% dosed QPM, from –6.6 to –8.1 mmHg for AL-6221 0.004% dosed QPM, from –6.2 to -8.1 mmHg for Xalatan 0.005% dosed QPM, and from –4.7 to –7.1 mmHg dosed BID for Timoptic 0.5%. Note: since the baseline mean IOP values of AL-6221 0.0015% as compared to the values of Timoptic 0.5% are not comparable, it is highly questionable as to what can be concluded about AL-6221 0.0015% from this study.*

APPEARS THIS WAY
ON ORIGINAL

Mean IOP per Visit and Time

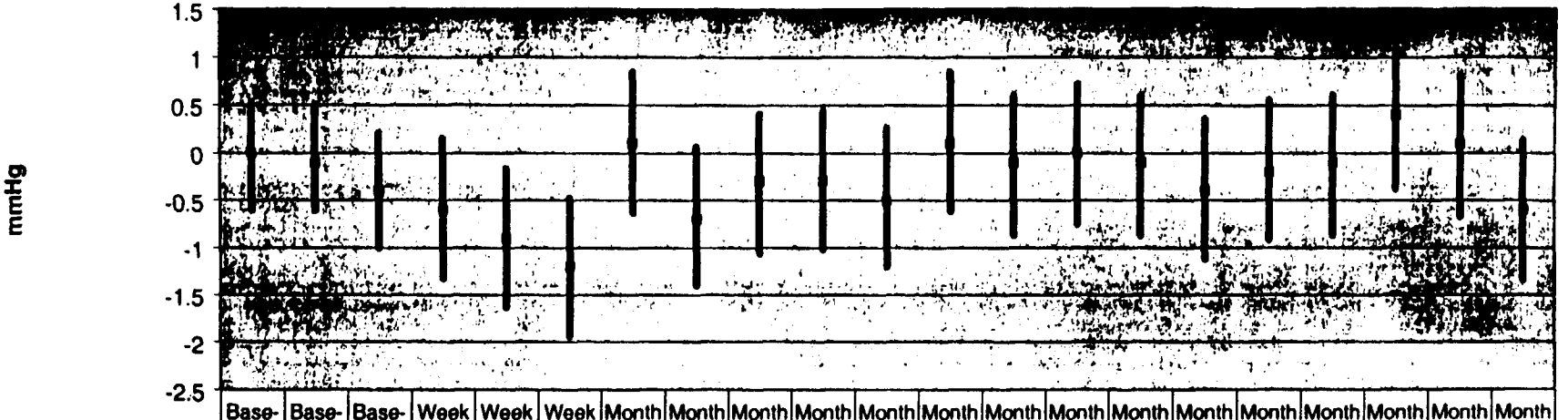


	Baseline 8AM	Baseline 10AM	Baseline 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
AL-6221 0.004%	26.8	25.2	24.6	18.9	17.5	17.4	18.8	17.4	18.7	17.7	17.7	19	17.9	19.4	17.6	18	19.5	18.3	19.8	18.2	17.9
Xalatan 0.005%	26.9	25.2	24.9	19.5	18.5	18.7	18.6	18.2	19	18.2	18.4	18.7	18.1	19.2	18	18.5	19.4	18.4	19.4	18.2	18.7

Reviewer's Comments: *Baseline mean IOP of the two treatment arms is similar. The mean IOP forAL-6221 0.004% and Xalatan 0.005% is similar at all time points measured. The treatment group with the lower mean IOP alternates between AL-6221 0.004% and Xalatan 0.005% over visit days and time in no discernable pattern.*

APPEARS THIS WAY
ON ORIGINAL

Mean Difference (AL-6221 0.004% - Xalatan 0.005%) with 95% Confidence Intervals

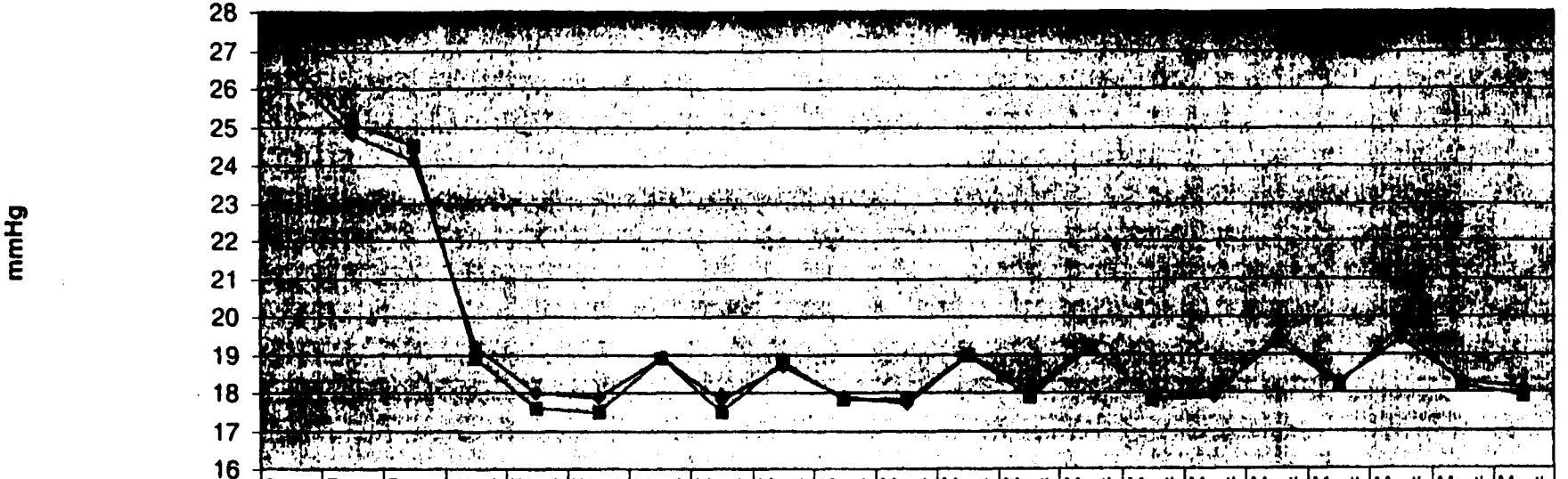


	Base-line 8AM	Base-line 10AM	Base-line 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
Lower CI	-0.6	-0.6	-1	-1.32	-1.63	-1.94	-0.63	-1.4	-1.06	-1.02	-1.2	-0.62	-0.87	-0.75	-0.87	-1.12	-0.91	-0.87	-0.38	-0.67	-1.34
Upper CI	0.5	0.5	0.2	0.14	-0.17	-0.48	0.84	0.06	0.4	0.44	0.26	0.84	0.59	0.71	0.59	0.34	0.55	0.6	1.09	0.8	0.13
■ Mean Difference	0	-0.1	-0.4	-0.6	-0.9	-1.2	0.1	-0.7	-0.3	-0.3	-0.5	0.1	-0.1	0	-0.1	-0.4	-0.2	-0.1	0.4	0.1	-0.6

Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean difference between the mean IOP of AL-6221 0.004% and Xalatan 0.005% is not statistically significant at almost all time points. The 95% confidence interval crosses zero at all time points, except at Week 2 10AM and 4PM.*

APPEARS THIS WAY
ON ORIGINAL

Mean IOP per Visit and Time

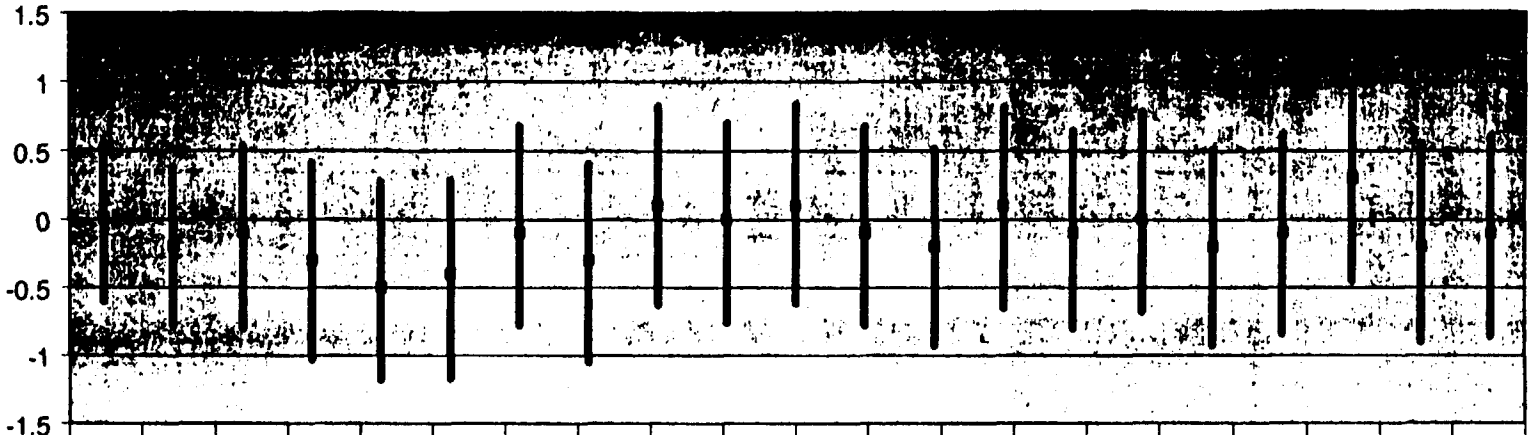


	Baseline 8AM	Baseline 10AM	Baseline 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
AL-6221 0.0015%	26.4	24.8	24.1	19.2	18	17.9	18.9	17.8	18.7	17.9	17.7	19	18.1	19.2	17.8	17.9	19.5	18.3	19.4	18.3	18.1
AL-6221 0.004%	26.8	25.1	24.5	18.9	17.6	17.5	18.9	17.5	18.8	17.8	17.8	19	17.9	19.2	17.8	18	19.3	18.2	19.7	18.2	17.9

Reviewer's Comments: *Baseline mean IOP of the two treatment arms is similar. The mean IOP of AL-6221 0.0015% and AL-6221 0.004% is similar over visit days and time. The treatment group with the lower mean IOP alternates between AL-6221 0.0015% and AL-6221 0.004% over visit days and time in no discernable pattern.*

APPEARS THIS WAY
ON ORIGINAL

Mean Difference (AL-6221 0.004% - AL-6221 0.0015%) with 95% Confidence Intervals

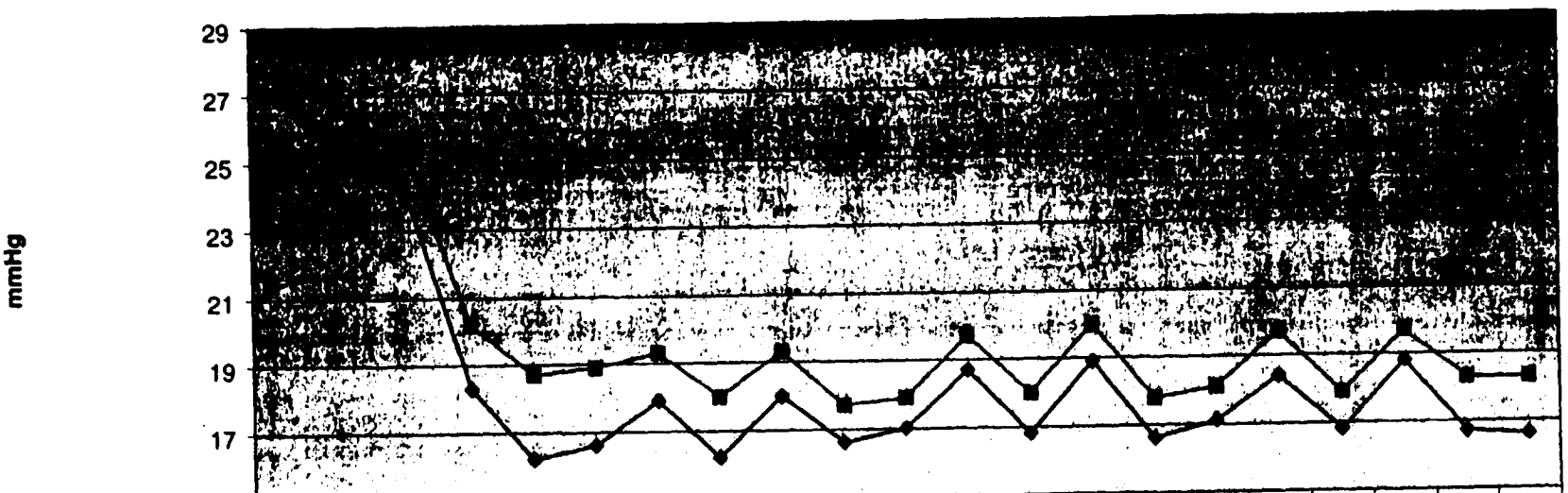


	Base-line 8AM	Base-line 10AM	Base-line 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
Lower CI	-0.6	-0.78	-0.8	-1.03	-1.18	-1.17	-0.78	-1.05	-0.63	-0.76	-0.78	-0.93	-0.65	-0.8	-0.68	-0.93	-0.84	-0.45	-0.9	-0.86
Upper CI	0.55	0.37	0.53	0.41	0.27	0.28	0.67	0.4	0.82	0.69	0.67	0.51	0.8	0.64	0.77	0.51	0.61	0.99	0.54	0.59
■ Mean Difference	0	-0.2	-0.1	-0.3	-0.5	-0.4	-0.1	-0.3	0.1	0	-0.1	-0.2	0.1	-0.1	0	-0.2	-0.1	0.3	-0.2	-0.1

Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean difference between the mean IOP of AL-6221 0.0015% and AL-6221 0.004% is not statistically significant at all time points. AL-6221 0.0015% and AL-6221 0.004% each dosed once daily in the evening demonstrate equivalence in their ability to lower IOP.*

APPEARS THIS WAY
ON ORIGINAL

Mean IOP per Visit and Time for Black Patients

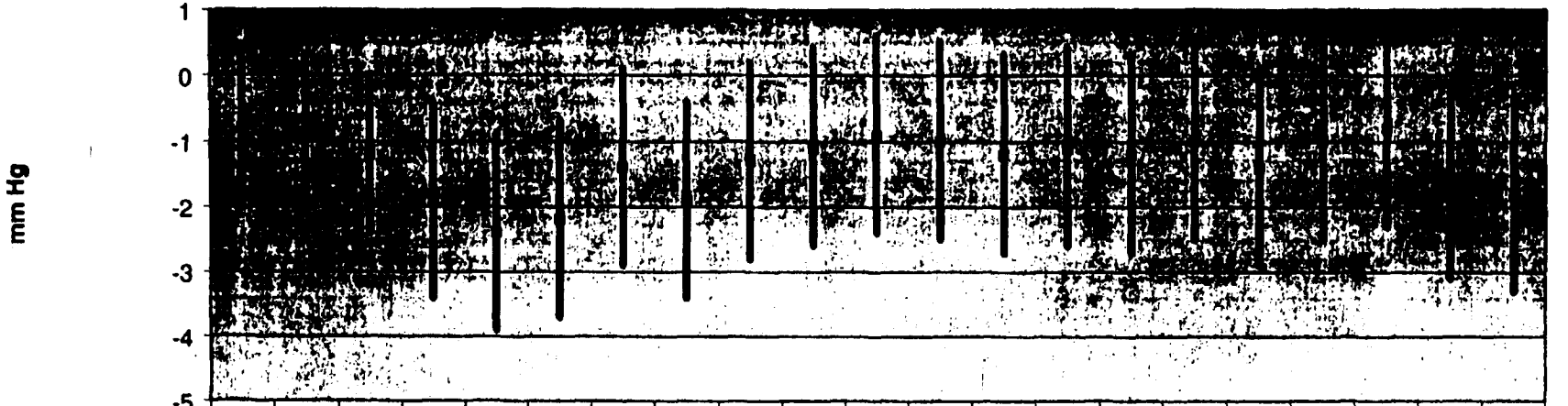


	Baseline 8AM	Baseline 10AM	Baseline 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
AL-6221 0.004%	26.8	25	24	18.3	16.2	16.6	17.9	16.2	18	16.6	17	18.7	16.8	18.9	16.6	17.1	18.4	16.8	18.8	16.7	16.6
Xalatan 0.005%	27.6	25	25.2	20.2	18.7	18.9	19.3	18	19.3	17.7	17.9	19.7	18	20	17.8	18.1	19.7	17.9	19.7	18.3	18.3

Reviewer's Comments: *Baseline mean IOP for AL-6221 0.004% and Xalatan 0.005% is similar. AL-6221 0.004% dosed QPM and Xalatan 0.005% dosed QPM demonstrate similar ability to lower IOP over visit days and time.*

APPEARS THIS WAY
ON ORIGINAL

Mean Difference (AL-6221 0.004% - Xalatan 0.005%) with 95% Confidence Intervals for Black Patients

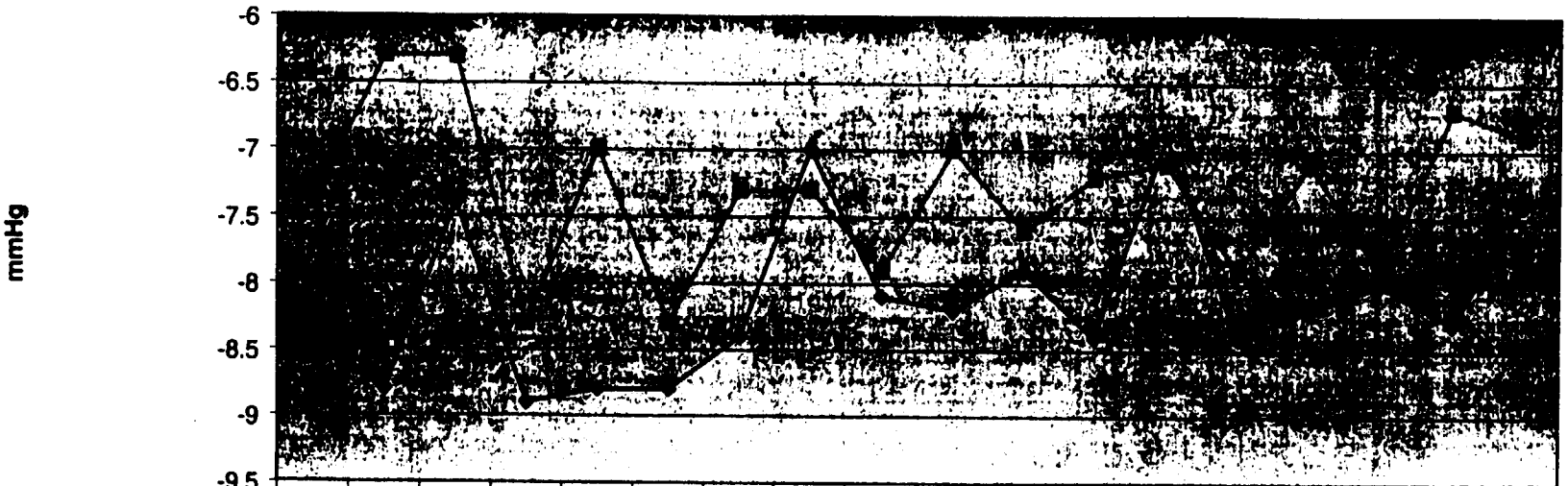


	Base-line 8AM	Base-line 10AM	Base-line 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
Lower CI	-2	-2	-2.4	-3.4	-3.9	-3.7	-2.9	-3.4	-2.8	-2.6	-2.4	-2.5	-2.7	-2.6	-2.7	-2.5	-2.9	-2.5	-2.3	-3.1	-3.3
Upper CI	0.4	0.3	0	-0.4	-0.9	-0.7	0.1	-0.4	0.2	0.4	0.6	0.5	0.3	0.4	0.3	0.5	0.1	0.5	0.7	-0.1	-0.3
■ Mean Difference	-0.8	-0.9	-1.2	-1.9	-2.4	-2.2	-1.4	-1.9	-1.3	-1.1	-0.9	-1	-1.2	-1.1	-1.2	-1	-1.4	-1	-0.8	-1.6	-1.8

Reviewer's Comments: *The mean IOP of the two treatment arms at baseline is comparable. The 95% confidence interval crosses zero at all time points measured at baseline. The mean difference between the mean IOP of AL-6221 0.004% dosed QPM and Xalatan 0.005% dosed QPM is not statistically significant at a majority of the time points measured and ranges from –0.8 to –2.4 mmHg.*

