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Clinical Evaluation of a New Formula of Timolol Maleate (WP-934 Ophthalmic Solution)

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Abstract: We investigated the ocular hypotensive effect and possible adverse reactions of a new timolol maleate formula, WP-934 ophthalmic solution, which is timolol maleate solution dissolved in a reversible thermo-setting gel. Once-daily instillation of 0.25 or 0.5% WP-934 ophthalmic solution was administered in a prospective, randomized manner at 29 institutions for 8 weeks to patients with primary open-angle glaucoma or ocular hypertension, and for another 16 weeks in a limited number of these patients. Patients were closely monitored throughout the study by ophthalmic and systemic examinations, and by continuous evaluation of symptoms. The new timolol formula demonstrated a significant ocular hypotensive effect throughout the study period. Adverse effects were minor. WP-934 ophthalmic solution, timolol maleate dissolved in a reversible thermo-setting gel, has a significant ocular hypotensive effect in eyes with primary open-angle glaucoma and ocular hypertension. **Jpn J Ophthalmol 1997;41:244–250** © 1997 Japanese Ophthalmological Society

Key Words: Glaucoma, intraocular pressure, reversible thermo-setting gel, timolol maleate.

Introduction

Timolol maleate, a beta adrenergic blocker, is a reliable ocular hypotensive medication for patients with glaucoma or ocular hypertension. Although twice-daily instillation of timolol ophthalmic solution is generally used, a new formulation, Timoptic XE® (Merck & Co., Inc., West Point, PA, USA), a timolol maleate ophthalmic solution dissolved with gellan gum (a gelling substance[1]) has recently become commercially available in some countries, including the United States. The new timolol formula is reported to be safe and to have a long-lasting ocular hypotensive effect, permitting once-daily administration of Timoptic XE®, which is as effective as the twice-daily instillation of ordinary timolol maleate ophthalmic solution.[1] Immediately after an instillation of Timoptic XE®, however, some patients complain of foggy vision or foreign body sensation, both probably related to the gellan gum and the high viscosity of the formula.[1]

Recently, a new gel, comprised of methylcellulose, citric acid, and polyethyleneglycol was developed in Japan. This gel has reversible gel form/solution form convertibility, depending on the temperature. It remains a solution when cold and becomes a gel as the temperature approaches body temperature. A new timolol formula has been developed using this gel as a solvent for timolol maleate. A phase one study conducted in Japan with healthy normal volunteers demonstrated that both a single-dose instillation and a 7-day, once-daily administration of the new timolol formula have a significant ocular hypotensive effect with no significant adverse reactions.[2] In order to further investigate the feasibility of the new timolol formula as a potential glaucoma medication, a multi-

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centered, prospective, randomized study was done in patients with primary open-angle glaucoma or ocular hypertension.

Subjects and Methods

The current study consisted of two phases: an 8-week, short-term efficacy study followed by a 16-week, mid-term phase. The first phase included all participants; the second, selected patients who had a favorable response without adverse reactions during the first phase. The second phase was intended to determine whether the ocular hypotensive effect confirmed during the first 8-week period would continue without change for all 24 weeks. The study protocol was approved by the investigational review board at each of the 29 participating institutions. Written informed consent was obtained from all patients before entry into the study, and again from patients selected to participate in the second phase. Selection criteria included age 20 or older; either gender; and a diagnosis of primary open-angle glaucoma or ocular hypertension with intraocular pressure (IOP), in at least one eye, equal to or greater than 21 mmHg and less than 30 mmHg at either 9 AM or 11 AM on the first day of the study. The washout period for previous ocular hypotensive medications was at least 14 days for pilocarpine, epinephrine, dipivefrin, and carbonic anhydrase inhibitors, and 28 days for topical beta-adrenergic blockers or any other ocular hypotensive agents. At the end of the 8-week, short-term phase, patients who had a favorable IOP response without any adverse reactions and who agreed to continued participation were enrolled in the 16-week phase.

Exclusion criteria included concomitant medication known to significantly affect IOP; a history of intraocular surgery; a history of argon laser trabeculoplasty within 3 months prior to the initiation of the drug administration; regular use of contact lenses; best corrected visual acuity at a distance equal to or worse than 20/100; signs of ocular infection or inflammation; and patients having any diseases contraindicating use of beta-blockers, such as bronchial asthma and congestive heart diseases. Because the selected patients were to continue monotherapy with a topical beta blocker for 24 weeks, patients with severe glaucomatous field defects were also excluded at the discretion of the participating ophthalmologists.

