Omidenepag Isopropyl Versus Latanoprost in Primary Open-Angle Glaucoma and Ocular Hypertension: The Phase 3 AYAME Study

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• PURPOSE: To evaluate the efficacy and safety of omidenepag isopropyl (OMDI), a selective, non-prostaglandin, prostanoid EP2 receptor agonist, in Japanese patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT).

• DESIGN: Phase III, randomized, investigator-masked, active-controlled, parallel-group, noninferiority study (ClinicalTrials.gov NCT02623738).

• METHODS: After a washout period of 1-4 weeks, eligible patients were randomized (1:1) to OMDI 0.002% or latanoprost 0.005% once daily for 4 weeks. Intraocular pressure (IOP) was measured at 9:00 AM, 1:00 PM, and 5:00 PM at weeks 1, 2, and 4. The primary endpoint was the change from baseline in mean diurnal IOP at week 4. The noninferiority margin for OMDI versus latanoprost was 1.5 mm Hg. Adverse events (AEs) were recorded.

• RESULTS: Of the 190 patients randomized, 189 had at least 1 post-baseline IOP measurement. At baseline, patients who received OMDI or latanoprost had a mean ± SD diurnal IOP of 23.78 ± 1.73 mm Hg and 23.40 ± 1.51 mm Hg, respectively. At week 4, least-squares mean ± SE reduction in IOP from baseline with OMDI (−5.93 ± 0.23 mm Hg) was noninferior to that of latanoprost (−6.56 ± 0.22 mm Hg; 95% confidence interval between groups: 0.01-1.26). The most frequently reported treatment-related ocular AEs (OMDI vs latanoprost) were conjunctival hyperemia (23/94 patients [24.5%] vs 10/96 patients [10.4%]), corneal thickening (11/94 patients [11.7%] vs 1/96 patients [1.0%]), and punctate keratitis (0/94 patients vs 5/96 patients [5.2%]). No serious AEs were observed in either group, and there were no discontinuations related to the study drug.

• CONCLUSIONS: OMDI 0.002% was noninferior to latanoprost 0.005% in reducing IOP in patients with OHT or POAG and was well tolerated. (Am J Ophthalmol 2020;220:53–63. © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

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GLAUCOMA IS A LEADING CAUSE OF IRREVERSIBLE vision loss worldwide.[1] Estimated to affect 64.3 million patients globally in 2013, the affected population is predicted to increase to 76 million by 2020 and to >110 million by 2040.[1] Glaucoma is a progressive optic neuropathy characterized by optic nerve head damage, retinal ganglion cell death, and progressive visual field loss.[2] Current therapeutic approaches aim to reduce intraocular pressure (IOP), the only strategy proven to reduce the risk of disease progression to date.[3–6] IOP may be lowered by reducing the production of aqueous humor or increasing its outflow. Drugs that reduce aqueous humor production include β-adrenergic receptor antagonists, carbonic anhydrase inhibitors, and α_2-adrenergic agonists.[7] Aqueous humor outflow may be increased by 2 routes: the conventional outflow pathway and the uveoscleral pathway.[8] The main outflow pathway is the conventional pathway, where aqueous humor passes through the trabecular meshwork, through Schlemm's canal, and into collector channels, aqueous veins, and episcleral veins.[8] Parasympathomimetics and rho kinase inhibitors enhance aqueous outflow through this pathway.[7,9] The uveoscleral pathway involves drainage of the aqueous humor through the interstitial spaces in the ciliary muscle and the suprachoroidal space to veins in the choroid and sclera or through scleral pores to episcleral tissue. This is believed to account for 3%-36% of total outflow and decreases with age.[8,10] Prostanoid FP receptor agonists (FP agonists), such as latanoprost, primarily increase aqueous outflow via the uveoscleral pathway.[7] FP agonists are generally recommended as first-line therapy for ocular hypertension (OHT) and primary open-angle glaucoma (POAG) because of their efficacy, generally favorable safety profile, and convenient once-daily dosing.[6,7,11,12]

Despite the availability of effective ocular hypertensive medications for OHT and POAG, novel agents are still required. This is because adequate IOP reduction cannot be achieved with FP agonists in all patients, necessitating adjunctive therapy or switching to an alternative agent.[7]

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In addition, approximately 40% of patients will require adjunctive treatment to adequately maintain IOP control within 2 years of initiating FP agonist monotherapy.[13] Furthermore, although systemic side effects are rare, FP agonists can be associated with ocular and periocular adverse events (AEs). In addition to the common AE of localized hyperemia, FP agonists are associated with prostaglandin-associated periorbitopathy, including loss of orbital fat and deepening of the upper eyelid sulcus, pigmentation of the periocular skin and iris, and abnormal growth of eyelashes.[2,6,14–16] The clinical and psychological burden of these appearance-altering AEs is currently unknown, but it has recently been suggested that deepening of the upper eyelid sulcus related to FP agonists may have an impact on IOP-lowering outcomes of trabeculectomy.[17] This suggests that this may have a clinical impact and that there may be a need for a topical IOP-lowering medication that has noninferior efficacy to the current standard of care, latanoprost, and does not contribute to these adverse events.

