Once-Daily Netarsudil Versus Twice-Daily Timolol in Patients With Elevated Intraocular Pressure: The Randomized Phase 3 ROCKET-4 Study

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• PURPOSE: To compare the intraocular pressure (IOP)-lowering efficacy and safety of netarsudil once daily (QD) and timolol twice daily (BID).

• DESIGN: Double-masked, randomized, phase 3, noninferiority study.

• METHODS: Patients with open-angle glaucoma or ocular hypertension (unmedicated baseline IOP >20 to <30 mm Hg at 8:00 AM) were randomized to netarsudil ophthalmic solution 0.02% QD (PM) or timolol ophthalmic solution 0.5% BID. The primary endpoint was mean IOP at 8:00 AM, 10:00 AM, and 4:00 PM at week 2, week 6, and month 3 in patients with baseline IOP <25 mm Hg (per-protocol population). Safety was recorded over the 6-month treatment period.

• RESULTS: A total of 186 patients from each treatment arm were included in the primary efficacy analysis. Netarsudil QD met the criteria for noninferiority to timolol BID. Mean treated IOP ranged from 16.3 to 17.9 mm Hg for netarsudil and 16.7 to 17.6 for timolol, with mean reductions from baseline of 3.9 to 4.7 mm Hg and 3.8 to 5.2 mm Hg, respectively. In prespecified secondary analyses, netarsudil demonstrated noninferiority to timolol in patients with baseline IOP <27 mm Hg and <30 mm Hg. The IOP-lowering effects of netarsudil were sustained over 6 months of treatment. No treatment-related serious adverse event (AE) was reported for either study drug. However, statistically significant reductions in mean heart rate were recorded at all study visits for the timolol group. The most frequent ocular AE among netarsudil-treated patients was conjunctival hyperemia (47.9%), which was predominately mild.

• CONCLUSIONS: Netarsudil QD (PM), a first-in-class IOP-lowering medication, was noninferior to timolol BID and was associated with tolerable ocular AEs. (Am J Ophthalmol 2019;204:97–104. © 2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

GLAUCOMA IS THE LEADING CAUSE OF IRREVERSIBLE blindness worldwide, affecting more than 64 million people aged 40-80 years.[1] Glaucoma can arise through various etiologies, but vision loss is ultimately due to optic nerve damage and the progressive death of retinal ganglion cells.[2,3] Intraocular pressure (IOP), which becomes elevated owing to abnormally high resistance to trabecular (conventional) outflow,[4] is currently the only modifiable risk factor for disease progression in patients with glaucoma or ocular hypertension.[5–9] A number of ocular hypotensive agents across different drug classes are available for clinical use, but none of the most commonly prescribed agents specifically target the diseased trabecular meshwork. Rather, these medications lower IOP primarily by increasing uveoscleral (nonconventional) outflow and/or by decreasing aqueous humor production.[3]

Netarsudil ophthalmic solution 0.02%, a topically administered Rho kinase (ROCK) inhibitor approved by the United States Food and Drug Administration in December 2017,[10] lowers IOP through a distinct mechanism of action: increasing trabecular outflow by decreasing actomyosin-driven cellular contraction and reducing production of extracellular matrix proteins.[11,12] In preclinical studies, netarsudil was shown not only to increase trabecular outflow facility,[12–15] but also to decrease episcleral venous pressure[16] and aqueous humor production.[13] The mechanisms of action of netarsudil were further explored in a phase 1 study of healthy human volunteers, in whom netarsudil once daily (QD) was

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demonstrated to lower IOP primarily by increasing outflow facility, but also by reducing episcleral venous pressure.[11]

In 2 phase 3 clinical studies, ROCKET-1 and ROCKET-2, the IOP-lowering effects of netarsudil 0.02% QD demonstrated noninferiority to timolol 0.5% twice daily (BID) over 3 months in patients with baseline IOP <25 mm Hg.[17] However, netarsudil did not meet the criteria for noninferiority to timolol when the analysis population included patients with baseline IOP <27 mm Hg, the upper IOP limit for inclusion into these studies. This result was unexpected given that, in a phase 2b study, netarsudil was similarly effective to latanoprost in patients with baseline IOP ≤26 mm Hg.[18] Unlike ROCKET-1 and ROCKET-2, the phase 2b study recruited patients with baseline IOP ≤35 mm Hg. To further explore the safety and efficacy of netarsudil, the phase 3 ROCKET-4 study was undertaken with broader IOP inclusion criteria (baseline >20 to <30 mm Hg) relative to ROCKET-1 and ROCKET-2. In this report, we compare the efficacy (month 3) and safety (month 6) of netarsudil ophthalmic solution 0.02% QD and timolol ophthalmic solution 0.5% BID in ROCKET-4.

