Reviewer's Comments:

A concentration related change in eyelash color, length, density, and thickness is consistent with an ocularly administered prostaglandin-type effect. The prevalence of an eyelash change increases with duration of therapy. Whether these changes are purely cosmetic or have safety related issues have not been determined.

Aqueous Flare and Inflammatory Cells

Aqueous flare and inflammatory cells assessment was performed at Eligibility 2 Visit (baseline), Week 2, Month 1.5, Month 3, Month 4.5, Month 6, Month 9, Month 12 Visits, and any unscheduled visits at 8AM. Any clinically significant increase of one or more units from baseline was reported as an adverse event.

Four subjects discontinued from the study due to aqueous flare or inflammatory cells. Two of 205 subjects (1.0%) receiving AL-6221 0.0015% discontinued from the study due to ocular inflammatory cells. One of 200 subjects (0.5%) receiving AL-6221 0.004% and one of 200 subjects (0.5%) receiving Timoptic 0.5% discontinued from the study due to aqueous flare and inflammatory cells. No subjects receiving Xalatan 0.005% discontinued from the study due to aqueous flare and inflammatory cells.

Cup/Disc Ratio

Cup/disc ratio assessment was performed at Screening (baseline) and Exit Visits. The mean change in cup/disc ratio from baseline to final was evaluated for each subject's eyes.

No clinically or statistically significant difference (p=0.3560) in increase of cup/disc ratio was observed among the treatment groups.

Visual Field

No clinically or statistically significant difference in visual field mean deviation/defect change or corrected loss variance change from baseline was observed among the treatment groups in subjects analyzed with the [redacted]

Fifty-four subjects (12 in AL-6221 0.0015%, 16 in AL-6221 0.004%, 14 in Timoptic 0.5%, 12 in Xalatan 0.005%) had no baseline or follow-up Mean Deviation [redacted] Mean Defect Data. Fifty-six subjects (12 in AL-6221 0.0015%, 18 in AL-6221 0.004%, 14 in Timoptic 0.5%, 12 in Xalatan 0.005%) had no baseline or follow-up Corrected Pattern Standard Deviation [redacted] There were eight adverse events reported for visual field defects (1 in AL-6221 0.0015%, 2 in AL-6221 0.004%, 2 in Timoptic 0.5%, 3 in Xalatan 0.005%.

Pachymetry

Endothelial cell health was assessed by measuring the potential increase in corneal thickness resulting from impaired endothelial cell function. Corneal thickness (mm) was measured at Eligibility 2 (baseline), Month 6, and Month 12. Sixty-seven subjects (17 in AL-6221 0.0015%, 19 in AL-6221 0.004%, 15 in Timoptic 0.5%, 16 in Xalatan 0.005%) had no baseline or follow-up data.

No clinically significant difference for corneal thickness change from baseline was observed among treatment groups, although a statistically significant difference was detected between treatment groups (p=0.0014). Comparison among the treatment groups indicated a statistically significant difference between AL-6221 0.0015% and AL-6221 0.004% compared to Timoptic 0.5%.

Endothelial Cell Density

Endothelial cell density was measured at Eligibility 2 (baseline), Month 6, and Month 12 (Exit) at 8AM. The mean change in endothelial cell density of both eyes from baseline was calculated at Month 6 and Month 12.

No clinically or statistically significant difference in the mean change of endothelial cell count was observed among treatment groups. Two-hundred six patients (25.7%) had no follow-up data (54 in AL-6221 0.0015%, 52 in AL-6221 0.004%, 49 in Timoptic 0.5%, 51 in Xalatan 0.005%).

Reviewer's Comment:

A very large number of subjects had no follow-up data and were not included in the analysis.

Ocular Signs

Ocular signs (cornea, iris/anterior chamber, lens, vitreous) were observed at Screening, Eligibility 1 8AM, Eligibility 2 8AM (baseline), and all subsequent visits. Any clinically increase of one or more units from baseline in ocular signs at any time during the study was reported as an adverse event.

One subject receiving AL-6221 0.0015% was discontinued from the study due to increase in ocular signs from baseline. Clinically significant increase in ocular signs from baseline was noted in 19 of 204 subjects (9.3%) receiving AL-6221 0.0015%, 22 of 200 subjects (11.0%) receiving AL-6221 0.004%, 15 of 199 subjects (7.5%), and 11 of 196 subjects (5.6%) receiving Xalatan 0.005%. Follow-up ocular sign data were unavailable for one subject receiving AL-6221 0.0015% and one subject receiving Timoptic 0.5%.

Dilated Fundus Examination

Dilated fundus examinations (retina/macula/choroid, optic nerve, disc pallor) were observed at Screening (baseline) and Month 12 (Exit) 10AM visits. Any clinically significant increase of one or more units from baseline in fundus parameters were reported as an adverse event.

No clinically or statistically significant difference in changes in retina, macula and choroid, optic nerve, and disc pallor were observed among treatment groups. Twenty-nine subjects had no follow-up data (6 in AL-6221 0.0015%, 6 in AL-6221 0.004%, 8 in Timoptic 0.5%, 9 in Xalatan 0.005%).

Three of 199 subjects (1.5%) receving AL-6221 0.0015%, three of 194 Subjects (1.5%) receiving AL-6221 0.004%, nine of 192 subjects (4.7%) receiving Timoptic 0.5%, and four of 187 subjects (2.1%) receiving Xalatan 0.005% experienced retinal changes.

Vital Signs

No clinically or statistically significant difference in systolic or diastolic blood pressure from baseline was observed between treatment groups.

No clinically or statistically significant difference in pulse was observed in the groups treated with AL-6221 0.0015%, AL-6221 0.004%, and Xalatan 0.005%. Timoptic 0.5% showed a statistical significant (p=0.0393) decrease in pulse measurements compared to AL-6221 0.0015% and AL-6221 0.004%. For subjects treated with Timoptic 0.5%, the mean change in the pulse was -1.3 BPM.

Clinical Laboratory Evaluation

No clinically significant change from baseline for laboratory values (hematology, blood chemistry, urinalysis) was observed among the treatment groups.

8.1.2 Reviewer's Summary of Efficacy and Safety

AL-6221 0.0015% and AL-6221 0.004% dosed one daily in the evening demonstrate equivalence in their ability to lower IOP.

AL-6221 0.0015% and AL-6221 0.004% demonstrate efficacy in the ability to lower IOP. The change in mean IOP from baseline ranges from –6.0 to –7.7 mmHg for AL-6221 0.0015% and from –6.6 to –8.1 mmHg for AL-6221 0.004% as compared to –4.7 to –7.1 for Timoptic 0.5%. Note: the baseline mean IOP values for AL-6221 0.0015% are questionable.

The IOP lowering ability of AL-6221 0.004% is not superior to Timoptic 0.5% by a clinically significant amount.

The IOP lowering ability of AL-6221 0.004% is not superior to Xalatan 0.005% by a clinically significant amount. The change in mean IOP from baseline ranges from –6.6 to –8.1 mmHg for AL-6221 0.004% as compared to –6.2 to –8.1 for Xalatan 0.005%. The mean difference between the mean IOP of the two treatment groups ranges from 0 to –1.3 mmHg.

The IOP lowering ability of AL-6221 0.004% is not superior to Xalatan 0.005% in Black patients. The change in mean IOP from baseline ranges from –6.9 to –8.9 mmHg for AL-6221 0.004% as compared to –6.3 to –8.3 mmHg for Xalatan 0.005% in Black patients. The mean difference between the mean IOP of the two treatment groups in Black patients ranges from –0.8 to –2.4 mmHg.

Both concentrations of AL-6221 are associated with ocular hyperemia. The prevalence and severity of ocular hyperemia are concentration related.

The iris/eyelash photographs read by masked independent readers reveal a statistically and clinically significant change in iris pigmentation. The onset of iris pigmentation change is 3 months after commencement of therapy and increases with duration of therapy.

The iris/eyelash photographs read by masked independent readers reveal a concentration related change in eyelash color, length, density, and thickness consistent with an ocularly administered prostaglandin-type effect. The prevalence increases with duration of therapy.

8.1.3 Study #3 Protocol C-97-72

Title: A Six-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% 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 6 months.

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
415	**Stuart Terry, M.D.** San Antonio, TX 78212	30	30	28
454	**Charles D. McMahon, M.D.** Colorado Springs, CO 80907	09	09	09
470	**Donald Brotherman, M.D.** Dallas, TX 75234	25	25	24
589	**Robert Shields, M.D.** Denver, CO 80210	32	30	27
648	**Alan Robin, M.D.** Baltimore, MD 21209	09	09	09
733	**E. George Rosanelli, Jr., M.D.** Tampa, FL 33609	04	04	03
943	**Robert A. Laibovitz, M.D.** Austin, TX 78731	29	29	29
1007	**Thomas R. Walters, M.D.** Austin, TX 78746	32	32	31
1064	**Steven Simmons, M.D.** Albany, NY 12204	17	17	14
1196	**Robert Rice, M.D.** Richmond, VA 23294	00	00	00
1733	**Donald P. McCurdy, M.D.** Birmingham, AL 35294	29	28	26
1909	**Jess Whitson, M.D.** Dallas, TX 75235	09	09	09
1911	**Karen Joos, M.D.** Nashville, TN 37232	09	09	08

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
1930	**Robert Freidman, M.D.** Sunrise, FL 33351	20	20	20
1946	**Leonard Cacioppo, M.D.** Brooksville, FL 34613	12	12	12
1952	**Kevin Greenidge, M.D.** New York, NY 10003	07	07	07
1971	**G. Richard Cohen, M.D.** Boca Raton, FL 33428	00	00	00
1999	**Marta Lopatynsky, M.D.** Morristown, NJ 07960	00	00	00
2162	**Karim F. Damji, M.D.** Ottawa, Ontario. Canada K1H 8L6	02	02	02
2181	**Catherine Birt, M.D.** Toronto, Ontario, Canada M4N 3M5	16	16	15
2192	**Richard Lehrer, M.D.** Alliance, OH 44601	01	01	01
2241	**Moira Burke, M.D.** Tampa, FL 33613	08	08	07
2417	**Neeru Gupta, M.D.** Toronto, Ontario, Canada M5B 1W8	16	15	15
2422	**Jon F. Dietlein, M.D.** Georgetown, TX 78626	29	29	29
2423	**William A. Pilchard, M.D.** Shawnee Mission, KS 66204	34	33	32
2431	**Hersh Chopra, M.D.** Marietta, GA 30060	05	04	02
2434	**Jason Bacharach, M.D.** Petaluma, CA 94954	11	11	08
2447	**Kathleen Lamping, M.D.** South Euclid, OH 44121	06	06	06
2448	**Ned Reinstein, M.D.** Tulsa, OK 74136	22	21	20
2449	**Barry Katzman, M.D.** San Diego, CA 92115	20	20	19
2464	**Daniel B. Thatcher, M.D.** Colorado Springs, CO 80907	19	17	17
2477	**Marc Weitzman, M.D.** New Haven, CT 06520	00	00	00

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
2488	**James E. Pickett, M.D.** San Marcos, TX 78666	02	02	02
2496	**Paul E. Michelson, M.D.** La Jolla, CA 92037	20	20	18
2534	**Ronald Fellman, M.D.** Dallas, TX 75231	15	15	15
2535	**Dean W. Carlson, M.D.** Colorado Springs, CO 80903	08	07	06
2537	**James Montgomery, M.D.** Austin, TX 78705	22	22	22
2557	**Thomas Croley, M.D.** Ocala, FL 32674	21	20	19
2569	**Michael Bernstein, M.D.** Birmingham, AL 35205	11	11	10
2590	**Mildred Olivier, M.D.** Hoffman Estates, IL 60194	13	13	10
2600	**David L. Wirta, M.D.** Newport Beach, CA 92663	14	14	14
2612	**Lisa F. Rosenberg, M.D.** Chicago, IL 60611	03	03	03
2630	**William Lagomarsino, M.D.** Corsicana, TX 75110	14	14	09

Reviewer's Comments:

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

8.1.3 Study Design

The study design was nearly identical to Study #2, Protocol C-97-71. The major differences were 1) the exclusion of a Xalatan 0.005% treatment arm, and 2) the study length was 6 months.

As in Protocol C-97-71, the primary efficacy parameter of the study was mean IOP measured at the 8AM, 10AM, and 4PM time points for the patient's worse eye.

Reviewer's Comments:

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

Study Medications

• AL-6221 0.0015%	Lot # ASE-2999A; ASE-2999B; ASE-2970A; ASE-2970B; ARE-2948B; 98-500007-2; and 99-500042-3
• AL-6221 0.004%	Lot # ASE-2998A; ASE-2998B; ASE-2971A; ASE-2971B; ARE-2946B; ARE-2946A; 98-500009-2; and 99-50044-3
AL-6221 Vehicle (Placebo)	ASE-2996A; ASE-2996B; ASE-2989; ASE-2972A; ASE-2972B; ARE-2947A; 98-500002-1; 99-500022-1; 99-500022-2; and 99-500050-1
• Timoptic 0.5%	ASE-3003B; ASE-2995; ASE-2977; ASE-2969; ARE-2949; 98-500013-1; 99-500023-1; and 99-500031-1

All masked test medications used during the treatment phase were supplied in a masked DROP-TAINER labeled with the appropriate patient number.

Protocol C-97-72
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		
		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
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
Hyperemia Assessment					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		
Visual Acuity (Best corrected) (logMAR scale)	X	X			X			X			X		X			X		X		
Biomicroscopy	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	
Dilated Fundus	X																		X	
Automated Perimetry	X[3]																		X[6]	
Gonioscopy[4]	X																			
Iris/eyelash photographs					X						X		X			X		X		
Hematology/blood chemistry		X																X		
Urinalysis		X																X		
Dispense study meds[5]							X			X		X			X		X			
Adverse Events								X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Rx																		X		
Exit Patient																				X

[1] 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

APPEARS THIS WAY
ON ORIGINAL

Subject Disposition and Demographics

All 605 randomized subjects received treatment and 512 subjects completed the study.

Subject Disposition

	Number of Subjects			
	AL-6221 0.0015%	AL-6221 0.004%	Timoptic 0.5%	Total
Randomized	202	201	202	605
Discontinued prematurely	30	33	30	93
Included in safety evaluations	202	201	202	605
Included in intent-to-treat analysis	198	197	199	594
Included in per protocol analysis	190	179	188	557

Reviewer's Comments:

The intent-to treat population excluded 11 subjects who received medication but had no on-treatment visit data.

Summary of Reasons for Premature Discontinuation from Study

Reason For Discontinuation	Treatment Group			
	AL6221 0.0015%	AL6221 0.004%	Timoptic 0.5%	Total
Adverse Event	7	9	7	23
Inadequate Control of IOP	2	2	4	8
Non-Qualifying IOP	3	7	2	12
Non-Qualifying Visual Fields	1	1	0	2
Patient Decision	2	3	0	5
Site Closed*	10	8	10	28
Use of Contraindicated Medications	1	1	6	8
Lost to Follow-up	1	0	0	1
Concurrent Investigational medication	0	0	1	1
Ineligible Visual Acuity	1	1	0	2
Inclusion Criteria – menopausal status	1	0	0	1
Inclusion Criteria – combined mechanism glaucoma	1	0	0	1
Inclusion Criteria - less than 1 month stable dosing	0	1	0	1
Total	**30**	**33**	**30**	**93**

*Investigator 943, due to ill health, had to close his clinical practice.

