MOR 1

Medical Officer's Review of NDA 21-114
Original

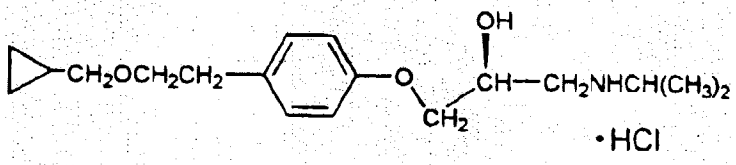
NDA 21-114
Medical Officer's Review

Submission: 8/26/99
Review Completed: 1/3/00

Proposed Tradename: Betaxon 0.5%

Generic Name: levobetaxolol hydrochloride suspension

Chemical Name: (S)-1-[p-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride



Empirical Formula: $C_{18}H_{29}NO_3 \bullet HCl$

Sponsor:

Alcon Universal, Ltd.
P.O. Box 62
Bosch 69
CH-6331 Hunenberg Switzerland

Authorized U.S. Agent
Alcon Research, Ltd.
6201 South Freeway
Ft. Worth, TX 76134
817-568-6296

Pharmacologic Category: Beta-1-adrenergic receptor blocking agent

Proposed Indication: Lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension

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

NDA Drug Classification: 2P

Related IND: IND

2 **Table of Contents**

3 **Material Reviewed**

NDA 21-114 Volumes 3.16-3.34

4 **Chemistry/Manufacturing Controls** – See Chemistry Review

Table 1 - Quantitative Composition

Ingredient	
Levobetaxolol Hydrochloride[a]	
Benzalkonium Chloride	
Poly(styrene-divinylbenzene) Sulfonic Acid[b] (PSA)	
Carbomer 974P	
Mannitol	
Boric Acid	
Edetate Disodium	
N-Lauroylsarcosine	
Tromethamine and/or Hydrochloric Acid	
Purified Water	

[a]The amount

These marketed products are a

6.1 Relevant Human Experience

Three studies of levobetaxolol ophthalmic suspension 0.5% (C-86-24, C-87-20 and C-87-78) were conducted in the late 1980's with a different formulation than the current formulation evaluated in this NDA.

Protocol C-86-24 was a comfort study that compared suspension formulations of betaxolol and levobetaxolol to marketed Betaxolol Solution 0.5%. Protocols C-87-20 and C-87-78 were pilot efficacy studies that compared IOP reduction from levobetaxolol 0.5% to IOP reduction from timolol 0.5%.

Further development of levobetaxolol was discontinued based upon a corporate decision at that time.

6.3 Foreign Experience

Betaxon (levobetaxolol hydrochloride ophthalmic suspension) 0.5% has not been marketed in any country nor has it been withdrawn from marketing in any country to date.

6.4 Human Pharmacology, Pharmacokinetics, & Pharmacodynamics – See Pharmacology Review

7 Description of Clinical Data Sources

Included in this medical officer's review are five clinical trials conducted in the United States or France under IND

- Two, 12-week trials to evaluate the safety and IOP-lowering efficacy of levobetaxolol ophthalmic suspension 0.5% compared to timolol 0.5% ophthalmic solution in patients with primary open-angle glaucoma or ocular hypertension (U.S.)

- A 4-week Dose-Response Trial placebo-controlled, dose-response study to evaluate the safety and IOP-lowering efficacy of levobetaxolol ophthalmic suspension compared to Timoptic® 0.5% and Betoptic® 0.5% in patients with primary open-angle glaucoma or ocular hypertension (U.S.)

- Two Phase 1 Trials [Cardiovascular Safety (U.S.) and Pulmonary Safety (France)].

Table 3 – Description of Clinical Data Sources

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Sites	No. Patients Randomized (Intent-to-Treat)	Status
Phase I Studies								
Cardiovascular Safety (C-97-68)	Double-masked, crossover	1 dose	Normal volunteers age 60 and over	Levobetaxolol 0.5% Timolol 0.5%	1 drop OU 1 drop OU	1	33	Completed
Pulmonary Safety (C-98-57)	Double-masked, crossover	1 dose	Adults with reactive airway disease	Levobetaxolol 0.5% Timolol 0.5%	1 drop OU 1 drop OU	1	30	Completed
Phases II/III Studies								
Dose-Response (C-97-40)	Double-masked, randomized, active and placebo controlled	1 month	Open-angle glaucoma and ocular hypertension	Levobetaxolol 0.25% Levobetaxolol 0.50% Levobetaxolol 0.75% BETOPTIC 0.5% TIMOPTIC 0.5% Placebo	1 drop BID OU 1 drop BID OU 1 drop BID OU 1 drop BID OU 1 drop BID OU 1 drop BID OU	18	43 43 44 41 43 42 (256 total)	Completed
Efficacy/ Safety #1 (C-97-67)	Double-masked, randomized, active controlled	3 months	Open-angle glaucoma and ocular hypertension	Levobetaxolol 0.5% Timolol 0.5%	1 drop BID OU 1 drop BID OU	22	182 177 (359 total)	Completed
Efficacy/ Safety #2 (C-97-80)	Double-masked, randomized, active controlled	3 months	Open-angle glaucoma and ocular hypertension	Levobetaxolol 0.5% Timolol 0.5%	1 drop BID OU 1 drop BID OU	25	174 174 (348 total)	Completed

8 Clinical Studies

8.1.1 Study #1 Protocol C-97-67

Title: A Twelve-Week, Multicenter, Triple-Masked Study of the Safety and IOP-Lowering Efficacy of Levobetaxolol 0.5% Suspension Compared to Timolol 0.5% Solution in the Treatment of Patients with Open-Angle Glaucoma or Ocular Hypertension.

Objective: To evaluate the safety and IOP-lowering efficacy of Levobetaxolol 0.5% Ophthalmic Suspension compared to Timolol 0.5% Ophthalmic Solution in patients with open-angle glaucoma or ocular hypertension.

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

Test Drug Schedule: Patients were instructed to instill one drop of study medication (either levobetaxolol 0.5% or timolol 0.5%) 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 12 weeks.