Materials

We used 0.25 or 0.5% timolol maleate ophthalmic solution dissolved in a reversible thermo-setting gel composed of 1.4% methylcellulose, 3.5% citric acid, and 2.0% polyethyleneglycol (WP-934 ophthalmic solution; Wakamoto Pharmaceutical Co. Ltd., Tokyo; patent number: WO94/23750). The viscosity depends on temperature: 26.2 m/second at 30°C, 42.0 m/second at 32°C, and over 100.0 m/second at 34°C.

Study Design

This multi-center, prospective, randomized, open-label study was conducted at 29 institutions throughout Japan. Patients were randomly assigned either 0.25 or 0.5% WP-934 ophthalmic solution according to an envelope method. One drop of the assigned solution was administered to both eyes once daily at 9 AM. Patients were asked to return for examinations every 2 weeks during the 8-week phase and every 4 weeks during the following 16-week phase (Table 1). Patients were monitored closely throughout the study by ophthalmic and systemic examinations, and by continuous evaluation of symptoms. Laboratory examinations, including hematology, urinalysis, and blood chemistry, were done at the initiation and the completion of each phase. Acceptability of the WP-934 ophthalmic solution was assessed on a point scale by evaluation of the subjective responses to administration of the drug. The day before each clinic visit, patients instilled the WP-934 ophthalmic solution at 9 AM; on the day of the clinic visit patients did not instill the medication. Following the scheduled examinations at 9 AM, one drop of WP-934 ophthalmic solution was administered to both eyes by the physician. Two hours later, IOP, pupillary diameter, visual acuity, blood pressure, and pulse rate were recorded and a slit lamp examination was done. On each clinic visit, compliance with the protocol was verified by specifically asking the patients if they had instilled drops at 9 AM on the preceding day. To evaluate the IOP effect accurately, the 9 AM dose was administered by the physician and all measurements of IOP for a given patient were performed by the same physician using the same Goldmann applanation tonometer. Patients whose IOP responded poorly to 0.25% WP-934 ophthalmic solution were allowed to change to the 0.5% preparation. Patients whose IOP responded poorly to 0.5% WP-934 ophthalmic solution were thereafter treated at the discretion of the responsible physician.

Statistical Methods

When one eye of a patient met the selection criteria, the IOP of that eye was studied; when both eyes

Jpn J Ophthalmol
Vol 41: 244–250, 1997

Table 1. Schedule of Examinations

	Follow-Up Period (Weeks)										
	Baseline		First Treatment Phase (Weeks)				Second Treatment Phase (Weeks)				
Examinations	−4/−2	0	2	4	6	8	12	16	20	24	On Cessation
History Taking	once at baseline										
Symptomatology	x	x	x	x	(x)	x	x	x	x	x	x
IOP Measurement	x	x	x	x	(x)	x	x	x	x	x	x
Slitlamp Examination	x	x	x	x	(x)	x	x	x	x	x	x
Pupillary Diameter	x	x	x	x	(x)	x	x	x	x	x	x
Visual Acuity[a]	x	x	x	x	(x)	x	x	x	x	x	x
Blood Pressure[a]	x	x	x	x	(x)	x	x	x	x	x	x
Pulse Rate[a]	x	x	x	x	(x)	x	x	x	x	x	x
Ophthalmoscopy[a]		x				x				x	x
Perimetry[a]		once at baseline				x				x	x
Blood Sample[a]		x				x				x	x
Urine Sample[a]		x				x				x	x
Schirmer Test[a]		once at baseline				(x)[b]				(x)[b]	(x)[b]

Parentheses: optional.

[a]Performed only once at each visit around 11 AM.

[b]Mandatory in cases where any changes were observed in cornea or conjunctiva.

met the criteria, the IOP of the "worse eye" was studied. The worse eye was defined as follows: (a) the eye with the higher IOP at 9 AM on the first day of the study; (b) if IOP was equal in both eyes at 9 AM on the first day of the study, then the worse eye was the one with the greater IOP at 11 AM on the same day; or (c) if IOP in both eyes was equal at both 9 and 11 AM, then the worse eye was defined as the right eye. Both eyes were evaluated for adverse reactions.