METHODS

• **PATIENTS AND STUDY DESIGN:** ROCKET-4 (www.clinicaltrials.gov identifier: NCT02558374) was a double-masked, randomized, multicenter (52 active sites in the United States), phase 3 study of adults (≥18 years) with open-angle glaucoma or ocular hypertension in both eyes. Patients were randomized (1:1) by a computer-generated method to receive either netarsudil ophthalmic solution 0.02% QD (PM) or timolol ophthalmic solution 0.5% BID for 6 months. Randomization was stratified by study site and maximum baseline IOP (<25 mm Hg vs ≥25 mm Hg). To maintain masking, patients randomized to netarsudil QD received vehicle in the morning and active drug in the evening.

Eligible participants had an unmedicated (postwashout, if needed) IOP >20 to <30 mm Hg per calibrated Goldmann applanation tonometer in both eyes at 8:00 AM at 2 qualification visits (2-7 days apart) and IOP >17 to <30 mm Hg in both eyes at 10:00 AM and 4:00 PM at the second qualification visit. The minimum washout period was 4 weeks for patients using prostaglandin analogues or beta-adrenoceptor antagonists prior to study entry, 2 weeks for those using adrenergic agonists, and 5 days for those using muscarinic agonists or topical carbonic anhydrase inhibitors.[19] Study participants also had a corrected visual acuity of 1.0 logarithm of the minimum angle of resolution or better per Early Treatment Diabetic Retinopathy Study criteria (equivalent to 20/200 or better Snellen). Excluded from the study were patients with clinically significant ocular or systemic disease, pseudoexfoliation or pigment dispersion glaucoma, history of angle closure or narrow angles, use of >2 ocular hypotensive medications within 30 days of screening, use of nonhypotensive ocular medication in either eye of any kind within 30 days of screening, changes in systemic medication that could have an effect on IOP in the 30 days prior to screening, hypersensitivity to any component of the study drugs, hypersensitivity or contraindication to beta-adrenergic antagonists, previous intraocular glaucoma or refractive surgery, previous glaucoma laser procedures, ocular trauma in the 6 months prior to screening, or ocular surgery or nonrefractive laser treatment in the 3 months prior to screening, as well as women of childbearing potential who were pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Also excluded were patients with recent or current ocular infection or inflammation in either eye, any abnormality preventing reliable applanation tonometry of either eye, mean central corneal thickness >620 μm at screening (related to tonometer accuracy), or clinically significant laboratory abnormalities at screening.

All participants provided written informed consent. ROCKET-4 was conducted in accordance with Good Clinical Practices guidelines and adhered to the Declaration of Helsinki. Institutional review board/ethics committee approval was obtained from all participating centers. Participating investigators and study sites are listed in the Acknowledgments.

• **ENDPOINTS:** Patients were evaluated at 8:00 AM, 10:00 AM, and 4:00 PM at weeks 2 and 6 and months 3, 4, 5, and 6. The primary efficacy endpoint was mean IOP at 8:00 AM, 10:00 AM, and 4:00 PM at week 2, week 6, and month 3 in patients with baseline IOP <25 mm Hg. In secondary efficacy analyses, mean IOP at 8:00 AM, 10:00 AM, and 4:00 PM at week 2, week 6, and month 3 was also examined in patients with baseline IOP <27 mm Hg and in the overall study population (baseline IOP <30 mm Hg). Two consecutive IOP measurements were obtained from each eye at each time point. If the 2 measurements differed by more than 2 mm Hg, a third measurement was obtained, with IOP analyzed as either the mean of 2 measurements or the median of 3 measurements. Mean diurnal IOP values were then calculated by averaging across patients within a treatment group at each of the 3 IOP measurement time points (8:00 AM, 10:00 AM, and 4:00 PM) at each study visit.

Assessment of safety and tolerability was based upon patient reports in response to open-ended questions (eg, "how are you feeling") and ophthalmic and systemic examinations. Ocular and systemic (heart rate, blood pressure, clinical laboratory examinations) adverse events (AEs) were recorded over the 6-month treatment period and coded per the Medical Dictionary for Regulatory Activities version 19.0. Conjunctival hyperemia was graded via biomicroscopy on a standardized, 4-point scale (0 [none] to 3 [severe]).

