

A Randomized Phase 2 Trial Comparing Omidenepag Isopropyl 0.002% Once and Twice Daily in Subjects With Primary Open-angle Glaucoma or Ocular Hypertension (SPECTRUM-6)

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Précis: No significant difference was found between the intraocular pressure (IOP) lowering of omidenepag isopropyl 0.002% once daily (QD) and twice daily (BID). However, adverse events (AEs) were higher in the BID arm; thus, QD dosing is the preferred dosing frequency for further investigation.

Purpose: This phase 2, randomized, double-masked, parallel-arm, multicenter study (NCT03858894) was conducted in the United States to examine whether the efficacy and safety of omidenepag isopropyl 0.002% BID dosing was superior to QD dosing in subjects with primary open-angle glaucoma or ocular hypertension.

Methods: Randomized subjects (1:1) received omidenepag isopropyl 0.002% QD (n = 50) or BID (n = 48) for 6 weeks (after a ≤ 4 -week washout period). IOP was measured at 8:00 AM, 12:00 PM, and 4:00 PM at baseline and weeks 2 and 6. The primary efficacy endpoint was IOP at each timepoint at weeks 2 and 6. AEs were evaluated.

Results: Baseline mean diurnal IOP (\pm SD) post washout was 25.4 \pm 2.9 mm Hg (BID) and 24.6 \pm 1.9 mm Hg (QD). At weeks 2 and 6, clinically significant IOP reductions from baseline were observed for omidenepag isopropyl BID and QD treatments. Least-squares mean (\pm SE) IOP differences (BID versus QD) were not statistically significant (week 2: 0.44 \pm 0.68 to 1.08 \pm 0.65 mm Hg; week 6: 0.36 \pm 0.63 to 0.68 \pm 0.68 mm Hg) at any timepoint (all $P > 0.05$). AEs were 3-fold greater in the BID arm (41.7%; QD: 14.0%); the most frequently reported AE was conjunctival/ocular hyperemia

(BID: 22.9%; QD: 2.0%). Five subjects discontinued omidenepag isopropyl prematurely, 4 of 5 owing to AEs (BID: 4; QD: 0).

Conclusion: In this study, the benefit-risk profile of omidenepag isopropyl 0.002% QD was more favorable than the benefit-risk profile of BID. This difference was driven by a higher incidence of local tolerability issues in the BID arm.

Key Words: EP2 receptor agonist, intraocular pressure, ocular hypertension, omidenepag isopropyl, primary open-angle glaucoma (*J Glaucoma* 2021;30:473–480)

Glaucoma describes a group of ocular disorders characterized by optic neuropathy often associated with elevated intraocular pressure (IOP).¹ Glaucoma is a progressive and chronic disease that is the leading cause of irreversible blindness globally, with an estimated worldwide prevalence of 3.54%.^{2,3} There are many subtypes of glaucoma, but the most common is primary open-angle glaucoma (POAG), which has an estimated global prevalence of 3.05%.²

Although there is currently no cure for glaucoma, progression can often be controlled, most frequently through reducing IOP by surgery, laser treatment, or pharmaceutical drops.³ Pharmaceutical treatments are the most common management method for POAG and ocular hypertension (OHT), of which prostanoid FP receptor agonists are generally prescribed as first-line therapy.³ FP agonists primarily reduce IOP by enhancing uveoscleral outflow⁴ and have a favorable efficacy and safety profile with convenient once-daily (QD) dosing.³ However, not all achieve sufficient IOP lowering with FP agonists and thus require adjunctive therapies, which reduces the likelihood of adherence.⁵ In addition, some individuals are termed FP agonist nonresponders (typically defined as $\leq 10\%$ IOP reduction rate)⁶ and thus require an alternative class of therapy.⁵ Low compliance with FP agonists can also occur as it is often associated with side effects such as conjunctival hyperemia, iris pigmentation, periocular skin pigmentation, eyelash changes, and deepening of the upper eyelid sulcus (DUES).^{5,7,8} Examples of current adjunctive and alternative therapy classes include β -blockers, α -agonists, Rho-kinase inhibitors, and carbonic anhydrase inhibitors (CAIs).^{5,9} However, consideration must be taken with regard to these alternative classes, as β -blockers are associated with pulmonary and cardiovascular side effects,

Received for publication September 8, 2020; accepted February 23, 2021.

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Santen, Emeryville, CA. The sponsor or funding organization participated in the design of the individual studies, the conducting of the studies, data collection, and data management. The analysis was sponsored by Santen, who participated in the data analysis, interpretation of the data, preparation, review, and approval of the manuscript.

Disclosure: F.L., P.D., N.O.-K., A.C., and N.K.S. are Santen (employee). The remaining authors declare no conflict of interest.