Omidenepag isopropyl (OMDI) is a topical ocular hypotensive agent that was approved in Japan in 2018 for the treatment of glaucoma and OHT.[18] Its active metabolite, omidenepag, is a selective, non-prostaglandin, prostanoid EP2 receptor agonist.[19,20] OMDI has been shown to reduce IOP by a novel mechanism; it binds to the EP2 receptor, which results in an increase in aqueous humor outflow via both the conventional and uveoscleral pathways.[21] Dose-finding studies have shown OMDI to be generally well tolerated and to demonstrate clinically relevant IOP-lowering effects in patients with POAG and OHT. In these studies, maximum IOP reductions were achieved within 1 week of treatment initiation, demonstrating an early onset of action, and were maintained for up to 3 months.[22] This study aimed to compare the IOP-lowering effects and safety of OMDI 0.002% versus latanoprost 0.005% over a 4-week treatment period. Latanoprost was chosen as a comparator because it has a well-established efficacy and safety profile and is the current standard of care for glaucoma treatment.[15]

METHODS

• **STUDY DESIGN:** This was a multicenter, investigator-masked, randomized, active-controlled, parallel-group phase III study conducted across 39 centers (see Supplemental Material Section) in Japan (ClinicalTrials.gov NCT02623738), which was undertaken to assess the noninferiority of the IOP-lowering effects of OMDI ophthalmic solution 0.002% versus latanoprost ophthalmic solution 0.005% (1 drop once daily at night for 4 weeks for both OMDI and latanoprost) in patients with POAG or OHT. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki, and prospectively approved by the institutional review boards responsible for each participating institution. Written informed consent was obtained from all patients before enrollment in the study.

The study design is shown in Figure 1. Patients were screened for eligibility before entering a washout period for previous IOP-lowering medications (≥4 weeks for α1-adrenergic antagonists, β-adrenergic antagonists, rho kinase inhibitors, prostamides, and prostaglandin analogs; ≥3 weeks for α2-adrenergic agonists; ≥2 weeks for parasympathomimetics and sympathomimetics; and ≥1 week for carbonic anhydrase inhibitors and no previous medication). The study medication randomization manager, who was not an investigator or observer, prepared the study medication randomization codes, which were sealed and stored. Following the washout period, patients were randomized (1:1) by the permuted block method (block size: 2) to receive OMDI or latanoprost, 1 drop once daily in both eyes at 9 PM ± 1 hour for 4 weeks. Because of the differences between the eyedrop bottles for the 2 study drugs, both the investigational treatment (OMDI) and the active control treatment (latanoprost) containers were packaged in the same secondary package (ie, cardboard carton) and over-labeled to mask the study treatment. Investigators, examiners, and sponsor personnel involved in the conduct of the study were masked to the study treatment and were instructed not to ask the patients about the contents of the cartons.

IOP was measured at visit 1 (the start of the washout period) at 9:00 AM and then at visit 2 (day 1), visit 3 (week 1), visit 4 (week 2), and visit 5 (week 4), at 9:00 AM, 1:00 PM, and 5:00 PM (12, 16, and 20 hours post-dose). IOP measurements were obtained using Goldmann applanation tonometry. The IOP values at each measurement time point were represented as the mean of 2 consecutive measurements. If the difference between the 2 measurements was ≥3 mm Hg, a third measurement was taken, and the median value was used. Evaluation of safety was based on assessment of AEs and ophthalmic evaluations, including visual acuity, slit-lamp biomicroscopy, fundoscopy, and central corneal thickness (CCT) measurement. Visual acuity was measured at the start of the washout period and every subsequent study visit. The particular visual acuity chart was not specified in the protocol; however, the Landolt ring chart is the standard used in Japan. At the start of the washout period and every subsequent study visit, evaluation of the eyelids, conjunctiva, cornea, anterior chamber, iris, and lens was performed using slit-lamp biomicroscopy. Worsening of at least 2 units compared with baseline was considered to be clinically significant. The grading for slit-lamp biomicroscopy is provided in Supplemental Material Section 2. Ophthalmoscopy (fundus examination) was performed at the start of the washout period and at the final study visit or at study withdrawal. CCT was measured using corneal pachymeters, including optical, ultrasound, and optical coherence tomography. Treatment compliance was checked at each scheduled visit by interviewing patients about study

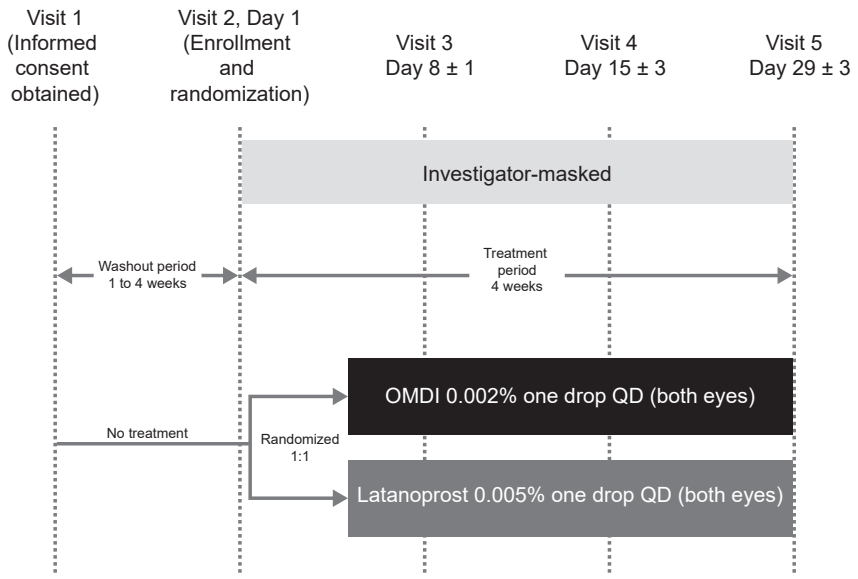

FIGURE 1. Study design. Treatment started at 9:00 PM ± 1 hour on visit 2 (day 1) and finished at 9:00 PM ± 1 hour on the night before visit 5 (day 29 ± 3). IOP = intraocular pressure; OMDI = omidenepag isopropyl; QD = once daily.

medication compliance from the previous to the current visit.

