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Phase 2b, Randomized, 3-Month, Dose-Finding Study of Sepetaprost in Patients with Primary Open-Angle Glaucoma or Ocular Hypertension: The ANGEL Study

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Abstract

Purpose: This phase 2b, randomized, observer-masked, placebo- and active-controlled, parallel-group, multinational (USA and Japan), multicenter study (NCT03216902) assessed the optimal dose of sepetaprost ophthalmic solution in patients with primary open-angle glaucoma or ocular hypertension.

Methods: After washout, patients ≥18 years (USA) or ≥20 years of age (Japan) received once-daily sepetaprost for 3 months [0.0005% ($n=43$); 0.001% ($n=43$); 0.002% ($n=44$); and 0.003% ($n=45$)], latanoprost 0.005% ($n=44$) or placebo until week 6, followed by sepetaprost 0.003% until month 3 ($n=22$). Safety assessments included adverse event (AE) occurrence.

Results: Baseline mean diurnal intraocular pressure (IOP) was 24.3 mmHg for latanoprost and ranged between 24.1 and 24.5 mmHg for the sepetaprost groups. Sepetaprost 0.002% had the lowest IOP at each month 3 time point (9:00 AM; 1:00 PM; 5:00 PM) of all sepetaprost concentrations (mean ± standard error: 17.6 ± 0.5; 17.4 ± 0.4; 16.7 ± 0.4 mmHg); similar values were observed with latanoprost (18.1 ± 0.6; 17.3 ± 0.5; 17.2 ± 0.5 mmHg). A positive dose–response relationship was observed with the 3 lower sepetaprost doses; sepetaprost 0.002% had numerically greater IOP-lowering effects than sepetaprost 0.003%. All sepetaprost doses had statistically significantly greater IOP reductions from baseline versus placebo at week 6 ($P<0.0001$). This IOP-lowering effect was consistent between Japan- and USA-based patients. Most AEs were mild and occurred numerically less frequently with sepetaprost 0.002% (34.1%) versus latanoprost (50.0%). The most frequently reported AE was conjunctival hyperemia.

Conclusion: In this study, sepetaprost 0.002% was the optimal concentration, showing comparable IOP-lowering efficacy and safety with latanoprost 0.005%. Most AEs were mild; occurrence was numerically lower with sepetaprost 0.002% than latanoprost 0.005%.

Keywords: FP and EP3 dual agonist, glaucoma, intraocular pressure, ocular hypertension, open-angle glaucoma, sepetaprost

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Introduction

Glaucoma is a group of optic neuropathies characterized by degeneration of retinal ganglion cells, optic nerve damage, and visual field loss; it is the leading cause of irreversible blindness worldwide.[1,2] The only proven method to treat primary open-angle glaucoma (POAG) and ocular hypertension (OHT) is through the reduction of intraocular pressure (IOP), occurring either through the increase of aqueous humor outflow or reduction in aqueous humor production.[1,3–12] A variety of topical hypotensive agents have been developed to lower IOP, including prostanoid FP receptor agonists (also known as prostaglandin analogs), beta-blockers, carbonic anhydrase inhibitors, alpha agonists, Rho kinase (ROCK) inhibitors, and EP2 agonists.[3,13–16]

FP receptor agonists, such as latanoprost, travoprost, bimatoprost, and tafluprost, lower IOP by increasing aqueous humor outflow, primarily through the uveoscleral outflow.[17] FP receptor agonists are currently the most commonly used first-line therapy to treat POAG, because of their effective IOP-lowering ability, convenience of once-daily (QD) dosing, limited systemic side effects, and good tolerability.[1,3,13,18,19]

However, despite being the most effective monotherapy for glaucoma treatment, it is estimated that 35%–40% of patients require adjunctive treatment to effectively manage their IOP.[20–22] Fixed-dose combinations of different ocular hypotensives have been utilized to improve adherence and achieve improvements in IOP reduction compared with either monotherapy alone.[23,24] In addition, the percentage of patients who are inadequate responders to currently approved FP agonists (IOP reductions of ≤15% from baseline) has been estimated to be up to 10%.[25] Therefore, there is an unmet need for POAG and OHT treatments with novel mechanisms of action that produce sustained and clinically significant reduction of IOP.

Sepetaprost [previously named ONO-9054 (Ono Pharmaceutical, Osaka, Japan) and DE-126 (Santen, Osaka, Japan)] is a novel investigative prodrug that is rapidly hydrolyzed by esterases to its active metabolite, a dual agonist of the FP and EP3 receptors.[26,27] It has been suggested that targeting both the FP and EP3 receptors simultaneously can enhance IOP reduction versus targeting only the FP receptor.[28] In preclinical studies, single and repeat administration of sepetaprost for 7 days caused IOP reductions in normotensive monkeys.

The maximum IOP reductions on day 7 with sepetaprost 0.003% were statistically significantly greater than those observed with latanoprost 0.005% or travoprost 0.004% in the monkey model.[27] In addition, a 4-week (2 14-day crossover regimens), single-center study comparing the effect of morning versus evening dosing of sepetaprost 0.003% in patients with POAG or OHT found that sepetaprost reduced IOP and was well tolerated regardless of dosing schedule.[29]

In a previous phase 1, randomized, double-masked, 14-day dose-escalating study of sepetaprost in adults with POAG or OHT, a single instillation of sepetaprost, administered at a dose of 0.0003%, 0.001%, 0.002%, or 0.003%, led to effective IOP lowering from baseline, which was sustained for ≥24 hours, with the greatest effect observed with sepetaprost 0.003% (22.9 ± 4.0 to 15.9 ± 2.3 mmHg). With multiple-day dosing, peak IOP reduction was achieved with sepetaprost 0.001% (23.3 ± 0.6 to 15.1 ± 2.4 mmHg).[26] Given the mixed results in identifying the optimal dose of sepetaprost, a longer study duration with a larger sample size was considered necessary to determine the optimal dose of sepetaprost in patients with POAG and OHT.

This phase 2b dose-finding study aimed to determine the optimal dose of sepetaprost by assessing the efficacy and safety of 4 concentrations of sepetaprost ophthalmic solution (0.0005%, 0.001%, 0.002%, and 0.003%) compared with placebo, as well as with the standard of care, latanoprost 0.005%, over 3 months of treatment in patients with POAG or OHT. The study also assessed the efficacy of all sepetaprost concentrations versus placebo (up to 6 weeks after treatment initiation) and the dose–response relationship of sepetaprost with IOP reduction.

