ORIGINAL STUDY

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# Ocular Hypotensive Effect of ONO-9054, an $EP_3$/FP Receptor Agonist: Results of a Randomized, Placebo-controlled, Dose Escalation Study

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**Purpose:** To assess pharmacodynamic and safety profiles of ONO-9054 following single and multiple day dosing in subjects with ocular hypertension or open-angle glaucoma.

**Materials and Methods:** This was a phase I, single-center, randomized, double-masked, placebo-controlled dose-escalation study. Nine subjects were randomized to each of ONO-9054 3, 10, 20, 30 μg/mL and 12 to placebo. Subjects received a single drop to each eye at 07:00 ± 30 minutes (single dose). Following a 4-day no-treatment period, subjects were dosed once daily for 14 consecutive days (multiple day dosing). Intraocular pressure (IOP) was measured regularly and compared with baseline measurements. Ocular examinations assessed safety and tolerability.

**Results:** Mean IOP decreased dose dependently. Following single dosing, IOP decreased from 22.9 ± 4.0 to 15.9 ± 2.3 mm Hg (ONO-9054, 30 μg/mL) at peak effect 9 hours postdose; the reduction in placebo-treated subjects was from 22.3 ± 2.4 to 21.5 ± 3.3 mm Hg. Following multiple day dosing, the greatest reduction in IOP occurred 1 hour postdose on day 18, from 23.3 ± 0.6 to 15.1 ± 2.4 mm Hg (ONO-9054, 10 μg/mL); the smallest reduction at this time was from 23.9 ± 0.8 to 18.6 ± 2.0 mm Hg (ONO-9054, 3 μg/mL). Pressures remained reduced on day 19, 25 hours after the last dose, when the lowest measurement was 15.8 ± 2.1 mm Hg (ONO-9054, 10 μg/mL). Anterior uveitis and vitreous detachment were each reported in 2 subjects and considered moderate by the Investigator. Ocular hyperemia and tolerability symptoms were generally mild and transient.

**Conclusions:** ONO-9054 was well-tolerated and elicited dose-dependent reductions in IOP, which were sustained for at least 24 hours following 2 weeks of consecutive daily dosing.

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Primary open-angle glaucoma (OAG) is a chronic ocular disease that is progressive, usually bilateral, but often asymmetric. Worldwide, approximately 44.7 million people are affected by this form of glaucoma and estimates put prevalence in the United States in the range of 1.87 to 2.5 million people, aged 40 years or older.[1] Clinical manifestations of glaucoma include raised intraocular pressure (IOP), optic disc or retinal nerve fiber layer structural anomalies or defects, and visual field abnormalities.[2]

Although glaucoma is not defined by raised IOP, the only treatment strategy approved and demonstrated to be effective for patients with glaucoma is to lower IOP in an effort to slow structural and visual degeneration.[3] Several classes of drugs have been indicated for topical therapy in the form of eye drops. These act locally to alter the homeostasis of the fluid dynamics of the aqueous humor, lowering IOP by a variety of mechanisms including facilitating aqueous outflow and decreasing aqueous production.[4] Where eye drops are considered insufficient, surgical interventions including laser surgery, minimally invasive glaucoma surgery, trabeculectomy, canaloplasty, and drainage implants can improve outflow.[5]

Prostaglandin analogs (PGAs) are highly effective topical drugs that lower IOP by acting directly on the ciliary muscles, promoting relaxation and remodelling of the extracellular matrix, thereby enhancing uveoscleral outflow, and are often prescribed as first-line treatment for ocular hypertension (OHT) and primary OAG.[6] Despite the variety of treatments, however, there are still unmet therapeutic needs: primary intervention often fails and so over 40% of patients on PGA monotherapy eventually require some form of adjunctive drug therapy to manage IOP within a 5-year period.[7]

The PGAs latanoprost, bimatoprost, travoprost, and tafluprost act primarily at the prostaglandin F (FP) receptor, although lower activity for other prostaglandin receptors has also been demonstrated.[8] ONO-9054, also known as sepetaprost, is a prodrug that is rapidly hydrolyzed by esterases to its active metabolite ONO-AG-367, which expresses high activity at both the prostaglandin E ($EP_3$) and FP receptors.[9] ONO-9054 is known to enhance trabecular outflow as well as uveoscleral outflow in animals.[10]

ONO-9054 has been demonstrated to be safe and well-tolerated in a single-dose escalation clinical study conducted in healthy volunteers.[11] The present phase I study

was completed to further assess safety and tolerability of ONO-9054, as well as to characterize its pharmacokinetic and pharmacodynamic profiles, following single and multiple day dosing in subjects with OHT or primary OAG.

## MATERIALS AND METHODS

### Subjects

The study population was comprised of men and women aged 18 to 80 years, who had a diagnosis of bilateral OHT or chronic primary OAG and were able to undergo washout of all ocular hypotensive and other ocular drugs. All subjects provided written, informed consent.

All subjects had IOP $\geq$ 22 mm Hg at 08:00 and $\geq$ 21 mm Hg at 10:00 in at least 1 eye, with $\leq$ 35 mm Hg at all measurements in both eyes on the 2 days preceding dosing (day $-2$ and $-1$) as measured by Goldmann applanation tonometry. Additional eligibility requirements for both eyes included central corneal thickness of 500 to 600 μm at screening; best-corrected visual acuity (BCVA) of at least 20/100 as measured by Early Treatment Diabetic Retinopathy Study chart and cup-to-disc ratio $\leq$ 0.8.