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DOI: 10.1097/IJG.0000000000001836

and are thus contraindicated in patients with asthma and bradycardia.^{5,10} Similarly, α -agonists are associated with local and systemic effects, such as allergic ocular reactions, dry eyes, and oral dryness.^{5,11} Rho-kinase inhibitors are associated with a high incidence of conjunctival hyperemia and the occurrence of cornea verticillata,⁹ and CAIs are contraindicated in those with low corneal endothelial cell counts.⁵ The occurrence of nonresponse and the prevalence of low adherence and compliance with available topical medications, and the side effects and contraindications associated with the available alternative classes, demonstrate that there is a need for a new class of therapy with a new mechanism of action.

Omidenepag isopropyl is an investigational topical prodrug that is hydrolyzed in the eye during corneal penetration to omidenepag, a highly selective, non-prostaglandin, prostanoid EP2 receptor agonist.¹² The EP2 receptor is a G-protein-coupled receptor found in many tissues including those involved in aqueous humor dynamics, such as the trabecular meshwork and ciliary muscle. Omidenepag, the active metabolite of omidenepag isopropyl, has been shown to reduce IOP by a novel mechanism that comprises the activation of the EP2 receptor, resulting in increased aqueous humor outflow through the conventional and uveoscleral pathways.^{12,13} Previous QD dose-finding studies conducted in the United States and Japan found that omidenepag isopropyl 0.002% was the optimal concentration for further investigation in terms of tolerability and IOP-lowering efficacy in subjects with POAG or OHT.¹⁴ Omidenepag isopropyl 0.002% QD was approved for use for the treatment of glaucoma and OHT in Japan in 2018¹⁵ and for the treatment of open-angle glaucoma and OHT in Korea (2019),¹⁶ Taiwan (2020),¹⁷ and Thailand (local affiliate, personal communication, 2020), and is currently being investigated in US populations.

It is unknown whether omidenepag isopropyl 0.002% twice daily (BID) would improve the IOP-lowering efficacy without compromising the safety/tolerability profile, compared with QD dosing. This phase 2 study aimed to identify whether BID or QD is the optimal dosing frequency of omidenepag isopropyl 0.002% over 6 weeks in subjects with POAG or OHT.

METHODS

Study Design

This was a phase 2, randomized, double-masked, multicenter, parallel-arm study assessing the safety and efficacy of omidenepag isopropyl 0.002% QD and BID in subjects with POAG or OHT (NCT03858894). The study was conducted at 13 investigational sites in the United States from January 2019 through June 2019. This study was conducted in accordance with the study protocol, Good Clinical Practice as required by US Food and Drug Administration regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, and Santen's standard operating procedures for clinical investigation. Compliance with these requirements is consistent with the ethical principles that have their origins in the Declaration of Helsinki. All subjects provided written informed consent before enrollment in the study.

Subjects were assessed for eligibility and then entered the screening phase, which included a washout period where previous topical IOP-lowering medications were discontinued for up to 28 days (plus a 7-d window) depending on the class of medication that the subject was receiving before the washout: 7 days for miotics and oral/topical CAIs; 14 days for α -agonists and α - β -agonists; 28 days for FP agonists, β -antagonists (β -blockers, including α - β -

blockers), α -antagonists (α -1 blockers), and Rho-kinase inhibitors; and ≥ 1 day for treatment-naïve subjects and those who used no IOP-lowering medications for the last 28 days between the screening visit and visit 2 (baseline). For subjects taking a combination of medications, the longest washout period of the individual components was applied. An interim safety visit (visit 1a) was performed if the investigator considered the subject's IOP to be of potential concern during the washout period. If subjects were treated with topical CAIs during the washout period, then a mid-washout visit (visit 1a) was recommended (CAI treatment was stopped 1 wk before visit 2).

Subjects were screened for inclusion (visit 1), assessed for baseline characteristics, and randomized into BID or QD treatment arms (day 1, visit 2). Subjects then returned for scheduled assessments at week 2 (visit 3) and week 6 (visit 4).

IOP was measured by a calibrated manual Goldmann applanation tonometer at visit 1 (screening) and visit 1a (optional mid-washout) at any time, and at 8:00 AM, 12:00 PM, and 4:00 PM (± 60 min) at visits 2, 3, and 4. Two consecutive measurements were obtained for each eye to determine IOP. If the 2 measurements differed by < 3 mm Hg, the average was recorded. However, if the difference in IOP measurements was > 3 mm Hg, a third measurement was taken, and the median of the 3 measurements was recorded.

Safety was evaluated by an assessment of adverse events (AEs). Safety parameters were assessed at scheduled visits by best-corrected visual acuity (BCVA) and slit-lamp biomicroscopy (performed before the 8:00 AM IOP measurement), and ophthalmoscopy (performed after the 4:00 PM IOP measurement).