Methods

Study design

This was a phase 2b, randomized, observer-masked, placebo- and active-controlled, parallel-group, multinational multicenter study (ClinicalTrials.gov Identifier: NCT03216902), which took place at 26 study centers in Japan and 11 in the USA from August 2017 to February 2018. The study was conducted in accordance with Good Clinical Practice as required by US Food and Drug Administration regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines.[30] Compliance with these requirements is consistent with the ethical principles that have their origins in the Declaration of Helsinki.[31] Institutional review board approval was obtained for each site. Patients provided written informed consent before their enrollment in the study.

Study design information is shown in Supplementary Fig. S1. At the screening visit, patients were selected per inclusion and exclusion criteria. Eligible patients were instructed to discontinue all IOP-lowering medications for the relevant washout period. The mandatory washout requirements were miotics and oral/topical carbonic anhydrase inhibitors (7 days); alpha agonists and alpha-beta agonists (14 days); and beta antagonists (including alpha-beta-blockers), alpha antagonists (alpha-1-blockers), FP agonists, and ROCK inhibitors (28 days). For combination medications, the longest washout period out of the individual components applied. If a patient did not require washout, a period of ≥1 day was required between screening and baseline visits (≥7 days if the patient used contact lenses). Final eligibility was determined at visit 2 (baseline) after washout was completed.

Randomization and masking

A central randomization schedule generated and implemented by an independent biostatistician was used to assign patients to treatment groups and was administered using an Interactive Response Technology system [Medidata BALANCE (New York, USA)]; Japan- and USA-based patients were allocated separately to ensure balance, using country as the stratifying factor. Patients were randomized in a ratio of 2:2:2:2:2:1 to receive sepetaprost 0.0005%, sepetaprost 0.001%, sepetaprost 0.002%, sepetaprost 0.003%, and latanoprost 0.005% for 3 months, or placebo for the first 6 weeks followed by sepetaprost 0.003% for the final 6 weeks, respectively.

Patients self-administered 1 drop of the study medication in each eye QD at 9:00 PM ±60 minutes. All sepetaprost concentrations and placebo had identical containers, but the latanoprost 0.005% container was different in appearance. As a result, the study was observer masked, whereby only an authorized study staff member, who was not the investigator/the examiner, was permitted to dispense and/or collect study medication. Patients were instructed not to show the study medication bottles to the investigator, the examiner, or other patients. The latanoprost 0.005% containers were overlabeled and packaged in the same secondary package as the test treatments. The masking of patients in the placebo group was maintained, owing to the identical containers, when they switched to sepetaprost 0.003% at week 6. Measures to facilitate compliance are in Supplementary Data S1.

Patients

Eligible patients were ≥18 years (USA) or ≥20 years of age (Japan) and had a diagnosis of POAG or OHT in both eyes. At all IOP measurement time points at baseline (visit 2; 9:00 AM, 1:00 PM, and 5:00 PM), an IOP ≥22 mmHg in at least 1 eye and ≤34 mmHg in both eyes were required, as well as corrected visual acuity of +0.60 logMAR or better in each eye, central corneal thickness between ≥480 and ≤620 μm in each eye, and an anterior chamber angle grade (Shaffer scale) of ≥2 in each eye.

The exclusion criteria included a history of ocular surgery specifically intended to lower IOP; any ocular surgery/laser treatment within the 90 days before screening or throughout the study in either eye; and initiation or modification of any systemic or topical medication known to affect IOP within 30 days before screening. Full inclusion/exclusion criteria are available on request.

Assessments and endpoints

IOP was assessed at baseline and each follow-up visit at 3 time points to account for the known diurnal fluctuation [9:00 AM, 1:00 PM, and 5:00 PM (±60 minutes)] using a Goldmann applanation tonometer. At each scheduled time point for IOP assessment, 2 consecutive IOP measurements were obtained, and the mean was used in the analysis; if the 2 measurements differed by ≥3 mmHg, a third IOP measurement was obtained, and the median was used. The policies for bias mitigation and tonometer calibration are in Supplementary Data S2.

The primary efficacy endpoint was the IOP at each time point at month 3. The key secondary efficacy endpoint was IOP at week 6 (significance vs. placebo; at all time points). Secondary efficacy endpoints included IOP at each visit and scheduled time point, mean diurnal IOP, and change and percentage change in mean diurnal IOP from baseline. Response rates at month 3, including the percentage of patients with a mean diurnal IOP reduction from baseline of ≥20%, ≥25%, and ≥30%, and the percentage of patients with a mean diurnal IOP ≤18 mmHg, were also assessed. Safety assessments included adverse event (AE) occurrence.

Ocular safety assessments consisted of biomicroscopy assessment of the anterior segment of the eye, corrected visual acuity, ophthalmoscopy assessment of the posterior segment of the eye, central corneal thickness measurement (in both eyes using any pachymeter, including optical pachymeter, ultrasound pachymeter, or optical coherence tomography, with the same pachymeter being used at the same site for consistency), ocular symptom severity scores [questionnaire assessing each of 6 ocular symptoms using a 4-point ordered categorical scale from 0 to 3 (none, mild, moderate, and severe): burning/stinging, foreign body sensation, tearing, itching, photophobia, and eye pain], and iris, eyelash, and eyelid change assessments (photographs).

Statistical methods

Efficacy analyses were based on the study eye data for the full analysis set (FAS). This population included patients who met all inclusion criteria, received ≥1 dose of any study medication, and recorded ≥1 postbaseline efficacy assessment. The study eye was the eye that qualified per eligibility criteria at visit 2. If both eyes met eligibility criteria, the eye with the higher mean diurnal IOP at baseline was designated as the study eye, and in instances where both eyes had the same mean diurnal IOP, the right eye was selected. Safety analyses were based on the safety population, which included all randomized patients who received ≥1 dose of any study medication.