PATIENTS

ELIGIBLE PATIENTS WERE AGE 20 YEARS OR OLDER AND HAD a diagnosis of bilateral POAG or OHT with a corrected decimal visual acuity of ≥0.2 (Snellen 20/100 or better), an anterior chamber angle grade ≥2 (Shaffer scale), and a CCT of 480-600 μm in both eyes. Following the washout period, a baseline IOP of ≥22 mm Hg in at least 1 eye and ≤34 mm Hg in both eyes at 3 time points (9:00 AM, 1:00 PM, and 5:00 PM) was required for study entry. Exclusion criteria included: visual field depression that was severe or at risk for progression during the study; any corneal abnormality or other condition potentially interfering with reliable Goldmann applanation tonometry; presence or history of iritis or uveitis; the presence of any active external ocular disease, inflammation, or infection of the eye or eyelids; the presence or history of macular edema, retinal detachment, diabetic retinopathy, or current retinal disease at risk for progression; history of refractive keratotomy; history of invasive surgery for glaucoma including laser therapy; history of intraocular surgery (other than for glaucoma) within 90 days before the washout period; history of severe eye injury; the use of contact lenses from 1 week before treatment phase initiation and during the study; the intended use of prohibited concomitant medications or treatments before treatment initiation or during the study; and participation in another clinical trial or instillation of a study medication within 90 days before the start of the washout phase. Women who were pregnant, potentially pregnant, or nursing were also excluded.

• **STATISTICAL ANALYSIS:** The target sample size was based on the SD of the change from baseline in mean diurnal IOP at week 4 in the OMDI 0.002% group in the first stage of this study, which was a phase II dose-finding study in Japanese patients.[22] Based on an SD of 2.9 mm Hg, a 2-sided significance level of .05, and a noninferiority margin of 1.5 mm Hg (assuming a 10% drop-out rate), a sample size of 180 randomized patients (90 patients per group) would provide approximately 90% power to demonstrate noninferiority of OMDI versus the active comparator, latanoprost.

The population for the analysis of efficacy (full analysis set) included all patients who met the study inclusion criteria, received at least 1 instillation of the study drug, and had baseline and at least 1 post-baseline IOP measurement in the study eye. The study eye was defined as the eye with the higher mean diurnal IOP at baseline; if both eyes had the same mean diurnal IOP, the right eye was designated as the study eye. The primary efficacy endpoint was the change in mean diurnal IOP from baseline (visit 2) to week 4 (visit 5). The least-squares mean change in diurnal IOP was determined using a mixed-effects model for repeated measures with treatment group, visit, and interaction between treatment group and visit as fixed effects, baseline IOP as a covariate, and the patient as a random effect. OMDI 0.002% was determined to be noninferior to latanoprost 0.005% if the upper limit of the 95% confidence interval (CI) was at or below the noninferiority margin of 1.5 mm Hg.

Secondary efficacy endpoints included the change in mean diurnal IOP at weeks 1 and 2 (visits 3 and 4); the

