

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-516

Statistical Review(s)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation CLINICAL STUDIES

NDA: 21-516
Name of drug: Timolol LA
Indication: Treatment of ocular hypertension
Applicant: Senju Pharmaceutical Co., Ltd.
17 Bridgegate Drive, San Rafael, CA 94903
Date of Submission: December 17, 2002
Review Status: Standard
Biometric Division: III
Statistical Reviewer: M. Atiar Rahman, Ph.D.
Concurring Reviewer: Stan Lin, Ph.D.
Documents reviewed
Submission: Submitted Volumes # 1.1 and 1.15 to 1.24
Data: Data stored in \\Cdsesub1\n21516\N_000\2003-01-10\Clinstat\Statistical\timla_301
Also supplied in one CD
Medical Division: Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products, HFD-550
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Keywords: NDA review, Clinical studies, Equivalence

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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

In this submission the sponsor included data from only one phase III study. The objective of this study was to demonstrate that Timolol-LA (TLA) once a day is equivalent in efficacy to Timolol Maleate (TIM) twice a day in treating intraocular pressure (IOP). Considering results of both the sponsor's and this reviewer's analyses, and using the operational definition of equivalence given in the protocol, this reviewer concludes that TLA and TIM have equivalent effect for the treatment of IOP in this study.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this submission the sponsor included only a single multicenter Phase III study, namely Study #301. This was a randomized, parallel-group, double-masked, multicenter study, designed to evaluate the safety and efficacy of Timolol-LA 0.5%. There were two arms in this study, namely Timolol-LA and Timolol maleate. A total of 332 patients were assigned in a random manner to a treatment arm. This study was conducted in 21 centers in the USA.

1.3 STATISTICAL ISSUES AND FINDINGS

The clinical objective of this trial was to demonstrate that Timolol-LA once a day is equivalent in efficacy to Timolol maleate twice a day. The operational definition of equivalence, as described in the protocol, was that the 95% confidence interval limits on the difference in mean change from baseline IOP between two treatment groups in per-protocol population were less than 1 mm Hg at the majority of time points and were less than 1.5 mm Hg at all time points during treatment. In addition both TLA and TIM should lower IOP by 25% at peak and 20% at trough testing times when compared to baseline. At the end of Phase-2 meeting with the agency, held on October 10, 2000, the medical officer Dr. Boyd proposed that instead of change from baseline, the actual value of IOP be analyzed in ITT population.

Both the sponsor's and this reviewer's analyses showed that the 95% confidence interval limits did not exceed 1.5 mm Hg at any visit. Also at most visits, these limits did not exceed 1.0 mm Hg. Mean reductions from baseline, starting at Week 1 and continuing through Week 12, were 7 mm Hg at peak, and 6 mm Hg at trough, approximately 28% and 23%, respectively.

2 INTRODUCTION

2.1 OVERVIEW

In this NDA the sponsor submitted data to support their claim that Timolol-LA is safe and efficacious for the treatment of ocular hypertension and that once a day Timolol LA (0.5%) has equivalent efficacy to twice a day Timolol maleate. The submission included only one pivotal Phase 3 study namely, Study #301.

2.2 DATA SOURCES

This reviewer reviewed sponsor's submitted Volumes # 1.1 and 1.15 to 1.24, and data submitted in CD. The submission was in hard copy and partially electronic. The quality of

data was within acceptable limit. The submitted data was also stored in the Division's electronic data file \\Cdsesub1\n21516\N_000\2003-01-10\Clinstat\Statistical\timla_301.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY #301

Title: "A double-masked, randomized, parallel study of the safety and efficacy of Timolol-LA in patients with ocular hypertension or open-angle glaucoma."

3.1.1.1 Design and Objectives

This was a randomized, parallel-group, double-masked, multicenter study, designed to evaluate the safety and efficacy of Timolol-LA 0.5%. The objective of this study was to demonstrate that Timolol-LA once daily is equivalent in efficacy to Timolol maleate (a commercially available eye-drop) twice daily in treating patients with open-angle glaucoma or ocular hypertension.

3.1.1.2 Primary Efficacy endpoint

The primary efficacy endpoint was intraocular pressure (mean intraocular pressure at each visit at each time point, peak and trough). Measurement taken in the morning prior to dosing presumed to be "trough" and measurement taken approximately two hours after dosing presumed to be "peak".

