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Pooled Efficacy and Safety Profile of Netarsudil Ophthalmic Solution 0.02% in Patients With Open-angle Glaucoma or Ocular Hypertension

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Precis: In pooled phase III analyses, once-daily netarsudil 0.02% resulted in intraocular pressure (IOP) reduction that was noninferior to twice-daily timolol 0.5%, with minimal treatment-related serious or systemic adverse events (AEs). Ocular AEs were generally tolerable.

Purpose: The purpose of this study was to assess the efficacy and safety of the Rho kinase inhibitor netarsudil in patients with open-angle glaucoma or ocular hypertension.

Patients and Methods: Pooled analysis of data from the ROCKET-1 to 4 phase III studies of once-daily (PM) netarsudil or twice-daily timolol in patients with open-angle glaucoma or ocular hypertension. The primary efficacy measure 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.

Results: In the pooled primary efficacy population (netarsudil, n = 494; timolol, n = 510), once-daily netarsudil was noninferior to twice-daily timolol at all 9 timepoints through month 3. Mean treated IOP ranged from 16.4 to 18.1 mm Hg among netarsudil-treated patients and 16.8 to 17.6 mm Hg among timolol-treated patients. In the pooled safety population (n = 839 in each treatment group), treatment-related serious AEs occurred at similar frequencies in each treatment group (netarsudil, 0.1%; timolol, 0%). The most common ocular AE, conjunctival hyperemia (netarsudil, 54.4%; timolol, 10.4%), was graded as mild in 77.6% (354/456) of affected netarsudil-treated patients.

Conclusions: Once-daily netarsudil resulted in IOP lowering that was noninferior to twice-daily timolol, with tolerable ocular AEs that were generally mild and self-resolving. As a first-in-class agent in the United States, with a novel mechanism of action, netarsudil may provide a useful therapeutic option for patients who would benefit from IOP lowering.

Key Words: open-angle glaucoma, ocular hypertension, netarsudil, timolol, head-to-head study

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Glaucoma is a complex and progressive disease that is ultimately caused by damage to optic nerve axons and subsequent destruction of retinal ganglion cells.[1] The aggregate health burden of this condition is particularly acute given its increasing prevalence in an aging global population; it is estimated that the number of people 40 to 80 years of age with glaucoma worldwide will increase from 76.0 million in 2020 to 111.8 million in 2040.[2] Intraocular pressure (IOP) is currently the only known modifiable risk factor for preventing disease progression and visual field loss in patients with glaucoma or ocular hypertension.[3–8] IOP is primarily regulated by the level of resistance to aqueous humor outflow through the trabecular (conventional) outflow pathway.[9] Although the specific mechanisms underlying the pathophysiology of elevated IOP have yet to be confirmed, increases in the stiffness of the trabecular meshwork have been proposed.[9,10] The most commonly used ocular hypotensive treatments do not affect trabecular outflow as a primary mechanism, but rather lower IOP by either increasing uveoscleral (nonconventional) outflow or decreasing aqueous humor production.[11,12] Thus, there is a long-standing need for an agent that directly targets the underlying etiology of elevated IOP, including functional

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defects in the trabecular outflow pathway. Existing ocular hypotensive treatments can also lead to systemic adverse events (AEs). For example, beta-blockers (such as timolol) have been associated with bronchospasm and bradycardia[11]; as a consequence, this class of agents may not be appropriate as first line for patients with certain respiratory or cardiac conditions.[13,14]

Rho kinase (ROCK), which is expressed by cells within the trabecular outflow pathway,[15] increases trabecular outflow resistance (and thus increases IOP) through activation of actin-myosin contraction.[16,17] ROCK inhibitors reduce actin-myosin contraction and represent a new class of ocular hypotensive agents. In preclinical studies, the ROCK inhibitor netarsudil has been shown to lower IOP primarily by increasing trabecular outflow,[18–20] but also by decreasing aqueous humor production[18] and lowering episcleral venous pressure.[21] In a phase I clinical study, netarsudil was found to lower IOP in healthy volunteers through a unique combination of increasing trabecular outflow facility and decreasing episcleral venous pressure.[22] A subsequent study confirmed this mechanism of action in patients with primary open-angle glaucoma or ocular hypertension, showing that netarsudil produced ~35% increase in outflow facility and a 9.5% decrease in episcleral venous pressure.[23]

