Randomized, Controlled, Phase 3 Trials of Carteolol/Latanoprost Fixed Combination in Primary Open-Angle Glaucoma or Ocular Hypertension

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• PURPOSE: To assess the intraocular pressure (IOP)-lowering effects and safety of a carteolol/latanoprost fixed combination drug (OPC-1085EL) vs latanoprost (Study 1) and carteolol (Study 2) in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OH).

• DESIGN: Multicenter, randomized, evaluator-masked (Study 1)/double-masked (Study 2), parallel-group studies.

• METHODS: SETTING: Twenty-eight clinical sites (Study 1) and 19 clinical sites (Study 2) in Japan. STUDY POPULATION: Outpatients with bilateral POAG or OH whose predose IOP was 18 to < 35 mm Hg in the study eye after 4 weeks' treatment with latanoprost (Study 1) or carteolol (Study 2) (defined as baseline). INTERVENTION: In Study 1, 237 patients applied OPC-1085EL (n = 118) or latanoprost (n = 119) for 8 weeks. In Study 2, 193 patients applied OPC-1085EL (n = 78), carteolol (n = 78), or carteolol/latanoprost concomitant therapy (n = 37) for 8 weeks. MAIN OUTCOME MEASURE: Adjusted mean IOP reduction at predose from baseline to week 8.

• RESULTS: In Study 1, the adjusted mean IOP reductions (95% confidence interval [CI]) were 2.9 (2.5-3.3) mm Hg and 1.6 (1.2-2.0) mm Hg in the OPC-1085EL and latanoprost groups, respectively ($P < .0001$). In Study 2, the adjusted mean IOP reductions (95% CI) were 3.5 (3.1-3.9) mm Hg and 1.6 (1.2-2.0) mm Hg in the OPC-1085EL and carteolol groups, respectively ($P < .0001$). All adverse drug reactions of OPC-1085EL observed in both studies were mild in severity and only 1 patient in each study discontinued because of an adverse drug reaction.

• CONCLUSIONS: OPC-1085EL is superior to latanoprost or carteolol alone in terms of lowering IOP, and was well tolerated.

GLAUCOMA IS THE SECOND-LEADING CAUSE OF blindness worldwide.[1] Open-angle glaucoma (OAG) is the commonest type of glaucoma, and it is estimated that it will affect around 59 million patients in 2020.[2] Elevated intraocular pressure (IOP) is the primary risk factor for the onset and progression of glaucoma. IOP-lowering treatment is the only therapeutic approach with clear evidence for preventing glaucoma and suppressing its progression.[1,3]

Patients with glaucoma are often treated with beta blockers or prostaglandin (PG) analogues. Treatment is initiated as monotherapy in the majority of the patients, but poor efficacy or intolerable adverse drug reactions (ADRs) may lead to a change in medication or the addition of a drug with a different mechanism of action.[1,4] However, concomitant therapies may be inconvenient for patients, fostering poor adherence to treatment. A fixed-combination drug has advantages over concomitant application of single-agent ophthalmic drugs. It can reduce the number of drugs and the frequency of the applications and may improve treatment adherence.[5,6] Less-frequent application also reduces exposure to potentially harmful preservatives in ophthalmic drugs.[6,7]

Carteolol hydrochloride is a nonselective beta blocker with intrinsic sympathomimetic activity that reduces IOP with twice-daily (BID) application. It increases blood flow in the fundus[8] and has less impact on the cardiovascular system[9] and respiratory function[10] than timolol maleate. It is also less likely to cause eye irritation[11] and has less impact on blood lipid profiles.[12] Once-daily (QD) carteolol (carteolol LA), which was formulated by adding alginic acid to prolong the IOP-lowering effects, is available in many countries.[13–16] Latanoprost, a $PGF_{2\alpha}$ analogue, is widely used for the treatment of glaucoma owing to its strong IOP-reducing activity and good safety profile, and was recently shown to have a visual

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field-preserving effect in a placebo-controlled trial.[17] Adding carteolol to latanoprost increases the IOP-lowering effect.[18] A fixed-combination treatment of carteolol and a PG analogue represents a new therapeutic option capable of improving convenience and adherence to concomitant therapy. OPC-1085EL is a newly developed ophthalmic solution containing carteolol hydrochloride 2% and latanoprost 0.005%. Because OPC-1085EL contains the same concentration of alginic acid as carteolol LA and the same dose of latanoprost as administered QD, the daily dose of each active ingredient is formulated to be the same as concomitant therapy with carteolol LA and latanoprost. It does not contain benzalkonium chloride, meaning that OPC-1085EL should be safer for the corneal epithelium.

The objectives of the 2 studies reported in this article were to assess the IOP-lowering effects and safety of OPC-1085EL compared with monotherapy with latanoprost (Study 1) or with carteolol LA (Study 2) in patients with primary OAG (POAG; including normal tension glaucoma [NTG]) or ocular hypertension (OH). In Study 2, OPC-1085EL was also compared with carteolol/latanoprost concomitant therapy.

METHODS

THESE WERE 2 PHASE 3, MULTICENTER, ACTIVE-controlled, randomized, evaluator-masked (Study 1)/double-masked (Study 2), parallel-group comparative studies in patients with POAG (including NTG) or OH. The studies were conducted in 28 clinical sites from April 28, 2014 to March 20, 2015 (Study 1) and in 19 clinical sites from April 27, 2014 to January 21, 2015 (Study 2) in Japan. Both studies were performed according to the tenets of the Helsinki Declaration and in compliance with the International Conference on Harmonization Good Clinical Practice and Japanese regulations. Prior to enrollment, written informed consent was obtained from the patients. The informed consent document covered all prospective treatments and study measures; it was not necessary to obtain retrospective consent for any procedures. The informed consent documents and the study protocols were reviewed and approved by the institutional review board of each study site. Both studies were registered on ClinicalTrials.gov (Study 1: NCT02105272; Study 2: NCT02105285). The list of investigators and participating sites is shown in the Supplemental Materials (available at AJO.com).

