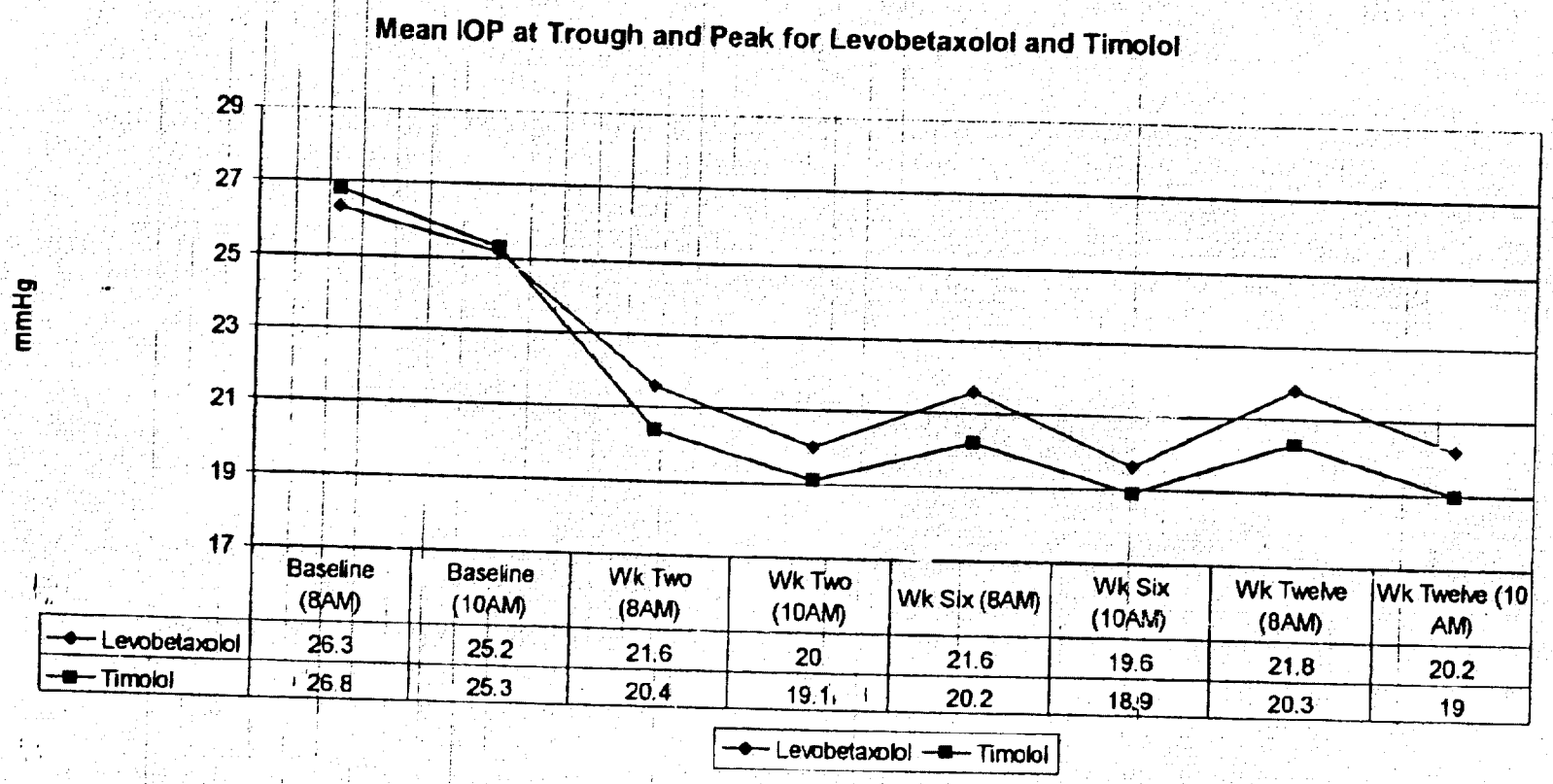
MOR2

8.1.2 Efficacy – Protocol C-97-80 Intent-to-Treat Population

Primary Efficacy Variable



	Baseline (8AM)	Baseline (10AM)	Wk Two (8AM)	Wk Two (10AM)	Wk Six (8AM)	Wk Six (10AM)	Wk Twelve (8AM)	Wk Twelve (10 AM)
Levobetaxolol	26.3	25.2	21.6	20	21.6	19.6	21.8	20.2
Timolol	26.8	25.3	20.4	19.1	20.2	18.9	20.3	19

Table C-97-80-5 - Comparison of Levobetaxolol 0.5% to Timolol 0.5%

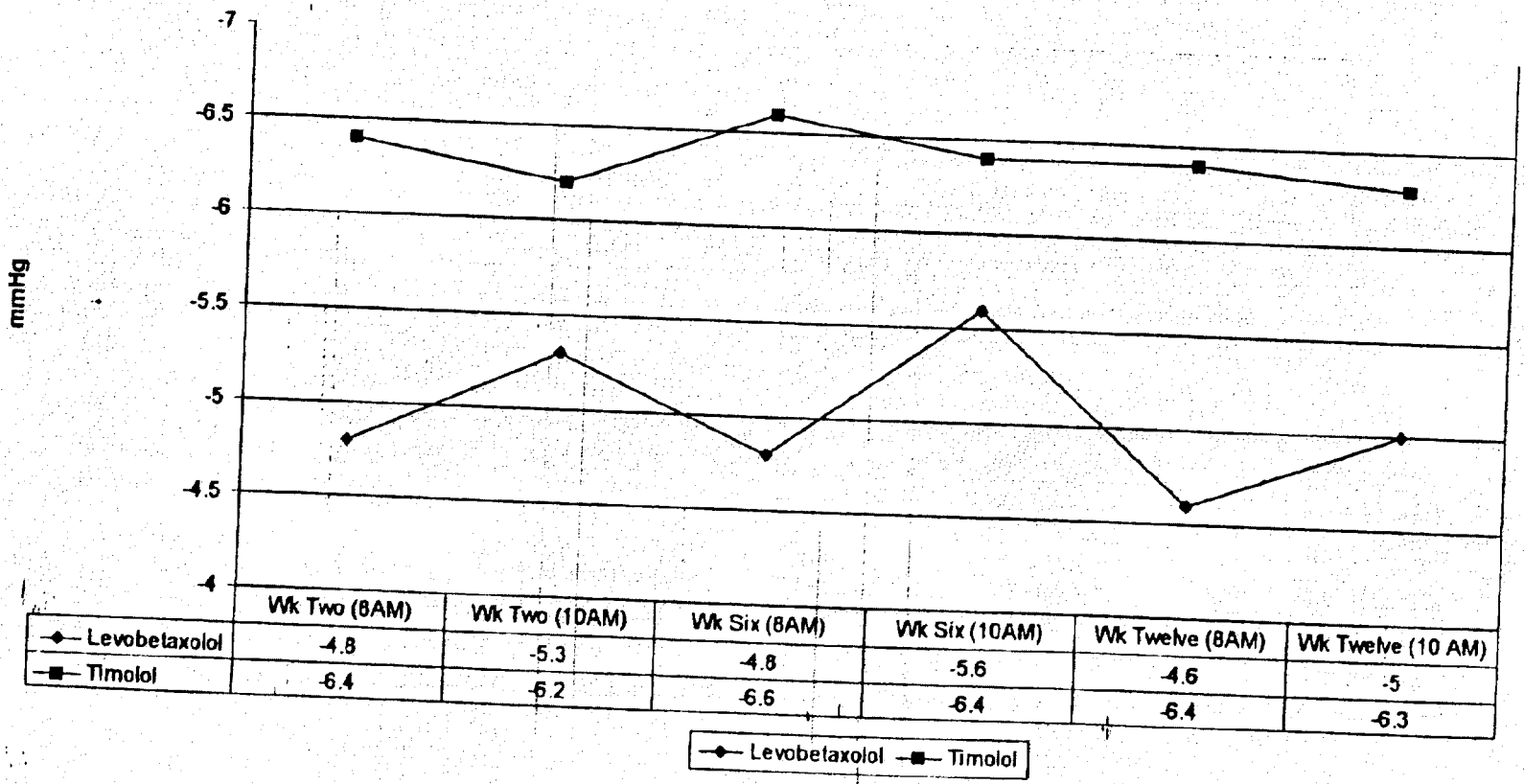
	Intent-to-Treat Data							
	Baseline		Wk 2		Wk 6		Wk 12	
	8	10	8	10	8	10	8	10
Treatment								
Levo	26.3	25.2	21.6	20.0	21.6	19.6	21.8	20.2
Tim	26.8	25.3	20.4	19.1	20.2	18.9	20.3	19.0
Levo-Tim	-0.4	-0.1	1.2	0.8	1.4	0.7	1.4	1.2
p-value	0.2255	0.7462	0.0008	0.0163	0.0003	0.0397	0.0003	0.0007
Upper 95% CI	0.26	0.57	1.87	1.51	2.08	1.39	2.10	1.89
Lower 95% CI	-1.10	-0.79	0.52	0.15	0.72	0.03	0.75	0.53