Once-daily netarsudil ophthalmic solution 0.02% (Rhopressa) was approved by the United States Food and Drug Administration in December 2017 for reducing elevated IOP in patients with open-angle glaucoma or ocular hypertension. In November 2019 it was approved by the European Medicines Agency under the trade name Rhokiinsa for primary open angle glaucoma and ocular hypertension.[24,25] To better characterize the clinical profile of netarsudil, data from the ROCKET series of phase III clinical trials[26–29] were pooled and analyzed to evaluate netarsudil efficacy (ROCKET-1, ROCKET-2, and ROCKET-4) and safety (ROCKET-1, ROCKET-2, ROCKET-3, and ROCKET-4).

PATIENTS AND METHODS

Patients and Study Design

Efficacy and safety data were pooled from the ROCKET trials, including ROCKET-1, ROCKET-2, and ROCKET-4 for efficacy (ROCKET-3 was solely a safety study), and ROCKET-1 (NCT02207491), ROCKET-2 (NCT02207621), ROCKET-3 (NCT02246764), and ROCKET-4 (NCT02558374) for safety.[26–29] These trials were similarly designed, randomized, phase III studies comparing once-daily (PM) netarsudil ophthalmic solution 0.02% with twice-daily timolol maleate ophthalmic solution 0.5%. To maintain masking, patients randomized to once-daily netarsudil received placebo in the morning and active drug in the evening. ROCKET-2 and ROCKET-3 also evaluated twice-daily netarsudil ophthalmic solution 0.02%, but because the approved dosage is once-daily in the evening, data on twice-daily treatment with netarsudil will not be presented. The ROCKET studies ranged in duration from 3 to 12 months (ROCKET-1, 3 mo; ROCKET-2, 12 mo; ROCKET-3, 12 mo; ROCKET-4, 6 mo); the pooled efficacy analysis includes 3-month data only (Fig. 1).

Inclusion/exclusion criteria have been previously described.[26,27] Briefly, eligible adults had open-angle glaucoma or ocular hypertension in both eyes, which was defined as untreated IOP ranging from >20 to <27 mm Hg (ROCKET-1, ROCKET-2, ROCKET-3) or from >20 to <30 mm Hg (ROCKET-4) at 8:00 AM at 2 qualification visits scheduled 2 to 7 days apart. Patients with known contraindications or hypersensitivity to timolol were excluded. The pretreatment washout period was ≥4 weeks for patients using prostaglandin analogs or beta-blockers before study entry, ≥2 weeks for those using alpha-agonists, and ≥5 days for those using muscarinic agonists or carbonic anhydrase inhibitors.

The ROCKET series of studies were conducted in accordance with Good Clinical Practice Guidelines and adhered to Declaration of Helsinki principles. All participants provided written informed consent, and approval was obtained from the institutional review board/ethics committee at all participating centers.

Statistical Analyses

The primary efficacy endpoint of the analysis was mean IOP at 8:00 AM, 10:00 AM, and 4:00 PM at week 2, week 6, and month 3 in the per-protocol population (patients who did not have major protocol violations likely to seriously affect the primary outcome of the study) with baseline IOP <25 mm Hg (primary efficacy population). As a secondary efficacy analysis, the primary efficacy analysis was repeated in the overall per-protocol population with baseline IOPs up to <30 mm Hg. For the primary efficacy analysis, noninferiority was concluded if the upper bound of the 95%