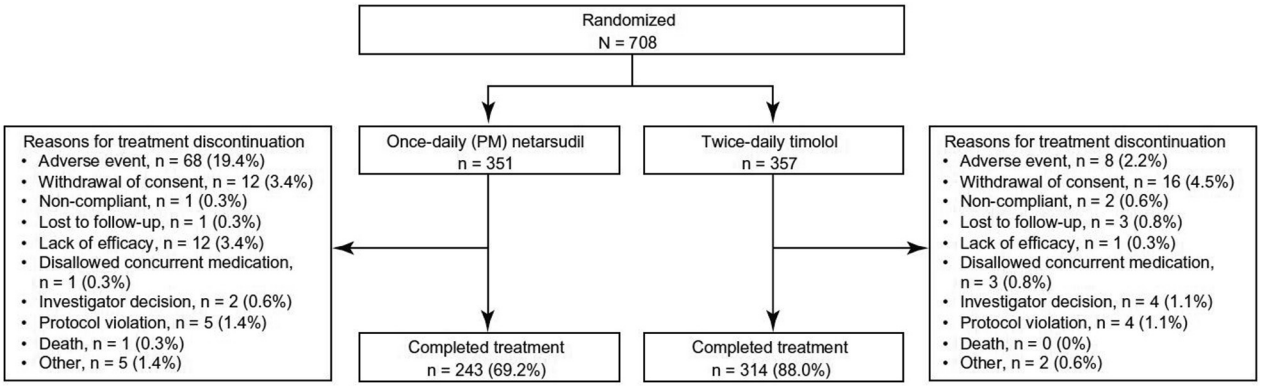

FIGURE 1. Patient disposition.

• **STATISTICS:** The primary efficacy analysis was performed on the per-protocol population using 2-sample 95% t-distribution confidence intervals (CIs) for each comparison at each time point (8:00 AM, 10:00 AM, and 4:00 PM at week 2, week 6, and month 3). For netarsudil QD to be considered noninferior to timolol BID, the upper bound of the 95% CI for the difference in mean IOP between the 2 treatments (netarsudil–timolol) had to be within 1.5 mm Hg at all 9 time points through month 3 and within 1.0 mm Hg for the majority of time points through month 3. Assuming zero difference between netarsudil QD and timolol BID, a 2-tailed alpha of 0.05 at each of the 9 study time points, a common standard deviation of 2.75 mm Hg, and a correlation between time points ≤0.60, 140 patients with baseline IOP <25 mm Hg in the per-protocol population of each treatment arm were needed to have 90% power to demonstrate noninferiority.

The safety analysis included all randomized patients who received ≥1 dose of study medication (safety population). Descriptive statistics were used to summarize safety outcomes in each treatment arm. All statistical analyses were performed using SAS version 9.2 or higher (SAS Institute, Cary, North Carolina, USA).

RESULTS

• **PATIENTS:** The ROCKET-4 study was undertaken between August 28, 2015 and December 16, 2016. In total, 708 patients were randomized, with 351 assigned to netarsudil QD and 357 assigned to timolol BID (Figure 1). Baseline demographics of randomized patients were similar between the 2 treatment arms (Table 1), with a mean age of approximately 64 years and a preponderance of women (59.3%–66.4%) and white patients (73.8%–76.8%). A total of 243 (69.2%) patients completed 6 months of treatment with netarsudil, and 314 (88.0%) completed 6 months of treatment with timolol. The reasons for treatment discontinuation are summarized in Figure 1.

• **EFFICACY:** A total of 186 patients in each treatment arm were included in the primary efficacy analysis, which was performed on patients with baseline IOP <25 mm Hg (per-protocol population). Mean baseline IOP at 8:00 AM, 10:00 AM, and 4:00 PM ranged from 20.7 to 22.4 mm Hg in both treatment arms (Table 2). Between week 2 and month 3, mean IOP ranged from 16.3 to 17.9 mm Hg among patients randomized to netarsudil QD and 16.7 to 17.6 mm Hg among those randomized to timolol BID, corresponding to mean decreases from baseline of 3.9 to 4.7 mm Hg and 3.8 to 5.2 mm Hg, respectively (Table 2, Figure 2). Percent reductions in IOP from baseline ranged from 18.7% to 21.4% for netarsudil QD and 18.1% to 22.9% for timolol BID. The reductions in IOP relative to baseline were significant for both netarsudil ($P < .0001$) and timolol ($P < .0001$). The upper bounds of the 95% CI for the differences in mean IOP between netarsudil and timolol were within 1.5 mm Hg at all 9 time points from the week 2, week 6, and month 3 study visits and within 1.0 mm Hg at the majority of time points (Table 2), indicating that netarsudil met the criteria for noninferiority to timolol. IOP measurements were collected beyond the primary efficacy analysis at month 3 as part of the safety evaluation. The IOP-lowering efficacy of netarsudil QD remained within the noninferiority range of timolol BID at all time points through month 6 (Figure 2, Table 2).