The primary efficacy parameters tested were change and percent change in IOP from baseline values at the same time point, and percent change in outflow pressure (OP), calculated by (baseline IOP − treated IOP)/(baseline IOP − episcleral venous pressure) × 100 (%), assuming an episcleral venous pressure of 10 mmHg. Primary efficacy parameters were tested using the Wilcoxon signed-rank test; $P < 0.01$ was considered statistically significant.

The IOP measurement on a day when the participant had failed to instill the eyedrops per protocol during the previous 2 days were excluded from analysis. When the IOP measurements were done 2 or more hours earlier or later than the baseline measurements, they were also excluded.

Results

Ninety-six patients initially entered the first phase of the study. Three (3.1%) were later excluded: two dropped out before the initiation of the drug and one declined to continue in the study after the 4-week examination although no adverse reactions or symptoms were observed. Another eight patients (8.3%) were also excluded during the study: one used contact lenses during the study period; one failed to use the eyedrops per protocol; three did not have IOP measured per protocol; two were withdrawn from the study because of adverse reactions on the 28th day (one with conjunctival hyperemia and itching, and the other with atrial fibrillation); and one dropped out without notice on the 31st day. Thus, 85 patients completed the study per protocol. Pretreatment demographics are shown in Table 2 for these 85 patients. There were 40 women (mean age, 55.2 years) and 45 men (mean age, 58.1 years). Overall, the mean (± SD) age was 56.7 ± 12.6 years ranging from 23 to 77 years. Pretreatment medications were: none in 42 patients, beta-blockers only in 28, pilocarpine only in 3, and combined therapy in 12. In the 12 cases with combined therapy, all received beta-blockers, nine patients received pilocarpine, five received dipivefrin, and one received a systemic carbonic anhydrase inhibitor. During the 8-week phase, no patients changed the assigned concentration of WP-934 ophthalmic solution because of poor IOP response or used other ocular hypotensive medications at the physician's discretion. Of the 85 patients completing the study per protocol, 46 had received the 0.25% WP-934 ophthalmic solution and the remaining 39 had received the 0.5% solution. The remaining eight patients (six in the 0.25% and two in the 0.5% treatment groups) were monitored only for adverse events because of incomplete IOP data.

Table 2. Pretreatment Demographics

	Treatment Group			
	0.25% WP-934		0.5% WP-934	
	First 8-Week Phase	Entire Period	First 8-Week Phase	Entire Period
Number	46	30	39	29
Sex (male/female)	24/22	20/10	21/18	15/14
Age[a] (years)	57.0 ± 11.5	55.1 ± 11.6	56.4 ± 14.0	54.2 ± 13.6
Type (POAG/OHT)	13/33	8/22	13/26	7/22

POAG: primary open-angle glaucoma, OHT: ocular hypertension.
[a]Mean ± standard deviation.

Sixty-four patients entered the second 16-week phase of the study. Five patients (7.8%) were excluded because of failure to meet the enrollment criteria for the second phase: one patient used contact lenses during the study period; two had not responded well to the eyedrops during the 8-week period; two had some missing data on the last day of the 8-week phase, which made judgment for compatibility with the criteria difficult. Hence, 59 patients completed the study according to the protocol (Table 2). There were 24 women (mean age, 53.4 years) and 35 men (mean age, 55.5 years). During the subsequent 16-week phase, no patients changed the assigned concentration of WP-934 ophthalmic solution because of poor IOP response. Of the 59 cases completing the study per protocol, 30 were treated with 0.25% WP-934 ophthalmic solution and the remaining 29 with 0.5% of the drug.

Intraocular Pressure

The mean IOPs and SDs before and during the first phase are shown in Tables 3 and 4. IOPs were significantly lower than the baseline values on the first day of the study at each time point ($P < 0.001$, Wilcoxon signed-rank test): the baseline IOP (mean ± SD) was 22.8 ± 2.3 mmHg at 9 AM and 22.3 ± 1.8 mmHg at 11 AM for the 0.25% treatment group, and was 22.9 ± 2.1 mmHg at 9 AM and 22.9 ± 2.2 mmHg at 11 AM for the 0.5% treatment group. Throughout the treatment period, both the 9 AM IOP before drug instillation and the IOP 2 hours after instillation remained remarkably stable.