• **PATIENTS:** Outpatients aged 20-80 years with bilateral POAG or OH and with a predose IOP of 18 to <35 mm Hg in the unilateral eye and IOP <35 mm Hg in the contralateral eye at the end of the screening period were eligible. Patients with the following were excluded: (1) best-corrected visual acuity (decimal unit) ≤0.2; (2) hypersensitivity to any ingredients in carteolol or latanoprost ophthalmic drug; (3) nonresponder to beta blockers (Study 1) or PG analogues (Study 2); (4) presence or history of ocular disease, such as progressive retinal disease, severe dry eye, angle closure, ocular infection, endophthalmitis, acute ocular inflammation, corneal foreign body, ocular trauma, herpes keratitis, or corneal ulcer; (5) cataract or intraocular surgery, aphakia, or intraocular lens; and (6) poorly controlled cardiac failure, sinus bradycardia, atrioventricular block, bronchial asthma, severe chronic obstructive pulmonary disease, or poorly controlled diabetes mellitus.

• **STUDY TREATMENTS:** The study drugs used during the evaluation period were carteolol hydrochloride 2%/latanoprost 0.005% fixed-combination ophthalmic solution (OPC-1085EL) and latanoprost 0.005% (Xalatan; Pfizer Japan Inc, Tokyo, Japan) in Study 1, and OPC-1085EL and carteolol hydrochloride 2% long-acting formulation (Mikelan LA 2%; Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan) and latanoprost 0.005% in Study 2. During the screening period, the run-in drugs (latanoprost in Study 1; carteolol in Study 2) were applied QD in the morning from the day after the screening period started to the last day of the screening period. During the evaluation periods, the study drugs were applied QD in the morning until the end of the last day of the evaluation period from the day after the last day of the screening period.

The study designs are shown in Figure 1. In Study 1, after application of latanoprost during a 4-week screening period, eligible patients were randomized to either OPC-1085EL (OPC group) or latanoprost (LAT group) in a 1:1 fashion and were treated for 8 weeks under evaluator-masked conditions. Patients in the LAT group received latanoprost for a total of 12 weeks from the start of the screening period until the end of the evaluation period. In Study 2, the patients applied carteolol during the screening period and were then randomized to OPC-1085EL (OPC group), carteolol (CAR group), or carteolol/latanoprost concomitant therapy (CAR-LAT group) in a 2:2:1 fashion and were treated for 8 weeks under double-masked conditions for OPC and CAR or under evaluator-masked conditions for CAR-LAT. Patients in the CAR and CAR-LAT groups received CAR for a total of 12 weeks from the start of the screening period until the end of the evaluation period.

During the screening and evaluation periods, the study drug was applied in both eyes, 1 drop, QD, between 9 AM and 11 AM. In the CAR-LAT group in Study 2, carteolol was applied 10 minutes after latanoprost. Patients were instructed to conduct nasolacrimal occlusion to both eyes for 1-5 minutes after application. The study drug was applied ≥10 minutes after any concomitant ophthalmic drug. Concomitant use of any IOP-lowering agents, systemic corticosteroids, topical corticosteroids applied to

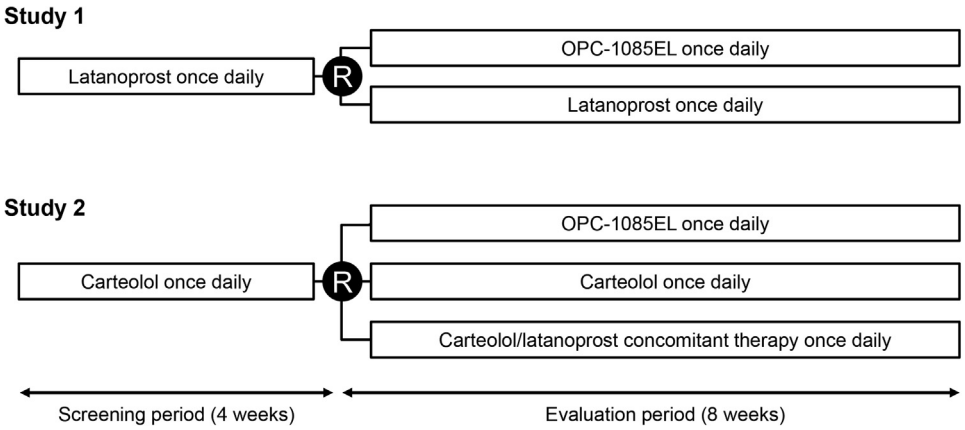

FIGURE 1. Study designs. Eligible patients were randomized to either OPC-1085EL or latanoprost in a 1:1 fashion in Study 1 and OPC-1085EL, carteolol, or carteolol/latanoprost concomitant therapy in a 2:2:1 fashion in Study 2. R, randomization.

the eyelids or eyes, and any other drugs that may affect IOP were prohibited. Topical corticosteroids applied elsewhere were permitted. Other prohibited concomitant therapies included ophthalmic surgery and treatment (eg, laser treatment, contact lens).

IOP was measured at the end of the screening period (baseline) and in week 8 of the evaluation period at the following times at both visits: predose (9 AM to 11 AM), 2 hours after dosing, and 8 hours after dosing. IOP was also measured at predose at week 4 after the start of treatment in the evaluation period. The IOP measurement at 8 hours was performed only for patients who consented to this procedure. IOP was measured once at each time point in a sitting position using the Goldmann applanation tonometer after topical anesthesia.

Central randomization was performed to assign patients to each group with a dynamic allocation method that included stratification by center and baseline IOP at predose (18 to <21 mm Hg; 21 to <24 mm Hg; and ≥24 mm Hg). The study drugs were coded based on the randomization list prepared by the controller.

Commercially available latanoprost (Xalatan) was used to ensure its quality. Measures were taken to maintain masking, including implementing procedures for packaging, allocation, supply, and collection of the study drugs; handling of patients; and topical application at the study sites.

• **EFFICACY PARAMETERS:** The study eye was defined as the eye with the highest IOP at predose at the end of the screening period, or the right eye if the IOP values of both eyes were equal. The primary endpoint was the adjusted mean IOP reduction at predose from baseline to week 8. Secondary efficacy endpoints included the mean IOP, adjusted mean IOP reduction at each time point at weeks 4 and 8, and the proportions of patients achieving the target IOPs (≤18, ≤16, or ≤14 mm Hg) or the target IOP reductions (≥2, ≥4, or ≥6 mm Hg) at week 8.

