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CLINICAL TRIAL REPORT

Omidenepag Isopropyl 0.002% versus Latanoprost 0.005% in Open-Angle Glaucoma/Ocular Hypertension: The Randomized Phase III PEONY Trial

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Purpose: To compare the efficacy and safety of omidenepag isopropyl (OMDI) 0.002% with latanoprost 0.005% once daily in Asian subjects with open-angle glaucoma (OAG)/ocular hypertension (OHT).

Methods: In this Phase III randomized, observer-masked, active-controlled, multinational trial (NCT02981446), subjects aged ≥18 years with OAG/OHT in both eyes and baseline intraocular pressure (IOP) ≥22 mmHg and ≤34 mmHg were randomized 1:1 to OMDI or latanoprost. IOP was measured at 9AM, 1PM, and 5PM at baseline, 1 week, 6 weeks, and 3 months. Adverse events (AEs) were recorded. Non-inferiority of OMDI to latanoprost was tested for primary and key secondary endpoints.

Results: Each group included 185 subjects. Mean diurnal IOP from baseline to month 3 was reduced 7.1 mmHg (28.8%) with OMDI and 7.8 mmHg (31.3%) with latanoprost, with the least-squares mean difference (OMDI minus latanoprost) being 0.6 mmHg (95% CI: 0.0, 1.2 mmHg; p = 0.0366), indicating non-inferiority. Mean IOP reductions at the nine timepoints were −5.8 to −7.3 mmHg (23.5–29.5%) for OMDI and −6.1 to −7.9 mmHg (24.3–31.7%) for latanoprost. Non-inferiority per FDA criteria was also met. Rates of all AEs, ocular AEs, and ocular AEs associated with treatment were 40.0%, 36.8%, and 23.2%, respectively, for OMDI and 29.7%, 21.1%, and 11.9%, respectively, for latanoprost. Conjunctival hyperemia rates were higher with OMDI than latanoprost (11.9% vs 5.4%). Most AEs were mild, with no serious ocular AEs.

Conclusion: OMDI safely and effectively reduces IOP in Asian subjects with OAG/OHT, with mean diurnal IOP at Month 3 and per-timepoint IOP reductions non-inferior to those of latanoprost.

Plain Language Summary: PEONY Study: Testing How Well and How Safely Omidenepag Isopropyl Eye Drops Treat People with Glaucoma or Ocular Hypertension Compared with Latanoprost.

Who took part in the study?

Three hundred and seventy participants average age of 57 years, from 34 centers across four Asian countries who had glaucoma or high pressure in both eyes were randomly divided into two groups. One group (185 people; 50%) was given OMDI, and the other group (185 people; 50%) latanoprost for 3 months. The intraocular pressure of both eyes was measured in all participants at three time points (9 AM, 1 PM, and 5 PM) after 1 week, 6 weeks, and 3 months of treatment. The primary endpoint was the average of the daily eye pressure after 3 months of treatment. The safety of OMDI was also assessed.

Study results.

After 3 months of treatment, OMDI decreased the eye pressure by 29%. This was similar to latanoprost, which decreased the eye pressure by 31% over the same time period. OMDI was safe and well tolerated by those participants who received it. The most

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common side-effect in people receiving OMDI or latanoprost was conjunctival hyperemia (red eye) (experienced by 22 people receiving OMDI, and 10 people receiving latanoprost).

Conclusions

After 3 months of use, OMDI was found to safely reduce high eye pressure to a similar level as latanoprost in Asian people with glaucoma or high eye pressure.

Keywords: omidenepag isopropyl, latanoprost, intraocular pressure, glaucoma, ocular hypertension

Introduction

Glaucoma is one of the leading causes of irreversible vision loss and blindness,[1] affecting more than 80 million people worldwide.[2] High intraocular pressure (IOP) is the primary risk factor and the only therapeutically modifiable factor for glaucoma. Lowering IOP has been shown to reduce the risk of developing glaucoma in high-risk ocular hypertensive patients[3] and to reduce the risk of disease progression in patients with manifest glaucoma.[4,5]

Topical medical therapy is a common first-line approach to glaucoma treatment, with prostaglandin analogues (PGAs) being the first choice of treatment owing to their superior efficacy and safety compared with other classes of drugs and their convenient once-daily dosing.[6,7] PGAs lower IOP by interacting with the prostaglandin $F_{2\alpha}$ receptors (FP receptors), activating a series of signaling pathways that upregulate the expression of matrix metalloproteinases, resulting in remodeling of the extracellular matrix of both the ciliary body and trabecular meshwork. This results in increased drainage of aqueous humor from the eye through the uveoscleral and, to a lesser extent, the trabecular outflow pathways.[6,7]

The use of PGAs has several drawbacks, for example, their chronic use can lead to appearance-altering changes, also known as prostaglandin-associated periorbitopathy (PAP).[8] PAP includes iris color changes and periorbital skin hyperpigmentation; vellus hair growth; eyelash changes including lengthening, thickening, and/or darkening; deepening of the upper eyelid sulcus (DUES), periorbital fat loss, ptosis, and in many cases enophthalmos.[7–14] The success rate of trabeculectomy at 24 months was found to be significantly lower in patients with than without DUES ($P < 0.0001$), suggesting that DUES can complicate ocular surgery due to eyelid changes and/or recession of the globe into the orbit.[15]

Omidenepag is a member of a new class of IOP-lowering drugs with non-prostaglandin structure, being a selective agonist of the prostanoid EP2 receptor.[16,17] Omidenepag is generated by hydrolysis of its prodrug omidenepag isopropyl (OMDI) by corneal esterases during ocular penetration.[16] Omidenepag exhibits agonist activity with high affinity at EP2 receptors, but no binding activity at FP receptors, reducing IOP by increasing both uveoscleral and trabecular outflow.[16,17] Omidenepag does not inhibit adipogenesis and should not cause DUES.[18] Additionally, a pre-clinical study in mice found that omidenepag did not cause eyelash changes.[19] Clinical trials showed that IOP reduction by OMDI was comparable to that of latanoprost, with OMDI showing a notable absence of FP receptor-mediated side effects such as skin hyperpigmentation and lash changes.[20–23] OMDI ophthalmic solution 0.002% has been approved for the reduction of IOP in patients with glaucoma/primary open-angle glaucoma (OAG) or ocular hypertension (OHT) in Japan, India, Singapore, South Korea, Taiwan, Malaysia, the Philippines, Thailand, and the United States.[20,24,25]

The Phase 3 PEONY trial was conducted in four Asian countries, India, Taiwan, Korea, and Singapore, to determine if the mean diurnal IOP reduction with OMDI ophthalmic solution 0.002% was non-inferior to that of latanoprost ophthalmic solution 0.005% (Xalatan®, Pfizer) at month 3 in subjects with OAG or OHT. This trial also compared mean IOP at 9AM, 1PM, and 5PM after treatment for 1 week, 6 weeks, and 3 months in patients treated with OMDI and latanoprost, with non-inferiority of OMDI relative to latanoprost defined as an upper limit of the 95% confidence intervals (CIs) for the difference between OMDI and latanoprost of ≤1.5 mmHg at all nine time points and ≤1.0 mmHg at five or more of the nine time points (ie FDA non-inferiority requirements).[26]

Materials and Methods

Study Design and Ethical Considerations

This phase 3, prospective, randomized, observer-masked, active-controlled, parallel-group, multinational, multicentre study (ClinicalTrials.gov identifier: NCT02981446) was conducted at 36 sites in Asia, including 13 in India, nine each in

South Korea and Taiwan, and five in Singapore. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The protocol was reviewed and approved by institutional ethics committees at each participating center (Supplementary Table 1), and all subjects provided written informed consent.