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Duration (Days)	Reason
415	4002	AL-6221 0.0015%	41	Adverse event-surgical/medical proc. synechiae
	4004	Timoptic 0.5%	140	D/C by Alcon-pt using steroid
	4005	AL-6221 0.0015%	23	Non-qualifying visual field
	4020	Timoptic 0.5%	16	Inadequate control of IOP
	4022	Timoptic 0.5%	50	Pt using steroid medication
470	1010	Timoptic 0.5%	34	Non-qualifying IOP
589	2301	Timoptic 0.5%	8	Non-qualifying IOP
	2302	AL-6221 0.004%	14	Adverse event-discomfort eye
	2303	AL-6221 0.0015%	28	Non-qualifying IOP
	2316	AL-6221 0.0015%	104	Pt using steroid medication
	2327	AL-6221 0.0015%	126	Subject decision unrelated to adverse event
	2329	Timoptic 0.5%	35	Concurrent investigational medication
733	4403	AL-6221 0.0015%	77	Inadequate control of IOP
943	1601	Timoptic 0.5%	62	Physician closed practice
	1602	AL-6221 0.004%	63	Physician closed practice
	1603	AL-6221 0.0015%	62	Physician closed practice
	1604	Timoptic 0.5%	62	Physician closed practice
	1605	AL-6221 0.0015%	62	Physician closed practice
	1606	AL-6221 0.004%	58	Physician closed practice
	1607	Timoptic 0.5%	63	Physician closed practice
	1608	AL-6221 0.0015%	63	Physician closed practice
	1609	AL-6221 0.004%	63	Physician closed practice
	1610	Timoptic 0.5%	68	Physician closed practice
	1611	AL-6221 0.0015%	63	Physician closed practice
	1612	AL-6221 0.004%	62	Physician closed practice
	1613	AL-6221 0.0015%	63	Physician closed practice
	1614	AL-6221 0.004%	62	Physician closed practice
	1615	Timoptic 0.5%	62	Physician closed practice
	1616	Timoptic 0.5%	63	Physician closed practice
	1617	AL-6221 0.004%	62	Physician closed practice
	1618	AL-6221 0.0015%	62	Physician closed practice
	1619	AL-6221 0.0015%	63	Physician closed practice
	1620	AL-6221 0.004%	55	Adverse event-hyperemia eye
	1621	Timoptic 0.5%	62	Physician closed practice
	1622	AL-6221 0.004%	58	Physician closed practice
	1623	Timoptic 0.5%	68	Physician closed practice
	1624	AL-6221 0.0015%	63	Physician closed practice
	1625	AL-6221 0.0015%	61	Physician closed practice
	1626	AL-6221 0.004%	61	Physician closed practice
	1627	Timoptic 0.5%	61	Physician closed practice
	1628	AL-6221 0.0015%	63	Physician closed practice
	1629	Timoptic 0.5%	61	Physician closed practice
1007	2604	Timoptic 0.5%	18	Adverse event-dizziness, asthenia, discomfort eye, dyspnea
	2616	AL-6221 0.0015%	133	Adverse event-dyspnea
	2621	AL-6221 0.0015%	26	Adverse event-hyperemia eye, hyphema, uveitis, decreased vision
1064	2409	Timoptic 0.5%	145	Adverse event-infarct myocardial (patient died)
1733	1811	AL-6221 0.004%	33	Adverse event-hyperemia eye, pain eye
	1815	Timoptic 0.5%	77	Adverse event-carcinoma GI, surgical/medical proc
	1820	AL-6221 0.004%	84	Pt using medication with less than 1month stable dosing
	1826	Timoptic 0.5%	126	Pt taking disallowed concomitant medication

Investigator	Patient	Treatment	Duration (Days)	Reason
1733	1829	AL-6221 0.0015%	0	Lost to follow-up
1909	2903	AL-6221 0.0015%	126	Subject decision unrelated to an adverse event
1930	1306	AL-6221 0.004%	83	Subject decision unrelated to an adverse event
	1312	AL-6221 0.004%	53	Adverse event-hyperemia eye, pain eye
2184	3105	AL-6221 0.004%	42	Non-qualifying IOP
	3107	AL-6221 0.004%	146	Subject decision unrelated to an adverse event
	3114	AL-6221 0.0015%	49	Adverse event-asthma, cough increase
2192	4101	Timoptic 0.5%	50	Inadequate control of IOP
2241	4806	AL-6221 0.004%	66	Inadequate control of IOP
2417	3406	AL-6221 0.0015%	4	Adverse event-headache, pain abdomen
	3411	AL-6221 0.0015%	96	Inadequate control of IOP
2423	2101	Timoptic 0.5%	28	Adverse event-lung disease
	2102	AL-6221 0.004%	14	Adverse event-foreign body sensation
	2114	AL-6221 0.004%	85	Non-qualifying IOP
	2128	Timoptic 0.5%	114	Adverse event-vision decrease
2431	5701	AL-6221 0.004%	6	Adverse event-arrhythmia, hypotension, asthenia
	5703	AL-6221 0.0015%	128	Diagnosis combined mechanism glaucoma
	5704	AL-6221 0.0015%	43	Non-qualifying IOP
2434	5101	Timoptic 0.5%	112	Pt using steroid inhaler
	5104	AL-6221 0.0015%	55	Non-qualifying IOP
	5105	AL-6221 0.0015%	66	Menopause status
	5110	Timoptic 0.5%	136	Inadequate control of IOP
2448	3008	AL-6221 0.004%	27	Non-qualifying IOP
	3010	AL-6221 0.0015%	15	Non-qualifying IOP
2449	3917	AL-6221 0.004%	126	Pt began taking exclusionary medication
2464	3807	AL-6221 0.004%	5	Adverse event-hyperemia eye, conjunctivitis
	3813	AL-6221 0.0015%	7	Adverse event-discomfort eye
	3819	Timoptic 0.5%	126	Use of exclusionary medication
2496	4706	AL-6221 0.004%	87	Non-qualifying visual field
	4711	AL-6221 0.004%	162	Non-qualifying IOP
	4719	AL-6221 0.004%	93	Non-qualifying IOP
2534	4606	AL-6221 0.004%	58	Adverse event-hyperemia eye
	4609	AL-6221 0.004%	23	Adverse event-hypermia eye, pain eye, malaise
	4610	AL-6221 0.0015%	30	Adverse event-hyperemia eye
2535	4502	Timoptic 0.5%	13	Adverse event-visual acuity decrease
2557	4901	Timoptic 0.5%	14	Adverse event-dizziness, bradycardia, hypotension
	4902	AL-6221 0.004%	43	Non-qualifying IOP
	4904	AL-6221 0.0015%	21	Ineligible visual acuity
2569	5004	Timoptic 0.5%	91	Inadequate control of IOP
	5008	AL-6221 0.004%	63	Subject decision unrelated to an adverse event
2590	5302	AL-6221 0.004%	39	Ineligible visual acuity
	5305	Timoptic 0.5%	83	Pt used glucocorticoid during eligibilty
	5312	AL-6221 0.004%	68	Inadequate control of IOP

Summary of Demographic Characteristics (Intent-to-Treat)

Treatment	Age Mean[a]	Std	N	Min	Max
AL-6221 0.0015%	62.9	12.4	198	21	87
AL-6221 0.004%	64.4	10.2	197	37	87
Timoptic 0.5%	63.9	11.2	199	30	91

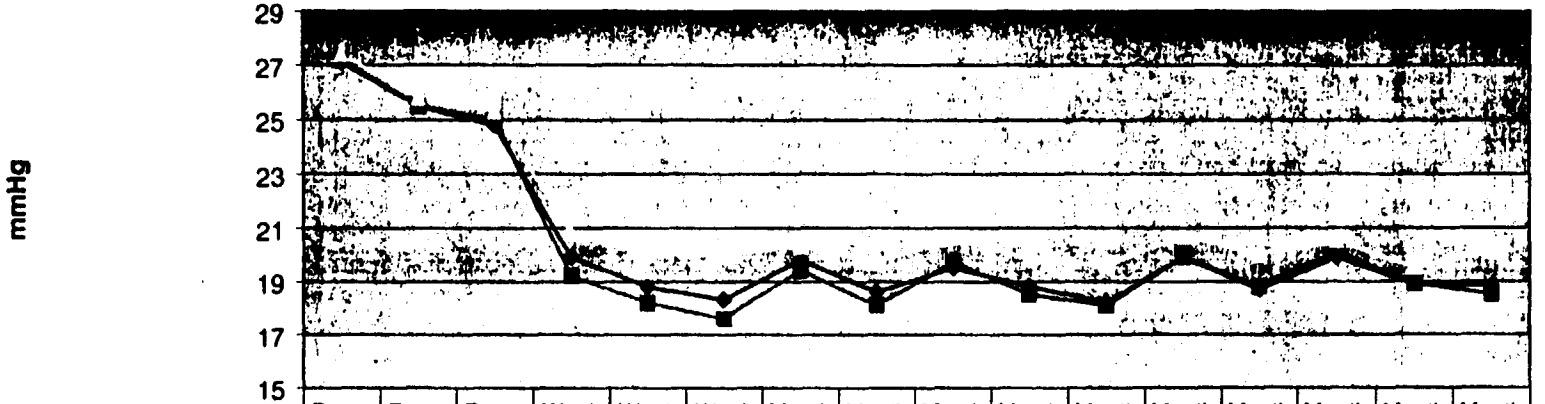
[a]p=0.368 for test of mean age differences among groups.

	Treatment: AL-6221 0.0015% N	%	AL-6221 0.004% N	%	Timoptic 0.5% N	%	P-value
Age Group							
<65	91	46.0	89	45.2	94	47.2	0.918
>=65	107	54.0	108	54.8	105	52.8	
<65	91	46.0	89	45.2	94	47.2	0.967
>=65-<75	71	35.9	76	38.6	68	34.2	
>=75-<85	34	17.2	29	14.7	34	17.1	
>=85-<95	2	1.0	3	1.5	3	1.5	
Sex							
MALE	105	53.0	94	47.7	94	47.2	0.441
FEMALE	93	47.0	103	52.3	105	52.8	
Race							
CAUCASIAN	161	81.3	166	84.3	161	80.9	0.942
BLACK	23	11.6	17	8.6	23	11.6	
ASIAN	1	0.5	1	0.5	2	1.0	
OTHER	13	6.6	13	6.6	13	6.5	
Iris Color							
BROWN	80	40.4	88	44.7	91	45.7	0.401
HAZEL	22	11.1	29	14.7	28	14.1	
GREEN	9	4.5	5	2.5	12	6.0	
BLUE	81	40.9	67	34.0	64	32.2	
GREY	6	3.0	8	4.1	4	2.0	
Diagnosis (ICD9)							
OCULAR HYPERTENSION	64	32.3	61	31.0	71	35.7	0.789
OPEN-ANGLE GLAUCOMA	131	66.2	129	65.5	122	61.3	
PIGMENTARY GLAUCOMA	3	1.5	6	3.0	5	2.5	
PSEUDOEXFOLIAT GLAUCOMA	--	--	1	0.5	1	0.5	

8.1.3 Efficacy – Protocol C-97-72 Intent-to-Treat Population

Efficacy Variable

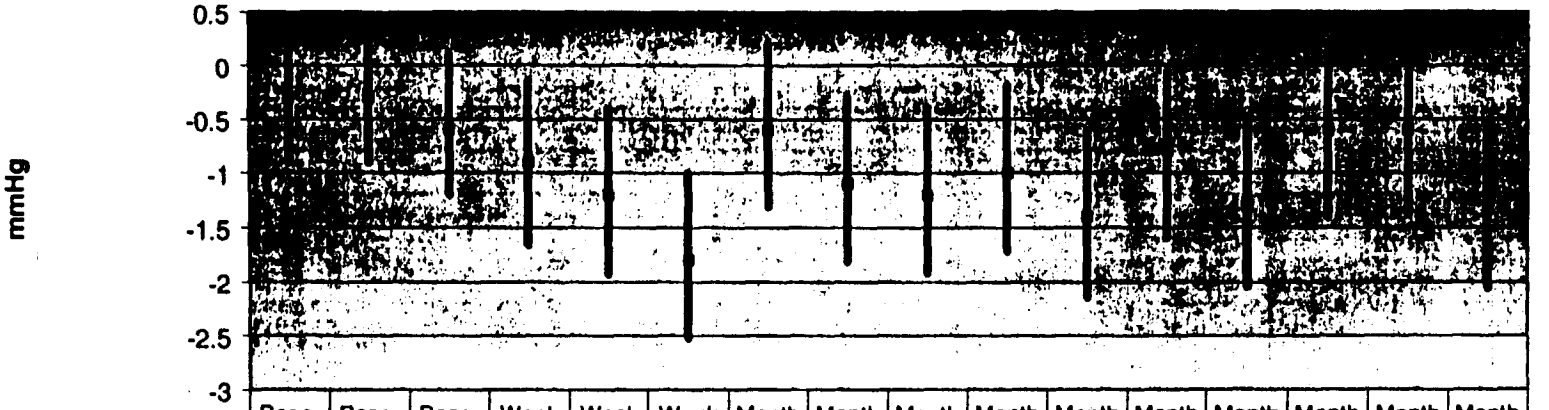
Mean IOP per Visit and Time



	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
AL-6221 0.0015%	27.1	25.5	24.8	19.9	18.8	18.3	19.8	18.6	19.5	18.8	18.2	19.9	18.7	19.9	18.9	18.8
AL-6221 0.004%	27.2	25.5	25	19.2	18.2	17.6	19.4	18.1	19.7	18.5	18.1	19.9	18.8	20.1	18.9	18.5
Timoptic 0.5%	27.4	25.8	25.3	20.8	20	20	20.3	19.7	20.7	19.8	19.6	20.7	20	20.5	19.5	20.1

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

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
Lower CI	-0.9	-0.9	-1.2	-1.66	-1.93	-2.52	-1.31	-1.82	-1.92	-1.72	-2.14	-1.59	-2.04	-1.4	-1.38	-2.06
Upper CI	0.3	0.3	0.1	-0.15	-0.41	-1	0.21	-0.3	-0.4	-0.2	-0.62	-0.07	-0.52	0.12	0.14	-0.54
■ Mean Difference	-0.3	-0.3	-0.6	-0.9	-1.2	-1.8	-0.6	-1.1	-1.2	-1	-1.4	-0.8	-1.3	-0.6	-0.6	-1.3

Reviewer's Comments: *The mean IOP of the two 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 Timoptic 0.5% is statistically significant at almost all time points and ranges from –0.6 to –1.8 mmHg. The 95% confidence interval crosses zero at Month 1.5 8AM, Month 6 8AM, and Month 6 10AM. The IOP lowering ability of AL-6221 0.0015% is not superior to Timoptic 0.5% by a clinically significant amount.*