Randomization and Masking

Permuted-block randomization was used to randomize eligible subjects 1:1 (by Interactive Response Technology) to receive omidenepag isopropyl 0.002% either QD (vehicle at 8:00 AM and omidenepag isopropyl at 8:00 PM ± 60 min), or BID (8:00 AM and 8:00 PM ± 60 min), 1 drop/eye for 6 weeks. Vehicle and omidenepag isopropyl 0.002% administration bottles were identical in appearance; both solutions were clear and colorless. This study had a double-masked design; the treatment was masked to the subjects, examiners, Santen personnel, and clinical investigators.

Subjects

Men and women were eligible for inclusion if they were aged 18 years or older and had a diagnosis of POAG or OHT in both eyes, or 1 eye with POAG and the other with OHT; BCVA $+0.60$ logarithm of the minimum angle of resolution (logMAR) or better in each eye; corneal thickness of ≥ 480 and ≤ 600 μ m in each eye; anterior chamber angle grade of ≥ 2 (Schaffer scale) in each eye; IOP of ≥ 22 mm Hg in at least 1 eye (the same eye, at all timepoints at visit 2), and of ≤ 34 mm Hg in both eyes at all timepoints on visit 2 and completion of appropriate washout period.

Key exclusion criteria included previous exposure to omidenepag isopropyl; ocular surgery/laser treatment within 180 days before visit 1; history of IOP-lowering surgery; presence of secondary or advanced glaucoma (eg pigmentary glaucoma, pseudoexfoliative glaucoma, or a visual field mean deviation worse than -12 dB); presence or history of macular edema or known risk factors for macular edema in either eye; presence of any corneal abnormality or other conditions interfering with or preventing reliable Goldmann applanation tonometry; presence of any active severe external ocular disease, inflammation, or infection; history of severe ocular

trauma, iritis, and/or uveitis; or female individuals who were pregnant, nursing, or planning a pregnancy.

Endpoints and Statistical Methods

The primary efficacy endpoint was the IOP in the study eye at 8:00 AM, 12:00 PM, and 4:00 PM at weeks 2 and 6. The secondary efficacy endpoints included the mean diurnal IOP in the study eye at week 6; the change and percentage change from baseline in IOP; the change and percentage change from baseline in mean diurnal IOP; the proportion of subjects achieving a mean diurnal IOP ≤ 18 mm Hg at each postbaseline visit; and percentage of responders (subjects with a mean diurnal IOP reduction of $\geq 20\%$, $\geq 25\%$, and $\geq 30\%$ from baseline) at weeks 2 and 6.

Safety endpoints included incidence of ocular and systemic AEs; BCVA; slit-lamp biomicroscopy findings including lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, keratic precipitates, anterior chamber cells, anterior chamber flare, anterior synechiae of iris, posterior synechiae of iris, and abnormal lens findings; and ophthalmoscopy (with particular attention paid to the macula).

Statistical analyses were performed with SAS System V.9.4 or higher (SAS Institute, Cary, NC) on locked databases. Assuming a 2-sided type I error rate of 5% and a standard deviation (SD) of 3.5 mm Hg, it was determined that 50 subjects per treatment arm (total of 100 subjects) would have an 80% power to detect a 2.0 mm Hg between-treatment difference.

The primary efficacy analyses were performed using the study eyes of the full analysis set (FAS) population, which included all randomized subjects who received at least 1 dose of the study medication and had at least one postbaseline IOP measurement of the study eye during the study. A mixed-effect model for repeated measures was carried out for each timepoint. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline IOP as a covariate. Within-subject errors were modeled using an unstructured covariance matrix. The least-squares (LS) means of the endpoints within each treatment arm were reported, and the 95% confidence intervals (CIs) for the differences in means between the 2 arms at each timepoint and the corresponding *P* values were provided. In the analysis of the primary endpoint, superiority of omidenepag isopropyl BID to omidenepag isopropyl QD with respect to the primary endpoint was achieved if the treatment differences were significantly > 0 at all 6 timepoints (8:00 AM, 12:00 PM, and 4:00 PM at weeks 2 and 6).

The study eye was the eye that qualified per the eligibility criteria at visit 2. If both eyes met the eligibility criteria, the eye with the higher diurnal IOP at visit 2 was designated as the study eye. If both eyes met the eligibility criteria and had the same mean diurnal IOP at visit 2, the right eye was designated as the study eye. Both eyes were treated with study medication for the study duration, even if only 1 eye was eligible per the IOP inclusion criteria.

Safety analysis was primarily assessed by AEs, BCVA, slit-lamp biomicroscopy findings, and ophthalmoscopy findings in the safety population (which included all randomized subjects who received at least one dose of study medication) and summarized descriptively. Each biomicroscopy parameter was given a rating score. In addition, clinically significant worsening was summarized and listed (defined as ≥ 1 category change from baseline for anterior chamber cells and flare, and ≥ 2 category changes from baseline for all other parameters).

