CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-214

STATISTICAL REVIEW(S)

Statistical Review

NDA#	21-214
Name of Drug:	Unoprostone isopropyl 0.15% ophthalmic solution
Applicant:	CIBA Vision Corporation
Indication:	The treatment of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension
Documents Reviewed:	Vol. 3.1--3.3, 3.5-3.75, 3.116-3.119/received on Feb. 16, 2000
Medical Reviewer:	William Boyd, MD
Statistical Reviewer:	Qian Li, Sc.D.
Period of Review:	February-June 2000

I. Introduction:

Sponsor of this NDA pursues the marketing approval of unoprostone isopropyl 0.15% ophthalmic solution (UIOS 0.15%) applied twice daily for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension. For efficacy evaluation, two similarly designed and conducted phase III studies, C97-UIOS-004 and C97-UIOS-005, were conducted to determine the IOP-lowering effect of UIOS 0.15%.

This statistical review focuses on the efficacy aspect of UIOS 0.15% treatment. The major issues in efficacy assessment were that there was no placebo control in the two phase III trials and there were higher drop out rate due to lack of efficacy in UIOS 0.15% treatment groups than the active control groups. Overall the two studies failed to provide sufficient evidence to show IOP lowering effect of UIOS 0.15% with patients with open angle glaucoma or ocular hypertension.

II. Study Design and Statistical Methodology:

The two phase III studies were similarly designed, randomized, parallel groups, multi-center, double blinded, and active control trials. In Study C97-UIOS-004 (Study 4), the primary objective was to determine if the IOP-lowering effect of UIOS 0.15% was equivalent to that of timolo maleate 0.5% ophthalmic solution (TMOS 0.5%) after six months of treatment. In Study C97-UIOS-005 (Study 5), the primary objective was to determine if the IOP-lowering effect of UIOS 0.15% was equivalent to that of TMOS 0.5% or betaxolol hydrochloride 0.5% ophthalmic solution (BHOS 0.5%) after six months of treatment. Subjects of either gender who were at least age of emancipation in the states in which the patient was to participate in the study, who presented with bilaterally or unilaterally elevated IOP due to POAG or OH had been recruited into the studies. Patients were randomized (stratified by center) in 2:1 ratio to UIOS 0.15%

treatment group and TMOS 0.5% group at baseline in Study 4 and 2:1:1 to UIOS 0.15%, TMOS 0.5% and BHOS 0.5% in Study 5. The patients were treated for 12 months.

1. Efficacy evaluation:

IOP of both eyes (regardless of whether only one eye was eligible for the study) assessed by [redacted]tonometry was obtained at baseline, weeks 2, 6, Month 3, 6, 9 and 12. For subjects with unilateral POAG or OH, only the eligible eye will be used for efficacy analysis.

Morning trough IOP was obtained at 8:00 ±1 hour at baseline, weeks 2, 6, months 3,6,9 and 12 before the use of study medication on the morning scheduled visit. Mid-morning IOP was taken +2 hours after study medication instillation. Afternoon IOP was measured +8 hours after study medication instillation. The mid-morning and afternoon IOPs were obtained at baseline, Week 2, and Months 3,6, and 12. Evening IOP was measured +12 hours after study medication instillation. The evening IOP measurements were taken at baseline, Month 6, and Month 12 for Study 4 and at Week 2 and Month 3 in addition for Study 5.

12-hour diurnal IOP was defined as the mean of four IOP measurements taken during the morning, midmorning, afternoon, and evening. The 12-hour diurnal IOP was obtained at Baseline, Month 6, and Month 12 for Study 4 and at baseline, Week 2, Month 3, Month 6 and Month 12 for Study 5. The baseline 12-hour diurnal IOP measurements should be taken at approximately +2, +8, and +12 hours after morning trough IOP. All diurnal measurements should be performed within ± 30 minutes of the expected time.

8-hour diurnal IOP was defined as the mean of three IOP measurements including the morning trough IOP, mid-morning and afternoon IOPs. 8-hour diurnal was not defined in Study 5.