Participants

Subjects were eligible if they were aged ≥18 years and had OAG, including pigmentary or pseudoexfoliation components, or OHT in both eyes with IOP ≥22 mmHg and ≤34 mmHg at 9AM, 1PM, and 5PM after washout of any IOP-lowering medication or were treatment naive. Additional eligibility criteria in both eyes included best-corrected visual acuity (BCVA) of 0.6 logMAR (Snellen equivalent 20/80) or better, central corneal thickness (CCT) between 480 and 600 microns, and open anterior chamber angles of Shaffer grade ≥2. Subjects with childbearing potential were required to utilize an acceptable form of birth control during study participation.

Key exclusion criteria included advanced glaucoma (visual field mean deviation worse than −12 dB) in either eye, any prior glaucoma laser or incisional procedures intended to lower IOP, inability to safely wash out existing IOP-lowering agents, any ocular surgery or ocular laser treatment within 90 days prior to screening, corneal abnormalities precluding accurate IOP assessment (including prior keratorefractive surgery), or any ocular or systemic comorbidity precluding safe use of either agent or that might confound study results. The continued use of systemic medications known to affect IOP was permitted by the investigator if no changes in therapy were anticipated during study participation, except that treatment with corticosteroids by any route was prohibited.

Visits and Assessments

This 3-month study included five scheduled visits: screening, eligibility/baseline, and 1 week, 6 weeks and 3 months after initiating treatment. The screening visit included a comprehensive eye examination to determine preliminary eligibility, at which time washout of all IOP-lowering therapy (4 weeks for prostaglandin analogues, rho kinase inhibitors, beta-blockers, and alpha-1 antagonists; 3 weeks for alpha-2 agonists; 2 weeks for non-selective alpha agonists; and 1 week for miotics and topical/oral carbonic anhydrase inhibitors) was initiated. If not performed within 3 months prior to the screening visit, gonioscopy was performed at screening to assess the angle of the anterior chamber, with the Shaffer scale used to rate the degree of angle closure.

At the eligibility/baseline visit, IOP was assessed at 9AM, 1PM, and 5PM by Goldmann applanation tonometry using the described two-person operator/recorder protocol, with 2–3 measurements taken per time point.[27] Upon final confirmation of eligibility (IOP 22–34 mmHg at all three time points), participants were randomized 1:1 to one drop of OMDI 0.002% or latanoprost 0.005%, instilled once per day at 9PM, for 3 months. While on therapy, IOP was measured at three time points (9AM, 1PM, and 5PM) at 1 week, 6 weeks, and 3 months after randomization, with visual acuity and slit-lamp biomicroscopic examination performed immediately before and CCT measured immediately after measuring IOP at 9AM.

Changes in appearance, including of the iris, eyelash, and eyelid, were assessed by standardized photographic documentation of the eyes at baseline and evaluated at each on-treatment visit. Ophthalmoscopy was performed at baseline and exit visits.

Randomization and Masking

The study utilized a blocked randomization schedule, with a fixed block size stratified by baseline mean diurnal IOP in the study eye (<25 mmHg and ≥ 25 mmHg) and diagnosis (OAG or OHT). Randomization was conducted via an Interactive Web Response System. Subjects received a study medication kit numbered using the randomization schedule. Because the shape of the eyedrop bottles of the OMDI and latanoprost ophthalmic solutions were different, they were placed in identical kits. To maintain masking of the investigator and examiner during this study, study medications were dispensed and collected by authorized study staff other than the investigator or examiner. Subjects were instructed not to show or tell the investigator, examiner, or any other study subject about the eyedrop bottles. When the study medications were collected, the kits containing the used and unused eyedrop bottles were sealed.

Primary and Secondary Endpoints

The primary efficacy endpoint was mean diurnal IOP at month 3. A key secondary efficacy endpoint was mean IOP at each of the nine on-treatment time points. Other secondary efficacy endpoints included mean diurnal IOP at weeks 1 and 6 and the proportions of participants with mean diurnal IOP ≤18 mmHg and with mean diurnal IOP reductions from baseline of ≥20%, ≥25%, and ≥30% at weeks 1 and 6 and month 3. Safety endpoints included the nature and incidence of treatment-emergent ocular and systemic adverse events, BCVA, and ocular examination findings.

Statistical Analysis

Sample Size Calculation

Based on a between-group difference in mean diurnal IOP at month 3 of 0 mmHg, with a standard deviation of 4.0 mmHg, 151 subjects per group would provide 90% power to demonstrate the non-inferiority of OMDI compared with latanoprost (two-sided $\alpha = 0.05$ and non-inferiority margin of 1.5 mmHg). Assuming a premature discontinuation rate of 16%, 360 subjects (180 per group) were scheduled to be randomized.

Other Statistical Analyses

Efficacy was analyzed in the full analysis set, consisting of all randomized subjects who received at least one dose of study medication and provided at least one on-treatment IOP measurement, as well as in the per protocol population, consisting of subjects in the full analysis set with no major protocol violations. One eye per subject was analyzed (the study eye): either the sole qualifying eye, the eye with the higher baseline mean diurnal IOP if both eyes qualified, or the right eye if the baseline mean diurnal IOP in the two eyes was equal. The primary endpoint was assessed using a mixed-effects model for repeated measures (MMRM), which included treatment, visit, diagnosis, country, and treatment–visit interaction as fixed effects, baseline mean diurnal IOP as a covariate, and subject as a random effect. Within-subject error was modeled using an unstructured covariance matrix. The least-squares (LS) means of the treatment response within each group and their differences (OMDI minus latanoprost) were reported with 95% CIs. Non-inferiority of OMDI relative to latanoprost was defined as an upper limit of the 95% CIs for the LS mean difference in mean diurnal IOP at month 3 of ≤1.5 mmHg. Mean IOP at each of the nine on-treatment time point (ie, 9AM, 1PM, and 5PM after treatment for 1 week, 6 weeks, and 3 months), was analyzed using a similar MMRM approach, with non-inferiority defined as an upper limit of the 95% CIs for the difference at all nine time points of ≤1.5 mmHg and at five or more of time points of ≤1.0 mmHg. If non-inferiority was demonstrated, a similar analysis was intended to test for the superiority of OMDI over latanoprost, with superiority defined as an upper limit of the 95% CI for the difference in mean diurnal IOP at week 1 of <0 mmHg. Safety was assessed in the safety population, defined as all randomized subjects who received at least one dose of study medication.