Reviewer's Comments:

Twice-daily-dosed levobetaxolol 0.5% ophthalmic suspension does not demonstrate equivalence in the ability to lower IOP compared to twice-daily-dosed timolol 0.5% ophthalmic solution.

Mean on-therapy IOPs for timolol 0.5% were statistically significantly lower than those observed for levobetaxolol 0.5% at most time points, and the differences between treatments ranged from 0.7 to 1.4 mmHg. The upper 95% confidence interval limits for the treatment differences ranged from 1.39 to 2.10. These were outside the 1-1.5 mmHg limit necessary to establish statistical equivalence at all but one time point (Wk 6 10AM).

Mean IOP Change From Baseline



	Wk Two (8AM)	Wk Two (10AM)	Wk Six (8AM)	Wk Six (10AM)	Wk Twelve (8AM)	Wk Twelve (10 AM)
Levobetaxolol	-4.8	-5.3	-4.8	-5.6	-4.6	-5
Timolol	-6.4	-6.2	-6.6	-6.4	-6.4	-6.3

Table C-97-80-6 - Mean IOP, Change From Baseline and Percent Change for Levobetaxolol and Timolol by Visit Day

IOP Analysis for Intent-to-Treat Data

Treatment		WK 2 8AM	WK 2 10AM	WK 6 8AM	WK 6 10AM	WK 12 8AM	WK 12 10AM
Tim 0.5%	Mean IOP	20.4	19.1	20.2	18.9	20.3	19.0
	Mean Change	-6.4	-6.2	-6.6	-6.4	-6.4	-6.3
	Percent Change	-23.6	-24.3	-24.5	-25.2	-23.8	-24.4
Levo 0.5%	Mean IOP	21.6	20.0	21.6	19.6	21.8	20.2
	Mean Change	-4.8	-5.3	-4.8	-5.6	-4.6	-5.0
	Percent Change	-18.0	-20.6	-18.2	-22.0	-17.5	-19.5

Reviewer's Comments:

IOP reduction in the timolol group was consistent with the amount of IOP lowering typically observed in other timolol studies.

Levobetaxolol IOP reductions at peak (2 hours post-dose) ranged from 5.0 to 5.6 mmHg (19.5 to 22.0% change) from a baseline of 25.2 mmHg. Levobetaxolol IOP reductions at trough (12 hours post-dose) ranged from 4.6 to 4.8 mmHg (17.5 to 18.2% change) from a baseline of 26.3 mmHg.

These reductions were less than those seen with timolol 0.5% and are consistent with those typically observed with betaxolol.

8.1.2 Safety

Adverse Events

Five of the 174 patients (2.9%) receiving levobetaxolol 0.5% discontinued from the study due to adverse events. See Table C-97-80-1, page 28.

Two of the 174 patients (1.1%) receiving timolol 0.5% discontinued from the study due to adverse events. See Table C-97-80-1, page 28.

One death was reported in a patient receiving levobetaxolol 0.5%. Patient 103 (inv. no. 1208), a 70-year old Caucasian male with a history of gout, high cholesterol, hypertension, cataract, and ocular hypertension who was receiving Levobetaxolol 0.5% experienced a fatal vascular anomaly (aneurysm) on Study Day 57. Concomitant medications included Allopurinol, Cardura, Ecotrin, Ziac, and Zocor.

All other serious adverse events are summarized in the following table.

Table C-97-80-7 - Other Serious Adverse Events

Investigator	Patient	Treatment	Coded Adverse Event	Outcome of Event	D/C Pt from Study
1783	614	Levobetaxolol 0.5%	Surgical/Medical Procedure	Resolved w/Tx	No
271	8332	Timolol 0.5%	Cerebrovasc Accident	Resolved w/Tx	No
1806	7323	Timolol 0.5%	Embolism Leg, Pain	Continuing w/Tx	No

No clinically significant differences in demographics were observed between the total patient population and the subgroups for each treatment, with or without adverse events.

The most frequent ocular events in levobetaxolol 0.5% treated subjects were transient ocular discomfort upon instillation (burning, stinging) which occurred in 11.5 % of patients and blurred vision, which occurred in 2.9 % of patients.

The most frequent ocular events in timolol 0.5% treated were ocular discomfort (burning, stinging) which occurred in 5.2 percent of patients and dry eye, which occurred in 1.7 percent of patients.

Table C-97-80-8 - Overall Frequency and Incidence of Adverse Events

	Levobetaxolol 0.5% N = 174		Timolol 0.5% N = 177	
	N	**%**	**N**	**%**
Ocular				
Discomfort Eye	20	11.5	9	5.2
Vision Blurred	5	2.9	1	0.6
Dry Eye	1	0.6	3	1.7
Foreign Body Sensation	1	0.6	2	1.1
Hem Conjunctivitis	1	0.6		
Keratitis	1	0.6	1	0.6
Pain Eye	1	0.6		
Pallor Optic Disc	1	0.6		
Visual Acuity Dec	1	0.6		
Corneal Lesion			1	0.6
Diplopia			1	0.6
Edema Conjunctival			1	0.6
Eye Discharge			1	0.6
Hem retinal			1	0.6
Hyperemia Eye			1	0.6
Injury Accident			1	0.6
Photophobia			1	0.6
Pruritis Eye			1	0.6
Tearing			1	0.6
Nonocular				
Body as a Whole				
Headache	3	1.7	1	0.6
Asthenia	2	1.1		
Pain Back	2	0.6	1	0.6
Allergy	1	0.6		
Cold Syndrome	1	0.6		
Injury Accident	1	0.6		
Surgical/Medical Proc	1	0.6		
Allergy			4	2.3
Pain			3	1.7
Infection			3	1.7
Pain Neck			2	1.1
			1	0.6

Table C-97-80-8 - Overall Frequency and Incidence of Adverse Events – Continued

	Levobetaxolol 0.5% N = 174		Timolol 0.5% N = 174	
	N	%	N	%
Cardiovascular System				
Bradycardia	2	1.1	1	0.6
Hypertension	2	1.1	3	1.7
Anomaly Vascular	1	0.6		
Heart Block	1	0.6		
Tachycardia	1	0.6		
Cerebrovasc Accid			1	0.6
Emb Leg			1	0.6
Digestive System				
Constipation	1	0.6		
Dyspepsia	1	0.6		
Diarrhea			1	0.6
Endocrine System				
Diabetes Mellitus	2	1.1		
Hypothyroidism			1	0.6
Metabolic/Nutritional Dis				
Gout	1	0.6		
Hypercholesteremia			1	0.6
Musculo-Skeletal System				
Arthritis	2	1.1	1	0.6
Fibro Tendon	1	0.6		
Bursitis			1	0.6
Nervous System				
Anxiety	1	0.6		
Dizziness	1	0.6	1	0.6
Hypertonia	1	0.6		
Respiratory System				
Bronchitis	2	1.1	1	0.6
Pneumonia	1	0.6		
Sinusitis	1	0.6		
Rhinitis			1	0.6
Skin and Appendages				
Alopecia	2	1.1		
Dermatitis	2	1.1		
Psoriasis	1	0.6		

Table C-97-80-8 - Overall Frequency and Incidence of Adverse Events – Continued

	Levobetaxolol 0.5% N = 174		Timolol 0.5% N = 174	
	N	%	N	%
Special Senses				
Pain Ear	1	0.6		
Taste Pervers	1	0.6		
Tinnitus	1	0.6		
Otitis Med			1	0.6

Visual Acuity, Ocular Signs, Dilated Fundus, Cup/Disc Ratio

Reviewer's Comments:

No statistically significant decrease in visual acuity change-from-baseline to final visit was observed between levobetaxolol 0.5% and timolol 0.5%.