"Study eye" was defined as the eye with the higher IOP on Day 1 based on the mean of the 0730-0930 and 1000-1200 hour measurements. In the event of the IOPs being equal, the left eye was designated as the study eye for patients with an even randomization number and the right eye if the number is odd.

The primary analysis for this study was efficacy after all patients completed three months of treatment. Patients were planned to continue until 12 months of treatment, at which time an additional efficacy and safety analysis was performed. The 12 month analysis is an unmasked extension of the 3 month trial.

3.1.1.3 Secondary Efficacy endpoint

Secondary measures of efficacy were change from baseline in mean defect (MD) score on perimetry and cup-to-disc ratio.

3.1.1.4 Patient Analyzed

Intent-to-Treat Population: The intent-to-treat population included those patients who received study medication.

Per-protocol population: The protocol deviations were used to define the per-protocol populations. Per-protocol population had 299 (148 in TLA and 151 in TIM).

Safety Population: The safety population included all randomized patients who received a study medication and had at least one post treatment assessment.

3.1.1.5 Disposition of Patients, Demography, and Baseline Characteristics

A total of 332 patients were assigned in a random manner to a treatment arm. Table 1 in the appendix shows the disposition of the patients. Most of the patients (93%, 309/332) completed the 12 weeks of the study. Of the 7% of patients (23/332) who did not complete the study, only 1% (2/332) were terminated for inadequate efficacy. Additional 12 patients (4%) were terminated for an adverse event, and 9 of patients (3%) were discontinued for reasons unrelated to the study. Table 2 in the appendix shows the demographics of the study population. The population of 332 patients with open-angle glaucoma or ocular hypertension had an average age in the mid 60's and was approximately 61% female. The population was 80% Caucasian, 13% Black, 5% Hispanic and 1% Asian. Approximately half of the patients had brown irides.

Patient disposition did not show any significant difference between the treatment groups.

3.1.1.6 Sponsor's Analysis of Primary Efficacy Data

The primary efficacy time point was Month 3. The primary efficacy population was the per-protocol population. As pointed out earlier, the clinical objective of this trial was to demonstrate that TLA q.d. is equivalent in efficacy to TIM b.i.d. According to the protocol, the operational definition of equivalence was that the 95% confidence interval limits on the difference in mean change from baseline IOP between two treatments groups were less than 1 mm Hg at the majority of time points, and were less than 1.5 mm Hg at all time points during treatment. In addition both TLA and TIM should lower IOP by 25% at peak and 20% at trough testing times when compared to baseline.

Following the statistical analysis plan, for continuous primary and secondary efficacy endpoints, the mean difference between treatments and its 95% confidence interval limits were estimated for each time point by a fixed effects model analysis of covariance with baseline as the covariate and with treatment as the single between patients factor. Calculation of percent reduction from baseline of IOP at the peak and trough at on-treatment time points used the adjusted least square means from the main effects model. The homogeneity of treatment effect across investigative sites was examined by a model containing the additional factors of investigative site and its interaction with treatment. However, in the final model the estimation of treatment effects was unadjusted for center. All statistical tests were two-sided with a significance level of $p \leq 0.05$.

3.1.2 SPONSOR'S RESULTS AND CONCLUSIONS

Table 3 in the appendix shows the mean IOP at each visit for both trough and peak. The sponsor concluded that the means at each visit (for both trough and peak) are comparable. Text Table 1 (next page) shows the sponsor's result of primary efficacy endpoint (Mean change from baseline IOP). The results show that at none of the visits did the 95% confidence interval limits for between treatment comparisons exceed 1.5 mm Hg. Also at most of the visits (4 out of 7), the confidence interval limits did not exceed 1.0 mm Hg.

Text Table 1: Test of Equivalence for Mean Change from Baseline, Per Protocol Population (Sponsor's Table)

	Visit	Estimate	S.S.M	P-value	C.I.	
					Lower	Upper
Trough	Week 1	0.2799	0.3413	0.4128	-0.3920	0.9518
	Week 2	0.4649	0.3032	0.1264	-0.1321	1.0620
	Week 6	0.7301	0.2988	0.0152	0.1420	1.3182
	Week 12	0.4460	0.3368	0.1866	-0.2171	1.1092
Peak	Week 2	0.0860	0.2978	0.7729	-0.5005	0.6726
	Week 6	0.1429	0.3091	0.6443	-0.4656	0.7513
	Week 12	-0.3309	0.3215	0.3042	-0.9638	0.3020

Source: Table 8

Change = TLA minus TIM. Calculated is the difference of least squares treatment means from reduced model analysis of covariance.