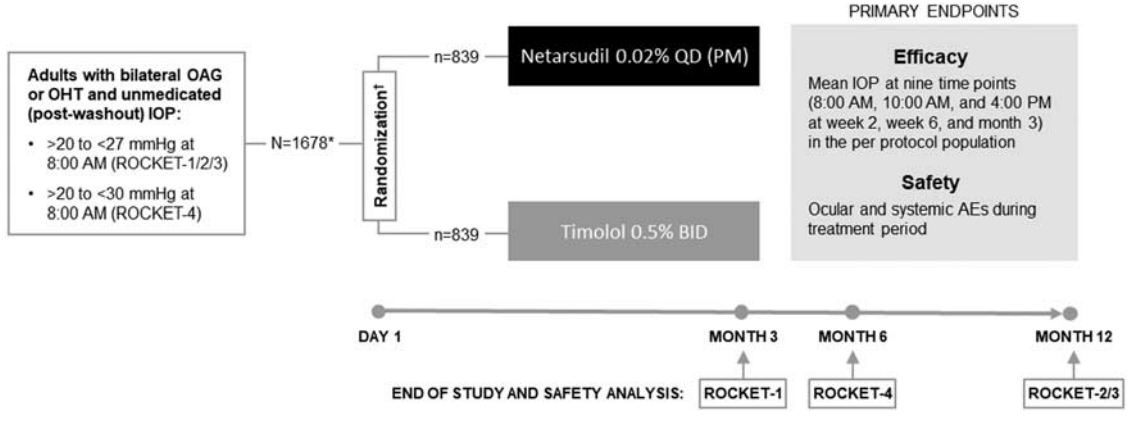


FIGURE 1. Pooled analysis population. *Numbers of patients shown are the safety population. †A netarsudil bid study arm was included in ROCKET-2 and ROCKET-3 but was not evaluated in this analysis. AE indicates adverse event; bid, twice daily; IOP, intraocular pressure; OAG, open-angle glaucoma; OHT, ocular hypertension; QD, once daily.

confidence interval (CI) for the difference in mean IOP between once-daily netarsudil and twice-daily timolol was within 1.5 mm Hg at all 9 timepoints and within 1.0 mm Hg for the majority of timepoints.

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. AEs were coded per the Medical Dictionary for Regulatory Activities version 19.0. Safety data (ocular and systemic AEs) for up to 12 months of treatment from ROCKET-1, ROCKET-2, ROCKET-3, and ROCKET-4 and were pooled by treatment arm, with patients analyzed according to the study treatment received. The safety analysis included all randomized patients who received ≥1 dose of study medication (safety population). Data are summarized using descriptive statistics.

RESULTS

Demographic and Baseline Characteristics: Pooled Efficacy and Safety Populations

The pooled efficacy population consisted of 804 patients randomized to once-daily netarsudil and 817 randomized to twice-daily timolol. Of these, 494 randomized to once-daily netarsudil and 510 randomized to twice-daily timolol had baseline IOP <25 mm Hg; 428 (86.6%) and 453 (88.8%), respectively, were included in the per-protocol population. A total of 86.6% (428/494) of the netarsudil group and 94.5% (482/510) of the timolol group with baseline IOP <25 mm Hg completed 3 months of study treatment. Similar proportions of patients with baseline IOP <30 mm Hg (overall population) completed 3 months of study treatment, 82.8% (666/804) of the netarsudil group and 94.0% (768/817) of the timolol group. There were no notable differences in baseline characteristics between treatment arms in either study population (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/IJG/A438).

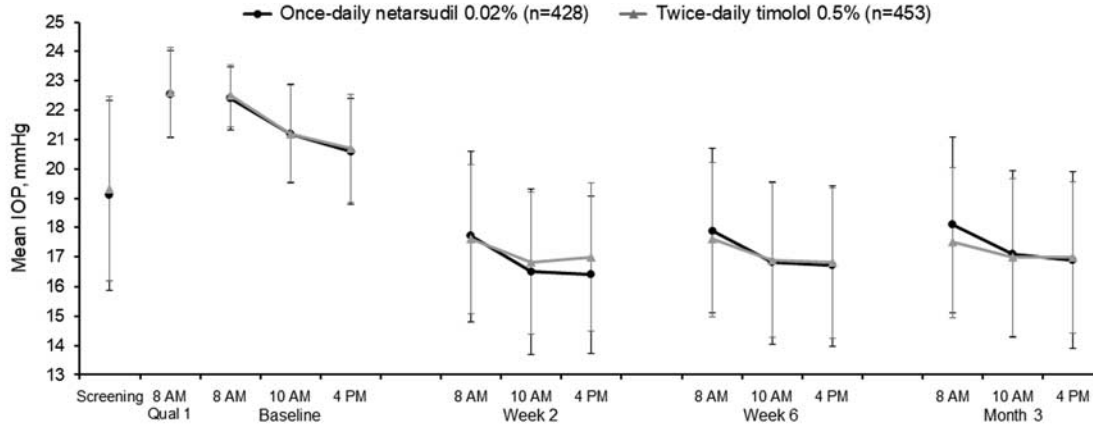
The pooled safety population included 839 patients treated with once-daily netarsudil and 839 treated with twice-daily timolol. Of these, 31.5% (264/839) of netarsudil patients and 12.6% (106/839) of timolol patients discontinued treatment before the end of their respective studies. There were no notable differences in baseline characteristics between treatment arms in this pooled analysis (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/IJG/A439).