Assuming that the minimal expected treatment difference in IOP between the optimal sepetaprost dose and placebo at week 6 across the 3 scheduled time points was −5.1 mmHg, and the standard deviation of the difference was 3.9 mmHg, with a 2:1 randomization allocation ratio and a 10% dropout rate, a sample size of 40 for each sepetaprost arm and 20 for the placebo arm would provide 92% power to detect such a difference at all time points using a *t*-test (2 sided, $\alpha = 0.0125$ adjusted by Bonferroni correction).

Comparisons of the IOP-lowering effects of sepetaprost (all concentrations) and latanoprost 0.005% were based on descriptive summaries. Comparisons of the IOP-lowering effect of sepetaprost (all concentrations; all postbaseline visits) and placebo (each postbaseline visit up to week 6) were based on a mixed-effect model for repeated measures, which included treatment, country, visit, and treatment by visit interaction as fixed effects, baseline IOP as a covariate, and patient as a random effect.

Within-patient errors were modeled using an unstructured covariance matrix. Least-squares means, differences between each sepetaprost concentration and placebo least-squares mean, and associated 95% confidence intervals and *P*-values were provided. For the IOP at week 6 (key secondary endpoint), adjusted *P*-values from the Hochberg step-up procedure were also provided to control the overall type I error rate at the 0.05 level (2 sided) across the comparisons of sepetaprost (all concentrations) with placebo. Descriptive summaries by country of enrollment (Japan and USA) were used to assess the homogeneity of treatment effects. Safety data were summarized descriptively.

Results

Patient demographics and baseline characteristics

The study was initiated on August 8, 2017, and concluded on February 27, 2018. A total of 301 patients were assessed for eligibility, and 241 were randomized to treatment groups (FAS; 114 from Japan-based and 127 from USA-based centers); patient disposition is shown in Fig. 1. A total of

8 patients (3%) prematurely discontinued from the study [3 (1%) owing to AEs; 2 (1%) owing to lack of efficacy; and 3 (1%) owing to protocol deviation]. Two patients discontinued because of lack of efficacy during the placebo treatment period. At each study visit, 84%–97% of patients reported 100% compliance with their assigned treatment regimens; however, patient-reported compliance is not an objective measure and may be inflated.

Baseline characteristics and demographics were evenly distributed across the 6 treatment groups (Table 1). Mean IOP at baseline was slightly lower in patients enrolled in Japan versus those enrolled in the USA.

Efficacy

In this study, treatment with the sepetaprost 0.002% concentration resulted in the numerically lowest mean ± standard error (SE) IOP of the 4 sepetaprost concentrations at all time points at month 3 (primary efficacy endpoint); this effect was sustained at every visit and time point from week 1 through month 3 (Table 2).

The mean ± SE IOP observed for sepetaprost 0.002% was similar to that observed for latanoprost 0.005% across all time points, including at month 3 overall (Table 2; Fig. 2). A positive dose–response relationship was observed across the 3 lower concentrations of sepetaprost (0.0005%, 0.001%, and 0.002%), but the sepetaprost 0.003% group did not exhibit greater IOP-lowering effects than the 0.002% concentration. The dose–response trend observed at month 3 was similar to that at week 6. In addition, the sepetaprost 0.002% concentration resulted in a mean ± SD IOP change from baseline similar to that with latanoprost 0.005% from week 1 to month 3 (Supplementary Table S1).

At week 6, mean diurnal IOP and absolute and percentage change from baseline in IOP at each time point and visit were statistically significantly lower with all 4 sepetaprost concentrations compared with placebo (all $P < 0.0001$; Table 2 and Supplementary Table S1). This effect was sustained at every visit and time point from week 1 through week 6 (the last visit at which placebo was included). At week 6, of the 4 sepetaprost concentrations, the sepetaprost 0.002% concentration resulted in the numerically lowest mean ± SE IOP at the 1:00 PM and 5:00 PM time points.

For all response criteria (≥20%, ≥25%, or ≥30% reduction in mean diurnal IOP at month 3), sepetaprost 0.002% resulted in the numerically greatest response rates (84%, 64%, and 36%, respectively) of the sepetaprost concentrations assessed (Supplementary Data S3; Supplementary Fig. S2). Sepetaprost 0.002% also had the numerically highest percentage of patients with a reduction in IOP to ≤18 mmHg (61%) at month 3 of all sepetaprost concentrations (Supplementary Data S3; Fig. 3).

For each efficacy endpoint, the IOP-lowering effects of sepetaprost and latanoprost were consistent between patients enrolled in the USA and those enrolled in Japan. The mean ± SD diurnal IOP at baseline across the 6 treatment groups for the Japan- and USA-based populations ranged from 22.9 ± 0.8 to 23.6 ± 2.0 mmHg and 24.8 ± 1.2 to 25.7 ±