Principal Investigator	Inv. No.	Dates of Participation	Number of Patients	
			Intent-to-Treat	Per-Protocol
Walter Atlas, M.D.	1986	5/6/98 to 12/31/98	19	19
Mark G. Bearman, M.D.	2443	5/18/98 to 9/3/98	2	2
Gregg J. Berdy, M.D.	1335	6/27/98 to 11/21/98	22	22
Richard O. Bessent, M.D.	2427	4/29/98 to 1/11/99	5	4
Moiz Carim, M.D.	2244	5/5/98 to 12/11/98	14	14
James Crabb, M.D.	1229	5/8/98 to 10/28/98	19	19
Timothy Crane, M.D.	1925	5/9/98 to 9/8/98	1	1
Randy E. Craven, M.D.	1236	4/22/98 to 1/29/99	22	22
Howard A. Doyle, M.D.	2441	5/5/98 to 12/3/98	9	9
Harvey DuBiner, M.D.	1927	4/13/98 to 12/31/98	47	47
*Lawrence Hurvitz, M.D.	1237	4/20/98 to 10/13/98	12	11
Robert Laibovitz, M.D.	943	No patients were enrolled	0	0
Scott Lanoux, M.D.	2538	5/27/98 to 11/17/98	22	22
Jeffrey Levensen, M.D.	2319	5/6/98 to 9/22/98	7	7
Solomon Luo, M.D.	2438	5/7/98 to 1/6/99	23	23
Paul Michelson, M.D.	2496	7/6/98 to 11/23/98	17	16
Paul G. Mitchell, M.D.	1716	4/30/98 to 12/21/98	36	34
Earl Nelson, M.D.	1978	6/15/98 to 1/27/99	32	27
William Roberts, M.D.	456	5/14/98 to 12/15/98	4	4
Shelly Temperley, M.D.	2489	6/2/98 to 9/22/98	1	1
Carl Tubbs, M.D.	1975	5/22/98 to 1/8/99	7	7

Principal Investigator	Inv. No.	Dates of Participation	Number of Patients Intent-to-Treat	Number of Patients Per-Protocol
Bonnie C. Weston, M.D.	2490	No patients were enrolled	0	0
Robert D. Williams, M.D.	2128	6/17/98 to 1/4/99	24	24
Brandon M. Wool, M.D.	2248	5/04/98 to 12/4/98	14	14

*Investigational site closed prematurely due to inconsistencies between the source documentation and the case report forms.

Reviewer's Comments:

Investigator 1237 was disqualified due to inconsistencies between the source documentation and case report forms observed during a Sponsor monitoring visit. This investigator's patients were discontinued from the study, and the investigational site was prematurely closed.

The Sponsor asserts that an analysis of the per-protocol data performed with and without Investigator 1237 did not change the results of this study. Therefore, the data from this investigator's patients were included in all other analyses. After review of these analyses, this reviewer concurs.

See Review Section 8.1.1 Efficacy – Protocol C-97-67.

8.1.1 Study Design

This study was a prospective, multicenter (24 sites), triple-masked, parallel-group, active-controlled, pivotal trial designed to compare the safety and efficacy of twice-daily-dosed levobetaxolol 0.5% ophthalmic suspension compared to twice-daily-dosed timolol 0.5% ophthalmic solution and to demonstrate their equivalence. Target enrollment to support the statistical power of the study was 150 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 two (2) treatments; levobetaxolol 0.5% twice-daily or timolol 0.5% twice-daily for a treatment period of twelve (12) weeks.

The eligibility phase included informed consent, evaluation of patient history, and ophthalmic and systemic assessments in order to establish safety baselines and exclude patients who would be considered at unacceptable risk by participation in the study. The eligibility phase included a washout period from current ocular hypotensive medications. The length of the washout periods for various ocular hypotensives is listed in Table C-97-67-1. To minimize potential risk to the patient due to IOP elevation during the washout period, investigators were allowed to substitute a miotic in place of a beta-blocker, sympathomimetic, or alpha agonist. Patients had to be washed out of these medications for the minimum period stated above prior to the Eligibility Visit 1.

Table C-97-67-1 - Minimum Washout Periods By Drug Class

Ocular Hypotensive Medication	Washout Period Prior to Eligibility Visit 1
beta-antagonists and prostaglandins: e.g.; betaxolol timolol carteolol metipranolol levobunolol latanoprost	3 weeks
alpha and alpha/beta agonists: e.g.; epinephrine dipivefrin apraclonidine brimonidine	2 weeks
miotics: e.g.; pilocarpine carbachol	5 days
oral/topical carbonic anhydrase inhibitors: e.g.; acetazolamide methazolamide dorzolamide brinzolamide	5 days
no ocular hypotensive medication	3 days

The treatment duration of the study (12 weeks) was considered sufficient to ensure stabilization of the efficacy endpoint, IOP, based on the applicant's previous experience in evaluating beta-blockers.

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 timolol and levobetaxolol. The trough IOP was measured at the end of the dosing period, prior to instillation of the next dose and compared the efficacy of levobetaxolol 0.5%, 12 hours post-dose, to timolol 0.5%, 12 hours post-dose. Peak IOP was measured two (2) hours after dose instillation.

Patients meeting all qualifying criteria entered the triple-masked treatment phase and were randomized to receive either Levobetaxolol 0.5% or Timolol 0.5% twice-daily. Patients were instructed to instill one drop of study medication into each eye in the morning at 8 am, and one drop of study medication into each eye in the evening at 8 pm. If any portion of the drop did not fall into the eye, patients were instructed to instill another drop into that eye. Both eyes were dosed with study medication even if only one eye qualified based upon the IOP entry criteria.

Patients were instructed by the investigator/staff to follow protocol guidelines and dose themselves as indicated. The time of last drug instillation prior to the 8 am visit was documented. Dosing at 8am on study visit days was conducted by study staff to ensure compliance. If the patient had dosed with study medication on the morning of the study visit, the visit was to be rescheduled, since the 8 am IOP measurement was a measure of trough IOP, to be assessed at the end of the dosing period.

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-97-67-2 - Study Medications

Treatment Group	Levobetaxolol 0.5%	Timolol 0.5%
Levobetaxolol 0.5% twice-daily	ARE-2956	-
Timolol 0.5% twice-daily	-	ARE-2959* ASE-2981*

*Sterile transfer of commercial TIMOPTIC®

Study Masking

The study was triple-masked, with patient, Investigator and Alcon study staff masked as to the patients' treatment codes (the term "triple-masked" is synonymous with the ICH definition of double masked). A sealed envelope containing the description of the test article was provided for each subject. The investigator was instructed to open the envelope in cases of medical emergencies, if it became necessary to know which test article the subject received. During the study, no study medication was unmasked.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

1) Patients of either sex, of any race, diagnosed with open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension.

2) Females must be surgically sterilized at least three (3) months prior to study start, one (1) year postmenopausal or utilizing suitable contraceptives.

   All females of childbearing potential must have a negative pregnancy test result at the Screening Exam and also must not intend to become pregnant during the study.