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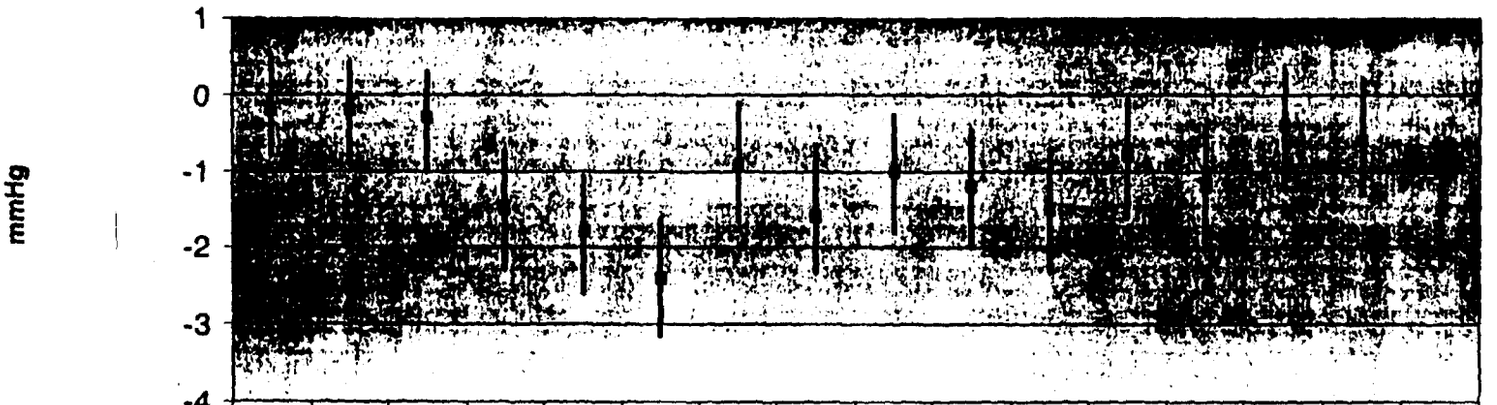
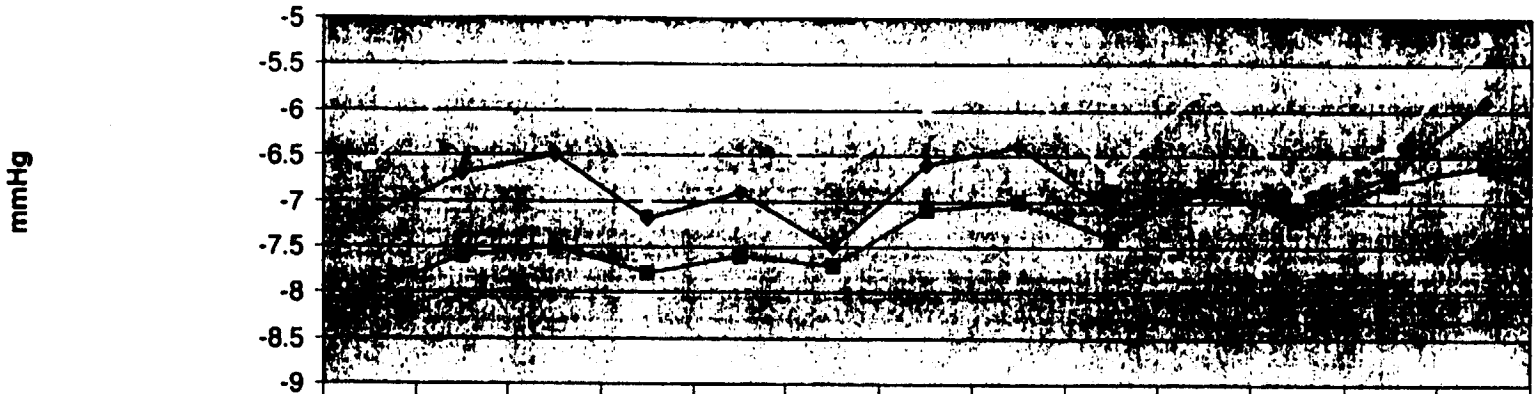
Mean Difference (AL-6221 0.004% - Timoptic 0.5%) with 95% Confidence Intervals



	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
Lower CI	-0.8	-0.9	-1	-2.28	-2.6	-3.16	-1.65	-2.32	-1.79	-2	-2.3	-1.6	-1.94	-1.18	-1.31	-2.29
Upper CI	0.5	0.4	0.3	-0.76	-1.08	-1.63	-0.12	-0.8	-0.27	-0.48	-0.78	-0.08	-0.42	0.34	0.21	-0.77
■ Mean Difference	-0.2	-0.2	-0.3	-1.5	-1.8	-2.4	-0.9	-1.6	-1	-1.2	-1.5	-0.8	-1.2	-0.4	-0.6	-1.5

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 almost all time points and ranges from –0.4 to –2.4 mmHg. The 95% confidence interval crosses zero at Month 6 8AM and 10AM. The lowering ability of AL-6221 0.0004% is not superior to Timoptic 0.5% by a clinically significant amount.*

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
AL-6221 0.0015%	-7.2	-6.7	-6.5	-7.2	-6.9	-7.5	-6.6	-6.4	-7.1	-6.9	-7.1	-6.7	-5.9
AL-6221 0.004%	-8	-7.6	-7.5	-7.8	-7.6	-7.7	-7.1	-7	-7.4	-6.8	-7.2	-6.8	-6.6
Timoptic 0.5%	-6.6	-5.7	-5.3	-7	-6.2	-6.7	-6	-5.7	-6.7	-5.7	-6.9	-6.4	-5.2

Reviewer's Comments: *When corrected for baseline, although both concentrations of AL-6221 (0.0015% and 0.004%) lower IOP more than Timoptic 0.5% over visit days and time, the difference is not clinically significant. The IOP lowering ability of AL-6221 0.0015% and AL-6221 0.004% is similar. The change in mean IOP from baseline ranges from –5.9 to –7.5 mmHg for AL-6221 0.0015%, from –6.6 to –8.0 mmHg for AL-6221 0.004%, and from –5.2 to –7.0 mmHg for Timoptic 0.5%.*

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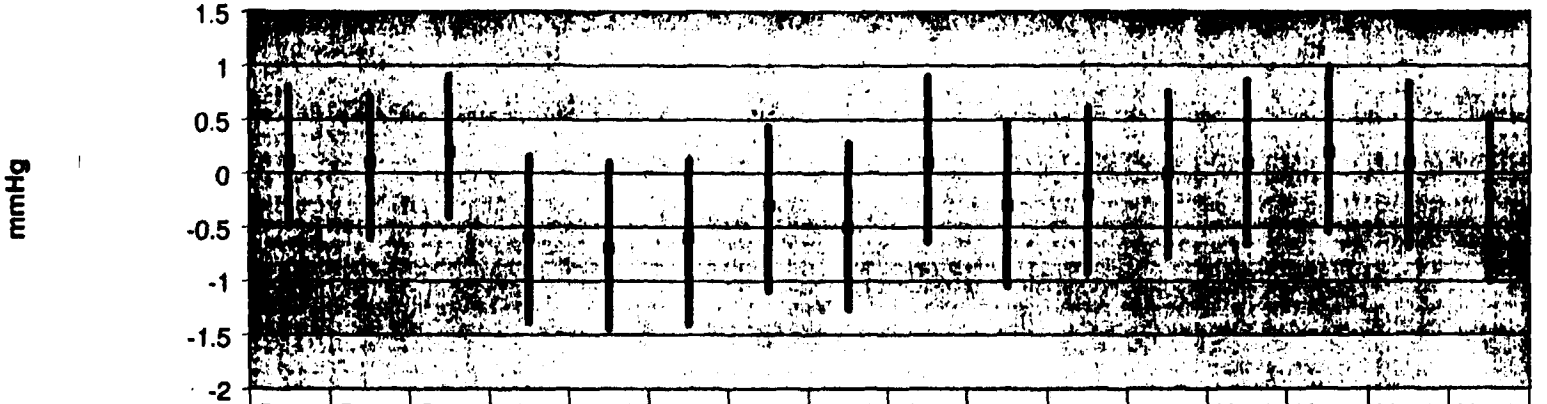
Mean Difference (AL-6221 0.004% - AL-6221 0.0015%) with 95% Confidence Intervals



	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 3 4PM	Month 4.5 8AM	Month 4.5 10AM	Month 6 8AM	Month 6 10AM	Month 6 4PM
Lower CI	-0.5	-0.6	-0.4	-1.38	-1.44	-1.4	-1.09	-1.26	-0.64	-1.05	-0.93	-0.77	-0.66	-0.54	-0.69	-1
Upper CI	0.8	0.7	0.9	0.15	0.09	0.12	0.43	0.27	0.89	0.48	0.6	0.75	0.86	0.98	0.83	0.53
■ Mean Difference	0.1	0.1	0.2	-0.6	-0.7	-0.6	-0.3	-0.5	0.1	-0.3	-0.2	0	0.1	0.2	0.1	-0.2

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 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.*

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8.1.3 Safety

Adverse Events

Serious adverse events other than death were reported for 20/202 (9.9%) subjects treated with AL-6221 0.0015%, 7/201 (3.5%) subjects treated with AL-6221 0.004%, and 11/202 (5.4%) subjects treated with Timoptic 0.5%. These other serious adverse events resulted in the premature discontinuation from the study for one subject treated with Timoptic 0.5%. No subjects treated with AL-6221 0.0015% and AL-6221 0.004% were discontinued from the study due to other serious adverse events.

Other Serious Adverse Events

Investigator Number	Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
2448	3003	AL-6221 0.0015%	Carcinoma Bladder	Continuing w/Tx	No
470	1017	AL-6221 0.0015%	Infection Urinary Tract	Resolved w/Tx	No
			Dehydration	Resolved w/Tx	No
	1005	AL-6221 0.0015%	Carcinoma Skin	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2496	4715	AL-6221 0.0015%	Pneumonia	Resolved w/Tx	No
2537	2005	AL-6221 0.0015%	Bone Fract Spontaneous	Resolved w/Tx	No
			Injury Accidental	Resolved w/Tx	No
			Pain Chest	Resolved w/Tx	No
415	4013	AL-6221 0.0015%	Hypokalemia	Resolved w/Tx	No
			Hyponatremia	Resolved w/Tx	No
2630	5608	AL-6221 0.0015%	Colitis	Resolved wo/Tx	No
			Hemorrhage Rectal	Resolved wo/Tx	No
			Surgical/Medical Proc	Resolved wo/Tx	No
1007	2603	AL-6221 0.0015%	Arrhythmia	Continuing w/Tx	No
			Infection	Resolved w/Tx	No
1733	1823	AL-6221 0.0015%	Pain	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2630	5611	AL-6221 0.0015%	Surgical/Medical Proc	Resolved w/Tx	No
2590	5306	AL-6221 0.0015%	Thrombosis Retinal Vein	Continuing wo/Tx	No
1733	1802	AL-6221 0.004%	Carcinoma Prostate	Continuing w/Tx	No
2569	5008	AL-6221 0.004%	Pneumonia	Resolved w/Tx	No
2422	1210	AL-6221 0.004%	Bone Fract Spontaneous	Resolved w/Tx	No
			Injury Accidental	Resolved w/Tx	No
2448	3021	AL-6221 0.004%	Pain Abdomen	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
2600	5207	AL-6221 0.004%	Surgical/Medical Proc	Resolved w/Tx	No
1733	1824	Timoptic 0.5%	Carcinoma Prostate	Resolved w/Tx	No
	1815	Timoptic 0.5%	Carcinoma GI	Continuing w/Tx	Yes
			GI Disease	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	Yes
2496	4701	Timoptic 0.5%	Ischemia Cerebral	Resolved w/Tx	No
	4712	Timoptic 0.5%	Surgical/Medical Proc	Resolved w/Tx	No
			Pain Back	Resolved w/Tx	No

D/C Pt = Discontinued Patient

One death occurred during the study:

Subject 2409 (Timoptic 0.5%) was a 67 year-old black female who entered the study with a history of hypertension, insulin dependent diabetes mellitus, arthritis, gastric reflux, incontinence, oophorectomy, open-angle glaucoma, diabetic retinopathy, blurred vision, ocular pruritus, and nuclear sclerosis cataracts. On Study Day 142, she experienced a fatal myocardial infarction.

Seven subjects (3.5%) receiving AL-6221 0.0015%, nine subjects (4.5%) receiving AL-6221 0.004%, and seven subjects (3.5%) receiving Timoptic 0.5% 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=202	AL-6221 0.004% N=201	Timoptic 0.5% N=202
	N (%)	N (%)	N (%)
All Events	126 (62.4)	134 (66.7)	98 (48.5)
OCULAR			
Hyperemia Eye	59 (29.2)	86 (42.8)	18 (8.9)
Visual Acuity Decrease	9 (4.5)	10 (5.0)	9 (4.5)
Pruritus Eye	7 (3.5)	12 (6.0)	5 (2.5)
Keratitis	6 (3.0)	8 (4.0)	4 (2.0)
Discomfort Eye	5 (2.5)	5 (2.5)	9 (4.5)
Pain Eye	3 (1.5)	12 (6.0)	
Vision Blurred	6 (3.0)	5 (2.5)	6 (3.0)
Dry Eye	3 (1.5)	6 (3.0)	4 (2.0)
Foreign Body Sensation	4 (2.0)	6 (3.0)	
Conjunctivitis		3 (1.5)	3 (1.5)
Hemorrhage Subconjunctival	3 (1.5)	3 (1.5)	
Vision Decrease			4 (2.0)
Inflammatory Cells Aqueous		3 (1.5)	
Blepharitis		3 (1.5)	
Aqueous Flare		3 (1.5)	
Tearing		4 (2.0)	
Lid Margin Crusting		3 (1.5)	
NON-OCULAR			
Body As A Whole			
Infection	12 (5.9)	7 (3.5)	8 (4.0)
Surgical/Medical Proc	10 (5.0)	5 (2.5)	6 (3.0)
Pain	5 (2.5)		5 (2.5)
Headache	6 (3.0)		3 (1.5)
Injury Accidental		6 (3.0)	-
Cold Syndrome	4 (2.0)		3 (1.5)
Allergy	3 (1.5)		
Pain Chest		3 (1.5)	
Cardiovascular System			
Hypertension	4 (2.0)		3 (1.5)
Bradycardia			3 (1.5)

Coded Adverse Event	AL-6221 0.0015% N=202	AL-6221 0.004% N=201	Timoptic 0.5% N=202
Digestive System			
GI Disease		3 (1.5)	
Metabolic & Nutrition			
Hypercholesterolemia		6 (3.0)	3 (1.5)
Hyperlipidemia			3 (1.5)
Musculo-Skeletal System			
Bone Fracture Spontaneous		3 (1.5)	
Respiratory System			
Bronchitis	3 (1.5)		3 (1.5)
Cough Increase	3 (1.5)		3 (1.5)
Pneumonia			3 (1.5)
Sinusitis	3 (1.5)		
Pharyngitis	4 (2.0)		
Urogenital System			
Infection Urinary Tract	3 (1.5)		
Prostate Disease		3 (1.5)	

Ocular Hyperemia

A statistically significant difference in ocular hyperemia among the 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%.

