MOR3

Table C–97-68-2 - Study Plan for Protocol C-97-67
(Levobetaxolol Cardiovascular Safety Study)

Activity	Screening and Baseline Exam	Study Period 1 (At least 7 days after Baseline)		7 - Day Washout	Study Period 2	
		PreDose	Post Dose Testing		PreDose	Post Dose Testing
Medical History	X					
Demographics	X					
Study Eligibility	X					
Subject Consent	X					
Laboratory Testing	X					X
History	X					
Stethoscopic Exam	X					
BP, Heart Rate, ECG	X	X	X		X	X
Stress Test	X		X			X
Adverse Events			X		X	X
Complete Exit Form*		X*	X*	X*	X*	X*

*Complete an Exit Form at any time if the subject exits the study prematurely or when subject completes the study successfully.

Subject Disposition and Demographics

One subject discontinued the study prematurely after Timolol 0.5% administration due to an irregular ECG reading.

All subjects were evaluable for safety and efficacy. Thirty-two (N=32) subjects were evaluated for safety for Levobetaxolol, and thirty-three (N=33) for Timolol.

Table C-97-68-3 – Discontinued Patients and Reason

Investigator No.	Subject No.	Treatment Group	Reason for Discontinuation
1965	1004	Timolol 0.5%	Irregular ECG (a-fib)

There were no statistically significant differences between treatment sequence groups in the demographic subgroup composition. The demographic statistics for the Intent-to-Treat subjects are shown in Table C-97-68-4.

Table C-97-68-4 - Demographic Statistics for Intent -To-Treat Patients

	Age				
	Mean	Std	N	Min	Max
Treatment					
Levo-Tim	64.6	3.8	16	60	72
Tim-Levo	64.5	4.3	17	60	72

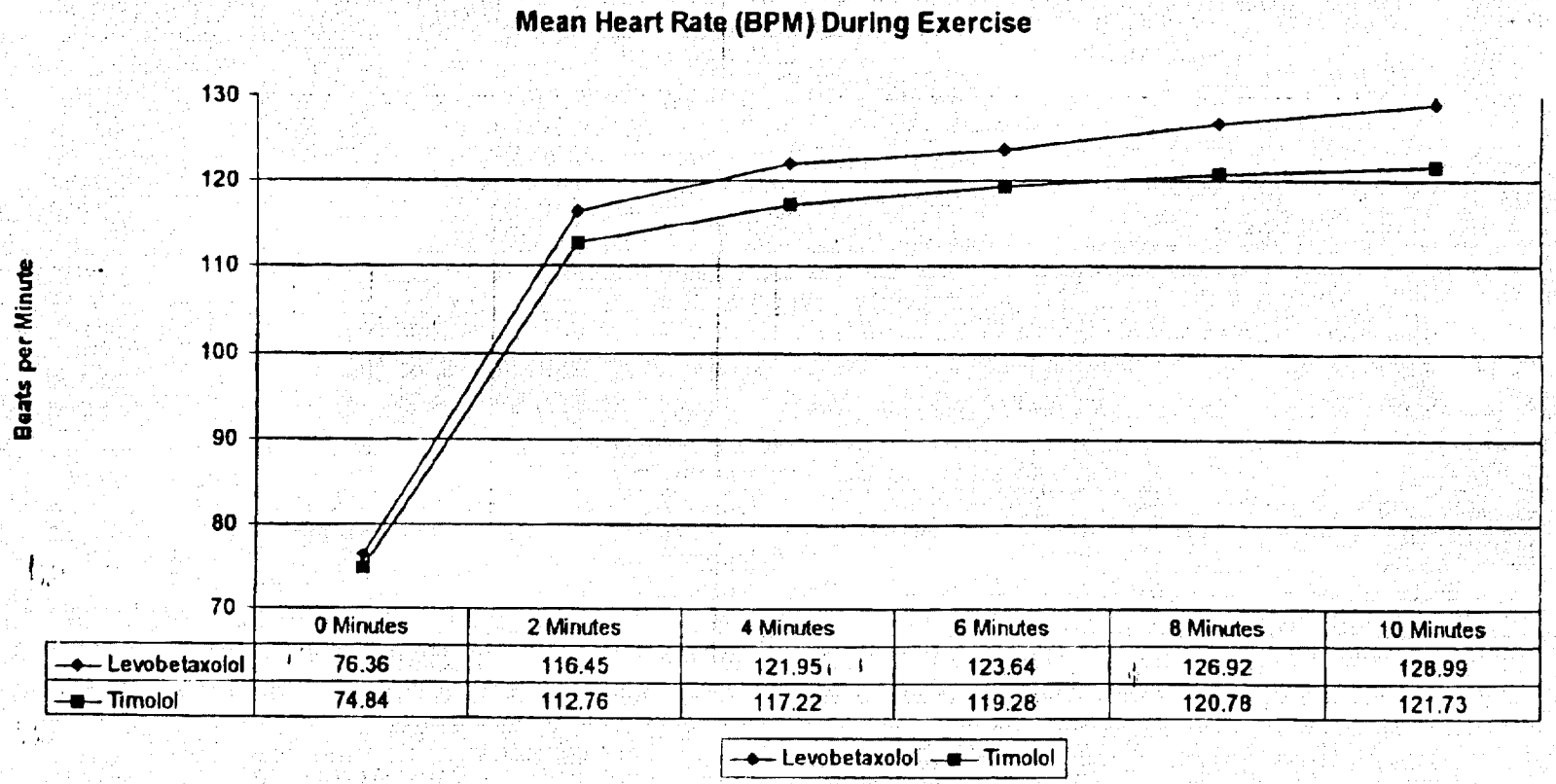
p=0.9463 in the one-way analysis of variance.

