Two Phase 3 Clinical Trials Comparing the Safety and Efficacy of Netarsudil to Timolol in Patients With Elevated Intraocular Pressure: Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2)

JANET B. SERLE, L. JAY KATZ, EUGENE MCLAURIN, THERESA HEAH, NANCY RAMIREZ-DAVIS, DALE W. USNER, GARY D. NOVACK, AND CASEY C. KOPCZYNSKI, FOR THE ROCKET-1 AND ROCKET-2 STUDY GROUPS

• PURPOSE: To evaluate the efficacy and ocular and systemic safety of netarsudil 0.02% ophthalmic solution, a rho-kinase inhibitor and norepinephrine transporter inhibitor, in patients with open-angle glaucoma and ocular hypertension.

• DESIGN: Double-masked, randomized noninferiority clinical trials: Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2).

• METHODS: After a washout of all pre-study ocular hypotensive medications, eligible patients were randomized to receive netarsudil 0.02% once daily (q.d.), timolol 0.5% twice a day (b.i.d.), and (ROCKET-2 only) netarsudil 0.02% b.i.d. Data through 3 months from both studies are provided in this report.

• RESULTS: Enrolled into the 2 studies were 1167 patients. Treatment with netarsudil q.d. produced clinically and statistically significant reductions from baseline intraocular pressure ($P < .001$), and was noninferior to timolol in the per-protocol population with maximum baseline IOP < 25 mm Hg in both studies (ROCKET-2, primary outcome measure and population, ROCKET-1, post hoc outcome measure). Netarsudil b.i.d. was also noninferior to timolol (ROCKET-2). The most frequent adverse event was conjunctival hyperemia, the incidence of which ranged from 50% (126/251, ROCKET-2) to 53% (108/203, ROCKET-1) for netarsudil q.d., 59% (149/253, ROCKET-2) for netarsudil b.i.d., and 8% (17/208, ROCKET-1) to 11% (27/251, ROCKET-2) for timolol ($P < .0001$ for netarsudil vs timolol).

• CONCLUSIONS: In 2 large, randomized, double-masked trials reported here, once-daily dosing of netarsudil 0.02% was found to be effective and well tolerated for the treatment of patients with ocular hypertension and open-angle glaucoma. The novel pharmacology and aqueous humor dynamic effects of this molecule suggest it may be a useful addition to the armamentarium of ocular hypotensive medications. (Am J Ophthalmol 2018;186:116–127. © 2017 The Authors. 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 A LEADING CAUSE OF IRREVERSIBLE blindness that affects more than 60 million people worldwide.[1,2] Longitudinal studies of treatment of glaucoma and ocular hypertension demonstrate that lowering intraocular pressure (IOP) decreases the development of glaucomatous visual field loss.[3–7] Current treatment guidelines for the management of glaucomatous disease center on the reduction of IOP, be it by pharmacological, surgical, or laser methods.

Although current ocular hypotensive medications are generally effective at lowering IOP, many patients do not achieve target IOPs with a single ocular hypotensive medication.[5,8] The medical treatment regimen for these patients typically requires co-administration of 2 or more glaucoma medications, 1 or more of which requires dosing 2–3 times per day. As glaucoma treatment regimens increase in complexity, patients become less compliant with their therapy.[9,10] Novel pharmacotherapies that can produce effective IOP lowering while providing a convenient, once-daily dosing regimen are needed.

A new class of topical agents being evaluated for the treatment of glaucoma are Rho kinase (ROCK) inhibitors.[11] The most commonly prescribed ocular hypotensive medications reduce IOP by increasing uveoscleral aqueous outflow (prostaglandin analogues) or decreasing aqueous

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From the Icahn School of Medicine at Mount Sinai, New York, New York (J.B.S.); Wills Eye Hospital, Philadelphia, Pennsylvania (L.J.K.); Total Eye Care, Memphis, Tennessee (E.M.); Aerie Pharmaceuticals, Inc, Bedminster, New Jersey, and Durham, North Carolina (T.H., N.R.-D., C.C.K.); SDC, Tempe, Arizona (D.W.U.); PharmaLogic Development, Inc, San Rafael, California (G.D.N.); and Departments of Pharmacology and Ophthalmology, University of California, Davis, School of Medicine, Sacramento, California (G.D.N.).