Exclusion criteria included history of severe ocular trauma in either eye, intraocular or ocular laser surgery within the previous 3 months; refractive surgery within the previous 6 months; and significant changes in visual fields within 6 months of dosing as measured by 24-2 perimetry. Subjects were excluded if any condition preventing reliable screening or performance of ocular assessments was discovered upon physical examination, as were those who had received recent ocular, inhaled, intranasal, or systemic administration of steroids, β-adrenergic blockers, adrenergic agonists, ocular allergy medications, carbonic anhydrase inhibitors, or cholinergic agonists.

### Study Design

This was a phase I, single-center, randomized, double-masked, placebo-controlled dose escalation study (clintrials.gov: NCT01670266), which took place from October 5, 2012 to May 9, 2013, inclusive, at a clinical research organization (West Coast Clinical Trials, Costa Mesa, CA). The study protocol was approved by the Aspire Institutional Review Board (Santee, CA). The study was conducted in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act.

Subjects were screened for eligibility in the 45 days preceding the study. Washout of topical or systemic IOP-lowering medications was performed according to the following schedules: 28 days for PGAs, β-adrenergic blockers, or local or systemic steroids and glucocorticoids; 14 days for adrenergic agonists or drugs for the treatment of ocular allergy; 5 days for cholinergic agonists or carbonic anhydrase inhibitors.

The study consisted of 3 parts: a single-dose period of 4 days (subjects received 1 dose of drug in the morning on day 1 and no treatment on days 2 to 4); a multiple day dosing period during which subjects received treatment once daily in the morning for 14 days (days 5 to 19); and a follow-up visit on day 25 (± 3 d).

A randomized treatment assignment schedule was prepared by an independent Statistician and Programmer at the Contract Research Organisation, which assigned each subject to either active or placebo treatment in a 3:1 ratio (active:placebo). Nine subjects were randomized to each of ONO-9054 3, 10, 20, or 30 μg/mL; and 12 subjects were randomized to placebo as control. One drop (approximately 30 μL) was administered to both eyes of each subject once daily at 07:00 ± 30 minutes.

### Pharmacodynamics

All IOP measurements were obtained by 2 examiners using calibrated Goldmann applanation tonometry: the masked operator viewed the mires and applanated by rotating the tonometer dial while the second operator recorded the result. Baseline IOP was measured on day $-1$ at 5 timepoints (08:00, 10:00, 12:00, 16:00, and 19:00). During the single-dose period, IOP was assessed 1, 3, 5, 9, 12, 25, 27, 29, and 33 hours postdose. During the multiple day dosing period, IOP was assessed on days 5, 6, 11, 18, and 19 at 1, 3, 5, and 9 hours postdose. All IOP measurements were compared with corresponding measurements taken at baseline on day $-1$. On day 18, following the conclusion of multiple day dosing, IOP was assessed 1, 3, 5, 9, 12, 25, 27, 39, and 33 hours postdose. In all IOP analyses, only data from the eligible eye was used (eligibility was defined as IOP $\geq$ 22 mm Hg at 08:00 and $\geq$ 21 mm Hg at 10:00, but $\leq$ 35 mm Hg at all timepoints on days $-2$ and $-1$). If both eyes were eligible, the eye with the higher IOP at 08:00 on day $-1$ was selected, and if both had the same IOP the right eye was selected.

### Pharmacokinetics

Peripheral blood samples were taken on days 1 and 18 predose and 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 4, and 6 hours postdose. On day 11, a sample was taken 10 minutes postdose. Plasma concentrations of ONO-9054 and the active metabolite ONO-AG-367 were determined using validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) methods at Quintiles BioSciences Inc. (Ithaca, NY).

Plasma concentration versus time data were analyzed using Phoenix WinNonlin version 6.2.1, utilizing a standard noncompartmental model. When concentrations allowed, the following plasma pharmacokinetic parameters were derived for ONO-9054 and ONO-AG-367: maximum observed concentration ($C_{max}$), area under the concentration-time curve from time 0 to the last sampling point ($AUC_{last}$; day 1 and day 18) and time 0 to infinity ($AUC_{inf}$; day 1 only), time to $C_{max}$ ($T_{max}$), elimination half-life ($T_{½}$), apparent clearance (CL/F; day 1 only), and corrected $C_{max}$ and $AUC_{last}$ for dose per kg of body weight (BW) [$C_{max}$/(dose/BW) and $AUC_{last}$/(dose/BW)].

### Safety

Adverse events were recorded from day 1 to follow-up and coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary (version 15.1). Clinical laboratory evaluations, vital signs, and 12-lead electrocardiographs were also assessed.

Ocular hyperemia was evaluated grossly by comparison of each eye to standardized photographs of conjunctival hyperemia in subjects on glaucoma drug therapy (use of Ora Calibra Redness Scale #6.0b, Ora Inc., Andover, MA, was made under license from Ora Inc.). The hyperemia scale was: $\geq$ 0 or 0.5 = none; 1 or 1.5 = mild; 2 or 2.5 = moderate; 3 = severe. Scores were gathered on days $-1$, 1, 2, 4, 5, 6, 11, 18, 19, and at follow-up. When

each eye had a different score, the worst score recorded from both eyes was used.

The tolerability of the eye drop was assessed by a subjective rating of photophobia, itching, tearing, dryness, and discharge. Subjects rated each parameter as 0 (absent), 1 (mild), 2 (moderate), 3 (severe with stinging or burning) or 4 (severe with blurred or dim vision). The worst scores from both eyes were recorded on days −1, 1, 2, 4, 5, 6, 11, 18, and 19 and follow-up.