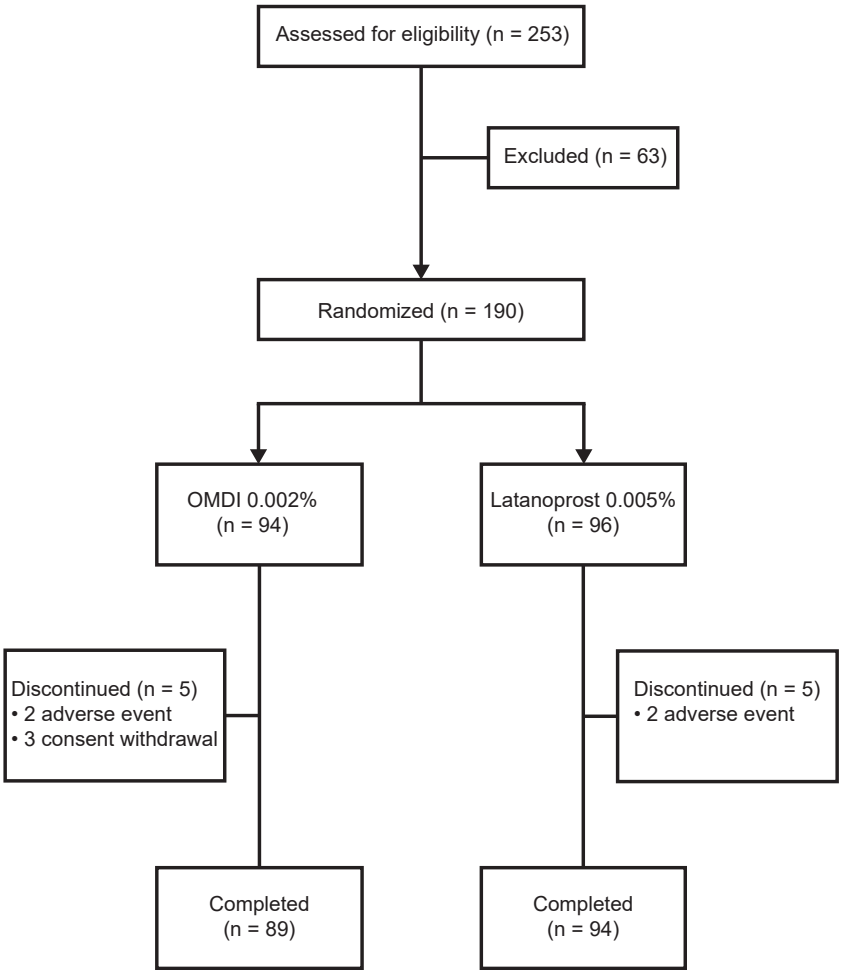

FIGURE 2. Patient disposition. OMDI = omidenepag isopropyl.

change in IOP at each scheduled assessment time point; and the percentage of responders (percentage reduction from baseline in diurnal IOP: ≥20%, ≥25%, ≥30%) at week 4. Secondary endpoints were analyzed by the mixed-effects model for repeated measures in the same manner as the primary efficacy endpoint. For responder rates, intergroup comparisons were performed using Fisher's exact method. The population for the analysis of safety included all patients who received at least 1 instillation of study drug and for whom any safety information was available.

RESULTS

• **PATIENT DISPOSITION AND DEMOGRAPHICS:** The study was conducted between July 2016 and February 2017. Subject disposition is shown in Figure 2. Of the 253 patients who provided informed consent, 190 (75%) were randomized and included in the safety analysis set (94 in the OMDI group and 96 in the latanoprost group). Of these, 189 had at least 1 post-baseline IOP measurement and were included in the full analysis set (94 and 95 patients in the 2 groups, respectively). In all, 183 patients completed the study; 7 patients withdrew because of AEs (2 patients in each group) or withdrawal of consent (3 patients in the OMDI group). In addition, 187 patients were included in the per-protocol analysis, 92 of whom were in the OMDI group and 95 of whom were in the latanoprost group. The demographic and baseline characteristics between the 2 study groups were balanced (Table 1). Patients were a mean ± SD age of 63.6 ± 11.9 years, 103/189 (54.5%) were women, and 110/189 (58.2%) had a primary diagnosis of OHT. In terms of previous use of IOP-lowering medications, 97/198 (51.3%) patients had received prostamides or prostaglandin analogs and 73/189 (38.6%) had received β-adrenergic antagonists; almost one-third (59/189 patients [31.2%]) were previously untreated. Except for 1 patient in the OMDI group at week 2, patient-reported treatment compliance rates were high (≥75%) in both treatment groups; full compliance over the study period was achieved by ≥80% of patients in each group.

TABLE 1. Demographics and Baseline Characteristics (Full Analysis Set)

Characteristic	OMDI 0.002% (n = 94)	Latanoprost 0.005% (n = 95)
Age (y), mean ± SD	65.7 ± 9.8	61.4 ± 13.4
Age ≥65 y, n (%)	57 (60.6)	53 (55.8)
Female, n (%)	51 (54.3)	52 (54.7)
Race		
Japanese, n (%)	94 (100)	95 (100)
Primary diagnosis, n (%)		
Primary open-angle glaucoma	37 (39.4)	42 (44.2)
Ocular hypertension	57 (60.6)	53 (55.8)
Previous use of IOP-lowering medications, n (%)		
None	28 (29.8)	31 (32.6)
Prostamides or prostaglandin analogs	49 (52.1)	48 (50.5)
β-adrenergic antagonists	40 (42.6)	33 (34.7)
Carbonic anhydrase inhibitors	17 (18.1)	10 (10.5)
α-adrenergic agonists	3 (3.2)	3 (3.2)
Other	4 (4.3)	1 (1.1)
Diurnal IOP (mm Hg), mean ± SD	23.78 ± 1.73	23.40 ± 1.51
Central corneal thickness (μm), mean ± SD	553.4 ± 32.0	552.9 ± 28.4
Shaffer grade of angle width, n (%)		
Grade 3	17 (18.1)	15 (15.8)
Grade 4	77 (81.9)	80 (84.2)
Glaucomatous visual field loss, n (%)	31 (33.0)	33 (34.7)

IOP = intraocular pressure; OMDI = omidenepag isopropyl.