Pooled Efficacy Results

In the per-protocol population of patients with baseline IOP <25 mm Hg, once-daily netarsudil met the criteria for noninferiority to twice-daily timolol at all 9 timepoints through month 3 (Fig. 2). Mean treated IOP ranged from 16.4 to 18.1 mm Hg among netarsudil-treated patients, and 16.8 to 17.6 mm Hg among timolol-treated patients, with mean IOP reductions from baseline up to 4.8 and up to 5.0 mm Hg, respectively.

Once-daily netarsudil also met the criteria for noninferiority to twice-daily timolol through month 3 in patients with baseline IOP <30 mm Hg. Mean treated IOP in this population ranged from 17.5 to 19.5 mm Hg among netarsudil-treated patients and 17.6 to 18.4 mm Hg among timolol-treated patients, with mean IOP reductions from baseline up to 4.8 and up to 5.3 mm Hg, respectively (Table 1).

The IOP-lowering efficacy of once-daily netarsudil was stable across subgroups of patients with different baseline IOPs at study entry, whereas twice-daily timolol became progressively less effective in the subgroups with lower baseline IOPs (Fig. 3A). Similarly, a larger proportion of patients with lower baseline pressures achieved ≥20% reduction in mean diurnal IOP at month 3 when treated with once-daily netarsudil as compared with twice-daily timolol (Fig. 3B). In per-protocol patients with baseline IOP <25 mm Hg, 49.7% (188/378) of those randomized to once-daily netarsudil and 50.9% (223/438) of those randomized to twice-daily timolol achieved ≥20% reduction in mean diurnal IOP at month 3. The corresponding values in the overall population (IOP <30 mm Hg) were 45.0% (263/585) and 53.4% (370/693), respectively. Overall, achievement of ≥20% reduction in mean diurnal IOP was greater with



		8:00 AM	10:00 AM	4:00 PM	Diurnal Mean	8:00 AM	10:00 AM	4:00 PM	Diurnal Mean	8:00 AM	10:00 AM	4:00 PM	Diurnal Mean	8:00 AM	10:00 AM	4:00 PM	Diurnal Mean
Mean IOP, mmHg	Netarsudil	22.4	21.2	20.6	21.4	17.7	16.5	16.4	16.9	17.9	16.8	16.7	17.1	18.1	17.1	16.9	17.3
	Timolol	22.5	21.2	20.7	21.5	17.6	16.9	17.0	17.1	17.6	16.9	16.8	17.1	17.5	17.0	17.0	17.2
Difference of netarsudil vs. timolol (95% CI)		-	-	-	-	0.08 (-0.29, 0.44)	-0.34 (-0.69, 0.01)	-0.54 (-0.89, -0.20)	-0.29 (-0.60, 0.02)	0.28 (-0.09, 0.64)	-0.02 (-0.38, 0.35)	-0.11 (-0.47, 0.25)	0.04 (-0.28, 0.36)	0.56 (0.18, 0.94)	0.09 (-0.29, 0.47)	-0.07 (-0.45, 0.32)	0.18 (-0.16, 0.51)

FIGURE 2. Mean IOP through month 3 in the per-protocol population of patients with baseline IOP <25 mm Hg (primary efficacy population). Error bars are ± SD. CI indicates confidence interval; IOP, intraocular pressure; SD, standard deviation.