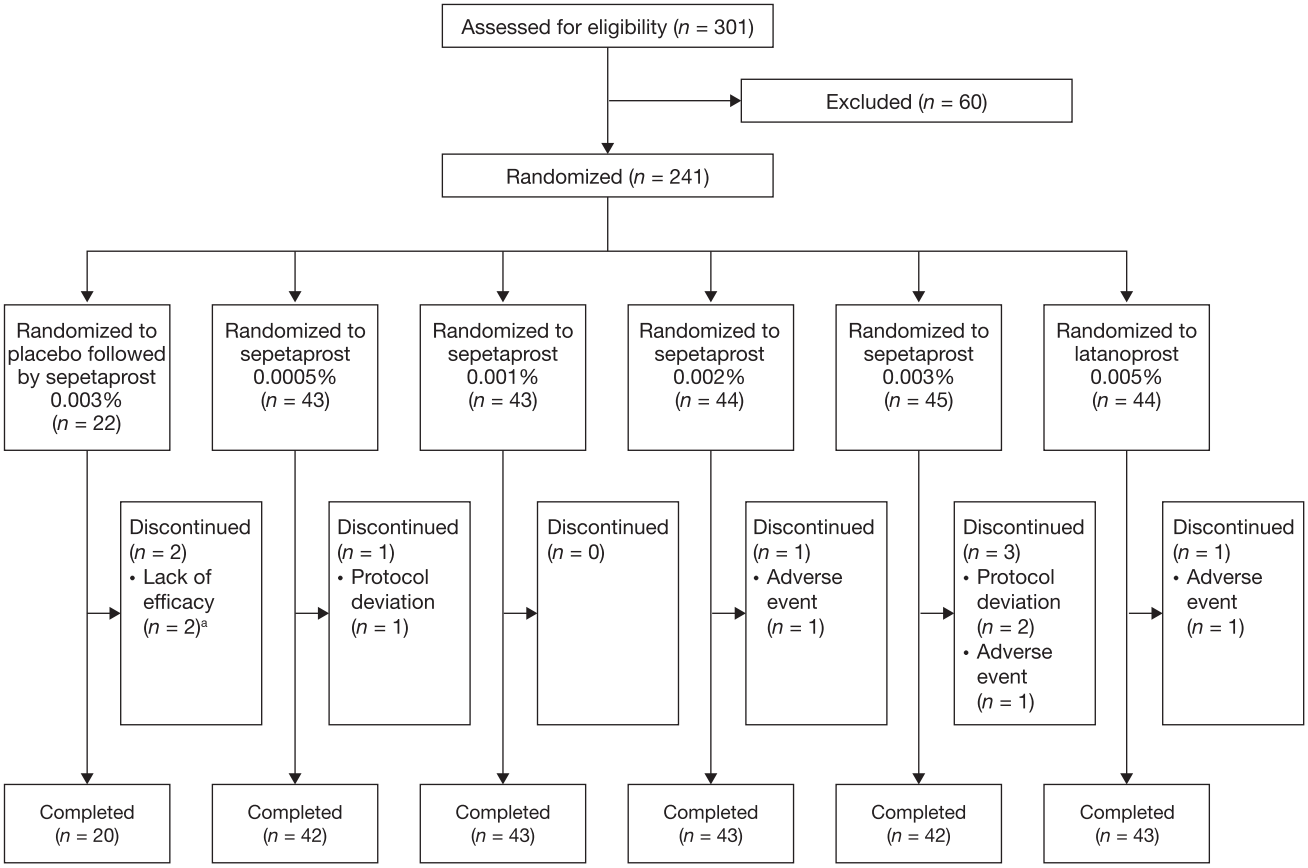

FIG. 1. Patient disposition. [a]Both patients who discontinued because of lack of efficacy withdrew during the placebo treatment period.

Table 1. Baseline Characteristics and Demographic Information (Full Analysis Set)

	Placebo to SEP 0.003%[a] *(n=22)*	*LAT 0.005% (n=44)*	*SEP 0.0005% (n=43)*	*SEP 0.001% (n=43)*	*SEP 0.002% (n=44)*	*SEP 0.003% (n=45)*
Country of enrollment, *n* (%)						
Japan	11 (50.0)	21 (47.7)	20 (46.5)	20 (46.5)	21 (47.7)	21 (46.7)
USA	11 (50.0)	23 (52.3)	23 (53.5)	23 (53.5)	23 (52.3)	24 (53.3)
Mean age, years ± SD	63.2 ± 11.2	64.4 ± 9.3	65.5 ± 13.3	63.7 ± 9.4	61.0 ± 11.8	63.8 ± 11.8
Min, max, years	39, 79	40, 79	26, 87	47, 82	33, 79	32, 87
≥65 years, *n* (%)	11 (50.0)	25 (56.8)	27 (62.8)	19 (44.2)	22 (50.0)	26 (57.8)
Male, *n* (%)	9 (40.9)	20 (45.5)	17 (39.5)	21 (48.8)	19 (43.2)	20 (44.4)
Primary diagnosis,[b] *n* (%)						
POAG	9 (40.9)	26 (59.1)	22 (51.2)	24 (55.8)	21 (47.7)	23 (51.1)
OHT	13 (59.1)	18 (40.9)	21 (48.8)	19 (44.2)	23 (52.3)	22 (48.9)
Mean diurnal IOP, mmHg ± SD	24.5 ± 2.3	24.3 ± 2.0	24.4 ± 2.3	24.2 ± 2.1	24.1 ± 2.2	24.2 ± 1.7
Japan	23.2 ± 1.1	23.4 ± 1.8	23.4 ± 1.2	23.6 ± 2.0	22.9 ± 0.8	23.4 ± 1.8
USA	25.7 ± 2.6	25.1 ± 1.8	25.2 ± 2.8	24.8 ± 2.0	25.3 ± 2.5	24.8 ± 1.2
9:00 AM,[b] mmHg ± SD	25.0 ± 2.7	25.0 ± 2.9	24.9 ± 2.6	24.9 ± 2.5	24.8 ± 2.9	24.7 ± 2.3
1:00 PM,[b] mmHg ± SD	24.0 ± 1.9	24.2 ± 2.2	24.5 ± 2.6	24.2 ± 2.4	24.1 ± 2.6	24.3 ± 2.2
5:00 PM,[b] mmHg ± SD	24.5 ± 2.9	23.5 ± 1.8	23.8 ± 2.4	23.6 ± 2.0	23.6 ± 2.3	23.6 ± 1.9
Mean CCT,[b] μm ± SD	552.4 ± 39.7	555.6 ± 31.5	551.5 ± 33.7	568.1 ± 28.7	549.1 ± 27.6	555.3 ± 30.9
Mean VA, logMAR score ± SD	0.006 ± 0.0768	0.013 ± 0.0874	0.020 ± 0.1027	0.029 ± 0.1339	0.019 ± 0.1144	–0.002 ± 0.1022
Glaucomatous optic nerve findings,[b] *n* (%)						
Mild	7 (31.8)	15 (34.1)	16 (37.2)	15 (34.9)	11 (25.0)	14 (31.1)
Moderate	1 (4.5)	4 (9.1)	2 (4.7)	3 (7.0)	5 (11.4)	4 (8.9)
Prior use of IOP-lowering medication(s),[b] *n* (%)						
None	8 (36.4)	14 (31.8)	10 (23.3)	10 (23.3)	14 (31.8)	14 (31.1)
Beta-adrenergic antagonist	1 (4.5)	11 (25.0)	15 (34.9)	11 (25.6)	6 (13.6)	14 (31.1)
Prostamide or PGA	11 (50.0)	21 (47.7)	24 (55.8)	25 (58.1)	25 (56.8)	20 (44.4)
Alpha-adrenergic agonist	1 (4.5)	0	4 (9.3)	2 (4.7)	2 (4.5)	5 (11.1)
CAI	2 (9.1)	8 (18.2)	8 (18.6)	10 (23.3)	4 (9.1)	5 (11.1)
ROCK inhibitor	1 (4.5)	0	1 (2.3)	0	0	0

[a]Placebo to SEP 0.003% arm received placebo by week 6, then sepetaprost 0.003% from week 6 to month 3.
[b]Data from study eye (FAS).
CAI, carbonic anhydrase inhibitor; CCT, central corneal thickness; FAS, full analysis set; IOP, intraocular pressure; LAT, latanoprost; OHT, ocular hypertension; PGA, prostaglandin analog; POAG, primary open-angle glaucoma; ROCK, Rho kinase; SD, standard deviation; SEP, sepetaprost; VA, visual acuity.