Slit-lamp examination and pupillometry were conducted as additional evaluators of safety and tolerability predose and 1, 3, 5, 9, 12, and 25 hours postdose during the single-dose period; and predose and 1, 3, 5, 9, hours postdose on days 5, 6, 11, and 18 during multiple day dosing. Measurements were also taken 12 hours postdose on day 5, and 12 and 25 hours after the final dose. Other ocular safety assessments included BCVA, central corneal thickness by pachymetry, indirect ophthalmoscopy, fundus imaging, impression cytology, and visual fields and were assessed before the first dose of study medication and postdose at various timepoints throughout the study.

## Statistical Considerations

No a priori statistical assumptions were made for sample size, which was based on including sufficient subjects to assess pharmacodynamics, pharmacokinetics, and safety, while minimizing the risk to subjects in early drug development, and was typical of similar phase I trials investigating OAG.[12,13] The Safety Set comprised all subjects enrolled in the study who received at least 1 drop of study medication of any strength (including placebo) instilled in either eye. The Safety Set was used for analysis of pharmacodynamic endpoints. The Pharmacokinetic Analysis Population included all enrolled subjects who received ONO-9054 and had at least 1 postdose PK blood sample.

Two post hoc analyses were performed. An analysis was conducted to evaluate the extent of IOP lowering in subgroups of subjects that presented at baseline with IOP ≥ 24 mm Hg as it has been identified that subjects with a higher baseline IOP respond better to PGAs.[14] A second post hoc analysis evaluated mean diurnal IOP (08:00, 10:00, 12:00, 16:00, 19:00) in all subjects at baseline and day 18 and assessed for statistical significance using Tukey's (least squares means) test. All *P*-values $<0.05$ were considered statistically significant.

# RESULTS

## Disposition and Demographics

A total of 113 subjects were screened and 48 subjects were randomized; 36 received ONO-9054, 12 received placebo. One subject discontinued study medication on day 8 after receiving 4 doses of ONO-9054 30 μg/mL because of moderate bilateral anterior uveitis judged probably related. The subject completed all safety assessments through day 18 and the bilateral uveitis was monitored until it resolved without sequelae on day 32. All remaining subjects completed the study and received active drug and placebo as planned. Subject demographics can be seen in Table 1.

## Pharmacodynamics

Mean baseline IOP at 08:00 on day −1 ranged from 23.3 ± 0.6 mm Hg in the ONO-9054 10 μg/mL group to 25.2 ± 2.5 mm Hg in the 30 μg/mL group.

### Single Dose

Following a single dose, ONO-9054 dose-dependently reduced mean IOP. Peak effect occurred 9 hours postdose on day 1, when the greatest reduction was from a baseline value of 22.9 ± 4.0 to 15.9 ± 2.3 mm Hg (−29.6% ± 11.6%) in the ONO-9054 30 μg/mL cohort. The smallest reduction in mean IOP was from a baseline value of 22.6 ± 1.3 to 19.3 ± 3.0 mm Hg (−14.4% ± 12.1%) in the ONO-9054 10 μg/mL cohort at this time and there was a reduction from 22.3 ± 2.4 to 21.5 ± 3.3 mm Hg (−3.0% ± 14.8% mm Hg) in placebo-treated subjects (Fig. 1). The lowest mean IOP (15.0 ± 3.0 mm Hg) was observed in the 20 μg/mL dose group at 12 hours postdose. In all active treatment groups, IOP increased slightly in the absence of continued dosing on days 2 to 4, although IOP did not return to baseline values.

### Multiple Day Dosing

Mean IOP was decreased throughout the multiple day dosing phase (days 5 to 18) and reductions in all active treatment groups were greater than placebo. All subjects who received ONO-9054 experienced a reduction in IOP to ≤18 mm Hg after the multiple dosing phase, whereas all placebo-treated subjects had IOP of ≥18 mm Hg at all measurement times. The peak reduction in mean IOP on day 18 was from a baseline value of 22.1 ± 0.8 to 13.8 ± 1.8 mm Hg (−37.6% ± 6.5%) at 12 hours postdose for the ONO-9054 10 μg/mL cohort; mean IOP in the placebo group changed from a baseline value of 21.9 ± 2.5 to 21.9 ± 1.9 mm Hg must be an error in these #s there is no change in the mean here? (+ 0.9% ± 12.1%) at this time (Figs. 2, 3).

Mean percent reductions in IOP from baseline at 08:00 (1 h postdose) on day 18 ranged from −35.4% ± 10.5% (ONO-9054, 10 μg/mL) to −22.5% ± 6.7% (ONO-9054, 3 μg/mL). The IOP in the ONO-9054 10 μg/mL group at 08:00 after multiple day dosing was 15.1 ± 2.4 mm Hg. The reduction from baseline in the placebo group was from 24.7 ± 2.1 to 23.5 ± 2.3 mm Hg (−5.0% ± 6.8%) at the same time on this day (Figs. 2, 3). The numbers of subjects who responded to multiple day dosing with IOP measurements of ≤16 mm Hg at 1 hour postdose on day 18 in each dose group were: 0/12 (0%) for placebo; 1/9 (11.1%) for ONO-9054 3 μg/mL; 7/9 (77.8%) for 10 μg/mL; 4/9 (44.4%) for 20 μg/mL; and 6/9 (66.7%) subjects in the 30 μg/mL cohort (Table 2).

Morning pressure remained at least 25% below baseline on day 19, 25 hours after the last dose, in all active treatment groups. The lowest mean IOP at this time was 15.8 ± 2.1 mm Hg observed in the ONO-9054 10 μg/mL cohort. The percent reduction from baseline remained greater than 30% in this dose group for all timepoints on day 19 through 33 hours postdose. In the ONO-9054 10 μg/mL dose group, >50% of subjects had IOPs lower than 16 mm Hg at all timepoints on day 18 (Table 2). In the doses above 10 μg/mL, >50% of subjects had IOPs lower than 18 mm Hg at all timepoints on this day. Mean IOP had increased at follow-up (7 ± 3 d after termination of dosing) in all cohorts; mean IOP measurements were 24.1 ± 3.3, 21.7 ± 2.0, 23.7 ± 3.5, 22.1 ± 1.2, and 24.3 ± 3.1 mm Hg for the ONO-9054 3, 10, 20, 30 μg/mL and placebo cohorts, respectively.