APPEARS THIS WAY
ON ORIGINAL

Change in Mean IOP from Baseline per Visit and Time for Black Patients



	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
AL-6221 0.004%	-8.5	-8.8	-7.4	-8.9	-8.8	-8.8	-8.4	-7	-8.1	-8.2	-7.9	-8.4	-6.9	-8.4	-8.2	-8	-8.3	-7.4
Xalatan 0.005%	-7.4	-6.3	-6.3	-8.3	-7	-8.3	-7.3	-7.3	-7.9	-7	-7.6	-7.2	-7.1	-7.9	-7.1	-7.9	-6.7	-6.9

Reviewer's Comments: *When corrected for baseline, the IOP lowering ability of AL-6221 0.004% and Xalatan 0.005% is similar. The change in mean IOP from baseline ranges from –6.9 to –8.9 mmHg for AL-6221 0.004% dosed QPM and from –6.3 to –8.3 mmHg for Xalatan 0.005% dosed QPM.*

APPEARS THIS WAY
ON ORIGINAL

8.1.2 Safety

Adverse Events

Serious adverse events other than death were reported for 21/205 (10.2%) subjects treated with AL-6221 0.0015%, 15/200 (7.5%) subjects treated with AL-6221 0.004%, 23/200 (11.5%) subjects treated with Timoptic 0.5%, and for 18/196 (9.2%) subjects treated with Xalatan 0.005%. These other serious adverse events resulted in premature discontinuation from the study for four (4) subjects treated with AL-6221 0.0015%, one (1) subject treated with AL-6221 0.004%, four (4) subjects treated with Timoptic 0.5%, and for two (2) subjects treated with Xalatan 0.005%.

Other Serious Adverse Events

Investigator Number	Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
1393	5006	AL-6221 0.0015%	Carcinoma Skin	Resolved w/Tx	No
2479	5414	AL-6221 0.0015%	Atelectasis	Resolved wo/Tx	No
			Pneumonia	Resolved w/Tx	No
			Illeus	Resolved wo/Tx	No
			Abdomen Enlargement	Resolved wo/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2247	3420	AL-6221 0.0015%	Carcinoma Lung	Continuing w/Tx	Yes
1806	1210	AL-6221 0.0015%	Joint Disease	Resolved w/Tx	No
1340	4607	AL-6221 0.0015%	Colitis	Resolved wo/Tx	No
			Hemorrhage Rectal	Resolved wo/Tx	No
1806	1205	AL-6221 0.0015%	Angina Pectoris	Resolved w/Tx	Yes
			Infarct Myocardial	Resolved w/Tx	Tes
1973	1040	AL-6221 0.0015%	Cardiovascular Disease	Resolved w/Tx	No
			Surgical/Med Proc	Resolved w/Tx	No
1972	7106	AL-6221 0.0015%	Heart Block	Resolved w/Tx	No
1973	1012	AL-6221 0.0015%	Heart Failure	Resolved w/Tx	No
2128	1117	AL-6221 0.0015%	Vasculitis	Resolved w/Tx	No
2558	5605	AL-6221 0.0015%	Pain Back	Resolved w/Tx	Yes
0649	1506	AL-6221 0.0015%	Surgical/Medical Proc	Resolved w/Tx	No
0731	2309	AL-6221 0.0015%	Surgical/Medical Proc	Resolved w/Tx	No
2353	3110	AL-6221 0.0015%	Surgical/Medical Proc	Resolved w/Tx	No
2247	3410	AL-6221 0.0015%	Surgical/Medical Proc	Resolved w/Tx	No
2247	3424	AL-6221 0.0015%	Surgical/Medical Proc	Resolved w/Tx	No
1892	4402	AL-6221 0.0015%	Surgical/Medical Proc	Resolved wo/Tx	No
2346	2823	AL-6221 0.0015%	Retinal Detachment	Resolved w/Tx	Yes
1973	1042	AL-6221 0.0015%	Pneumonia	Resolved w/Tx	No
1973	1013	AL-6221 0.0015%	Surgical/Medical Proc	Resolved w/Tx	No
1393	5001	AL-6221 0.0015%	Melanoma Skin	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2346	2825	AL-6221 0.004%	Infection Urinary Tract	Resolved w/Tx	No
1913	9006	AL-6221 0.004%	Arithritis	Continuing w/Tx	No
			Pain Chest	Resolved w/Tx	No
0731	2314	AL-6221 0.004%	Gastroenteritis	Resolved w/Tx	No
			Nausea Vomit	Resolved w/Tx	No

Investigator Number	Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
2128	1113	AL-6221 0.004%	Obstruction Intestinal	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
0983	1419	AL-6221 0.004%	Aneurysm Intracranial	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2128	1107	AL-6221 0.004%	Angina Pectoris	Resolved w/Tx	No
0649	1519	AL-6221 0.004%	Angina Pectoris	Resolved w/Tx	No
0553	1705	AL-6221 0.004%	Surgical/Medical Proc	Resolved w/Tx	No
0750	1801	AL-6221 0.004%	Surgical/Medical Proc	Resolved w/Tx	No
0362	2124	AL-6221 0.004%	Surgical/Medical Proc	Resolved w/Tx	No
0386	3014	AL-6221 0.004%	Surgical/Medical Proc	Resolved w/Tx	No
1565	3505	AL-6221 0.004%	Surgical/Medical Proc	Resolved w/Tx	No
1393	5002	AL-6221 0.004%	Surgical/Medical Proc	Resolved w/Tx	No
1939	6023	AL-6221 0.004%	Surgical/Medical Proc	Resolved w/Tx	No
			Hemorrhage Retinal	Resolved w/Tx	No
1939	6007	AL-6221 0.004%	Retinal Detachment	Resolved w/Tx	Yes
2153	4206	Timoptic 0.5%	Carcinoma Prostate	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
1973	1010	Timoptic 0.5%	Carcinoma Skin	Resolved w/Tx	No
0989	2514	Timoptic 0.5%	Cough Increase	Continuing w/Tx	No
			Weight Decrease	Continuing w/Tx	No
1393	5008	Timoptic 0.5%	Edema Lung	Resolved w/Tx	No
0553	1731	Timoptic 0.5%	Pneumonia	Resolved w/Tx	No
0989	2507	Timoptic 0.5%	Pneumonia	Resolved w/Tx	No
			Pain Chest	Resolved w/Tx	No
1927	3923	Timoptic 0.5%	Carcinoma GI	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
1473	2706	Timoptic 0.5%	GI Disease	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2346	2816	Timoptic 0.5%	Obstruction Intestinal	Resolved w/Tx	No
2353	3123	Timoptic 0.5%	Ulcer Stomach Hemorrhage	Continuing wo/Tx	No
			Surgical/Medical Proc	Resolved wo/Tx	No
1973	1031	Timoptic 0.5%	Angina Pectoris	Resolved w/Tx	No
2128	1104	Timoptic 0.5%	Angina Pectoris	Resolved w/Tx	Yes
0331	4016	Timoptic 0.5%	Angina Pectoris	Resolved w/Tx	No
			Coronary Artery Disease	Continuing w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2346	2822	Timoptic 0.5%	Cardiovascular Disease	Resolved w/Tx	Yes
0362	2114	Timoptic 0.5%	Heart Block	Resolved w/Tx	Yes
			Surgical/Medical Proc	Resolved w/Tx	Yes
2346	2803	Timoptic 0.5%	Cyst	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved wo/Tx	No
1973	1039	Timoptic 0.5%	Infection	Resolved w/Tx	No
2558	5602	Timoptic 0.5%	Injury Accidental	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
0386	3004	Timoptic 0.5%	Surgical/Medical Proc	Resolved w/Tx	No
2418	3807	Timoptic 0.5%	Surgical/Medical Proc	Resolved w/Tx	No
1939	6022	Timoptic 0.5%	Surgical/Medical Proc	Resolved w/Tx	No
2133	1914	Timoptic 0.5%	Pain Chest	Resolved w/Tx	No
2353	3107	Timoptic 0.5%	Retinal Detachment	Resolved w/Tx	Yes
1973	1011	Xalatan 0.005%	Surgical/Medical Proc	Resolved wo/Tx	No
			Carcinoma Breast	Resolved w/Tx	No