• **EFFICACY:** The mean ± SD diurnal IOP at baseline and week 4 was 23.78 ± 1.73 mm Hg and 17.81 ± 2.41 mm Hg, respectively, in the OMDI group, and 23.40 ± 1.51 mm Hg and 16.96 ± 2.24 mm Hg, respectively, in the latanoprost group. As shown in Table 2, the least-squares mean ± SE change from baseline diurnal IOP at week 4 (primary endpoint) was −5.93 ± 0.23 mm Hg in the OMDI group and −6.56 ± 0.22 mm Hg in the latanoprost group. The IOP reduction achieved with OMDI was found to be noninferior to that achieved with latanoprost. The difference in the change in mean ± SE diurnal IOP from baseline to week 4 for OMDI versus latanoprost was 0.63 ± 0.32 mm Hg (95% CI: 0.01-1.26) in favor of latanoprost. The treatment difference between the 2 groups was statistically significant ($P = .048$) but was not considered to be clinically significant. The analysis of the per-protocol population led to the same conclusion, in which the difference was 0.65 ± 0.32 mm Hg (95% CI: 0.02-1.28). Analysis of the mean diurnal IOP reduction achieved at weeks 1 and 2 (secondary endpoints) revealed no statistically significant differences between the 2 groups and demonstrated the noninferiority of OMDI versus latanoprost at both visits (95% CI: −0.96 to 0.25 at week 1 and 95% CI: −0.32 to 0.89 at week 2).

OMDI and latanoprost showed clinically significant IOP reduction from baseline at all assessment time points during each study visit (Figure 3). The reduction in IOP was numerically greater in the OMDI group than in the latanoprost group at all week 1 assessment time points, except 9:00 AM, when they were similar. At week 2, reductions in IOPs were numerically greater in the latanoprost group at 9:00 AM and 1:00 PM and greater in the OMDI group at 5:00 PM. IOP reductions in the OMDI and latanoprost groups were similar at all week 2 assessment time points, and were numerically greater in the latanoprost group than in the OMDI group at all week 4 assessment time points, with a statistically significant difference at 9:00 AM (least-squares mean ± SE IOP reduction: −6.62 ± 0.23 mm Hg compared with −5.70 ± 0.24 mm Hg, respectively; $P = .0061$) (Figure 3). At week 4, the 20%, 25%, and 30% responder rates (corresponding to ≥20%, ≥25%, and ≥30% reductions from baseline in mean diurnal IOP) were numerically greater in the latanoprost group than those in the OMDI group, but there were no significant between-group differences ($P > .05$ for all). Respective responder rates were 76.6%, 56.4%, and 26.6% in the OMDI group and 81.1%, 66.3%, and 40.0% in the latanoprost group.

In patients who were treatment-naïve, the least-squares mean ± SE change from baseline diurnal IOP at week 4 was −6.43 ± 0.45 mm Hg in the OMDI group and −6.77 ± 0.43 in the latanoprost group. The difference in IOP reduction between the OMDI and latanoprost groups was 0.34 ± 0.62 mm Hg in favor of latanoprost; this was not considered clinically significant. These results were similar to those observed in the overall population.

TABLE 2. Results of Analysis Using Mixed-Effects Model for Repeated Measures (Full Analysis Set, Study Eye)

Change From Baseline (mm Hg)	OMDI 0.002% (n = 94)	Latanoprost 0.005% (n = 95)
Week 1		
LS mean ± SE	−6.37 ± 0.22	−6.02 ± 0.22
Difference, mean ± SE[a]	−0.35 ± 0.31	
95% CI of difference	−0.96 to 0.25	
P-value	.2530	
Week 2		
LS mean ± SE	−5.98 ± 0.22	−6.27 ± 0.22
Difference, mean ± SE[a]	0.29 ± 0.31	
95% CI of difference	−0.32 to 0.89	
P-value	.3535	
Week 4		
LS mean ± SE	−5.93 ± 0.23	−6.56 ± 0.22
Difference, mean ± SE[a]	0.63 ± 0.32	
95% CI of difference	0.01 to 1.26	
P-value	.0477	

CI = confidence interval; LS = least squares; OMDI = omidenepag isopropyl; [a]OMDI compared with latanoprost.

• **SAFETY:** No serious AEs were reported in either treatment group during this study (Table 3). Four patients discontinued study treatment as a result of AEs: 2 who received OMDI (both with adenoviral conjunctivitis) and 2 who received latanoprost (1 with adenoviral conjunctivitis and 1 with palpitations). None of these AEs were considered by the investigator(s) to be causally related to study medication. The patient with palpitations was on numerous concomitant medications, including a calcium channel blocker. The incidence of AEs and adverse drug reactions was higher in the OMDI group than that in the latanoprost group (OMDI: 48.9% and 39.4%, respectively; latanoprost: 27.1% and 18.8%, respectively). In both the OMDI and the latanoprost groups, all treatment-related AEs were mild in severity, except for 1 case in each group of conjunctival hyperemia that was moderate in severity. The most frequently reported treatment-related ocular AE was conjunctival hyperemia (mostly mild), which occurred in 23 (24.5%) and 10 (10.4%) patients in the OMDI and latanoprost groups, respectively, followed by corneal thickening in 11 and 1 patients (11.7% and 1.0%) and photophobia in 4 and 0 patients (4.3% and 0%). Punctate keratitis was not observed in the OMDI group, but there were 5 (5.2%) cases related to treatment reported in the latanoprost group. All AEs resolved or recovered during the study or following study drug discontinuation. All treatment-related AEs (adverse drug reactions) were ocular AEs; no non-ocular adverse drug reactions were reported in either group.