Inquiries to Gary D. Novack, PharmaLogic Development, Inc, 17 Bridgegate Dr, San Rafael, CA 94903; e-mail: gary_novack@pharmalogic.com

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humor production (ß-adrenoceptor antagonists, α-adrenoceptor agonists, and carbonic anhydrase inhibitors). ROCK inhibitors lower IOP through a different mechanism of action, increasing aqueous outflow through the trabecular outflow pathway by decreasing actomyosin-driven cellular contraction and reducing production of fibrotic extracellular matrix proteins.[12–16]

Netarsudil (previously AR-13324) is a new compound under development for the treatment of glaucoma that is a potent ROCK inhibitor and also an inhibitor of the norepinephrine transporter.[17,18] In preclinical models, netarsudil has been shown to lower IOP through 3 effects on aqueous humor dynamics: (1) it increases trabecular outflow facility, (2) it decreases production of aqueous humor,[15] and (3) it decreases episcleral venous pressure.[19] In a clinical study in normal healthy volunteers, once-daily dosing of netarsudil ophthalmic solution 0.02% lowered IOP relative to baseline primarily by increasing outflow facility and it appeared to reduce episcleral venous pressure.[20]

In a 28-day, randomized, double-masked, dose-ranging phase 2 study of 224 patients with open-angle glaucoma or ocular hypertension, netarsudil ophthalmic solution 0.02% and latanoprost produced clinically significant reductions in mean diurnal IOP of 5.7 mm Hg and 6.8 mm Hg, respectively. In a prespecified subset analysis of patients with baseline IOPs ≤ 26 mm Hg, netarsudil 0.02% and latanoprost were similarly effective at all time points, producing decreases in mean diurnal IOP of 5.7 and 6.0 mm Hg, respectively. This suggested that the ocular hypotensive efficacy of netarsudil may be less dependent upon baseline IOP than has been reported for other ocular hypotensive medications.[21]

Here we present the 3-month efficacy and ocular and systemic safety results from 2 large phase 3 trials, Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2), comparing netarsudil ophthalmic solution 0.02% dosed once nightly (q.d., PM) to the active comparator timolol maleate ophthalmic solution 0.5% dosed twice daily (b.i.d.). In the ROCKET-2 trial, a treatment arm of netarsudil ophthalmic solution 0.02% dosed twice daily (bid) was also included.

METHODS

• **STUDY DESIGN:** The ROCKET-1 and ROCKET-2 studies were double-masked, randomized, multicenter, parallel-group studies that compared netarsudil ophthalmic solution 0.02% (netarsudil) to timolol maleate ophthalmic solution 0.5% (timolol) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). Netarsudil was dosed q.d. PM (ROCKET-1 and ROCKET-2) or b.i.d. (ROCKET-2 only). Timolol was dosed b.i.d. in both studies. Data through 3 months from both studies are provided in this report. ROCKET-2 continued through 12 months, and will be reported subsequently.

These studies are registered with clinicaltrials.gov as NCT02207491 and NCT02207621. The studies were conducted in accordance with Good Clinical Practices Guidelines and adhered to the Declaration of Helsinki. A list of investigators and sites that participated in these studies is provided as an Appendix (Supplemental Material available at AJO.com).

Eligible patients were randomized by a computer-generated method to receive netarsudil or timolol in both eyes. Patients and study site personnel were fully masked to treatment assignments. A vehicle bottle was provided for AM dosing in the netarsudil q.d. PM treatment groups to maintain masking. Study visits were screening, qualification 1 (after medication washout, if required), a second qualification visit 2/day 1 (2–7 days later) (to ensure unmedicated IOP stability, which was also baseline and the first day of dosing), week 2, week 6, and month 3. Examinations at day 1, week 2, week 6, and month 3 included diurnal IOP measurements (8:00 AM, 10:00 AM, and 4:00 PM hours), best-corrected visual acuity by Early Treatment Diabetic Retinopathy Study (ETDRS), biomicroscopy, and assessment of adverse events. Dilated ophthalmoscopy and static automated visual fields were performed at screening and at month 3.

IOP was measured using a calibrated Goldmann applanation tonometer. Two consecutive IOP measurements of each eye were obtained. If the 2 measurements differed by more than 2 mm Hg, a third measurement was to be obtained. IOP was to be recorded as the mean of 2 measurements or as the median of 3 measurements.[22] Biomicroscopic grading was performed on 4-point scales, from 0 = none to 3 = severe, for erythema and edema of the lid, hyperemia and edema of the conjunctiva, edema and staining of the cornea, anterior chamber flare, and lens opacity (phakic only). In further detail, conjunctival hyperemia was scored as follows: None (0) = Normal. Appears white with a small number of conjunctival blood vessels easily observed; Mild (+1) = Prominent, pinkish-red color of both the bulbar and palpebral conjunctiva; Moderate (+2) = Bright, scarlet red color of the bulbar and palpebral conjunctiva; Severe (+3) = "Beefy Red" with petechiae. Dark red bulbar and palpebral conjunctiva with evidence of subconjunctival hemorrhage. For anterior chamber cells, a 5-point scale was to be used with Grade 4 = ++++ cells and hypopyon formation.

• **PATIENTS:** Eligible patients were adults (18 years of age or greater) or, to meet U.S. Food and Drug Law, children aged 0–2 years with a diagnosis of bilateral OAG or OHT. Unmedicated IOP (after washout, if required)[23] was required to be >20 mm Hg and <27 mm Hg at 8:00 AM in at least 1 eye at both qualification visits. At the second qualification visit, IOP was also required to be >17 mm Hg and <27 mm Hg at 10:00 AM and 4:00 PM. If both eyes

qualified for all criteria, the eye with the higher IOP was selected to be the study eye for statistical purposes. If both eyes had the same IOP, the right eye was selected as the study eye. Corrected visual acuity in each eye was required to be +1.0 logMAR or better by the ETDRS system in each eye. Individuals were required to be able and willing to give signed Institutional Review Board–approved informed consent (parent or guardian consent for pediatric patients) and follow study instructions.