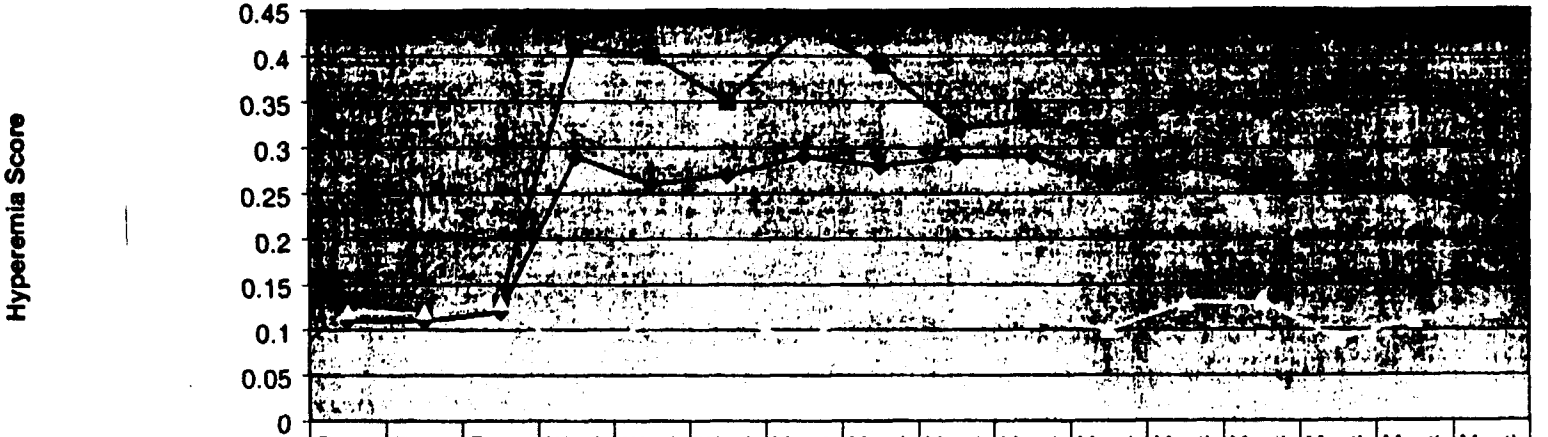
Frequency and Incidence of Ocular Hyperemia

Treatment	Number Randomized	N	%
AL-6221 0.0015%	202	59	29.2
AL-6221 0.004%	201	86	42.8
Timoptic 0.5%	202	18	8.9

Frequency and Incidence of Discontinued Patients Due to Ocular Hyperemia

Treatment	Number Randomized	N	%
AL-6221 0.0015%	202	2	1.0
AL-6221 0.004%	201	6	3.0
Timoptic 0.5%	202	0	0.0

Mean Hyperemia Score per Visit Day 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
AL-6221 0.0015%	0.11	0.11	0.12	0.29	0.26	0.27	0.29	0.28	0.29	0.29	0.26	0.28	0.26	0.26	0.25	0.23
AL-6221 0.004%	0.13	0.12	0.13	0.41	0.4	0.35	0.43	0.39	0.32	0.33	0.31	0.35	0.34	0.36	0.36	0.32
Timoptic 0.5%	0.12	0.12	0.13	0.07	0.11	0.11	0.09	0.13	0.11	0.11	0.1	0.13	0.13	0.09	0.11	0.12

Reviewer's Comments: *Baseline mean hyperemia score for the three treatment arms is similar. The mean hyperemia score for AL-6221 0.0015% and AL-6221 0.004% dosed QPM is consistently higher than for Timoptic 0.5% dosed BID. A concentration related increase in mean hyperemia score is associated with AL-6221.*

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Visual Acuity

No statistically significant difference (p=0.928) 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 (%)
N	199	199	200
≥ 2 lines loss	13 (6.5)	21 (10.6)	10 (5.0)
1 line loss	49 (24.6)	46 (23.1)	44 (22.9)
No Change	130 (65.3)	116 (58.3)	129 (64.5)
1 line gain	7 (3.5)	12 (6.0)	16 (8.0)
≥ 2 lines gain	0 (0)	4 (2.0)	1 (0.5)

Patients 1829, 3813, 4403 (AL-6221 0.0015%); 4401, 4901 (AL-6221 0.004%); 4402, 4404 (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 (%)
N	199	199	200
≥ 2 lines loss	58 (29.1)	84 (42.2)	61 (30.5)
1 line loss	92 (46.2)	61 (30.7)	76 (38.0)
No Change	47 (23.6)	45 (22.6)	59 (29.5)
1 line gain	2 (1.0)	8 (4.0)	4 (2.0)
≥ 2 lines gain	0 (0)	1 (0.5)	0 (0)

Patients 1829, 3813, 4403 (AL-6221 0.0015%); 4401, 4901 (AL-6221 0.004%); 4402, 4404 (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 and Month 6.

Percent of Patients with Iris Pigmentation Change by Visit

Treatment		Visit MONTH 1.5-8AM	MONTH 3-8AM	MONTH 4.5-8AM	MONTH 6-8AM	EARLY EXIT
AL-6221 0.0015% + Vehicle	%	0.0	0.0	0.0	0.0	0.0
	N	0	0	0	0	0
	Total N	190	176	170	172	29
AL-6221 0.004% + Vehicle	%	0.0	0.6	0.6	1.2	0.0
	N	0	1	1	2	0
	Total N	188	168	165	166	32
Timoptic 0.5%	%	0.0	0.0	0.0	0.0	0.0
	N	0	0	0	0	0
	Total N	190	177	170	172	26

p≥ 0.106 at any visit from Fisher's Exact test comparing treatment groups.
Early Exit denotes patients who did not complete the study.
Twelve AL-6221 0.0015% patients (1829, 2303, 2621, 3010, 3406, 3813, 4002, 4005, 4403, 4610, 4904, 5704), 13 AL-6221 0.004% patients (1306, 1312, 1811, 2102, 2302, 3008, 3105, 3807, 4404, 4609, 4902, 5302, 5701) and 12 Timoptic 0.5% patients (1007, 1010, 2101, 2301, 2329, 2604, 3019, 4020, 4502, 4901, 4918, 5001) had missing Month 1.5 data.
Patients 1829 (AL-6221 0.0015%), 1312 (AL-6221 0.004%), and 2301 (Timoptic 0.5%) 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 for the group treated with AL-6221 0.004%.

Eyelashes

Eyelash photographs of each eye were taken at Eligibility 2 8AM (baseline), Month 1.5, Month 3, Month 4.5, and Month 6.

A statistically significant (p=0.001) difference was observed between the treatment groups and include changes in color, length, density, and thickness.

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	73	36.3	55	27.4	73	36.3	68	33.8	57	28.4
AL-6221 0.004% + Vehicle	200	102	51.0	81	40.5	102	51.0	100	50.0	92	46.0
Timoptic .5%	201	4	2.0	3	1.5	4	2.0	4	2.0	1	0.5

p≤ 0.001 in all categories from chi-square test comparing treatment groups.
Patients 1829 (AL-6221 0.0015%), 1312 (AL-6221 0.004%), and 2301 (Timoptic 0.5%) 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	EARLY EXIT
AL-6221 0.0015% + Vehicle	%	1.6	22.7	32.4	41.9	3.4
	N	3	40	55	72	1
	Total N	190	176	170	172	29
AL-6221 0.004% + Vehicle	%	2.7	38.7	50.3	57.8	18.8
	N	5	65	83	96	6
	Total N	188	168	165	166	32
Timoptic 0.5%	%	0.0	0.6	1.2	2.3	0.0
	N	0	1	2	4	0
	Total N	190	177	170	172	26

p = 0.056 for Month 1.5 and p <= 0.02 for other visits from Fisher's Exact test comparing treatment groups.
Early Exit denotes patients who did not complete the study.
Twelve AL-6221 0.0015% patients (1829, 2303, 2621, 3010, 3406, 3813, 4002, 4005, 4403, 4610, 4904, 5704), 13 AL-6221 0.004% patients (1306, 1312, 1811, 2102, 2302, 3008, 3105, 3807, 4404, 4609, 4902, 5302, 5701) and 12 Timoptic 0.5% patients (1007, 1010, 2101, 2301, 2329, 2604, 3019, 4020, 4502, 4901, 4918, 5001) had missing Month 1.5 data.
Patients 1829 (AL-6221 0.0015%), 1312 (AL-6221 0.004%), and 2301 (Timoptic 0.5%) had no follow-up data.

Reviewer's Comments:

A concentration related change in eyelash color, length, density, and thickness is consistent with an ocularly administered prostaglandin-type effect. The prevalence of eyelash change increases with duration of therapy. Whether these changes are purely cosmetic or have safety related issues have not been determined.

Aqueous Flare and Inflammatory Cells

Aqueous flare and inflammatory cells assessment was performed at Eligibility 2 Visit (baseline), Week 2, Month 1.5, Month 3, Month 4.5, Month 6 Visits, and any unscheduled visits at 8AM.

No subjects discontinued from the study due to aqueous flare or inflammatory cells. One of 201 subjects (0.5%) treated with AL-6221 0.0015% and three of 201 subjects (1.5%) treated with AL-6221 0.004% experienced clinically significant flare. No subject treated with Timoptic 0.5% experienced clinically significant flare. Two of 201 subjects (1.0%) treated with AL-6221 0.0015%, four of 201 subjects (2.0%) treated with AL-6221 0.004%, and two of 201 subjects (1.0%) treated with Timoptic 0.5% experienced clinically significant cells.

Cup/Disc Ratio

No clinically or statistically significant difference (p=0.5466) in increase of cup/disc ratio was observed among the treatment groups.

Visual Field

Although no clinically or statistically significant difference in visual field mean deviation/defect change or corrected loss variance change from baseline was observed among the treatment groups in subjects analyzed with the [redacted] no conclusion could be drawn due to the limited sample size.

Ocular Signs

No clinically or statistically significant difference (p=0.954) in ocular signs was observed among the treatment groups.

One of 201 subjects receiving Timoptic 0.5% discontinued from the study due to decreased vision secondary to cataracts. Clinically significant increase in ocular signs from baseline was observed in six of the 201 subjects (3.0%) receiving AL-6221 0.0015%, eight of the 201 subjects (4.0%) receiving AL-6221 0.004%, and eight of the 201 subjects (4.0%) receiving Timoptic 0.5%.

Dilated Fundus Examination

Dilated fundus examinations (retina/macula/choroid, optic nerve, disc pallor) were observed at Screening (baseline) and Month 6 (Exit) 10AM visits.

No clinically or statistically significant difference for retina/macula/choroid (p=0.324), for optic nerve (p=1.0) or for disc pallor (p=0.553) in increase of fundus parameters was observed among the treatment groups.

Three of the 200 subjects (1.5%) receiving AL-6221 0.0015% experienced retina/macula/choroid changes (retinal hemorrhage, retinal vein thrombosis). Three of the 201 subjects (1.5%) receiving AL-6221 0.004% experienced retina/macula/choroid changes (increased fibrin, retinal vascular disorder) and disc pallor. One of the 198 subjects (0.5%) receiving Timoptic 0.5% experienced optic disc pallor.

Vital Signs

Timoptic 0.5% showed a statistically significant (p=0.0001) decrease in pulse measurements compared to AL-6221 (0.0015% and 0.004%).

Timoptic 0.5% showed a statistically significant decrease in systolic blood pressure from AL-6221 0.0015% (p=0.0006) and AL-6221 0.004% (p=0.0219).

No statistically significant (p=0.1684) difference in diastolic blood pressure was observed among treatment groups.

Pulse Change from Baseline (Beats Per Minute)

Treatment		Baseline	Change From Baseline: WEEK 2 8AM	WEEK 2 10AM	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
Al-6221	MEAN	71.9	-0.5	-0.5	-0.9	-0.9	-0.3	-0.4	0.2	0.0	-1.3	-0.3
0.0015% +	STD	10.4	9.7	9.3	10.0	10.5	9.9	9.7	10.9	9.5	11.1	9.6
Vehicle	N	201	197	194	190	188	177	176	173	172	171	171
	MIN	47	-31	-24	-25	-32	-32	-32	-33	-24	-31	-32
	MAX	108	36	34	34	48	30	24	33	31	41	42
AL-6221	MEAN	71.8	-0.2	0.3	-0.5	-0.4	1.0	1.2	0.7	1.1	0.0	1.5
0.004% +	STD	9.1	9.2	7.8	9.5	9.3	9.0	8.8	10.2	9.9	10.4	9.9
Vehicle	N	200	196	195	191	189	172	172	167	168	167	166
	MIN	52	-24	-22	-29	-30	-26	-24	-36	-36	-36	-36
	MAX	100	28	24	32	32	24	30	29	28	36	36
Timoptic	MEAN	72.1	-3.2	-3.9	-3.1	-4.9	-2.6	-4.3	-2.0	-3.4	-2.3	-2.7
0.5%	STD	9.8	9.1	8.6	9.2	8.8	9.3	9.0	9.8	9.2	9.6	9.8
	N	201	197	195	193	192	178	178	173	173	171	169
	MIN	40	-30	-30	-34	-30	-32	-30	-36	-28	-40	-40
	MAX	100	25	20	20	24	28	28	28	24	20	24

p=0.0001 from repeated measures analysis of variance comparing treatment groups.
The following patients had no baseline data: AL-6221 0.0014%: 3022; AL-6221 0.004%: 4404; Timoptic 0.5%: 4913.
Patients 1829, 3022 (AL-6221 0.0015%); 4404 (AL-6221 0.004%); 2301, 4901, 4913 (Timoptic 0.5%) had no follow-up data.

Systolic Blood Pressure Change from Baseline (mmHg)

Treatment		Baseline	Change From Baseline: WEEK 2 8AM	WEEK 2 10AM	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
AL 6221	MEAN	133.7	1.8	1.0	0.3	0.0	2.6	1.2	2.8	1.7	2.0	1.8
0.0015% +	STD	16.1	15.3	14.4	17.6	15.6	17.3	17.4	16.8	15.0	17.4	15.9
Vehicle	N	202	198	195	191	189	178	177	174	173	172	172
	MIN	90	-32	-31	-62	-40	-40	-38	-48	-32	-40	-40
	MAX	190	56	41	56	48	70	46	60	48	68	50
AL 6221	MEAN	135.7	0.6	0.1	0.4	-0.8	0.7	-1.0	-1.1	-1.9	1.6	-0.1
0.004% +	STD	19.4	16.6	16.4	16.6	16.5	17.8	15.1	17.2	16.7	16.3	17.3
Vehicle	N	200	195	194	191	189	172	172	167	168	167	166
	MIN	97	-45	-45	-42	-41	-81	-55	-60	-60	-58	-91
	MAX	227	43	45	48	50	77	48	50	50	44	50
Timoptic	MEAN	138.3	-0.9	-4.1	-2.8	-4.2	-2.4	-2.5	-1.6	-3.8	-1.6	-4.2
0.5%	STD	18.6	14.9	15.2	15.8	17.0	15.8	15.8	17.4	17.1	18.8	17.3
	N	201	197	195	193	191	178	178	173	173	171	169
	MIN	93	-41	-53	-75	-77	-75	-44	-61	-65	-67	-79
	MAX	205	48	56	44	48	40	40	48	45	60	40

p=0.0022 from repeated measures analysis of variance comparing treatment groups.
The following patients had no baseline data: AL-6221 0.004%: 4404 and Timoptic 0.5%: 2908.
Patients 1829, 3022 (AL-6221 0.0015%); 4404 (AL-6221 0.004%); 2301, 4901, 4913 (Timoptic 0.5%) had no follow-up data.

Clinical Laboratory Evaluation

No clinically significant change from baseline in laboratory values (hematology, blood chemistry, urinalysis) was observed among treatment groups.

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8.1.3 Reviewer's Summary of Efficacy and Safety

AL-6221 0.0015% and AL-6221 0.004% dosed once daily in the evening demonstrate equivalence in their ability to lower IOP.

AL-6221 0.0015% and AL-6221 0.004% demonstrate efficacy in the ability to lower IOP. The change in mean IOP from baseline ranges from –5.9 to –7.5 mmHg for AL-6221 0.0015% and from –6.6 to –8.0 mmHg for AL-6221 0.004% as compared to –5.2 to –7.0 mmHg for Timoptic 0.5%.

The IOP lowering ability of AL-6221 0.004% is not superior to Timoptic 0.5% by a clinically significant amount.

Both concentrations of AL-6221 are associated with ocular hyperemia. The prevalence and severity of ocular hyperemia are concentration related.

The iris/eyelash photographs read by masked independent readers reveal iris pigmentation change beginning at 3 months after commencement of therapy and increases with duration of therapy for the AL-6221 0.004% treatment group only.

The iris/eyelash photographs read by masked independent readers reveal a concentration related change in eyelash color, length, density, and thickness consistent with an ocularly administered prostaglandin-type effect. The prevalence increases with duration of therapy.

8.1.4 Study #4 Protocol C-97-73

Title: A Six-Month, Multicenter, Triple-Masked, Placebo-Controlled Adjunctive Therapy Study of the Safety and Efficacy of AL-6221 0.0015% and AL-6221 0.004% Ophthalmic Solution in Patients with Open-Angle Glaucoma or Ocular Hypertension Maintained on Timoptic 0.5%

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

Test Drug Schedule: Patients instilled one drop of Timoptic 0.5% twice daily at approximately 8AM and 8PM into each eye for 6 months. Patient also instilled one drop of masked medication daily into each eye five minutes after administration of Timoptic 0.5% at 8PM for 6 months.