• **SAFETY PARAMETERS:** Safety variables included adverse events (AEs), physical examination findings, subjective ocular symptoms, comfort in the use of the study drug, vital signs (blood pressure, pulse rate), visual acuity, slit-lamp microscopy, fundus examinations, and clinical laboratory tests. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.0., and were classified as mild (discomfort, but no disruption of normal daily activity), moderate (sufficient discomfort to reduce or affect daily activity), and severe (unable to work or perform normal daily activity). The comfort in the use of the study drug was rated on a 4-point scale by clinical interview: 0: "No problems with application at all"; 1: "Some trouble with application, but no problems"; 2: "Trouble with application, but bearable"; and 3: "Unbearable trouble with application". ADRs were defined as AEs that occurred during the evaluation period for which a causal relationship with the study drug could not be ruled out.

• **STATISTICAL ANALYSIS:** To determine the sample size in both studies, the difference in IOP reduction between the OPC and LAT groups was assumed to be 1.5 mm Hg[18–21] and that between the OPC and CAR groups to be 2 mm Hg.[22–24] The standard deviation for IOP reduction in the 2 studies was estimated to be 3.2 mm Hg. Based on these assumptions, 97 patients per group for Study 1 and 55 per group for Study 2 were required to detect a difference with a 2-sided significance level of .05 and a power of 90%. Moreover, allowing for exclusions, discontinuations, and dropouts, 220 patients (with a ratio for OPC:LAT of 1:1) were required for Study 1 and 175 patients (with a ratio for OPC:CAR:CAR-LAT of 2:2:1; 70, 70, and 35 patients, respectively) for Study 2.

The efficacy population included all randomized patients who received any dose of the study drug, had an IOP measurement at the end of screening, and had at least 1 postbaseline IOP measurement (full analysis set, FAS).

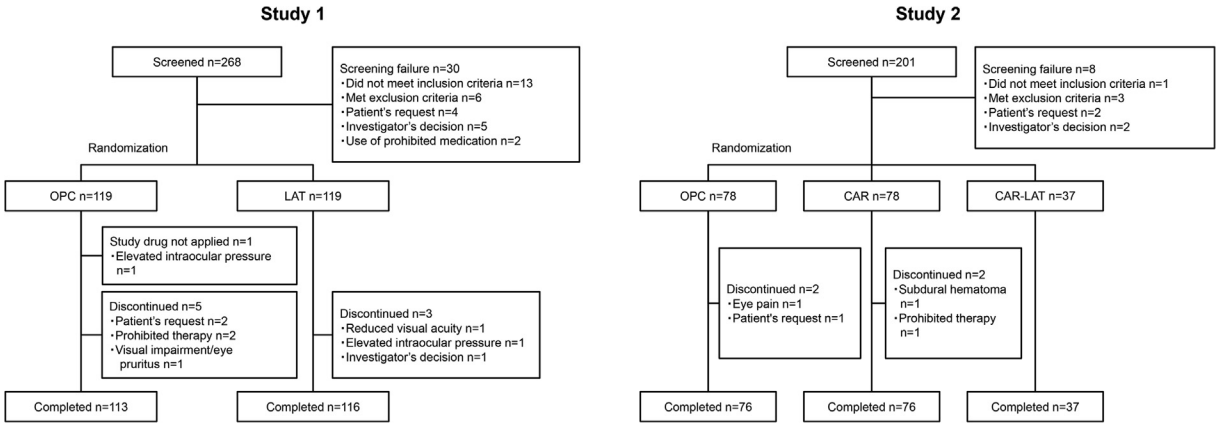

FIGURE 2. Flow charts showing patient dispositions in Study 1 and Study 2. OPC = OPC-1085EL; LAT = latanoprost; CAR = carteolol; CAR-LAT = carteolol/latanoprost concomitant therapy.

Analysis of covariance was performed to compare the mean IOP and the mean IOP reduction between OPC and LAT (Study 1) and between OPC and CAR (Study 2), with treatment group as a fixed factor and baseline IOP as a covariate. These analyses yielded baseline-adjusted mean changes in IOP. The proportions of patients achieving the target criteria were compared using logistic regression models.

The safety population included all patients who received any dose of the study drug (safety set, SS). The number of patients with AEs was tabulated for each treatment group.

Missing values in the efficacy analyses were imputed using the last-observation-carried-forward (LOCF) approach. Values obtained before topical application of the study drug were not used for imputation. At each visit, for patients with poor compliance with the study drug treatment, categorized as "No application on the day before the visit," the data at the visit were used in the analysis. For patients with poor compliance with the study drug treatment, categorized as "Visited the site after application on the day of visit," the data obtained at "2 hours after morning application" and "8 hours after morning application" at the visit were used in the analysis, but the data obtained "predose, before morning application" were excluded.

The SAS software package version 9.2 (SAS Institute Inc, Cary, North Carolina, USA) was used for all analyses.

RESULTS

• **STUDY SETTINGS AND PATIENTS:** In Study 1, of 238 patients (119 in each group) who were randomized, 237 received the study drugs (118 and 119 in the OPC and LAT groups, respectively), and 229 (113 and 116 in the OPC and LAT groups, respectively) completed the 8-week treatment (Figure 2). In terms of patient characteristics, there were no obvious differences between groups except for sex (significance level: 15%; $P = .0661$) (Table 1).

In Study 2, 193 patients (78 in each of the OPC and CAR groups and 37 in the CAR-LAT group) were randomized and received the study drugs, and 189 (76 in each of the OPC and CAR groups and 37 in the CAR-LAT group) completed the 8-week treatment (Figure 2). There were no obvious differences in patient characteristics among the 3 groups (Table 1).

• **EFFICACY:** The mean IOPs at each time point are shown in Figure 3 and Table 2. The mean baseline IOPs at predose and at 2 and 8 hours postdose were similar in both groups in Study 1 and in all 3 groups in Study 2.