The mean IOPs and SDs before and during the second phase are shown in Tables 5 and 6. IOPs in this phase were significantly lower than the baseline values ($P < 0.001$, Wilcoxon signed-rank test): the mean baseline IOP (mean ± SD) was 23.3 ± 2.1 mmHg at 9 AM and 22.5 ± 2.0 mmHg at 11 AM for the 0.25% treatment group, and was 23.0 ± 2.2 mmHg at 9 AM and 23.0 ± 2.2 mmHg at 11 AM for the 0.5% treatment group. Throughout the treatment period, the IOPs were remarkably stable.

The IOP decrease, expressed as percent change, was consistent throughout the two phases of treatment (Tables 3–6). The mean (± SD) percent IOP reduction during the 8-week phase was 17.1 ± 11.6% at 9 AM and 20.3 ± 9.3% 2 hours after instillation

Table 3. Change in Intraocular Pressure During First 8 Weeks (0.25% WP-934 Treated Group)

	0 Weeks	2 Weeks	4 Weeks	6 Weeks	8 Weeks
IOP (mmHg)					
9 AM	22.8 ± 2.3 (46)	19.0 ± 2.0[b] (45)	18.8 ± 2.0[b] (42)	18.1 ± 2.3[b] (16)	18.6 ± 2.1[b] (43)
11 AM	22.3 ± 1.8 (46)	17.7 ± 2.0[b] (45)	17.6 ± 1.9[b] (42)	16.4 ± 2.5[b] (16)	17.6 ± 2.0[b] (43)
ΔIOP (mmHg)					
9 AM		3.8 ± 2.7	4.1 ± 2.5	4.7 ± 2.9	4.1 ± 2.7
11 AM		4.7 ± 2.4	4.9 ± 2.2	5.6 ± 2.9	4.7 ± 2.1
ΔIOP (%)					
9 AM		15.9 ± 11.7	17.1 ± 10.0	20.2 ± 11.3	17.1 ± 11.6
11 AM		20.6 ± 9.6	21.4 ± 9.0	25.0 ± 11.6	20.3 ± 9.3
ΔOP[a] (%)					
9 AM		27.3 ± 23.4	30.0 ± 17.6	35.8 ± 19.1	30.3 ± 22.0
11 AM		37.1 ± 16.6	38.6 ± 15.7	46.1 ± 20.2	37.7 ± 16.0

Values are shown in mean ± standard deviation. Parentheses: number of eyes studied.
[a](baseline IOP − treated IOP)/(baseline IOP − 10) × 100.
[b]$P < 0.001$ (versus baseline; Wilcoxon signed-rank test).

Jpn J Ophthalmol
Vol 41: 244–250, 1997

Table 4. Change in Intraocular Pressure During First 8 Weeks (0.5% WP-934 Treated Group)

	0 Weeks	2 Weeks	4 Weeks	6 Weeks	8 Weeks
IOP (mmHg)					
9 AM	22.9 ± 2.1 (39)	18.3 ± 2.8[b] (37)	18.3 ± 2.7[b] (37)	17.4 ± 2.3[b] (17)	18.2 ± 2.4[b] (38)
11 AM	22.9 ± 2.2 (39)	17.2 ± 2.8[b] (37)	17.4 ± 2.5[b] (37)	16.2 ± 2.5[b] (17)	17.0 ± 2.7[b] (38)
ΔIOP (mmHg)					
9 AM		4.6 ± 2.9	4.7 ± 2.6	5.7 ± 3.4	4.8 ± 2.9
11 AM		5.5 ± 3.1	5.5 ± 3.2	7.1 ± 3.3	6.0 ± 3.4
ΔIOP (%)					
9 AM		19.6 ± 12.1	20.1 ± 10.6	23.7 ± 12.6	20.3 ± 11.7
11 AM		24.0 ± 12.3	23.5 ± 11.9	29.9 ± 11.7	25.5 ± 12.7
ΔOP[a] (%)					
9 AM		34.8 ± 21.0	35.6 ± 18.6	41.6 ± 20.3	35.7 ± 20.2
11 AM		42.9 ± 21.6	41.6 ± 19.7	52.4 ± 18.8	45.2 ± 21.1

Values are shown in mean ± standard deviation. Parentheses: number of eyes studied.
[a](baseline IOP − treated IOP)/(baseline IOP − 10) × 100.
[b]$P < 0.001$ (versus baseline; Wilcoxon signed-rank test).