3) Patients must be able to discontinue use of all ocular hypotensive medication(s) and undergo a minimum washout period of twelve (12) days to four (4) weeks.

4) Mean IOP measurements must be 24 to 36 mmHg, inclusive, in at least one eye, the same eye, at the 8:00 a.m. IOP measurements at both Eligibility Visits 1 and 2. Additionally, the 10:00 a.m. mean IOP measurement must be 21 to 36 mmHg, inclusive, in at least one eye, the same eye that qualified previously. Mean IOP

measurements in each eye must be less than or equal to 36 mmHg at all times. These IOP criteria must be met at both Eligibility Visits 1 and 2.

5) Informed consent read, signed, and dated (including the time of day) by the patient or legally authorized representative, before conducting the Screening exam. If the patient is less than 18 years of age, the informed consent must also be signed and dated by a parent or legal guardian.

Exclusion Criteria

1) Best corrected visual acuity worse than 0.60 LogMAR in either eye.

2) Current or history of chronic or recurrent uveitis or other inflammatory eye disease (i.e., scleritis).

3) History of ocular trauma within the past six (6) months.

4) Current or history of ocular infection within the past three (3) months.

5) Any history of clinically significant retinal disease such as retinal degeneration, diabetic retinopathy, retinal detachment or progressive retinal disease.

6) Any abnormality preventing reliable applanation tonometry of either eye.

7) History of severe ocular pathology (including severe dry eye) in either eye that would preclude the administration of a topical beta-blocker.

8) Patients with a cup-disc ratio greater than 0.8 in either eye.

9) Patients with severe central field loss in either eye defined as a sensitivity $\leq$ 10 dB in at least two (2) of the four (4) visual field points closest to the point of fixation.

10) Intraocular surgery within the past six (6) months as determined by patient history and/or examination.

11) Ocular laser surgery within the past three (3) months as determined by patient history and/or examination.

12) History of severe or serious hypersensitivity to beta-blockers (oral or topical) or to any components of these medications.

13) History of severe, unstable or uncontrolled cardiovascular, pulmonary, hepatic or renal disease (e.g., bronchial asthma, severe chronic obstructive pulmonary disease, clinically relevant bradycardia, overt cardiac failure, greater than first degree atrioventricular block, cardiogenic shock, clinically relevant angina or uncontrolled hypertension) that would preclude the safe administration of a topical beta-blocker.

14) Less than thirty (30) days stable dosing regimen prior to the screening visit, of any systemic or topical medication used on a chronic basis that may affect IOP (i.e., sympathomimetic agents, beta-adrenergic blocking agents, alpha agonists, alpha-adrenergic blocking agents, calcium channel blockers, angiotensin converting enzyme inhibitors, etc.). Patients must be on a stable dosing regimen of these medications at least thirty (30) days prior to the Screening Visit and must not change the dosing regimen during the Eligibility period. Any changes in dosage or addition of such medication(s) following randomization must be documented in the patient's chart.

15) Use of any glucocorticoid during the Eligibility phase. Patients must have washed out of any chronic glucocorticoid therapy for at least four (4) weeks or intermittent glucocorticoid use for at least two (2) weeks prior to the Eligibility 1 Visit.

16) History of ineffective IOP response to a topical beta-blocker.

17) Any form of glaucoma other than open-angle glaucoma (with or without a pigment dispersion or pseudoexfoliation component).

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

19) Women who are pregnant, nursing, or of childbearing potential who are not utilizing suitable birth control measures.

20) Patients who cannot be dosed in both eyes.

21) Use of any adjunctive therapy, either topical or systemic, for lowering IOP.

Additionally, the Alcon Medical Monitor could declare any patient ineligible for a valid medical reason.

Efficacy Variables

The primary efficacy parameter was an assessment of mean IOP at the 8 a.m. and 10 a.m. time points for the patient's worse eye. Worse eye was defined as follows:

1) The eye with the higher intraocular pressure at 8 am averaged across both eligibility visits. If both eyes were equal then,

2) The eye with the higher intraocular pressure at 10 am averaged across both eligibility visits. If both eyes were equal then, the right eye was selected for analysis.

Safety Variables

This study included the following safety variables:

Adverse Events
Subjects were queried at each follow-up 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.

Visual Acuity
Best-corrected visual acuity was measured at each study visit using an ETDRS or modified ETDRS chart.

Slit-Lamp Examination (Biomicroscopy)
A biomicroscopic evaluation was performed at each 8 am study visit, and included the cornea, iris/anterior chamber, lens and vitreous.

Fundus Examination (Ophthalmoscopy)
A dilated fundus examination was performed at the Screening Visit and at the 10 am study visit at Week 12 and included the retina/macula/choroid, optic nerve, disc pallor, and cup/disc ratio.

Gonioscopy
Graded with the Schaffer Classification (0-3) at the Screening.

Resting Pulse and Blood Pressure
Measured after patient seated for 4 minutes at the Screening and 8 am and 10 am study visits.

Automated Perimetry
Humphrey or Octopus evaluation at Screening (if not conducted within the last 9 months).

Table C-97-67-3 - Study Plan for Protocol C-97-67 (Efficacy/Safety Study 1)

Activity	Screening	Eligibility 1[A]		Eligibility 2[B]		Week 2		Week 6		Week 12	
		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										
Instill Masked Medication						X		X		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

Subject Disposition and Demographics

Three hundred fifty-nine (359) patients were enrolled into the study and randomized to drug at 22 sites. All 359 patients were included in the safety and intent-to-treat analyses. Three hundred thirty-five (335) patients completed the study. Twenty-four (12 in Levobetaxolol 0.5%; 12 in Timolol 0.5%) patients were discontinued from the study for various reasons including adverse events (9 patients); inadequate control of IOP (1 patient); lost to follow-up (2 patients); protocol non-compliance (4 patients); and other, non-medical reasons (8 patients).