	Treatment				
	Levo-Tim		Tim-Levo		p-value*
	N	%	N	%	
Age					
<65	10	62.5	10	58.8	0.829
>=65	6	37.5	7	41.2	
Sex					
MALE	8	50.0	7	41.2	0.611
FEMALE	8	50.0	10	58.8	
Race					
CAUCASIAN	13	81.3	14	82.4	0.547
BLACK	.	.	1	5.9	
OTHER	3	18.8	2	11.8	
Iris					
BROWN	8	50.0	4	23.5	0.433
HAZEL	3	18.8	5	29.4	
GREEN	1	6.3	3	17.6	
BLUE	4	25.0	4	23.5	
GREY	.	.	1	5.9	

* p-values from chi-square test of independence

8.1.4 Efficacy – Protocol C-97-68 Intent-to-Treat Population

Primary Efficacy Variable



	0 Minutes	2 Minutes	4 Minutes	6 Minutes	8 Minutes	10 Minutes
Levobetaxolol	76.36	116.45	121.95	123.64	126.92	128.99
Timolol	74.84	112.76	117.22	119.28	120.78	121.73

Table C-97-68-5 - Comparison of Mean Heart Rate (BPM) During Exercise Phase (Intent to Treat Data)

	Minutes					
Treatment	**0**	**2**	**4**	**6**	**8**	**10**
Levobetaxolol 0.5%	76.36	116.45	121.95	123.64	126.92	128.99
Timolol 0.5%	74.84	112.76	117.22	119.28	120.78	121.73
Levo-Tim	1.52	3.70	4.73	4.36	6.14	7.26
P Value	0.3062	0.0137	0.0017	0.0038	0.0001	0.0001

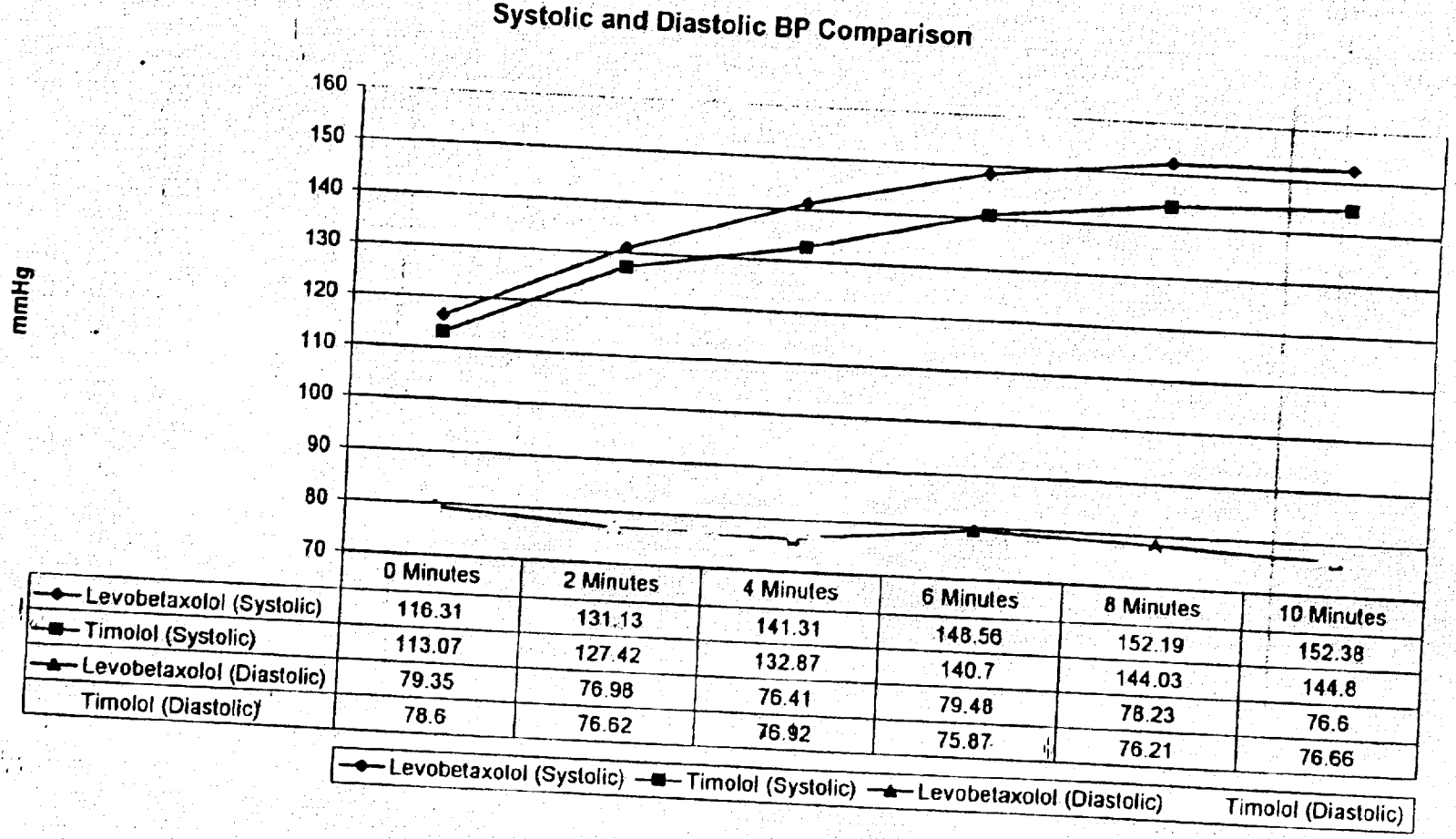
All values are least squares means.

Reviewer's Comments:

Subjects treated with timolol 0.5% demonstrated statistically significantly lower mean heart rates in response to exercise compared to those treated with levobetaxolol 0.5%.

The differences between treatment ranged from [redacted] *and were significantly different at each time point over the 10 minute evaluation period. Baseline difference between treatments was 1.52 bpm, but this was not statistically significant.*

Secondary Efficacy Variables



	0 Minutes	2 Minutes	4 Minutes	6 Minutes	8 Minutes	10 Minutes
Levobetaxolol (Systolic)	116.31	131.13	141.31	148.56	152.19	152.38
Timolol (Systolic)	113.07	127.42	132.87	140.7	144.03	144.8
Levobetaxolol (Diastolic)	79.35	76.98	76.41	79.48	78.23	76.6
Timolol (Diastolic)	78.6	76.62	76.92	75.87	76.21	76.66

Table C-97-68-6 - Comparison of Systolic Blood Pressure and Diastolic Blood Pressure (Intent to Treat Data)

Systolic Blood Pressure (mmHg)

	Minutes					
Treatment	**0**	**2**	**4**	**6**	**8**	**10**
Levobetaxolol 0.5%	116.31	131.13	141.31	148.56	152.19	152.38
Timolol 0.5%	113.07	127.42	132.87	140.70	144.03	144.80
Levo-Tim	3.25	3.70	8.45	7.86	8.16	7.58
P Value	0.3061	0.2430	0.0087	0.0144	0.0112	0.0182

Diastolic Blood Pressure (mmHg)

	Minutes					
Treatment	**0**	**2**	**4**	**6**	**8**	**10**
Levobetaxolol 0.5%	79.35	76.98	76.41	79.48	78.23	76.60
Timolol 0.5%	78.60	76.62	76.92	75.87	76.21	76.66
Levo-Tim	0.75	0.36	-0.51	3.61	2.02	-0.06
P Value	0.6798	0.8431	0.7806	0.0482	0.2662	0.9748

All values are least square means.