### Post Hoc Analyses

The number of subjects with high IOP at baseline (≥24 mm Hg at 23 h predose on day −1) was 27: 8 for placebo, 6 for ONO-9054 3 μg/mL, 2 for 10 μg/mL, 5 for 20 μg/mL, and 6 for 30 μg/mL (Fig. 4). Mean baseline

**TABLE 1.** Subject Demographics

| Patient Characteristics | Placebo (n = 12) | ONO-9054 3 μg/mL (n = 9) | ONO-9054 10 μg/mL (n = 9) | ONO-9054 20 μg/mL (n = 9) | ONO-9054 30 μg/mL (n = 9) | Total (n = 48) |
|---|---|---|---|---|---|---|
| Mean age in years ± SD [range] | 65.7 ± 8.2 [55-79] | 67.8 ± 8.2 [55-80] | 51.3 ± 13.5 [30-72] | 65.7 ± 6.6 [58-77] | 64.1 ± 6.8 [50-74] | 63.1 ± 10.4 [30-80] |
| Sex [n (%)] | | | | | | |
| Male | 3 (25.0) | 2 (22.2) | 4 (44.4) | 3 (33.3) | 3 (33.3) | 15 (31.2) |
| Female | 9 (75.0) | 7 (77.8) | 5 (55.6) | 6 (66.7) | 6 (66.7) | 33 (68.8) |
| Race [n (%)] | | | | | | |
| White | 10 (83.3) | 7 (77.8) | 7 (77.8) | 7 (77.8) | 7 (77.8) | 38 (79.2) |
| Black or Afro-American | 1 (8.3) | 1 (11.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.2) |
| Asian | 1 (8.3) | 1 (11.1) | 2 (22.2) | 2 (22.2) | 2 (22.2) | 8 (16.7) |
| Prior use of IOP-lowering medications [n (%)] | | | | | | |
| PGA | 5 (41.7) | 2 (22.2) | 0 (0.0) | 2 (22.2) | 4 (44.4) | 13 (27.1) |
| TCAI | 3 (25.0) | 4 (44.4) | 0 (0.0) | 5 (55.6) | 0 (0.0) | 12 (25.0) |
| β-blocker | 0 (0.0) | 1 (11.1) | 1 (11.1) | 4 (44.4) | 0 (0.0) | 6 (12.5) |
| $\alpha_2$ agonist | 0 (0.0) | 1 (11.1) | 1 (11.1) | 0 (0.0) | 0 (0.0) | 2 (4.2) |
| Fixed combinations | 2 (16.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.2) |

IOP indicates intraocular pressure; PGA, prostaglandin analog; TCAI, topical carbonic anhydrase inhibitor.

values for IOP ranged from 24.0 ± 0.0 mm Hg (ONO-9054, 10 μg/mL cohort) to 26.5 ± 2.1 mm Hg (ONO-9054, 30 μg/mL cohort) at 08:00 on day −1. The greatest mean reductions in IOP from baseline in this population occurred 1 hour postdose on day 6 for the 3 μg/mL [−7.5 ± 3.2 mm Hg (−30.9% ± 14.8%)] and 20 μg/mL [−8.6 ± 2.3 mm Hg (−33.8% ± 8.8%)] cohorts; 1 hour postdose on day 11 for the 30 μg/mL cohort [−10.1 ± 2.2 mm Hg (−38.1% ± 7.2%)]; and 9 hours postdose on day 11 in the 10 μg/mL cohort [−11.0 ± 2.8 mm Hg (−46.0% ± 8.5%)]. At the end of the study, after multiple day dosing, the mean IOP of subjects with a high IOP at baseline and who received active treatment ranged from 15.5 ± 2.1 mm Hg (ONO-9054, 10 μg/mL) to 19.3 ± 1.7 mm Hg (ONO-9054, 3 μg/mL) 1 hour postdose on day 18. The greatest percent reduction from baseline in IOP was observed in the 30 μg/mL group (36.8% ± 7.6%) at this time.

For all subjects, mean diurnal IOP (08:00, 10:00, 12:00, 16:00, and 19:00) at baseline ranged from 22.0 ± 1.4 mm Hg (ONO-9054, 20 μg/mL) to 23.9 ± 2.6 mm Hg (ONO-9054, 30 μg/mL). Mean diurnal IOP values on day 18 were as follows: 22.5 ± 2.1 mm Hg (−2.7% ± 6.6%) for placebo,