Netarsudil was also noninferior to timolol in prespecified secondary analyses of patients with baseline IOP <27 mm Hg (per-protocol population) and baseline IOP <30 mm Hg (overall per-protocol population). In these analyses, the upper bounds of the 95% CI for the differences in mean IOP between netarsudil and timolol were within 1.5 mm Hg at all 9 time points from the week 2, week 6, and month 3 study visits and within 1.0 mm Hg at the majority of time points (Supplemental Tables 1 and 2, available at www.AJO.com).

• **SAFETY:** All treated patients were included in the safety population. AEs were reported more frequently in

TABLE 1. Baseline Demographics of All Randomized Patients

	Once-Daily Netarsudil 0.02% (N = 351)	Twice-Daily Timolol 0.5% (N = 357)
Study eye diagnosis, n (%)		
OAG	223 (63.5)	244 (68.3)
OHT	128 (36.5)	113 (31.7)
Sex, n (%)		
Female	208 (59.3)	237 (66.4)
Male	143 (40.7)	120 (33.6)
Mean age, years (SD)	64.1 (11.6)	64.5 (11.0)
Age, n (%)		
<65 years	165 (47.0)	164 (45.9)
≥65 years	186 (53.0)	193 (54.1)
Race, n (%)		
White	259 (73.8)	274 (76.8)
Black/African American	84 (23.9)	75 (21.0)
Asian	7 (2.0)	6 (1.7)
Other[a]	1 (0.3)	2 (0.6)
Iris color of study eye, n (%)		
Brown/black	241 (68.7)	227 (63.6)
Blue/gray/green	74 (21.1)	90 (25.2)
Hazel	36 (10.3)	40 (11.2)
Mean time since diagnosis, weeks (SD)	364.1 (367.3)	344.2 (341.1)
Prior hypotensive therapy, n (%)		
Combination therapy	24 (6.8)	21 (5.9)
Prostaglandin monotherapy	163 (46.4)	167 (46.8)
Other monotherapy	34 (9.7)	34 (9.5)
No prior therapy	130 (37.0)	135 (37.8)

IOP = intraocular; OAG = open-angle glaucoma; OHT = ocular hypertension; SD = standard deviation.

[a] "Other" includes patients self-identified as Native Hawaiian or other Pacific Islander, multiple race, or other.

netarsudil-treated vs timolol-treated patients. Between baseline and month 6, 80.1% (281/351) of patients treated with netarsudil QD and 60.2% (215/357) of patients treated with timolol BID reported an AE. The majority of patients with AEs had a maximum severity of mild (netarsudil, 58.4% [164/281]; timolol, 73.0% [157/215]). The most frequent ocular AE was conjunctival hyperemia (physician- and patient-reported) (Table 3), with an incidence of 47.9% (168/351) in the netarsudil group and 9.2% (33/357) in the timolol group. Of note, 22.2% (78/351) of netarsudil-treated patients and 20.7% (74/357) of timolol-treated patients had conjunctival hyperemia at baseline (4:00 PM). Among patients with an AE of conjunctival hyperemia, the event was mild in 76.8% (129/168) of those treated with netarsudil and 97.0% (32/33) of those treated with timolol. When examined via biomicroscopy, the severity of conjunctival hyperemia did not increase with continued dosing of netarsudil, as there was no significant change in mean hyperemia score between week 2 and month 6 (Figure 3). Based on biomicroscopy, conjunctival hyperemia occurred intermittently. In total, 12.5% (21/168) of netarsudil-treated patients and 9.1% (3/33) of timolol-treated patients had conjunctival hyperemia at each study visit to month 3, the timing of the primary endpoint analysis; only 1 (0.6%) patient, who was treated with netarsudil, had conjunctival hyperemia at every study visit to month 6. In the netarsudil treatment arm, more physicians (45.0% [158/351]) than patients (9.4% [33/351]) reported conjunctival hyperemia; the corresponding values in the timolol treatment arm were 8.4% (30/357) and 1.4% (5/357). A total of 4.0% (14/351) of study participants discontinued netarsudil owing to conjunctival hyperemia.

Other common ocular AEs in netarsudil-treated patients were cornea verticillata and conjunctival hemorrhage. Cornea verticillata were reported in 24.5% (86/351) of netarsudil-treated patients and in no timolol-treated patient. Cornea verticillata were reported as mild (87.2% [75/86]) or moderate (12.8% [11/86]) in affected netarsudil-treated patients. They predominantly occurred bilaterally and did not have a clinically meaningful impact on visual acuity. The mean time to onset of cornea verticillata was 109.2 (range, 30-183) days. By study end, cornea verticillata had resolved in 60.5% (52/86) of affected patients following treatment cessation, with a mean time to resolution following treatment cessation of 87.3 (range, 0-264) days. Based on the investigator's decision, 4.0% (14/351) of patients were discontinued from netarsudil owing to cornea verticillata.