Reviewer's Comments:

Treatment with Timolol 0.5% resulted in significantly lower systolic blood pressure after four (4) minutes of exercise which remained significant throughout the ten (10) minute treatment period compared to Levobetaxolol 0.5%. The systolic blood pressure difference between treatments ranged [redacted] Baseline difference between treatments was 3.25 mmHg, but this was not statistically significant.

There were no treatment differences for the diastolic blood pressures except at the six (6) minute time point.

8.1.4 Safety

Adverse Events

None of the 32 patients receiving levobetaxolol 0.5% discontinued from the study due to adverse events.

One of the 33 patients (3.03%) receiving timolol 0.5% discontinued from the study due to an adverse event. See Table C-97-68-7 below.

No deaths were reported during the study.

All serious adverse events are summarized in the following table.

Table C-97-68-7 - Serious Adverse Events

Prot No	Inv No	Pt No	Treatment	Coded Adverse Event	Outcome of Event	D/C Study
C9768	1965	1004	Timolol 0.5%	Fibrilat Atr	Resolved wo/Tx	Yes

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 overall adverse event with Levobetaxolol 0.5% was transient ocular discomfort (burning; 3.1%) upon instillation.

Table C-97-68-8 - Overall Frequency and Incidence of Adverse Events

	Levobetaxolol 0.5% N = 32		Timolol 0.5% N = 33	
	N	%	N	%
Ocular				
Discomfort Eye	1	3.1		
Dry Eye			1	3.0
Foreign Body Sensation			1	3.0
Vision Blurred			1	3.0
Nonocular				
Cardiovascular System				
Fibrillat Atrial			1	3.0
Vasodilatation			1	3.0
Special Senses				
Ear Disorder			1	3.0

Clinical Laboratory Evaluation

No clinically relevant changes from baseline in clinical laboratory data were observed during the study.

Reviewer's Comments:

There are sporadic statistically significant lab value changes from baseline (increase in fasting chloride levels, decrease in fasting glucose levels, decrease in fasting cholesterol levels) in subjects receiving levobetaxolol 0.5% and timolol 0.5%. These are not clinically significant.

Electrocardiogram

No clinically relevant or statistically significant difference in change from baseline of electrocardiogram parameters was observed between levobetaxolol 0.5% and timolol 0.5%. One subject (1004) receiving timolol 0.5% during period 1 experienced an abnormal electrocardiogram (atrial fibrillation) and was discontinued from the study.

Reviewer's Comments:

There are no statistically significant differences in change from baseline for Ventricular Rate, PR Interval, QRS Duration, or QT Interval.

8.1.4 Reviewer's Summary of Efficacy and Safety

Subjects treated with timolol 0.5% demonstrated statistically significantly lower mean heart rates in response to exercise compared to those treated with levobetaxolol 0.5%.

Adverse experiences appeared generally mild-moderate in nature.

8 **Clinical Studies**

8.1.5 **Study #5 Protocol C-98-57**

Title: A Single-Drop, Two-Period, Crossover Comparison of Levobetaxolol 0.5% Ophthalmic Suspension versus Timolol 0.5% Ophthalmic Solution in Patients With Reactive Airway Disease.

Objective: To compare the effects of Levobetaxolol 0.5% Ophthalmic Suspension and Timolol 0.5% Ophthalmic Solution on airflow (pulmonary function) as measured by forced expiratory volume in one second (FEV_1) and FVC in patients with reversible reactive airway disease.

Study Design: A randomized, double-masked, single center, active-controlled, two-way crossover study.

Test Drug Schedule: Subjects were randomized to receive either one drop in each eye Timolol 0.5% or Levobetaxolol 0.5% at Study Visit 1 and vice versa at Study Visit 2.

PRINCIPAL INVESTIGATOR	INVESTIGATOR No.	DATES OF PARTICIPATION	No. SUBJECTS
Catherine Mayolle, M.D. 5 boulevard Henri Becquerel 14052 Caen Cedex 4, FRANCE	2253	30 Nov 98-18 Feb 99	30

Reviewer's Comments:

A financial certification or disclosure statement not received from this investigator.

8.1.5 **Study Design**

The study was a prospective, single center (1 site), double-masked, active-controlled, randomized safety trial designed to compare the acute effects of levobetaxolol 0.5% and timolol 0.5% on pulmonary function. Patients enrolled in the study were adults of any race and either sex diagnosed with reactive airway disease. Target enrollment for this study was 24 completed patients. In order to ensure this, 30 patients were randomized. The volunteer patients were randomized into one of two treatment sequences (Levobetaxolol 0.5%-Timolol 0.5% or Timolol 0.5%-Levobetaxolol 0.5%) in an equal 1:1 ratio.

The maximum total length of the study was twenty-nine (29) days and consisted of three (3) phases: Screening, Eligibility and Study Visits.

The Eligibility Visit was carried out to document the pulmonary patient's response to Timolol 0.5% and to perform entry level testing. Baseline FEV_1 and FVC were measured for each patient. Baseline blood pressure and resting pulse rate were also obtained in the sitting position after a 5-minute rest period and an ECG (12 leads) was conducted. In order to qualify for participation in the study, patients had to demonstrate a baseline FEV_1 not greater than 60% of normal predicted values for the patient's age, sex and height, and a FEV_1 of at least 1.5 Liters. The investigator then instilled one drop of Timolol 0.5% in both eyes.

Spirometry testing was performed at 15, 30, 60, 90, 120 and 180 minutes after drug instillation. If the on-drug FEV_1 values were reduced by 15% compared to baseline at any observation time, the patient qualified for participation in the study and returned one week later for Study Visit 1.