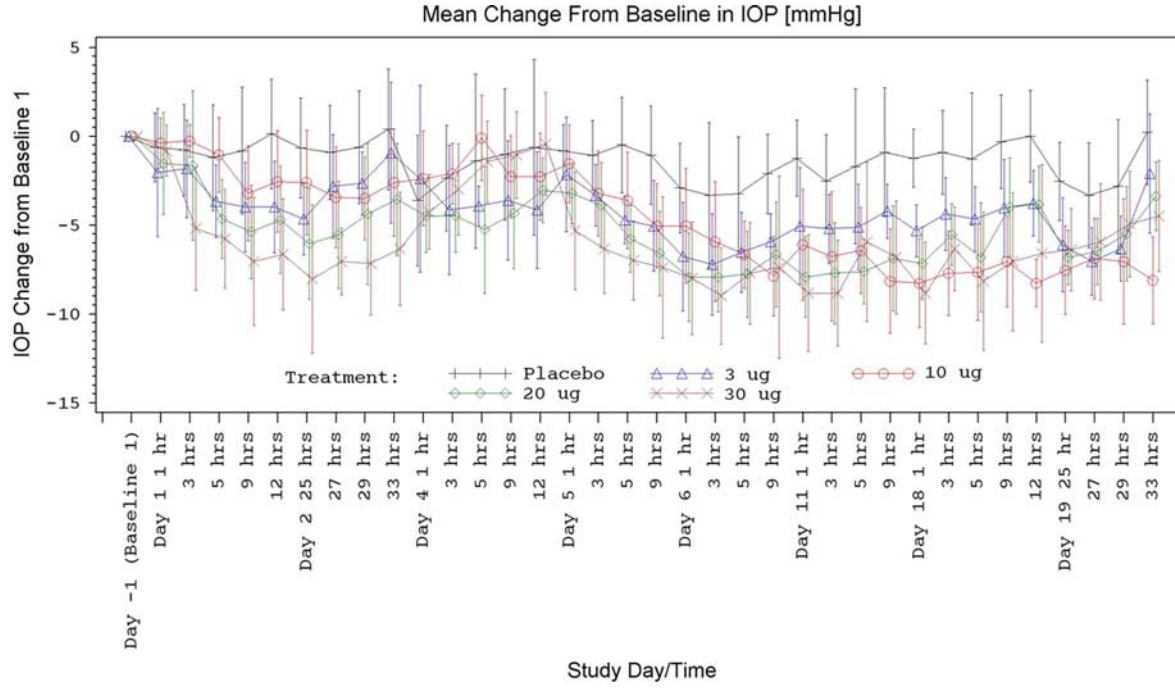


**FIGURE 1.** Mean change from baseline in intraocular pressure (IOP) (mm Hg ± SD) in subjects receiving ONO-9054 3 μg/mL (△), 10 μg/mL (○), 20 μg/mL (◇) or 30 μg/mL (X) or placebo (+) during single dose (days 1 to 4) and 14 consecutive days dosing (days 5 to 18). Subjects receiving ONO-9054 displayed reduced IOP following both treatment periods, whereas those receiving placebo did not.

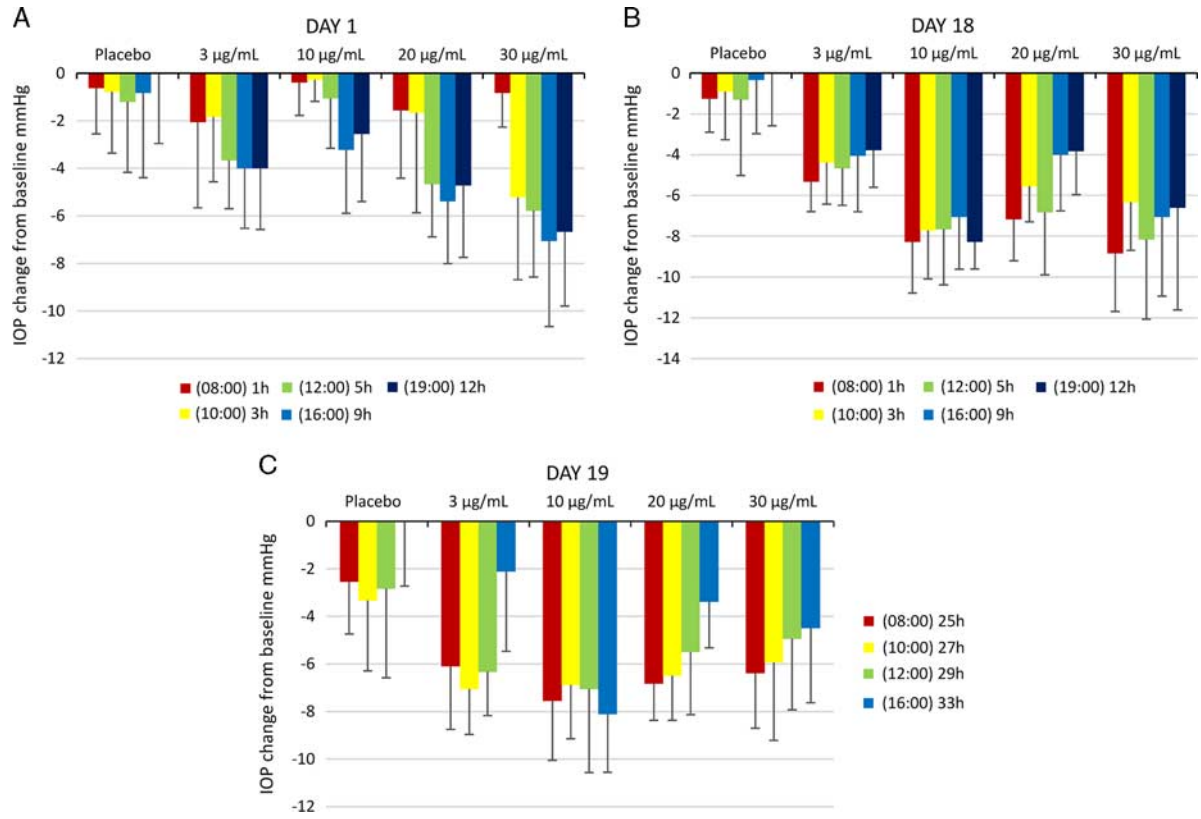


**FIGURE 2.** Mean reductions in intraocular pressure (IOP) (mm Hg ± SD) from baseline at various timepoints on days 1 (A), 18 (B), or 19 (C) following treatment with ONO-9054 3, 10, 20, or 30 µg/mL or placebo. Reduced IOP was sustained for 12 hours following single dose and was still markedly reduced 33 hours postdose (day 19, 16:00) following 14 consecutive days dosing.