Investigator Number	Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
1552	1310	Xalatan 0.005%	Pneumonia	Lost to F/U	No
2247	3421	Xalatan 0.005%	Cholecystitis	Resolved w/Tx	No
			Dyspepsia	Resolved w/Tx	No
			Eructation	Resolved w/Tx	No
			Vomit	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved wo/Tx	No
1973	1014	Xalatan 0.005%	Cholelithiasis	Resolved w/Tx	No
0386	3002	Xalatan 0.005%	Coronary Artery Disease	Continuing w/Tx	No
			Pain Chest	Continuing w/Tx	No
2128	1118	Xalatan 0.005%	Infarct Myocardial	Resolved w/Tx	No
2247	3402	Xalatan 0.005%	Infarct Myocardial	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved wo/Tx	No
1806	1237	Xalatan 0.005%	Surgical/Medical Proc	Resolved w/Tx	No
1939	6029	Xalatan 0.005%	Surgical/Medical Proc	Resolved w/Tx	No
2353	3104	Xalatan 0.005%	Neuropathy	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
0731	2305	Xalatan 0.005%	Cardiovasc Disease	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved wo/Tx	No
1973	1020	Xalatan 0.005%	Cerebrovascular Accident	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved wo/Tx	No
			Vision Decrease	Resolved w/Tx	No
			Visual Field Defect	Resolved w/Tx	No
2558	5601	Xalatan 0.005%	Embolism	Resolved w/Tx	Yes
2479	5404	Xalatan 0.005%	Carcinoma	Resolved w/Tx	No
2353	3113	Xalatan 0.005%	Surgical/Medical Proc	Resolved w/Tx	No
1927	3931	Xalatan 0.005%	Surgical/Medical proc	Resolved w/Tx	No
1973	1045	Xalatan 0.005%	Carcinoma Bladder	Resolved w/Tx	No
1973	1002	Xalatan 0.005%	Surgical/Medical Proc	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	Yes

D/C Pt = Discontinued Patient

Fatal Serious Adverse Events

Investigator Number	Patient Number	Treatment	Duration (Days)	Coded Adverse Event
1973	1042	AL-6221 0.0015%	287	Leukemia
1973	1013	AL-6221 0.0015%	89	Arrhythmia Coronary Artery Disease
0983	1402	AL-6221 0.0015%	301	Cardiovascular Disease
1393	5001	AL-6221 0.0015%	302	Infarct Myocardial
0983	1407	AL-6221 0.004%	35	Injury Accidental
2133	1904	Timoptic 0.5%	287	Edema Lung Infarct Myocardial Shock
1927	3925	Timoptic 0.5%	264	Cardiovascular Disease
1393	5011	Timoptic 0.5%	352	Heart Failure Infarct Myocardial
1973	1002	Xalatan 0.005%	383	Pneumonia
0983	1420	Xalatan 0.005%	173	Cardiovascular Disease
1552	1306	Xalatan 0.005%	131	Heart Arrest
2133	1925	Xalatan 0.005%	149	Tachycardia Ventricular

Fifteen subjects (7.3%) receiving AL-6221 0.0015%, fifteen subjects (7.5%) receiving AL-6221 0.004%, eleven subjects (5.5%) receiving Timoptic 0.5%, and six subjects (3.1%) receiving Xalatan 0.005% discontinued from the study due to adverse events.

Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	Al-6221 0.0015% N=205	AL-6221 0.004% N=200	Timoptic 0.5% N=200	Xalatan 0.005% N=196
	N (%)	N (%)	N (%)	N (%)
All Events	158 (77.1)	166 (83.0)	140 (70.0)	141 (71.9)
OCULAR				
Hyperemia eye	78 (38.0)	99 (49.5)	28 (14.0)	54 (27.6)
Visual Acuity Decrease	12 (5.9)	17 (8.5)	19 (9.5)	9 (4.6)
Discomfort Eye	11 (5.4)	15 (7.5)	15 (7.5)	5 (2.6)
Iris Discoloration	10 (4.9)	6 (3.0)		10 (5.1)
Pruritus Eye	8 (3.9)	15 (7.5)	4 (2.0)	12 (6.1)
Eye Disease	7 (3.4)	3 (1.5)	3 (1.5)	4 (2.0)
Cataract	6 (2.9)	5 (2.5)	3 (1.5)	
Pain Eye	6 (2.9)	16 (8.0)	3 (1.5)	7 (3.6)
Dry Eye	5 (2.4)	9 (4.5)	3 (1.5)	