Conjunctival hemorrhage was observed in 16.0% (56/351) of patients randomized to netarsudil and 3.1% (11/357) of patients randomized to timolol. Conjunctival hemorrhage, which was typically described by investigators as small petechial hemorrhages, was reported as mild (98.2% [55/56]) or moderate (1.8% [1/56]) in netarsudil-treated patients and as mild in timolol-treated patients. Conjunctival hemorrhage did not have a clinically meaningful effect on visual acuity (ie, all reports were asymptomatic) and was self-resolving. One netarsudil-treated patient discontinued owing to conjunctival hemorrhage.

Specific nonocular AEs were infrequent (each had an incidence of <4%) and similar between treatment arms. Across both treatment arms, 18 patients reported a total of 23 serious AEs, but none was considered related to study drug, and none was ocular. Mean changes in systolic and diastolic blood pressure were <4 mm Hg for each treatment arm throughout the duration of the study. Mean changes in heart rate were <1 beat per minute in the netarsudil QD group and not statistically significant at any time point. In contrast, the timolol BID group showed statistically significant ($P < .01$) reductions in mean heart rate of up to 3 beats per minute across all on-treatment study visits (Figure 4). One patient randomized to netarsudil QD died of cardiac arrest, but this death was considered unrelated to study medication.

TABLE 2. Mean Intraocular Pressure and Mean Change in Intraocular Pressure in the Primary Efficacy Population[a]

	Once-Daily Netarsudil 0.02% (N = 186)		Twice-Daily Timolol 0.5% (N = 186)		
	Mean IOP	Mean Change in IOP From Baseline	Mean IOP	Mean Change in IOP From Baseline	Difference vs Timolol (95% CI)
Baseline		—		—	—
8:00 AM	22.40		22.44		
10:00 AM	21.06		21.27		
4:00 PM	20.69		20.69		
Week 2					
8:00 AM	17.68	−4.74	17.51	−4.94	0.17 (−0.43 to 0.77)
10:00 AM	16.55	−4.51	16.71	−4.55	−0.16 (−0.73 to 0.41)
4:00 PM	16.32	−4.37	16.92	−3.77	−0.60 (−1.16 to −0.04)
Week 6					
8:00 AM	17.84	−4.55	17.60	−4.85	0.25 (−0.34 to 0.83)
10:00 AM	16.75	−4.27	16.98	−4.29	−0.22 (−0.82 to 0.37)
4:00 PM	16.57	−4.09	16.67	−4.01	−0.10 (−0.66 to 0.46)
Month 3					
8:00 AM	17.86	−4.52	17.29	−5.17	0.56 (−0.02 to 1.15)
10:00 AM	16.90	−4.10	16.69	−4.56	0.21 (−0.37 to 0.79)
4:00 PM	16.73	−3.88	16.80	−3.89	−0.07 (−0.68 to 0.55)

CI = confidence interval; IOP = intraocular pressure.
Data are expressed as mmHg.
[a]Baseline IOP <25 mm Hg, per-protocol population.

DISCUSSION

IN THE PHASE 3 ROCKET-4 STUDY, NETARSUDIL ophthalmic solution 0.02% QD (PM) achieved clinically relevant and statistically significant reductions in mean IOP from baseline at all time points. The reductions in IOP with netarsudil QD met the criteria for noninferiority to those of timolol BID in the primary efficacy analysis (patients with baseline IOP <25 mm Hg) and in 2 prespecified secondary efficacy analyses (patients with baseline IOP <27 mm Hg and <30 mm Hg). Furthermore, the consistent level of IOP lowering seen across baseline pressures was maintained (stable) over 6 months.

The primary efficacy outcome in ROCKET-4 is consistent with the results of the 2 large phase 3 ROCKET-1 and ROCKET-2 studies, where the IOP-lowering effects of netarsudil QD met the criteria for noninferiority to timolol BID in patients with baseline IOP <25 mm Hg over 3 months.[17] However, unlike ROCKET-1 and ROCKET-2, ROCKET-4 demonstrated noninferiority of netarsudil QD to timolol BID when the analysis population included patients with maximum baseline IOP <27 mm Hg and also <30 mm Hg. These results are consistent with a phase 2b study that showed the efficacy of netarsudil to be similar to that of latanoprost in patients with baseline IOP ≤26 mm Hg.[18] The ROCKET-4 and phase 2b studies recruited patients with higher baseline pressures (up to <30 mm Hg and <36 mm Hg, respectively) than the ROCKET-1 and ROCKET-2 studies (<27 mm Hg). It is possible that the more restrictive IOP inclusion criterion in ROCKET-1 and ROCKET-2 was not effective at excluding patients with higher unmedicated IOP, but inadvertently selected for patients with lower unmedicated IOP on the day of enrollment than was typical for them. Notably, this phenomenon would have been expected to favor the timolol treatment arm, as timolol produces larger IOP reductions at higher baseline IOP.[20] However, in ROCKET-4, netarsudil demonstrated noninferiority to timolol across the entire range of baseline pressures.