18.0 ± 2.1 mm Hg (−19.7% ± 6.7%) for the ONO-9054 3 µg/mL cohort, 15.0 ± 2.0 mm Hg (−34.3% ± 8.2%) for the ONO-9054 10 µg/mL cohort, 16.5 ± 2.1 mm Hg (−24.5% ± 8.3%) for the ONO-9054 20 µg/mL cohort, and 16.5 ± 2.9 mm Hg (−30.4% ± 12.4%) for the ONO-9054 30 µg/mL cohort. On day 18, diurnal IOPs for all subjects displayed statistically significant reductions compared with placebo at all doses (ONO-9054, 3 µg/mL: $P = 0.001$; ONO-9054, 10 µg/mL: $P < 0.0001$; ONO-9054, 20 µg/mL: $P < 0.0001$; ONO-9054, 30 µg/mL: $P < 0.0001$). A statistically significantly greater treatment effect was observed in both the ONO-9054 10 µg/mL ($P = 0.007$) and 30 µg/mL ($P = 0.023$) cohorts compared with the ONO-9054 3 µg/mL cohort.

## Pharmacokinetics

The plasma concentration of ONO-9054 was below the limit of quantification in all subjects who received

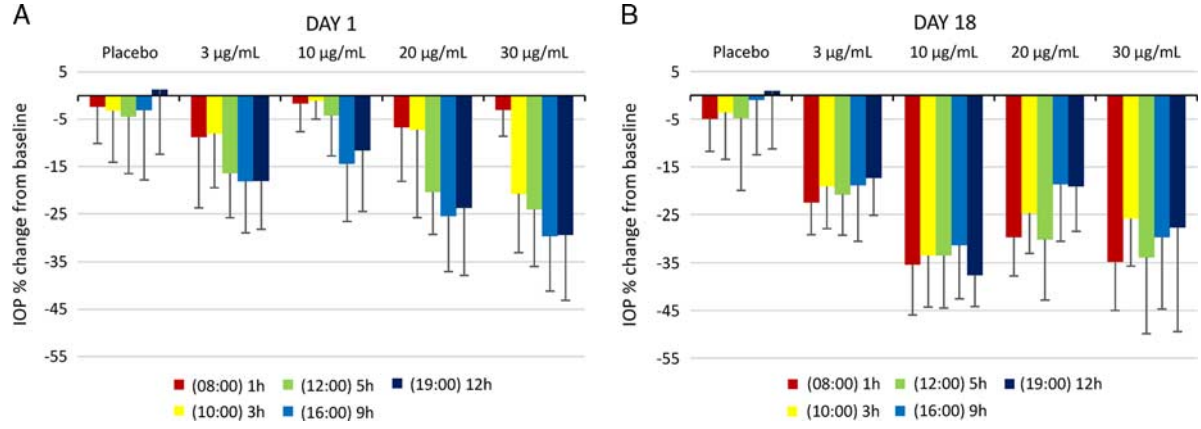


**FIGURE 3.** Percent change in intraocular pressure (IOP) (% ± SD) from baseline at various timepoints on days 1 (A) and 18 (B) following treatment with ONO-9054 3, 10, 20, or 30 µg/mL or placebo. Administration of ONO-9054 resulted in a greater reduction in IOP than placebo after single dose and 14 consecutive days dosing.

**TABLE 2.** Categorical Analysis of Target IOPs on Day 18 at 1 Hour Postdose (08:00)

| Timepoint (Hours Postdose) | Target IOP (mm Hg) | Placebo (N = 12) | ONO-9054 [n/N (%)] 3 µg/mL (N = 9) | 10 µg/mL (N = 9) | 20 µg/mL (N = 9) | 30 µg/mL (N = 9) |
|---|---|---|---|---|---|---|
| 1 | ≤18 | 0/12 (0.0) | 4/9 (44.4) | 8/9 (88.9) | 7/9 (77.8) | 7/9 (77.8) |
| | ≤16 | 0/12 (0.0) | 1/9 (11.1) | 7/9 (77.8) | 4/9 (44.4) | 6/9 (66.7) |
| 3 | ≤18 | 0/12 (0.0) | 4/9 (44.4) | 7/9 (77.8) | 5/9 (55.6) | 5/9 (55.6) |
| | ≤16 | 0/12 (0.0) | 2/9 (22.2) | 5/9 (55.6) | 4/9 (44.4) | 2/9 (22.2) |
| 5 | ≤18 | 1/12 (8.3) | 5/9 (55.6) | 8/9 (88.9) | 7/9 (77.8) | 7/9 (77.8) |
| | ≤16 | 0/12 (0.0) | 2/9 (22.2) | 8/9 (88.9) | 5/9 (55.6) | 6/9 (66.7) |
| 9 | ≤18 | 0/12 (0.0) | 7/9 (77.8) | 8/9 (88.9) | 6/9 (66.7) | 6/9 (66.7) |
| | ≤16 | 0/12 (0.0) | 2/9 (22.2) | 6/9 (66.7) | 4/9 (44.4) | 5/9 (55.6) |
| 12 | ≤18 | 0/12 (0.0) | 5/9 (55.6) | 9/9 (100.0) | 8/9 (88.9) | 6/9 (66.7) |
| | ≤16 | 0/12 (0.0) | 2/9 (22.2) | 8/9 (88.9) | 6/9 (66.7) | 5/9 (55.6) |

IOP indicates intraocular pressure.

ONO-9054 and no pharmacokinetic parameters were calculated.