Coded Adverse Event	Al-6221 0.0015% N=205	AL-6221 0.004% N=200	Timoptic 0.5% N=200	Xalatan 0.005% N=196
	N (%)	N (%)	N (%)	N (%)
OCULAR				
Foreign Body Sensation	5 (2.4)	14 (7.0)		6 (3.1)
Keratitis	5 (2.4)	7 (3.5)	5 (2.5)	4 (2.0)
Cataract Nos	4 (2.0)	9 (4.5)	4 (2.0)	5 (2.6)
Inflammatory Cells Aqueous	4 (2.0)	4 (2.0)	4 (2.0)	
Vitreous Disease	4 (2.0)			
Aqueous Flare	3 (1.5)	3 (1.5)	3 (1.5)	
Hemorrhage Subconjunctival	3 (1.5)	3 (1.5)		8 (4.1)
Iritis	3 (1.5)			
Vision Abnormal	3 (1.5)	4 (2.0)		
Blepharitis		7 (3.5)		7 (3.6)
Conjunctivitis		4 (2.0)		
Retinal Pigment			3 (1.5)	
Surgical/Medical Proc		4 (2.0)		
Vitreous Detachment		3 (1.5)		
Photophobia		4 (2.0)	3 (1.5)	3 (1.5)
Vision Blurred		6 (3.0)	6 (3.0)	9 (4.6)
Visual Field Defect				3 (1.5)
Hemorrhage Retinal			5 (2.5)	
Pallor Optic Disc			3 (1.5)	
Retinal Disease				3 (1.5)
Tearing			4 (2.0)	3 (1.5)
NON-OCULAR				
Body As A Whole				
Surgical/Medical Proc	22 (10.7)	19 (9.5)	24 (12.0)	26 (13.3)
Cold Syndrome	9 (4.4)	6 (3.0)	7 (3.5)	
Infection	9 (4.4)	11 (5.5)	14 (7.0)	10 (5.1)
Injury Accidental	6 (2.9)	8 (4.0)	5 (2.5)	4 (2.0)
Pain	5 (2.4)	8 (4.0)	6 (3.0)	3 (1.5)
Flu Syndrome	4 (2.0)	3 (1.5)	6 (3.0)	3 (1.5)
Headache	4 (2.0)	8 (4.0)	5 (2.5)	5 (2.6)
Pain Back		3 (1.5)		6 (3.1)
Allergy			3 (1.5)	5 (2.6)
Cardiovascular System				
Hypertension	12 (5.9)	13 (6.5)	9 (4.5)	7 (3.6)
Arrhythmia	5 (2.4)			
Bradycardia		4 (2.0)		
Cardiovascular Disease				4 (2.0)
Angina Pectoris		4 (2.0)	3 (1.5)	
Hypotension		3 (1.5)		3 (1.5)
Digestive System				
GI Disease	3 (1.5)	3 (1.5)	3 (1.5)	
Diarrhea				3 (1.5)
Nausea				4 (2.0)
Dyspepsia		3 (1.5)	3 (1.5)	3 (1.5)
Endocrine System				
Diabetes Mellitus				5 (2.6)
Metabolic And Nutrition				
Hypercholesterolemia	7 (3.4)	4 (2.0)	4 (2.0)	5 (2.6)
Hyperlipidemia			3 (1.5)	

Coded Adverse Event	Al-6221 0.0015% N=205	AL-6221 0.004% N=200	Timoptic 0.5% N=200	Xalatan 0.005% N=196
	N (%)	N (%)	N (%)	N (%)
NON-OCULAR				
Musculo-Skeletal System				
Arthritis	6 (2.9)	4 (2.0)	4 (2.0)	3 (1.5)
Myalgia	5 (2.4)			
Nervous System				
Insomnia	3 (1.5)			
Anxiety		3 (1.5)		
Depression		5 (2.5)	4 (2.0)	
Respiratory System				
Rhinitis	7 (3.4)			
Sinusitis	4 (2.0)	10 (5.0)	5 (2.5)	5 (2.6)
Bronchitis	3 (1.5)	5 (2.5)		3 (1.5)
Cough Increase	3 (1.5)			
Pharyngitis	3 (1.5)			
Pneumonia	3 (1.5)		3 (1.5)	
Skin And Appendages				
Dermatitis				3 (1.5)
Urogenital System				
Infection Urinary Tract	6 (2.9)	5 (2.5)	3 (1.5)	10 (5.1)
Cystitis			3 (1.5)	
Incontinence Urinary		3 (1.5)		

Ocular Hyperemia

Ocular hyperemia assessment was performed at all time points and at all visits beginning with the Eligibility 2 Visit (baseline). A scale ranging from 0 to 3 units in 0.5 increments was used to assess ocular hyperemia. The ocular hyperemia scale was 0=None or Trace, 1=Mild, 2=Moderate, and 3=Severe. Clinically significant change from baseline in ocular hyperemia was defined as an increase of one or more units from the maximum hyperemia score recorded at any time point at the baseline. Adverse events were reported for a clinically significant increase in ocular hyperemia.

A statistically significant difference in ocular hyperemia among treatment groups was observed (p=0.0001). A concentration-related increase in mean ocular hyperemia was observed between AL-6221 0.0015% and AL-6221 0.004% compared to Timoptic 0.5%.

Frequency and Incidence of Ocular Hyperemia

Treatment	Number Randomized	N	%
AL-6221 0.0015%	205	78	38.0
AL-6221 0.004%	200	99	49.5
Timoptic 0.5%	200	28	14.0
Xalatan 0.005%	196	54	27.6

Frequency and Incidence of Discontinued Patients Due to Ocular Hyperemia

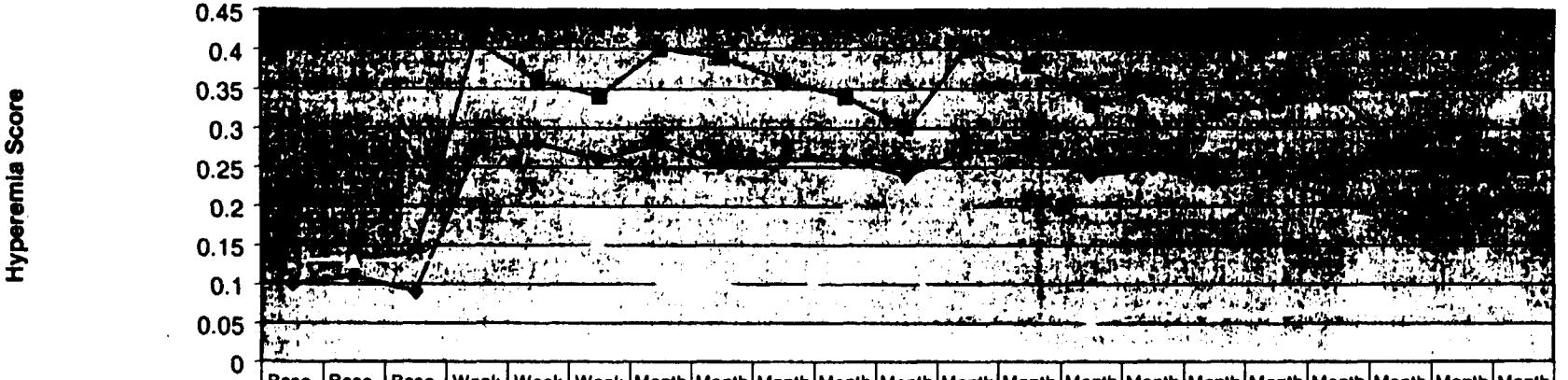
Treatment	Number Randomized	N	%
AL-6221 0.0015%	205	2	1.0
AL-6221 0.004%	200	6	3.0
Timoptic 0.5%	200	0	0.0
Xalatan 0.005%	196	0	0.0