Although more AEs were reported in the netarsudil vs timolol treatment arm, the large majority of AEs among netarsudil-treated patients were mild and considered manageable. The discontinuation rate for netarsudil was higher than for timolol, but was similar to that reported in registration studies for other approved glaucoma products.[21,22] Of note, patients with known contraindications or hypersensitivity to timolol were ineligible for participation in ROCKET-4, which may have contributed to the lower observed discontinuation rate for timolol. The most frequent ocular AE among netarsudil-treated patients was conjunctival hyperemia. The majority of reports of conjunctival hyperemia were mild and intermittent and the severity did not increase over 6 months of dosing (mean severity score via biomicroscopy <1 at all time points). However, this AE may be intolerable to some patients and, in the current study, led to discontinuation in 4.0% of netarsudil-treated patients. Although conjunctival hyperemia is an expected consequence of the known vasodilatory effects of ROCK inhibition,[23–25] this ocular AE is not specific to ROCK inhibitors. In a meta-analysis of randomized clinical trials of

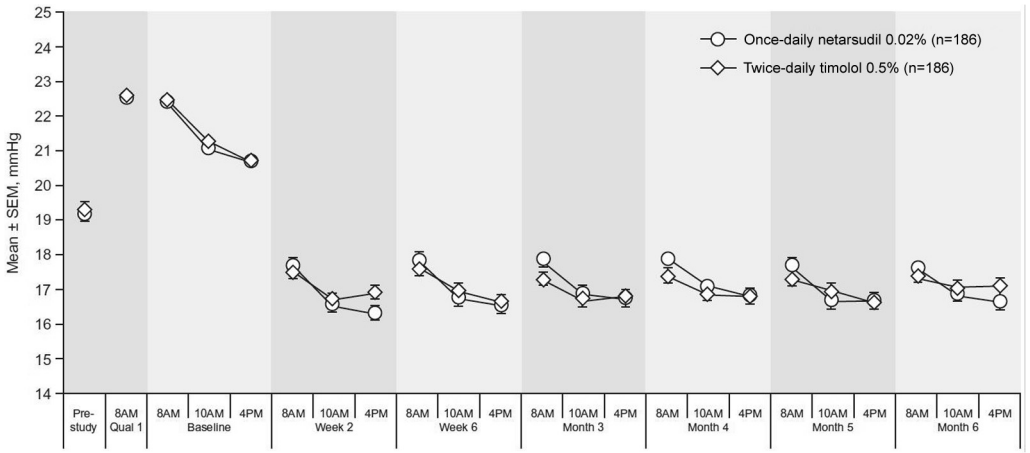

FIGURE 2. Mean intraocular pressure in the primary efficacy population (baseline intraocular pressure < 25 mm Hg, per-protocol population). SEM = standard error of the mean.

TABLE 3. Adverse Events Occurring in ≥5% of Patients in Either Treatment Arm

	Once-Daily Netarsudil 0.02% (N = 351)	Twice-Daily Timolol 0.5% (N = 357)
≥1 AE	281 (80.1)	215 (60.2)
≥1 ocular AE	267 (76.1)	180 (50.4)
Eye disorders		
Conjunctival hyperemia	168 (47.9)	33 (9.2)
Cornea verticillata	86 (24.5)	0 (0)
Conjunctival hemorrhage	56 (16.0)	11 (3.1)
Lacrimation increased	26 (7.4)	5 (1.4)
Erythema of eyelid	26 (7.4)	2 (0.6)
Vision blurred	22 (6.3)	4 (1.1)
General disorders and administration site conditions		
Instillation site pain	83 (23.6)	92 (25.8)
Instillation site erythema	36 (10.3)	4 (1.1)
Investigations		
Vital dye staining cornea present	34 (9.7)	24 (6.7)
≥1 nonocular AE	82 (23.4)	91 (25.5)

AE = adverse event.
Data are expressed as n (%).