RESULTS

Subject Disposition

A total of 98 subjects were randomized into the study and were included in the intention-to-treat population (QD, *n* = 50; BID, *n* = 48). All randomized subjects received the study drug and were included in the FAS and safety population (subject disposition information is shown in Fig. 1). There was a high rate of subjects completing the study (95.9% at week 6) and 100% compliance in 91% of subjects at week 6 (97% of subjects at week 2). Five subjects (5.1%) prematurely discontinued the study drug (4 owing to AEs and one owing to subject withdrawal). All discontinuations occurred in the BID arm.

Subject Demographics and Baseline Characteristics

Subject demographics and baseline characteristics for the FAS population are shown in Table 1. Overall, the demographic characteristics of the FAS were well balanced between the 2 treatment arms. Subjects in both arms were predominantly white and phakic. IOP-lowering medications had not been previously used in 36.7% of subjects. In those who had previously used IOP-lowering medications, the most common medication was FP agonists (51.0%), followed by β -blockers (13.3%).

Efficacy

The primary efficacy endpoint was IOP at all timepoints at weeks 2 and 6, which is displayed in Table 2. The BID arm had numerically lower LS mean IOP at all timepoints at weeks 2 and 6 compared with the QD arm; however, the between-arm differences [\pm standard error (SE); BID – QD] were not significant (all timepoints *P* > 0.05). The first and second secondary efficacy endpoints were the mean diurnal IOP at weeks 6 and 2, respectively, in the FAS. At week 2, the mean (\pm SE) diurnal IOP was 17.52 ± 0.44 mm Hg for the BID arm and 18.40 ± 0.42 mm Hg for the QD arm. The between-arm difference (BID – QD; \pm SE) at week 2 was -0.89 ± 0.61 mm Hg. The LS mean diurnal IOP in the BID and QD arms were not significantly different at week 2 (95% CI, -2.1 to 0.3 ; *P* = 0.1490). The LS mean (\pm SE) diurnal IOP scores at week 6 were 17.77 ± 0.43 mm Hg for the BID arm and 18.37 ± 0.41 mm Hg for the QD arm. The between-arm difference (\pm SE) at week 6 was not significant (-0.60 ± 0.60 mm Hg; 95% CI, -1.80 to 0.59 ; *P* = 0.3199).

Consistent with the primary endpoint, the change in IOP from baseline to all timepoints was numerically, but not statistically significantly, greater in the BID arm compared with the QD arm (Fig. 2; raw mean (\pm SE) change in IOP; all timepoints, *P* > 0.05). This was also evident in the percentage change from baseline in mean diurnal IOP. At week 2, the LS mean (\pm SE) change and percentage change (\pm SE) from baseline in IOP ranged from -7.14 ± 0.49 to -7.68 ± 0.47 mm Hg ($-28.54 \pm 1.91\%$ to $-31.19 \pm 1.87\%$) in the BID arm and from -6.43 ± 0.45 to -6.70 ± 0.46 mm Hg ($-25.30 \pm 1.71\%$ to $-27.01 \pm 1.81\%$) in the QD arm. The mean IOP reductions were stable between weeks 2 and 6. The LS mean (\pm SE) change and percentage change from baseline in IOP across all timepoints at week 6 ranged from -7.11 ± 0.45 to -7.25 ± 0.49 mm Hg ($-28.66 \pm 1.80\%$ to $-29.17 \pm 1.87\%$) in the BID arm and from -6.52 ± 0.43 to -6.75 ± 0.43 mm Hg ($-25.55 \pm 1.75\%$ to $-27.35 \pm 1.77\%$) in the QD arm. The difference of LS mean (\pm SE) IOP values