Primary efficacy endpoints:

Change in 12-hour diurnal IOP from baseline at Month 6 was prospectively defined as the primary efficacy endpoints in both studies. For patients who were treated bilaterally, average value from both eyes was used in the analysis.

Secondary efficacy variables:

1) the change from baseline in 8-hour diurnal IOP (not defined in Study 5),
2) the change from baseline in morning trough (8:00±1 hour) IOP,
3) the change from baseline in mid morning (+2 hours after medication instillation) IOP,
4) the change from baseline in afternoon (+8 hours after medication instillation) IOP,
5) the change from baseline in evening (+12 hours after medication instillation) IOP,

6) the percentage of patients responding to therapy. A patient was defined as having responded to therapy if the average of their IOP measurement(s) in the study eye(s) was below 20 mmHg.
7) Percent of response defined to have greater than and equal to 15% morning IOP reduction from baseline.

2. Analysis populations:

Intent-to-treat (ITT): this population included all patients who received at least one drop of the study medication and who had their IOP measured at least once following treatment. This population was used for primary analysis.

Per-protocol population: this population included all patients in ITT population who followed the protocol without significant violation.

3. Statistical Analyses:

Analysis of covariance model with treatment and center as the main factors and baseline IOP as covariate was used to analyze the mean change from baseline. Interaction between treatment and center, treatment and baseline were also included in the model.

For missing data due to premature discontinuation, the last observation would be carried forward (LOCF) in primary and secondary analyses. The method of LOCF was to be applied as follows:
1) No data were to be carried forward from baseline.
2) Data were to be carried forward by hourly assessment (i.e., +0, +2, +8, +12).
3) The 8- and 12-hour diurnal IOPs were to be calculated following step 2.

Equivalence between UIOS 0.15% and TMOS 0.5% would be concluded if the upper limit of two sided 95% confidence interval about the difference between treatment group means was less than or equal to +1.5 mmHg (i.e., non-inferiority).

In order to adjust for multiple comparisons (i.e., UIOS 0.15% vs. TMOS 0.5% and UIOS 0.15% vs. BHOS 0.5%) in Study 5, Dunnett's procedure was used in the calculation of 95% simultaneous confidence intervals for determining equivalence of IOP reduction. The overall significance level was maintained at the 5% level.

Subgroup analyses based on gender, age (<60, ≥60), race (caucasian, non-caucasuan), iris color (dark, mixed, light), diagnosis (POAG, OH, pseudoexfoliation), baseline IOP (IOP≤26, IOP>26mmHg), and previous β-blocker therapy (yes, no) were performed.

III. Study Results

1. Study 4 (C97-UIOS-004):

Thirty study centers in USA and Canada screened 796 patients. Five hundred and seventy-one patients (571) were randomized to receive UIOS 0.15% (379) and TMOS 0.5% (192) treatments. Among the randomized patients, 562 patients satisfied the ITT population definition. Patient accounting information was summarized in Table 1-1.

Table 1-1: Patient accounting information for Study 4.

Number of subjects	UIOS 0.15%	TMOS 0.5%	Total
Randomised	379	192	571
ITT population	373	189	562
Completed Month 6	296	168	464
Discontinued before Month 6:	83	24	107
due to AE	22(5.8%)	11(5.7%)	
therapy failure	29 (7.7%)	3 (1.6%)	
protocol violation	17 (4.5%)	7 (3.6%)	
lost to follow-up	5 (1.3%)	2 (1.0%)	
death	2 (0.5%)	0 (0.0%)	
withdrawal of consent	7 (1.8%)	0 (0.0%)	
other	1 (0.3%)	1 (0.5%)	

Source: Based on Text Tables 3 & 4 on page 58 vol. 3.34 and Text Table 8 on page 138 vol. 3.2.

Demographic characteristics for the intent-to-treat population showed that the treatment groups were comparable for age, gender, and race; however, the treatment groups were significantly different for the frequency distribution of eye color (P=0.014). The percentages of subjects with a specific iris color were similar for all iris colors except hazel and blue. The percentage of subjects with hazel eyes was 16% and 24% for the UIOS 0.15% and TMOS 0.5% groups, respectively, and the percentage of subjects with blue eyes was 30% and 21%, respectively.