Study 1. The adjusted mean IOP reductions (95% confidence interval [CI]) in the OPC and LAT groups at predose at week 8 (primary endpoint) were 2.9 (2.5, 3.3) and 1.6 (1.2, 2.0) mm Hg, respectively. The difference in adjusted mean IOP reduction (95% CI) between the 2 groups (OPC − LAT) was 1.3 (0.7, 1.8) mm Hg (Table 3). The IOP reduction in the OPC group was significantly greater than that in the LAT group at all time points. The reductions in IOP with OPC vs LAT were also reflected in the subgroup analysis (Table 4). The proportions of patients achieving the target criteria (ie, ≤18, ≤16, and ≤14 mm Hg for IOP; or ≥2, ≥4, and ≥6 mm Hg for IOP reduction) at predose at week 8 were significantly greater in the OPC group than in the LAT group (Table 5).

Study 2. The adjusted mean IOP reductions (95% CI) in the OPC and CAR groups at predose at week 8 (primary endpoint) were 3.5 (3.1, 3.9) mm Hg and 1.6 (1.2, 2.0) mm Hg, respectively. The difference in adjusted mean IOP reduction (95% CI) between the 2 groups

TABLE 1. Patient Characteristics in Phase 3 Trials of Carteolol/Latanoprost Fixed Combination

	Study 1			Study 2			
	OPC	LAT		OPC	CAR		CAR-LAT
Characteristics	N (%)	N (%)	*P* Value[a]	N (%)	N (%)	*P* Value[a]	N (%)
Sex							
Male	57 (48.3)	43 (36.1)		38 (48.7)	39 (50.0)		16 (43.2)
Female	61 (51.7)	76 (63.9)	.0661[b]	40 (51.3)	39 (50.0)	1.0000[b]	21 (56.8)
Age							
Mean ± SD, y	59.9 ± 11.4	60.8 ± 11.5	.5344[c]	57.9 ± 12.1	60.6 ± 10.6	.1416[c]	56.6 ± 12.8
Diagnosis							
POAG	72 (61.0)	71 (59.7)		39 (50.0)	42 (53.8)		22 (59.5)
NTG	9 (7.6)	7 (5.9)		4 (5.1)	8 (10.3)		4 (10.8)
OH	37 (31.4)	41 (34.5)	.7964[b]	35 (44.9)	28 (35.9)	.3414[b]	11 (29.7)
Baseline IOP[d]							
≥18 to <21 mm Hg	80 (67.8)	78 (65.5)		59 (75.6)	59 (75.6)		28 (75.7)
≥21 to <24 mm Hg	30 (25.4)	34 (28.6)		15 (19.2)	13 (16.7)		6 (16.2)
≥24 mm Hg	8 (6.8)	7 (5.9)	.8613[b]	4 (5.1)	6 (7.7)	.8109[b]	3 (8.1)
Prior medication[e]							
Present	102 (86.4)	103 (86.6)		61 (78.2)	65 (83.3)		29 (78.4)
Absent	16 (13.6)	16 (13.4)	1.0000[b]	17 (21.8)	13 (16.7)	.5427[b]	8 (21.6)

CAR = carteolol; CAR-LAT = carteolol/latanoprost concomitant therapy; IOP = intraocular pressure; LAT = latanoprost; NTG = normal tension glaucoma; OH = ocular hypertension; OPC = OPC-1085EL; POAG = primary open-angle glaucoma.

[a]Study 1: OPC vs LAT; Study 2: OPC vs CAR.

[b]Fisher exact test.

[c]*t* test.

[d]For the study eye.

[e]Medication for POAG, NTG, or OH.

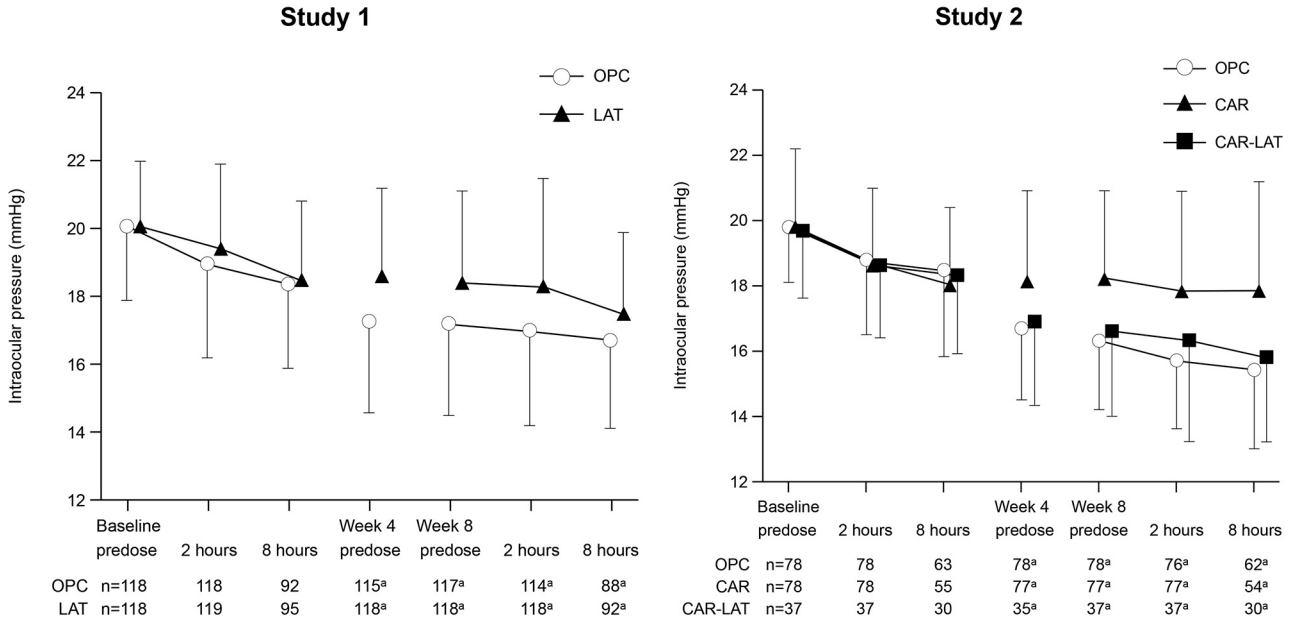

FIGURE 3. Time course of intraocular pressure in Study 1 and Study 2. Values are presented as the mean ± standard deviation (standard deviations are presented in a 1-sided manner for clarity). Missing values were imputed using the last-observation-carried-forward method. OPC = OPC-1085EL; LAT = latanoprost; CAR = carteolol; CAR-LAT = carteolol/latanoprost concomitant therapy. [a]Number of subjects with both nonmissing baseline values and nonmissing values at each time point.