for the 0.25% treatment group, and was 20.3 ± 11.7% at 9 AM and 25.5 ± 12.7% at 11 AM for the 0.5% treatment group. For the 24-week study subjects, the mean ± SD percent IOP reduction during the last 16 weeks was 21.7 ± 7.5% at 9 AM and 20.6 ± 10.9% 2 hours after instillation for the 0.25% treatment group, and was 21.1 ± 15.0% at 9 AM and 23.2 ± 14.0% at 11 AM for the 0.5% treatment group. There were no statistically significant day-to-day differences in either IOP values or percent change in IOP.

The percent change in OP is also shown in Tables 3–6. The mean percent OP change during the 8 weeks ranged from 27.3% to 35.8% at 9 AM and 37.1% to 46.1% 2 hours after instillation for the 0.25% treatment group, and ranged from 34.8% to 41.6% at 9 AM and 41.6% to 52.4% at 11 AM for the 0.5% treatment group. Percent changes in OP were similar during the second phase.

Ocular Signs and Symptoms

WP-934 ophthalmic solution was well tolerated in most subjects. Exceptions during the first phase included one patient withdrawn from the study because of subjective ocular symptoms: this 64-year-old woman in the 0.25% treatment group complained of itching and conjunctival hyperemia. Another patient in the 0.25% treatment group was found to have corneal epithelial erosions at the end of the first phase and the drug was discontinued. The signs and symptoms disappeared within 14 days in both cases. One patient in the 0.25% treatment group complained of dryness of the eyes and two patients (one from the

Table 5. Change in Intraocular Pressure During Second 16 Weeks (0.25% WP-934 Treated Group)

	0 Weeks	12 Weeks	16 Weeks	20 Weeks	24 Weeks
IOP (mmHg)					
9 AM	23.3 ± 2.1 (30)	18.6 ± 1.7[b] (27)	18.6 ± 2.4[b] (28)	18.9 ± 2.0[b] (28)	18.1 ± 1.9[b] (29)
11 AM	22.5 ± 2.0 (30)	17.2 ± 2.3[b] (27)	17.0 ± 2.3[b] (28)	17.4 ± 2.0[b] (28)	17.7 ± 2.2[b] (29)
ΔIOP (mmHg)					
9 AM		4.8 ± 1.9	4.7 ± 2.8	4.5 ± 2.2	5.1 ± 2.0
11 AM		5.3 ± 2.4	5.4 ± 2.3	5.0 ± 2.1	4.7 ± 2.5
ΔIOP (%)					
9 AM		20.2 ± 7.2	19.7 ± 11.1	18.9 ± 8.6	21.7 ± 7.5
11 AM		23.5 ± 10.2	24.1 ± 9.3	22.1 ± 8.8	20.6 ± 10.9
ΔOP[a] (%)					
9 AM		35.2 ± 12.0	34.3 ± 18.8	32.9 ± 14.7	38.3 ± 12.8
11 AM		42.5 ± 18.5	43.7 ± 16.9	39.8 ± 15.3	37.0 ± 19.8

Values are shown in mean ± standard deviation. Parentheses: number of eyes studied.
[a](baseline IOP − treated IOP)/(baseline IOP − 10) × 100.
[b]$P < 0.001$ (versus baseline; Wilcoxon signed-rank test).

Table 6. Change in Intraocular Pressure During Second 16 Weeks (0.5% WP-934 Treated Group)

	0 Weeks	12 Weeks	16 Weeks	20 Weeks	24 Weeks
IOP (mmHg)					
9 AM	23.0 ± 2.2 (29)	17.9 ± 2.0[b] (28)	17.9 ± 2.3[b] (27)	17.4 ± 2.1[b] (27)	18.0 ± 2.3[b] (27)
11 AM	23.0 ± 2.2 (29)	16.9 ± 2.4[b] (28)	16.9 ± 2.5[b] (27)	16.9 ± 2.2[b] (27)	17.6 ± 2.4[b] (27)
ΔIOP (mmHg)					
9 AM		4.9 ± 2.4	5.1 ± 2.9	5.7 ± 3.0	5.0 ± 3.3
11 AM		5.9 ± 2.9	6.2 ± 3.6	6.2 ± 3.3	5.6 ± 3.3
ΔIOP (%)					
9 AM		21.0 ± 10.4	22.3 ± 12.9	24.9 ± 13.8	21.1 ± 15.0
11 AM		25.2 ± 11.8	26.7 ± 15.6	26.6 ± 14.3	23.2 ± 14.0
ΔOP[a] (%)					
9 AM		37.3 ± 17.1	38.3 ± 17.8	42.1 ± 16.9	36.7 ± 20.7
11 AM		45.3 ± 18.6	45.8 ± 21.1	45.9 ± 19.7	41.2 ± 20.3