At Study Visit 1, baseline FEV_1 and FVC were measured for each patient. Baseline blood pressure and resting pulse rate were also obtained in the sitting position after a 5-minute rest period. The investigator instilled one drop of masked test medication labeled for Visit 1 in both eyes. Follow-up spirometry testing was performed at 15, 30, 60, 90, 120 and 180 minutes after drug instillation. Blood pressure and resting pulse rates in the sitting position were monitored at each observation time.

These steps were repeated seven (7) days later at Study Visit 2 with the investigator instilling one drop of masked test medication labeled for Visit 2 in both eyes.

If any patient demonstrated a $\geq$ 50% reduction in the pulmonary parameters tested and/or in the opinion of the investigator intervention was warranted, a bronchodilator could be given to reverse the effect of the ocular medication. In such cases, one to two aerosol puffs of a beta-sympathomimetic (salbutamol)/anticholinergic (ipratropium bromide) combination (COMBIVENT®, Boehringer Ingelheim) were administered.

Study Medications

Alcon planned to provide the investigational site with open labeled timolol 0.5% in sterile transfer bottles for the Eligibility test procedures. Due to the early start at the site the first 17 patients received marketed timolol 0.5% in commercial bottles. The next 50 patients received sterile transferred timolol 0.5% as planned. The last nine (9) patients were tested again with marketed timolol 0.5% in commercial bottles.

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 and the exam number.

Table C-98-57-1 - Study Medications

Drug	Timolol 0.5% Open label	Levobetaxolol 0.5% Masked	Timolol 0.5% masked[b]
Lot number	ASE-3012 403610[a]	ASE-3013	ASE-3012

[a]Commercial Lot of Timolol 0.5% [b]Sterile transfer of Timoptic.

Study Masking

Identical to Protocol C-97-68.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

Study subjects included adults of either sex and any race, aged eighteen (18) years or older, with reversible reactive airway disease. Qualified patients must have demonstrated a systemic response to topical Timolol as evidenced by at least a 15% reduction in FEV_1 in order to participate in this study.

Exclusion Criteria

Patients with any of the following conditions were not eligible for participation in the study:

1) History of sensitivity to oral or topical beta-blockers, beta-agonists, anticholinergics, vasoconstrictors, antihistamines, or any component of these medications that in the opinion of the investigator, would preclude the safe administration of a topical beta-blocker

2) Spirometry baseline FEV_1 or baseline FVC at the Eligibility Visit which was < 60% of normal predicted values for that patient's age, sex and height.

3) Baseline FEV_1 at the Eligibility Visit which was < 1.5 Liter.

4) Any ocular pathological condition which might have been adversely affected by the topical test treatments.

5) Systemic beta-blockers used within the past 30 days.

6) Oral beta-stimulants used within the past 30 days.

7) Systemic beta-sympathomimetic agents used within 30 days prior to Study start.

8) Participation in any other investigational drug study within 30 days prior to Study start.

9) Pregnant or nursing women and women of childbearing potential who were not using adequate contraceptive methods.

10) History of current or clinically relevant cardiovascular disease, diabetes, hyperthyroidism, or neurological, hepatic, and/or renal disease. Patients with clinically significant hematologic, electrolyte, renal or hepatic abnormalities based upon laboratory testing performed at the Eligibility Visit.

11) Resting pulse greater than 100 or less than 60 beats per minute as measured prior to spirometry test at the Eligibility Visit.

12) Any history of pulmonary surgery.

13) Inability to perform correctly spirometry tests as described in study procedures.

14) Inability to discontinue smoking during the test procedures.

15) Patients using topical beta-blocker therapy were not excluded from participation in the study; however, drops had to be withdrawn for at least 5 days prior to the start of the study and during the study.

16) Patients could continue to receive their oral or inhaled medication, either bronchodilators (except oral beta-sympathomimetic agents), steroids, or both, as prescribed by their physicians. However, patients were not allowed to use their inhaled medications on the day of testing. Additionally, patients had to withdraw use of inhaled beta-sympathomimetic agents at least 24 hours prior to each study exam.

17) In order to eliminate possible intrapatient variability, the investigator urged each patient to use his/her systemic and/or inhaled medication as uniformly as possible during the course of the study.

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

Reviewer's Comments:

The study design for this protocol is fundamentally flawed – this should be taken into consideration when interpreting its results. The Inclusion Criteria preselect subjects sensitive to Timoptic, but Timoptic is used as the comparator for levobetaxolol in this protocol.

Table C-98-57-2 - Study Plan for Protocol C-98-57 (Levobetaxolol Pulmonary Study)

	Screening Visit	Eligibility Visit	Study Period 1	7-Day Washout	Study Period 2	Exit Visit
Patient Consent	X					
Medical History	X					
Demographic Information	X					
Screening Stethoscopic Exam	X					
Pregnancy Test[a]	X					X
Patient Eligibility Determined		X				
Baseline FEV/FVC		X	X		X	
BP, Pulse	X	X[b]	X[c]		X[c]	
Instill Test Med		X[d]	X		X	
Postdose FEV_1 + FVC						
15 min.		X	X		X	
30 min.		X	X		X	
60 min.		X	X		X	
90 min.		X	X		X	
120 min.		X	X		X	
180 min.		X	X		X	
Lab Tests		X				X
ECG		X				X
Administer COMBIVENT® when indicated		X	X		X	
Dismiss Subject			X[e]			X

[a]Women of childbearing potential.
[b]Blood pressure and pulse not required at the eligibility exam if conducted on the same day as the screening exam.
[c]Blood pressure and pulse will be obtained before dosing and at each observation time.
[d]Open-label Timolol 0.5%.
[e]Complete exit exam if patient exits during period one.

Efficacy Variables

The primary efficacy variable was pulmonary airflow as measured by forced expiratory volume in one second (FEV_1).

Forced vital capacity (FVC) was a secondary efficacy variable.

Safety Variables

This study included the following safety variables:

Examination of Heart and Lungs
Stethoscopic examination at screening.

Laboratory Testing
Hematology (CBC, platelet count) and blood chemistry (glycemia, creatininemia, ionogram including Na, K, Cl, ASAT, ALAT, alkaline phosphatase, γGT, direct/indirect and total bilirubinemia, triglycerides, total cholesterol, HIV, Hepatitis B and C) on patients qualifying after spirometry. Performed at Eligibility and at 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 Eligibility and at exit.

Subject Disposition and Demographics

A total of thirty (30) patients in one (1) single investigational site were randomized to treatment. All are evaluable for efficacy and safety. All 30 patients received both treatments in this cross-over study and were thus included in the efficacy analyses.