Excluded from the study were individuals currently treated with >2 ocular hypotensive medications, with pseudoexfoliation or pigment dispersion component glaucoma, a history of angle closure or narrow iridocorneal angles (including previous peripheral iridotomy), previous glaucoma incisional or laser surgery, refractive surgery, central corneal thickness greater than 600 μm, or known hypersensitivity to or contraindications to netarsudil or timolol or their excipients. Also excluded were individuals with clinically significant ocular disease in either eye or with systemic disease that might interfere with the study, as well as women of childbearing potential who were pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. At screening, individuals were observed to assure proper performance of eyedrop instillation.[24]

• **STATISTICS:** In both studies, the primary efficacy outcome was mean IOP at the following time points: 8:00 AM, 10:00 AM, and 4:00 PM at the week 2, week 6, and month 3 visits. Netarsudil was compared to the marketed control product, timolol. Netarsudil was considered to be at least as effective as timolol (ie, noninferior) if the upper limit of the 2-sided 95% confidence intervals around the difference (netarsudil − timolol) was within 1.5 mm Hg at all time points and was within 1.0 mm Hg at a majority of the time points.[25] In ROCKET-2, in order to preserve an overall 2-sided type I error of 0.05, the primary analysis was completed in a hierarchical fashion, first testing netarsudil q.d. to timolol, then, if q.d. demonstrated clinical noninferiority, secondarily testing netarsudil bid for noninferiority to timolol.

In ROCKET-2, the primary analysis population for efficacy was the per-protocol (PP) population with IOP < 25 mm Hg at all baseline time points. In ROCKET-1, the primary analysis population was the full PP population and analysis of the population with baseline IOP < 25 mm Hg was post hoc.

In ROCKET-2, a sample size of approximately 122 PP population patients per arm with baseline IOP < 25 mm Hg was necessary to have 85% power to show statistical noninferiority of netarsudil q.d. to timolol b.i.d. and to show statistical noninferiority of netarsudil b.i.d. to timolol b.i.d. in the mean study eye IOP. The power calculation assumed a zero difference between netarsudil q.d. and timolol b.i.d. and a zero difference between netarsudil b.i.d. and timolol b.i.d., a 2-tailed alpha of 0.05 at each of 9 time points for each of the 2 comparisons, a common standard deviation (SD) of 2.75 mm Hg, and a correlation of 0.60 or less between time points. To achieve the required sample size, approximately 252 patients were to be randomized per arm on the assumption that 80% of enrolled patients would complete through month 3 and would be considered in the PP population, and that approximately 65% of randomized patients would have baseline IOP < 25 mm Hg. Thus, a total of approximately 756 patients were to be randomized.

In ROCKET-1, a sample size of 170 PP patients per arm was needed to have 90% power to show noninferiority of netarsudil q.d. to timolol b.i.d., assuming a 2-tailed alpha of 0.05 at each of 9 time points, a common SD of 3.0 mm Hg, and a correlation between time points of 0.60 or less. To achieve the required sample size, approximately 200 patients were to be randomized per arm on the assumption that 85% of enrolled patients would complete through month 3 and considered in the PP population.

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. Adverse events were defined *a priori* as any untoward change in medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Discontinuation of the study medication for any reason was at the discretion of the investigator. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Versions 17.0-19.0). The safety population included all randomized patients who received at least 1 dose of study medication.

RESULTS

• **DEMOGRAPHICS AND DISPOSITION:** Enrolled into ROCKET-2 were 756 patients and into ROCKET-1 were 411 patients. The demographics for the respective safety populations are shown in Table 1 and Table 2. Each study population had a mean age in the mid-60s, was predominantly female, and was approximately three fourths white and one fourth African-American. The only characteristic that was statistically significantly different between treatment groups was iris color in ROCKET-1 ($P = .0085$), with the timolol group having a 14.5% higher frequency of brown/black iris color. Although eligible for enrollment, no patients 0–2 years of age were enrolled. At the time of pre-study screening, approximately half of the patients were on prostaglandin therapy (monotherapy or combination therapy) and the remainder were on a non-prostaglandin therapy or were untreated. One patient in ROCKET-2 randomized to the netarsudil b.i.d. treatment group did not receive study medication.