Table 2. Least Squares Mean[a] ± Standard Error Intraocular Pressure by Analysis Visit and Time Point (Full Analysis Set)

	Placebo to SEP 0.003%[b] *(n = 22)*	*LAT 0.005% (n = 44)*	*SEP 0.0005%*[c] *(n = 43)*	*SEP 0.001%*[c] *(n = 43)*	*SEP 0.002%*[c] *(n = 44)*	*SEP 0.003%*[c] *(n = 45)*
Mean ± SE IOP, mmHg (baseline)						
9:00 AM	25.0 ± 0.6	25.0 ± 0.4	24.9 ± 0.4	24.9 ± 0.4	24.8 ± 0.4	24.7 ± 0.3
1:00 PM	24.0 ± 0.4	24.2 ± 0.3	24.5 ± 0.4	24.2 ± 0.4	24.1 ± 0.4	24.3 ± 0.3
5:00 PM	24.5 ± 0.6	23.5 ± 0.3	23.8 ± 0.4	23.6 ± 0.3	23.6 ± 0.3	23.6 ± 0.3
LS mean ± SE IOP, mmHg (week 1)						
9:00 AM	22.8 ± 0.6	17.6 ± 0.4	19.4 ± 0.4	18.8 ± 0.4	18.1 ± 0.4	18.1 ± 0.4
1:00 PM	22.8 ± 0.6	17.4 ± 0.4	18.7 ± 0.5	18.6 ± 0.4	17.1 ± 0.4	17.6 ± 0.4
5:00 PM	21.4 ± 0.6	17.4 ± 0.4	18.1 ± 0.4	18.5 ± 0.4	16.9 ± 0.4	17.2 ± 0.4
LS mean ± SE IOP, mmHg (week 2)						
9:00 AM	23.2 ± 0.7	17.6 ± 0.5	19.4 ± 0.5	18.7 ± 0.5	17.9 ± 0.5	18.3 ± 0.5
1:00 PM	22.4 ± 0.6	17.4 ± 0.4	18.1 ± 0.4	18.1 ± 0.4	17.3 ± 0.4	17.6 ± 0.4
5:00 PM	21.8 ± 0.6	16.9 ± 0.4	18.1 ± 0.4	17.8 ± 0.4	16.7 ± 0.4	17.3 ± 0.4
LS mean ± SE IOP, mmHg (week 6)						
9:00 AM	23.2 ± 0.7	17.9 ± 0.5	19.0 ± 0.5	18.5 ± 0.5	18.7 ± 0.5	18.7 ± 0.5
1:00 PM	22.2 ± 0.6	17.1 ± 0.4	18.2 ± 0.4	17.9 ± 0.4	17.3 ± 0.4	17.4 ± 0.4
5:00 PM	21.6 ± 0.6	16.8 ± 0.4	17.8 ± 0.4	17.9 ± 0.4	16.6 ± 0.4	17.4 ± 0.4
LS mean ± SE IOP, mmHg (month 3)						
9:00 AM		18.1 ± 0.5	19.7 ± 0.5	19.1 ± 0.5	17.6 ± 0.5	19.2 ± 0.5
1:00 PM		17.3 ± 0.4	18.4 ± 0.4	18.1 ± 0.4	17.4 ± 0.4	18.6 ± 0.4
5:00 PM		17.2 ± 0.4	18.2 ± 0.4	17.8 ± 0.4	16.7 ± 0.4	17.9 ± 0.4

[a]LS means are obtained by fitting an MMRM model to the IOP at each time point. The model includes treatment, country, visit, and treatment-by-visit interaction as fixed effects, with baseline IOP as a covariate. Patient is a random effect, and within-patient errors are modeled using an unstructured covariance matrix.
[b]Placebo to SEP 0.003% arm received placebo by week 6, then sepetaprost 0.003% from week 6 to month 3.
[c]$P < 0.0001$ for all sepetaprost concentrations versus placebo at all time points from week 1 to 6.
LS, least squares; MMRM, mixed model for repeated measures; SE, standard error.

2.6 mmHg, respectively. At month 3, mean ± SD diurnal IOP was comparable between the 2 populations (16.6 ± 2.3 to 18.5 ± 2.7 mmHg in Japan and 17.8 ± 2.6 to 19.3 ± 3.6 mmHg in the USA) (Supplementary Table S2).

Safety

Safety data are shown in Table 3. Most AEs were mild in severity. There was 1 serious nonocular AE and 1 severe nonocular AE reported, neither of which was considered related to the study drug or occurred while the patients were receiving the study drug. Three patients experienced AEs leading to discontinuation: 1 patient from the latanoprost 0.005% group withdrew because of sudden hearing loss (not considered to be treatment related), 1 patient from the sepetaprost 0.002% group withdrew because of conjunctival hyperemia and conjunctival edema (not considered to be treatment related), and 1 patient from the sepetaprost 0.003% group withdrew because of treatment-related allergic conjunctivitis.

These AEs either resolved or were resolving at the last follow-up. The type and frequency of AEs were similar between all sepetaprost populations (45.1%) and the latanoprost population (50.0%), while the incidence of AEs with sepetaprost 0.002% was 34.1%. Similarly, suspected adverse reactions (SARs) occurred with a frequency of 20.5% in the sepetaprost 0.002% treatment group, 22.6% in the total sepetaprost population, and 29.5% in the latanoprost group. There was no relationship between sepetaprost dose and SAR or AE incidence.