As for ophthalmic evaluations for safety monitoring, clinically significant worsening of visual acuity (change of ≥0.2 LogMAR units) in the study and/or non-study eye was reported in 5 patients in the OMDI group and in 1 patient in the latanoprost group. No AEs were reported in these patients, except for 1 patient with adenoviral conjunctivitis, which was not related to the study treatment. No clinically significant visual field changes were reported. Slit-lamp biomicroscopy revealed worsening of at least 2 U in redness of the eyelid compared with baseline in 1 patient in the OMDI group at weeks 2 and 4. This patient also had adenoviral conjunctivitis reported as an AE, but this AE was not causally related to the study medication. Worsening of at least 2 U in conjunctival hyperemia compared with baseline was reported in 7 patients in the OMDI group and in 3 patients in the latanoprost group; all patients also had AEs reported, including conjunctival hyperemia, conjunctivitis, and adenoviral conjunctivitis. All AE cases of adenoviral conjunctivitis (OMDI group: 3/7 patients with conjunctival hyperemia; latanoprost, 1/3 patients with conjunctival hyperemia) were unrelated to the study treatment. The incidence of worsening of conjunctival hyperemia by at least 2 U at each study visit is shown in Supplemental Table 1. Worsening of at least 2 U in corneal staining compared with baseline was observed in 1 patient in the latanoprost group at week 4. This patient also experienced an AE of punctate keratitis that was considered related to the study medication. There was no worsening of glaucomatous fundoscopy reported in any patients.

Increased CCT was reported more frequently in the OMDI group than in the latanoprost group. The CCT increase in the OMDI group was observed at the first postdose assessment (week 1). The mean change from baseline in CCT in OMDI-treated patients ranged from 13.0 to 18.7 μm (approximately 3%) and remained constant throughout the study period (Supplemental Table 2). A

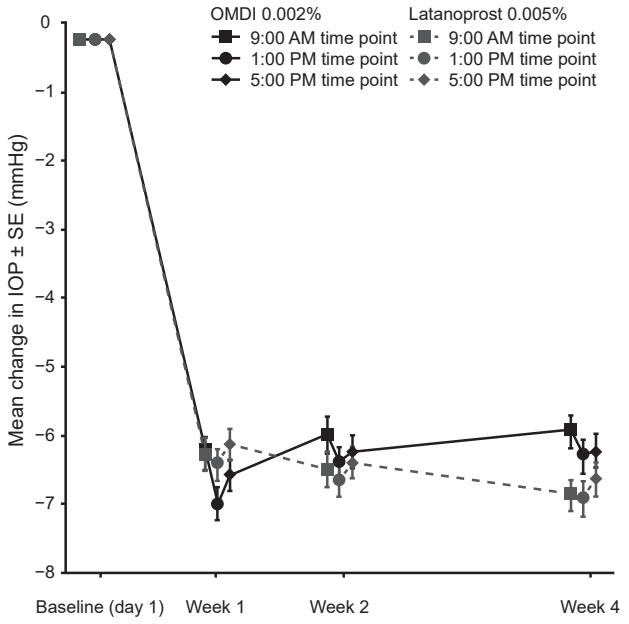

FIGURE 3. Change in mean ± SE diurnal IOP from baseline at each study assessment time point. IOP = intraocular pressure; OMDI = omidenepag isopropyl.

≥50 μm increase from baseline in measured CCT was observed in 3/188 eyes (1.6%) in the OMDI group at week 1, with no cases reported in week 2. At week 4, a ≥50 μm increase in measured CCT from baseline was reported in 6/180 eyes (3.3%) in the OMDI group and in 1/188 eyes (0.5%) in the latanoprost group. There was no reported corneal edema associated with CCT changes as evaluated by slit-lamp biomicroscopy, and no impact on visual acuity was observed. No additional safety issues were identified based on the other ocular safety parameters assessed.

DISCUSSION

THIS PHASE III STUDY BASED IN JAPAN ASSESSED THE EFFICACY and safety of OMDI ophthalmic solution 0.002% compared with latanoprost ophthalmic solution 0.005% in patients with POAG and OHT. OMDI (1 drop at night in each eye once daily) was found to provide clinically significant reductions in mean diurnal IOP from baseline that were noninferior to latanoprost after 4 weeks of treatment. Although the treatment difference between OMDI and latanoprost in mean diurnal IOP reduction at week 4 was statistically significant, from a clinical perspective, the 0.63 mm Hg difference was not considered to be clinically meaningful. This was because it was below the noninferiority margin, which was comparable with the differences observed among the FP agonists (eg, bimatoprost, latanoprost, tafluprost, and travoprost) (range: −0.90 to 0.87 mm Hg), was smaller than the observed reduction from the placebo effect (−1.3 mm Hg), and was within the measurement limit threshold by the Goldmann applanation tonometer (1 mm Hg).[23–25] In addition, the IOP-lowering effect from baseline was similar between OMDI and latanoprost in patients who were treatment-naïve. A previous dose-finding study suggested that the similar IOP-lowering effect observed between OMDI 0.002% and latanoprost persisted for up to 12 weeks.[22] However, a randomized phase III study with a larger patient population would provide more substantial evidence of this.