Distribution of Maximum Hyperemia Score

			Maximum Hyperemia Score									
			0		>0 to <1		>=1 to 2		>=2 to 3		3	
Treatment		Total	N	%	N	%	N	%	N	%	N	%
AL-6221	Week 2	201[a]	125	62.2	33	16.4	40	19.9	3	1.5	--	--
0.0015%	Month 1.5	199	129	64.8	37	18.6	27	13.6	6	3.0	--	--
+ Vehicle	Month 3	189	120	63.5	34	18.0	31	16.4	4	2.1	--	--
	Month 4.5	190	118	62.1	43	22.6	25	13.2	4	2.1	--	--
	Month 6	184	116	63.0	37	20.1	28	15.2	3	1.6	--	--
	Month 9	181	125	69.1	28	15.5	24	13.3	4	2.2	--	--
	Month 12	180	112	62.2	37	20.6	26	14.4	5	2.8	--	--
AL-6221	Week 2	196[b]	100	51.0	33	16.8	52	26.5	11	5.6	--	--
0.004%	Month 1.5	190	97	51.1	41	21.6	45	23.7	7	3.7	--	--
+ Vehicle	Month 3	183	93	50.8	38	20.8	48	26.2	4	2.2	--	--
	Month 4.5	174	91	52.3	39	22.4	36	20.7	8	4.6	--	--
	Month 6	172	93	54.1	39	22.7	35	20.3	5	2.9	--	--
	Month 9	165	90	54.5	42	25.5	28	17.0	5	3.0	--	--
	Month 12	166	94	56.6	44	26.5	24	14.5	4	2.4	--	--
Timoptic	Week 2	195[c]	144	73.8	32	16.4	17	8.7	1	0.5	1	0.5
0.5%	Month 1.5	188	156	83.0	19	10.1	13	6.9	--	--	--	--
	Month 3	179	144	80.4	20	11.2	15	8.4	--	--	--	--
	Month 4.5	180	159	88.3	14	7.8	7	3.9	--	--	--	--
	Month 6	178	158	88.8	13	7.3	7	3.9	--	--	--	--
	Month 9	168	150	89.3	12	7.1	6	3.6	--	--	--	--
	Month 12	170	141	82.9	21	12.4	8	4.7	--	--	--	--
Xalatan	Week 2	193[d]	130	67.4	31	16.1	29	15.0	3	1.6	--	--
0.005%	Month 1.5	188	119	63.3	39	20.7	27	14.4	3	1.6	--	--
+ Vehicle	Month 3	187	119	63.6	44	23.5	20	10.7	4	2.1	--	--
	Month 4.5	183	127	69.4	35	19.1	18	9.8	3	1.6	--	--
	Month 6	180	121	67.2	41	22.8	16	8.9	2	1.1	--	--
	Month 9	173	116	67.1	35	20.2	21	12.1	1	0.6	--	--
	Month 12	175	125	71.4	31	17.7	16	9.1	3	1.7	--	--

Patients 1205 (AL-6221 0.0015%) and 2503, 3304 (Timoptic 0.5%) had no follow-up data.
[a] Patients 1205, 2916, 3607, 8036 (AL-6221 0.0015%) had missing data.
[b] Patients 1043, 1410, 3417, and 5215 (AL-6221 0.004%) had missing data.
[c] Patients 2004, 2103, 2503, 3107 and 3304 (Timoptic 0.5%) had missing data.
[d] Patients 1616, 2104, and 2105 (Xalatan 0.005%) had missing data.

Mean Hyperemia Score per Visit Day and Time



	Base-line 8AM	Base-line 10AM	Base-line 4PM	Week 2 8AM	Week 2 10AM	Week 2 4PM	Month 1.5 8AM	Month 1.5 10AM	Month 3 8AM	Month 3 10AM	Month 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM	Month 9 8AM	Month 9 10AM	Month 12 8AM	Month 12 10AM	Month 12 4PM
AL-6221 0.0015%	0.1	0.11	0.09	0.27	0.28	0.26	0.28	0.25	0.26	0.26	0.24	0.27	0.27	0.24	0.25	0.23	0.24	0.23	0.27	0.24	0.25
AL-6221 0.004%	0.13	0.13	0.14	0.41	0.36	0.34	0.4	0.39	0.36	0.34	0.3	0.4	0.38	0.33	0.35	0.32	0.33	0.34	0.27	0.3	0.25
Timoptic 0.5%	0.13	0.13	0.13	0.13	0.14	0.15	0.1	0.1	0.09	0.11	0.11	0.07	0.07	0.05	0.07	0.06	0.06	0.07	0.07	0.08	0.07
Xalatan 0.005%	0.13	0.14	0.13	0.2	0.22	0.21	0.25	0.24	0.23	0.2	0.2	0.2	0.21	0.18	0.18	0.17	0.23	0.21	0.17	0.19	0.17

Reviewer's Comments: *Baseline mean hyperemia score for the four treatment arms is similar. The mean hyperemia score for AL-6221 0.0015%, AL-6221 0.004%, and Xalatan 0.005% dosed QPM is consistently higher than for Timoptic 0.5% dosed BID. Both concentrations of AL-6221 have higher mean hyperemia score than Xalatan 0.005% at all time points. A concentration related increase in mean hyperemia score is associated with AL-6221.*

Visual Acuity

Best corrected visual acuity was measured as logMAR values at Screening, Eligibility 1 8AM, Eligibility 2 8AM (baseline), and all subsequent visits. The maximum change in visual acuity for the worse eye in each patient (either the right or the left eye which had the greatest decrease in visual acuity acuity) was calculated as the change in logMAR lines (0.1 = 1 logMAR line) from baseline to the final visit and any visit. Any clinically decrease in visual acuity (three or more logMAR lines) from baseline was reported as an adverse event.

No statistically significant difference (p=0.829) in visual acuity change from baseline to final visit was observed among the treatment groups.

Change in Visual Acuity (logMAR) from Baseline to Final Visit

	Treatment Group				
Line Changes	AL-6221 0.0015% N (%)	AL-6221 0.004% N (%)	Timoptic 0.5% N (%)	Xalatan 0.005% N (%)	Total N (%)
N	203	200	198	196	797
≥ 2 lines loss	18 (8.9)	24 (12.0)	25 (12.6)	19 (9.7)	86 (10.8)
1 line loss	48 (23.6)	41 (20.5)	35 (17.7)	30 (15.3)	154 (19.3)
No Change	119 (58.6)	123 (61.5)	125 (63.1)	131 (66.8)	498 (62.5)
1 line gain	15 (7.4)	8 (4.0)	11 (5.6)	15 (7.7)	49 (6.1)
≥ 2 lines gain	3 (1.5)	4 (2.0)	2 (1.0)	1 (0.5)	10 (1.3)

Patients 1205, 3607 (AL-6221 0.0015%) had no follow-up data.
Patients 3107, 3304 (Timoptic 0.5%) had no follow-up data.