The most frequently observed AE was conjunctival hyperemia, which occurred with a frequency of 20.5% in the sepetaprost 0.002% group and 27.3% in the latanoprost group. The overall percentage of patients with at least 1 appearance-altering AE (growth of eyelashes, blepharal pigmentation, eyelash thickening, and iris hyperpigmentation) reported was 2.3% in the sepetaprost 0.002% group and 6.8% in the latanoprost 0.005% group.

No safety issue was identified by ocular safety assessments. Three patients (sepetaprost 0.002%: 2 and sepetaprost 0.003%: 1) experienced a 2-unit worsening of conjunctival hyperemia and/or anterior chamber cell severity scores from baseline; all but one of these occurred before month 3 and had resolved or declined in severity by study conclusion (Supplementary Data S4). One patient in the sepetaprost 0.003% group experienced reduced visual acuity at week 6, which had resolved without intervention at month 3. The most frequently reported symptoms from ocular symptom severity scores were mild-to-moderate itching, tearing, and burning/stinging, and were reported as worsening from baseline in <10% of patients for any given combination of treatment, dose, and follow-up visit.

Assessment of appearance-altering effects found that 1 patient had a change in iris color with sepetaprost 0.003%. A total of 12 patients (sepetaprost 0.0005%: $n = 4$; sepetaprost 0.001%: $n = 3$; sepetaprost 0.003%: $n = 2$; and latanoprost 0.005%: $n = 3$) had an increase from baseline in at least 1 of the following effects: eyelash length, thickness, pigment, number, and/or eyelid pigmentation or hair growth; a sepetaprost dose-related trend was not observed.

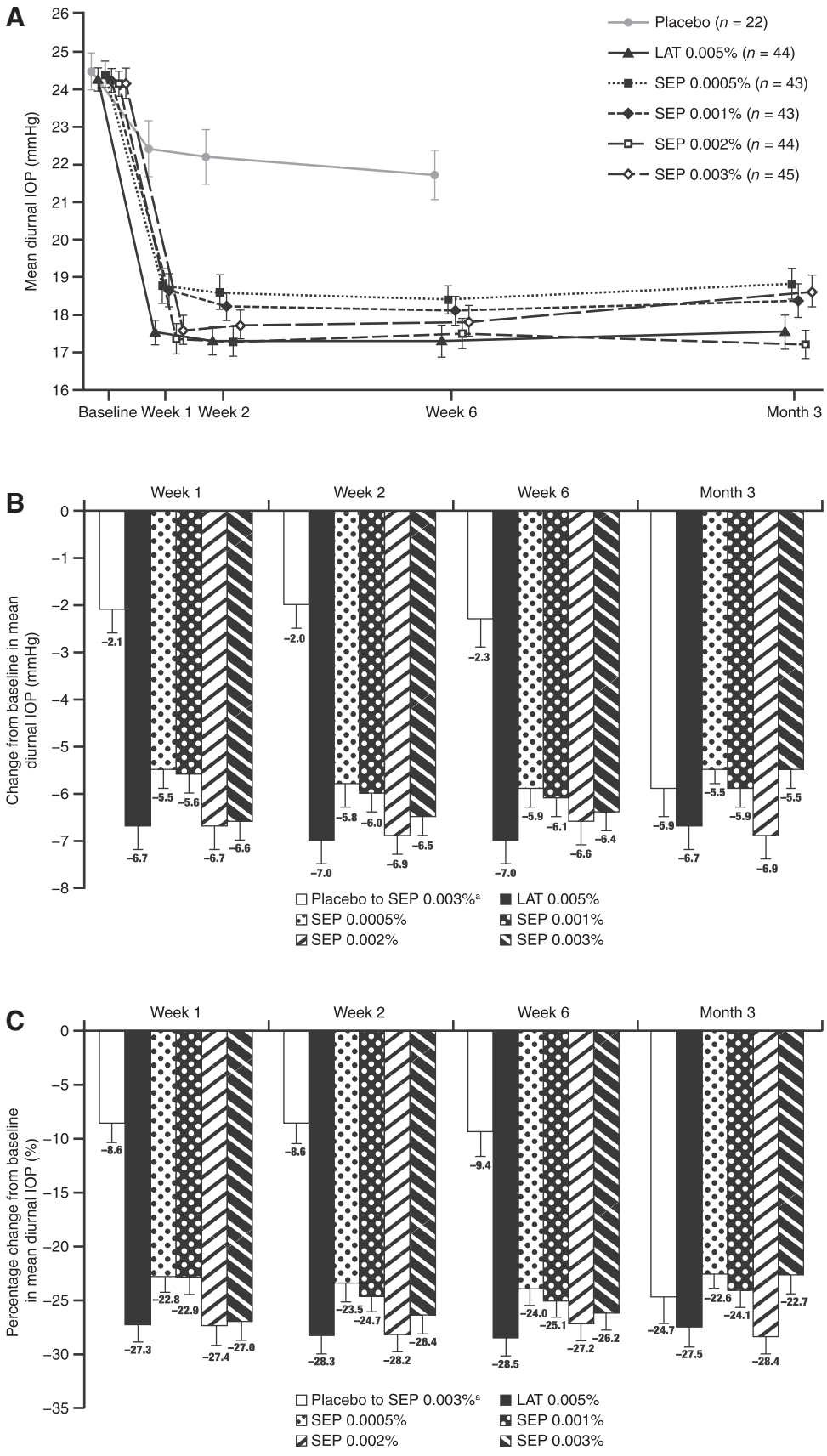

FIG. 2. Mean ± SE diurnal IOP (**A**), and mean change (**B**) and percentage change (**C**) in diurnal IOP from baseline by analysis visit (FAS). [a]Placebo to SEP 0.003% arm received placebo by week 6, then sepetaprost 0.003% from week 6 to month 3. FAS, full analysis set; IOP, intraocular pressure; LAT, latanoprost; SE, standard error; SEP, sepetaprost.