No statistically significant difference in worsening of ocular signs (cornea, iris/anterior chamber, lens, vitreous) was observed between levobetaxolol 0.5% and timolol 0.5%.

No statistically significant difference in fundus parameters (retina/macula/choroid, optic nerve) was observed between levobetaxolol 0.5% and timolol 0.5%.

No statistically significant difference in cup/disc ratio was observed levobetaxolol 0.5% and timolol 0.5%.

Systolic/Diastolic Blood Pressure

Reviewer's Comments:

No statistically significant difference in systolic blood pressure was noted between levobetaxolol 0.5% and timolol 0.5%.

No statistically significant difference in diastolic blood pressure was noted between levobetaxolol 0.5% and timolol 0.5%.

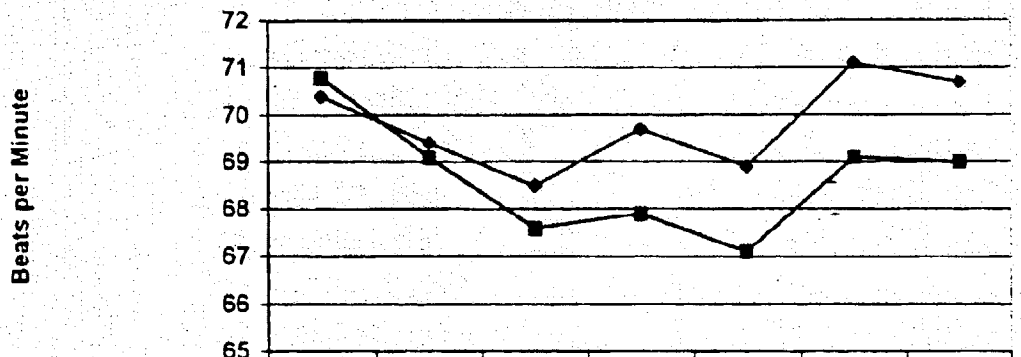
Pulse

A statistically significant ($p = 0.02$) difference was found for pulse change from baseline, with the timolol 0.5% group having a greater reduction in pulse compared to the levobetaxolol 0.5% group.

Reviewer's Comments:

There was also a statistically significant difference found between mean heart rates by treatment group ($p = 0.0023$). This is not a clinically significant difference.

Mean Heart Rate (BPM)



	Baseline (10AM)	Wk Two (8AM)	Wk Two (10AM)	Wk Six (8AM)	Wk Six (10AM)	Wk 12 (8AM)	Wk 12 (10 AM)
Levobetaxolol	70.4	69.4	68.5	69.7	68.9	71.1	70.7
Timolol	70.8	69.1	67.6	67.9	67.1	69.1	69

8.1.2 Reviewer's Summary of Efficacy and Safety

Twice-daily-dosed levobetaxolol 0.5% ophthalmic suspension does not demonstrate equivalence in the ability to lower IOP compared to twice-daily-dosed timolol 0.5% ophthalmic solution. Levobetaxolol IOP reductions at peak [redacted] and at trough [redacted] are clinically relevant.

Adverse experiences appeared generally mild-moderate in nature.

8 Clinical Studies

8.1.3 Study #3 Protocol C-97-40

Title: A Four-Week, Multicenter, Triple-Masked, Placebo-Controlled, Dose-Response Study of the Safety and Efficacy of (S)- Betaxolol Suspension Compared to TIMOPTIC 0.5% and BETOPTIC 0.5% in the Treatment of Patients with Primary Open-Angle Glaucoma or Ocular Hypertension.

[Note: S-Betaxolol was the original drug substance designation; this has since been changed to Levobetaxolol]

Objective: The objective of this placebo-controlled, dose-response study was to evaluate the safety and IOP-lowering efficacy of S-Betaxolol Ophthalmic Suspension compared to TIMOPTIC® 0.5% and BETOPTIC® 0.5% in patients with primary open-angle glaucoma or ocular hypertension.

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

Test Drug Schedule: Patients were instructed to instill one drop of study medication (either S-Betaxolol 0.75%, S-Betaxolol 0.5%, S-Betaxolol 0.25%, TIMOPTIC 0.5%, BETOPTIC 0.5%, or Placebo) into each eye in the morning at 8 AM, and one drop of study medication into each eye in the evening at 8 PM for twenty-eight (28) days.

Principal investigator Name	Inv. No.	No. Enrolled	Dates of participation
John J. Alpar, M.D.	623	4	8/22/97 to 11/24/97
Gregg Berdy, M.D.	1335	15	8/20/97 to 11/22/97
Moira J. Burke, M.D.	2241	18	8/05/97 to11/04/97
Robert Caine, M.D.	1208	15	8/18/97 to 11/18/97
Moiz Carim, M.D.	2244	7	8/13/97 to 11/14/97
Marcel Estopinal, M.D.	2134	18	8/08/97 to 10/28/97
James Ferguson, Jr.,M.D.	2250	8	8/21/97 to 11/05/97
Mitchell Friedlaender, M.D.	501		IRB approval not obtained No patients enrolled
Gregory M. Hoffpauir, M.D.	2255	13	8/25/97 to 11/06/97
Thomas Mundorf, M.D.	1473	21	8/19/97 to 11/21/97
Al O'Byrne, M.D.	2245	3	8/29/97 to 10/15/97
David S. Rothberg, M.D.	2242	19	8/21/97 to 11/19/97
Kenneth Sall, M.D.	1806	28	8/05/97 to 11/25/97
Martin Schoenberger, M.D.	2246	26	8/14/97 to 12/01/97
J.O. Logan Smith, M.D.	2252		No patients were enrolled
John Snead, M.D.	2251	11	8/21/97 to 11/25/97

Principal investigator Name	Inv. No.	No. Enrolled	Dates of participation
Richard T. Sturm, M.D.	2247	26	8/02/97 to 11/26/97
Brandon Wool, M.D.	2248	24	8/20/97 to 11/24/97

8.1.3 Study Design

This study was a prospective, multicenter (18 sites), triple-masked, parallel-group, active and placebo-controlled, dose-response trial designed to evaluate the safety and efficacy of several concentrations of twice-daily-dosed S-Betaxolol compared to twice-daily-dosed TIMOPTIC 0.5%, BETOPTIC 0.5% and Placebo. Target enrollment to support the statistical power of the study was 30 patients per treatment arm.

Patients enrolled in the study were adults diagnosed with primary open-angle glaucoma (with or without a pseudoexfoliation or pigment dispersion component) or ocular hypertension. Eligible patients who met all inclusion criteria including entry IOP requirements were randomized to one of six treatments, S-Betaxolol 0.25%, S-Betaxolol 0.5%, S-Betaxolol 0.75% twice-daily, or TIMOPTIC 0.5%, twice-daily, or BETOPTIC 0.5%, twice-daily or Placebo Ophthalmic Solution twice-daily for a treatment period of twenty-eight (28) days.