Table C-97-67-4 - Discontinued Patients and Reason

Investigator	Patient	Treatment	Reason
1335	2604	Tim	INADEQUATE CONTROL OF IOP
1236	4714	Levo	ADVERSE EVENT (open heart surgery)
1236	4719	Levo	ADVERSE EVENT (vertigo)
1229	5809	Tim	LOST TO FOLLOW-UP
1229	5812	Tim	NONCOMPLIANCE
2427	6903	Levo	ADVERSE EVENT (asthenia, dyspnea)
1927	7905	Tim	NONCOMPLIANCE
1927	7909	Levo	ADVERSE EVENT (discomfort eye)
1927	7910	Tim	INADEQUATE WASHOUT
1927	7918	Tim	NONCOMPLIANCE
1237	8707	Tim	NONQUALIFYING IOP
1237	8711	Levo	PATIENT DECISION
1237	8712	Tim	SITE CLOSED
2319	8801	Tim	ADVERSE EVENT (discomfort eye)
2438	8909	Levo	PATIENT DECISION
1716	9702	Levo	ADVERSE EVENT (dyspnea)
1716	9704	Levo	ADVERSE EVENT (pain chest)
1716	9716	Tim	NONCOMPLIANCE
1716	9720	Tim	ADVERSE EVENT (iritis)
1978	9807	Levo	LOST TO FOLLOW-UP
1978	9809	Levo	NONQUALIFYING IOP
1978	9816	Levo	NONQUALIFYING IOP
1978	9819	Levo	NONQUALIFYING IOP
456	9901	Tim	ADVERSE EVENT (arrhythmia, bone fx, accidental injury)

Three hundred forty-nine (349) 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-97-67-5 - Patients Excluded from the Per-Protocol Analysis

Investigator	Patient	Treatment	Evaluable for Efficacy	Evaluable for Safety	Reason
2427	6904	Tim	NO	YES	NON QUALIFYING IOPS
2496	8210	Levo	NO	YES	INADEQUATE WASHOUT
1237	8707	Tim	NO	YES	NON QUALIFYING IOP
1716	9707	Tim	NO	YES	INADEQUATE WASHOUT
1716	9710	Levo	NO	YES	INADEQUATE WASHOUT
1978	9809	Levo	NO	YES	NON QUALIFYING IOPS
1978	9814	Tim	NO	YES	NON QUALIFYING IOPS
1978	9816	Levo	NO	YES	NON QUALIFYING IOPS
1978	9819	Levo	NO	YES	NON QUALIFYING IOPS
1978	9820	Tim	NO	YES	NON QUALIFYING IOPS

There were no statistically significant differences in demographic subgroup membership between treatments. The demographic statistics for the Intent-to-Treat patients are shown in Table C-97-67-7.

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

Table C-97-67-6 - Baseline IOP Comparison (mmHg)

Treatment	8 AM	10 AM
Levobetaxolol 0.5%	26.6	25.4
Timolol 0.5%	26.8	25.6

Table C-97-67-7 - Demographic Statistics for Intent -To-Treat Patients

	Age				
Treatment	**Mean**	**Std**	**N**	**Min**	**Max**
Timolol 0.5%	64.1	11.9	177	35	92
Levobetaxolol 0.5%	64.3	11.8	182	35	89