A total of eighty (80) patients were screened to get thirty (30) eligible patients. Four patients were not eligible because of predose spirometry requirements. Seventy-six (76) patients received open labeled Timolol 0.5% during the Eligibility phase. Forty-five (45) of these patients were not randomized to treatment because they did not meet the Eligibility criteria of postdose spirometry. One (1) patient was not randomized because already thirty (30) patients were eligible for the study. CRFs were only collected from the randomized patients. Only data from patients who were randomized to treatment are presented in this report.

Only one (1) patient was discontinued from the study following randomization.

Table C-98-57-3 - Discontinued Patients and Reason

Investigator No.	Subject No.	Treatment Group	Reason for Discontinuation
2253	103	Levo-Tim	Dyspnea

There were no statistically significant differences between treatment sequence groups in their demographic composition. Also, there were no differences between treatments in their mean pulmonary or cardiovascular parameters.

Table C-98-57-4 - Demographic Statistics

	Age				
	Mean	Std	N	Min	Max
Treatment					
Tim-Levo	24.0	7.1	15		
Levo-Tim	29.7	9.7	15		

p = 0.0763 from one-way analysis of variance

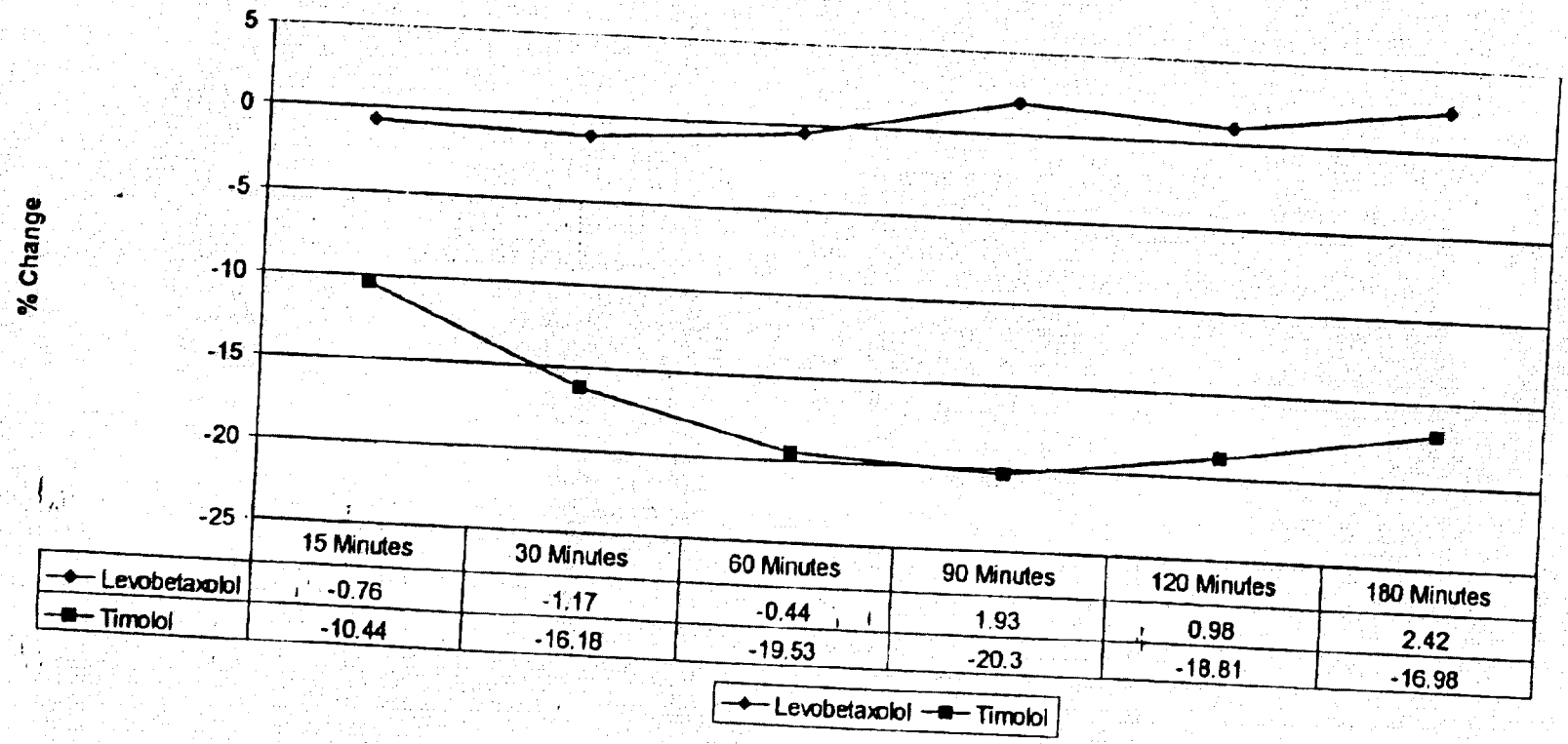
	Treatment Sequence				
	Tim-Levo		Levo-Tim		
	N	%	N	%	p-value*
Age					
<65	15	100.0	15	100.0	1.000
Sex					
MALE	7	46.7	9	60.0	0.464
FEMALE	8	53.3	6	40.0	
Race					
CAUCASIAN	15	100.0	13	86.7	0.143
BLACK	.	.	2	13.3	
Iris					
BROWN	6	40.0	8	53.3	0.390
GREEN	.	.	1	6.7	
BLUE	9	60.0	6	40.0	
Diagnosis					
ASTHMA	15	100.0	15	100.0	1.000

*p-values from chi-square test of independence

8.1.5 Efficacy – Protocol C-98-57 Intent-to-Treat Population

Primary Efficacy Variable

Mean Percent Change From Baseline in FEV1



	15 Minutes	30 Minutes	60 Minutes	90 Minutes	120 Minutes	180 Minutes
Levobetaxolol	-0.76	-1.17	-0.44	1.93	0.98	2.42
Timolol	-10.44	-16.18	-19.53	-20.3	-18.81	-16.98

Table C-98-57-5 - Mean Percent Change From Baseline in FEV_1
(Intent-to-Treat Data)