Results

Disposition and Demographics

A total of 370 subjects were randomized, 185 to each treatment, with all receiving at least one dose of study medication (Figure 1). One subject in the OMDI group was excluded due to having no on-treatment IOP measurements, ie, this subject never returned for follow-up visits after receiving the medication. Overall, 23 subjects did not complete the study: four in the OMDI group and two in the latanoprost group for adverse events (AEs); two in the OMDI group for protocol violations; eight in the OMDI and five in the latanoprost group who withdrew from the study; and one in each group for other reasons.

Table 1 shows the baseline demographic and clinical characteristics of the 369 subjects in the full analysis set. Their mean (standard deviation) age was 53.6 (13.0) years, 52.6% were male, and 100% were Asian, with 54.5% enrolled at sites in India, followed by Taiwan (27.4%), Korea (11.1%) and Singapore (7.0%). Of these subjects, 64.5% had OAG and 33.1% had OHT; 46.9% were not using IOP-lowering medication during enrollment, 98.6% had brown eyes, and 90% were phakic. No clinically meaningful differences between treatment groups were observed.

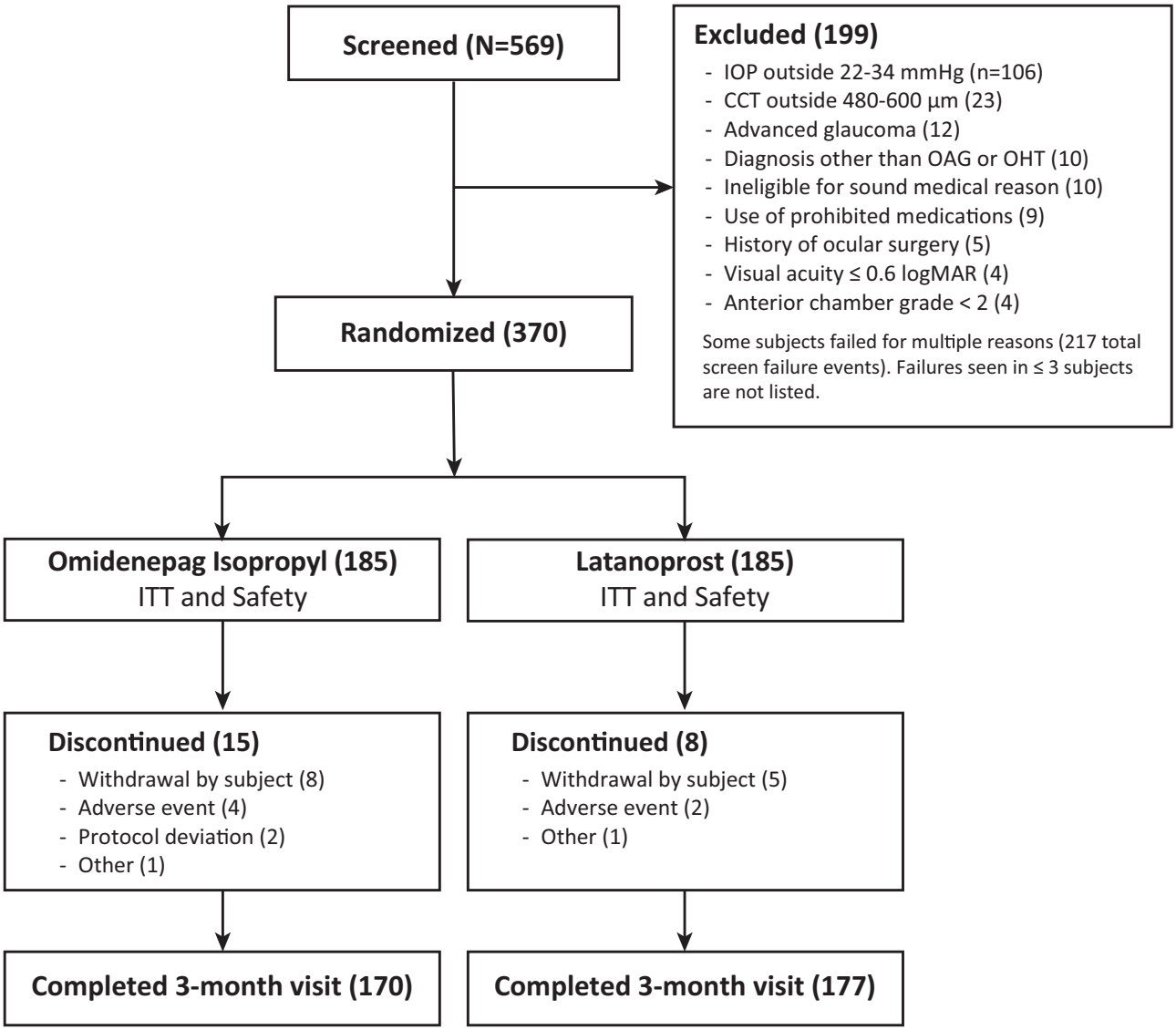

Figure 1 Patient Disposition.

Primary Efficacy Endpoint

Figure 2 shows the mean diurnal IOP in each group at baseline and at each on-treatment visit. Baseline mean (standard error [SE]) diurnal IOPs were 24.6 (0.17) mmHg in the OMDI group and 24.5 (0.15) mmHg in the latanoprost group. At month 3, the LS

Table 1 Demographic Characteristics of the Subjects in the Full Analysis Set (N = 369)

	OMDI (N=184)	Latanoprost (N=185)	Overall (N=369)
Age (year), mean (SD)	54.6 (12.9)	52.6 (13.1)	53.6 (13.0)
Gender, n (%)			
Male	106 (57.6)	88 (47.6)	194 (52.6)
Female	78 (42.4)	97 (52.4)	175 (47.4)

(*Continued*)

Table 1 (Continued).

	OMDI (N=184)	Latanoprost (N=185)	Overall (N=369)
Ethnicity, n (%)			
Asian	184 (100.0)	185 (100.0)	369 (100.0)
Country, n (%)			
India	98 (53.3)	103 (55.7)	201 (54.5)
Taiwan	48 (26.1)	53 (28.6)	101 (27.4)
Korea	21 (11.4)	20 (10.8)	41 (11.1)
Singapore	17 (9.2)	9 (4.9)	26 (7.0)
Glaucoma diagnosis, n (%)			
Primary open-angle	120 (65.2)	118 (63.8)	238 (64.5)
Exfoliation	2 (1.1)	4 (2.2)	6 (1.6)
Pigmentary	3 (1.6)	0	3 (0.8)
Ocular hypertension	59 (32.1)	63 (34.1)	122 (33.1)
Prior use of IOP-lowering medications, n (%)			
None	76 (41.3)	97 (52.4)	173 (46.9)
Carbonic anhydrase inhibitors*	64 (34.8)	55 (29.7)	119 (32.2)
Prostaglandin analogues	41 (22.3)	29 (15.7)	70 (19.0)
Beta-blockers	38 (20.7)	32 (17.3)	70 (19.0)
Alpha agonists	14 (7.6)	6 (3.2)	20 (5.4)
Miotics	1 (0.5)	1 (0.5)	2 (0.5)
Other	3 (1.6)	0	3 (0.8)
Iris color, n (%)			
Brown	181 (98.4)	183 (98.9)	364 (98.6)
Other	3 (1.6)	2 (1.1)	5 (1.4)
Lens status, n (%)			
Phakic	159 (86.4)	173 (93.5)	332 (90.0)
Pseudophakic	25 (13.6)	12 (6.5)	37 (10.0)