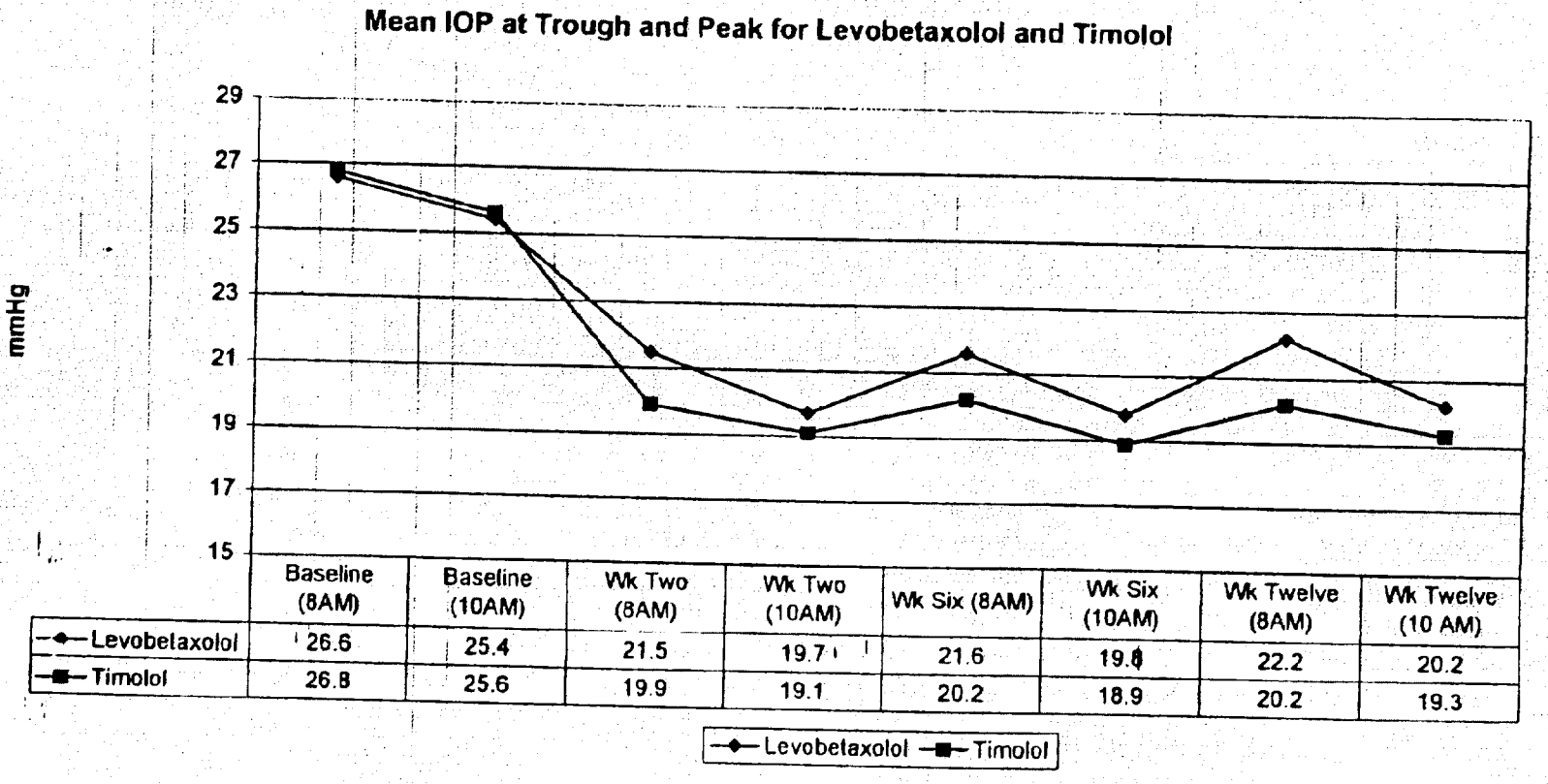
p=0.8441 from the analysis of variance

	Treatment				
	Timolol 0.5%		Levobetaxolol 0.5%		p-value
	N	%	N	%	
Age					
< 65	81	45.8	80	44.0	0.731
>=65	96	54.2	102	56.0	
Sex					
MALE	84	47.5	81	44.5	0.575
FEMALE	93	52.5	101	55.5	
Race					
CAUCASIAN	139	78.5	131	72.0	0.348
BLACK	37	20.9	50	27.5	
OTHER	1	0.6	1	0.5	
Iris					
BROWN	87	49.2	96	52.7	0.930
HAZEL	31	17.5	27	14.8	
GREEN	7	4.0	7	3.8	
BLUE	49	27.7	50	27.5	
GREY	3	1.7	2	1.1	
Diagnosis					
OCULAR HYPERTENSION	30	16.9	39	21.4	0.560
OPEN-ANGLE GLAUCOMA	146	82.5	142	78.0	
OPEN-ANGLE GLAUCOMA WITH PSEUDOEXFOLIATION	1	0.6	1	0.5	

p-values from chi-square test of independence

8.1.1 Efficacy – Protocol C-97-67 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	26.6	25.4	21.5	19.7	21.6	19.8	22.2	20.2
Timolol	26.8	25.6	19.9	19.1	20.2	18.9	20.2	19.3

Table C-97-67-8 - Comparison of Levobetaxolol 0.5% to Timolol 0.5%

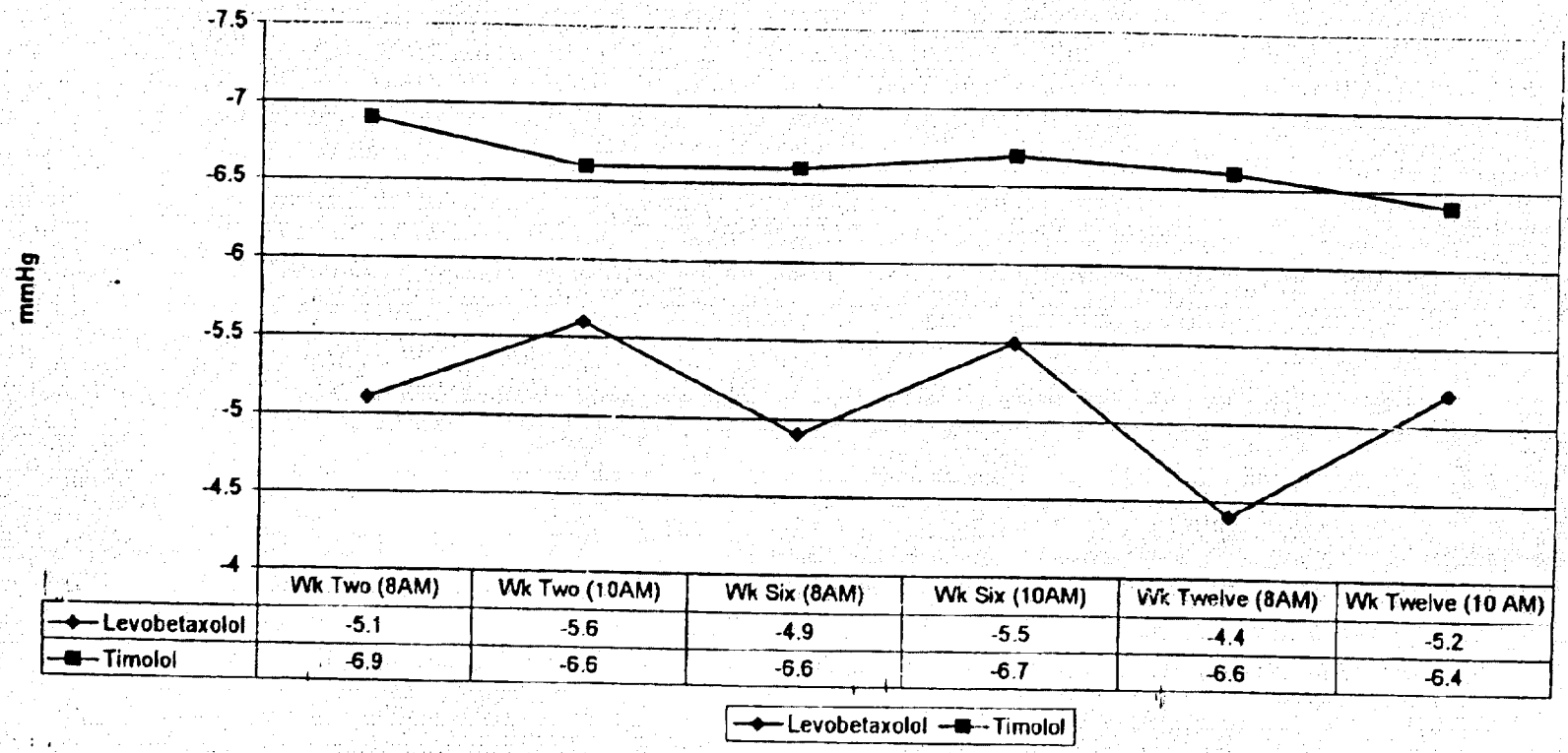
	Intent-to-Treat Data							
	Baseline		Wk 2		Wk 6		Wk 12	
Treatment	8	10	8	10	8	10	8	10
Levo	26.6	25.4	21.5	19.7	21.6	19.8	22.2	20.2
Tim	26.8	25.6	19.9	19.1	20.2	18.9	20.2	19.3
Levo-Tim	-0.2	-0.3	1.6	0.7	1.4	0.9	2.0	0.9
p-value	0.5062	0.4580	0.0003	0.0709	0.0003	0.0127	0.0003	0.0106
Upper 95% CI	0.47	0.44	2.31	1.37	2.13	1.62	2.74	1.65
Lower 95% CI	-0.95	-0.98	0.88	-0.06	0.70	0.20	1.31	0.22

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 2.0 mmHg. The upper 95% confidence interval limits for the treatment differences ranged from 1.37 to 2.74. These were outside the 1-1.5 mmHg limit necessary to establish statistical equivalence at all but one time point (Wk 2 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	-5.1	-5.6	-4.9	-5.5	-4.4	-5.2
Timolol	-6.9	-6.6	-6.6	-6.7	-6.6	-6.4

Table C-97-67-9 - 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	19.9	19.1	20.2	18.9	20.2	19.3
	Mean Change	-6.9	-6.6	-6.6	-6.7	-6.6	-6.4
	Percent Change	-25.5	-25.2	-24.3	-25.9	-24.5	-24.6
Levo 0.5%	Mean IOP	21.5	19.7	21.6	19.8	22.2	20.2
	Mean Change	-5.1	-5.6	-4.9	-5.5	-4.4	-5.2
	Percent Change	-19.1	-22.1	-18.6	-21.7	-16.5	-20.3

Reviewer's Comments:

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

Levobetaxolol IOP reductions at peak (2 hours post-dose) ranged from 5.2 to 5.6 mmHg (20.3 to 22.1% change) from a baseline of 25.4 mmHg. Levobetaxolol IOP reductions at trough (12 hours post-dose) ranged from 4.4 to 5.1 mmHg (16.5 to 19.1% change) from a baseline of 26.6 mmHg.