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
1986	**Walter Atlas, M.D.** Charlotte, NC 28207	13	13	13
2443	**Mark G. Bearman, M.D.** Birmingham, AL 35235	01	01	0
470	**Donald Brotherman, M.D.** Dallas, TX 75234	02	02	02
1208	**Robert Caine, M.D.** Fredericksburg, VA 22405	07	07	05
2431	**Hersh Chopra, M.D.** Marietta, GA 30060	01	01	01
2442	**Charles E. Cox, M.D.** Fort Meyers, FL 33901	11	11	11
1236	**E. Randy Craven, M.D.** Littleton, CO 80120	14	13	10
2348	**Douglas Day, M.D.** Atlanta, GA 30342	27	27	23
2441	**Howard Doyle, M.D.** Boca Raton, FL 33486	07	06	06
1927	**Harvey DuBiner, M.D.** Morrow, GA 30260	06	06	06
2564	**Robert Feldman, M.D.** Houston, TX 77030	03	03	02
2534	**Ronald Fellman, M.D.** Dallas, TX 75231	0	0	0

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
2555	**Brian Francis, M.D.** New Orleans, LA 70211	28	28	26
2440	**David E. Hall, M.D.** St. Petersburg, FL 33707	05	05	04
1098	**Harold A. Helms, M.D.** Birmingham, AL 35205	04	04	01
2182	**Raymond Hernandez, M.D.** San Antonio, TX 78240	20	20	20
1237	**Lawrence M. Hurvitz, M.D.** Sarasota, FL 34233	01	01	0
1250	**Adam Kaufman, M.D.** Cincinnati, OH 45242	09	09	07
2439	**Joseph Krug, Jr., M.D.** Leawood, KS	0	0	0
943	**Robert A. Laibovitz, M.D.** Austin, TX 78731	0	0	0
432	**Norman Levy, M.D.** Gainesville, FL 32605	0	0	0
2438	**Solomon C. Luo, M.D.** Pottsville, PA 17901	15	15	15
2565	**William McMullen, M.D.** Webster, TX 77598	07	07	01
1716	**Paul Mitchell, M.D.** Marietta, GA 30060	12	12	09
1978	**Earl Nelson, M.D.** New Orleans, LA 70127	12	11	07
2133	**Silvia Orengo-Nania, M.D.** Houston, TX 77030	06	06	04
1780	**Richard Patchett, M.D.** Marshfield, WI 54449	08	08	08
2445	**Mitchell Porias, D.O.** Houston, TX 77009	04	04	04
2436	**James Roberts, M.D.** Palm Harbor, FL 34684	0	0	0
733	**Edward G. Rosanelli, Jr., M.D.** Tampa, FL 33609	0	0	0
1393	**Michael Rotberg, M.D.** Charlotte, NC 28204	04	04	03

Investigator Number	Investigator	Number Randomized	Number Randomized	Number in Per Protocol Population
2242	**David S. Rothberg, M.D.** Palm Harbor, FL 34684	06	06	05
1806	**Kenneth Sall, M.D.** Bellflower, CA 90706	31	31	29
1939	**Howard Schenker, M.D.** Rochester, NY 14618	15	15	15
1892	**Shannon Smith, M.D.** Nacogdoches, TX 75961	10	09	09
1972	**Dara Stevenson, M.D.** New Orleans, LA 70019	01	01	0
989	**William C. Stewart, M.D.** Charleston, SC 29412	41	38	36
2247	**Richard T. Sturm, M.D.** Lynbrook, NY 11563	21	21	20
1455	**Joseph Tauber, M.D.** Kansas City, MO 64111	02	01	01
2353	**George C. Thorne, Jr., M.D.** Austin, TX 78756	01	01	01
2491	**David P. Tingey, M.D.** London, Ontario, Canada N6A4G5	07	07	05
1007	**Thomas R. Walters, M.D.** Austin, TX 78746	29	29	28
1913	**Jeffrey Wasserstrom, M.D.** La Mesa, CA 91942	02	01	01
394	**Mark Weiss, M.D.** Tulsa, OK 74104	09	09	05
2435	**Jeffrey C. Whitsett, M.D.** Houston, TX 77055	14	14	13
2128	**Robert Williams, M.D.** Louisville, KY 40217	10	10	09

Reviewer's Comments:

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

8.1.4 Study Design

This was a randomized, multicenter, triple-masked, placebo (vehicle)-controlled, parallel group comparison of two concentrations of AL-6221 (0.0015% and 0.004%) to placebo (vehicle) (1:1:1 randomization) to evaluate their efficacy and safety when used adjunctively with Timoptic 0.5% in patients with open-angle glaucoma or ocular hypertension. The three treatment groups were 1) AL-6221 0.0015% + Timoptic 0.5%, 2) AL-6221 0.004% + Timoptic 0.5%, and 3) AL-6221 Vehicle +Timoptic 0.5%.

The study consisted of two phases. Phase 1 consisted of a Screening Visit, Eligibility 1 Visit, and Eligibility 2 Visit. At the Screening Visit, patients who qualified began dosing twice a day (8AM and 8PM) with open-label Timoptic 0.5% and discontinued all other topical or systemic hypotensive medications. After being treated with Timoptic 0.5% for three weeks, patients returned for the Eligibility 1 Visit followed by the Eligibility 2 Visit one week later. All eligible patients were on twice daily Timoptic 0.5% and were required to have a mean IOP of 24 mmHg to 36 mmHg at 8AM at both Eligibility 1 and 2 Visits. Ten (10) AM and 4PM IOP measurements were required to be 21 mmHg to 36 mmHg in the same eye at both Eligibility 1 and 2 Visits.

Follow-up visits were scheduled for Week 2, Month 1.5, Month 3, Month 4.5, and Month 6. Patient's IOP was measured at 8AM, 10AM, and 4PM on Week 2, Month 3, and Month 6 and at 8AM and 10AM at Month 1.5 and Month 4.5.

Reviewer's Comments:

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

Study Population

The inclusion and exclusion criteria were nearly identical to Protocol C-97-71. The major difference is that the entrance IOP criteria were required while the patient was on twice daily Timoptic 0.5% therapy.

Study Medications

• AL-6221 0.0015%	Lot # ARE-2948B; 99-500042-3; ASE-2999A; ASE-2999B; 98-500007-2
• AL-6221 0.004%	Lot # ARE-2946A; ARE-2946B; ASE-2998B; 99-500044-3; 98-500009-2; ASE-2998A
• AL-6221 Vehicle	Lot # ARE-2947A; 99-500022-2; 98-500002-1; 99-500050-1; ASE-2996B
• Timoptic 0.5%	Lot # 1465H; 0347H; 1623H; 0074E; 1289E; 0073E; 1690E; 0858E; 0630E; 1899H; 1289E

Protocol C-97-73
Study Plan

Activity	Screen	Eligibility Visit 1			Eligibility Visit 2			Week 2 ± 1 day			Month 1.5 ± 3days		Month 3 ± 3 days			Month 4.5 ± 3 days		Month 6 ± 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
Screen Patients	X																			
Informed Consent	X																			
Demographics	X																			
Medical History	X																			
Discontinue All Glaucoma Rx	X																			
IOP[a]		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
Flare/Cells Assessment[b]					X			X			X		X			X		X		
Visual Acuity (Best Corrected) (LogMAR Scale)	X	X			X			X			X		X			X		X		
Biomicroscopy	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	
Dilated Fundus	X																		X	
Automated Perimetry[c,f]	X																		X[F]	
Gonioscopy[d]	X																			
Dispense TIMOPTIC[e]	X						X			X		X			X		X			
Iris/Eyelash Photographs					X						X		X			X		X		
Dispense Masked Meds[e]							X			X		X			X		X			
Adverse Events								X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Rx																		X		
Exit Patients																				X

[a] IOP measurements should be ±30 minutes of the required time.
[b] Flare/cells will be assessed at all sites according to the grading provided in the Manual of Definitions.
[c] 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.
[d] Gonioscopy will be conducted only if this procedure has not been performed and documented within the last six months.
[e] Dispense meds as needed.
[f] Exit automated perimetry may be performed after the 8 AM exam and before the 4 PM exam.

Efficacy Variable

The primary efficacy variable was mean IOP measured at 8AM. 10AM, and 4PM at Week 2, Month 3, and Month 6 and at 8AM and 10AM at Month 1.5 and Month 4.5.

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 at Week 2 and Months 1.5, Month3, Month 4.5, and Month 6.

Safety Variables

The safety variables that were assessed were the same ones examined in Study #2, Protocol C-97-71.

Subject Disposition and Demographics

Four hundred twenty-six of the 427 randomized subjects received treatment and 349 subjects completed the study.

Subject Disposition

	Number of Subjects			
	T1/2 + AL-6221 0.0015%	T1/2 + AL-6221 0.004%	T1/2 + AL-6221 Vehicle	Total
Randomized	142	146	139	427
Discontinued prematurely	21	18	39	78
Included in safety evaluations	142	145	139	426
Included in intent-to-treat efficacy analysis	139	137	134	410
Included in per protocol efficacy analysis	122	123	117	362

T1/2 =Timoptic 0.5%

Reviewer's Comments:

The intent-to-treat population excluded 17 subjects who received treatment but had no-on-treatment visit data.

Summary of Reasons for Premature Discontinuation from Study

	Number (%) of Subjects			
	T1/2 + AL-6221 0.0015%	T1/2 + AL-6221 0.004%	T1/2 + AL-6221 Vehicle	Total
Inadequate control of IOP	2 (9.5)	1 (5.6)	21 (53.9)	24
Adverse event	6 (28.6)	8 (44.4)	2 (5.1)	16
Patient decision	2 (9.5)	1 (5.6)	1 (2.6)	4
Lost to follow-up	1 (4.8)	0 (0)	3 (7.7)	4
Noncompliance	0 (0)	1 (5.6)	2 (5.1)	3
Other	10 (47.6)	7 (38.9)	10 (25.6)	27
Total	21	18	39	78

T1/2 =Timoptic 0.5%

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Duration (Days)	Reason
394	7404	AL-6221 0.004%+T1/2	35	Unqualifying IOPs
	7406	AL-6221 0.0015%+T1/2	94	Protocol violation
	7407	AL-6221 Vehicle+T1/2	49	Protocol violation
989	5402	AL-6221 Vehicle+T1/2	166	Inadequate control of IOP
	5405	AL-6221 0.004% +T1/2	34	Adverse event-pain eye
	5406	AL-6221 Vehicle +T1/2	55	Lost to follow-up
	5415	AL-6221 Vehicle+T1/2	84	Inadequate control of IOP
	5418	AL-6221 0.004%+T1/2	12	Adverse event-cells, flare, uveitis
	5421	AL-6221 Vehicle+T1/2	125	Inadequate control of IOP
	542 4	AL-6221 Vehicle +T1/2	5	Inadequate control of IOP
	5435	AL-6221 0.0015%+T1/2	98	Adverse event-surgical/medical proc
	5436	AL-6221 0.004%+T1/2	77	Protocol violation
	5439	AL-6221 Vehicle+T1/2	21	Inadequate control of IOP
	5440	AL-6221 Vehicle+T1/2	7	Inadequate control of IOP
1098	3903	AL-6221 Vehicle+T1/2	202	Protocol violation
1208	7002	AL-6221 0.0015%+T1/2	91	Alcon's decision
	7005	AL-6221 0.0015%+T1/2	126	IOP did not qualify
1236	3602	AL-6221 Vehicle+T1/2	21	Inadequate control of IOP
	3603	AL-6221 0.004%+T1/2	19	Adverse event-pain eye
	3605	AL-6221 0.004%+T1/2	27	Ineligible pt entered in error
	3610	AL-6221 Vehicle+T1/2	10	Inadequate control of IOP
	3613	AL-6221 0.0015%+T1/2	87	Adverse event-pain eye
1237	4101	AL-6221 0.0015%+T1/2	165	Study terminated per Alcon
1250	4202	AL-6221 Vehicle+T1/2	73	IOP did not meet eligibility
1455	5601	AL-6221 0.0015%+T1/2	6	Adverse event-discomfort eye
1716	4607	AL-6221 Vehicle+T1/2	72	IOP too low at eligibility visit
	4611	AL-6221 0.0015%+T1/2	84	Did not meet eligibility criteria. Decreased IOP
1780	4804	AL-6221 Vehicle+T1/2	89	Inadequate control of IOP
	4807	AL-6221 Vehicle+T1/2	126	Inadequate control of IOP
1806	5202	AL-6221 Vehicle+T1/2	294	Lost to follow-up
	5207	AL-6221 Vehicle+T1/2	28	Sponsor requests pt exit study due to VF results
	5208	AL-6221 0.0015%+T1/2	37	Adverse event-cells, flare, iritis
	5209	AL-6221 0.004%+T1/2	372	Visual field failed criteria
	5212	AL-6221 Vehicle+T1/2	61	Inadequate control of IOP
	5213	AL-6221 Vehicle+T1/2	167	Noncompliance
	5221	AL-6221 0.004%+T1/2	125	Noncompliance

Investigator	Patient	Treatment	Duration (Days)	Reason
1806	5222	AL-6221 Vehicle+T1/2	56	Inadequate control of IOP
	5228	AL-6221 Vehicle+T1/2	27	Inadequate control of IOP
1892	8107	AL-6221 0.004%+T1/2	24	Adverse event-foreign body sensation, sticky sensation
1913	7302	AL-6221 0.0015%+T1/2	29	Ineligibile visual field
1939	7901	AL-6221 0.004%+T1/2	91	Pt already enrolled in Alcon C-97-71 study
	7913	AL-6221 Vehicle+T1/2	24	Inadequate control of IOP
1978	4707	AL-6221 Vehicle+T1/2	176	Noncompliance
	4708	AL-6221 0.0015%+T1/2	169	Sponsor requested subject termination
	4709	AL-6221 0.004%+T1/2	45	IOPs did not qualify
	4710	AL-6221 Vehicle+T1/2	311	Non-qualifying IOPs
	4711	AL-6221 0.0015%+T1/2	38	IOPs did not qualify
	4712	AL-6221 0.004%+T1/2	35	Sponsor requested
2128	8005	AL-6221 Vehicle+T1/2	85	Inadequate control of IOP
	8006	AL-6221 0.0015%+T1/2	182	Subject decision unrelated to an adverse event
	8008	AL-6221 0.004%+T1/2	9	Adverse event-hyperemia eye, photophobia
2133	7702	AL-6221 0.0015%+T1/2	15	Non-qualifying IOPs
	7705	AL-6221 Vehicle+T1/2	41	Inadequate control of IOP
2242	5106	AL-6221 Vehicle+T1/2	119	Pressures too low at eligibility 2
2247	5505	AL-6221 Vehicle+T1/2	42	IOP less than 20 on eligibility 1
	5517	AL-6221 0.004%+T1/2	14	Inadequate control of IOP
2348	7107	AL-6221 Vehicle+T1/2	66	Non-qualifying IOPs
	7109	AL-6221 0.0015%+T1/2	133	Adverse event-hypertension
	7111	AL-6221 0.0015%+T1/2	49	Inadequate control of IOP
	7112	AL-6221 Vehicle+T1/2	84	Inadequate control of IOP
	7113	AL-6221 0.0015%+T1/2	133	Lost to follow-up
	7115	AL-6221 Vehicle+T1/2	28	Inadequate control of IOP
	7116	AL-6221 Vehicle+T1/2	7	Adverse event-cells, uveitis
	7125	AL-6221 Vehicle+T1/2	91	Inadequate control of IOP
2438	4501	AL-6221 0.0015%+T1/2	130	Adverse event-hyperemia eye
2440	3805	AL-6221 0.004%+T1/2	3	Adverse event-pain eye, photophobia, tearing
2441	3706	AL-6221 0.004%+T1/2	16	Adverse event-cells, iritis
	3707	AL-6221 Vehicle+T1/2	143	Inadequate control of IOP
2442	3508	AL-6221 Vehicle+T1/2	78	Adverse event-infarct myocardial(patient died)
	3509	AL-6221 0.0015%+T1/2	84	Subject decision unrelated to an adverse event
2491	6001	AL-6221 0.0015%+T1/2	42	Protocol violation
	6002	AL-6221 Vehicle+T1/2	7	Non-qualifying IOP
	6004	AL-6221 0.004%+T1/2	0	Subject decision unrelated to an adverse event
	6007	AL-6221 0.004%+T1/2	16	Adverse event-hyperemia eye, conjunctivitis
2555	6105	AL-6221 Vehicle+T1/2	35	Inadequate control of IOP
	6110	AL-6221 Vehicle+T1/2	102	Lost to follow-up
	6119	AL-6221 0.0015%+T1/2	88	Inadequate control of IOP
	6121	AL-6221 Vehicle+T1/2	42	Subject decision unrelated to an adverse event