The maximal IOP-lowering effect was achieved within 1 week of treatment initiation, which was similar to the previous dose-finding studies,[22] and remained stable over the 4-week study period in both treatment groups. The study duration of 4 weeks was chosen based on 1 of the dose-finding studies in the USA in which the IOP reduction was stable from month 1 to month 3.[22] In addition, this study duration was agreed with the Japanese regulatory agency, the Pharmaceuticals and Medical Devices Agency. In previous studies of latanoprost in Japanese patients, the IOP reductions observed were similar to those reported in the present study. In a 12-week study of Japanese patients with POAG or OHT, treatment with latanoprost (n = 80) lowered mean ± SD IOP from a baseline value of 23.1 ± 1.9 mm Hg by 6.2 ± 2.7 mm Hg to 16.8 ± 2.3 mm Hg.[26] Similarly, in a 12-month study of 124 Japanese patients with POAG or OHT, latanoprost treatment resulted in a 5.7 ± 2.4 mm Hg reduction after 4 weeks from a baseline value of 23.5 ± 2.2 mm Hg.[27] The IOP reduction observed with OMDI treatment was within the range of previous dose-finding studies.[22] However, the IOP reduction appeared to be numerically greater in the US studies than the Japanese studies. This difference might be because of the lower IOP values typically observed in Japanese patients compared with White populations at study entry.[28] More studies are required to investigate the treatment response in different patient populations.

Responder rates after 4 weeks of treatment were similar in both study groups, with most patients achieving a reduction in mean diurnal IOP from baseline of at least 20%. The observed responder rates were numerically greater than previously reported 4-week results for bimatoprost and latanoprost treatment in patients with similar baseline IOPs (66.9% and 47.1%, respectively).[29] A 20% reduction in IOP, or a target of <21 mm Hg, is recommended for patients with early glaucoma, and these results suggest that treatment with OMDI may be useful in this patient population.[7] Sommer reported that 78% of patients with glaucoma had IOPs of <25 mm Hg at the time of POAG diagnosis.[30] In late-stage glaucoma, a 30% reduction, or a target of <18 mm Hg, in IOP is recommended. In this study, the 30% response rate was numerically smaller in the OMDI group than that in the latanoprost group. However, the mean diurnal IOP value at week 4 was <18 mm Hg in both groups. The proportion of patients who

TABLE 3. Summary of AEs (Safety Analysis Set)

Patients with any AEs	OMDI 0.002% (n = 94) n (%)	Latanoprost 0.005% (n = 96) n (%)
AEs	46 (48.9)	26 (27.1)
Serious AEs	0	0
Ocular AEs	43 (45.7)	21 (21.9)
Ocular adverse drug reactions	37 (39.4)	18 (18.8)
AEs leading to study discontinuation	2 (2.1)	2 (2.1)
Non-ocular AEs	11 (11.7)	9 (9.4)
Ocular AEs occurring in ≥2 patients in either treatment group		
Conjunctival hyperemia	23 (24.5)	10 (10.4)
Corneal thickening	11 (11.7)	1 (1.0)
Eye pain	4 (4.3)	1 (1.0)
Photophobia	4 (4.3)	0
Adenoviral conjunctivitis	3 (3.2)	1 (1.0)
Eye pruritus	2 (2.1)	2 (2.1)
Foreign body sensation in eyes	2 (2.1)	0
Vision blurred	2 (2.1)	0
Eye irritation	1 (1.1)	4 (4.2)
Punctate keratitis	0	7 (7.3)
Non-ocular AEs occurring in ≥2 patients in either treatment group		
Nasopharyngitis	4 (4.3)	2 (2.1)
Glucose present in urine	2 (2.1)	1 (1.0)
Headache	2 (2.1)	0
Pharyngitis	0	2 (2.1)

AE = adverse event; OMDI = omidenepag isopropyl.

achieved <18 mm Hg was not a pre-specified analysis. More than one-half of patients did not achieve 30% IOP reduction with either treatment. These findings continue to confirm the need of new ocular hypotensive agents with different mechanisms of action, particularly in patients with advanced glaucoma who require a lower target IOP level.

OMDI ophthalmic solution demonstrated acceptable safety and tolerability in this study. The overall incidence of ocular AEs and adverse drug reactions was numerically higher in the OMDI group than in the latanoprost group. This difference was mostly due to a higher incidence of mild conjunctival hyperemia in this group; however, there were no study discontinuations due to conjunctival hyperemia. No serious AEs were reported, and few (2 in each group) patients discontinued the study due to AEs in either group. None of the AEs that led to study discontinuation were related to either treatment. Conjunctival hyperemia, a well-recognized side effect of ocular hypotensive treatment,[31] was the most frequently reported AE in both treatment groups. The incidence of conjunctival hyperemia in the OMDI group in this study (24.5%) was within the range observed for FP agonists.[32–35] Conjunctival hyperemia has been reported with all FP agonists, with varying incidences (~4%-20%, ~8%, ~31%, and ~30%-50% of patients who received tafluprost, latanoprost, bimatoprost, and travoprost, respectively).[32–35] Similarly, conjunctival hyperemia has been reported in up to 20% of patients who received brimonidine and up to 53% of patients who received netarsudil.[36,37] Topical administration of FP agonists has been shown to induce conjunctival hyperemia within 2 days of treatment commencement and generally diminishes within 4 weeks of treatment.[38,39] A longer study would be required to determine the time course of hyperemia during OMDI treatment.