The selection of doses (S-Betaxolol 0.75%, S-Betaxolol 0.5%, S-Betaxolol 0.25%, TIMOPTIC 0.5%, RS-Betaxolol 0.5% and Placebo, (one drop twice-daily) was based on the objectives of this clinical study. The first objective to test the hypothesis that a formulation containing only the S-isomer of Betaxolol had ≥ IOP-lowering efficacy than the racemic mixture. The second objective was to compare the IOP-lowering efficacy of S-Betaxolol to TIMOLOL as an established reference standard for IOP-lowering efficacy.

The IOP measurement times selected represent trough (end of the BID dosing period at 8 AM) and peak (2 hours post-dose at 10 AM) activity for all test drugs. The trough IOP was measured at the end of the dosing period, prior to instillation of the next dose. The peak IOP was measured two (2) hours after dose instillation.

Study Medications

The masked test medications used during the treatment phase were supplied in masked 5 mL [redacted] labeled with the appropriate patient number. The drug lot numbers used in this study according to treatment group are displayed below.

Reviewer's Comments:

The identity of the placebo used in this trial is unclear. The Study Report and Protocol refer to it only as an "ophthalmic solution." A phone message left by Scott Kruger of Alcon indicated the placebo was probably the vehicle of Betoptic.

Table C-97-40-1 - Study Medications

Treatment Group	**S-Betaxolol 0.75%**	**S-Betaxolol 0.5%**	**S-Betaxolol 0.25%**
S-Betaxolol 0.75% twice-daily	ARE-2918	-	-
S-Betaxolol 0.5% twice-daily	-	ARE-2919	-
S-Betaxolol 0.25% twice-daily	-	-	ARE-2920
Treatment Group	**TIMOPTIC 0.5%**	**BETOPTIC 0.5%**	**Placebo**
TIMOPTIC 0.5% twice-daily	ARE-2908	-	-
BETOPTIC 0.5% twice-daily	-	ARE-2907	-
Placebo Twice-daily	-	-	ARE-2917

Study Masking

Identical to Protocols C-97-67 and C-97-80.

Study Population – Inclusion and Exclusion Criteria

Essentially identical to Protocols C-97-67 and C-97-80.

Efficacy and Safety Variables

Essentially identical to Protocols C-97-67 and C-97-80.

The primary efficacy variable was mean IOP measured at 8 AM and 10 AM at all treatment visits.

Table C-97-40-2 - Study Plan for Protocol C-97-40 (Levobetaxolol Dose-Response Study)

Activity	Screening	Eligibility 1[A]		Eligibility 2[B]		Day 7		Day 14		Day 28	
		8am	10am	8am	10am	8am	10am	8am	10am	8am	10am
Informed Consent	X										
Demographics	X										
Medical History	X										
Pregnancy Test	X										
Discontinue All Glaucoma Medications	X									X	
IOP		X	X	X	X	X	X	X	X	X	X
LogMar Visual Acuity (Best Corrected)	X	X		X		X		X		X	
Biomicroscopy	X	X		X		X		X		X	
Resting Pulse	X	X	X	X	X	X	X	X	X	X	X
Resting Blood Pressure	X	X	X	X	X	X	X	X	X	X	X
Dilated Fundus Examination	X										X
Automated Perimetry			X								
Gonioscopy	X										
Dispense Study Medication					X		X		X		
Monitor Adverse Events						X	X	X	X	X	X
Collect Study Medication										X	
Complete Exam Form											X
Dismiss Patient											X

[A] scheduled three (3) days to three (3) weeks after Screening
[B] scheduled one (1) week after Eligibility 1

Reviewers Comments:

The Study Plan shown on the previous page is taken from the original protocol found in the NDA on page 8-02969 and appears correct.

The Study Plan for Protocol C-97-40 found in the NDA Study report on page 8-012131 as Table 8 appears incorrect. There should be no scheduled 12-noon return on the Eligibility 2 visit.

Subject Disposition and Demographics

Two hundred fifty-six (256) patients were enrolled into the study and randomized to drug at 16 sites. All 256 patients were included in the safety and intent-to-treat analyses. Two hundred forty-four (244) patients completed the study. Twelve (2 in S-Betaxolol 0.25%, 3 in S-Betaxolol 0.5%, 1 in S-Betaxolol 0.75%, 1 in TIMOPTIC 0.5%, 3 in BETOPTIC 0.5%, and 2 in Placebo) patients were discontinued from the study for various reasons including adverse event (4 patients) inadequate control of IOP (1 patient); patient decision (1 patient); and other, non-medical reasons (6 patients).

Table C-97-40-3 - Discontinued Patients and Reason –

Inv. No.	Patient	Treatment	Reason Discontinued
1208	201	S BETAX 0.25%	PATIENT DECISION
1473	606	S BETAX 0.5%	INADEQUATE WASHOUT
1806	719	PLACEBO	INADEQUATE CONTROL OF IOP
1806	725	PLACEBO	NONQUALIFYING VISUAL FIELD
2245	1201	S BETAX 0.25%	NON-COMPLIANCE
2245	1202	BETOPTIC 0.5%	PATIENT ISSUED WRONG TEST DRUG
2245	1203	S BETAX 0.5%	PATIENT ISSUED WRONG TEST DRUG
2246	1303	S BETAX 0.5%	CONTRAINDICATED MEDICATION
2247	1414	BETOPTIC 0.5%	ADVERSE EVENT (allergy, dermatitis)
2248	1506	TIMOPTIC 0.5%	ADVERSE EVENT (prostate disorder)
2248	1513	BETOPTIC 0.5%	ADVERSE EVENT (infection, urinary tract infection)
2255	2212	S BETAX 0.75%	ADVERSE EVENT (cerebrovascular accident)

Two hundred forty-seven (247) patients were included in the per-protocol analysis. A listing of patients excluded from the per-protocol analysis, with reasons for exclusion, is found below.

Table C-97-40-4 - Patients Excluded from the Per-Protocol Analysis

Investigator	Patient	Treatment	Evaluable for Efficacy	Evaluable for Safety	Reason
1473	606	S BETAX 0.5%	NO	YES	NON QUAL IOP/INADEQUATE WASHOUT
2241	801	S BETAX 0.25%	NO	YES	NON-QUAL IOP > 36
2244	1102	BETOPTIC 0.5%	NO	YES	CONTRA MED
2245	1202	BETOPTIC 0.5%	NO	YES	DOSED WITH RX FOR #1211
2245	1203	S BETAX 0.5%	NO	YES	DOSED WITH RX FOR #1213
2246	1310	S BETAX 0.75%	NO	YES	NON-QUAL IOP'S
2246	1313	S BETAX 0.5%	NO	YES	NON-QUAL IOP'S
2246	1315	TIMOPTIC 0.5%	NO	YES	CONTRA MED
2251	1905	S BETAX 0.5%	NO	YES	NON-QUAL IOP

No statistical differences were observed in demographic characteristics between the six treatments, except for sex. There was a statistically significant (p=0.016) difference in sex distribution between treatments. This is due to the S-Betaxolol 0.5% group having a majority of males (67.4%) while the other treatment groups had a minority of males (<46%). The demographic statistics for the Intent-to-Treat patients are shown in Table C-97-40-6.

There was no significant difference in baseline IOP between the treatment groups for each IOP time.