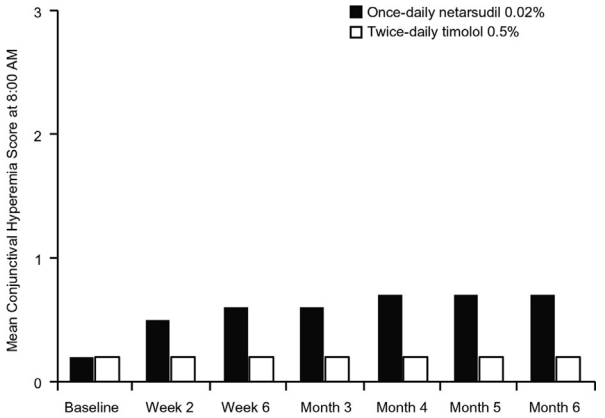

FIGURE 3. Mean hyperemia score (8:00 AM), as measured via biomicroscopy. Grading of the severity of conjunctival hyperemia was performed on a standardized, 4-point scale, where 0 = none (normal; appears white with a small number of conjunctival blood vessels easily observed); 1 = mild (prominent pinkish red color of both the bulbar and palpebral conjunctiva); 2 = moderate (bright, scarlet red color of the bulbar and palpebral conjunctiva); and 3 = severe ("beefy red" with petechiae; dark red bulbar and palpebral conjunctiva with evidence of subconjunctival hemorrhage).

prostaglandin analogues, rates of conjunctival hyperemia ranged from 3.3% to 47.1% among patients administered latanoprost, 14.3% to 68.6% among those administered bimatoprost, and 6.2% to 58.0% among those administered travoprost.[26]

Other commonly observed ocular AEs among netarsudil-treated patients were cornea verticillata and conjunctival hemorrhage. Cornea verticillata are benign lipid microdeposits that collect in the corneal epithelium. They form through a process known as phospholipidosis, which occurs when cationic amphiphilic drugs such as netarsudil complex with lysosomal phospholipids.[27–29] They are a result of the chemical properties of the drug and are not metabolic in nature. Cornea verticillata are a common occurrence with amiodarone[30] and other treatments that have been approved by the United States Food and Drug Administration.[29] Cornea verticillata were reported as mild or moderate in all affected ROCKET-4 study participants and were not associated

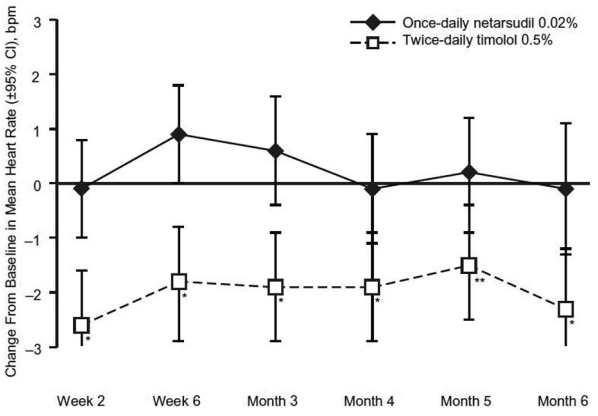

FIGURE 4. Change in mean heart rate (±95% CI) relative to baseline. CI derived from paired *t* tests of differences. **P* < .001; ***P* < .01. bpm = beats per minute; CI = confidence interval.

with decreases in visual function; they were only observed at the biomicroscope (ie, patients were asymptomatic and unaware of the presence of cornea verticillata) and resolved following treatment cessation in most (60.5%) affected patients by study end. Conjunctival hemorrhage, which was typically described by investigators as small petechial hemorrhages, was reported as mild or moderate in all cases and generally resolved with continued use of netarsudil.

In ROCKET-4, there was no evidence of netarsudil-related serious AEs. No treatment-related serious AE was reported among timolol-treated patients either; however, there were reductions in heart rate that were statistically significant and consistent with the known adverse effects of timolol.[31] Overall, the safety profile of netarsudil in ROCKET-4 was consistent with observations from ROCKET-1 and ROCKET-2 (ie, no new safety issues were uncovered).[17]

In conclusion, netarsudil QD is effective at lowering IOP in patients with open-angle glaucoma or ocular hypertension, with tolerable ocular AEs. The IOP-lowering efficacy of netarsudil QD is noninferior to that of timolol BID, is consistent across lower and higher baseline pressures, and is sustained over 6 months of treatment. As a new class of treatment with a novel mechanism of action, netarsudil QD has the potential to be used both as a single agent and as an adjunct to currently used IOP-lowering treatments.