T1/2 = Timoptic 0.5%

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Summary of Demographic Characteristics (Intent-to-Treat)

	Age				
	Mean	Std	N	Min	Max
Treatment					
AL-6221 0.0015%	63.9	11.7	139	11	84
AL-6221 0.004%	63.9	11.1	137	29	89
Vehicle	63.3	11.3	134	37	88

p=0.8780 in analysis of variance

Demographic Statistics By Treatment Group
Intent-to-Treat

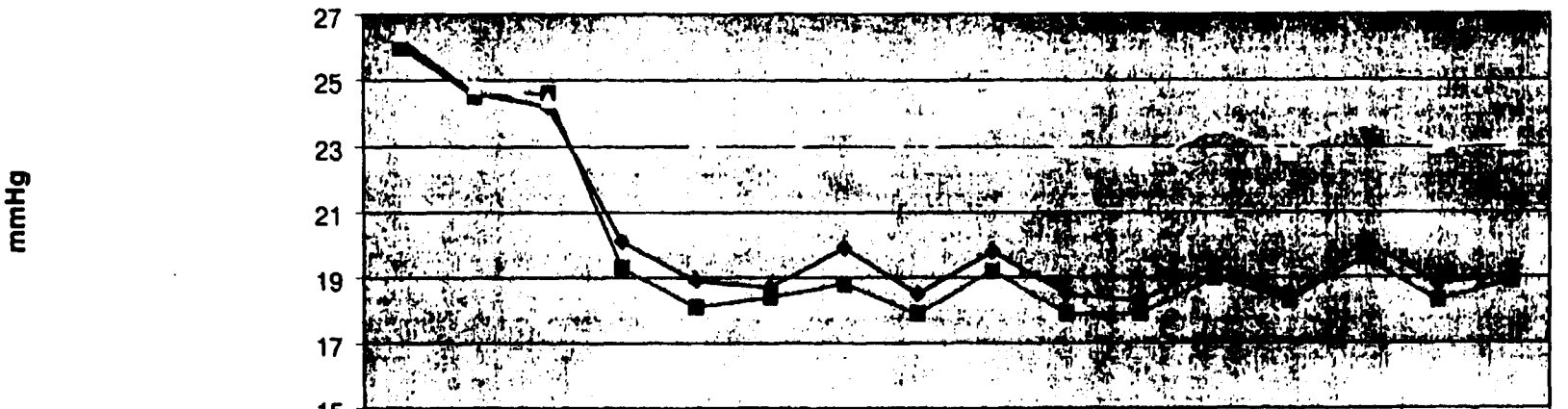
	Treatment						
	AL-6221 0.0015%		AL-6221 0.004%		Vehicle		p-value
	N	%	N	%	N	%	
Age							
<65	70	50.4	65	47.4	71	53.0	0.659[a]
>=65	69	49.6	72	52.6	63	47.0	
Age (>=65)							
>=65 - < 75	45	65.2	47	65.3	39	61.9	0.721[b]
>=75 - < 85	24	34.8	23	31.9	22	34.9	
>=85 - < 95	--	--	2	2.8	2	3.2	
Sex							
MALE	59	42.4	65	47.4	56	41.8	0.588[a]
FEMALE	80	57.6	72	52.6	78	58.2	
Race							
CAUCASIAN	103	74.1	86	62.8	94	70.1	0.301[b]
BLACK	27	19.4	35	25.5	32	23.9	
ASIAN	--	--	2	1.5	1	0.7	
OTHER	9	6.5	14	10.2	7	5.2	
Iris Color							
BROWN	72	51.8	85	62.0	64	47.8	0.309[c]
HAZEL	17	12.2	16	11.7	17	12.7	
GREEN	6	4.3	2	1.5	5	3.7	
BLUE	44	31.7	33	24.1	46	34.3	
GREY	--	--	1	0.7	2	1.5	
Diagnosis (ICD9)							
OCULAR HYPERTENSION	8	5.8	14	10.2	13	9.7	0.447[b]
OPEN-ANGLE GLAUCOMA NOS	126	90.6	118	86.1	116	86.6	
PIGMENTARY GLAUCOMA	4	2.9	1	0.7	2	1.5	
PSEUDOEXFOLIAT GLAUCOMA	1	0.7	4	2.9	3	2.2	

a. p-value from chi square test of independence
b. p-value from Fisher's exact test
c. p-value from chi-square test of independence since execution time for the exact test was too long.

8.1.4 Efficacy – Protocol C-97-73 Intent-to-Treat Population

Primary Efficacy Variable

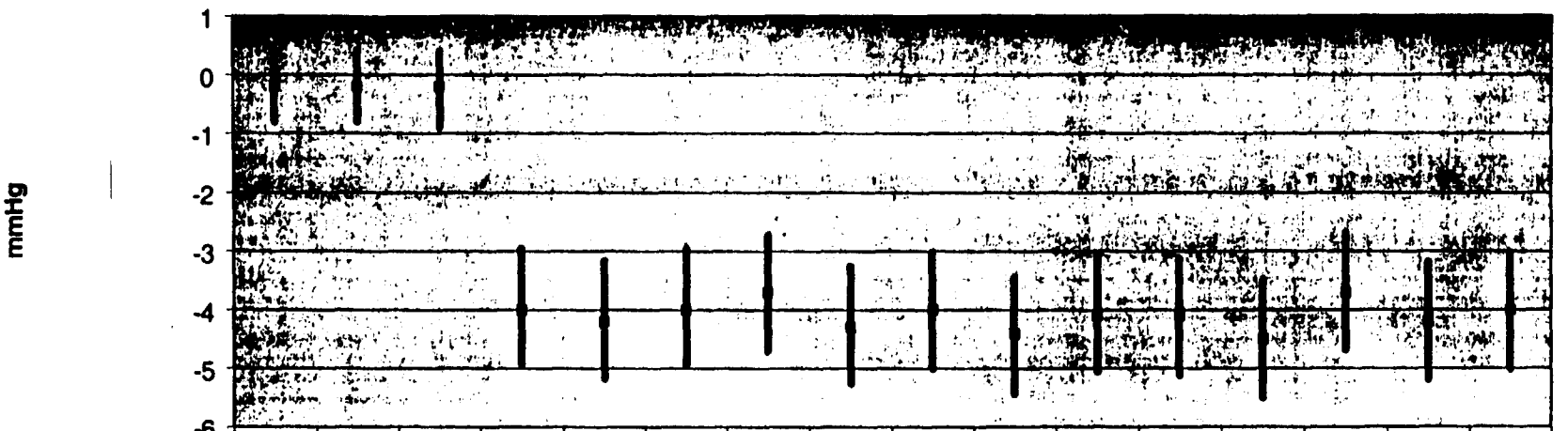
Mean IOP per Visit and Time



	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
AL-6221 0.0015% + T1/2	26.2	24.6	24.2	20.1	18.9	18.7	19.9	18.5	19.8	18.5	18.3	19.4	18.3	20.1	18.8	19.1
AL-6221 0.004% + T1/2	26	24.5	24.6	19.3	18.1	18.4	18.8	17.9	19.2	17.9	17.9	19	18.3	19.6	18.3	18.9
AL-6221 Vehicle + T1/2	26.4	24.8	24.4	24.1	23.1	22.6	23.6	22.8	23.8	22.9	22.4	23.6	22.8	23.8	23	23.1

Reviewer's Comments: *Baseline mean IOP of the three treatment arms is similar. In patients with mean baseline IOP of 24.2 to 26.4 mmHg, the mean IOP of both concentrations of AL-6221 (0.0015% and 0.004%) + Timoptic 0.5% is lower than AL-6221 Vehicle + Timoptic 0.5% at all time points measured. AL-6221 0.0015% + Timoptic 0.5% and AL-6221 0.004% + Timoptic 0.5% demonstrate similar ability to lower IOP over visit days and time.*

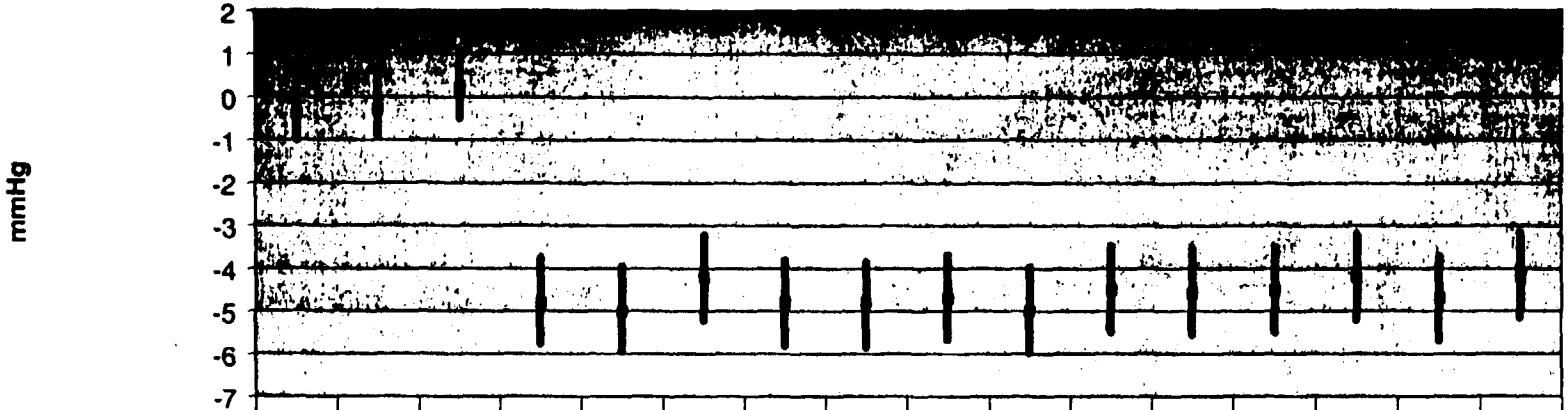
Mean Difference (AL-6221 0.0015% + Timoptic 0.5% - AL-6221 Vehicle + Timoptic 0.5%) with 95% Confidence Intervals



	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
Lower CI	-0.8	-0.8	-0.9	-4.94	-5.17	-4.94	-4.71	-5.25	-5.01	-5.43	-5.06	-5.12	-5.5	-4.68	-5.19	-5.02
Upper CI	0.4	0.4	0.4	-2.96	-3.18	-2.96	-2.73	-3.27	-3.02	-3.45	-3.07	-3.14	-3.52	-2.69	-3.2	-3.03
■ Mean Difference	-0.2	-0.2	-0.2	-4	-4.2	-4	-3.7	-4.3	-4	-4.4	-4.1	-4.1	-4.5	-3.7	-4.2	-4

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% + Timoptic 0.5% and AL-6221 Vehicle + Timoptic 0.5% is statistically significant at all time points and ranges from –3.7 to –4.5 mmHg. AL-6221 0.0015% dosed QPM when used adjunctively with Timoptic 0.5% BID demonstrates additional IOP lowering by a clinically significant amount.*

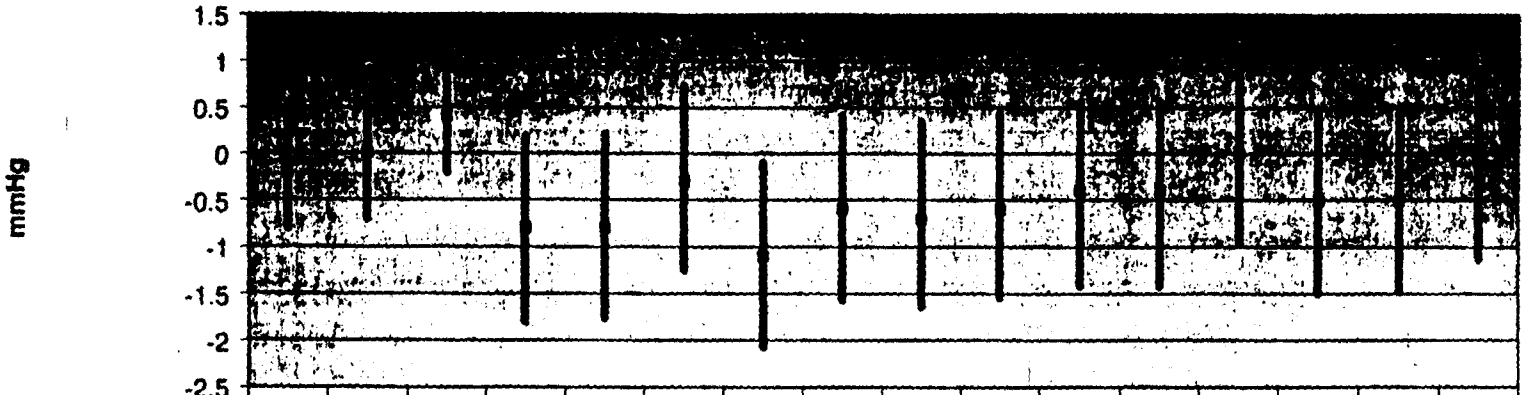
Mean Difference (AL-6221 0.004% + Timoptic 0.5% - AL-6221 Vehicle + Timoptic 0.5%) with 95% Confidence Intervals



	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
Lower CI	-1	-0.9	-0.5	-5.76	-5.95	-5.21	-5.81	-5.84	-5.66	-5.99	-5.49	-5.55	-5.49	-5.2	-5.69	-5.16
Upper CI	0.3	0.4	0.8	-3.77	-3.96	-3.22	-3.82	-3.85	-3.67	-4	-3.5	-3.56	-3.5	-3.21	-3.7	-3.17
■ Mean Difference	-0.4	-0.3	0.2	-4.8	-5	-4.2	-4.8	-4.8	-4.7	-5	-4.5	-4.6	-4.5	-4.2	-4.7	-4.2

Reviewer's Comments: *Baseline 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% + Timoptic 0.5% and AL-6221 Vehicle + Timoptic 0.5% is statistically significant at all time points and ranges from –4.2 to –5.0 mmHg. AL–6221 0.004% dosed QPM when used adjunctively with Timoptic 0.5% BID demonstrates additional IOP lowering by a clinically significant amount.*

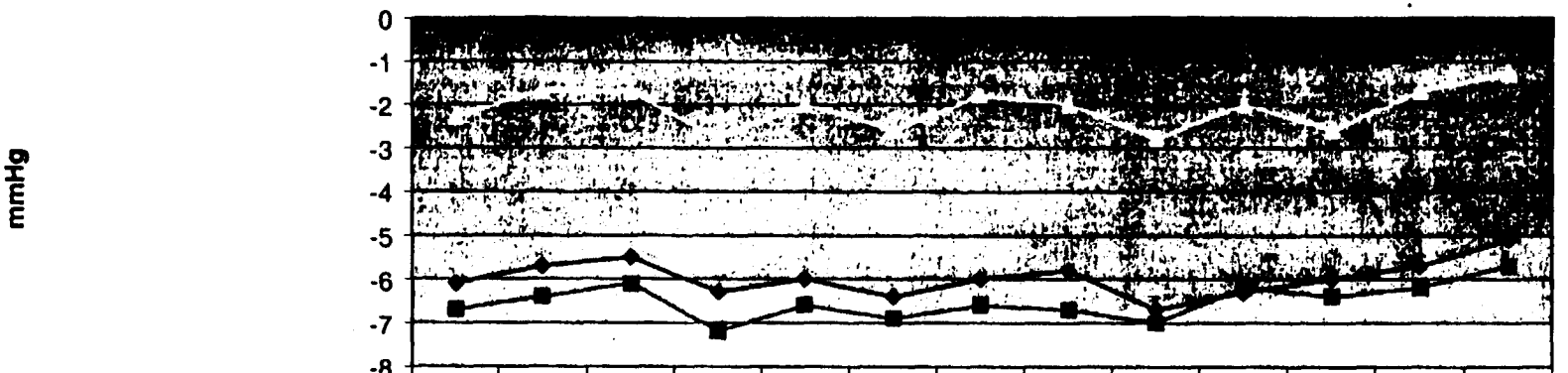
Mean Difference (AL-6221 0.004% + Timoptic 0.5% - AL-6221 0.0015% + Timoptic 0.5%) with 95% Confidence Intervals