For medical history, the treatment groups were significantly different for the distribution of subjects with drug allergies/hypersensitivities (P=0.004). The percentage of subjects with a history of drug allergies/hypersensitivities was smaller for the UIOS 0.15% group (29%) than for the TMOS 0.5% group (42%).

The overall discontinuous rates at Month 6 were 22.0% and 12.5% for UIOS 0.15% and TMOS 0.5% respectively. The discontinue rates due to therapy failure were 7.7% for UIOS 0.15% treatment group and 1.6% for TMOS 0.5%. Two deaths were observed in UIOS 0.15% group.

Sponsor's efficacy results of primary endpoint:

The mean 12-hour diurnal IOP at baseline were 23.0 mmHg and 23.1 mmHg for UIOS 0.15% and TMOS 0.5% respectively. Difference between treatment groups at baseline was not statistically significant.

The adjusted difference for mean change from baseline was statistically significantly in favor of TMOS 0.5% compared with UIOS 0.15% after six months of treatment (Δ = +1.44 mm Hg, p-value<0.001). The upper limit of 95% CI was 1.87. The unadjusted mean difference was 1.5 with 95% CI (1.04, 1.95) (Calculated by the reviewer based on Table 6 on page 125 vol.3.34). The prospectively defined criterion for equivalence between UIOS 0.15% and TMOS 0.5% (upper limit of the 95% confidence interval for the difference between treatments < 1.50 mm Hg) was not met. Table 2-1 listed the results of this primary efficacy analysis.

Table 2-1: Results of primary efficacy variable for Study 4– 12-hour diurnal at Month 6.

		UIOS 0.15%	TMOS 0.5%	Difference[1]	95% CI[2]
Baseline	N	373	189		
	Mean	23.0	23.1	-0.16	(-0.59, 0.27)
Month 6	N	373	189		
	Mean	20.0	18.5		
Change from Baseline	N	373	189		
	Mean change	-3.0	-4.5	1.44	(1.00, 1.87)
	% change	-13.0%	-19.4%		

[1] Difference between treatments (UIOS-TMOS) based on adjusted means from ANCOVA
[2] 95% confidence interval for the difference between treatments (lower bound, upper bound)

Source: Based on Text Table 10 in Vol 3.34 page 68.

There was no treatment by center interaction. However, the center effect was statistically significant with p-value <0.001.

Secondary analysis:

Per protocol analysis yielded similar results as the ITT analysis.

The results for 8-hour diurnal IOP at Week 2, Month 3 and Month 6 were consistent with the primary analysis.

The results for morning IOP showed larger treatment difference than the averaged 12-hour diurnal IOP at Month 6. The treatment difference (UIOS 0.15%-TMOS 0.5%) was 2.06 mmHg with 95%CI (1.51, 2.61). Mid-morning IOP (treatment difference=1.57 with 95%CI (1.05,2.09)), afternoon IOP (treatment difference=1.00 95%CI (0.49, 1.51)), and evening IOP (treatment difference=0.46 95%CI (-0.08, 1.00)) at Month 6 showed a tendency of decreased treatment difference from morning to evening. The evening IOP of UIOS 0.15% was equivalent to that of TMOS 0.5% at Month 6. (see Page 79 Vol.34).

Both responder analyses support the conclusion that TMOS 0.5% was statistically significantly superior to UIOS 0.15%.

Subgroup analyses:

It was found in subgroup analyses, there were statistically significant baseline effect and race effect. The mean change from baseline in 12-hour diurnal IOP was larger for subjects with a baseline IOP>26 mmHg than it was for subjects with a baseline IOP≤26 mmHg (p-value <0.001) in both treatment groups. Also in both treatment groups, the mean change from baseline in 12-hour diurnal IOP was larger for Caucasian than for non-Caucasians. The magnitude of the difference between subgroups was smaller for UIOS 0.15% than for TMOS 0.5% in all subgroups. No significant interaction with subgroups was observed.