In ROCKET-2, 82% (205/251), 60% (153/254), and 94% (237/251) of patients completed the first 3 months

TABLE 1. ROCKET-2: Demographics and Baseline Characteristics

Characteristic	Netarsudil 0.02% q.d. N = 251	Netarsudil 0.02% b.i.d. N = 254	Timolol 0.5% b.i.d. N = 251	All Subjects N = 756	*P* Value
Study eye diagnosis, n (%)					.3465
Ocular hypertension	84 (33.5)	96 (37.8)	80 (31.9)	260 (34.4)	
Open-angle glaucoma	167 (66.5)	158 (62.2)	171 (68.1)	496 (65.6)	
Sex, n (%)					.3256
Male	103 (41.0)	89 (35.0)	101 (40.2)	293 (38.8)	
Female	148 (59.0)	165 (65.0)	150 (59.8)	463 (61.2)	
Age (y)					.1051
Mean	65.3	64.1	63.0	64.1	
SD	11.48	12.46	11.81	11.95	
Median	67.0	65.0	64.0	65.0	
Range (min, max)	(14, 86)	(18, 92)	(11, 88)	(11, 92)	
Age (y), n (%)					.1949
<65	111 (44.2)	126 (49.6)	131 (52.2)	368 (48.7)	
≥65	140 (55.8)	128 (50.4)	120 (47.8)	388 (51.3)	
Race, n (%)					.4447
Asian	2 (0.8)	6 (2.4)	6 (2.4)	14 (1.9)	
Black or African American	69 (27.5)	69 (27.2)	76 (30.3)	214 (28.3)	
Native American	2 (0.8)	0	0	2 (0.3)	
White	178 (70.9)	177 (69.7)	166 (66.1)	521 (68.9)	
Multiple	0	1 (0.4)	2 (0.8)	3 (0.4)	
Other	0	1 (0.4)	1 (0.4)	2 (0.3)	
Ethnicity, n (%)					.9922
Hispanic or Latino	41 (16.3)	43 (16.9)	42 (16.7)	126 (16.7)	
Not Hispanic or Latino	210 (83.7)	211 (83.1)	209 (83.3)	630 (83.3)	
Iris color, study eye, n (%)					.0836
Blue/gray/green	60 (23.9)	57 (22.4)	69 (27.5)	186 (24.6)	
Brown/black	155 (61.8)	169 (66.5)	165 (65.7)	489 (64.7)	
Hazel	35 (13.9)	28 (11.0)	17 (6.8)	80 (10.6)	
Other	1 (0.4)	0	0	1 (0.1)	
Prior hypotensive therapy					.1898
Prostaglandin therapy[a]	125 (49.8)	111 (43.7)	129 (51.4)	365 (48.3)	
No prostaglandin therapy	126 (50.2)	143 (56.3)	122 (48.6)	391 (51.7)	
β-adrenoceptor antagonists	29 (11.6)	30 (11.9)	21 (8.4)	80 (10.6)	
β-adrenoceptor antagonists (oral)	51 (20.3)	49 (19.3)	45 (17.9)	145 (19.2)	

P values are from tests of differences across treatment groups and are 2-sided. Fisher exact tests were used for the categorical variables and 1-way ANOVAs were used for the continuous variables.

[a]Defined as use of prostaglandin analogues at screening.

of the study in the netarsudil q.d., netarsudil b.i.d., and timolol groups, respectively. The proportion of patients discontinuing owing to an adverse event was 12% (31), 30% (77), and 1% (2), respectively. In ROCKET-1, 85% (171/202) and 94% (196/209) of patients completed the study in the netarsudil q.d. and timolol groups, respectively. The proportion of patients discontinuing owing to an adverse event was 10% (20) and 2% (4), respectively.

• **INTRAOCULAR PRESSURE:** In the ROCKET-2 primary efficacy population (PP population with maximum baseline IOP < 25 mm Hg), baseline IOPs at 8:00 AM, 10:00 AM, and 4:00 PM were similar among the treatment groups, ranging from 20.4 to 22.5 mm Hg and 20.6 to 22.6 mm Hg in the netarsudil q.d. and b.i.d. groups, respectively, and from 20.7 to 22.5 mm Hg in the timolol group (Table 3, Figure 1, $P \geq .1931$, 2 sample *t* test). All 3 treatment groups produced statistically significant mean reductions from baseline IOP ($P < .0001$, paired *t* test) at all 9 treatment time points over the 3-month efficacy assessment, with mean IOP ranging from 16.7 to 18.2 mm Hg and 15.7 to 17.6 mm Hg in the netarsudil q.d. and b.i.d. groups, respectively, and 16.6 to 17.7 mm Hg in the timolol group. The mean decreases from baseline IOP ranged from 3.3 to 4.6 mm Hg and 4.1 to 5.4 mm Hg for netarsudil q.d. and b.i.d., respectively, and those for timolol ranged from 3.7 to 5.1 mm Hg. Both netarsudil q.d. and b.i.d. met the prespecified criteria for noninferiority to timolol, with