	Minutes					
	15	30	60	90	120	180
Levobetaxolol 0.5%	-0.76	-1.17	-0.44	1.93	0.98	2.42
p-value	0.7416	0.6107	0.8484	0.4023	0.6702	0.2951
Lower 95% CI	-5.3	-5.7	-5.0	-2.6	-3.6	-2.2
Timolol 0.5%	-10.44	-16.18	-19.53	-20.30	-18.81	-16.98
p-value	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Upper 95% CI	-5.9	-11.6	-15.0	-15.7	-14.2	-12.4

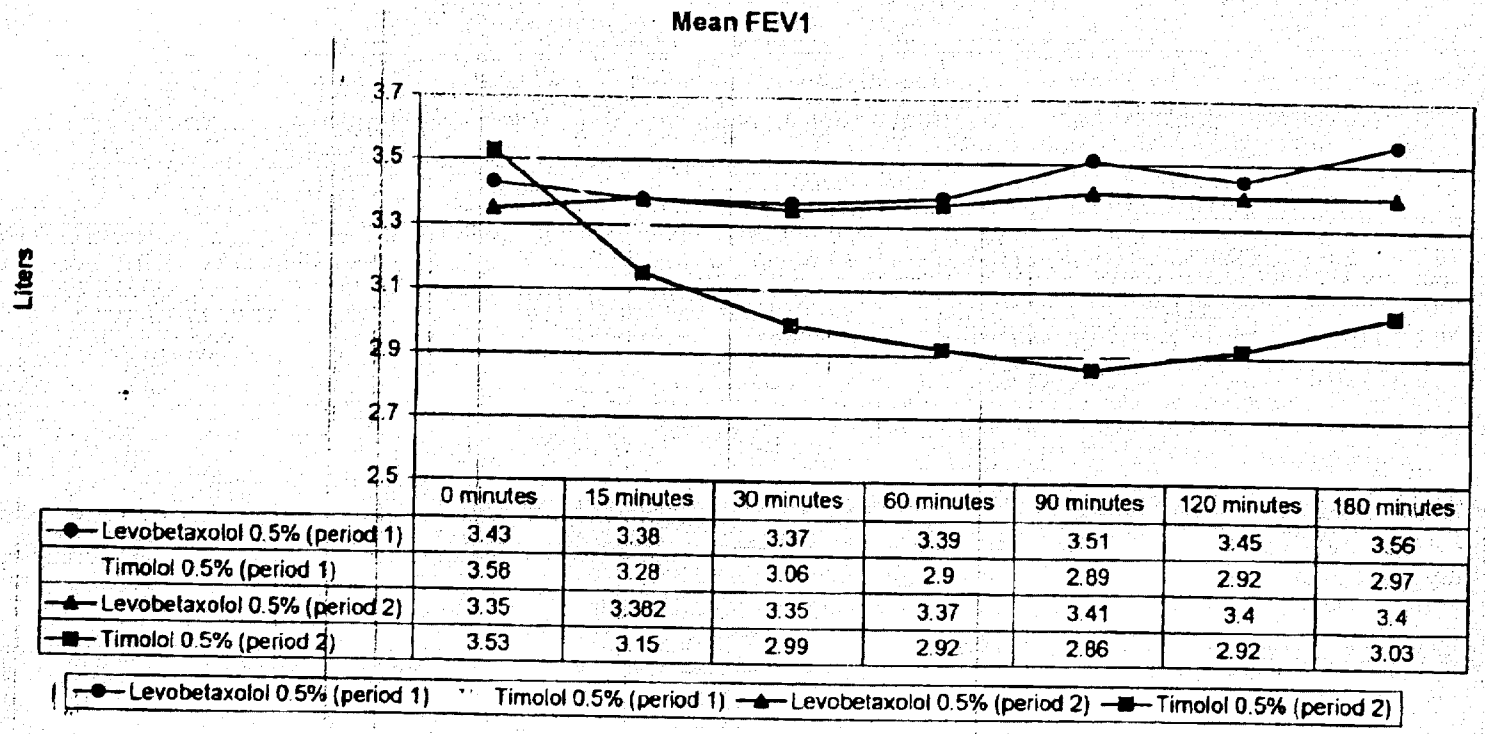
p-value from analysis of variance test that least squares mean is zero

Reviewer's Comments:

No statistically significant effect on FEV_1 was observed in study patients following a single administration of 1 (one) drop of levobetaxolol 0.5%.

For levobetaxolol, the mean percent change from baseline in FEV_1 was never statistically different from 0 (baseline).

Timolol 0.5% significantly reduced FEV_1 at all time points, with a 10.4% drop in mean percent change from 0 (baseline) at 15 minutes.