2. Study 5 (C97-UIOS-005):

Twenty-seven study centers in Europe and Israel screened 661 patients. Five hundred and fifty-six patients were randomized to receive UIOS 0.15% (278), TMOS 0.5% (138), and BHOS 0.5% (140). Among the randomized patients, 552 satisfied the ITT population definition. Patient accounting information was summarized in Table 1-2.

Table 1-2: Patients accounting information for Study 5

Number of subjects	UIOS 0.15%	TMOS 0.5%	BHOS 0.5%	Total
Randomised	278	138	140	556
ITT population	276	137	139	552
Completed Month 6	238	126	126	490
Discontinued before Month 6:	40 (14.4%)	12(8.7%)	14(10.0%)	66
due to AE	9 (3.2%)	5(3.6%)	2(1.4%)	16
therapy failure	19 (6.8%)	1(0.7%)	5(3.6%)	25
protocol violation	2 (0.7%)	3 (2.2%)	1 (0.7%)	6
lost to follow-up	1 (0.36%)	2 (1.4%)	1 (0.7%)	4
death	1 (0.36%)	0 (0.0%)	0 (0.0%)	1
withdrawal of consent	4 (1.4%)	0 (0.0%)	3 (2.1%)	7
other	4 (1.4%)	1 (0.7%)	2 (1.4%)	7

Source: Based on Text Tables 5 & 6 on page 45 vol. 3.46.

Demographic information and baseline characteristics showed reasonable balances between treatment groups.

The discontinuous rate in UIOS 0.15% (14.4%) was higher than that in TMOS 0.5% (8.7%) and BHOS 0.5% (10%). Similarly, the rate of discontinuation due to therapy failure was high in UIOS 0.15% group (6.8%) than the other two groups (0.7% for TMOS 0.5% and 3.6% for BHOS 0.5%). One death was observed in UIOS 0.15% treatment group.

Sponsor's efficacy results of the primary endpoint:

The mean 12-hour diurnal IOP at baseline were 23.3 mm Hg, 23.5 mm Hg and 23.6 mm Hg for the UIOS 0.15%, TMOS 0.5% and BHOS 0.5% treatment groups, respectively. Differences between treatment groups at baseline were not statistically significant.

The mean change from baseline was statistically significantly in favour of TMOS 0.5% compared with UIOS 0.15% after six months of treatment (Δ = +1.57 mm Hg, p-value<0.001). The prospectively defined criterion for equivalence between UIOS 0.15% and TMOS 0.5% (upper limit of the adjusted 95% confidence interval for the difference between treatments < 1.50 mm Hg) was not met. While the comparison between BHOS 0.5% and UIOS 0.15% showed equivalent effect in lowering IOP, BHOS 0.5% was numerically better. The results of primary efficacy variable at Month 6 were summarized in Table 2-2.

Results of the primary efficacy variable obtained at Week 2 and Month 3 were consistent with the results at Month 6.

Table 2-2: Results of primary efficacy variable for Study 5– 12-hour diurnal at Month 6.

		UIOS 0.15%		**TMOS 0.5%**		**BHOS 0.5%**	
	N	276		137		139	
Baseline:	Mean (SD)	23.3	(2.2)	23.5	(2.4)	23.6	(2.4)
Month 6:	Mean (SD)	18.9	(2.9)	17.7	(2.4)	18.8	(2.7)
Change from baseline:	Mean (SD)	-4.3	(2.5)	-5.8	(2.7)	-4.9	(2.6)
% change from baseline:	Mean (SD)	-18.6	(10.2)	-24.3	(10.0)	-20.4	(10.3)
		UIOS 0.15% - TMOS 0.5%				**UIOS 0.15% - BHOS 0.5%**	
Mean treatment difference		1.57				0.53	
95% CI – adjusted by Dunnett's procedure		[1.00, 2.13]				[-0.03, 1.09]	

Source: Based on Text Tables 12 & 13 on pages 53 & 54 vol. 3.46.