A mean increase in CCT of approximately 15 μm (2.7%) was observed in patients treated with OMDI at week 4, a finding that was not observed in the latanoprost group. Similar increases in CCT have been reported in previous studies of OMDI and another EP2 receptor agonist, taprenepag isopropyl (<24 μm for both).[22,40] The increase in CCT seen in OMDI-treated patients in this study was not considered clinically significant, because it was within the range of normal physiologic change that occurs after 1 night of sleep (3%-8% overnight corneal swelling).[41] Furthermore, there was no corneal edema, as evaluated by slit-lamp biomicroscopy, and no impact on visual acuity was observed. However, further investigation on the impact of CCT increase on corneal health, including corneal endothelial cell count, in a long-term follow-up

study is warranted. Other glaucoma medications have also been shown to affect corneal thickness. Treatment with carbonic anhydrase inhibitors has been shown to increase CCT.[42–44] This likely occurs because of treatment-related changes in fluid transport from the corneal stroma to the aqueous humor.[42] Treatment with FP agonists can lead to a significant but reversible decrease in CCT.[44–47] FP agonists are known to lower collagen production in the ciliary muscle, and it has been shown that latanoprost affects collagen distribution and decreases fibronectin in cultured corneal stromal cells.[48,49] The precise mechanism by which OMDI increases CCT is not yet known, and further investigation is required. Studies suggested that changes to CCT might influence IOP measurements, with a thicker cornea leading to an overestimation of IOP.[47,50,51] However, the effect of CCT changes on IOP measurements was not analyzed in this study. It was unknown whether these small increases in CCT had an effect on the reported IOP values in this study. However, the modest increases in CCT observed were in the normal physiologic range.[41] In addition, the observed increases in CCT were stable from week 1 to week 4, and therefore, were not thought to contribute to the small difference in IOP lowering between OMDI and latanoprost at week 4.

The differences observed in local AE profiles and incidence rates between OMDI and latanoprost could be attributed to the different mechanisms of action of the active compounds. In some cases, the components of ophthalmic solutions (eg, a preservative like benzalkonium chloride) and the concentrations of components or combination of the components could cause several local AEs (eg, punctate keratitis). All 7 cases of punctate keratitis, including 5 related to treatment, were reported in the latanoprost group only, and both treatments contained benzalkonium chloride.

The safety and tolerability findings in the present study were in line with the results of other previous studies of OMDI in US and Japanese patients with glaucoma and OHT.[22] Pharmacokinetic studies have shown a similar safety profile in Japanese and Caucasian patients.[52] Additional phase III studies are being conducted in Asia (outside of Japan; ClinicalTrials.gov NCT02981446) and in the USA (ClinicalTrials.gov NCT03691649; ClinicalTrials.gov NCT03691662; ClinicalTrials.gov NCT03697811) to investigate these findings in diverse patient populations.

Key strengths of this study were the investigator-masked, randomized, controlled design and use of latanoprost ophthalmic solution, the gold standard of care, as an active comparator. Latanoprost has a well-established efficacy and safety profile, being the first of the currently available FP agonists to be approved for the treatment of glaucoma and OHT and widely used as a first-line therapy worldwide.[15] Although studies in the USA typically use timolol as an active comparator, the greater IOP-lowering efficacy and wide use of latanoprost suggest that the presented comparison is more informative of the efficacy and safety profile of OMDI compared with the current standard of care.[53] There are currently 2 ongoing phase III studies that are comparing the IOP-lowering efficacy of OMDI with timolol.[54,55] Although the short duration of this study was sufficient for the efficacy comparison with latanoprost, it was limited in providing information on whether this IOP-lowering effect was sustained over a long-term period. However, a 12-month, open-label study on the efficacy and safety of OMDI was recently completed (ClinicalTrials.gov NCT02822729), and showed sustained IOP lowering (Aihara M, et al. 2018; AAO Poster PO100. https://aao.scientificposters.com/epsAbstractAAO.cfm?id=1). Another potential limitation of this study was the investigator-masked design. Because different containers were used for OMDI and latanoprost, it was not feasible to establish double-masked study conditions. However, several procedures and efforts were in place to minimize bias. Investigators, examiners (including individuals who measured the primary endpoint of IOP), and sponsor personnel involved in the conduct of the study were masked to the study treatment, and an authorized unmasked study staff member, who was not the investigator or examiner, dispensed the study medication. Furthermore, the study drug containers were overlabeled and inserted into identical secondary packaging, and the investigators, examiners, and sponsor personnel involved in the conduct of the study were instructed not to ask about the contents of the cartons.

In conclusion, results of this study showed the IOP-lowering effect of once daily OMDI to be noninferior to that of latanoprost in Japanese patients with POAG or OHT. OMDI had an acceptable safety and tolerability profile because no serious treatment-related AEs were reported, and there were no discontinuations related to the treatment. Therefore, OMDI could be considered a candidate for first-line treatment of glaucoma and OHT. As a result, in 2018, OMDI was approved for the treatment of glaucoma and OHT in Japan.[18] Further phase III studies with longer duration are ongoing in Asia (outside of Japan) and the USA.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

MAKOTO AIHARA: METHODOLOGY, INVESTIGATION, SUpervision, Writing - original draft, Writing - review & editing. **Fenghe Lu:** Methodology, Investigation, Supervision, Formal analysis. **Hisashi Kawata:** Methodology, Investigation, Supervision, Formal analysis. **Akihiro Iwata:** Methodology, Investigation, Supervision, Formal analysis. **Noriko Odani-Kawabata:** Methodology, Investigation, Supervision, Formal analysis. **Naveed K. Shams:** Methodology, Writing - original draft, Writing - review & editing.

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