TABLE 1. Mean Intraocular Pressure (IOP) Through Month 3 in the Per-protocol Population of Patients With Baseline IOP <30 mm Hg (Overall Population)

	Once-daily Netarsudil 0.02% (n = 694)	Twice-daily Timolol 0.5% (n = 722)
Mean baseline IOP (mm Hg)*	21.9-23.7	21.8-23.6
Mean treated IOP (week 2 to month 3) (mm Hg)†	17.5-19.5	17.6-18.4
Mean IOP decrease from baseline (mm Hg)*	3.7-4.8	4.0-5.3

*On the basis of mean IOP at 8:00 AM, 10:00 AM, and 4:00 PM at the baseline visit.

†On the basis of mean IOP at 8:00 AM, 10:00 AM, and 4:00 PM at the week 2, week 6, and month 3 visits.

once-daily netarsudil at lower baseline IOPs and greater with twice-daily timolol at higher baseline IOPs.

Pooled Safety Analysis

A total of 83.3% (699/839) and 60.3% (506/839) of patients treated with once-daily netarsudil and twice-daily timolol, respectively, experienced an AE; 79.3% (665/839) and 49.3% (414/839), respectively, experienced an ocular AE. The proportion of patients experiencing a systemic AE was 26.3% (221/839) for netarsudil and 26.6% (223/839) for timolol (Supplemental Table 3, Supplemental Digital Content 3, http://links.lww.com/IJG/A440), with no systemic AE occurring in >2% of patients in either treatment arm, except for upper respiratory tract infection in 2.7% of timolol patients. The most frequently reported systemic AEs were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, headache, dermatitis contact, cough, and hypertension. Once-daily netarsudil had no clinically meaningful effect on mean heart rate, whereas the beta-blocker timolol reduced mean heart rate by 1.5 to 2.8 bpm at each study visit ($P < 0.01$) (Fig. 4).

Serious AEs were reported in 3.3% (28/839) of netarsudil-treated patients and 3.2% (27/839) of timolol-treated patients. One serious AE was considered treatment related by the study investigator, but not the medical monitor. Serious AEs reported in ≥2 study participants are presented in Supplemental Table 4 (Supplemental Digital Content 4, http://links.lww.com/IJG/A441).

No serious ocular AE was reported among patients administered once-daily netarsudil. Cataract was considered serious in one timolol-treated patient.

The most frequent ocular AE was conjunctival hyperemia [netarsudil, 54.4% (456/839); timolol, 10.4% (87/839)] (Table 2). Mean hyperemia score was <1 for both treatment arms at all study visits up to month 12 (Fig. 5A). Among patients in the once-daily netarsudil group who experienced conjunctival hyperemia, the severity of conjunctival hyperemia was graded as mild in 77.6% (354/456), moderate in 20.8% (95/456), and severe in 1.5% (7/456) of patients. The severity of conjunctival hyperemia by study visit and time point among patients administered once-daily netarsudil is summarized in Figure 5B. The severity of conjunctival hyperemia did not increase with continued dosing (Fig. 5A).