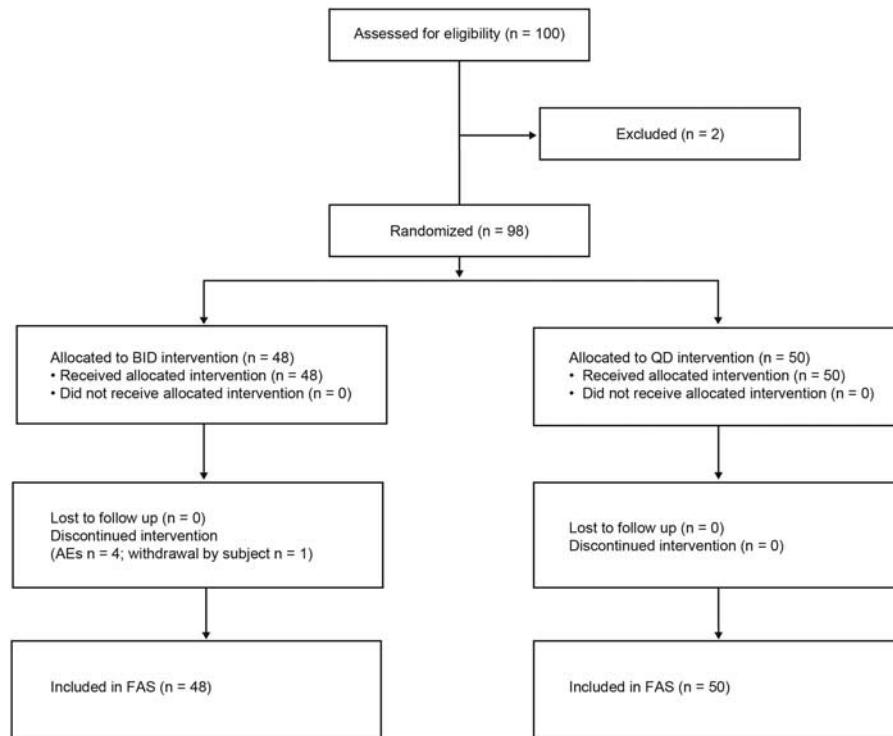


FIGURE 1. Subject disposition. AE indicates adverse event; BID, twice daily; FAS, full analysis set; QD, once daily.

TABLE 1. Subject Demographics and Baseline Characteristics (FAS Population)

Characteristic	Omidenepeg Isopropyl	
	BID (N = 48)	QD (N = 50)
Age (y), mean (SD)	67.3 (9.5)	66.3 (8.7)
Female, n (%)	27 (56.3)	25 (50.0)
Primary diagnosis, n (%)		
POAG	30 (62.5)	35 (70.0)
OHT	18 (37.5)	15 (30.0)
BCVA (logMAR), mean (SD)	0.12 (0.13)	0.11 (0.12)
Central corneal thickness (µm), mean (SD)	553.67 (36.21)	548.62 (28.45)
Race, n (%)		
Black or African American	13 (27.1)	14 (28.0)
Native Hawaiian or Other Pacific Islander	0	1 (2.0)
White	35 (72.9)	35 (70.0)
Lens status, n (%)		
Aphakic	0	1 (2.0)
Pseudophakic	10 (20.8)	6 (12.0)
Phakic	38 (79.2)	43 (86.0)
Diurnal IOP (mm Hg), mean (SD)	25.39 (2.92)	24.55 (1.86)
Prior use of IOP-lowering medication(s), n (%)		
Oral/topical CAIs	4 (8.3)	3 (6.0)
α-agonists	1 (2.1)	1 (2.0)
β-blockers	5 (10.4)	8 (16.0)
FP agonists	25 (52.1)	25 (50.0)
None	17 (35.4)	19 (38.0)

BCVA indicates best-corrected visual acuity; BID, twice daily; CAI, carbonic anhydrase inhibitor; FAS, full analysis set; FP, F-prostanoid receptor; IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution; OHT, ocular hypertension; POAG, primary open-angle glaucoma; QD, once daily; SD, standard deviation.

(BID – QD) at weeks 2 and 6 was 0.44 ± 0.68 to 1.08 ± 0.65 and from 0.36 ± 0.63 to 0.68 ± 0.68 , respectively.

The percentage of subjects achieving a mean diurnal IOP reduction of $\geq 20\%$, $\geq 25\%$, or $\geq 30\%$ from baseline or achieving a mean diurnal IOP of ≤ 18 mm Hg at weeks 2 or 6 is displayed in Figure 3. There were no significant between-arm differences in the proportion of subjects achieving a mean diurnal IOP reduction of $\geq 20\%$, $\geq 25\%$, or $\geq 30\%$ from baseline at weeks 2 or 6 (all $P > 0.05$). More than 75% of subjects in both arms at week 2, and $\geq 80\%$ of subjects at week 6, achieved an IOP reduction from baseline of 20%. There were also no significant between-arm differences in the proportion of subjects achieving a mean diurnal IOP of ≤ 18 mm Hg at weeks 2 or 6 (all $P > 0.05$), with $> 50\%$ of subjects in both dosing schedules achieving a mean diurnal IOP of ≤ 18 mm Hg by week 2, which remained stable to week 6.

Safety

The AEs reported in each treatment arm are summarized in Table 3. A total of 4 subjects (8.3%) in the BID arm discontinued the study drug prematurely owing to 5 AEs (ocular hyperemia, iritis and nausea, conjunctival hyperemia, and ocular discomfort). None of the AEs leading to study drug discontinuation were serious; all were moderate aside from the mild cases of iritis and nausea. All discontinuations because of AEs were considered related to the study drug except for the single case of nausea, and none occurred in the QD arm.