TABLE 2. Time Course of Intraocular Pressure in Phase 3 Trials of Carteolol/Latanoprost Fixed Combination

		Study 1				Study 2					
		OPC		LAT		OPC		CAR		CAR-LAT	
Visit	Time Point	N	IOP,[a] mm Hg	N	IOP,[a] mm Hg	N	IOP,[a] mm Hg	N	IOP,[a] mm Hg	N	IOP,[a] mm Hg
Baseline	Predose	118	20.1 ± 2.2	119	20.1 ± 1.9	78	19.8 ± 1.7	78	19.8 ± 2.4	37	19.7 ± 2.1
	2 hours	118	19.0 ± 2.8	119	19.4 ± 2.5	78	18.8 ± 2.3	78	18.6 ± 2.4	37	18.6 ± 2.2
	8 hours	92	18.4 ± 2.5	95	18.5 ± 2.3	63	18.5 ± 2.7	55	18.0 ± 2.4	30	18.3 ± 2.4
Week 4	Predose	115	17.3 ± 2.7	118	18.6 ± 2.6	78	16.7 ± 2.2	77	18.1 ± 2.8	35	16.9 ± 2.6
Week 8	Predose	117	17.2 ± 2.7	118	18.4 ± 2.7	78	16.3 ± 2.1	77	18.2 ± 2.7	37	16.6 ± 2.6
	2 hours	114	17.0 ± 2.8	118	18.3 ± 3.2	76	15.7 ± 2.1	77	17.8 ± 3.1	37	16.3 ± 3.1
	8 hours	88	16.7 ± 2.6	92	17.5 ± 2.4	62	15.4 ± 2.4	54	17.8 ± 3.4	30	15.8 ± 2.6

CAR = carteolol; CAR-LAT = carteolol/latanoprost concomitant therapy; IOP = intraocular pressure; LAT = latanoprost; OPC = OPC-1085EL.

Missing values were imputed using the last-observation-carried-forward method.

[a]Mean ± standard deviation.

TABLE 3. Adjusted Mean Intraocular Pressure Reduction From Baseline in Phase 3 Trials of Carteolol/Latanoprost Fixed Combination

Study 1		OPC		LAT			
Visit	Time Point	N[a]	IOP Reduction,[b] mm Hg	N[a]	IOP Reduction,[b] mm Hg	Difference[b]	*P* Value[c]
Week 4	Predose	115	2.7 ± 0.2 (2.3, 3.1)	118	1.5 ± 0.2 (1.1, 1.8)	1.3 ± 0.3 (0.7, 1.8)	<.0001
Week 8	Predose	117	2.9 ± 0.2 (2.5, 3.3)	118	1.6 ± 0.2 (1.2, 2.0)	1.3 ± 0.3 (0.7, 1.8)	<.0001
	2 hours	114	2.1 ± 0.2 (1.7, 2.4)	118	1.0 ± 0.2 (0.6, 1.4)	1.0 ± 0.3 (0.5, 1.6)	.0003
	8 hours	88	1.7 ± 0.2 (1.3, 2.1)	92	1.0 ± 0.2 (0.6, 1.3)	0.7 ± 0.3 (0.2, 1.3)	.0108
Study 2		OPC		CAR			
Visit	Time Point	N[a]	IOP Reduction,[b] mm Hg	N[a]	IOP Reduction,[b] mm Hg	Difference[b]	*P* Value[c]
Week 4	Predose	78	3.1 ± 0.2 (2.7, 3.6)	77	1.8 ± 0.2 (1.3, 2.2)	1.3 ± 0.3 (0.7, 2.0)	<.0001
Week 8	Predose	78	3.5 ± 0.2 (3.1, 3.9)	77	1.6 ± 0.2 (1.2, 2.0)	1.9 ± 0.3 (1.3, 2.5)	<.0001
	2 hours	76	2.9 ± 0.2 (2.5, 3.3)	77	0.8 ± 0.2 (0.4, 1.2)	2.1 ± 0.3 (1.6, 2.7)	<.0001
	8 hours	62	3.0 ± 0.3 (2.5, 3.6)	54	0.3 ± 0.3 (−0.3, 0.8)	2.7 ± 0.4 (1.9, 3.5)	<.0001

CAR = carteolol; IOP = intraocular pressure; LAT = latanoprost; OPC = OPC-1085EL.

Missing values were imputed using the last-observation-carried-forward method.

[a]Number of subjects with both nonmissing baseline values and nonmissing values at each time point.

[b]Mean ± standard error (95% confidence interval).

[c]Analysis of covariance.

(OPC − CAR) was 1.9 (1.3, 2.5) mm Hg (Table 3). The IOP reduction in the OPC group was significantly greater than that in the CAR group at all time points ($P < .0001$). The reductions in IOP with OPC vs CAR were also reflected in the subgroup analysis (Table 4). The proportions of patients achieving the target criteria were significantly greater in the OPC group than in the CAR group (Table 5). In addition, the IOP reduction at each time point in the OPC group was similar to that in the CAR-LAT group (Table 6).

• **SAFETY:** *Study 1.* AEs were observed in 30 of 118 patients (25.4%) in the OPC group and 23 of 119 patients (19.3%) in the LAT group. ADRs occurred in 8 of 118 patients (6.8%) in the OPC group and 5 of 119 patients (4.2%) in the LAT group (Table 7). All ADRs were mild in severity. ADRs leading to discontinuation of the study drug were "visual impairment" and "eye pruritus" in 1 patient in the OPC group. Both events were mild in severity and resolved without treatment. The visual impairment was considered to be subjective, because the visual acuity test results showed no decrease. There were no clinically significant laboratory abnormalities in any group. Pulse rate and blood pressure in the OPC group tended to decrease after application, but the magnitude of these changes was small and not clinically significant

TABLE 4. Subgroup Analysis of the Mean Intraocular Pressure Reductions at Predose From Baseline to Week 8 in Phase 3 Trials of Carteolol/Latanoprost Fixed Combination