	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
Lower CI	-0.8	-0.7	-0.2	-1.8	-1.76	-1.25	-2.08	-1.57	-1.64	-1.54	-1.42	-1.42	-0.97	-1.5	-1.48	-1.13
Upper CI	0.5	0.6	1.1	0.17	0.21	0.72	-0.11	0.4	0.33	0.43	0.55	0.55	1	0.47	0.49	0.84
■ Mean Difference	-0.2	0	0.4	-0.8	-0.8	-0.3	-1.1	-0.6	-0.7	-0.6	-0.4	-0.4	0	-0.5	-0.5	-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. The mean difference between the mean IOP of AL-6221 0.0015% + Timoptic 0.5% and AL-6221 0.004% + Timoptic 0.5% is not statistically significant at almost all time points. The 95% confidence interval crosses zero at all time points except Month 1.5 8AM. The IOP reduction produced by AL-6221 0.015% dosed QPM + Timoptic 0.5% and AL-6221 0.004% + Timoptic 0.5% does not differ by a clinically significant amount.*

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
AL-6221 0.0015% + T1/2	-6.1	-5.7	-5.5	-6.3	-6	-6.4	-6	-5.8	-6.7	-6.3	-6	-5.7	-5.1
AL-6221 0.004% + T1/2	-6.7	-6.4	-6.1	-7.2	-6.6	-6.9	-6.6	-6.7	-7	-6.2	-6.4	-6.2	-5.7
AL-6221 Vehicle + T1/2	-2.3	-1.7	-1.7	-2.8	-2	-2.6	-1.8	-2	-2.8	-2	-2.6	-1.7	-1.3

Reviewer's Comments: *When corrected for baseline, AL-6221 0.0015% + Timoptic 0.5% and AL-6221 0.004% + Timoptic 0.5% consistently lower IOP more than AL-6221 Vehicle + Timoptic 0.5% over visit days and time, in patients with mean baseline IOP of 24.2 to 26.4 mmHg. The IOP lowering ability of the two concentrations of AL-6221 (0.0015% and 0.004%) dosed QPM when used adjunctively with Timoptic 0.5% dosed BID is similar. The change in mean IOP from baseline ranges from –5.1 to –6.7 mmHg for AL-6221 0.0015% + Timoptic 0.5% and from –5.7 to –7.2 mmHg for AL-6221 0.004% + Timoptic 0.5% as compared to –1.3 to -2.8 mmHg for AL-6221 Vehicle + Timoptic 0.5%.*

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8.1.4 Safety

Adverse Events

Serious adverse events other than death were reported for 6/142 (4.2%) subjects treated with AL-6221 0.0015% + Timoptic 0.5%, 2/145 (1.4%) subjects treated with AL-6221 0.004% + Timoptic 0.5%, and 4/139 (2.9%) subjects treated with AL-6221 Vehicle + Timoptic 0.5%. These other serious adverse events did not result in premature discontinuation from the study for any of the subjects.

Other Serious Adverse Events

Investigator Number	Patient Number	Treatment	Coded Adverse Event	Outcome of Event	D/C from Study
2348	7109	AL-6221 0.0015%+T1/2	Lung Disease	Resolved w/Tx	No
1236	3606	AL-6221 0.0015%+T1/2	Pneumonia	Resolved w/Tx	No
			Neuralgia	Resolved w/Tx	No
			Arthritis	Resolved w/Tx	No
			Pain Chest	Resolved w/Tx	No
989	5401	AL-6221 0.0015%+T1/2	Pneumonia	Resolved w/Tx	No
1939	7906	AL-6221 0.0015%+T1/2	Hypoglycemia	Resolved w/Tx	No
1007	5721	AL-6221 0.0015%	Accidental Injury	Resolved w/Tx	No
			Pain	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
394	7406	AL-6221 0.0015%+T1/2	Surgical/Medical Proc	Resolved w/Tx	No
1806	5221	AL-6221 0.004%+T1/2	Heart Failure	Resolved w/Tx	No
1806	5203	AL-6221 0.004%+T1/2	Thrombosis Retinal Vein	Resolved wo/Tx	No
2182	7201	Al-6221 Vehicle+T1/2	Carcinoma breast	Resolved w/Tx	No
989	5431	Al-6221 Vehicle+T1/2	Dyspnea	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
989	5430	Al-6221 Vehicle+T1/2	Cholecystitis	Resolved w/Tx	No
			Surgical/Medical Proc	Resolved w/Tx	No
1892	8101	Al-6221 Vehicle+T1/2	Surgical/Medical Proc	Resolved w/Tx	No

T1/2 = Timoptic 0.5%
D/C Pt = Discontinued Patient

One death occurred during the study:

Subject 3508 (AL-6221 Vehicle + Timoptic 0.5%) was an 85 year-old Caucasian male with a history of hypertension, open-angle glaucoma, and cataracts who experienced a severe myocardial infarction on Study Day 79 while playing golf and died that day.

Six subjects (4.2%) receiving AL-6221 0.0015% + Timoptic 0.5%, eight subjects (5.5%) receiving AL-6221 0.004% + Timoptic 0.5%, and two subjects (1.4%) receiving AL-6221 Vehicle + Timoptic 0.5% 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	Timoptic 0.5% + AL-6221		
	0.0015% N=142	0.004% N=145	Vehicle N=139
	N (%)	N (%)	N (%)
All events	83 (58.4)	84 (57.9)	60 (43.2)
OCULAR			
Hyperemia Eye	33 (23.2)	52 (35.9)	13 (9.4)
Inflammatory Cells Aqueous	7 (4.9)	6 (4.1)	
Discomfort Eye	7 (4.9)	7 (4.8)	3 (2.2)
Keratitis	7 (4.9)	3 (2.1)	5 (3.6)
Aqueous Flare	5 (3.5)	2 (1.4)	
Pruritus Eye	4 (2.8)	5 (3.4)	2 (1.4)
Visual Acuity Decrease	4 (2.8)	6 (4.1)	5 (3.6)
Blepharitis	3 (2.1)	2 (1.4)	
Eye Disease	3 (2.1)		
Foreign Body Sensation	3 (2.1)	4 (2.8)	
Pain Eye	3 (2.1)	6 (4.1)	
Vision Blurred	3 (2.1)	3 (2.1)	2 (1.4)
Conjunctivitis	2 (1.4)	2 (1.4)	
Hemorrhage Retinal	2 (1.4)		
Iritis	2 (1.4)		
Surgical/Medical Proc	2 (1.4)		
Vitreous Disease	2 (1.4)		
Dry Eye		8 (5.5)	
Tearing		3 (2.1)	
Eye Fatigue		2 (1.4)	
Lid Disease		3 (2.1)	
Optic Nerve Disease			2 (1.4)
Photophobia		4 (2.8)	
Sticky Sensation		2 (1.4)	
Vision Abnormal			2 (1.4)
Body As A Whole			
Infection	7 (4.9)	3 (2.1)	3 (2.2)
Injury Accidental	5 (3.5)		3 (2.2)
Surgical/Medical Proc	5 (3.5)	4 (2.8)	6 (4.3)
Cold Syndrome	4 (2.8)	3 (2.1)	
Allergy	3 (2.1)	2 (1.4)	
Pain back	3 (2.1)		
Allergic Reaction	2 (1.4)		
Headache	2 (1.4)	2 (1.4)	
Pain			4 (2.9)
Flu Syndrome		2 (1.4)	2 (1.4)
Cardiovascular System			
Hypertension	5 (3.5)	2 (1.4)	2 (1.4)
Hypotension	2 (1.4)		
Coronary Artery Disease			2 (1.4)
Digestive System			
Constipation	2 (1.4)		
Dyspepsia			2 (1.4)
GI Disease			3 (2.2)

Coded Adverse Event	Timoptic 0.5% + AL-6221		
	0.0015% N=142	0.004% N=145	Vehicle N=139
	N (%)	N (%)	N (%)
NON-OCULAR			
Musculo-Skeletal System			
Arthritis	3 (2.1)		
Bone Fract Spontaneous	2 (1.4)		
Nervous System			
Dizziness	2 (1.4)		
Insomnia	2 (1.4)		
Anxiety			2 (1.4)
Depression		2 (1.4)	
Respiratory System			
Sinusitis	3 (2.1)	3 (2.1)	2 (1.4)
Dyspnea	2 (1.4)		
Pneumonia	2 (1.4)		
Rhinitis			3 (2.2)
Skin And Appendages			
Dermatitis	2 (1.4)		
Special Senses			
Otitis Media	3 (2.1)		
Urogenital System			
Infection Urinary Tract		3 (2.1)	
Prostate Disease		2 (1.4)	

Ocular Hyperemia

A statistically significant difference (p=0.0001) in ocular hyperemia was observed among the treatment groups. A study drug concentration-related increase in ocular hyperemia was observed in subjects receiving AL-6221 (0.0015% and 0.004%) + Timoptic 0.5% compared to subjects receiving AL-6221 Vehicle + Timoptic 0.5%.

Frequency and Incidence of in Ocular Hyperemia

Treatment	Number Randomized	N	%
AL-6221 0.0015% + T1/2	142	33	23.2
AL-6221 0.004% + T1/2	145	52	35.9
AL-6221 Vehicle + T1/2	139	13	9.4

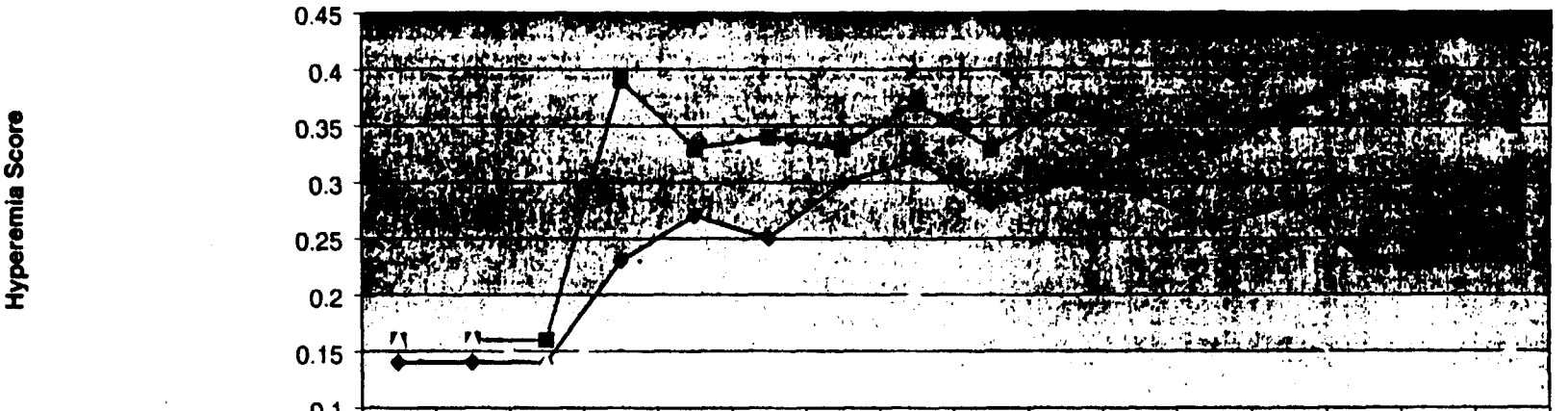
T1/2 = Timoptic 0.5%

Frequency and Incidence of Discontinued Patients Due to Ocular Hyperemia

Treatment	Number Randomized	N	%
AL-6221 0.0015% + T1/2	142	1	0.7%
AL-6221 0.004% + T1/2	145	2	1.4%
AL-6221 Vehicle + T1/2	139	0	0

T1/2=Timoptic 0.5%

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
AL-6221 0.0015% + T1/2	0.14	0.14	0.14	0.23	0.27	0.25	0.3	0.32	0.28	0.3	0.29	0.26	0.28	0.23	0.23	0.23
AL-6221 0.004% + T1/2	0.16	0.16	0.16	0.39	0.33	0.34	0.33	0.37	0.33	0.37	0.33	0.33	0.36	0.4	.0.39	0.35
AL-6221 Vehicle + T1/2	0.16	0.16	0.14	0.16	0.16	0.16	0.19	0.2	0.17	0.17	0.17	0.17	0.17	0.13	0.14	0.15

Reviewer's Comments: *Baseline mean hyperemia score for the three treatment arms is similar. The mean hyperemia score for AL-6221 0.0015% dosed QPM + Timoptic 0.5% dosed BID and AL-6221 0.004% dosed QPM + Timoptic 0.5% dosed BID is consistently higher than for AL-6221 Vehicle dosed QPM + Timoptic 0.5% dosed BID. A concentration related increase in mean hyperemia score is associated with AL-6221.*

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Visual Acuity

No statistically significant difference (p=0.379) in visual acuity from baseline to final visit was observed among treatment groups.

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

	Treatment Group			
Line Changes	T1/2 + AL-6221 0.0015% N (%)	T1/2 + AL-6221 0.004% N (%)	T1/2 + AL-6221 Vehicle N (%)	Total N (%)
N	139	143	139	421
≥ 2 lines loss	4 (2.9)	9 (6.3)	6 (4.3)	19 (4.5)
1 line loss	25 (18.0)	34 (23.8)	29 (20.9)	88 (20.9)
No Change	97 (69.8)	93 (65.0)	90 (64.7)	280 (66.5)
1 line gain	12 (8.6)	6 (4.2)	10 (7.2)	28 (6.7)
≥ 2 lines gain	1 (0.7)	1 (0.7)	4 (2.9)	6 (1.4)

T1/2=Timoptic 0.5%
Patients 4711, 7302 (AL-6221 0.0015%) and 3805 (AL-6221 0.004%) had no follow-up data.
Patients 4708 (AL-6221 0.0015%) and 4712 (AL-6221 0.004%) had no baseline data.

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

	Treatment Group			
Line Changes	T1/2 + AL-6221 0.0015% N (%)	T1/2 + AL-6221 0.004% N (%)	T1/2 + AL-6221 Vehicle N (%)	Total N (%)
N	139	143	139	421
≥ 2 lines loss	9 (6.5)	9 (6.3)	9 (6.5)	27 (6.4)
1 line loss	32 (23.0)	36 (25.2)	19 (13.7)	87 (20.7)
No Change	56 (40.3)	63 (44.1)	56 (40.3)	175 (41.6)
1 line gain	40 (28.8)	33 (23.1)	52 (37.4)	125 (29.7)
≥ 2 lines gain	2 (1.4)	2 (1.4)	3 (2.2)	7 (1.7)

T1/2=Timoptic 0.5%
Patients 4711, 7302 (AL-6221 0.0015%) and 3805 (AL-6221 0.004%) had no follow-up data.
Patients 4708 (AL-6221 0.0015%) and 4712 (AL-6221 0.004%) had no baseline data.

Iris Pigmentation Change

No iris pigmentation change was observed for any subject over the course of the study.

Eyelashes

A statistically significant ($p \leq 0.001$) difference in the percent of patients with eyelash change at Months 3, 4.5 and 6 were observed between treatment groups. Additionally, a statistically difference in changes in eyelash color, length, density, and thickness ($p=0.001$) was observed among treatment groups.

A study drug concentration related increase in eyelash change (color, length, density, and thickness) from baseline was observed in subjects receiving AL-6221 (0.0015% and 0.004%) + Timoptic 0.5%.