Overall, AEs were more frequent in the BID arm (41.7%) than the QD arm (14.0%), including ocular AEs (BID, 37.5%; QD, 10.0%) and suspected adverse reactions (BID, 29.2%; QD, 6.0%). The most commonly reported AEs by preferred term were conjunctival hyperemia (BID, 12.5%; QD, 0%) and ocular hyperemia (BID, 10.4%; QD,

TABLE 2. LS Mean (\pm SE) IOP at Weeks 2 and 6 (FAS Population, Study Eye)

Analysis Visit	Analysis Timepoint	Statistics	Omidenepag Isopropyl, n (%)		
			BID (N = 48)	QD (N = 50)	
Week 2	8:00 AM	LS mean (SE)	18.19 (0.46)	19.15 (0.45)	
		Difference (SE; BID – QD)	–0.96 (0.64)		
		95% CI of difference	–2.24 to 0.32		
			P	0.1403	
	12:00 PM	LS mean (SE)	17.73 (0.49)	18.17 (0.46)	
		Difference (SE; BID – QD)	–0.44 (0.68)		
		95% CI of difference	–1.79 to 0.91		
			P	0.5174	
	4:00 PM	LS mean (SE)	16.73 (0.47)	17.81 (0.44)	
Difference (SE; BID – QD)		–1.08 (0.65)			
95% CI of difference		–2.37 to 0.21			
		P	0.0994		
Week 6	8:00 AM	LS mean (SE)	18.33 (0.49)	19.01 (0.47)	
		Difference (SE; BID – QD)	–0.68 (0.68)		
		95% CI of difference	–2.04 to 0.68		
			P	0.3238	
	12:00 PM	LS mean (SE)	17.77 (0.45)	18.35 (0.43)	
		Difference (SE; BID – QD)	–0.58 (0.62)		
		95% CI of difference	–1.82 to 0.66		
			P	0.3523	
	4:00 PM	LS mean (SE)	17.30 (0.45)	17.66 (0.43)	
Difference (SE; BID – QD)		–0.36 (0.63)			
95% CI of difference		–1.61 to 0.88			
		P	0.5633		

BID indicates twice daily; CI, confidence interval; FAS, full analysis set; LS, least squares; QD, once daily; SE, standard error.

2.0%). Most AEs were mild (there were 3 cases of moderate AEs in the BID arm only, all of which led to study discontinuation), and 1 serious AE was reported in the QD arm (cholelithiasis), which was not considered related to the study drug. The rate of nonocular AEs was similar in the BID and QD treatment arms (10% and 8%, respectively), all of which were not considered to be causally related to study treatment. For the biomicroscopy parameters, clinically significant worsening from baseline occurred in 3 subjects owing to conjunctival hyperemia (1 BID, 2 QD) and in 2 subjects owing to corneal staining (1 BID, 1 QD). One occurrence of worsening of anterior chamber cells and one occurrence of worsening of anterior chamber flare were also reported (both BID). A baseline to week 6 change in

ophthalmoscopy assessments (including evaluation of the retina, macula, choroid, and vitreous) from normal to abnormal occurred in 1 subject; this was not considered related to the treatment.

DISCUSSION

This phase 2, double-masked, randomized study based in the United States evaluated whether the benefit-risk profile of omidenepag isopropyl 0.002% BID or QD is more favorable, and thus establishing the optimal dosing frequency of omidenepag isopropyl 0.002% over 6 weeks in subjects with POAG or OHT. It was found that omidenepag isopropyl administered QD or BID resulted in clinically

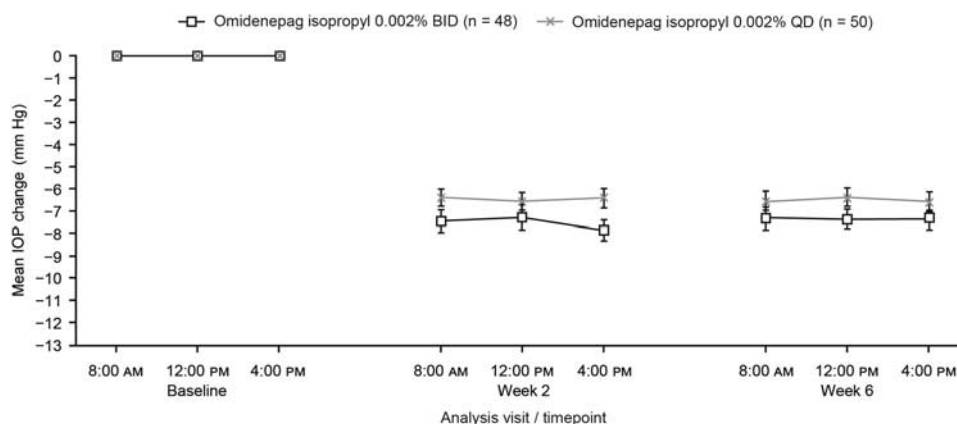


FIGURE 2. Raw mean change in IOP from baseline at each study visit and timepoint (\pm SE; FAS population). All values are raw mean (\pm SE). BID indicates twice daily; FAS, full analysis set; IOP, intraocular pressure; QD, once daily; SE, standard error.