TABLE 2. ROCKET-1: Demographics and Baseline Characteristics

Characteristic	Netarsudil 0.02% N = 202	Timolol 0.5% N = 209	All Subjects N = 411	*P* Value
Study eye diagnosis, n (%)				.8355
Open-angle glaucoma	134 (66.3)	136 (65.1)	270 (65.7)	
Ocular hypertension	68 (33.7)	73 (34.9)	141 (34.3)	
Sex, n (%)				.0857
Male	88 (43.6)	73 (34.9)	161 (39.2)	
Female	114 (56.4)	136 (65.1)	250 (60.8)	
Age (y)				.1525
Mean	65.8	64.2	65.0	
SD	11.65	11.34	11.50	
Median	67.0	65.0	66.0	
Range (min, max)	(20, 96)	(26, 90)	(20, 96)	
Age (y), n (%)				.1359
<65	78 (38.6)	96 (45.9)	174 (42.3)	
≥65	124 (61.4)	113 (54.1)	237 (57.7)	
Race, n (%)				.5078
Asian	2 (1.0)	4 (1.9)	6 (1.5)	
Black or African American	43 (21.3)	51 (24.4)	94 (22.9)	
White	157 (77.7)	153 (73.2)	310 (75.4)	
Other	0	1 (0.5)	1 (0.2)	
Ethnicity, n (%)				>.9999
Hispanic or Latino	27 (13.4)	28 (13.4)	55 (13.4)	
Not Hispanic or Latino	175 (86.6)	181 (86.6)	356 (86.6)	
Iris color of study eye, n (%)				.0085
Blue/gray/green	71 (35.1)	54 (25.8)	125 (30.4)	
Brown/black	107 (53.0)	141 (67.5)	248 (60.3)	
Hazel	24 (11.9)	14 (6.7)	38 (9.2)	
Prior hypotensive therapy				.4904
Prostaglandin therapy[a]	99 (49.0)	110 (52.6)	209 (50.9)	
No prostaglandin therapy	103 (51.0)	99 (47.4)	202 (49.1)	
β-adrenoceptor antagonists	35 (17.2)	39 (18.8)	74 (18.0)	
β-adrenoceptor antagonists (oral)	38 (18.8)	46 (22.0)	84 (20.4)	

P values are from tests of differences across treatment groups and are 2-sided. Fisher exact tests were used for the categorical variables and 1-way ANOVAs were used for the continuous variables.

[a]Defined as use of prostaglandin analogues at screening.

the upper limit of the 2-sided 95% confidence interval for the differences in mean IOP from timolol being within 1.5 mm Hg at all of the 9 time points and within 1.0 mm Hg at the majority of time points. This reduction in IOP with netarsudil q.d. was 16%–21%, compared with netarsudil b.i.d. (22%–24%) and timolol (18%–23%).

In ROCKET-1, the primary efficacy population was the per-protocol population with maximum baseline IOP < 27 mm Hg, and analysis of the per-protocol population with baseline IOP < 25 mm Hg was a post hoc endpoint. In the primary analysis, baseline IOPs at 8:00 AM, 10:00 AM, and 4:00 PM ranged from 21.8 to 23.4 mm Hg and 21.5 to 23.4 mm Hg in the netarsudil q.d. and timolol groups ($P \geq .0986$), respectively, and mean IOPs subsequently decreased to 17.2–19.8 and 17.4–18.5 mm Hg, respectively, across the 9 treatment time points ($P < .0001$, paired t test). The mean decreases from baseline IOP ranged from 3.3 to 5.0 mm Hg and 3.7 to 5.1 mm Hg for netarsudil q.d. and timolol, respectively. In this primary efficacy analysis, the upper limit of the 2-sided 95% confidence interval for the difference between netarsudil q.d. and timolol was greater than 1.5 mm Hg at 3 of the 9 time points, and therefore netarsudil did not meet the criteria for noninferiority to timolol (Table 4). This reduction in IOP with netarsudil q.d. was 15%–22%, compared with timolol at 17%–22%.

In the ROCKET-1 analysis of PP patients with maximum baseline IOP < 25 mm Hg (N = 237), baseline IOPs at 8:00 AM, 10:00 AM, and 4:00 PM were similar among the treatment groups, ranging from 20.6 to 22.4 mm Hg and 20.5 to 22.5 mm Hg in the netarsudil q.d. and timolol groups ($P \geq .3235$), respectively (Table 4, Figure 2). Both treatment groups produced statistically significant mean reductions from baseline IOP

TABLE 3. ROCKET-2: Mean Intraocular Pressure (mm Hg) by Visit: Primary Efficacy Population[a]