Sponsor's analysis of ITT population showed similar results. Sponsor's results for ITT population are given in Table 4 in the appendix.

Table 5 in the appendix shows that the mean reductions from baseline, starting at Week 1 and continuing through Week 12, were 7 mm Hg at peak, and 6 mm Hg at trough (approximately 28% and 24%, respectively). The sponsor concluded that as with mean IOP, there was little difference in mean reduction between treatments.

3.1.2.1 Sponsor's Analysis of Secondary Efficacy Data

Automated threshold visual fields were conducted at baseline and Week 12. Table 6 in the appendix shows results of sponsor's analysis of mean defect (MD) in visual field. At entry, the mean MD was approximately -2 dB. At Week 12, there was little change (less than 0.3 dB). The ITT population had similar results.

Cup-disc ratio was measured at baseline and Week 12. Table 7 in the appendix shows results of sponsor's analysis of mean cup-disc ratio. At entry, the mean ratio was approximately 0.5. At Week 12, there was little change (mean of 0.0). The maximum change seen in any patient was a worsening of 0.2 units, and an improvement of 0.20 units.

3.1.2.2 Sponsor's Analysis of Safety Data

Treatment emergent adverse events were cross tabulated by system organ class, by preferred term, by causality, and by severity (COSTART). The incidence of AEs grouped under preferred terms for each active treatment were compared to placebo using Fisher's exact test as a screening tool for events that may be treatment related.

Adverse events were reported in 112 (68%) patients in the TLA treatment group, and in 87 (52%) patients in the TIM treatment group. The most frequent adverse events in the TLA treatment group were: burning/stinging upon instillation (38%), injection (6%), hypertension and ocular itching (5% each), allergic reaction, asthenia, headache, infection and ocular discomfort (3% each). The corresponding incidences for the TIM group were: burning/stinging upon instillation (22%), injection (6%), hypertension (4%), ocular itching (3%), allergic reaction (2%), asthenia (0%), headache (2%), infection (1%) and ocular discomfort (3%). There were no deaths in the first 12 weeks of the study. Seventeen (17) serious adverse events were reported in 11 patients. Out of these

only one was judged by the investigator to be possibly related (Congestive heart failure in Patient 101-10 in TLA). Other events were judged as not related to treatment.

3.1.3 REVIEWER'S FINDINGS AND CONCLUSION

Following the protocol, the sponsor analyzed the change from baseline IOP as the primary efficacy endpoint. However, at the end of Phase-2 meeting with the agency, held on October 10, 2000, the medical officer Dr. Boyd proposed that instead of change from baseline, the actual value of IOP be analyzed. In a personal discussion Dr. Boyd told this reviewer that he wanted his proposed analysis in ITT population. In sponsor's submission this analysis was not included. Text Tables 2 contains this reviewer's analysis of observed cases of actual values of IOP for ITT populations.

Text Table 2: Test of Equivalence for Actual OIP, ITT Population Observed cases only (Reviewer's Table)

Visit	Timolol LA			Timolol maleate			95% C.I. on difference between means			
	n	Mean	SD	n	Mean	SD	Lower	Upper	Length	
Trough	Week 1	155	19.529	3.177	158	19.272	3.217	-0.452	0.965	1.417
	Week 2	149	19.423	2.537	149	18.846	2.804	-0.030	1.184	1.214
	Week 6	159	19.616	2.841	163	18.804	2.863	0.190	1.436	1.246
Peak	Week 12	151	19.358	3.078	155	18.890	2.880	-0.200	1.135	1.335
	Week 2	142	18.331	2.537	146	18.171	2.506	-0.423	0.742	1.165
	Week 6	157	18.440	2.772	161	18.137	2.847	-0.315	0.921	1.236
	Week 12	149	18.074	2.682	155	18.219	2.899	-0.774	0.483	1.257

- Confidence interval was for TLA minus TIM

This reviewer's analysis showed that in ITT populations all upper 95% confidence interval limits were below 1.5, and most (4 out of 7) of the upper 95% confidence interval limits were below 1. Therefore, results from ITT population satisfied the efficacy specification.