	Study 1				Study 2			
	OPC		LAT		OPC		CAR	
Characteristics	N[a]	IOP Reduction,[b] mm Hg	N[a]	IOP Reduction,[b] mm Hg	N[a]	IOP Reduction,[b] mm Hg	N[a]	IOP Reduction,[b] mm Hg
IOP at baseline								
≥18 to <21 mm Hg	79	2.7 ± 1.7	78	1.7 ± 2.0	59	3.3 ± 1.7	58	1.5 ± 1.7
≥21 to <24 mm Hg	30	3.1 ± 2.2	34	1.2 ± 2.3	15	3.8 ± 2.1	13	1.6 ± 2.3
≥24 mm Hg	8	4.5 ± 2.9	6	3.7 ± 4.9	4	5.8 ± 3.4	6	3.0 ± 2.2
Diagnosis								
POAG	71	3.0 ± 2.2	70	1.5 ± 2.1	39	3.8 ± 2.0	42	1.4 ± 1.9
NTG	9	3.7 ± 1.7	7	2.0 ± 2.1	4	3.5 ± 1.0	7	2.3 ± 1.3
OH	37	2.5 ± 1.7	41	1.7 ± 2.7	35	3.1 ± 1.9	28	1.9 ± 2.0

CAR = carteolol; IOP = intraocular pressure; LAT = latanoprost; NTG = normal tension glaucoma; OH = ocular hypertension; OPC = OPC-1085EL; POAG = primary open angle glaucoma.

Missing values were imputed using the last-observation-carried-forward method.

[a]Number of subjects with both nonmissing baseline values and nonmissing values at each time point.

[b]Mean ± standard deviation.

(Table 8). In the OPC group, 97.4% and 99.2% of patients reported "No problems with application at all" regarding the comfort of OPC-1085EL (Table 9) at weeks 4 and 8, respectively.

Study 2. AEs were observed in 25 of 78 patients (32.1%) in the OPC group, 12 of 78 patients (15.4%) in the CAR group, and 8 of 37 patients (21.6%) in the CAR-LAT group. Of these, ADRs occurred in 15 of 78 patients (19.2%) in the OPC group, 2 of 78 patients (2.6%) in the CAR group, and 6 of 37 patients (16.2%) in the CAR-LAT group (Table 7). One patient with eye pain discontinued the study in the OPC group, but this AE resolved without treatment. There were no clinically significant laboratory abnormalities in any group. There were no notable differences in vital signs among the 3 groups (Table 8). In the OPC group, 93.5% and 93.6% of patients reported "No problems with topical application at all" regarding the comfort of OPC-1085EL (Table 9) at weeks 4 and 8, respectively.

DISCUSSION

THE IOP-LOWERING EFFECT WAS SIGNIFICANTLY GREATER with OPC than with LAT or CAR, and similar in the OPC and CAR-LAT groups, at all measured time points. More patients achieved the target IOPs or target IOP reductions in the OPC group than in the LAT and CAR groups. The IOP reductions in the OPC group were numerically greater than those in the LAT and CAR groups in the subgroups of patients with POAG, NTG, or OH. The prevalence of NTG is higher in Japanese individuals than in other populations[25]; therefore, the greater IOP reduction observed with OPC in this population is an important result. IOP reductions were also observed in the control groups in both studies. These changes might be owing to the screening period of 4 weeks being insufficient to reach a plateau in some patients; alternatively, the reductions could represent regression to the mean.

A study to investigate the efficacy of the latanoprost/timolol fixed combination vs latanoprost using a similar design to Study 1 in Japanese patients with POAG and OH showed an IOP reduction from baseline in the morning (8 AM to 11 AM) at week 8 of 2.59 mm Hg with the latanoprost/timolol fixed combination and 1.61 mm Hg with latanoprost—a between-group difference of 0.97 mm Hg.[26] In Study 1, the IOP reduction at predose (9 AM to 11 AM) was 2.9 mm Hg with OPC-1085EL and 1.6 mm Hg with latanoprost, and the between-group difference was 1.3 mm Hg. Another study showed that concomitant therapy with latanoprost and carteolol LA was similar to latanoprost/timolol fixed combination in terms of the IOP-lowering effect.[27] These results, combined with the result of Study 2 showing that the IOP-lowering effect of OPC-1085EL was similar to that of the carteolol/latanoprost concomitant therapy, suggest that OPC-1085EL is as effective as the latanoprost/timolol fixed combination. However, a direct comparison between OPC-1085EL and the latanoprost/timolol fixed combination may be required to prove noninferiority of OPC-1085EL.

A prior meta-analysis showed that a fixed combination of a PG analogue and timolol had weaker IOP-lowering effects than concomitant therapy.[28] These results were considered to be due to a difference in the daily dose between fixed-combination therapy and concomitant therapy.[20] Noninferiority of a latanoprost/timolol fixed

TABLE 5. Number and Percentage of Patients in Phase 3 Trials of Carteolol/Latanoprost Fixed Combination who Achieved the Target of Intraocular Pressure and Intraocular Pressure Reduction From Baseline at Predose at Week 8

	Study 1			Study 2		
	OPC ($n^a = 117$)	LAT ($n^a = 118$)	Wald[de] χ^2 test	OPC ($n^a = 78$)	CAR ($n^a = 77$)	Wald[de] χ^2 test
Target value	N[b] (%)[c]	N[b] (%)[c]	*P* Value	N[b] (%)[c]	N[b] (%)[c]	*P* Value
IOP						
≤18 mm Hg	88 (75.2)	66 (55.9)	.0004	66 (84.6)	45 (58.4)	<.0001
≤16 mm Hg	47 (40.2)	27 (22.9)	.0038	48 (61.5)	19 (24.7)	<.0001
≤14 mm Hg	18 (15.4)	8 (6.8)	.0634	14 (17.9)	5 (6.5)	.0313
IOP reduction						
≥2 mm Hg	89 (76.1)	61 (51.7)	.0002	68 (87.2)	39 (50.6)	<.0001
≥4 mm Hg	42 (35.9)	25 (21.2)	.0201	36 (46.2)	11 (14.3)	<.0001
≥6 mm Hg	10 (8.5)	4 (3.4)	.2417	13 (16.7)	4 (5.2)	.0215

CAR = carteolol; IOP = intraocular pressure; LAT = latanoprost; OPC = OPC-1085EL.