Notes: *During the required washout period, subjects at sites in India who discontinued their current treatment were allowed treatment with a topical CAI for up to 1 week prior to randomization (baseline).
Abbreviations: SD, standard deviation; OMDI, omidenepag isopropyl; IOP, intraocular pressure.

mean (SE) diurnal IOPs were 17.5 (0.25) mmHg in the OMDI group (change from baseline −7.1 mmHg, 28.8%) and 16.8 (0.25) mmHg in the latanoprost group (change from baseline −7.8 mmHg, 31.3%), with a between-group difference in mean diurnal IOP of 0.6 mmHg (95% CI: 0.0–1.2 mmHg; p = 0.0366). Because the upper limit of the 95% CI between the two groups was ≤1.5 mmHg, OMDI was deemed non-inferior to latanoprost. This primary analysis was also supported by four prespecified non-inferiority sensitivity analyses: 1) MMRM analysis based on per-protocol population (PPP), in which the mean difference in mean diurnal IOP was 0.7 mmHg (95% CI: 0.1–1.3 mmHg; p = 0.0332); 2) analysis by ANCOVA based on FAS, in which the

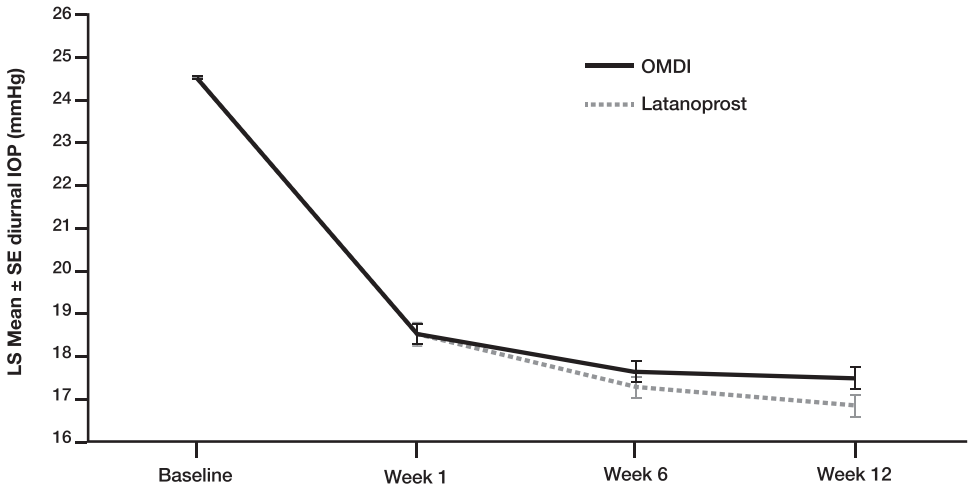

Figure 2 Baseline mean diurnal IOP and least-squares mean diurnal IOP ± standard error at each on-treatment study visit by treatment group.

mean difference in mean diurnal IOP was 0.5 mmHg (95% CI: −0.0–1.1 mmHg; p = 0.0729); 3) analysis by ANCOVA based on PPP, in which the mean difference in mean diurnal IOP was 0.6 mmHg (95% CI: −0.0–1.2 mmHg; p = 0.0561); and 4) analysis by ANCOVA of completers, in which the mean difference in mean diurnal IOP was 0.7 mmHg (95% CI: 0.1–1.3 mmHg; p = 0.0213).

Key Secondary Efficacy Endpoints

Figure 3 shows the mean (SE) IOP at each time point in both groups, measured at 9AM, 1PM, and 5PM during the baseline visit and after treatment for 1 week, 6 weeks, and 3 months. The LS mean IOPs across all 9 time points ranged from 17.2 to 19.0 mmHg in the OMDI group and from 16.7 to 18.8 mmHg in the latanoprost group; these represented mean IOP reductions from the baseline of −5.8 to −7.3 mmHg (23.5–29.5%) in the OMDI group and of −6.1 to −7.9 mmHg (24.3–31.7%) in the latanoprost group. Differences in mean IOP between the two groups ranged from −0.2 to +0.9 mmHg. The prespecified criteria for non-inferiority of OMDI to latanoprost were satisfied, in that the upper limit of 95% CIs of these differences in mean IOP were ≤1.5

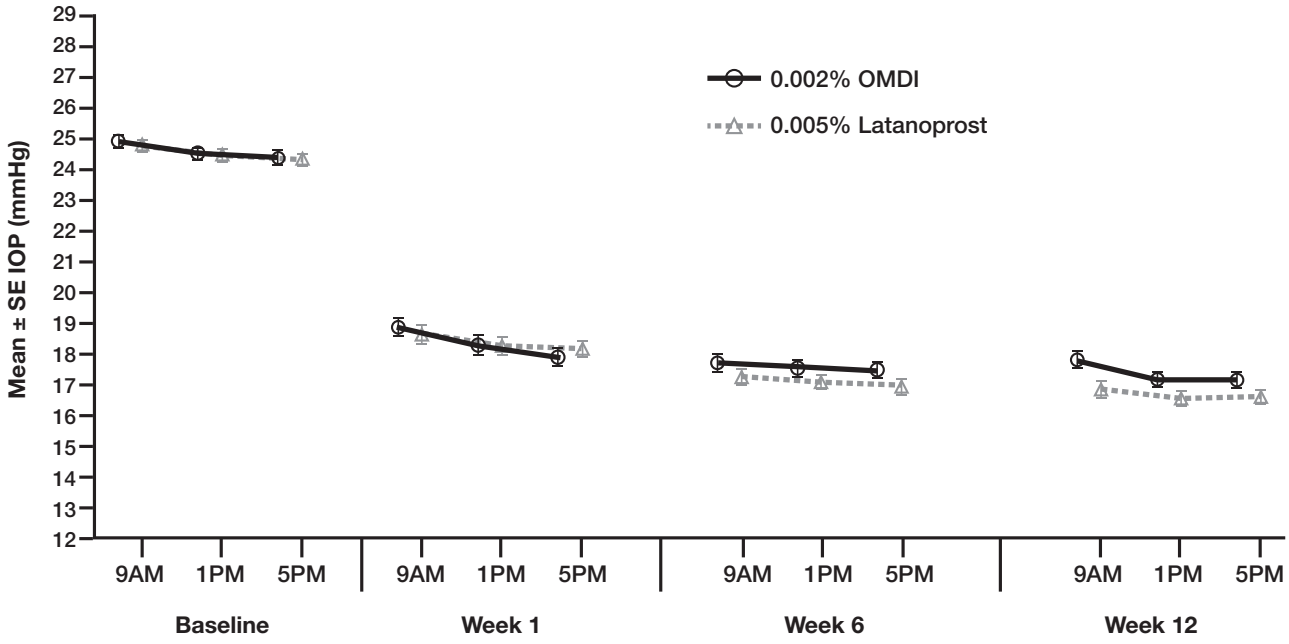

Figure 3 Mean baseline and on-treatment IOP ± standard error at each study time point by treatment group.