	Netarsudil q.d.		Netarsudil b.i.d.		Timolol		Netarsudil q.d. − Timolol		Netarsudil b.i.d − Timolol	
Day and Time	N	Mean IOP	N	Mean IOP	N	Mean IOP	Mean Difference	95% CI	Mean Difference	95% CI
Baseline										
8:00 AM	129	22.54	132	22.55	142	22.54	0.00	(−0.25, 0.25)	0.01	(−0.24, 0.26)
10:00 AM	129	21.29	132	21.27	142	21.27	0.02	(−0.37, 0.41)	−0.01	(−0.40, 0.38)
4:00 PM	129	20.43	132	20.56	142	20.71	−0.28	(−0.71, 0.14)	−0.15	(−0.58, 0.29)
Week 2										
8:00 AM	127	18.07	122	17.21	142	17.69	0.37	(−0.25, 0.99)	−0.48	(−1.19, 0.22)
10:00 AM	126	16.72	120	16.35	141	16.93	−0.21	(−0.82, 0.41)	−0.57	(−1.24, 0.09)
4:00 PM	126	16.68	118	15.65	141	16.83	−0.15	(−0.75, 0.46)	−1.18	(−1.82, −0.54)
Week 6										
8:00 AM	122	17.95	111	17.64	141	17.46	0.49	(−0.13, 1.12)	0.17	(−0.51, 0.86)
10:00 AM	120	16.95	106	16.28	141	16.63	0.32	(−0.31, 0.95)	−0.34	(−1.02, 0.33)
4:00 PM	120	17.00	106	15.75	141	16.60	0.40	(−0.22, 1.02)	−0.85	(−1.53, −0.17)
Month 3										
8:00 AM	116	18.24	91	17.58	140	17.47	0.77	(0.03, 1.50)	0.11	(−0.64, 0.86)
10:00 AM	114	17.03	88	16.94	140	16.92	0.10	(−0.59, 0.80)	0.02	(−0.72, 0.77)
4:00 PM	114	17.13	88	16.51	139	16.95	0.18	(−0.55, 0.91)	−0.44	(−1.16, 0.27)

CI = confidence interval; IOP = intraocular pressure.

Difference from timolol and 2-sided CIs and *P* values are based on 2-sample *t* tests comparing netarsudil vs timolol.

[a]Primary efficacy population: per-protocol subjects with baseline IOP < 25 mm Hg.

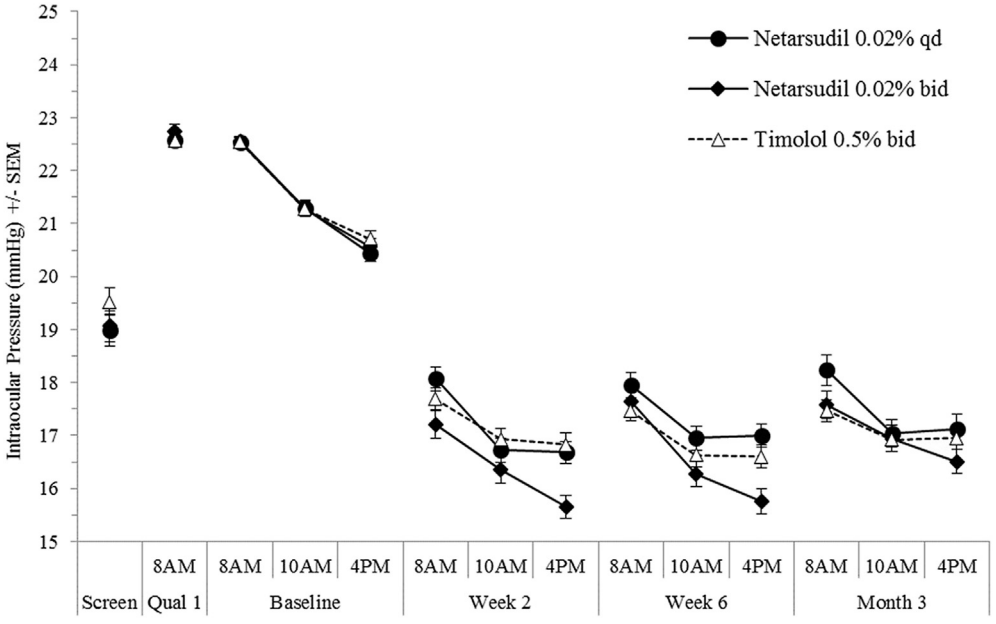

FIGURE 1. ROCKET-2: Ocular hypotensive effect of netarsudil once daily (q.d.) and twice daily (b.i.d.) compared with timolol b.i.d. in the primary efficacy population (subjects with baseline IOP < 25 mm Hg).

($P < .0001$, paired *t* test) at all 9 treatment time points, with mean IOP ranging from 16.2 to 18.2 mm Hg and 17.0 to 17.9 mm Hg in the netarsudil q.d. and timolol groups, respectively. The mean decreases from baseline IOP ranged from 3.7 to 5.1 mm Hg and 3.2 to 4.7 mm Hg for netarsudil q.d. and timolol, respectively. Netarsudil q.d. met the criteria for noninferiority to timolol in patients with maximum baseline IOP < 25 mm Hg, with the upper limit of the 2-sided 95% confidence interval for the differences in mean IOP from timolol being within 1.5 mm Hg at all of the 9 time points and within 1.0 mm Hg at the majority of the 9 time points.