Missing values were imputed using the last-observation-carried-forward method.

[a]Number of subjects with both nonmissing baseline values and nonmissing values at each time point.

[b]Number of subjects who achieved the target value at week 8.

[c]Percentage of patients with the target value according to the number of patients with IOP data at week 8.

[d]Logistic regression model: the response variable was set as the proportion, and the fixed effects were baseline intraocular pressure and treatment group.

[e]*P* values were with treatment group as a fixed effect.

TABLE 6. Mean Intraocular Pressure Reductions in Study 2 of Phase 3 Trials of Carteolol/Latanoprost Fixed Combination

		OPC		CAR-LAT	
Visit	Time Point	N[a]	IOP Reduction,[b] mm Hg	N[a]	IOP Reduction,[b] mm Hg
Week 4	Predose	78	3.1 ± 2.0	35	2.7 ± 2.1
Week 8	Predose	78	3.5 ± 1.9	37	3.1 ± 2.3
	2 hours	76	2.9 ± 1.8	37	2.3 ± 2.4
	8 hours	62	3.1 ± 2.1	30	2.5 ± 2.4

CAR = carteolol; CAR-LAT = carteolol/latanoprost concomitant therapy; IOP = intraocular pressure; LAT = latanoprost; OPC = OPC-1085EL.

Missing values were imputed using the last-observation-carried-forward method.

[a]Number of subjects with both nonmissing baseline values and nonmissing values at each time point.

[b]Mean ± standard deviation.

combination to concomitant therapy with latanoprost QD plus timolol BID was not confirmed.[29] Although a travoprost/timolol fixed combination was noninferior to travoprost QD plus timolol QD,[30] the effect was not assessed by comparison to a standard daily dose of concomitant therapy (ie, travoprost QD plus timolol BID). In addition, in a study comparing BID application of a dorzolamide/timolol fixed combination and a concomitant therapy with dorzolamide 3-times-daily plus timolol BID, the IOP-lowering effect was similar between the 2 treatments at 2 hours after application, but the percent reduction from baseline was lower at 0 and 8 hours after application in the fixed combination group than in the concomitant therapy group.[31] The daily dose of the active ingredients of OPC-1085EL is the same as that in concomitant therapy with carteolol LA and latanoprost. A pharmacokinetic study in rabbits confirmed that the concentrations of each active ingredient of OPC-1085EL in the aqueous humor and iris/ciliary body are not lower than carteolol LA or latanoprost (unpublished data: ClinicalTrials.gov NCT02108288). In Study 2, OPC-1085EL displayed similar efficacy to concomitant therapy with carteolol LA and latanoprost. Therefore, we believe that switching from concomitant therapy to OPC-1085EL may improve convenience for patients while maintaining the IOP-lowering effects.

In the present studies, the ophthalmic drugs were applied in the morning. Because studies of beta blocker/PG analogue fixed-combination drugs have reported better IOP reduction with evening than with morning application,[32,33] OPC-1085EL may exert greater IOP-lowering effects when applied in the evening. It may be necessary to further investigate the relationship between the time of application and the IOP-lowering effect.

No new safety concerns, other than known ADRs for each single agent, were identified in the OPC group in either of our studies. All ADRs, including the ADRs that led to study discontinuation in 1 patient, were rated as mild in severity. Although the incidence of ADRs in

TABLE 7. Adverse Drug Reactions in Phase 3 Trials of Carteolol/Latanoprost Fixed Combination

	Study 1		Study 2		
	OPC (N = 118)	LAT (N = 119)	OPC (N = 78)	CAR (N = 78)	CAR-LAT (N = 37)
	N (%)	N (%)	N (%)	N (%)	N (%)
Patients with adverse drug reactions	8 (6.8)	5 (4.2)	15 (19.2)	2 (2.6)	6 (16.2)
Ocular events					
Growth of eyelashes	2 (1.7)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Blepharal pigmentation	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Vision blurred	2 (1.7)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Eye pruritus	1 (0.8)	1 (0.8)	2 (2.6)	0 (0.0)	0 (0.0)
Erythema of eyelid	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (2.7)
Eye discharge	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye irritation	0 (0.0)	1 (0.8)	2 (2.6)	0 (0.0)	1 (2.7)
Punctate keratitis	1 (0.8)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Visual impairment	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Foreign body sensation in eyes	1 (0.8)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)
Conjunctival hyperemia	0 (0.0)	1 (0.8)	2 (2.6)	1 (1.3)	2 (5.4)
Ciliary hyperemia	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye pain	0 (0.0)	0 (0.0)	3 (3.8)	0 (0.0)	0 (0.0)
Ocular hyperemia	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	1 (2.7)
Abnormal sensation in eye	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)
Blepharitis	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)
Corneal disorder	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (2.7)
Conjunctivitis allergic	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Instillation site irritation	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertrichosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)
Nonocular events					
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)

CAR = carteolol; CAR-LAT = carteolol/latanoprost concomitant therapy; LAT = latanoprost; OPC = OPC-1085EL.
Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 17.0.
All events were mild in severity.

Study 2 was higher in the OPC group than in the CAR group, all of the ADRs in the OPC group were rated as mild in intensity and were tolerable. The incidence was similar to that in the CAR-LAT group, and there were no AEs with an unexpectedly high incidence.

Major eye disorders reported to be specific to PG analogues include "conjunctival hyperemia," "blepharal pigmentation," and "keratitis punctuate." In our studies, the incidence of "conjunctival hyperemia" was lower than was previously reported for latanoprost,[34] and other specific disorders (eg, blepharal pigmentation, iris pigmentation, hypertrichosis of eyelid, and prostaglandin-associated periorbitopathy) were not reported in the OPC group. The lower incidence of these eye disorders may be attributable to the short observation period. Our results suggest no significant safety concerns based on the class effects associated with PG analogues, but this should be confirmed in long-term observation.