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

Disqualified Investigator

Investigator 1237 was disqualified due to inconsistencies between the source documentation and the case report forms. This investigator's patients were discontinued from the study and the investigational site was prematurely closed. An analysis of the per-protocol and intent-to-treat data was performed both with and without investigator 1237. Removing this investigator did not change the results of this study. Therefore, the data from this investigator's patients were included in all other analyses.

Reviewer's Comments:

After reviewing reanalyzed intent-to-treat data, agree that removing this investigator did not change the results of this study.

8.1.1 Safety

Adverse Events

Six of the 182 patients (3.3%) receiving levobetaxolol 0.5% discontinued from the study due to adverse events. See Table C-97-67-4, page 14.

Three of the 177 patients (1.7%) receiving timolol 0.5% discontinued from the study due to adverse events. See Table C-97-67-4, page 14.

No deaths were reported during the study.

All serious adverse events are summarized in the following table.

Table C-97-67-10 - Serious Adverse Events

Inv No	Pt No	Treatment	Coded Adverse Event	Outcome of Event	D/C Pt from Study
1236	4714	Levobetaxolol 0.5%	Surgical/Medical Procedure	Resolved w/Tx	Yes
1716	9704	Levobetaxolol 0.5%	Chest Pain	Resolved w/Tx	Yes
456	9901	Timolol 0.5%	Bone Fracture	Resolved w/Tx	Yes
1236	4721	Timolol 0.5%	Accidental Injury	Resolved w/Tx	No
1927	7914	Timolol 0.5%	Pneumonia	Resolved w/Tx	No
			Hem Eye, Visual Acuity Decrease	Resolved 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 adverse events in levobetaxolol 0.5% treated subjects were transient or temporary ocular discomfort (burning, stinging) upon instillation (11.0%) and blurred vision (2.2%).

The most frequent ocular adverse event in timolol 0.5% treated subjects was ocular discomfort (burning, stinging) (1.7%).

Table C-97-67-11 - Overall Frequency and Incidence of Adverse Events

	Levobetaxolol 0.5% N = 182		Timolol 0.5% N = 177	
	N	%	N	%
Ocular				
Discomfort Eye	20	11.0	3	1.7
Vision Blurred	4	2.2	1	0.6
Cataract	2	1.1	2	1.1
Discharge Eye Nos	2	1.1	1	0.6
Vitreous Disorder	2	1.1	1	0.6
Cells	1	0.5		
Conjunctivitis	1	0.5		
Foreign Body Sensation	1	0.5	1	0.6
Hem Conjunctival	1	0.5		
Hyperemia Eye	1	0.5	1	0.6
Tearing	1	0.5	2	1.1
Injury Accident	1	0.5	1	0.6
Irritation Eye	1	0.5		
Lid Margin Crusting	1	0.5		
Pain Eye	1	0.5	1	0.6
Pruritis Eye	1	0.5		
Scotoma	1	0.5		
Staining Corneal	1	0.5		
Tearing	1	0.5	2	1.1
Visual Acuity Dec	1	0.5	2	1.1
Dry Eye			2	1.1
Optic Nerve Disorder			2	1.1
Retinal Disorder			2	1.1
Blepharitis			1	0.6
Chalazion			1	0.6
Follicles Conjunctivitis			1	0.6
Hem Eye			1	0.6
Hordeolum			1	0.6
Iritis			1	0.6
Keratitis			1	0.6
Vision Abnorm			1	0.6
Vision Change			1	0.6

Table C-97-67-11 - Overall Frequency and Incidence of Adverse Events – Continued

	Levobetaxolol 0.5% N = 182		Timolol 0.5% N = 177	
	N	%	N	%
Nonocular				
Body as a Whole				
Surgical/Medical Proc	3	1.6	1	0.6
Infection	2	1.1	2	1.1
Pain Chest	2	1.1		
Anaphylaxis	1	0.5		
Asthenia	1	0.5		
Cyst	1	0.5		
Flu Syndrome	1	0.5		
Headache	1	0.5	2	1.1
Injury Accident	1	0.5	1	0.6
Pain Back			2	1.1
Cardiovascular System				
Hypotension	1	0.5		
Hypertension			3	1.7
Ischemia Cerebral			2	1.1
Arrhythmia			1	0.6
Digestive System				
Dyspepsia	3	1.6		
Cholelithiasis			1	0.6
Gingivitis			1	0.6
Ulcer Mouth			1	0.6
Endocrine				
Hypothyroidism	1	0.5		
Diabetes Mellitus			1	0.6
Metabolic/Nutritional Dis				
Hypercholesterolemia	1	0.5		
Hyperlipidemia	1	0.5		
Musculoskeletal				
Bone Frac Spontan			1	0.6
Myalgia			1	0.6
Nervous System				
Anxiety	1	0.5		
Vertigo	1	0.5		
Hypertonia			1	0.6
Insomnia			1	0.6
Somnolence			1	0.6

Table C-97-67-11 - Overall Frequency and Incidence of Adverse Events – Continued

	Levobetaxolol 0.5% N = 182		Timolol 0.5% N = 177	
	N	%	N	%
Nonocular				
Respiratory System				
Dyspnea	3	1.6		
Pharyngitis	1	0.5		
Sinusitis			4	2.3
Bronchitis			2	1.1
Pneumonia			1	0.6
Rhinitis			1	0.6
Skin and Appendages				
Herpes Zoster			1	0.6
Infect Nail			1	0.6
Pruritis			1	0.6
Special Senses				
Otitis Media	1	0.5		
Urogenital System				
Abscess Breast	1	0.5		
Cystitis			1	0.6
Infect Urin Tract			1	0.6

Visual Acuity, Ocular Signs, Dilated Fundus

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 increase of fundus parameters (retina macula choroid, optic nerve) was observed between levobetaxolol 0.5% and timolol 0.5%.