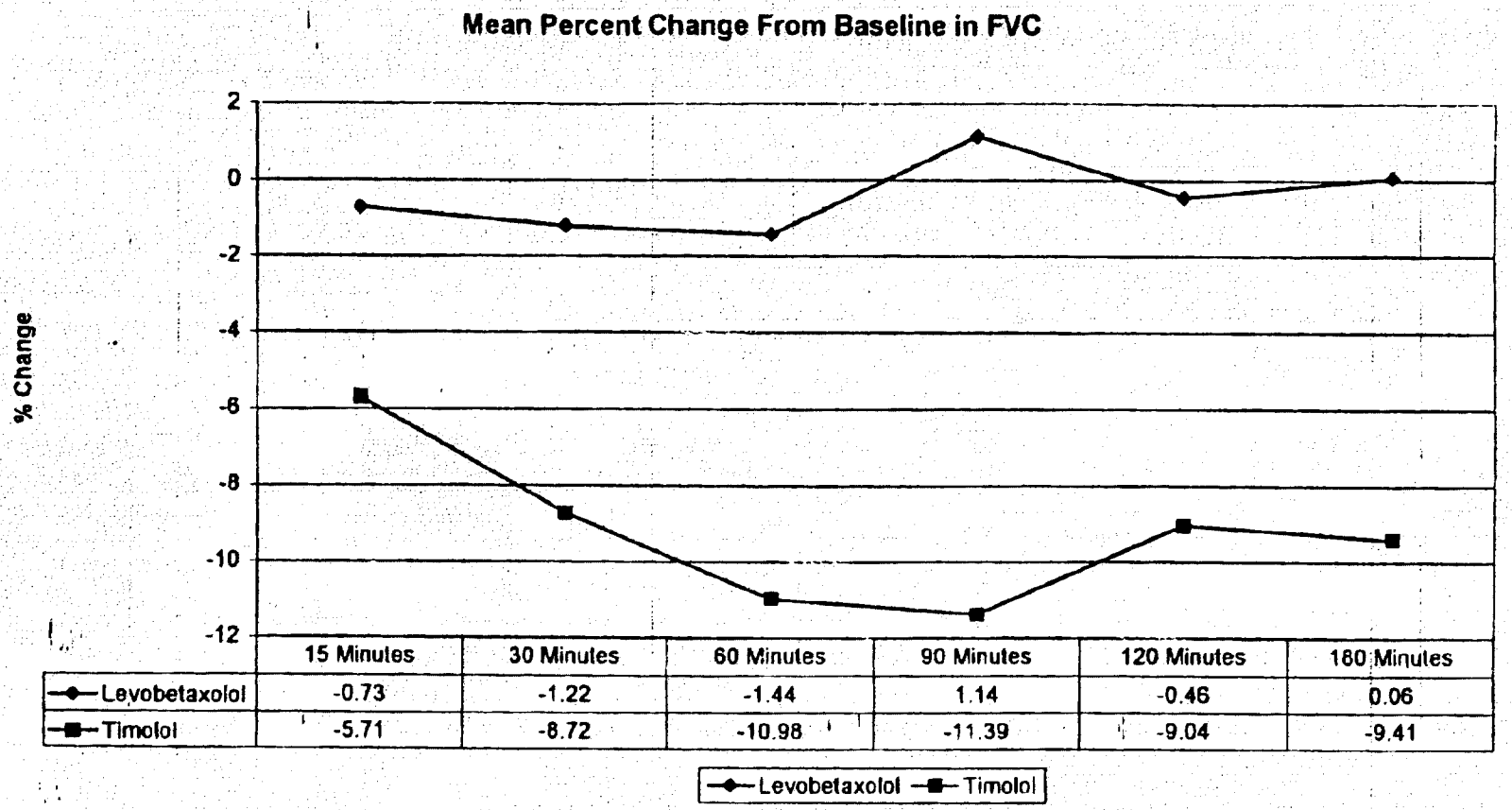


	0 minutes	15 minutes	30 minutes	60 minutes	90 minutes	120 minutes	180 minutes
Levobetaxolol 0.5% (period 1)	3.43	3.38	3.37	3.39	3.51	3.45	3.56
Timolol 0.5% (period 1)	3.58	3.28	3.06	2.9	2.89	2.92	2.97
Levobetaxolol 0.5% (period 2)	3.35	3.382	3.35	3.37	3.41	3.4	3.4
Timolol 0.5% (period 2)	3.53	3.15	2.99	2.92	2.86	2.92	3.03

Reviewer's Comments:

There was also a statistically significant difference found between mean FEV1 by treatment group (p = 0.0001).

Secondary Efficacy Variables



	15 Minutes	30 Minutes	60 Minutes	90 Minutes	120 Minutes	180 Minutes
Levobetaxolol	-0.73	-1.22	-1.44	1.14	-0.46	0.06
Timolol	-5.71	-8.72	-10.98	-11.39	-9.04	-9.41

Table C-98-57-6 - Mean Percent Change From Baseline for FVC

FVC Percent Change From Baseline	Minutes					
	15	30	60	90	120	180
Levobetaxolol 0.5%	-0.73	-1.22	-1.44	1.14	-0.46	0.06
p-value	0.6749	0.4811	0.4066	0.5112	0.7897	0.9727
Lower 95% CI	-4.16	-4.66	-4.88	-2.29	-3.90	-3.38
Timolol 0.5%	-5.71	-8.72	-10.98	-11.39	-9.04	-9.41
p-value	0.0014	0.0001	0.0001	0.0001	0.0001	0.0001
Upper 95% CI	-2.27	-5.29	-7.54	-7.96	-5.61	-5.98

p-value from analysis of variance test that least squares mean is zero

Reviewer's Comments:

The mean percent change from baseline in FVC was not significantly different from 0 (baseline) in the levobetaxolol 0.5% group.

The mean percent change from baseline in FVC was significantly different from 0 (baseline) at all time points in the timolol 0.5% group.

8.1.5 Safety

Adverse Events

One patient receiving timolol 0.5% was discontinued from the study due to an adverse event. See Table C-98-57-3, page 77.

No patient receiving levobetaxolol 0.5% was discontinued from the study due to an adverse event.

No death related or unrelated to levobetaxolol 0.5% or timolol 0.5% was reported during the study.

All serious adverse events are summarized in the following table.

Table C-98-57-8 - Serious Adverse Events

Prot No	Inv No	Pt No	Treatment	Coded Adverse Event	Outcome of Event	D/C Study
C9857	2253	103	Timolol 0.5%	Dyspnea	Resolved w/Tx	Yes

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

Table C-98-57-9 - Overall Frequency and Incidence of Adverse Events

	Levobetaxolol 0.5% N = 30		Timolol 0.5% N = 30	
	N	%	N	%
Nonocular				
Respiratory System				
Dyspnea			2	6.7
Bronchitis			1	3.3

Clinical Laboratory Evaluation

No clinically relevant changes from baseline in clinical laboratory data were observed during the study.

Reviewer's Comments: *Concur.*

Pulse, Systolic/Diastolic Blood Pressure

There was a statistically significant difference between the two treatments in systolic blood pressure at 180 minutes ($p = 0.0370$). However, there was no difference in systolic blood pressure by treatment.

Reviewer's Comments:

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

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

8.1.5 Reviewer's Summary of Efficacy and Safety

No statistically significant effect on FEV_1 was observed in these study patients following a single administration of 1 (one) drop of levobetaxolol 0.5%. However, due to the inclusion criteria, this study is significantly flawed.

Adverse experiences appeared generally mild-moderate in nature.

9 Reviewer's Overview of Efficacy

Although not equivalent to timolol 0.5% ophthalmic solution in the ability to lower IOP, levobetaxolol 0.5% produced IOP reductions at trough (12 hours post-dose) ranging from [redacted] and at peak (2 hours post-dose) ranging from [redacted] equivalent to the amount expected from betaxolol.

10 Reviewer's Overview of Safety

Adequate safety has been established for the use of levobetaxolol 0.5% in lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

The most frequent ocular adverse events in levobetaxolol 0.5% treated subjects were transient ocular discomfort (burning, stinging) upon instillation (11.0%) and blurred vision (2.5%).