Table C-97-40-5 - Baseline IOP Comparison (mmHg)

Treatment	8 AM	10 AM
S-Betaxolol 0.25%	25.94	24.74
S-Betaxolol 0.5%	26.19	25.12
S-Betaxolol 0.75%	26.12	25.19
TIMOPTIC 0.5%	26.57	25.36
BETOPTIC 0.5%	26.13	25.31
Placebo	26.25	24.71

Table C-97-40-6 - Demographic Statistics for Intent -To-Treat Patients

Treatment	Age Mean	Std	N	Min	Max
S-BETAXOLOL 0.25%	66.8	11.9	43	38	85
S-BETAXOLOL 0.5%	66.3	11.4	43	36	89
S-BETAXOLOL 0.75%	65.9	13.0	44	39	89
TIMOPTIC 0.5%	63.0	11.8	43	28	84
BETOPTIC 0.5%	64.9	12.2	41	34	87
PLACEBO	65.9	10.7	42	39	85

p=0.7132 in analysis of variance

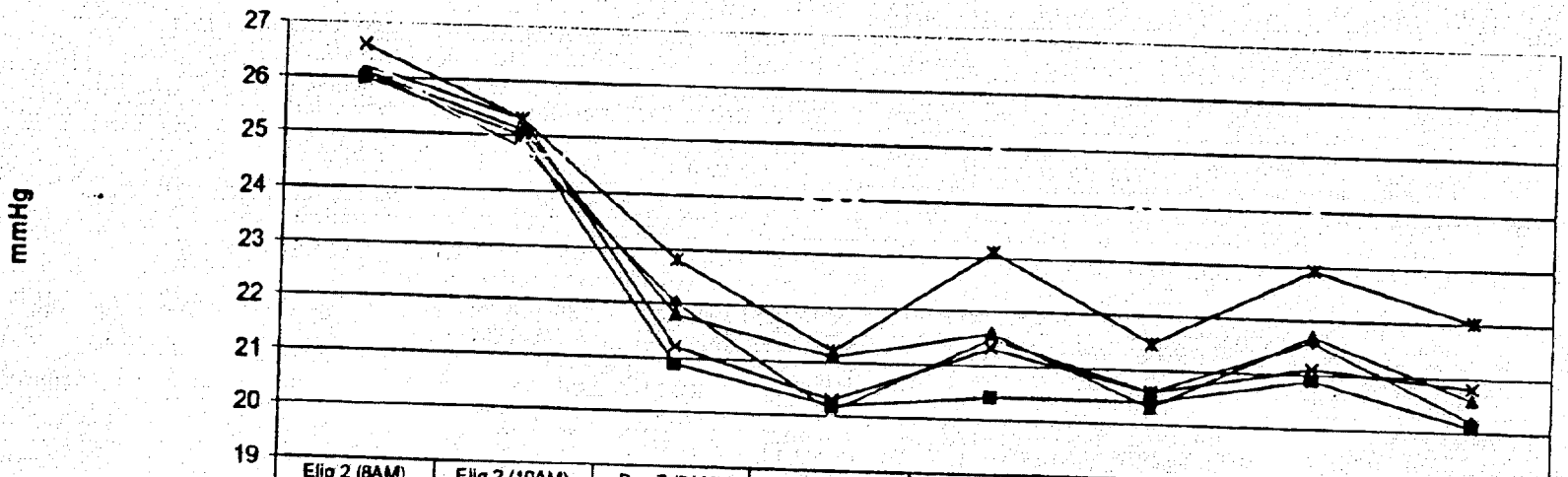
	Treatment: S-BETAX 0.25% N	%	S-BETAX 0.5% N	%	S-BETAX 0.75% N	%	TIMOPTIC 0.5% N	%	BETOPTIC 0.5% N	%	PLACEBO N	%	p-value
Age													
<65	15	34.9	17	39.5	17	38.6	21	48.8	14	34.1	17	40.5	0.780
≥ 65	28	65.1	26	60.5	27	61.4	22	51.2	27	65.9	25	59.5	
Sex													
MALE	19	44.2	29	67.4	15	34.1	18	41.9	13	31.7	19	45.2	0.016
FEMALE	24	55.8	14	32.6	29	65.9	25	58.1	28	68.3	23	54.8	
Race													
CAUCASIAN	36	83.7	37	86.0	34	77.3	36	83.7	37	90.2	36	85.7	0.508
BLACK	6	14.0	2	4.7	6	13.6	5	11.6	3	7.3	3	7.1	
ASIAN	1	2.3											
OTHER			4	9.3	4	9.1	2	4.7	1	2.4	3	7.1	
Iris Color													
BROWN	27	62.8	17	39.5	22	50.0	24	55.8	17	41.5	22	52.4	0.678
HAZEL	7	16.3	7	16.3	4	9.1	6	14.0	6	14.6	3	7.1	
GREEN	1	2.3	3	7.0	3	6.8	2	4.7	2	4.9	3	7.1	
BLUE	8	18.6	15	34.9	14	31.8	11	25.6	15	36.6	11	26.2	
GREY			1	2.3	1	2.3			1	2.4	3	7.1	
Diagnosis													
Ocular Hypertension	13	30.2	12	27.9	13	29.5	14	32.6	14	34.1	12	28.6	0.852
Prim Open Angle Glaucoma	29	67.4	31	72.1	31	70.5	29	67.4	27	65.9	30	71.4	
Pseudoexfoliation Glaucoma	1	2.3											

p-values from chi-square test of independence

8.1.3 Efficacy – Protocol C-97-40 Intent-to-Treat Population

Primary Efficacy Variable

Mean IOP at Trough and Peak



	Elig 2 (8AM)	Elig 2 (10AM)	Day 7 (8AM)	Day 7 (10AM)	Day 14 (8AM)	Day 14 (10AM)	Day 28 (8AM)	Day 28 (10AM)
Levobetaxolol 0.25%	26.1	24.8	22	20.1	21.5	20.6	21.6	20.2
Levobetaxolol 0.5%	26	25	20.9	20.2	20.4	20.4	20.9	20.1
Levobetaxolol 0.75%	26.1	25.1	21.8	21.1	21.6	20.3	21.7	20.6
Timoptic 0.5%	26.6	25.3	21.2	20.3	21.3	20.6	21.1	20.8
Betoptic 0.5%	26.2	25.3	22.8	21.2	23.1	21.5	22.9	22
Placebo	26.3	24.7	24.5	23.9	24.9	23.9	23.9	23.7

Levobetaxolol 0.25% Levobetaxolol 0.5% Levobetaxolol 0.75% Timoptic 0.5% Betoptic 0.5% Placebo

Comparisons to Placebo

Table C-97-40-7- Mean IOP Treatment Difference vs. Placebo and 95% Confidence Limits

Intent to Treat

S-Betaxolol 0.25% and Placebo

	Day 7		Day 14		Day 28	
	8AM	10AM	8AM	10AM	8AM	10AM
Treatment						
S-Betaxolol 0.25%[1]	22.0	20.1	21.5	20.6	21.6	20.2
Placebo	24.5	23.9	24.9	23.9	23.9	23.7
SBX25-PLCBO[2]	-2.5	-3.8	-3.5	-3.3	-2.3	-3.5
p-value	0.0015	0.0000	0.0000	0.0000	0.0034	0.0000
Upper 95% CI	-0.95	-2.26	-1.92	-1.80	-0.76	-1.94
Lower 95% CI	-4.01	-5.32	-4.98	-4.87	-3.82	-5.00

S-Betaxolol 0.5% and Placebo

	Day 7		Day 14		Day 28	
	8AM	10AM	8AM	10AM	8AM	10AM
Treatment						
S-Betaxolol 0.5%[1]	20.9	20.2	20.4	20.4	20.9	20.1
Placebo	24.5	23.9	24.9	23.9	23.9	23.7
SBX50-PLCBO[2]	-3.6	-3.7	-4.5	-3.5	-3.0	-3.5
p-value	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000
Upper 95% CI	-2.07	-2.16	-3.00	-2.01	-1.47	-1.98
Lower 95% CI	-5.14	-5.23	-6.06	-5.08	-4.53	-5.05

S-Betaxolol 0.75% and Placebo

	Day 7		Day 14		Day 28	
	8AM	10AM	8AM	10AM	8AM	10AM
Treatment						
S-Betaxolol 0.75%[1]	21.8	21.1	21.6	20.3	21.7	20.6
Placebo	24.5	23.9	24.9	23.9	23.9	23.7
SBX75-PLCBO[2]	-2.7	-2.7	-3.3	-3.6	-2.1	-3.0
p-value	0.0005	0.0004	0.0000	0.0000	0.0059	0.0001
Upper 95% CI	-1.18	-1.22	-1.78	-2.05	-0.62	-1.50
Lower 95% CI	-4.23	-4.27	-4.82	-5.10	-3.66	-4.54

[1]Least squares means (mmHg) from the analysis of variance
[2]Differences may not be exact due to rounding

Reviewer's Comments:

The differences in mean IOP for all three levobetaxolol (S-Betaxolol) concentrations were statistically significantly ($p \leq 0.003$) lower at all visits compared to Placebo.