Table 8 in the appendix shows the analysis of the actual OIP in ITT population with LOCF for the missing values. Table 9 in the appendix shows the analysis of the actual OIP in the per-protocol population. Results in Table 8 show that in ITT populations with last observation carried forward, all upper 95% confidence interval limits were below 1.5, and most (4 out of 7) of the upper 95% confidence interval limits were below 1. Results from Table 9 show that in per-protocol populations also all upper 95% confidence interval limits were below 1.5, however most (4 out of 7) of the upper 95% confidence interval limits were above 1.

This reviewer's calculation of percent reduction from baseline in ITT population is given in Table 10 in the appendix. Results shows more than 22% reduction in mean IOP at trough more than 25% at peak.

4 FINDINGS IN SPECIAL SUBGROUPS

4.1 GENDER

The sponsor or this reviewer did not perform any sub-group analysis by gender.

4.2 RACE

The sponsor or this reviewer did not perform any sub-group analysis by race.

4.3 AGE

The sponsor or this reviewer did not perform any sub-group analysis by age.

4.4 OTHER SPECIAL/SUBGROUP POPULATIONS

The sponsor or this reviewer did not perform any sub-group analysis by any other sub-group criteria.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

There was only a single Phase III study included in this submission. Therefore, this reviewer's overall evaluation was based on the one submitted study only.

In the original protocol the primary efficacy end point was change from baseline IOP at Month 3. The primary efficacy population was the per-protocol population. The clinical objective of this trial was to demonstrate that TLA q.d. is equivalent in efficacy to TIM b.i.d. The operational definition of equivalence, as described in the protocol, was that the 95% confidence interval limits on the difference in mean change from baseline IOP between two treatments groups were less than 1 mm Hg at the majority of time points and were less than 1.5 mm Hg at all time points during treatment. In addition both TLA and TIM should lower IOP by 25% at peak and 20% at trough testing times when compared to baseline. Use of this operational definition, showed equivalent effect of TLA and TIM.

However, at the end of Phase-2 meeting with the agency, held on October 10, 2000, the medical officer Dr. Boyd proposed that instead of change from baseline, the actual value of IOP be analyzed in ITT population. The sponsor did not perform such analysis. This reviewer reanalyzed the data according to Dr. Boyd's proposal. Use of the same operational definition given in the protocol, results of this reviewer's analysis also showed equivalent effect of Timolol-LA and Timolol maleate.

5.2 CONCLUSION AND RECOMMENDATIONS

Considering results of both the sponsor and this reviewer, and using the operational definition of equivalence given in the protocol, this reviewer concludes that Timolol-LA and Timolol maleate has equivalent effect for the treatment of IOP.

6 APPENDICES

There is only one appendix (Appendix 1) attached to this review.

7 PRIMARY, CONCURRING REVIEWERS, DISTRIBUTION LIST

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8 APPENDIX-1

**Table 1: Patient's Disposition
 (Sponsor's Table)**

Status	Treatment		All
	Timolol LA	Timolol mmaleate	
Entered	166	166	332
Completed	154 (93%)	155 (93%)	309 (93%)
Not completed	12 (7%)	11 (7%)	23 (7%)
Terminated: Inadequate efficacy	1 (1%)	1 (1%)	2 (1%)
Terminated: Adverse event	7 (5%)	5 (3%)	12 (4%)
Discontinued:	4 (2%)	5 (3%)	9 (3%)
Protocol violation	1 (1%)	2 (1%)	3 (1%)
Patient withdrew consent	1 (1%)	0 (0%)	1 (1%)
Other	2 (1%)	3 (2%)	5 (2%)

Source: Table 4 of sponsor's analysis

**Table 2: Demographics Characteristics, Intent-to-treat population
 (Sponsor's Table)**

Measure	Timolol-LA	Timolol maleate	All
N	166	166	332
Age (y)			
Mean ± s.e.m.	64.3 ± 12.4	64.9 ± 11.1	64.6 ± 11.8
Range	29-92	32-85	29-92
Gender			
Female	102 (61%)	101 (61%)	203 (61%)
Male	64 (39%)	65 (39%)	129 (39%)
Race			
Caucasian	135 (81%)	132 (80%)	267 (80%)
Asian	2 (1%)	2 (1%)	4 (1%)
Black	21 (13%)	21 (13%)	42 (13%)
Hispanic	7 (4%)	11 (7%)	18 (5%)
Other	1 (1%)	0 (-)	1 (1%)
Iris Color			
Brown	79 (48%)	88 (53%)	167 (50%)
Hazel	23 (14%)	23 (14%)	46 (14%)
Blue	53 (32%)	44 (27%)	97 (29%)
Gray	5 (3%)	3 (2%)	8 (2%)
Other	6 (4%)	8 (5%)	14 (4%)
Glaucoma diagnosis ¹			
OAG	116 (70%)	114 (69%)	230 (69%)
OHT	50 (30%)	51 (31%)	101 (31%)

Source: Table 6 of sponsor's analysis

¹ Based upon 331 study eyes.