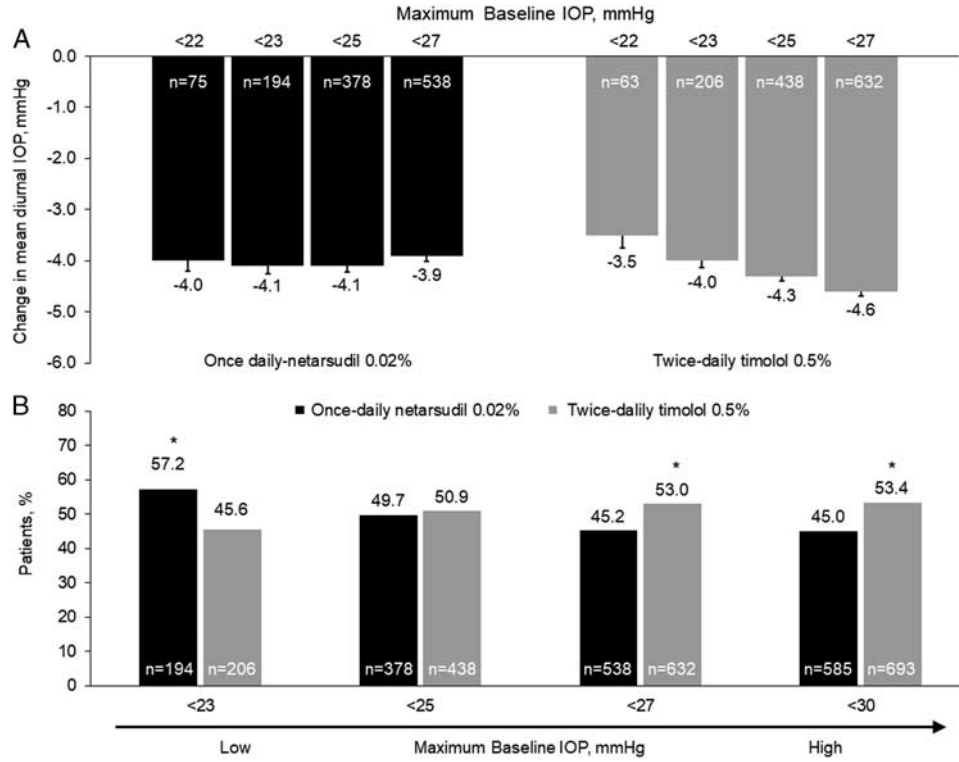


FIGURE 3. A, Change from baseline in mean diurnal intraocular pressure (IOP) at month 3 for subgroups with different baseline IOP thresholds (per-protocol population). B, Percentage of patients at month 3 achieving ≥20% reduction in mean diurnal IOP for subgroups with different baseline IOP thresholds (per-protocol populations). *$P < 0.05$ (once-daily netarsudil 0.02% vs. twice-daily timolol 0.5%). Error bars are SEM. SEM indicates standard error of the mean.

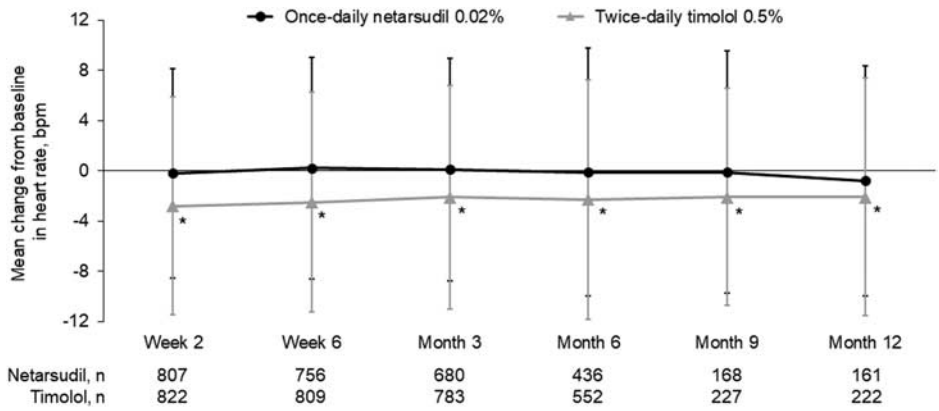


FIGURE 4. Mean change from baseline in heart rate. *$P < 0.01$ versus baseline. Error bars are ± SD. SD indicates standard deviation.

Conjunctival hyperemia occurred intermittently, with only 10.1% (46/456) of affected netarsudil-treated patients reporting this AE during 3 consecutive visits. Treatment discontinuation due to conjunctival hyperemia occurred in 6.0% (50/839) of netarsudil patients and 0% (0/839) of timolol patients.