The upper confidence intervals of the mean treatment differences between the three levobetaxolol (S-Betaxolol) concentrations and placebo were all less than zero.

Comparisons Among Levobetaxolol Treatment Groups

Table C-97-40-8 - Mean IOP, IOP Change from Baseline, and Percent Change from Baseline
Intent to Treat Data

		Visit							
		ELIG2 8AM	ELIG2 10AM	DAY7 8AM	DAY7 10AM	DAY14 8AM	DAY14 10AM	DAY28 8AM	DAY28 10AM
S-Betaxolol 0.25%	Mean IOP	26.1	24.8	22.0	20.1	21.5	20.6	21.6	20.2
	Mean Change	.	.	-4.1	-4.7	-4.7	-4.2	-4.6	-4.6
	Percent Change	.	.	-15.8	-18.9	-18.1	-16.9	-17.5	-18.2
	N	43	43	43	43	43	43	43	43
S-Betaxolol 0.5%	Mean IOP	26.0	25.0	20.9	20.2	20.4	20.4	20.9	20.1
	Mean Change	.	.	-5.1	-4.8	-5.6	-4.6	-5.2	-4.8
	Percent Change	.	.	-19.7	-19.1	-21.5	-18.3	-19.6	-19.3
	N	43	43	43	43	43	43	43	43
S-Betaxolol 0.75%	Mean IOP	26.1	25.1	21.8	21.1	21.6	20.3	21.7	20.6
	Mean Change	.	.	-4.3	-4.0	-4.5	-4.8	-4.3	-4.5
	Percent Change	.	.	-16.5	-16.1	-17.2	-19.1	-16.9	-18.1
	N	44	44	44	44	44	44	44	44

Reviewer's Comments:

Levobetaxolol 0.5% (S-Betaxolol) produced the lowest mean IOPs and greatest IOP-lowering efficacy compared to the levobetaxolol 0.25% and 0.75% formulations.

Comparisons to Betoptic 0.5%

Table C-97-40-9 - Mean IOP Treatment Difference vs. Placebo and 95% Confidence Limits

Intent to Treat

S-Betaxolol 0.5% and BETOPTIC 0.5%

	Day 7		Day 14		Day 28	
	8AM	10AM	8AM	10AM	8AM	10AM
Treatment						
S-Betaxolol 0.5%[1]	20.9	20.2	20.4	20.4	20.9	20.1
BETOPTIC 0.5%	22.8	21.2	23.1	21.5	22.9	22.0
SBX50-BET50[2]	-1.8	-1.1	-2.8	-1.2	-2.0	-1.8
p-value	0.0187	0.1736	0.0004	0.1342	0.0094	0.0203
Upper 95% CI	-0.31	0.47	-1.23	0.36	-0.50	-0.28
Lower 95% CI	-3.39	-2.61	-4.31	-2.72	-3.58	-3.36

[1]Least squares means (mmHg) from the analysis of variance
[2]Differences may not be exact due to rounding

Reviewer's Comments:

The mean IOP of the levobetaxolol 0.5% (S-Betaxolol) group was lower at all visits than the Betoptic 0.5% group and was statistically significantly lower at 8AM on Days 14 and 28 and at 10AM on Day 28.

Comparisons to Timolol

Table –97-40-10 - Mean IOP Treatment Difference vs. Timoptic 0.5% and 95% Confidence Limits

Intent to Treat

S-Betaxolol 0.25% and TIMOPTIC 0.5%

	Day 7		Day 14		Day 28	
	8AM	10AM	8AM	10AM	8AM	10AM
Treatment						
S-Betaxolol 0.25%[1]	22.0	20.1	21.5	20.6	21.6	20.2
TIMOPTIC 0.5%	21.2	20.3	21.3	20.6	21.1	20.8
SBX25-TIM50[2]	0.8	-0.3	0.2	0.0	0.4	-0.6
p-value	0.2874	0.7191	0.8221	0.9522	0.5792	0.4358
Upper 95% CI	2.35	1.24	1.70	1.48	1.95	0.92
Lower 95% CI	-0.70	-1.80	-1.35	-1.57	-1.09	-2.13

S-Betaxolol 0.5% and TIMOPTIC 0.5%

	Day 7		Day 14		Day 28	
	8AM	10AM	8AM	10AM	8AM	10AM
Treatment						
S-Betaxolol 0.5%[1]	20.9	20.2	20.4	20.4	20.9	20.1
TIMOPTIC 0.5%	21.2	20.3	21.3	20.6	21.1	20.8
SBX50-TIM50[2]	-0.3	-0.2	-0.9	-0.3	-0.3	-0.7
p-value	0.6968	0.8105	0.2425	0.7416	0.7191	0.4014
Upper 95% CI	1.22	1.34	0.61	1.27	1.24	0.87
Lower 95% CI	-1.82	-1.71	-2.43	-1.78	-1.80	-2.17