**Table 3: Mean IOP, Per Protocol Population
 (Sponsor's Table)**

Time	Visit	Treatment	N	Mean	SD	Min	Max
Trough	Baseline	TLA	148	25.43	2.89	21	35
		TIM	151	25.20	2.74	22	35
	Week 1	TLA	135	19.57	3.21	10	30
		TIM	143	19.20	3.16	13	32
	Week 2	TLA	130	19.35	2.55	14	28
		TIM	133	18.75	2.86	11	31
	Week 6	TLA	139	19.60	2.92	13	27
		TIM	148	18.78	2.80	12	27
	Week 12	TLA	131	19.39	3.16	11	36
		TIM	143	18.79	2.85	10	25
Peak	Baseline	TLA	147	24.95	2.75	22	36
		TIM	151	24.95	2.54	22	35
	Week 2	TLA	125	18.23	2.52	12	27
		TIM	130	18.04	2.54	11	28
	Week 6	TLA	139	18.35	2.79	11	30
		TIM	147	18.10	2.80	10	26
	Week 12	TLA	130	18.07	2.78	13	30
		TIM	141	18.24	2.88	9	27

Source: Table 7 of sponsor's analysis
 Among-group p-values: Baseline: 0.9089; Trough: 0.4404, 0.2211, 0.0165, and 0.3567 at Weeks 1, 2, 6 and 12, respectively; Peak: 0.9503, 0.4246, and 0.0.1218at Weeks 2, 6 and 12, respectively.

Baseline for analysis and change from baseline is the mean of the trough (0 hour) and peak (2.5) measures at Visit 1 (Day 1).

**Table 4: Test of Equivalence for Mean Change from Baseline, ITT population
 (Sponsor's Table)**

Time	Visit	Estimate	s.e.m.	P-value	C.I.	
					Lower	Upper
Trough	Week 1	0.1986	0.3270	0.5441	-0.4449	0.8421
	Week 2	0.4634	0.2833	0.1029	-0.0941	1.0208
	Week 6	0.0683	0.2809	0.8082	-0.4847	0.6212
	Week 12	0.7328	0.2860	0.0109	0.1700	1.2955
Peak	Week 2	0.2308	0.2983	0.4396	-0.3561	0.8178
	Week 6	0.3403	0.3197	0.2880	-0.2888	0.9695
	Week12	-0.2623	0.3017	0.3853	-0.8560	0.3314

Source: Table 11 of sponsor's analysis
 Change = TLA minus TIM. Calculated is the difference of least squares treatment means from reduced model analysis of covariance

**Table 5: Mean Change from Baseline in IOP, Per Protocol Population
 (Sponsor's Table)**

Time	Visit	Treatment	N	Mean	SD	Min	Max
Trough	Baseline	TLA	148	0.25	1.09	-3	4
		TIM	151	0.12	1.01	-4	3
	Week 1	TLA	135	-5.66	3.08	-16	2
		TIM	142	-5.89	3.00	-15	3
	Week 2	TLA	130	-5.87	2.58	-12	-1
		TIM	132	-6.21	2.94	-16	3
	Week 6	TLA	139	-5.63	2.86	-13	2
		TIM	147	-6.28	2.72	-14	-1
	Week 12	TLA	131	-5.94	3.19	-16	6
		TIM	142	-6.23	3.03	-16	1
Peak	Baseline	TLA	147	-0.24	1.10	-4	3
		TIM	150	-0.13	1.01	-3	4
	Week 2	TLA	125	-7.00	3.03	-17	2
		TIM	129	-6.94	2.65	-16	0
	Week 6	TLA	139	-6.89	3.08	-18	0
		TIM	146	-6.92	2.99	-15	3
	Week 12	TLA	130	-7.25	3.26	-17	5
		TIM	140	-6.73	2.82	-14	-1