Percent of Subjects with Eyelash Change by Category

Treatment	Total N	Change Reported N[a]	Change Reported %	Color Change N[a]	Color Change %	Length Change N[a]	Length Change %	Density Change N[a]	Density Change %	Thickness Change N[a]	Thickness Change %
AL-6221 0.0015%+Tim	136	51	37.5	39	28.7	51	37.5	48	35.3	40	29.4
AL-6221 0.004%+Tim	139	72	51.8	58	41.7	72	51.8	69	49.6	65	46.8
Vehicle+Tim	131	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

p <= 0.001 in all categories from chi-square test comparing treatment groups.
Twenty patients contributed no eyelash change data: 6 AL-6221 0.0015%, 6 AL-6221 0.004% and 8 Vehicle patients.
Tim = TIMOPTIC 0.5%
[a]N=patients with eyelash change by category at any visit after Eligibility 2 (baseline).

Percent of Subjects with Eyelash Change by Visit

Treatment		Visit MONTH 1.5[a]	MONTH 3	MONTH 4.5	MONTH 6	EARLY EXIT
AL-6221 0.0015% + TIMOPTIC 0.5%	%	0.0	17.2	32.5	40.9	23.1
	N[b]	0	21	38	47	3
	Total N	126	122	117	115	13
AL-6221 0.004% + TIMOPTIC 0.5%	%	0.8	46.0	48.4	56.3	9.1
	N[b]	1	57	60	71	1
	Total N	123	124	124	126	11
Vehicle + TIMOPTIC 0.5%	%	0.0	0.0	0.0	0.0	0.0
	N[b]	0	0	0	0	0
	Total N	113	102	101	96	28
	p-value	0.652	0.001	0.001	0.001	0.023

p-values from Fisher's Exact test comparing treatment groups.
Twenty patients contributed no eyelash change change data: 6 AL-6221 0.0015%, 6 AL-6221 0.004% and 8 Vehicle patients. See **Error! Bookmark not defined.** for a listing of these 20 patient numbers.
[a]The following patients had no eyelash data at Month 1.5: AL-6221 0.0015%- Pats. 3601, 3804, 4708, 4711, 5208, 5231, 5601, 6001, 6501, 6804, 7102, 7111, 7113, 7124, 7302, 7702; AL-6221 0.004%-3603, 3605, 3611, 3614, 3706, 3805, 4702, 4706, 4709, 4712, 5209, 5403, 5405, 5418, 5517, 6007, 6803, 7101, 7104, 7404, 8008, 8107; and Vehicle-Pats. 3602, 3610, 4202, 4607, 4703, 4707, 4710, 5207, 5228, 5406, 5424, 5430, 5439, 5440, 5505, 6002, 6105, 6121, 7103, 7105, 7107, 7115, 7116, 7407, 7705, 7913.
[b]N=number of patients with eyelash change at that visit only.

Reviewer's Comments:

A change in eyelash color, length, density, and thickness is consistent with an ocularly administered prostaglandin-type effect. Whether the changes are purely cosmetic or have safety implications have not been determined.

Aqueous Flare and Inflammatory Cells

No statistically significant difference in increase from baseline for ocular flare (p=0.55) or inflammatory cells (p=0.053) were observed among treatment groups.

Five of the 134 subjects (3.6%) receiving AL-6221 0.0015% + Timoptic 0.5%, two of the 141 subjects (1.4%) receiving AL-6221 0.004% + Timoptic 0.5%, and no subjects receiving AL-6221 Vehicle + Timoptic 0.5% experienced an increase from baseline in ocular flare.

Eight of the 131 subjects (5.8%) receiving AL-6221 0.0015% + Timoptic 0.5%, six of the 137 subjects (4.2%) receiving AL-6221 + Timoptic 0.5%, and one of the 137 subjects (0.7%) receiving AL-6221 Vehicle + Timoptic 0.5% experienced an increase from baseline in inflammatory cells.

One of the 142 subjects (0.7%), two of the 145 subjects (1.4%) receiving AL-6221 0.004% + Timoptic 0.5%, and one of the 139 subjects (0.7%) receiving AL-6221 Vehicle + Timoptic 0.5% discontinued from the study due to ocular cells and/or flare.

Cup/Disc Ratio

No clinically or statistically significant difference (p=0.7997) in increase of cup/disc ratio from baseline was observed among treatment groups.

Visual Field

For subjects analyzed with the [redacted] (425 subjects), no clinically or statistically significant difference was observed among treatment groups for visual field mean deviation (p=0.9379) or corrected pattern standard deviation (p=0.3341) change from baseline.

Seven of the subjects receiving AL-6221 0.0015% + Timoptic 0.5%, four of the subjects receiving AL-6221 0.004% + Timoptic 0.5%, and twelve of the subjects receiving AL-6221 Vehicle + Timoptic 0.5% had no baseline of exit data for mean deviation. Eight of the subjects receiving AL-6221 0.0015% + Timoptic 0.5%, nine of the subjects receiving AL-6221 0.004% + Timoptic 0.5%, and fourteen of the subjects receiving AL-6221 Vehicle + Timoptic 0.5% had no baseline or exit data for corrected pattern standard deviation.

Ocular Signs

No statistically significant difference for cornea (p=0.332), for iris/anterior chamber (p=0.553). lens (p=1.000), or for vitreous (p=1.000) in increase of ocular signs was observed among treatment groups.

A clinically significant increase from baseline in ocular signs was observed in nine of the 139 subjects (6.5%) receiving AL-6221 0.0015% + Timoptic 0.5%, six of the 143 subjects (4.2%) receiving AL-6221 0.004% + Timoptic 0.5%, and seven of the 138 subjects (5.1%) receiving AL-6221 Vehicle + Timoptic 0.5%.

Dilated Fundus Examination

No statistically significant difference was observed among treatment groups for retina/macula/choroid (p=0.650), optic nerve (p=0.102), or disc pallor (p=0.320) in increase of fundus parameters.

One of the 135 subjects (0.7%) receiving AL-6221 0.0015% + Timoptic 0.5% experienced retina/macula/choroid changes. Three of the 131 subjects (2.3%) receiving AL-6221 Vehicle + Timoptic 0.5% experienced optic nerve changes or optic disc pallor.

Vital Signs

No clinically or statistically significant difference in pulse (p=0.6808), systolic blood pressure (p=0.5226%), and diastolic blood pressure (p=0.5510) was observed among treatment groups.

Clinical Laboratory Evaluation

No clinical laboratory evaluations were performed.

8.1.4 Reviewer's Summary of Efficacy and Safety

In patients with mean baseline IOP of 24.2 to 26.4 mmHg, AL-6221 0.0015% and AL-6221 0.004% dosed once daily in the evening when used adjunctively with Timoptic 0.5% dosed twice daily produce additional IOP reduction by a clinically significant amount.

The IOP lowering ability of both concentrations of AL-6221 (0.0015% and 0.004%) when used adjunctively with Timoptic 0.5% is similar. The amount of additional IOP reduction ranges from –3.7 to –4.5 mmHg for AL-6221 0.0015% and from –4.2 to –5.0 mmHg for AL-6221 0.004%.

Both concentrations of AL-6221 (0.0015% and 0.004%) are associated with ocular hyperemia. The prevalence of ocular hyperemia is concentration related.

The iris/eyelash photographs read by masked independent readers reveal no iris pigmentation change after six months of therapy with AL-6221 0.0015% and AL-6221 0.004%.

The iris/eyelash photographs read by masked independent readers reveal a concentration related change in eyelash color, length, density, and thickness consistent with an ocularly administered prostaglandin-type effect. The prevalence increases with duration of therapy.

APPEARS THIS WAY
ON ORIGINAL

8.1.5 Study #5 Protocol C-97-79

Title: A Nine-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% 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 9AM and 9PM for 9 months.

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
707	**Jacqueline Collignon Brach, M.D.** Domaine du Sart Tilman B-4000 Liege, Belgium	08	08	05
766	**Ivan Goldberg, M.D.** 187 Macquarie St Sydney NSW 2001, Australia	29	29	27
906	**Jose Cunha-Vaz, M.D.** Azinhaga Santa Comba-Celas 3000 Coimbra, Portugal	30	30	30
1218	**Philippe Denis, M.D.** 5 place d'Arsonval 69003 Lyon, France	03	03	02
1487	**Alain Bron, M.D.** 3, rue du Faubourg Raines 21030 Dijon, France	06	06	05
1493	**Luigi Cardia, M.D.** Piazza Giulio Cesare, 11 70124 Bari, Italy	06	06	02
1608	**Pedro Corsino Fernandez-Vila, M.D.** 15705-Santiago de Compostela La Coruna, Spain	16	16	12
1663	**Jose Carlos Pastor, M.D.** Avda. Ramon y Cajal 5-7 47033 Valladolid, Spain	04	04	03
1685	**Alain Bechetoille, M.D.** Avda. Ramon y Cajal 5-7 47005 Valladolid, Spain	12	12	12
1687	**C.A.B. Webers, M.D.** NL-6206 AZ Maastricht Netherland	0	0	0

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
1696	**Miquel Angel Teus Guezala, M.D.** 28805 – Alcal de Henares Madrid, Spain	10	10	09
1700	**Colm J. O'Brien, M.D.** Eccles Street Dublin 7, Eire	0	0	0
1714	**Adrian Farinelli, M.D.** Marquarie St Sydney NSW 2001, Australia	06	06	02
1715	**Julian Rait, M.D.** 32 Gisborne St East Melbourne 3002, Australia	10	10	08
1717	**Mark Loane, M.D.** Auchenflower 4066 Brisbane, Australia	11	11	10
1729	**Hans-Joachim Belger, M.D.** Domhof 15-21 48683 Ahaus, Germany	07	07	07
1732	**Jean-Philippe Nordmann, M.D.** 4, rue de la Chine 75970 Paris Cedex 20, France	12	12	12
1764	**Jose Jordano Perez, M.D.** Ctra. Nacional IV, Km. 665 11510 – Cadiz, Spain	10	10	09
1792	**Jean-Francois Rouland, M.D.** 2 av. Oscar Lambret 59037 Lille Cedex, France	04	03	02
1802	**Marc Pericoi, M.D.** 1, Place de Belgique 92400 Courbevoie, France	01	01	01
1804	**Andreas Matt, M.D.** Im Weidenbruch 145 51061 Koln, Germany	06	06	06
1820	**Allan Bank, M.D.** 303 Pacific Highway Lindfield 2070 Sydney, Australia	19	19	19
1824	**Philippe Kestelijn, M.D.** De Pintelaan 185 B-9000 Gent, Belgium	01	01	01
1829	**Danielle Sangers, M.D.** Esdoornenlaan 14 B-3090 Overijse, Belgium	10	10	08

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
1833	**Peter Wiedemann, M.D.** Liebigstr. 10-14 04103 Leipzig, Germany	11	11	09
1836	**Rosario Brancato, M.D.** Via Olgettina, 60 20100 Milano, Italy	09	09	09
1841	**Peter K. Wishart, M.D.** Prescott Street Liverpool L7 8LX, United Kingdom	08	08	08
1896	**Gilles Lesieur, M.D.** 4 rue Patus Cremat 81000 Albi, France	08	08	07
1897	**Jean-Paul Renard, M.D.** 74, Boulevard de Port-Royal 75230 Paris Cedex 05, France	02	02	02
1898	**Jean-Luc George, M.D.** Rue du Morvan 54511 Vandoeuvre, France	12	12	12
1905	**Hans G. Lemij, M.D.** Schiedamsevest 180 NL-3011 BH Rotterdam, Netherland	0	0	0
1906	**Michele Detry-Morel, M.D.** 10, Ave. Hippocrate B-1200 Bruxelles, Belgium	01	01	01
1984	**Pedro Abrantes, M.D.** Rua Jose A. Serrano 1150 Lisbon, Portugal	12	12	12
1988	**Denis Gruber, M.D.** 34, Place de l'Hotel de Ville 76600 Le Havre, France	04	04	04
2025	**Louis G. Glearkin, M.D.** Arrowe Park Road Upton Wirral L49 5PE United Kingdom	18	18	15
2040	**Anders Heijl, M.D.** Ogonkliniken S-205 02 Malmo, Sweden	02	02	02
2041	**Juhani Airaksinen, M.D.** University Eye Clinic FIN-90220 Oulu, Finland	10	10	09
2042	**John Thygesen, M.D.** Blegdamsvej 9 DK-2100 Kobenhavn O, Denmark	08	08	06

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
2104	**William Huxley Morgan, M.D.** Verdun St Nedlands WA 6009 Perth, Australia	03	03	03
2130	**Peter Wanger, M.D.** Flemminggatan 22 S-112 82 Stockholm, Sweden	0	0	0
2144	**Jon Erik Slagsvoid, M.D.** Postboks 302 N-4801 Arendal, Norway	11	11	10
2149	**Jeremy Diamond, M.D.** Lower Maudlin Street Bristol BS1 2LX, United Kingdom	13	13	09
2154	**Simon Rankin, M.D.** Grosvenor Road Belfast BT12 6BA, United Kingdom	03	03	02
2156	**Ian Cunliffe, M.D.** Bordesley Green East Birmingham B9 5SS, United Kingdom	08	08	08
2168	**Stefano Gandolfi, M.D.** Universita di Parma Via Gramsci 14 43100 Parma, Italy	10	10	10
2178	**Gilles Kretz, M.D.** 150, rue Raymond Losserand 75014 Paris, France	08	08	08
2181	**Alan Dorrer, M.D.** 3, Place Saint Leger 68500 Guebwiller, France	0	0	0
2312	**Paul Stadion, M.D.** 75, rue Lambert Fortune B-1300 Wavre, Belgium	10	10	06
2343	**Bjorn Fristrom, M.D.** I Linkoping Ogonkliniken S-581 85 Linkoping, Sweden	23	23	23
2350	**Jan Erik Jakobsen, M.D.** Kirkeveien 166 N-0407 Oslo, Norway	17	17	16
2351	**Thordur Sverrisson, M.D.** Oldugata 17 IS-101 Reykjavik, Iceland	08	08	08
2352	**Clive Migdal, M.D.** Marylebone Road London NW1 5YE, United Kingdom	03	03	03

Investigator Number	Investigator	Number Randomized	Number in Intent-to-Treat Population	Number in Per Protocol Population
2408	**Joachim Nasemann, M.D.** Weinstrasse 4 80333 Munchen, Germany	06	06	05
2409	**Karin Kernt, M.D.** Sendlingen-Tor-Platz 7 80336 Munchen, Germany	12	12	11
2411	**Wendy Franks, M.D.** City Road London EC1V 2PD, United Kingdom	14	14	14
2412	**Lieve Dralands, M.D.** Kapucijnenvoer 33 B-3000 Leuven, Belgium	22	22	22
2413	**Yves Lachkar, M.D.** 45/47 rue Vineuse 75016 Paris, France	06	06	04
2419	**Paivi Puska, M.D.** Haartmanninkatu 4C FIN-00290 Helsinki, Finland	10	10	10
2425	**Marc de Smet, M.D.** Meibergdreef 9 NL-1105 AZ Amsterdam, Netherlands	07	07	03
2457	**Selim Orgul, M.D.** Mittlere Strasse 91 CH-4012 Basel, Switzerland	10	10	08
2473	**R.J.F. Verkaart, M.D.** 'sGravenpolderseweg 114 NL-4462 RA Goes, Netherlands	12	12	08
2476	**Jean Ferraton, M.D.** 62, rue de Bonnel 69448 Lyon Cedex 03, France	18	18	15
2493	**Robert W.A.M. Kuypers, M.D.** Dr. Molewaterplein 40 NL-3015 GD Rotterdam, Netherlands	02	02	02
2494	**Nils Maren, M.d.** Flemminggatan 22 S-112 82 Stockholm, Sweden	11	11	11

Reviewer's Comments:

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