TABLE 4. ROCKET-1: Mean Intraocular Pressure (mm Hg) by Visit: Primary[a] and Post Hoc[b] Efficacy Populations

	< 27 mm Hg (Primary)						< 25 mm Hg (Post Hoc)					
	Netarsudil		Timolol		Netarsudil − Timolol		Netarsudil		Timolol		Netarsudil − Timolol	
	N	Mean IOP	N	Mean IOP	Mean Difference	95% CI	N	Mean IOP	N	Mean IOP	Mean Difference	95% CI
Baseline												
8:00 AM	182	23.42	188	23.37	0.06	(−0.29, 0.41)	113	22.39	124	22.50	−0.11	(−0.39, 0.18)
10:00 AM	182	22.28	188	21.92	0.36	(−0.07, 0.79)	113	21.28	124	21.07	0.21	(−0.21, 0.64)
4:00 PM	182	21.78	188	21.45	0.33	(−0.15, 0.82)	113	20.62	124	20.52	0.10	(−0.36, 0.56)
Week 2												
8:00 AM	177	18.68	187	18.33	0.35	(−0.27, 0.96)	108	17.34	123	17.78	−0.44	(−1.10, 0.22)
10:00 AM	176	17.29	186	17.55	−0.26	(−0.87, 0.36)	107	16.18	122	16.98	−0.81	(−1.44, −0.17)
4:00 PM	176	17.24	186	17.70	−0.45	(−1.08, 0.17)	107	16.22	122	17.14	−0.92	(−1.58, −0.26)
Week 6												
8:00 AM	170	19.35	184	18.24	1.11	(0.42, 1.80)	105	17.85	121	17.81	0.05	(−0.68, 0.77)
10:00 AM	170	18.14	184	17.44	0.70	(0.04, 1.36)	105	16.88	121	16.96	−0.08	(−0.74, 0.58)
4:00 PM	170	17.86	183	17.71	0.15	(−0.52, 0.83)	105	16.57	120	17.26	−0.69	(−1.40, 0.02)
Month 3												
8:00 AM	157	19.81	181	18.47	1.33	(0.64, 2.03)	99	18.22	119	17.91	0.31	(−0.40, 1.02)
10:00 AM	158	18.92	181	17.96	0.96	(0.26, 1.66)	99	17.34	119	17.43	−0.09	(−0.82, 0.63)
4:00 PM	158	18.48	181	17.74	0.74	(0.07, 1.42)	99	17.02	119	17.37	−0.35	(−1.03, 0.34)

CI = confidence interval; IOP = intraocular pressure.
Difference from timolol and 2-sided CIs and *P* values are based on 2-sample *t* tests comparing netarsudil vs timolol.
[a]Primary efficacy population: per-protocol subjects with baseline IOP < 27 mm Hg.
[b]Post hoc efficacy population: per-protocol subjects with baseline IOP < 25 mm Hg.

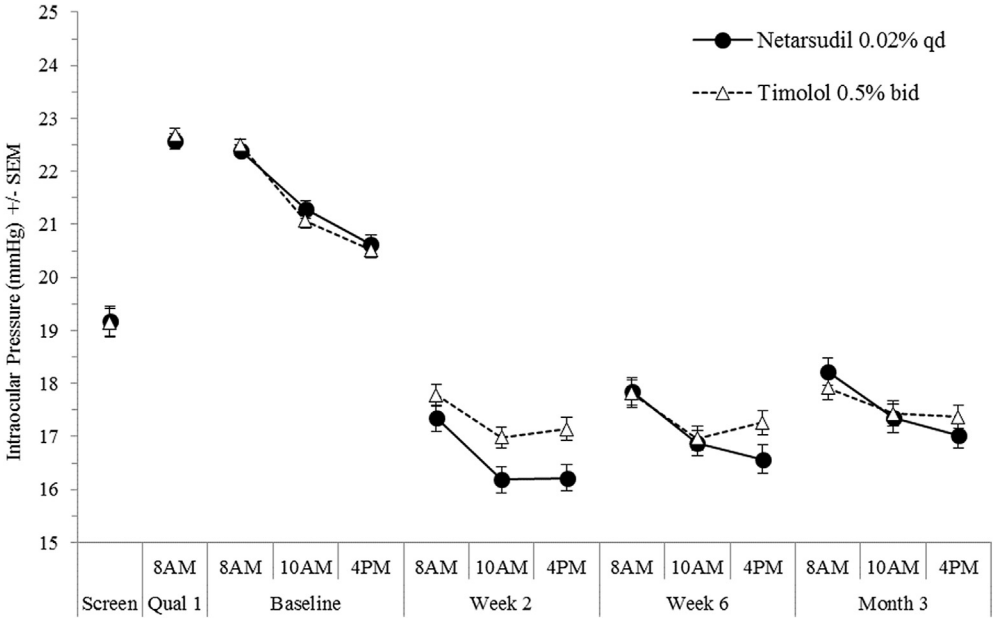

FIGURE 2. ROCKET-1: Ocular hypotensive effect of netarsudil once daily (q.d.) compared with timolol twice daily (b.i.d.) in subjects with baseline IOP < 25 mm Hg: Secondary analysis.