Table 2 Mean (SD) IOP at Baseline, Measured at 9AM, 1PM, and 5PM, and LS Mean (SE) IOP at 9AM, 1PM, and 5PM in Both Groups After Treatment for 1 Week, 6 Weeks, and 3 Months

	Time point	OMDI 0.002%	Latanoprost 0.005%	Difference (95% CI)	P-value
Baseline Mean IOP (SD), mmHg	9:00 AM	24.9 (2.56)	24.7 (2.37)	N/A	N/A
	1:00 PM	24.5 (2.40)	24.5 (2.27)	N/A	N/A
	5:00 PM	24.3 (2.46)	24.3 (2.21)	N/A	N/A
Week 1 LS Mean IOP (SE), mmHg	9:00 AM	19.0 (0.28)	18.8 (0.29)	0.2 (−0.5, 0.9)	0.5253
	1:00 PM	18.4 (0.28)	18.4 (0.29)	0.0 (−0.7, 0.7)	0.9759
	5:00 PM	18.0 (0.28)	18.3 (0.28)	−0.2 (−0.9, 0.5)	0.5038
Week 6 LS Mean IOP (SE), mmHg	9:00 AM	17.8 (0.26)	17.4 (0.26)	0.4 (−0.3, 1.0)	0.2479
	1:00 PM	17.6 (0.27)	17.2 (0.27)	0.4 (−0.3, 1.0)	0.2695
	5:00 PM	17.5 (0.26)	17.1 (0.27)	0.4 (−0.3, 1.0)	0.2415
Month 3 LS Mean IOP (SE), mmHg	9:00 AM	17.9 (0.27)	17.0 (0.27)	0.9 (0.2, 1.5)	0.0113
	1:00 PM	17.2 (0.25)	16.7 (0.26)	0.6 (−0.0, 1.2)	0.0661
	5:00 PM	17.2 (0.26)	16.7 (0.27)	0.5 (−0.2, 1.1)	0.1350

Abbreviations: SD, standard deviation; IOP, intraocular pressure; LS, least squares; SE, standard error; OMDI, omidenepag isopropyl; CI, confidence interval.

mmHg at all nine time points and ≤1.0 mmHg at five of these nine time points, including all three time points at week 1 and 9AM at week 6 and month 3 (Table 2, Figure 4).

Other Secondary Efficacy Endpoints

Mean diurnal IOPs at weeks 1 and 6 were also compared in the two groups. At week 1, the LS mean (SE) diurnal IOPs were 18.5 (0.26) mmHg (change from baseline −6.1 mmHg, 24.8%) in the OMDI group and 18.5 (0.27) mmHg (change from baseline −6.1 mmHg, 24.7%) in the latanoprost group, a difference of 0.0 mmHg (95% CI: −0.7, 0.7 mmHg; p = 0.9911). At week 6, the LS mean (SE) diurnal IOPs were 17.6 (0.25) mmHg (change from baseline −7.0 mmHg, 28.2%) in the OMDI

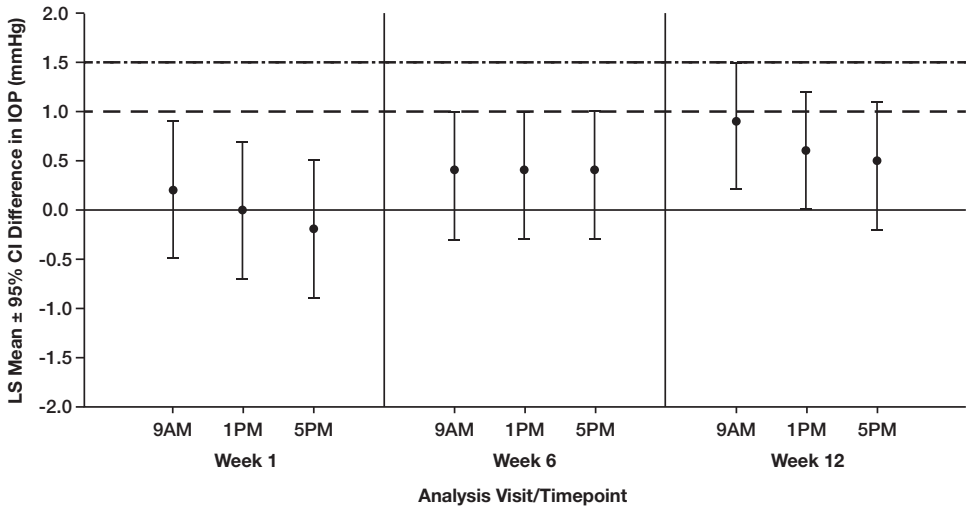

Figure 4 Difference in least squares mean IOP between omidenepag isopropyl and latanoprost at each time point, showing that OMDI met the prespecified criteria for non-inferiority to latanoprost. That is, the upper limit of 95% CIs of these differences in mean IOP were ≤1.5 mmHg at all nine time points and ≤1.0 mmHg at five time points, including all three time points at week 1 and 9AM at week 6 and month 3.

Table 3 Mean Diurnal IOP Outcomes at Week 1, Week 6 and Month 3 in Eyes Treated with Omidenepag Isopropyl (OMDI) and Latanoprost. The Percentages of Eyes Achieving Each Endpoint at Each Time Point are Shown

Mean diurnal IOP outcomes	Week 1		Week 6		Month 3	
	OMDI (N=184)	Latanoprost (N=185)	OMDI (N=184)	Latanoprost (N=185)	OMDI (N=184)	Latanoprost (N=185)
≤18 mmHg	50.3	47.3	54.0	60.6	58.2	66.5
≥20% reduction	64.5	66.8	74.7	82.8	78.2	86.4
≥25% reduction	50.3	51.1	56.3	65.0	61.8	72.7
≥30% reduction	38.3	34.2	43.1	52.2	45.3	61.4

Abbreviation: IOP, intraocular pressure.

group and 17.2 (0.25) mmHg (change from baseline −7.3 mmHg, 29.7%) in the latanoprost group, a difference of 0.4 mmHg (95% CI: −0.2, 1.0 mmHg; p = 0.2244). The comparison of mean diurnal IOP at week 1 was the efficacy endpoint for assessing the superiority of OMDI over latanoprost; superiority was not achieved (95% CI included 0, p > 0.05).

Table 3 shows the proportions of subjects in each treatment group achieving mean diurnal IOPs ≤18 mmHg and reductions from baseline of ≥20%, ≥25%, and ≥30%. In both treatment groups, the proportion of subjects achieving each endpoint increased slightly over time.