Values are shown in mean ± standard deviation. Parentheses: number of eyes studied.
[a](baseline IOP − treated IOP)/(baseline IOP − 10) × 100.
[b]$P < 0.001$ (versus baseline; Wilcoxon signed-rank test).

0.25% treatment group and one from 0.5% treatment group) had mild discomfort; these three continued the instillations during the entire study period with little difficulty. Overall, five patients (5.4%) complained of mild to moderate discomfort and/or had abnormalities in the outer segment during the first phase.

During the second phase, one patient in the 0.25% treatment group developed allergic conjunctivitis on the 104th day. Another patient in the 0.5% treatment group complained of an itchy sensation. Both continued instillations during the entire study period without difficulty. Only these two patients (3.4%) had mild to moderate discomfort and/or abnormalities in the outer segment during the second phase.

Systemic Findings

During the first phase, we found the following: a slight decrease in white blood cell count (50-year-old female, 0.25% group), atrial fibrillation (47-year-old male, 0.5% group), mild hypoglycemia (70-year-old male on insulin therapy, 0.5% group), and mild cerebral infarction (56-year-old female, 0.5% group). In all cases, except the atrial fibrillation, the use of WP-934 ophthalmic solution was continued without difficulty. No causal relationship between the systemic abnormalities and the study medication was seen. On the last day of the 16-week phase, one patient was found to have bradycardia (48 beats/minute; baseline: 66 beats/minute). This 23-year-old woman was treated by another nonselective beta-blocker and the pulse rate returned to normal.

Other physical and laboratory examinations revealed no abnormal changes attributable to the use of the drug with a few exceptions: pulse rate was significantly lower than baseline in the 0.5% treatment group at 2, 4, and 8 weeks during the first phase and systolic blood pressure was significantly lower than baseline in the 0.5% treatment group at 12 weeks during the second phase.

Discussion

The reversible thermo-setting gel used in the current study forms a solution in cold temperature and turns into a gel as the temperature approaches body temperature. The constituents (methylcellulose, citric acid, and polyethyleneglycol) are known to be safe for ocular tissues.[4] WP-934 ophthalmic solution is now undergoing several clinical trials in Japan.[2,5,6] It has been demonstrated that once-daily instillation of 0.5% WP-934 ophthalmic solution has a significant ocular hypotensive effect in normal subjects[2] and is as effective as twice-daily use of commercially-available 0.5% timolol ophthalmic solution.[6] The enhanced effect may be due to the gel-induced increase in drug-cornea contact time, although methylcellulose does not stay in tear film as long as gellan gum.[7]

The ocular hypotensive effect found in the current study is almost identical to that already reported for twice-daily use of 0.5% timolol ophthalmic solution as well as once-daily use of Timoptic XE®. A 28% reduction in IOP was reported following twice-daily timolol instillations for approximately 10 weeks.[8] In eyes with less milder elevations in pretreatment IOP, in a Japanese population, a 20–25% reduction in IOP following twice-daily use of 0.5% timolol maleate aqueous solution has been reported.[9,10]

Most adverse reactions detected in the current study have no definite causal relationship to the use of the drug and some adverse effects, such as brady-

Jpn J Ophthalmol
Vol 41: 244–250, 1997

cardia and conjunctival hyperemia, have been reported since the introduction of timolol eyedrops.[11] The adverse effects of WP-934 ophthalmic solution, therefore, appear to be minor in nature and no more serious than those associated with the timolol ophthalmic solution now available. Based on the current results, WP-934 ophthalmic solution merits further clinical evaluation as a potential once-a-day ocular hypotensive medication.

The authors and the members of the Study Group have no proprietary interest in the development and marketing of any products mentioned in the article or of competing drugs.

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Appendix

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