Secondary analyses:

Per protocol analysis yielded similar results as the ITT analysis.

The analysis results for morning IOP, mid-morning IOP, afternoon IOP, and evening IOP at Week 2, Month 3 and Month 6 were consistent with the result of primary efficacy variable obtained at Month 6. Both responder analyses support the conclusion that TMOS 0.5% was statistically significantly superior to UIOS 0.15% and BHOS 0.5% was equivalent to UIOS 0.15%, although numerically slightly better in reducing IOPs.

Subgroup analyses:

The results in each subgroup were consistent with the overall results. The subgroup effect was not statistically significant in any subgroup analysis.

IV. Reviewer's Comments:

1. Reviewer's analysis:

The results of the reviewer's analysis on the primary efficacy endpoint were consistent with that of the sponsor's analyses on ITT populations. By fisher's exact test, The drop out rates due to therapy failure were statistically significant higher in UIOS 0.15% treatment group than that in TMOS 0.5% group in both studies (p-value were 0.002 and 0.005 for Studies 4 and 5 respectively). The drop out rates were not statistically significantly different between UIOS 0.15% and BHOS 0.5% treatment groups in Study 5.

2. Consistency between the two studies:

Compared Study 4 to Study 5, the IOP lowering effects of UIOS 0.15% and TMOS 0.5% in Study 5 were consistently better than that in Study 4 numerically. Since Study 4 was conducted in north American while Study 5 was conducted in Europe, only 74% of the patients was white in Study 4 while the majority patients in Study 5 (99%) was white. In Study 4, statistically significant race effect was observed and there was no statistically significant race by treatment interaction. In this study, Caucasian subgroup had better IOP lowering effect than non-Caucasian subgroup in both treatment groups. Race difference could be the explanation why Study 5 showed better IOP lowering effect than Study 4.

3. No placebo control:

The lack of placebo control created difficulty in evaluating the IOP lowering effect of UIOS 0.15% treatment since the study results showed UIOS 0.15% was not equivalent to TMOS 0.5% in lowering IOP and UIOS 0.15% was statistically significantly inferior to TMOS 0.5%. Only in one study that UIOS 0.15% showed to be equivalent to BHOS 0.5% in IOP lowering effect. If placebo control was included, the decision making could be easier by using the comparison between UIOS 0.15% and placebo.

V. Conclusion:

The results from both Phase III studies showed that the IOP lowering effect of UIOS 0.15% was not equivalent to TMOS 0.5%. As a matter of fact, it was statistically significantly inferior to the active control TMOS 0.5% by almost all the efficacy variables and analyses. The mean treatment differences between UIOS 0.15% and TMOS 0.5% for the primary efficacy variable on ITT population were 1.5 mmHg with 95%CI (1.04, 1.95)

and 1.57 mmHg with 95%CI (1.00, 2.13) mmHg in Studies 4 & 5 respectively. The upper limits of the two sided 95% CI exceeded the pre-specified equivalence region +1.5 mmHg in both studies. The rate of drop out due to lack of therapeutic effect was statistically significantly higher in UIOS 0.15% treatment group than that in TMOS 0.5% group.

Treatment with UIOS 0.15% showed equivalent therapeutic effect with BHOS 0.5% in Study 5. Since Study 4 did not have BHOS 0.5% as a control arm, the result in Study 5 was not confirmed in another study. Since Study 5 was conducted in Europe and the study population was primarily Caucasian, it was not clear if the results obtained in Study 5 for the comparison between UIOS 0.15% and BHOS 0.5% can be generalized in US.

It was shown in the two phase III studies that UIOS 0.15% lowered IOP about 3-4 mmHg, it was unclear if such lowering effect was different from placebo.

Overall, the two phase III studies did not provide convincing evidence for IOP lowering effect of UIOS 0.15% in patients with open angle glaucoma or ocular hypertension.

/S/

Qian Li, Sc.D
Mathematical Statistician

Disagree. See medical officer's Review. Placebo would be expected to have a maximum of 2 mm Hg.
/S/

Concur:

/S/ 7/10/00.

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