Cup/Disc Ratio

Table C-97-67-12 - Summary Statistics for Cup/Disc Ratio Change from Baseline

		Baseline	Change at Exit
Levobetaxolol	**MEAN**	0.447	0.007
	STD	0.177	0.038
	N	182	180
	MIN		
	MAX		
Timolol	**MEAN**	0.450	-0.001
	STD	0.163	0.034
	N	177	173
	MIN		
	MAX		

p=0.0429 from analysis of variance comparing treatments

Reviewer's Comments:

A statistically significant (p = 0.0419) difference in the increase of cup disc ratio was observed between levobetaxolol 0.5% and timolol 0.5%.

The difference between treatment means is approximately 0.008 and is not clinically significant.

Systolic/Diastolic Blood Pressure

Reviewer's Comments:

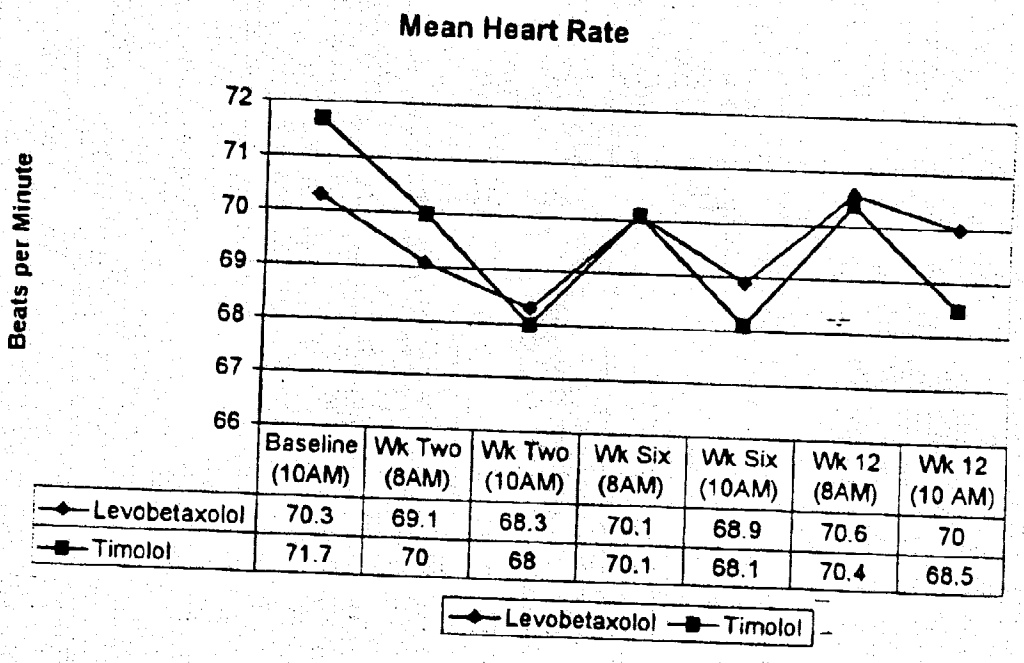
No statistically significant difference in systolic or diastolic blood pressure was noted between levobetaxolol 0.05% and timolol 0.5%.

Pulse

A statistically significant (p = 0.0307) 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 no statistically significant difference or clinically significant difference found between mean heart rates by treatment group.



	Baseline (10AM)	Wk Two (8AM)	Wk Two (10AM)	Wk Six (8AM)	Wk Six (10AM)	Wk 12 (8AM)	Wk 12 (10 AM)
Levobetaxolol	70.3	69.1	68.3	70.1	68.9	70.6	70
Timolol	71.7	70	68	70.1	68.1	70.4	68.5

8.1.1 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 (5.2 to 5.6 mmHg) and at trough (4.4 to 5.1 mmHg) are clinically relevant.

Adverse experiences appeared generally mild-moderate in nature.

8 **Clinical Studies**

8.1.2 **Study #2** **Protocol C-97-80**

Title: Identical to Protocol C-97-67

Objective: Identical to Protocol C-97-67

Study Design: Identical to Protocol C-97-67

Test Drug Schedule: Identical to Protocol C-97-67

Principal Investigator	Inv. No.	Dates of Participation	Number of Patients Intent to Treat	Per Protocol
Robert Caine, M.D.	1208	3/17/98 to 11/25/98	16	15
William Caldwell, M.D.	2465	5/28/98 to 11/20/98	6	6
Stephen J. Capps, M.D.	2466	No patients were enrolled	0	0
Hersh Chopra, M.D.	2431	4/28/98 to 11/16/98	8	7
Andrew A. Dahl, M.D.	2452	4/14/98 to 1/6/99	29	26
Andrew Dannemann, M.D.	2468	4/27/98 to 11/23/98	3	2
Marcel Estopinal, M.D.	2134	5/27/98 to 11/17/98	16	16
James G. Ferguson, M.D.	2250	4/2/98 to 9/2/98	5	5
Gregory Hoffpauir, M.D.	2255	6/19/98 to 11/4/98	3	3
Alan Kohn, M.D.	2453	3/17/98 to 12/29/98	15	15
Harry Kolodner, M.D.	1783	4/8/98 to 10/9/98	14	14
Joseph Krug, M.D.	2439	4/20/98 to 11/6 98	16	14
Stephen Leff, M.D.	2553	6/24/98 to 11/11/98	4	3
Albert Munn III, M.D.	2437	4/15/98 to 9/1/98	3	3
Kenneth Olander, M.D.	750	5/21/98 to 10/20/98	8	8
Mitchell Porias, M.D.	2445	3/31/98 to 1/21/99	23	21
Michael H. Rotberg, M.D.	1393	10/1/98 to 2/22/99	5	5
Kenneth Sall, M.D.	1806	6/16/98 to 2/15/99	23	23
Morris Segall, M.D.	738	3/30/98 to 7/13/98	4	0
Harold Skalka, M.D.	2432	5/14/98 to 12/2/98	4	4
*Alfred Solish, M.D.	2454	3/30/98 to 12/15/98	23	20
John F. Stamler, M.D.	2444	3/16/98 to 9/10/98	10	9
Robert Stewart, M.D.	271	6/15/98 to 1/19/99	36	36
Richard Sturm, M.D.	2247	3/17/98 to 1/13/99	40	39
Jonathan Till, M.D.	2467	3/30/98 to 12/28/98	14	11
Jeffrey Whitsett, M.D.	2435	3/25/98 to 8/25/98	20	20

*financial certification or disclosure statement not received from investigator

8.1.2 Study Design

Identical to Protocol C-97-67 except 25 investigational sites utilized.