Safety

The rates of all AEs, ocular AEs, and ocular AEs associated with treatment were 40.0%, 36.8%, and 23.2%, respectively, in the OMDI group and 29.7%, 21.1%, and 11.9%, respectively, in the latanoprost group. Both treatments were generally safe and well tolerated, with Table 4 showing the types and incidence of ocular AEs. The most common ocular AE in both groups was conjunctival hyperemia, occurring in 11.9% of the subjects in the OMDI group and 5.4% of the subjects in the latanoprost group. Four patients in the OMDI group discontinued treatment due to AEs (one each with uveitis,

Table 4 Nature and Incidence of Ocular Adverse Events in the Safety Population (N = 370) in the Omidenepag Isopropyl (OMDI) and Latanoprost Groups

	Incidence, n (%)	
	OMDI (N=185)	Latanoprost (N=185)
Patients with ocular AEs	74 (40.0%)	55 (29.7%)
Conjunctival hyperemia	22 (11.9)	10 (5.4)
Photophobia	10 (5.4)	1 (0.5)
Dry eye	9 (4.9)	4 (2.2)
Corneal thickening	7 (3.8)	2 (1.1)
Eye pain	5 (2.7)	6 (3.2)
Ocular hyperemia	4 (2.2)	4 (2.2)
Vision blurred	4 (2.2)	2 (1.1)
Conjunctival irritation	3 (1.6)	1 (0.5)
Corneal deposits	3 (1.6)	0
Eye irritation	3 (1.6)	2 (1.1)

(*Continued*)

Table 4 (Continued).

	Incidence, n (%)	
	OMDI (N=185)	**Latanoprost (N=185)**
Corneal pigmentation	2 (1.1)	0
Iritis	1 (0.5)	0
Punctate keratitis	1 (0.5)	2 (1.1)
Uveitis	1 (0.5)	0
Blepharal pigmentation	0	2 (1.1)
Eyelash thickening	0	1 (0.5)
Growth of eyelashes	0	1 (0.5)
Investigator-reported IOP increase	1 (0.5)	0
Increased optic nerve cup/disc ratio	1 (0.5)	0

Abbreviation: IOP, intraocular pressure.

iritis, photophobia and foreign body sensation); two patients in the latanoprost group also discontinued study medication due to AEs (one with headache and one with blurred vision plus eye pain). The patient that developed uveitis had mild anterior chamber inflammation in both eyes from day 12 to day 29, which resolved following discontinuation from OMDI on day 22 and betamethasone sodium phosphate treatment. The patient with iritis experienced mild iritis in both eyes from day 8 to day 17, which resolved without treatment following discontinuation from OMDI on day 8.

Four AEs (in 3 subjects) of appearance-altering changes (blepharal pigmentation, eyelash thickening, growth of eyelashes) related to the PGAs were reported in the latanoprost group only, with 2 of 3 patients treatment-naïve at baseline, as well as the other patient PGA treatment naïve.

Mean CCTs in both groups were within typical ranges (547 µm in the OMDI group and 540 µm in the latanoprost group) and mean (SD) changes in CCT at month 3 were 3.4 (18.1) µm in the OMDI group and −1.7 (15.5) µm in the latanoprost group. Four subjects (seven eyes) in the OMDI group showed an increase in CCT (>50 µm) during the study, with three eyes resolved (within 50 µm of baseline); at month 3, CCT change from baseline ranged from 25 to 65 µm. One subject (one eye) in the latanoprost group showed an increase in CCT (>50 µm) and returned to 37 µm by month 3. None of the eyes in the present study experienced a change in visual acuity from the baseline greater than 10 letters/0.2 logMAR. In addition, none of these eyes manifested corneal edema or other ocular symptoms. No serious ocular AEs occurred in either group.

Discussion

OMDI constitutes a new class of IOP-lowering agents,[16,17] with an efficacy similar to that of latanoprost in patients with OAG/OHT.[21] OMDI acts by binding to the EP2 receptor, a G protein-coupled transmembrane receptor found in the ciliary body and trabecular meshwork, increasing both trabecular and uveoscleral outflow.[17,28] OMDI specifically stimulates the EP2 receptor but does not bind to other prostanoid receptors.[16] The current trial compares OMDI to latanoprost, a standard first-line treatment and a PGA, the most effective existing class of glaucoma medication therapy.[29,30]

This phase 3, multicenter, observer-masked, randomized, active-controlled clinical trial in subjects from four Asian countries, India, Taiwan, Korea, and Singapore, demonstrated that OMDI was non-inferior to latanoprost, as shown by mean diurnal IOP at Month 3 and by mean IOP at nine on-treatment time points, the US FDA IOP endpoint.[26] The reduction in mean diurnal IOP was comparable for OMDI (6.1–7.1 mmHg, 24.8–28.8%) and latanoprost (6.1–7.8 mmHg,

21.7–31.3%) during 3 months of once-daily dosing. The Safety profiles of the two drugs were comparable with low rates of AEs and treatment discontinuations due to AEs events. There were no serious ocular AEs in either group.

The efficacy outcomes reported in this study are consistent with prior reports. The phase 3 AYAME study compared OMDI 0.002% with latanoprost 0.005% each once daily in Japanese patients with POAG or OHT.[21] The AYAME study was similar to the current study in that the comparator was latanoprost, the primary outcome was the change from baseline in mean diurnal IOP, and the analysis was designed to assess non-inferiority of OMDI compared with latanoprost. In the AYAME study, the baseline mean diurnal IOP was 23.8 mmHg in the OMDI group and 23.4 mmHg in the latanoprost group (slightly lower than the current study). The study demonstrated mean diurnal IOP reductions after 4 weeks of therapy of 5.9 mmHg and 6.6 mmHg, respectively, a treatment difference similar to that in the current study, confirming the non-inferiority of OMDI to latanoprost. Two Phase 2 studies in the United States with relatively small sample size (15–30 subjects per arm) reported mean diurnal IOP reductions with OMDI 0.002% of 7.4 mmHg at 4 weeks (from baseline 24.8 mmHg) and 5.5 mmHg at 3 months (from baseline 25.4 mmHg).[22] Together, these studies show a consistent IOP-lowering effect of OMDI 0.002% across several ethnic populations including Asian, Japanese and US patients.

In this study the reduction in mean diurnal IOP was comparable for OMDI and latanoprost during 3 months of once-daily dosing. Similarly, when assessed across all nine on-treatment time points, the mean IOP reductions from baseline ranged from 5.8 to 7.3 mmHg (23.5–29.5%) in the OMDI group and 6.1–7.9 mmHg (24.3–31.7%) in the latanoprost group, indicating IOP control from morning (9AM) to afternoon (5PM). This magnitude of IOP reduction has been shown to reduce the risk of glaucoma progression[4,5] and is consistent with both the US and European glaucoma treatment guidelines for initial IOP reduction in eyes with mild-to-moderate OAG.[30,31]