For ONO-AG-367, median $T_{max}$ for all cohorts was 0.17 hours on days 1 and 18. Plasma mean $T_{½}$ of ONO-AG-367 ranged from 0.41 to 0.67 hours for all cohorts on days 1 and 18. Increases in the plasma mean peak and total exposures of ONO-AG-367 were observed with increased concentrations on both days 1 and 18 (Fig. 5). Both $C_{max}$ and $AUC_{last}$ on days 1 and 18 exhibited approximate dose proportionality across the ONO-9054 dose range of 3 to 30 µg/mL and there was no accumulation following 14 days of dosing across all concentrations.

## Safety and Tolerability

There were no deaths, serious or severe adverse events, and only 1 subject (in the ONO-9054, 30 µg/mL group) experienced an adverse event (bilateral anterior uveitis) that led to study drug discontinuation and withdrawal from the study.

Overall, 17 subjects reported 23 adverse events; 6 who received placebo and 11 who received ONO-9054; all but 2 were considered mild. The proportion of subjects with one or more ocular or systemic adverse events was: 6/12 (50%) in the placebo group, which was greater than the 3 µg/mL treatment group (0/9, 0%), 10 µg/mL treatment group (4/9, 44%), and 20 µg/mL treatment group (2/9, 22.2%). In the 30 µg/mL cohort, the proportion was 5/9 (55.6%), a proportion similar to placebo. The most frequently reported systemic adverse event was headache (3/48), and the most frequently reported ocular adverse events were anterior uveitis (2/48) and vitreous detachment (2/48). There was no

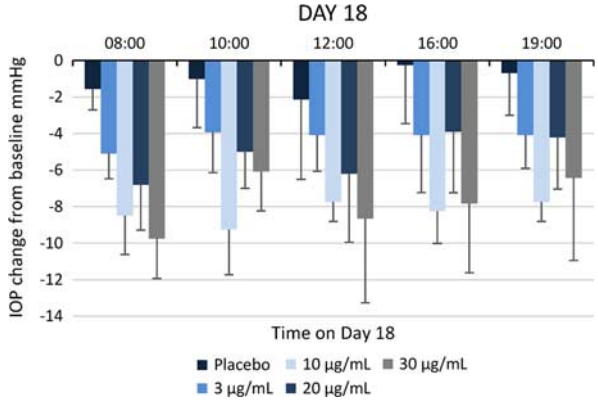


**FIGURE 4.** Mean reductions in intraocular pressure (IOP) (mm Hg ± SD) from baseline at all 5 timepoints on day 18 following 14 consecutive days treatment with ONO-9054 3, 10, 20, or 30 µg/mL or placebo in patients with high baseline values (≥ 24 mm Hg). Reduced IOP was observed in all patients with high baseline values who received ONO-9054.

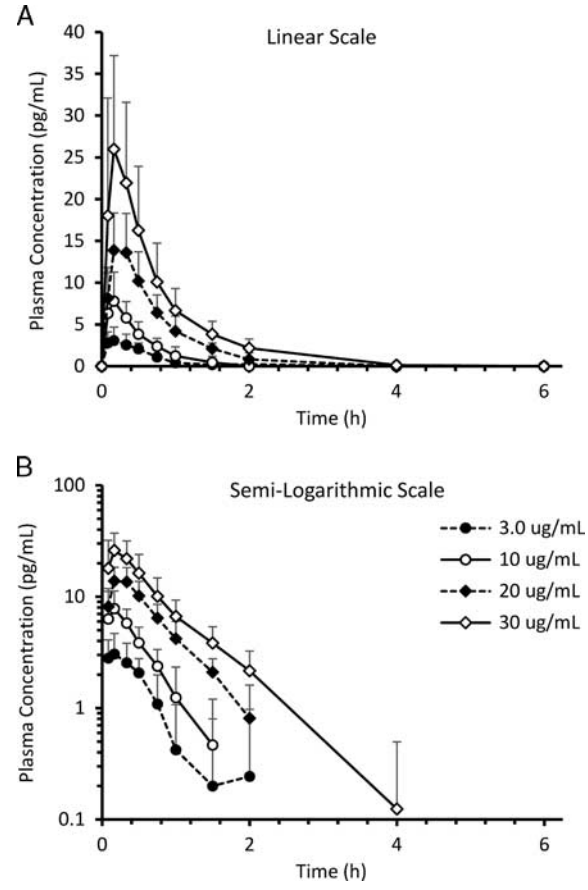


**FIGURE 5.** Mean plasma ONO-AG-367 concentration time profile presented on a linear (A) and semilogarithmic scale (B) of patients receiving ONO-9054 3 µg/mL (○), 10 µg/mL (●), 20 µg/mL (◇), or 30 µg/mL (△). Metabolite displayed a dose-proportionate decrease in plasma concentration over time.

evidence of a dose-response trend for any local (ocular) or systemic adverse event.

One event of moderate intensity presented as bilateral anterior uveitis and was considered by the Investigator to be probably related to the study medication. This occurred on day 8; the subject was discontinued from study medication on the same day and completed all other safety assessments through day 18. The subject was treated with a tapering course of steroid eye drops and the bilateral uveitis was monitored until it resolved without sequelae on day 32. This subject was randomized to receive ONO-9054 30 μg/mL. The second moderate adverse event was anterior uveitis of the right eye which occurred in the ONO-9054 10 μg/mL cohort on day 11. The study drug was withdrawn from the affected eye, which was treated with a tapering course of steroid eye drops and the event resolved without sequelae. The subject completed the study.