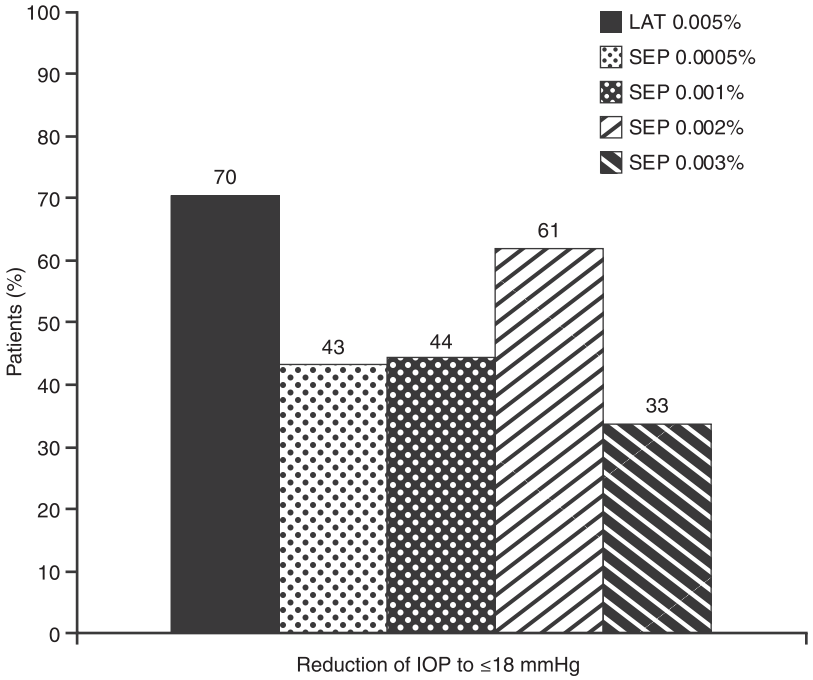

FIG. 3. Percentage of patient population with reduction to ≤18 mmHg from baseline in mean diurnal IOP in the study eye (FAS; month 3).

Mean changes in central corneal thickness ± SD from baseline to month 3 were minimal, with a value of −4.4 ± 9.9 μm for latanoprost and a range of −7.9 ± 15.6 μm to 0.7 ± 11.3 μm across the sepetaprost treatment groups.

The distribution of SARs for the sepetaprost 0.002% group, the total sepetaprost groups, and the latanoprost 0.005% group was similar between Japan- and USA-based patients (Japan: 19.0%, 23.7%, and 23.8% and USA: 21.7%, 21.6%, and 34.8%). The distribution of AEs across these same groups was 28.6%, 45.2%, and 42.9% for Japan-based patients and 39.1%, 45.1%, and 56.5% for USA-based patients.

Discussion

In this study, sepetaprost, a dual agonist of the FP and EP3 receptors, was efficacious at all concentrations assessed, and provided sustained IOP reductions in patients with POAG or OHT. Sepetaprost 0.002% was identified as the optimal dose for IOP lowering, which is within the range of potential optimal doses (0.001%–0.003%) identified in previous studies.[26,28] This study had a larger patient population and longer study duration; therefore, given the alignment of these data with previous studies, sepetaprost 0.002% may be considered the optimal dose.

A positive dose–response relationship was generally observed across the 3 lower concentrations of sepetaprost, but sepetaprost 0.003% did not outperform sepetaprost 0.002% in IOP-lowering efficacy. It has been shown that the IOP-lowering dose–response of other FP agonists such as latanoprost and bimatoprost also either plateaus or numerically decreases at higher doses in patients with OHT and POAG.[32,33]

All sepetaprost study concentrations demonstrated a stable, clinically significant IOP reduction from baseline over 3 months. All doses of sepetaprost statistically significantly reduced IOP from baseline versus placebo at week 6 ($P < 0.0001$ for all). The IOP-lowering effect and responder rates (≥20%, ≥25%, and ≥30% IOP reduction) of sepetaprost 0.002% were similar to those observed for latanoprost 0.005% at month 3; however, this study was not statistically powered to demonstrate noninferiority between latanoprost 0.005% and sepetaprost.

When comparing US and Japan population data, the numerically lower IOP observed in Japanese patients may be attributed to the lower baseline IOP in this population. Despite the lower baseline IOP, sepetaprost 0.002% was still able to clinically significantly reduce IOP at month 3. Although the mean ± SE IOP showed some diurnal fluctuation, decreasing across the time points during the day (Table 2), the mean ± SD change from baseline at the same time was consistent for all treatment groups (Supplementary Table S2).

The percentage IOP reduction for latanoprost in this study ranged from 27% to 29% over week 1 to month 3; these reductions aligned with a meta-analysis of ≤12 clinical trials of patients with open-angle glaucoma (OAG) and OHT ($n = 3,090$), which reported a peak and trough IOP reduction of 31% and 28%, respectively, for latanoprost 0.005%.[34] The similar IOP-lowering efficacy observed with latanoprost 0.005% and sepetaprost 0.002% treatment throughout this study suggests that sepetaprost 0.002% could offer an alternative treatment for POAG and OHT with a novel, dual FP and EP3 receptor agonistic mechanism of action.[27] A large phase 3 study would be required to further confirm its comparable efficacy to latanoprost. Prostaglandin analogs such as tafluprost and travoprost have also shown similar IOP-lowering efficacy to latanoprost 0.005%.[35,36]

There was no apparent dose–response relationship with AE frequency. When sepetaprost 0.003% and latanoprost 0.005% were compared in a previous phase 2 study, the prevalence of treatment-emergent AEs was numerically higher for sepetaprost 0.003% (35.5% overall and 33.9% ocular AEs) than for latanoprost 0.005% (29.5% overall and 23.0% ocular AEs).[37] Conjunctival hyperemia was reported in 19.4% of patients with sepetaprost 0.003% treatment and in 8.2% of patients with latanoprost 0.005% treatment.[37]

Table 3. Overall Occurrence of Adverse Events (Safety Population)