This study also found that OMDI was generally safe and well tolerated, at least in the short term. Common adverse events included conjunctival hyperemia, photophobia, and dry eye, consistent with previous reports.[20–24] Mean CCT was essentially unchanged (mean increase, 3.4 μm) through 3 months of OMDI treatment. Measured increases in CCT >50 μm were observed in four studies or fellow eyes in the OMDI group and one eye in the latanoprost group. At month 3 there were CCT increases in four eyes in the OMDI group, and none in the latanoprost group. The average CCT increase was subclinical, within the ranges of measurement variability and normal diurnal variation due to overnight corneal swelling,[32] and manifested only as pachymetric measurements without any clinical signs or symptoms. These findings are consistent with past reports of subclinical increases in CCT during OMDI treatment, which were not associated with other safety variables including vision.[21–23] Endothelial cell density, which could be affected by the glaucoma disease process as well as by medical, laser, and surgical interventions for glaucoma,[33] was not assessed in this study. No cases of macular edema were observed in this study, although OCT was not planned in the study protocol, except in patients with diagnosed or suspected macular edema during the study. However, pseudophakia was observed in only 10.0% (37/369) of the study population, specifically 13.6% (25/184) in the OMDI group and 6.5% (12/185) in the latanoprost group. In a prior phase 3 long-term safety study conducted in Japanese patients, macular edema was observed only in pseudophakic eyes,[23] leading the Japanese regulatory authority to list pseudophakia as a contraindication to OMDI treatment.[34] Additional phase 3 studies have been performed in the US to further characterize the safety profile of OMDI.[35,36]

Appearance-altering AEs, including periocular pigmentation and eyelash thickening, lengthening, and/or darkening, were observed in only a few latanoprost-treated subjects, underscoring likely differences in receptor activity, signal cascade, and mechanism of action of these two drugs. None of the subjects in the latanoprost group experienced DUES, which was not surprising as this was a short-term study, although latanoprost inhibits adipogenesis.[18] However, OMDI, as an EP2 agonist, does not inhibit adipogenesis,[18] and therefore DUES is not expected to develop in OMDI-treated eyes and has not been observed in studies of this drug including longer exposure.[20–24] Widespread use of PGAs for glaucoma may increase the incidence of appearance altering AEs or PAP.[37] Once-daily treatment with an agent having an efficacy similar to latanoprost, but with reduced incidence of PAP or appearance-altering effects on eyelids and lashes, may have potential value in the treatment of glaucoma.[38] Further studies of longer durations are necessary to confirm this finding.

This study had several advantages, including its being an observer-masked, randomized phase 3 clinical trial; its use of a common first-line glaucoma medication, latanoprost, as an active comparator that has proven IOP-lowering efficacy,

and its large sample size with sufficient statistical power. Additionally, the study utilized primary and key secondary efficacy endpoints to satisfy both the US (mean IOP at nine individual time points) and global (mean diurnal IOP at the last visit) regulatory requirements. Even though both latanoprost and timolol are acceptable as the active control in Phase 3 registration trials per the FDA,[26] OMDI is the first US-approved ocular hypertensive agent, a new chemical entity, to successfully achieve non-inferiority to latanoprost with the FDA's restrictive non-inferiority requirements.

The key limitation of the study was its relatively short duration of 3 months. Although this duration enabled adequate characterization of efficacy, it may not reveal safety issues associated with chronic exposure. Another limitation was its inclusion of only Asian subjects, including those from India, Taiwan, Korea, and Singapore, thus limiting the ability of the study results to be generalized to other ethnic/racial groups. However, phase 2 and 3 trials completed in the US and Japanese populations demonstrated similar IOP lowering efficacy and safety profiles.[20–24] Additionally, although no cases of macular edema were noted in this study, relatively few patients with pseudophakia were enrolled, and the treatment duration was only 3 months. Moreover, OCT was not planned in the study protocol, except in patients with diagnosed or suspected macular edema during the study. Additional phase 3 studies with longer durations are warranted to further characterize the drug profile in other populations that differ by race, iris color and eyelid color.

In summary, OMDI safely and effectively lowered IOP in Asian subjects with OAG or OHT, with mean diurnal IOP reductions and reductions at nine individual time points that were non-inferior to latanoprost over 3 months. The incidence of all AEs (including ocular AEs) was numerically higher with OMDI than with latanoprost. OMDI lowers IOP through interaction with the EP2 receptor, indicating that OMDI is a novel and safe option for the treatment of glaucoma.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the institutional ethics committees at each of the 36 participating centers and conformed to the Declaration of Helsinki. All subjects provided written informed consent.

Data Sharing Statement

Requests should be directed to publications@santen.com. To gain access, data requestors will need to sign a data access agreement.

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Disclosure

Tsing Hong Wang is a consultant to AbbVie, Bausch & Lomb, Santen, and Viatris. Tin Aung is a consultant to Santen, AbbVie, Belkin Laser, Sun Pharma, and Novartis. Ronnie George is a consultant to AbbVie, Alcon, Santen, Sun Pharma, and Novartis. Ki Ho Park is a consultant to Santen, AbbVie, Novartis, and Sensimed. Noriko Odani-Kawabata is an employee of Santen. Fenghe Lu was an employee of Santen at the time of the study. The authors report no other conflicts of interest in this work.