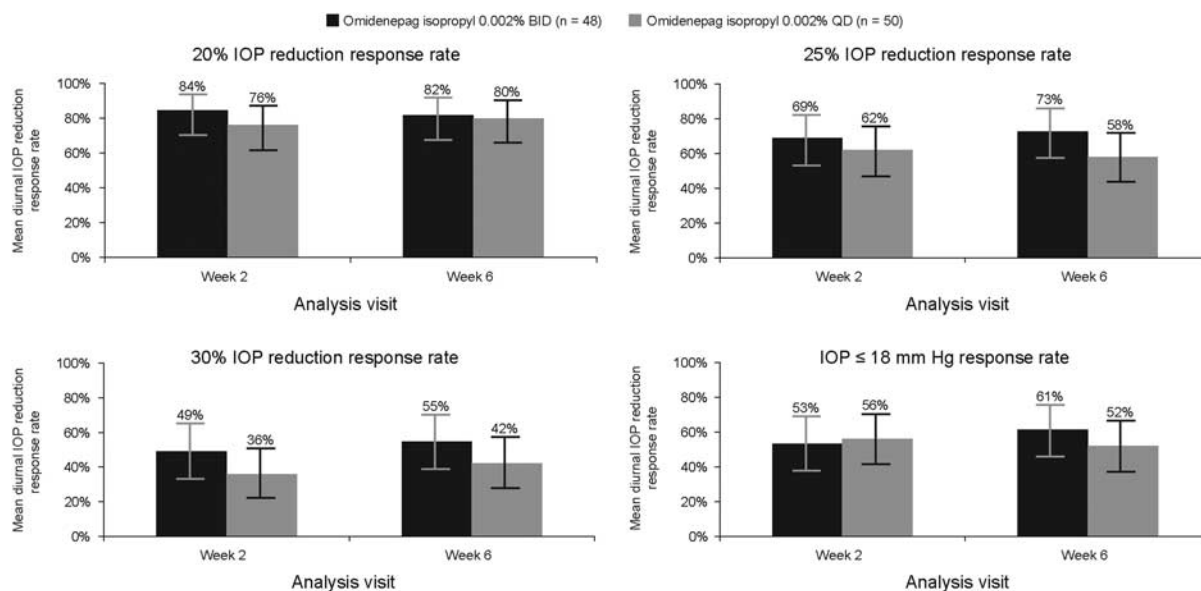


FIGURE 3. Percentage of subjects achieving a mean (\pm 95% CI) diurnal IOP reduction of \geq 20%, \geq 25%, or \geq 30% from baseline, or achieving a mean diurnal IOP \leq 18 mm Hg. All between-arm differences were not significantly different ($P > 0.05$). BID indicates twice daily; CI, confidence interval; IOP, intraocular pressure; QD, once daily.

TABLE 3. Summary of AEs

Type of Event	Omidenepag Isopropyl, n (%)	
	BID (N = 48)	QD (N = 50)
AE(s)	20 (41.7)	7 (14.0)
Serious AE(s)*	0	1 (2.0)
Suspected adverse reaction(s)	14 (29.2)	3 (6.0)
AE(s) leading to study drug discontinuation†	4 (8.3)	0
Ocular AE(s)	18 (37.5)	5 (10.0)
Serious AE(s)	0	0
Suspected adverse reaction(s)	14 (29.2)	3 (6.0)
AE(s) leading to study drug discontinuation	4 (8.3)	0
Nonocular AE(s)	5 (10.4)	4 (8.0)
Serious AE(s)	0	1 (2.0)
Suspected adverse reaction(s)	0	0
AE(s) leading to study drug discontinuation	1 (2.1)	0
AEs reported in \geq 2 subjects, by MedDRA system organ class and preferred term		
Eye disorders	16 (33.3)	4 (8.0)
Conjunctival hyperemia	6 (12.5)	0
Ocular hyperemia	5 (10.4)	1 (2.0)
Photophobia	1 (2.1)	2 (4.0)
Investigations	2 (4.2)	1 (2.0)
Vital dye staining cornea present	2 (4.2)	1 (2.0)
Nervous system disorders	1 (2.1)	2 (4.0)
Headache	1 (2.1)	2 (4.0)

*One subject experienced cholelithiasis, which was reported as a serious AE.

†One subject discontinued the study drug owing to 2 AEs, iritis and nausea.