Ocular hyperemia occurred acutely on days 1 or 2 after dosing, and in most cases resolved within 24 hours. Of the scores reported on days 1 or 2 postdose, the highest graded score of 2 (moderate hyperemia) was observed in the ONO-9054 20 and 30 μg/mL cohorts. Mean hyperemia scores indicated that redness was mild or absent throughout the study and all hyperemia scores had returned to baseline ranges by follow-up (day 25).

The majority of parameters assessed for ocular tolerability were mild and transient. Severe dryness was reported by 1 subject in the ONO-9054 10 μg/mL cohort predose on day 5. The most common symptoms were itching and dryness. There was no obvious relationship between dose of ONO-9054 and ocular tolerability findings.

Corneal pachymetry revealed that the thickness of the central cornea of 4 subjects was $>600$ μm (placebo n = 1; ONO-9054, 3 μg/mL, n = 1) and 1 subject $<500$ μm (placebo) on day 19, 25 hours postdose. All corneal thicknesses were between 500 and 600 μm at follow-up (day 25). Fifteen subjects had slightly abnormal or abnormal impression cytology scores at follow-up, which was an increase in severity from baseline, although these scores were considered consistent with the age of the study population. There were no clinically significant findings of BCVA, indirect ophthalmoscopy, fundus imaging, or visual field assessments.

## DISCUSSION

This was the first clinical study that investigated the pharmacodynamic potential of ONO-9054 in subjects with early primary OAG or OHT. ONO-9054 is a prodrug that is hydrolyzed to its active prostaglandin receptor agonist form, ONO-AG-367, by esterases known to be present in the cornea and other tissues. Preclinical data suggest that the efficacy of ONO-9054 in reducing IOP may be greater than that of PGAs such as latanoprost,[9,15] the most commonly prescribed single-agent topical therapy for glaucoma. Single doses of ONO-9054 resulted in marked reductions in IOP across all treatment groups that were proportionate with dose concentration. The sustained reduction of IOP in the absence of continued dosing in subjects receiving ONO-9054 10 μg/mL and 30 μg/mL was consistent with the requirements for once-daily administration. This could be attributable to the costimulation by the metabolite ONO-AG-367 of both the $EP_3$ and FP receptors.[9] Following multiple day dosing, all cohorts receiving ONO-9054 demonstrated a reduction in mean IOP, which was sustained even after cessation of drug instillation for the 3 highest doses. It should be noted that the baseline IOP at day −1 after washout of IOP reducing drugs was used throughout as the baseline. Following the single dose part of the study, the 3-day washout of ONO-9054 was not sufficient for the IOP to return to predose levels; however, the day −1 timepoint was considered an appropriate baseline for both parts as it represents the IOP before administration of ONO-9054.

This study was conducted in subjects with elevated IOP; however, studies of other PGAs have used baseline IOP entry criteria for phase II studies are usually higher than those used in this phase I study. One reason for this difference may be that subjects with more severe (mild-moderate) glaucoma and higher untreated IOPs are routinely included in these studies. A meta-analysis of the efficacy of latanoprost revealed that a higher baseline IOP is significantly associated with a greater mean reduction in IOP.[14] To assess the IOP reducing capacity of ONO-9054 in subjects with higher baselines, a subgroup analysis of those with IOP $\geq 24$ mm Hg, 23 hours predose, on day −1 was conducted. Mean percent reductions in IOP from baseline to day 18 were similar or greater in the higher baseline IOP group (Fig. 4 compared with Fig. 2B), although as the sample size in some of the dose groups was low, the relevance of this information is unclear.

Pharmacological studies have shown that drugs applied topically to the eye are only minimally absorbed into the eye (2% to 10%) where they exert their local effect.[16,17] The remainder of the topically applied drug can enter the systemic circulation through the extensive network of conjunctival vessels and through the nasolacrimal duct through the highly vascularized nasal mucosa. Both of these routes are rapid and bypass first pass metabolism. In addition, drug entering the nasolacrimal system may be swallowed and absorbed via the stomach.[16] In these ways a large proportion of drug administered topically (over 80% in some studies)[18] may enter the systemic circulation rapidly, with peak plasma concentrations reached between 5 and 30 minutes after instillation.[17,19]

Plasma concentrations of ONO-9054 were below the assay's limit of quantification in all subjects who received the drug. However, it was possible to characterize the plasma profile of ONO-AG-367. Not only was mean peak concentration reached rapidly, it also declined rapidly with no measureable concentrations after 6 hours on day 1 and 4 hours on day 18 with no accumulation following 14 days of dosing across all doses. As minimal concentrations of active metabolite were measured for very short periods of time following dosing, systemic side effects would not be expected and were not observed.

Current prostaglandin therapies available in the United States, United Kingdom, and Japan include bimatoprost, latanoprost, travoprost, and tafluprost. This class of drugs is recognized as having an excellent systemic safety and tolerability profile. Although there is extensive evidence on the efficacy of the individual prostaglandin drugs, data determining the comparative effectiveness of the 4 drugs are limited, but suggest similar efficacy effects.[7,20] PGAs are associated with ocular adverse effects, which are typically observed after 3 to 6 months of dosing, including ocular hyperemia, stimulation of eyelash growth, iris and periocular pigmentary changes, and prostaglandin associated periorbitopathy.[20–22] These side effects were not reported in this study, although this could possibly be due to the short duration of dosing. With the exception of the highest dose

group, the proportion of subjects with one or more ocular or systemic adverse events was similar to those reported in the placebo group and the majority were mild and 2 were moderate in intensity. All concentrations of ONO-9054 were well tolerated over 2 weeks of dosing.

This study indicates that topical administration of ONO-9054, a novel dual receptor agonist PGA, effectively lowers IOP in subjects with early primary OAG or OHT following single and multiple day dosing, which was sustained for at least 24 hours following 2 weeks of consecutive once-daily morning dosing.

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