Subject Disposition and Demographics

Three hundred forty-eight (348) patients were enrolled into the study and randomized to drug at 25 sites. All 348 patients were included in the safety and intent-to-treat analyses. Three hundred twenty-five (325) patients completed twelve weeks of therapy. Twenty-three (13 in Levobetaxolol 0.5%; 10 in Timolol 0.5%) patients were discontinued from the study for various reasons, including adverse events (7 patients); lost to follow-up (2 patients); protocol non-compliance (4 patients); non-qualifying IOP (9 patients); and patient decision (1 patient).

Table C-97-80-1 - Discontinued Patients and Reason

Investigator	Patient	Treatment	Reason
1208	103	Levobetaxolol 0.5%	ADVERSE EVENT (anomaly vascular)
2431	201	Levobetaxolol 0.5%	NONCOMPLIANCE
2452	301	Levobetaxolol 0.5%	ADVERSE EVENT (anxiety, asthenia, tachycardia)
2452	328	Levobetaxolol 0.5%	NONQUALIFYING IOP
2453	510	Levobetaxolol 0.5%	ADVERSE EVENT (bradycardia, dizziness, heart block)
1783	609	Timolol 0.5%	ADVERSE EVENT (tearing)
2439	703	Timolol 0.5%	NONQUALIFYING IOP
738	1301	Timolol 0.5%	NONCOMPLIANCE
738	1302	Levobetaxolol 0.5%	NONQUALIFYING IOP
738	1303	Levobetaxolol 0.5%	NONQUALIFYING IOP
738	1304	Timolol 0.5%	NONQUALIFYING IOP
2454	1606	Levobetaxolol 0.5%	ADVERSE EVENT (alopecia)
2454	1619	Levobetaxolol 0.5%	ADVERSE EVENT (alopecia)
2247	1821	Levobetaxolol 0.5%	NONQUALIFYING IOP
2465	2701	Timolol 0.5%	ADVERSE EVENT (edema, hyperemia, pruritus eye)
2465	2706	Levobetaxolol 0.5%	NONCOMPLIANCE
2468	2813	Timolol 0.5%	NONQUALIFYING IOP
2467	2903	Timolol 0.5%	NONQUALIFYING IOP
2553	7201	Levobetaxolol 0.5%	NONCOMPLIANCE
2553	7202	Timolol 0.5%	NONQUALIFYING IOP
1806	7303	Timolol 0.5%	PATIENT DECISION
1806	7323	Timolol 0.5%	LOST TO FOLLOW-UP
1393	9605	Levobetaxolol 0.5%	LOST TO FOLLOW-UP

Three hundred twenty-five (325) 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-97-80-2 - Patients Excluded from the Per-Protocol Analysis

Investigator	Patient	Treatment	Evaluable for Efficacy	Evaluable for Safety	Reason
1208	104	Tim	NO	YES	INADEQUATE WASHOUT
2431	201	Levo	NO	YES	NONCOMPLIANCE
2452	314	Levo	NO	YES	CONTRAINDICATED RX
2452	322	Levo	NO	YES	CONTRAINDICATED RX
2452	328	Levo	NO	YES	NONQUALIFYING IOPS
2439	703	Tim	NO	YES	NONQUALIFYING IOPS
2439	706	Levo	NO	YES	INADEQUATE WASHOUT
2445	1201	Tim	NO	YES	INADEQUATE WASHOUT
2445	1202	Levo	NO	YES	NONQUALIFYING IOPS
738	1301	Tim	NO	YES	NONQUALIFYING IOPS
738	1302	Levo	NO	YES	NONQUALIFYING IOPS
738	1303	Levo	NO	YES	NONQUALIFYING IOPS
738	1304	Tim	NO	YES	NONQUALIFYING IOPS
2454	1604	Tim	NO	YES	CONTRAINDICATED RX
2454	1612	Levo	NO	YES	CONTRAINDICATED RX
2454	1614	Tim	NO	YES	CONTRAINDICATED RX
2444	1707	Tim	NO	YES	INADEQUATE WASHOUT
2247	1821	Levo	NO	YES	NONQUALIFYING IOPS
2468	2813	Tim	NO	YES	NONQUALIFYING IOPS
2467	2901	Tim	NO	YES	NONQUALIFYING IOPS
2467	2903	Tim	NO	YES	NONQUALIFYING IOPS
2467	2904	Levo	NO	YES	INADEQUATE WASHOUT
2553	7202	Tim	NO	YES	NONQUALIFYING IOPS

There were no statistically significant differences in demographic subgroup membership between treatments. The demographic statistics for the Intent-to-Treat patients are shown in Table C-97-80-4.

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

Table C-97-80-3 - Baseline IOP Comparison (mmHg)

Treatment	8 AM	10 AM
Levobetaxolol 0.5%	26.3	25.2
Timolol 0.5%	26.8	25.3

Table C-97-80-4 - Demographic Statistics for Intent -To-Treat Patients

	Age				
	Mean	Std	N	Min	Max
Treatment					
Levobetaxolol 0.5%	62.1	13.3	174	22	92
Timolol 0.5%	61.8	13.1	174	25	87

p=0.8299 in the analysis of variance

	Treatment				
	Levobetaxolol 0.5%		Timolol 0.5%		p-value
	N	%	N	%	
Age					
< 65	91	52.3	91	52.3	1.000
>=65	83	47.7	83	47.7	
Sex					
MALE	74	42.5	74	42.5	1.000
FEMALE	100	57.5	100	57.5	
Race					
CAUCASIAN	128	73.6	120	69.0	0.421
BLACK	31	17.8	31	17.8	
ASIAN	1	0.6	4	2.3	
OTHER	14	8.0	19	10.9	
Iris					
BROWN	93	53.4	94	54.0	0.869
HAZEL	22	12.6	23	13.2	
GREEN	7	4.0	8	4.6	
BLUE	52	29.9	48	27.6	
GREY	.	.	1	0.6	
Diagnosis					
OCULAR HYPERTENSION	55	31.6	69	39.7	0.192
OPEN-ANGLE GLAUCOMA	118	67.8	102	58.6	
OPEN-ANGLE GLAUCOMA WITH PIGMENTARY COMPONENT	.	.	2	1.1	
OPEN-ANGLE GLAUCOMA WITH PSEUDOEXFOLIATION COMPONENT	1	0.6	1	0.6	

p-values from chi-square test of independence