AE indicates adverse event; BID, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily.

significant reductions in IOP from baseline that remained stable through the study duration. At the end of the 6-week study, the LS mean IOP in the BID arm was numerically lower than the QD arm; however, no between-arm differences in the LS mean IOP were statistically significant at any timepoint (all $P > 0.05$). Consistent findings were also observed for all IOP-lowering endpoints; there were no significant between-arm differences in the mean diurnal IOP at weeks 2 and 6, or at any timepoint in the change and percentage change in IOP. In addition, no significant between-arm differences were observed in the proportion of subjects achieving mean diurnal IOP reductions of \geq 20%, \geq 25%, or \geq 30% from baseline, or in the proportion of subjects achieving an IOP \leq 18 mm Hg. At week 6, ~80% of subjects achieved a mean diurnal IOP reduction of \geq 20% from baseline in both treatment arms, and more than half of the subjects achieved an on-treatment IOP of \leq 18 mm Hg. Based on these findings, the BID dosing schedule of omidenepag isopropyl does not significantly improve IOP lowering compared with QD dosing in the studied population. This is in line with previous FP agonist dose-regimen studies, where QD dosing was generally found to be at least as, or more, effective at lowering IOP than BID dosing.^{18–20} In healthy and ocular hypertensive eyes, latanoprost QD was found to provide a numerically greater IOP reduction compared with BID application.^{21,22} In addition, in eyes that were inadequately controlled with timolol, latanoprost 0.006% QD concomitantly administered with timolol for 12 weeks in 50 patients with POAG or capsular glaucoma was found to be at least as effective at reducing IOP as BID dosing.²⁰ Similarly, in 3-month, randomized trials, QD dosing of bimatoprost 0.03% demonstrated greater IOP lowering and a better safety profile than BID dosing in patients with glaucoma or OHT.^{18,19}

With regard to the safety profile of omidenepag isopropyl 0.002% QD and BID, most AEs reported were mild

and occurred 3 times more frequently in the BID arm compared with the QD arm. In addition, all 4 discontinuations of study drug because of AEs occurred in the BID arm. No nonocular AEs considered to be related to the study drug were reported in either arm, and one serious AE (cholelithiasis) was reported (QD arm), which was deemed not related to the study drug. The most frequently reported AEs were conjunctival and ocular hyperemia, which occurred more frequently in the BID arm compared with the QD arm. Overall, QD dosing of omidenepag isopropyl was better tolerated in the studied population than BID dosing. Likewise, these findings are consistent with studies of other topical treatments for POAG and OHT, including FP agonists,¹⁹ where QD dosing usually has a better tolerability profile compared with BID dosing, with lower rates of reported AEs in the QD arm versus the BID arm.¹⁸ These studies also found that QD dosing generally resulted in a higher rate of adherence and fewer discontinuations because of AEs than BID dosing, although time of day and frequency of administration may also play a role.^{18,23} There were no issues with adherence reported with either dosing schedule of omidenepag isopropyl in the present study. No iris pigmentation, periocular skin pigmentation, eyelash changes, or DUES that are frequently associated with FP agonist administration⁸ were reported in this study; however, this finding was based only on investigator reports and was not assessed with systematic, independently graded photos. In addition, the study duration may not have been long enough to detect these changes. However, in a 12-month, open-label, multicenter, phase 3 study in Japan (n = 125), after administration of omidenepag isopropyl as a monotherapy QD, or in combination with timolol 0.5%, there were no reports of appearance-altering AEs in patients with OAG and OHT (Aihara, et al 2018; AAO Poster PO100. <https://www.aao.org/annual-meeting/meeting-archives>). In addition, in an independent 1-year follow-up study of 12 subjects with DUES after the administration of FP agonists for a mean duration of 61 months, 6 subjects had improvement in DUES after 12 months of omidenepag isopropyl administration (assessed by digital facial images).²⁴ The lack of DUES and eyelash changes with omidenepag isopropyl has also been assessed and confirmed in nonclinical studies, including in mouse 3T3-L1 cells in vitro and in C57BL/6J mice in vivo.^{25,26} These studies suggested that unlike FP agonists, omidenepag isopropyl did not lead to abnormal eyelash growth, or changes in adipocyte differentiation (leading to DUES).^{25,26} Thus, no new safety signals for omidenepag isopropyl were identified in this phase 2 study, in line with previous observations,¹⁴ and omidenepag isopropyl 0.002% QD dosing was better tolerated overall compared with BID dosing. Because glaucoma is a lifelong and chronic disease, it is likely that less study drug exposure with QD dosing is also preferred.

Key strengths of this study include its double-masked, randomized, multicenter study design with 80% statistical power, and the high rate of completion (95.9%) and compliance of subjects (100% compliance in 91% of subjects at week 6). However, there was no placebo or active comparator because of the nature of dose frequency studies where BID versus QD are compared.

In conclusion, the IOP lowering of omidenepag isopropyl 0.002% BID was not statistically superior to QD dosing after 6 weeks of treatment in individuals with POAG or OHT. However, BID dosing was associated with a 3-fold higher incidence of AEs compared with QD dosing in the studied population. Therefore, omidenepag isopropyl QD was identified and confirmed as the optimal dose frequency.

ACKNOWLEDGMENTS

Medical writing was provided by Katherine Hardy, PhD, Helios Medical Communications, Oxfordshire, United Kingdom, which was funded by Santen. The study was sponsored by Santen.

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