Other ocular AEs among netarsudil-treated patients were cornea verticillata and conjunctival hemorrhage. Cornea verticillata were reported in 20.9% (175/839) of patients administered once-daily netarsudil and 0.2% (2/839) of those administered twice-daily timolol. Cornea verticillata were graded as either mild [89.7% (157/175)] or moderate [10.3% (18/175)] in all affected patients administered once-daily netarsudil and did not have a meaningful impact on visual acuity. The proportion of netarsudil-treated patients experiencing reduced visual acuity was comparable in the overall safety population [5.2% (44/839)] and in the subset of patients who developed cornea verticillata [7.4% (13/175)]. Discontinuations due to cornea verticillata were considered to be treatment related and occurred in 31 patients (3.7%). Conjunctival hemorrhage was reported in 17.2% (144/839) of patients administered once-daily netarsudil and 1.8% (15/839) of those administered twice-daily timolol. Of those treated with once-daily netarsudil affected by conjunctival hemorrhage, the event was graded as mild in 92.4% (133/144), moderate in 6.3% (9/144), and severe in 1.4% (2/144). Conjunctival hemorrhage occurred intermittently and was typically self-limiting, with only 4.2% (6/144) of affected netarsudil-treated patients reporting this AE during 3 consecutive visits. Treatment discontinuation due to conjunctival hemorrhage occurred in 1.0% (8/839) and 0% (0/839) of netarsudil and timolol patients, respectively.

Reduced visual acuity was reported in 5.2% (44/839) of the netarsudil-treated patients, and 3.5% (29/839) were considered treatment-related. All cases of reduced visual acuity were sporadic (in > 77% cases, the AE did not persist > 1 or 2 consecutive visits) and resolved at subsequent visits; only 1.2% (10/839) of netarsudil-treated patients discontinued the study drug as a result of this AE. Reduction in visual acuity may have been the result of concurrent AEs in some cases.

TABLE 2. Ocular Adverse Events Reported in ≥ 5% of Patients in Either Treatment Arm

	Once-daily Netarsudil 0.02% (n = 839)	Twice-daily Timolol 0.5% (n = 839)
Eye disorders		
Conjunctival hyperemia	456 (54.4)	87 (10.4)
Cornea verticillata	175 (20.9)	2 (0.2)
Conjunctival hemorrhage	144 (17.2)	15 (1.8)
Vision blurred	62 (7.4)	12 (1.4)
Lacrimation increased	60 (7.2)	5 (0.6)
Erythema of eyelid	57 (6.8)	6 (0.7)
Visual acuity reduced	44 (5.2)	13 (1.5)
Administration site conditions		
Instillation site pain	167 (19.9)	181 (21.6)
Instillation site erythema	76 (9.1)	13 (1.5)
Investigations		
Vital dye staining cornea present	79 (9.4)	64 (7.6)

Data are expressed as number (%) of patients.

DISCUSSION

Pooled analyses of the phase III ROCKET clinical trials found that once-daily netarsudil had IOP-lowering efficacy that was noninferior to that of twice-daily timolol and was generally well-tolerated with respect to both systemic and ocular events, findings that were consistent with the results from the individual ROCKET trials.

In the pooled efficacy analysis of 3 phase III ROCKET clinical trials, once-daily netarsudil achieved statistically significant and clinically relevant reductions in mean IOP from baseline, meeting the criteria for noninferiority to twice-daily timolol at all 9 timepoints over 3 months. Efficacy was shown across a range of baseline pressures, with once-daily netarsudil demonstrating noninferiority to timolol in the primary efficacy analysis of patients with baseline IOP <25 mm Hg, as well as in the overall patient population, which included patients with baseline IOP up to 30 mm Hg. Of note, the IOP-lowering efficacy of once-daily netarsudil was stable across baseline pressures, whereas the efficacy of twice-daily timolol varied with baseline IOP. The greater efficacy of timolol at higher versus lower baseline IOPs has previously been reported, with every 1 mm Hg decrease in baseline IOP associated with 0.5 mm Hg less effectiveness in IOP lowering.[30] A similar loss of IOP-lowering efficacy at lower baseline IOPs has been reported for prostaglandin analogs.[30,31]