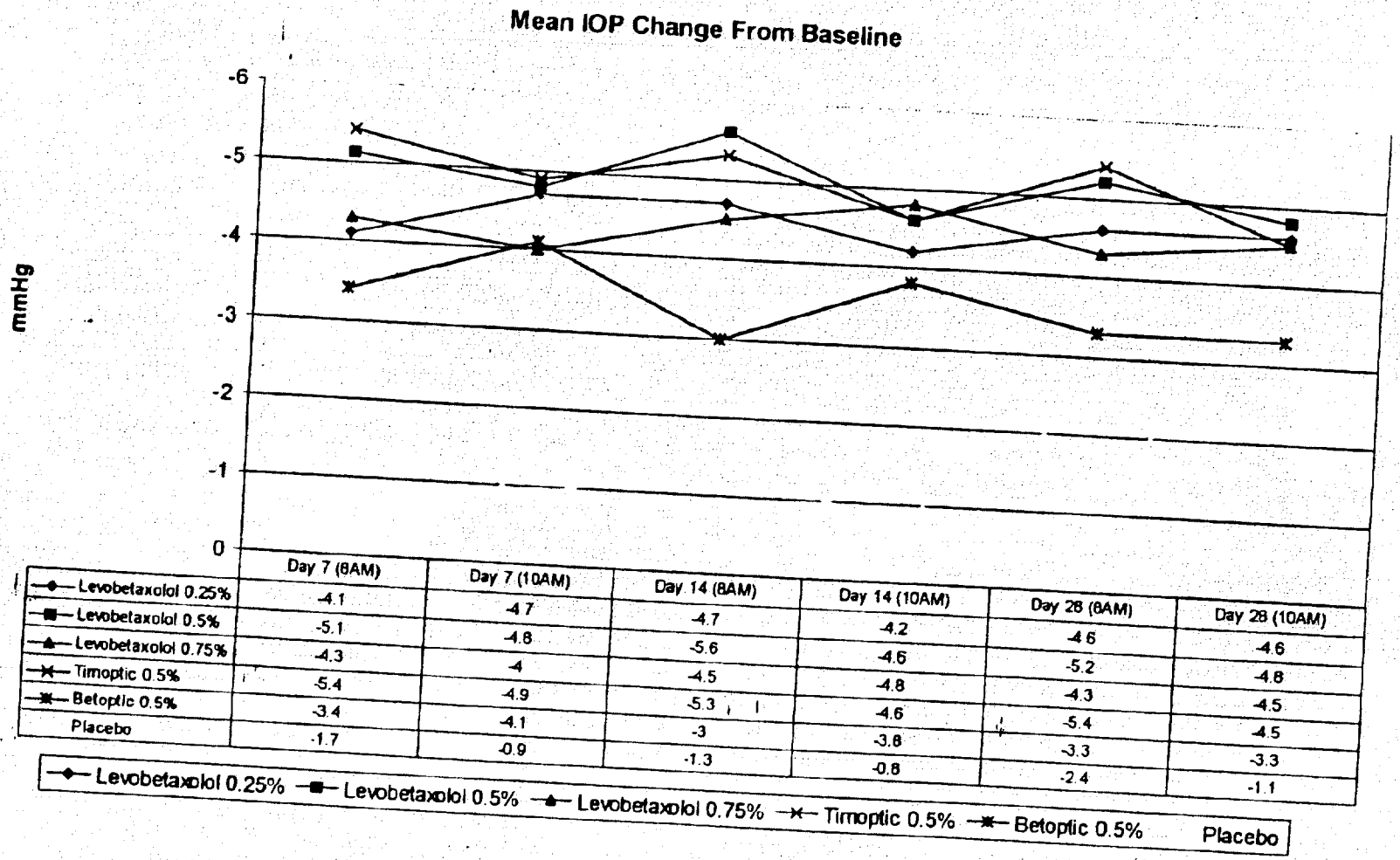
S-Betaxolol 0.75% and TIMOPTIC 0.5%

	Day 7		Day 14		Day 28	
	8AM	10AM	8AM	10AM	8AM	10AM
Treatment						
S-Betaxolol 0.75%[1]	21.8	21.1	21.6	20.3	21.7	20.6
TIMOPTIC 0.5%	21.2	20.3	21.3	20.6	21.1	20.8
SBX75-TIM50[2]	0.6	0.8	0.3	-0.3	0.6	-0.2
p-value	0.4387	0.3216	0.6753	0.7099	0.4550	0.8414
Upper 95% CI	2.11	2.28	1.84	1.23	2.09	1.36
Lower 95% CI	-0.92	-0.75	-1.19	-1.80	-0.94	-1.67

[1]Least squares means (mmHg) from the analysis of variance
[2]Differences may not be exact due to rounding.

Reviewer's Comments:

There were no statistically significant differences in mean IOP, but levobetaxolol 0.5% produced the lowest mean IOPs at all visits.



	Day 7 (8AM)	Day 7 (10AM)	Day 14 (8AM)	Day 14 (10AM)	Day 28 (8AM)	Day 28 (10AM)
Levobetaxolol 0.25%	-4.1	-4.7	-4.7	-4.2	-4.6	-4.6
Levobetaxolol 0.5%	-5.1	-4.8	-5.6	-4.6	-5.2	-4.8
Levobetaxolol 0.75%	-4.3	-4	-4.5	-4.8	-4.3	-4.5
Timoptic 0.5%	-5.4	-4.9	-5.3	-4.6	-5.4	-4.5
Betoptic 0.5%	-3.4	-4.1	-3	-3.8	-3.3	-3.3
Placebo	-1.7	-0.9	-1.3	-0.8	-2.4	-1.1

Reviewer's Comments:

This study is limited by its short duration and the limited number of patients per group. Levobetaxolol 0.5% appears to be at the top of the dose-response curve.

8.1.3 Safety

Adverse Events

Four patients discontinued from the study due to adverse events; one in the S-Betaxolol 0.75% group, one in the Timoptic 0.5% group, and two in the Betoptic 0.5% group. See Table C-97-40-3, page 44.

No deaths were reported during the study.

All serious adverse events are summarized in the following table.

Table C-97-40-11 - Serious Adverse Events

Investigator	Patient	Treatment	Coded Adverse Event	Outcome of Event	D/C Pt from Study
2255	2212	S-Betaxolol 0.75%	Cerebrovascular Accident	Resolved with Treatment	Yes
2248	1513	BETOPTIC 0.5%	Infection, Urinary Tract Infection	Resolved with Treatment	Yes
2246	1307	BETOPTIC 0.5%	Surgical/Medical Procedure, Back Pain	Resolved with Treatment	No

No clinically significant differences in demographics were observed between the total patient population and the subgroups for each treatment, with or without adverse events.

The most frequent ocular event in levobetaxolol 0.25% (S-Betaxolol) treated subjects was transient ocular discomfort upon instillation (burning, stinging) which occurred in 14% of patients.

The most frequent ocular event in levobetaxolol 0.5% treated subjects was transient ocular discomfort upon instillation (burning, stinging) which occurred in 16.3% of patients.

The most frequent ocular event in levobetaxolol 0.75% treated subjects was transient ocular discomfort upon instillation (burning, stinging) which occurred in 25% of patients.

The most frequent ocular events in Timoptic 0.5% treated subjects were hyperemia, keratitis, pruritus, corneal staining, and trichiasis, all of which occurred in only 2.3% of patients.

The most frequent ocular event in Betoptic 0.5% treated subjects was transient ocular discomfort upon instillation (burning, stinging) which occurred in 19.5% of patients.

The most frequent ocular events in Placebo treated subjects were hyperemia and conjunctival edema, each of which occurred in only 2.4% of patients.

Table C-97-40-12 - Overall Frequency and Incidence of Adverse Events

	Lev 0.25%		Lev 0.5%		Lev 0.75%		Tim 0.5%		Bet 0.5%		Placebo	
	N = 43		N = 43		N = 44		N = 43		N = 41		N = 42	
	N	%	N	%	N	%	N	%	N	%	N	%
Ocular												
Discomfort Eye	6	14.0	7	16.3	11	25.0			8	19.5		
Blepharitis			1	2.3	1	2.3			1	2.4		
Hordeolum			1	2.3								
Hyperemia Eye			1	2.3	2	4.5	1	2.3			1	2.4
Infiltrate Corneal			1	2.3								
Vision Blurred	1	2.3	1	2.3	1	2.3						
Foreign Body Sensat	1	2.3										
Keratitis	1	2.3			1	2.3	1	2.3				
Papill Conjunctivitis	1	2.3										
Pruritus Eye	1	2.3					1	2.3	1	2.4		
Spasm Lid	1	2.3										
Tearing	1	2.3							1	2.4		
Vitreous Disorder	1	2.3										
Conjunctivitis					1	2.3			1	2.4		
Discharge Eye Nos					1	2.3						
Edema Lid					1	2.3						
Eye Fatigue					1	2.3						
Glare					1	2.3						
Staining Corneal							1	2.3				
Trichiasis							1	2.3				
Edema Conjunctival											1	2.4
Nonocular												
Body as a Whole												
Headache	2	4.7							1	2.4		
Infection	1	2.3			2	4.5	1	2.3	1	2.4		
Flu Syndrome					1	2.3	2	4.7				
Surgical/Medical Pro					1	2.3			1	2.4		
Allergy									2	4.9		
Pain Back									1	2.4		
Cardiovasc System												
Cerebrovasc Acci					1	2.3						
Tachycardia									1	2.4		
Hypertension											1	2.4
Digestive System												
Tooth Caries					1	2.3						
Dyspepsia							1	2.3				
GI Disorder											1	2.4
Endocrine												
Diabetes Mellitus							1	2.3				

Table C-97-40-12 - Overall Frequency and Incidence of Adverse Events - Continued

	Lev 0.25%		Lev 0.5%		Lev 0.75%		Tim 0.5%		Bet 0.5%		Placebo	
	N = 43		N = 43		N = 44		N = 43		N = 41		N = 42	
	N	%	N	%	N	%	N	%	N	%	N	%
Metab/Nutri Disord												
Hypercholesteremia	1	2.3					1	2.3			1	2.4
Hyperglycemia					1	2.3						
Hyperlipidemia					1	2.3						
Musculo-Skel Sys												
Pain Bone									1	2.4		
Arthritis											1	2.4
Nervous System												
Coordinat Abnorm					1	2.3						
Respiratory System												
Bronchitis					1	2.3						
Lung Disorder					1	2.3						
Rhinitis									1	2.4		
Sinusitis									1	2.4		
Skin and Append									1	2.4		
Dermatitis												
Urticaria							1	2.3				
Special Senses												
Otitis Media									1	2.4		
Urogenital System												
Prostate Disorder							1	2.3				
Infect Urin Tract									1	2.4		

Visual Acuity, Ocular Signs, Dilated Fundus, Cup/Disc Ratio

Reviewer's Comments:

No statistically significant decrease in visual acuity change-from-baseline to final visit was observed between the treatment groups.