Change in Visual Acuity (logMAR) from Baseline to Worse Visit

	Treatment Group				
Line Changes	AL-6221 0.0015% N (%)	AL-6221 0.004% N (%)	Timoptic 0.5% N (%)	Xalatan 0.005% N (%)	Total N(%)
N	203	200	199	196	798
≥ 2 lines loss	61 (30.0)	71 (35.5)	75 (37.7)	65 (33.2)	272 (34.1)
1 line loss	89 (43.8)	92 (46.0)	82 (41.2)	76 (38.8)	339 (42.5)
No Change	36 (17.7)	36 (18.0)	42 (21.1)	53 (27.0)	167 (20.9)
1 line gain	7 (3.4)	1 (0.5)	0 (0)	2 (1.0)	10 (1.3)
≥ 2 lines gain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Patients 1205, 3607 (AL-6221 0.0015%) had no follow-up data.
Patient 3304 (Timoptic 0.5%) had no follow-up data.

Iris Pigmentation Change

Iris photographs of each eye were taken at Eligibility 2 8AM (baseline), Month 1.5, Month 3, Month 4.5, Month 6, Month 9, and Month 12. The photographs were evaluated for any change from baseline in iris pigmentation. Any confirmed iris pigmentation change from baseline was reported as an adverse event.

A statistically significant difference (p=0.014) in iris color change was noted in AL-6221 0.015%, AL-6221 0.004%, and Xalatan 0.005% compared to Timoptic 0.5%.

Percent of Patients with Iris Pigmentation Change by Visit

		Visit						
Treatment		MONTH 1.5-8AM[a]	MONTH 3-8AM[a]	MONTH 4.5-8AM[a]	MONTH 6-8AM[a]	MONTH 9-8AM[b]	MONTH 12-8AM[b]	EARLY EXIT[a]
AL-6221	%	0.0	0.0	1.6	2.8	3.3	5.7	0.0
0.0015%	N	0	0	3	5	6	10	0
+ Vehicle	Total N	193[c]	186	188	180	180	175	18
AL-6221	%	0.0	0.6	0.6	1.8	3.1	3.7	0.0
0.004%	N	0	1	1	3	5	6	0
+ Vehicle	Total N	187[d]	178	172	168	162	161	25
Timoptic	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.5%	N	0	0	0	0	0	0	0
	Total N	181[e]	175	177	174	165	164	25
Xalatan	%	0.0	0.5	1.7	2.9	4.1	5.9	0.0
0.005%	N	0	1	3	5	7	10	0
+ Vehicle	Total N	184[f]	187	181	175	170	169	16

[a] p>=0.102 from Fisher's Exact test comparing treatment groups.
[b] p<=0.038 from Fisher's Exact test comparing treatment groups.
Early Exit denotes patients who did not complete the study.
[c] Patients 1205, 2515, 3108, 3607 (AL-6221 0.0015%) had no follow-up data.
[d] Patients 1407, 4403, 4414, 5604 (AL-6221 0.004%) had no follow-up data.
[e] Patients 2503, 3304, 4404, 4406 (Timoptic 0.5%) had no follow-up data.
[f] Patients 1310, 2413 (Xalatan 0.005%) had no follow-up data.

Reviewer's Comments:

Iris pigmentation change is consistent with an ocularly administered prostaglandin-type effect. A change is detected as early as 3 months following commencement of therapy. The prevalence of iris pigmentation change increases with duration of therapy.

Eyelashes

Eyelash photographs of each eye were taken at Eligibility 2 8AM (baseline), Month 1.5, Month 3, Month 4.5, Month 6, Month 9, and Month 12. The photographs were evaluated for any changes from baseline in eyelash length, eyelash color, eyelash density, and eyelash thickness. Any eyelash change from baseline and any complaints in eyelash change were reported as an adverse event.

Percent of Subjects with Eyelash Change by Category

Treatment	Total N	Change Reported		Color Change		Length Change		Density Change		Thickness Change	
	N	N	%	N	%	N	%	N	%	N	%
AL-6221 0.0015% + Vehicle	201[a]	89	44.3	70	34.8	89	44.3	82	40.8	62	30.8
AL-6221 0.004% + Vehicle	196[b]	112	57.1	89	45.4	112	57.1	103	52.6	96	49.0
Timoptic 0.5%	196[c]	6	3.1	5	2.6	6	3.1	5	2.6	0	0.0
Xalatan 0.005% + Vehicle	194[d]	50	25.8	32	16.5	50	25.8	43	22.2	34	17.5

p= 0.883 for Month 1.5 and p<=0.001 from chi-square test comparing treatment groups in all categories of eyelash change.
[a] Patients 1205, 2515, 3108, 3607 (AL-6221 0.0015%) had no follow-up data
[b] Patients 1407, 4403, 4414, 5604 (AL-6221 0.004%) had no follow-up data
[c] Patients 2503, 3304, 4404, 4406 (Timoptic 0.5%) had no follow-up data
[d] Patients 1310, 2413 (Xalatan 0.005%) had no follow-up data.

Percent of Subjects with Eyelash Change by Visit

Treatment		Visit MONTH 1.5-8AM	MONTH 3-8AM	MONTH 4.5-8AM	MONTH 6-8AM	MONTH 9-8AM	MONTH 12-8AM	EARLY EXIT
AL-6221	%	1.6	22.6	27.1	30.6	35.6	47.1	16.7
0.0015%	N	3	42	51	55	64	82	3
+ Vehicle	Total N[a]	193	186	188	180	180	174	18
AL-6221	%	1.6	29.8	40.7	48.8	51.9	62.7	24.0
0.004%	N	3	53	70	82	84	101	6
+ Vehicle	Total N[a]	187	178	172	168	162	161	25
Timoptic	%	0.6	1.1	1.1	1.1	1.8	2.4	4.0
0.5%	N	1	2	2	2	3	4	1
	Total N[a]	181	175	177	174	165	164	25
Xalatan	%	1.1	7.0	11.0	14.9	18.2	29.0	6.3
0.005%	N	2	13	20	26	31	49	1
+ Vehicle	Total N[a]	184	187	181	175	170	169	16

p=0.883 for Month 1.5 and p<=0.001 for all other visits from chi-square test comparing treatment groups.
Early Exit denotes patients who did not complete the study.
[a] Patients 1205, 2515, 3108, 3607 (AL-6221 0.0015%); 1407, 4403, 4414, 5604 (AL-6221 0.004%); 2503, 3304, 4404, 4406 (Timoptic 0.5%); 1310, 2413 (Xalatan 0.005%) had no follow-up data.

A concentration-related change in eyelash color, length, density, and/or thickness was observed between subjects receiving AL-6221 0.0015% and AL-6221 0.004% compared to subjects receiving Timoptic 0.5%. Patients receiving Xalatan 0.005% also experienced a change in eyelash color, length, density, and/or thickness comparable to a lesser extent than seen with AL-6221 0.0015% and AL-6221 0.004%.