10 pages redacted

DRAFT

LABELING

12 Conclusions

The submitted studies in NDA 21-114 demonstrate safety and efficacy for the use of levobetaxolol 0.5% in lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

13 Recommendations

1. *Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 21-114 is recommended for approval for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.*

2. *The applicant should submit revised labeling consistent with the recommendations in this review.*

3. *The NDA Study report on page 8-00837 and the Financial Certification/Disclosure Statement on page 16-00005 list the principal investigator of C-97-68 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. The applicant should clarify.*

4. *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. The Study Plan from the original protocol found in the NDA on page 8-02969 appears correct. The applicant should clarify.*

/S/

William M. Boyd, M.D.
Medical Officer, Ophthalmology

NDA 21-114
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers /S/ 4/1/00
HFD-550/Div Dir/Midthun
HFD-880/Biopharm/Lee
HFD-160/Micro/Hussong
HFD-550/Chem/Fenselau
HFD-550/Chem/Tso
HFD-550/PharmTox/Mukherjee
HFD-550/PM/Gorski
HFD-340/Carraras

MOR4

Medical Officer's Review of NDA 21-114

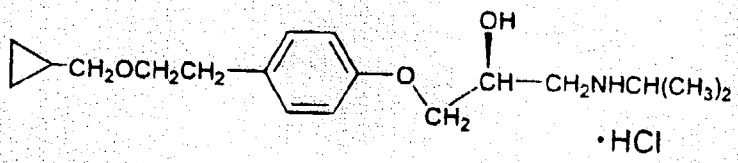
NDA 21-114
Medical Officer's Review #2

Submission: 1/12/00
Review Completed: 1/18/00

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

Submitted: Responses to Initial Review's Deficiencies.

1) *The NDA Study report on page 8-00837 and the Financial Certification/Disclosure Statement on page 16-00005 list the principal investigator of C-97-68 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. The applicant should clarify.*

The principal investigator for study C-97-68 was Thomas L. Hunt, M.D., Ph.D. Dr. Hunt was incorrectly listed as Robert Hunt, M.D. on page 8-00837 of the Clinical Study Report and on page 16-00005 of the Financial Certification or Disclosure Statement. The completed financial disclosure form in our study files reflects the correct name of Thomas L. Hunt.

Reviewer's Comments: *Acceptable.*

2) *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. The Study Plan from the original protocol found in the NDA on page 8-02969 appears correct. The applicant should clarify.*

The study plan for Protocol C-97-40 on page 8-02131 incorrectly listed a 12 noon visit at the Eligibility 2 visit. The study flow chart on page 8-02969 is correct indicating that the Eligibility 2 visit consisted of only 8 am and 10 am visits.

Reviewer's Comments: *Acceptable.*

Recommendations:

NDA 21-114 is recommended for approval for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

/S/

William M. Boyd, M.D.
Medical Officer, Ophthalmology

NDA 21-114
HFD-550/Div Files
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HFD-550/Dep Director/Chambers /S/ 2/1/00
HFD-550/Div Dir/Midthun
HFD-880/Biopharm/Lee
HFD-160/Micro/Hussong
HFD-550/Chem/Fenselau
HFD-550/Chem/Tso
HFD-550/PharmTox/Mukherjee
HFD-550/PM/Gorski
HFD-340/Carraras

Medical Officer's Review of NDA 21-114

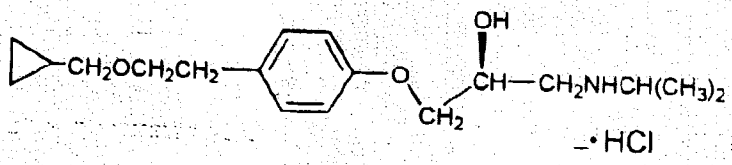
NDA 21-114
Medical Officer's Review #3

Submission: 2/17/00
Review Completed: 2/17/00

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

Submitted: Revised labeling based on previous review and discussion with the sponsor.

9 pages
REDACTED
DRAFT
LABELING

Recommendations:

NDA 21-114, Betaxon (levobetaxolol hydrochloride ophthalmic suspension) 0.5%, is recommended for approval for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

/S/

William M. Boyd
Medical Officer, Ophthalmology

NDA 21-114
HFD-550/Div Files
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HFD-550/Chem/Fenselau
HFD-550/Chem/Tso
HFD-550/PharmTox/Mukherjee
HFD-550/PM/Gorski
HFD-340/Carreras

Medical Officer's Review of NDA 21-114
120-Day Safety Update

NDA 21-114
Medical Officer's Review

Submission: 1/18/00
Review Completed: 2/1/00

Proposed Tradename: Betaxon 0.5%

Generic Name: levobetaxolol hydrochloride suspension

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 emulsion for topical ocular administration

Submitted: 120-Day Safety Information for Protocol C-97-82 and Overall Frequency and Incidence of Adverse Events for Protocols C-97-40, C-97-67, C-97-68, C-97-80, C-97-81, C-97-82, and C-98-57

Protocol C-97-82

The objective of this active-controlled, multi-center, double-masked, 12-month study was to evaluate the long-term safety and IOP-lowering efficacy of levobetaxolol ophthalmic suspension compared to timolol 0.5% ophthalmic solution in patients with primary open-angle glaucoma or ocular hypertension.

The most frequently reported ocular adverse events in the levobetaxolol 0.5% group included ocular discomfort (burning and stinging) (12%), transient blurred vision (7%), decreased visual acuity (5%), discharge (3%), pain (3%) and dry eye (3%).

The most frequently reported non-ocular adverse events in the levobetaxolol 0.5% group included surgical/medical procedures (7%), infection (3%), hypertension (3%) and insomnia (3%).

Reviewer's Comments and Conclusions:

Information contained in this safety update is comparable to previous safety information reviewed for the original NDA. When the overall frequency and incidence of adverse events are examined, there has been no new safety information learned about the drug that would reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

Original conclusions regarding the safety of levobetaxolol ophthalmic suspension, 0.5% for the indication of lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension are not altered.

APPEARS THIS WAY
ON ORIGINAL

/S/

William M. Boyd, M.D.
Medical Officer, Ophthalmology

NDA 21-114
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HFD-160/Micro/Hussong
HFD-550/Chem/Fenselau
HFD-550/Chem/Tso
HFD-550/PharmTox/Mukherjee
HFD-550/PM/Gorski
HFD-340/Carraras

APPEARS THIS WAY
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