No statistically significant difference in worsening of ocular signs (cornea, iris/anterior chamber, lens, vitreous) was observed between the treatment groups.

No statistically significant difference in fundus parameters (retina/macula/choroid, optic nerve) was observed between the treatment groups.

No statistically significant difference in cup/disc ratio was observed between the treatment groups.

Pulse, Systolic/Diastolic Blood Pressure

Reviewer's Comments:

No statistically significant difference in pulse change from baseline was noted between the treatment groups.

No statistically significant difference in systolic or diastolic blood pressure was noted between the treatment groups.

8.1.3 Reviewer's Summary of Efficacy and Safety

Levobetaxolol 0.5% (S-Betaxolol) produced the lowest mean IOPs and greatest IOP-lowering efficacy compared to the levobetaxolol 0.25% and 0.75% formulations.

Adverse experiences appeared generally mild-moderate in nature with increasing incidence associated with increasing concentrations of levobetaxolol.

8 **Clinical Studies**

8.1.4 **Study #4 Protocol C-97-68**

Title: A Single-Drop, Two Period, Crossover Comparison of the Cardiovascular Effects of Levobetaxolol 0.5% Ophthalmic Suspension versus Timolol 0.5% Ophthalmic Solution During Exercise in Normal Subjects Age 60 and Over.

Objective: The objective was to compare the cardiovascular effects of Levobetaxolol 0.5% Ophthalmic Suspension to Timolol 0.5% Ophthalmic Solution during exercise in normal subjects age 60 and over.

Study Design: A randomized, single-center, double masked, crossover design study.

Test Drug Schedule: Subjects were randomized to one (1) of two (2) treatment sequences; Levobetaxolol-Timolol or Timolol-Levobetaxolol. Subjects were dosed by site personnel with one drop of masked medication in each eye at approximately the same time each study day.

PRINCIPAL INVESTIGATOR	INVESTIGATOR No.	DATES OF PARTICIPATION	No. SUBJECTS
Thomas L. Hunt, M.D., Ph.D. 706-A Ben White Blvd West Austin, Tx 78746	1965	12/4/98 – 2/12/99	33

Reviewer's Comments:

The NDA Study report on page 8-00837 and the Financial Certification/Disclosure Statement on page 16-00005 list the principal investigator as Robert Hunt, M.D. The Curriculum Vitae found on page 8-01189 belongs to Thomas L. Hunt, M.D., Ph.D. at the same professional address. They are presumably the same individual.

8.1.4 **Study Design**

This study was a single-site, double-masked, randomized, two-period crossover comparison of Levobetaxolol 0.5% and Timolol 0.5%. Subjects enrolled in the study were healthy adults at least 60 years of age, of any race and either sex. Target enrollment to support the statistical power of the study was 30 subjects completing both treatment sequences. Eligible subjects who met all inclusion criteria were randomized to one of two treatment sequences (Levobetaxolol 0.5%-Timolol 0.5% or Timolol 0.5%-Levobetaxolol 0.5%). Successive treatments were scheduled one (1) week apart at approximately the

same time of day. Each subject completed a baseline and two treatment periods. Subjects underwent a qualifying baseline treadmill test prior to randomization in order to verify the existence of an unremarkable electrocardiogram during exercise and the ability to reach 80% of predicted maximum heart rate within ten (10) minutes of exercise. The treadmill test consisted of a constant speed of 2.7 mph at a 10% grade.

In the treatment phase, subjects received two drops of study drug (one drop in each eye) on both the mornings of Period One and Period Two. Thirty minutes after instillation of study drug, subjects underwent a 10 minute treadmill test at a speed of 2.7 mph and a grade of 10%. Heart rate, blood pressure and ECG results were monitored immediately prior to beginning exercise (time 0) and at two minute increments for the ten (10) minutes of exercise and for a ten minute recovery period.

The primary parameter in this study, heart rate, was measured via ECG recordings, captured by the treadmill attached monitoring hardware and software. This provided an objective measurement of heart rate, that could be validated through the review of ECG printouts. Heart rate was recorded at each study visit day in a supine and standing position approximately 30 minutes prior to drug instillation, and in 2 minute increments for 20 minutes during the exercise (10 min. standing) and recovery (10 min. supine) phases.

Study Medications

The masked test medications used during the treatment phase were supplied in masked 5 mL opaque DROP-TAINER®s labeled with the appropriate patient number. The drug lot numbers used in this study according to treatment group are displayed below.

Table C–97-68-1 - Study Medications

TEST ARTICLE	LOT NUMBER
Levobetaxolol 0.5%	ASE – 3013
Timolol 0.5%	ASE – 3012*

*Sterile transfer of commercial TIMOPTIC 0.5%

Study Masking

The study was double-masked with subject, investigator and Alcon study staff blinded as to the subjects' treatment codes. A sealed envelope containing the description of the test article was provided for each subject. The investigator was instructed to open the envelope only in cases of medical emergencies if it became necessary to know which test article the subject received.

In no case was masking broken during conduct of the study.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

Healthy adults of any race and either sex aged 60 or older.

Exclusion Criteria

Subjects with any of the following conditions will be ineligible for participation in this study:

1) History of previous illness affecting pulmonary or cardiac function including but not limited to hypertension, myocardial ischemia/infarction, clinically significant valvular heart disease, cardiomyopathy, asthma, chronic bronchitis, or emphysema.

2) Tachycardia (> 100 bpm), bradycardia (< 60 bpm), hypertension (> 140/90 mmHg), or abnormal electrocardiogram (ECG) tracings at rest or standing during the baseline exam.

3) Systemic or topical beta-blocking drug use within the previous 30 days and for the duration of the study.

4) History of treatment with any cardiovascular medication within the previous 30 days and for the duration of the study.

5) Hypersensitivity to beta-blockers, glucocorticoids (either topical or systemic), anticholinergics, vasoconstrictors, antihistamines or any component of the preparations.

6) History or presence of any current systemic disease that might be adversely affected by beta-blockade.

7) History or current diagnosis of diabetes, glaucoma, hyperthyroidism, neurological, hepatic, and/or renal disease.

8) Any ocular pathological condition which may be adversely affected by the topical ocular test treatments.

9) Therapy with another investigational agent within the past 30 days.

10) Any physical problem(s) which would interfere with completion of a treadmill stress test.

11) Heart rate that measures less than 80% of maximum targeted heart rate at the 10 minute mark of the screening treadmill stress test.

12) Age less than 60 years.

13) Current use of tobacco (must be free from tobacco use 6 months prior to screening).

14) Subjects exhibiting clinically significant signs or symptoms of orthostatic hypotension during the screening exam.

Additionally, the Medical Monitor could declare any subject ineligible for a valid medical reason detected during prescreening.

Efficacy Variables

The primary variable was heart rate, measured in two minute increments during a 10 minute exercise phase (treadmill test) and a 10 minute recovery phase (supine) on both Period One and Period Two visit days.

Blood pressure (Systolic/Diastolic) was captured at the same times as heart rate during exercise and recovery. These were secondary variables in this study.

The product of heart rate times systolic blood pressure [Double Product] was evaluated an indicator of overall cardiac ~~work. The units for double~~ product are BPM x mmHg.

Safety Variables

This study included the following safety variables:

Examination of Heart and Lungs
Stethoscopic examination at screening.

Laboratory Testing
Hematology, blood chemistry, urinalysis performed at screening and exit.

Adverse Events
Subjects were queried at each visit regarding occurrence of any adverse events. Adverse event information included a description of the event, onset, severity, treatment required, outcome, and relationship to use of the study medication.

12-Lead Electrocardiograms
Performed at screening and all pre-dose and post-dose visits.