Beta blockers can affect the cardiovascular system. Although carteolol may affect the cardiovascular system, its effects are weaker than those of timolol.[9] In the present studies, no cardiovascular ADRs were reported in the OPC, CAR, or CAR-LAT groups. In Study 2, changes in the pulse rate and blood pressure in the OPC group were similar to those observed in the CAR and CAR-LAT groups. These results are consistent with those of an OPC-1085EL pharmacokinetic study, in which the PK parameters of human plasma carteolol after application of OPC-1085EL were similar to those after application of carteolol LA (ClinicalTrials.gov NCT02108288). In each treatment group in Study 2, the pulse rate at week 8 tended to be lower than those observed at baseline and at week 4. This may be attributable to a transient increase in the blood drug concentration immediately after application in association with different measurement time points (predose at baseline and week 4, and at 2 hours after dosing at week 8).

Regarding ADRs that may affect treatment adherence, a previous study comparing latanoprost/timolol fixed combination and latanoprost[26] reported a higher incidence of "eye irritation" in the latanoprost/timolol group (16.7%) than in the latanoprost group (0.7%). In our studies, OPC-1085EL caused "eye irritation" and "eye pain," but

TABLE 8. Changes in Patient Vital Signs in Phase 3 Trials of Carteolol/Latanoprost Fixed Combination

		Study 1				Study 2					
		OPC		LAT		OPC		CAR		CAR-LAT	
Parameters	Visit	N[a]	Mean ± SD	N[a]	Mean ± SD	N[a]	Mean ± SD	N[a]	Mean ± SD	N[a]	Mean ± SD
Pulse rate, beats/min	Baseline[b]	118	75.0 ± 11.8	119	77.4 ± 11.5	78	71.0 ± 10.5	78	71.4 ± 10.8	37	75.2 ± 9.5
	Week 4[c]	115	70.7 ± 9.5	117	77.5 ± 10.4	77	72.0 ± 10.4	78	72.0 ± 10.3	35	74.6 ± 9.9
	Week 8[d]	117	68.9 ± 9.0	119	75.2 ± 11.4	78	68.2 ± 8.6	77	70.1 ± 9.4	37	70.8 ± 9.6
Systolic blood pressure, mm Hg	Baseline[b]	118	132.2 ± 17.5	119	132.2 ± 20.4	78	128.6 ± 18.6	78	128.2 ± 18.6	37	126.0 ± 19.2
	Week 4[c]	115	129.2 ± 16.4	117	132.6 ± 17.4	77	127.5 ± 18.3	78	126.7 ± 16.5	35	127.5 ± 20.3
	Week 8[d]	117	128.0 ± 17.4	119	132.3 ± 16.9	78	127.2 ± 19.1	77	126.0 ± 17.7	37	125.1 ± 20.2
Diastolic blood pressure, mm Hg	Baseline[b]	118	80.3 ± 11.3	119	79.5 ± 11.7	78	76.7 ± 12.0	78	77.5 ± 12.4	37	76.2 ± 12.3
	Week 4[c]	115	78.9 ± 10.9	117	80.4 ± 11.7	77	76.0 ± 11.2	78	77.3 ± 10.5	35	77.0 ± 13.5
	Week 8[d]	117	77.8 ± 11.3	119	80.5 ± 11.1	78	75.6 ± 10.7	77	77.3 ± 11.6	37	74.7 ± 11.6

CAR = carteolol; CAR-LAT = carteolol/latanoprost concomitant therapy; LAT = latanoprost; OPC = OPC-1085EL.
[a]Number of subjects with nonmissing values at each time point.
[b]Predose at the end of screening.
[c]Predose at week 4.
[d]Two hours after dosing at week 8 or at discontinuation.

TABLE 9. Comfort Scores at Weeks 4 and 8 of Phase 3 Trials of Carteolol/Latanoprost Fixed Combination

		Study 1		Study 2		
		OPC	LAT	OPC	CAR	CAR-LAT
Visit	Comfort Score[a]	N (%)[b]	N (%)[b]	N (%)[b]	N (%)[b]	N (%)[b]
Week 4[c]	0	112 (97.4)	112 (95.7)	72 (93.5)	75 (96.2)	29 (82.9)
	1	3 (2.6)	4 (3.4)	3 (3.9)	3 (3.8)	6 (17.1)
	2	0 (0.0)	1 (0.9)	1 (1.3)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Week 8[d]	0	117 (99.2)	116 (97.5)	73 (93.6)	74 (94.9)	33 (89.2)
	1	0 (0.0)	3 (2.5)	3 (3.8)	4 (5.1)	4 (10.8)
	2	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)

CAR = carteolol; CAR-LAT = carteolol/latanoprost concomitant therapy; LAT = latanoprost; OPC = OPC-1085EL.
[a]0: "No problems with application at all"; 1: "Some trouble with application, but no problems"; 2: "Trouble with application, but bearable"; and 3: "Unbearable trouble with application."
[b]Percentages calculated vs number of subjects with measured comfort of study drug values at each visit.
[c]Predose at week 4.
[d]Two hours after dosing at week 8 or at discontinuation.

all events were mild and infrequent. Regarding the comfort in the use of the study drug, most of the patients answered "No problems with application."

We consider that the incidence of corneal disorders was lower in the OPC group than in other groups in these studies because OPC-1085EL does not contain benzalkonium chloride.[7,35] However, it was not possible to compare the results because of the low incidence of these events; only 1 patient experienced corneal epithelium disorder, which is coded as "corneal disorder" in MedDRA, in each of the OPC and CAR-LAT groups in Study 2.

Taken together, these findings suggest that OPC-1085EL poses no greater safety risks than, and is tolerated as well as, latanoprost, carteolol, and their concomitant therapy.

These studies have some limitations. In both, the IOP-lowering effect was investigated only after morning application. Further studies are needed to assess the effect of OPC-1085EL applied at other times. Second, the treatment duration was short, and the efficacy and safety of

long-term treatment need to be further investigated. Third, both studies only enrolled Japanese patients.

In conclusion, in patients with POAG and OH, OPC-1085EL achieved a significantly greater IOP-lowering effect than latanoprost and carteolol and had comparable effects to carteolol/latanoprost concomitant therapy. OPC-1085EL posed no new safety concerns. These results indicate that OPC-1085EL is a useful IOP-lowering treatment in patients who respond poorly to monotherapy. Switching to OPC-1085EL from concomitant therapy may improve convenience for patients while maintaining IOP-lowering efficacy.

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