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REFERENCES

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014;121(11):2081–2090.
2. Vrabec JP, Levin LA. The neurobiology of cell death in glaucoma. *Eye (Lond)* 2007;21(Suppl 1):S11–S14.
3. Prum BE Jr, Rosenberg LF, Gedde SJ, et al. Primary open-angle glaucoma Preferred Practice Pattern(®) guidelines. *Ophthalmology* 2016;123(1):P41–P111.
4. Stamer WD, Acott TS. Current understanding of conventional outflow dysfunction in glaucoma. *Curr Opin Ophthalmol* 2012;23(2):135–143.
5. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol* 1998; 126(4):498–505.
6. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000;130(4):429–440.
7. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120(6):701–713.
8. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002;120(10): 1268–1279.
9. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2003;121(1):48–56.
10. RHOPRESSA® (netarsudil ophthalmic solution 0.02%) [prescribing information] Durham, NC: Aerie Pharmaceuticals, Inc; 2017.
11. Kazemi A, McLaren JW, Kopczynski CC, Heah TG, Novack GD, Sit AJ. The effects of netarsudil ophthalmic solution on aqueous humor dynamics in a randomized study in humans. *J Ocul Pharmacol Ther* 2018;34(5): 380–386.
12. Lin CW, Sherman B, Moore LA, et al. Discovery and preclinical development of netarsudil, a novel ocular hypotensive agent for the treatment of glaucoma. *J Ocul Pharmacol Ther* 2018;34(1-2):40–51.
13. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *J Glaucoma* 2015;24(1):51–54.
14. Ren R, Li G, Le TD, et al. Netarsudil increases outflow facility in human eyes through multiple mechanisms. *Invest Ophthalmol Vis Sci* 2016;57(14):6197–6209.
15. Li G, Mukherjee D, Navarro I, et al. Visualization of conventional outflow tissue responses to netarsudil in living mouse eyes. *Eur J Pharmacol* 2016;787:20–31.
16. Kiel JW, Kopczynski CC. Effect of AR-13324 on episcleral venous pressure in Dutch belted rabbits. *J Ocul Pharmacol Ther* 2015;31(3):146–151.
17. Serle JB, Katz LJ, McLaurin E, et al. Two phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure. *Am J Ophthalmol* 2018;186:116–127.
18. Bacharach J, Dubiner HB, Levy B, Kopczynski CC, Novack GD, AR-13324-CS202 Study Group. Double-masked, randomized, dose-response study of AR-13324 versus latanoprost in patients with elevated intraocular pressure. *Ophthalmology* 2015;122(2):302–307.
19. Hughes BA, Bacharach J, Craven ER, et al. A three-month, multicenter, double-masked study of the safety and efficacy of travoprost 0.004%/timolol 0.5% ophthalmic solution compared to travoprost 0.004% ophthalmic solution and timolol 0.5% dosed concomitantly in subjects with open angle glaucoma or ocular hypertension. *J Glaucoma* 2005; 14(5):392–399.
20. Hedman K, Alm A. A pooled-data analysis of three randomized, double-masked, six-month clinical studies comparing the intraocular pressure reducing effect of latanoprost and timolol. *Eur J Ophthalmol* 2000;10(2):95–104.
21. Chambers WA. Simbrinza™ (brinzolamide/brimonidine ophthalmic suspension) 1%/0.2%. NDA 204251. Center for Drug Evaluation and Research; 2012.
22. Food and Drug Administration, Freedom of Information Staff. Alphagan® (brimonidine tartrate ophthalmic solution) 0.2% sterile. NDA 20-613. Center for Drug Evaluation and Research; 1996.
23. Kopczynski CC, Epstein DL. Emerging trabecular outflow drugs. *J Ocul Pharmacol Ther* 2014;30(2):85–87.
24. Rao PV, Pattabiraman PP, Kopczynski C. Role of the Rho GTPase/Rho kinase signaling pathway in pathogenesis and treatment of glaucoma: bench to bedside research. *Exp Eye Res* 2017;158:23–32.
25. Watabe H, Abe S, Yoshitomi T. Effects of Rho-associated protein kinase inhibitors Y-27632 and Y-39983 on isolated rabbit ciliary arteries. *Jpn J Ophthalmol* 2011;55(4):411–417.
26. Honrubia F, García-Sánchez J, Polo V, de la Casa JM, Soto J. Conjunctival hyperaemia with the use of latanoprost versus other prostaglandin analogues in patients with ocular hypertension or glaucoma: a meta-analysis of randomised clinical trials. *Br J Ophthalmol* 2009;93(3):316–321.
27. Halliwell WH. Cationic amphiphilic drug-induced phospholipidosis. *Toxicol Pathol* 1997;25(1):53–60.
28. Hollander DA, Aldave AJ. Drug-induced corneal complications. *Curr Opin Ophthalmol* 2004;15(6):541–548.
29. Raizman MB, Hamrah P, Holland EJ, et al. Drug-induced corneal epithelial changes. *Surv Ophthalmol* 2017;62(3): 286–301.
30. CORDARONE® (amiodarone HCl) [prescribing information] Philadelphia, PA: Wyeth Pharmaceuticals Inc; 2017.
31. TIMOPTIC® 0.25% and 0.5% (timolol maleate ophthalmic solution) [prescribing information] Bridgewater, NJ: Bausch & Lomb Incorporated; 2016.