Patients, n *(%)*	*Placebo to SEP 0.003%*		*LAT 0.005%* (n=*44*)	*SEP 0.0005%* (n=*43*)	*SEP 0.001%* (n=*43*)	*SEP 0.002%* (n=*44*)	*SEP 0.003%* (n=*45*)	*SEP 0.003% Total*[b] (n=*65*)	*SEP Total*[c] (n=*195*)
	P1[a] (n=*22*)	*P2*[a] (n=*20*)							
AEs	5 (22.7)	10 (50.0)	22 (50.0)	21 (48.8)	19 (44.2)	15 (34.1)	23 (51.1)	33 (50.8)	88 (45.1)
SARs	1 (4.5)	4 (20.0)	13 (29.5)	9 (20.9)	11 (25.6)	9 (20.5)	11 (24.4)	15 (23.1)	44 (22.6)
Serious AEs	1 (4.5)	0	0	0	0	0	0	0	0
AE(s) leading to study discontinuation	0	0	1 (2.3)	0	0	1 (2.3)	1 (2.2)	1 (1.5)	2 (1.0)
Ocular AEs	3 (13.6)	5 (25.0)	18 (40.9)	16 (37.2)	14 (32.6)	13 (29.5)	18 (40.0)	23 (35.4)	66 (33.8)
Nonocular AEs	3 (13.6)	6 (30.0)	11 (25.0)	10 (23.3)	7 (16.3)	5 (11.4)	9 (20.0)	15 (23.1)	37 (19.0)
Prevalence of all recorded ocular AEs (reported by ≥3 patients; safety population)									
Conjunctival hyperemia	0	2 (10.0)	12 (27.3)	5 (11.6)	5 (11.6)	9 (20.5)	7 (15.6)	9 (13.8)	28 (14.4)
Eye pruritus	0	0	5 (11.4)	2 (4.7)	1 (2.3)	0	5 (11.1)	5 (7.7)	8 (4.1)
Growth of eyelashes	0	1 (5.0)	2 (4.5)	3 (7.0)	2 (4.7)	0	0	1 (1.5)	6 (3.1)
Instillation site pain	0	0	0	0	1 (2.3)	3 (6.8)	1 (2.2)	1 (1.5)	5 (2.6)
Conjunctival hemorrhage	0	0	0	2 (4.7)	1 (2.3)	1 (2.3)	1 (2.2)	1 (1.5)	5 (2.6)
Foreign body sensation	0	0	1 (2.3)	2 (4.7)	0	1 (2.3)	2 (4.4)	2 (3.1)	5 (2.6)
Punctate keratitis	0	0	1 (2.3)	1 (2.3)	2 (4.7)	1 (2.3)	1 (2.2)	1 (1.5)	5 (2.6)
Blepharitis	0	0	0	2 (4.7)	0	1 (2.3)	0	0	3 (1.5)
Dry eye	0	0	0	0	0	1 (2.3)	2 (4.4)	2 (3.1)	3 (1.5)
Eye irritation	1 (4.5)	0	2 (4.5)	0	3 (7.0)	0	0	0	3 (1.5)
Lacrimation increased	0	1 (5.0)	3 (6.8)	1 (2.3)	1 (2.3)	0	0	1 (1.5)	3 (1.5)
Photophobia	0	0	0	0	1 (2.3)	0	2 (4.4)	2 (3.1)	3 (1.5)
Vision blurred	0	0	0	0	2 (4.7)	0	1 (2.2)	1 (1.5)	3 (1.5)

[a]P1: AEs from placebo treatment to week 6; P2: AEs from SEP 0.003% treatment from week 6 to month 3.
[b]SEP 0.003% total summarizes columns "SEP 0.003%" and "Placebo to SEP 0.003% P2."
[c]SEP total summarizes columns "SEP 0.0005%," "SEP 0.001%," "SEP 0.002%," "SEP 0.003%," and "Placebo to SEP 0.003% P2."
AE, adverse event; SAR, suspected adverse reaction.

The comparable efficacy to latanoprost and lower incidence of AEs reported in this study, although of relatively small sample size, suggest that sepetaprost 0.002% is a preferable dose to the sepetaprost 0.003% solution.

Conjunctival hyperemia is the most frequently reported AE during treatment with glaucoma eye drops, including FP agonists[15,16,25,38]; however, the frequency observed in the latanoprost treatment group (27.3%) in this study was higher than previously reported in the prescribing information for latanoprost (8.0%).[39] The lower frequency of conjunctival hyperemia observed with sepetaprost (20.5% for sepetaprost 0.002%; 14.4% across all sepetaprost groups) compared with latanoprost in this study suggests that further research would be warranted to determine if sepetaprost may provide better tolerability over currently available FP agonists.

Conjunctival hyperemia score worsened by ≥2 units for 2 patients in the sepetaprost 0.002% group and the severity had been reduced from moderate to mild or none by the end of the study. However, limited conclusions can be drawn from this study because of the small sample size, and safety comparisons would be better made in a large phase 3 study.

A key strength of this study was the inclusion of both a placebo control group and an active control group. This provided the study with assay sensitivity, by validating efficacy of the active control relative to placebo in patients with OAG and OHT, and strengthened the validity of the comparisons in efficacy between sepetaprost and latanoprost, which is the current gold standard of treatment. The use of a 6-week placebo arm followed by the highest study concentration of sepetaprost was to limit the placebo phase. The study was designed to include 2 distinct populations, Japan- and USA-based patients, and showed similar efficacy and safety outcomes, increasing the validity and generalizability of the data. The observer masking of this study design was implemented to minimize the potential bias.

The randomization was stratified by both countries in which the study was conducted (USA and Japan), which helped to ensure balance across the treatment groups within each country, as the patients were evenly distributed. The overall sample sizes of between 43 and 45 patients in each sepetaprost group and the latanoprost group provided a robust assessment of efficacy and dose–response. The smaller sample sizes by treatment group within each country meant that the treatment estimates by country were less precise than overall estimates; however, this is a common limitation in phase 2 dose-finding studies.

There are 2 ongoing phase 2 studies for sepetaprost: the ANGEL-2 study in the USA is comparing sepetaprost 0.002% with timolol 0.5%, and a further study in the EU aims to further explore the safety and efficacy profile of sepetaprost compared with latanoprost.[40,41] Phase 3 studies investigating the optimal dose determined in this study would provide further evidence of the efficacy and safety of sepetaprost.

In conclusion, of the concentrations evaluated, the optimal dose of sepetaprost in this study was 0.002% in both Japan- and USA-based patients; the efficacy and safety outcomes of treatment observed with this dose were comparable to those of latanoprost 0.005%.

Author Disclosure Statement

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Supplementary Material

Supplementary Data S1
Supplementary Data S2
Supplementary Data S3
Supplementary Data S4
Supplementary Figure S1
Supplementary Figure S2
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