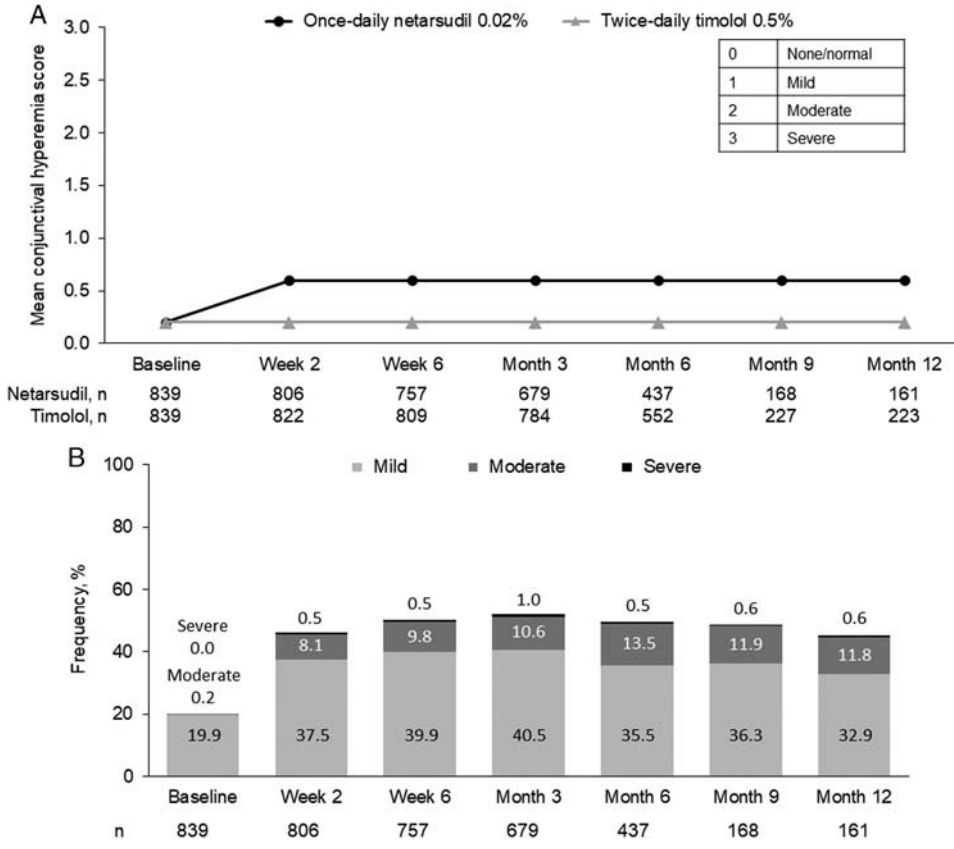


FIGURE 5. A, Mean conjunctival hyperemia score (8:00 AM) via biomicroscopy. B, Investigator-assessed maximum severity of conjunctival hyperemia (8:00 AM) among patients administered once-daily netarsudil. Biomicroscopic grading of conjunctival hyperemia was performed on a standardized, 4-point scale [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); 3 = severe ("beefy red" with petechiae; dark red bulbar and palpebral conjunctiva with evidence of subconjunctival hemorrhage)].[26]

In the pooled safety analysis of 4 phase III ROCKET trials, once-daily netarsudil was associated with a similar pattern of systemic AEs as timolol, minimal treatment-related serious AEs overall (1 case), and manageable ocular AEs. The most frequent AE among netarsudil-treated patients was conjunctival hyperemia, which was predominantly mild and intermittent. The severity of conjunctival hyperemia did not increase with continued dosing (mean score <1 at all study visits). However, the higher incidence of conjunctival hyperemia with netarsudil compared with timolol is not unexpected, for ROCK inhibitors have established vasodilatory effects.[12,32,33] Although ocular AEs are a common occurrence among topical ophthalmic agents, their acceptability differs among patients.

To conclude, treatment with once-daily netarsudil ophthalmic solution 0.02% resulted in IOP lowering that was noninferior to that of twice-daily timolol maleate ophthalmic solution 0.5% and was associated with minimal treatment-related serious AEs and manageable ocular AEs. Of note, the IOP-lowering efficacy of once-daily netarsudil was stable across patients with different baseline pressures and was sustained over 3 months of treatment. The novel pharmacology and aqueous humor dynamic effects of netarsudil suggest that it may be a useful treatment option for patients with open-angle glaucoma or ocular hypertension.

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