Source: Table 9 of sponsor's analysis

**Table 6: Visual Fields: Mean MD (dB), Per protocol
 (Sponsor's Table)**

Visit	Treatment	N	Mean	SD	Min	Max
Baseline	TLA	150	-1.92	3.32	-22.62	2.90
	TIM	153	-1.91	2.33	-9.96	3.00
Week 12	TLA	130	-1.57	2.86	-15.96	8.99
	TIM	140	-2.15	2.96	-13.55	7.56
Change	TLA	130	0.28	1.72	-7.45	6.49
	TIM	140	-0.29	2.23	-9.70	4.71

Source: Table 13 of sponsor's analysis
 The between treatment p-value at baseline was 0.9673, and at Week 12 was 0.1126.

**Table 7: Mean Cup-disc Ratio, Per protocol
 (Sponsor's Table)**

Visit	Treatment	N	Mean	SD	Min	Max
Baseline	TLA	149	0.45	0.19	0.10	0.90
	TIM	153	0.47	0.20	0.10	0.85
Week 12	TLA	129	0.45	0.19	0.10	0.90
	TIM	141	0.48	0.20	0.10	0.90
Change	TLA	129	0.00	0.02	-0.10	0.10
	TIM	141	0.00	0.05	-0.20	0.20

Source: Table 14 of sponsor's analysis
 The between treatment p-value at baseline was 0.8980, and at Week 12 was 0.9344.

**Table 8: Test of Equivalence for Actual OIP, ITT Population with LOCF
 (Reviewer's Table)**

Visit	Timolol LA			Timolol maleate			95% C.I. on difference between means			
	n	Mean	SD	n	Mean	SD	Lower	Upper	Length	
Trough	Week 1	166	19.856	3.358	166	19.518	3.346	-0.384	1.059	1.442
	Week 2	166	19.446	2.604	166	19.121	2.982	-0.277	0.928	1.205
	Week 6	166	19.602	2.864	166	18.795	2.910	0.186	1.428	1.242
	Week 12	166	19.343	3.064	166	18.934	2.965	-0.239	1.058	1.297
Peak	Week 2	166	19.241	3.473	166	19.084	3.536	-0.597	0.911	1.508
	Week 6	166	18.663	2.931	166	18.331	3.130	-0.321	0.984	1.305
	Week 12	166	18.301	2.857	166	18.434	3.163	-0.781	0.516	1.297

Confidence interval was for TLA minus TIM

**Table 9: Test of Equivalence for Actual OIP, Per Protocol Population
 (Reviewer's Table)**

Visit	Timolol LA			Timolol maleate			95% C.I.			
	n	Mean	SD	n	Mean	SD	Lower	Upper	Length	
Trough	Week 1	135	19.570	3.208	143	19.203	3.164	-0.382	1.117	1.498
	Week 2	130	19.354	2.545	133	18.752	2.856	-0.052	1.256	1.309
	Week 6	139	19.604	2.921	148	18.777	2.799	0.166	1.489	1.324
	Week 12	131	19.389	3.159	143	18.790	2.845	-0.112	1.310	1.422
Peak	Week 2	125	18.232	2.524	130	18.039	2.538	-0.428	0.815	1.243
	Week 6	139	18.345	2.789	147	18.095	2.805	-0.399	0.899	1.297
	Week 12	130	18.069	2.776	141	18.241	2.881	-0.847	0.503	1.349

Confidence interval was for TLA minus TIM

**Table 10: Percent Change in Mean IOP at Trough and Peak, ITT population
 (Reviewer's Table)**

Visit	Timolol LA			Timolol maleate			
	Mean Baseline	Mean Visit	Percent Change	Mean Baseline	Mean Visit	Percent Change	
Trough	Week 1	25.361	19.529	22.997	25.127	19.272	23.300
	Week 2	25.361	19.423	23.416	25.127	18.846	24.997
	Week 6	25.361	19.616	22.653	25.127	18.804	25.164
	Week 12	25.361	19.358	23.673	25.127	18.890	24.819
Peak	Week 2	24.898	18.331	26.375	24.904	18.171	27.034
	Week 6	24.898	18.440	25.939	24.904	18.137	27.173
	Week 12	24.898	18.074	27.407	24.904	18.219	26.841

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/s/

Atiar Rahman
5/30/03 10:12:19 AM
BIOMETRICS

Stan Lin
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