References

1. Vision Loss Expert Group of the Global Burden of Disease Study, Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(12):e1221–e1234. doi:10.1016/S2214-109X(17)30393-5
2. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90(3):262–267. doi:10.1136/bjo.2005.081224
3. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120(6):701–713. doi:10.1001/archopht.120.6.701
4. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. *Arch Ophthalmol*. 2002;120(10):1268–1279. doi:10.1001/archopht.120.10.1268
5. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial [published correction appears in *Lancet*. *Lancet*. 2015;385(9975):1295–1304. doi:10.1016/S0140-6736(14)62111-5
6. Toris CB, Gabelt BT, Kaufman PL. Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction. *Surv Ophthalmol*. 2008;53(SUPPL1):S107–S120. doi:10.1016/j.survophthal.2008.08.010
7. Alm A. Latanoprost in the treatment of glaucoma. *Clin Ophthalmol*. 2014;8:1967–1985. doi:10.2147/OPTH.S59162
8. Filippopoulos T, Paula JS, Torun N, et al. Periorbital changes associated with topical bimatoprost. *Ophthalmic Plast Reconstr Surg*. 2008;24:302–307. doi:10.1097/IOP.0b013e31817d81df
9. Tappeiner C, Perren B, Iliev ME, Frueh BE, Goldblum D. Orbital fat atrophy in glaucoma patients treated with topical bimatoprost–can bimatoprost cause enophthalmos? *Klin Monbl Augenheilkd*. 2008;225(5):443–445. doi:10.1055/s-2008-1027362
10. Peplinski LS, Albiani Smith K. Deepening of lid sulcus from topical bimatoprost therapy. *Optom Vis Sci*. 2004;81(8):574–577. doi:10.1097/01.opx.0000141791.16683.4a
11. Tan J, Berke S. Latanoprost-induced prostaglandin-associated periorbitopathy. *Optom Vis Sci*. 2013;90(9):e245–e247. doi:10.1097/OPX.0b013e31829d8dd7
12. Rabinowitz MP, Katz LJ, Moster MR, et al. Unilateral prostaglandin-associated periorbitopathy: a syndrome involving upper eyelid retraction distinguishable from the aging sunken eyelid. *Ophthal Plast Reconstr Surg*. 2015;31(5):373–378. doi:10.1097/IOP.0000000000000351
13. Zhang F, Liao S, Liu K, Duan XC. Prostaglandin-associated periorbitopathy. *Zhonghua Yan Ke Za Zhi*. 2017;53(8):637–640. doi:10.3760/cma.j.issn.0412-4081.2017.08.018
14. Yip IYM, Ramasamy B. Unilateral orbital fat change. *BMJ Case Rep*. 2018;2018:bcr2017223525. doi:10.1136/bcr-2017-223525
15. Miki T, Naito T, Fujiwara M, et al. Effects of pre-surgical administration of prostaglandin analogs on the outcome of trabeculectomy. *PLoS One*. 2017;12(7):e0181550. doi:10.1371/journal.pone.0181550
16. Kirihara T, Taniguchi T, Yamamura K, et al. Pharmacologic characterization of omidenepag isopropyl, a novel selective EP2 receptor agonist, as an ocular hypotensive agent. *Invest Ophthalmol Vis Sci*. 2018;59(1):145–153. doi:10.1167/iovs.17-22745
17. Fuwa M, Toris CB, Fan S, et al. Effects of a novel selective EP2 receptor agonist, omidenepag isopropyl, on aqueous humor dynamics in laser-induced ocular hypertensive monkeys. *J Ocul Pharmacol Ther*. 2018;34(7):531–537. doi:10.1089/jop.2017.0146
18. Yamamoto Y, Taniguchi T, Inazumi T, et al. Effects of the selective EP2 receptor agonist omidenepag on adipocyte differentiation in 3T3-L1 cells. *J Ocul Pharmacol Ther*. 2020;36(3):162–169. doi:10.1089/jop.2019.0079
19. Esaki Y, Katsuta O, Kamio H, et al. The antiglaucoma agent and EP2 receptor agonist omidenepag does not affect eyelash growth in mice. *J Ocul Pharmacol Ther*. 2020;36(7):529–533. doi:10.1089/jop.2020.0003
20. Olander KW, Sato MA, Abrams MA, et al. A randomized phase 2 trial comparing omidenepag isopropyl 0.002% once and twice daily in subjects with primary open-angle glaucoma or ocular hypertension (SPECTRUM-6). *J Glaucoma*. 2021;30(6):473–480. doi:10.1097/IJG.0000000000001836
21. Aihara M, Lu F, Kawata H, Iwata A, Odani-Kawabata N, Shams NK. Omidenepag isopropyl versus latanoprost in primary open-angle glaucoma and ocular hypertension: the phase 3 AYAME study. *Am J Ophthalmol*. 2020;220:53–63. doi:10.1016/j.ajo.2020.06.003
22. Aihara M, Lu F, Kawata H, et al. Phase 2, randomized, dose-finding studies of omidenepag isopropyl, a selective EP2 agonist, in patients with primary open-angle glaucoma or ocular hypertension. *J Glaucoma*. 2019;28(3):375–385. doi:10.1097/IJG.0000000000001221
23. Aihara M, Lu F, Kawata H, Iwata A, Odani-Kawabata N. Twelve-month efficacy and safety of omidenepag isopropyl, a selective EP2 agonist, in open-angle glaucoma and ocular hypertension: the RENGE study. *Jpn J Ophthalmol*. 2021;65(6):810–819. doi:10.1007/s10384-021-00868-y
24. Aihara M, Ropo A, Lu F, et al. Intraocular pressure-lowering effect of omidenepag isopropyl in latanoprost non-/low-responder patients with primary open-angle glaucoma or ocular hypertension: the FUJI study. *Jpn J Ophthalmol*. 2020;64(4):398–406. doi:10.1007/s10384-020-00748-x
25. Duggan S. Omidenepag isopropyl ophthalmic solution 0.002%: first global approval. *Drugs*. 2018;78(18):1925–1929. doi:10.1007/s40265-018-1016-1
26. Weinreb RN, Kaufman PL. The glaucoma research community and FDA look to the future: a report from the NEI/FDA CDER glaucoma clinical trial design and endpoints symposium. *Invest Ophthalmol Vis Sci*. 2009;50(4):1497–1505. doi:10.1167/iovs.08-2843
27. Gordon MO, Kass MA. The ocular hypertension treatment study: design and baseline description of the participants. *Arch Ophthalmol*. 1999;117(5):573–583. doi:10.1001/archopht.117.5.573
28. Aihara M. Prostanoid receptor agonists for glaucoma treatment. *Jpn J Ophthalmol*. 2021;65(5):581–590. doi:10.1007/s10384-021-00844-6
29. Li F, Huang W, Zhang X. Efficacy and safety of different regimens for primary open-angle glaucoma or ocular hypertension: a systematic review and network meta-analysis. *Acta Ophthalmol*. 2018;96(3):e277–e284. doi:10.1111/aos.13568
30. American Academy of Ophthalmology. *Primary Open-Angle Glaucoma: Preferred Practice Pattern*. San Francisco: American Academy of Ophthalmology; 2020.
31. European Glaucoma Society Terminology and Guidelines for Glaucoma. Chapter 3: treatment principles and options. supported by the EGS foundation; part 1: foreword; introduction; glossary; chapter 3: treatment principles and options. *Br J Ophthalmol*. 2017;101(6):130–195. doi:10.1136/bjophthalmol-2016-EGSguideline.003

32. Feng Y, Varikooty J, Simpson TL. Diurnal variation of corneal and corneal epithelial thickness measured using optical coherence tomography. *Cornea*. 2001;20(5):480–483. doi:10.1097/00003226-200107000-00008
33. Realini T, Gupta PK, Radcliffe NM, et al. The effects of glaucoma and glaucoma therapies on corneal endothelial cell density. *J Glaucoma*. 2021;30(3):209–218. doi:10.1097/IJG.0000000000001722
34. Santen Pharmaceutical. EYBELIS ophthalmic solution 0.002% prescribing information [Japanese]. http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/300237_13197C0Q1028_1_02. Accessed March 16, 2021.
35. Panarelli JF, Bowden EC, Tepedino ME, et al. Omidenepag isopropyl in latanoprost low/nonresponders with primary open angle glaucoma or ocular hypertension: a phase 3, nonrandomized, two-phase, open-label study. *J Glaucoma*. 2023;32(12):999–1005. doi:10.1097/IJG.0000000000002321
36. Bacharach J, Brubaker JW, Evans DG, et al. Omidenepag isopropyl versus timolol in patients with glaucoma or ocular hypertension: two randomized phase 3 trials (SPECTRUM 4 and 3). *Am J Ophthalmol*. 2024;263:23–34. doi:10.1016/j.ajo.2024.02.010
37. Sobel RK, Tienor BJ. The coming age of enophthalmos. *Curr Opin Ophthalmol*. 2013;24(5):500–505. doi:10.1097/ICU.0b013e3283642e7c
38. Sakata R, Chang PY, Sung KR, et al. Prostaglandin-associated periorbitopathy syndrome (PAPS): addressing an unmet clinical need. *Semin Ophthalmol*. 2022;37(4):447–454. doi:10.1080/08820538.2021.2003824