In ROCKET-2, netarsudil produced similar reductions in IOP across all 3 treatment study visits (week 2, week 6, and month 3; Figure 1, Table 3). In contrast, in ROCKET-1 the mean reductions in IOP for the netarsudil group were largest at week 2 and smaller at week 6 and month 3 (Figure 2, Table 4). In both studies, efficacy results in the intent-to-treat population (randomized patients receiving at least 1 dose of the drug) were

TABLE 5. ROCKET-2: Treatment-Emergent Adverse Events[a] (Safety Population) (Incidence ≥ 3%)

System Organ Class Preferred Term	Netarsudil 0.02% q.d. (N = 251) n (%)	Netarsudil 0.02% b.i.d. (N = 253) n (%)	Timolol 0.5% b.i.d. (N = 251) n (%)	*P* Value[b]
Eye disorders	163 (64.9)	198 (78.3)	63 (25.1)	<.0001/<.0001
Conjunctival hyperemia	126 (50.2)	149 (58.9)	27 (10.8)	<.0001/<.0001
Conjunctival hemorrhage	37 (14.7)	43 (17.0)	0	<.0001/<.0001
Corneal deposits	22 (8.8)	37 (14.6)	1 (0.4)	<.0001/<.0001
Vision blurred	18 (7.2)	41 (16.2)	7 (2.8)	.0382/<.0001
Lacrimation increased	12 (4.8)	17 (6.7)	0	.0004/<.0001
Visual acuity reduced	11 (4.4)	18 (7.1)	4 (1.6)	.1130/.0036
Eye pruritus	12 (4.8)	14 (5.5)	0	.0004/.0001
Punctate keratitis	10 (4.0)	10 (4.0)	5 (2.0)	.2944/.2944
Erythema of eyelid	12 (4.8)	7 (2.8)	2 (0.8)	.0118/.1758
Conjunctival edema	4 (1.6)	14 (5.5)	0	.1235/.0001
Eye pain	8 (3.2)	10 (4.0)	6 (2.4)	.7875/.4471
Eye irritation	7 (2.8)	9 (3.6)	4 (1.6)	.5443/.2606
Eyelid edema	8 (3.2)	7 (2.8)	2 (0.8)	.1059/.1758
Foreign body sensation in eyes	5 (2.0)	9 (3.6)	0	.0613/.0036
General disorders and administration site conditions	64 (25.5)	71 (28.1)	48 (19.1)	.1076/.0210
Instillation site pain	41 (16.3)	40 (15.8)	38 (15.1)	.8065/.9021
Instillation site erythema	14 (5.6)	31 (12.3)	5 (2.0)	.0586/<.0001
Infections and infestations	19 (7.6)	27 (10.7)	15 (6.0)	.5947/.0753
Upper respiratory tract infection	4 (1.6)	8 (3.2)	4 (1.6)	>.999/.3819
Investigations	24 (9.6)	18 (7.1)	16 (6.4)	.2484/.8594
Vital dye staining cornea present	10 (4.0)	11 (4.3)	12 (4.8)	.8280/.8345
Nervous system disorders	10 (4.0)	17 (6.7)	7 (2.8)	.6230/.0577
Headache	5 (2.0)	11 (4.3)	5 (2.0)	>.9999/.2028
Skin and subcutaneous tissue disorders	8 (3.2)	8 (3.2)	3 (1.2)	.2214/.2214
Injury, poisoning, and procedural complications	10 (4.0)	5 (2.0)	1 (0.4)	.0109/.2160
Respiratory, thoracic, and mediastinal disorders	8 (3.2)	2 (0.8)	8 (3.2)	>.9999/.0621

b.i.d. = twice a day; q.d. = once a day.

[a]Adverse events reported for 3.0% or more of subjects in any treatment group.

[b]*P* values are from Fisher exact test comparing the distribution of incidence across treatment groups. First number is netarsudil q.d. vs timolol and second number is netarsudil b.i.d. vs timolol.

similar to those in the PP population (primary efficacy population).

• **ADVERSE EVENTS:** In both studies, all treated subjects were included in the safety population. In ROCKET-2, 1 subject randomized to the netarsudil b.i.d. group was excluded from the safety population because no study medication was administered. Adverse events in patients treated with once-daily netarsudil were predominantly nonserious, were generally mild in intensity, and resulted in patient discontinuation from the study in 10%–12% of patients (12%, 31/251 in ROCKET-2 and 10%, 20/202 in ROCKET-1). Adverse events associated with twice-daily dosing of netarsudil in ROCKET-2 led to discontinuation in 30% (77/254) of patients. In both studies, the most frequently reported adverse events were ocular.

In ROCKET-2, the incidence of ocular adverse events was 73% (182/251) in the netarsudil q.d. group, 84% (213/253) in the netarsudil b.i.d. group, and 41% (102/251) in the timolol group. Similarly, in ROCKET-1, the incidence of ocular adverse events was 77% (156/203) in the netarsudil group and 44% (92/208) in the timolol group (Table 5 and Table 6).

In both studies, the most frequently reported ocular adverse event was conjunctival hyperemia. The incidence of hyperemia (physician-reported and patient-reported) ranged from 50% (126/251, ROCKET-2) to 53% (105/203, ROCKET-1) for netarsudil q.d., 59% (149/253, ROCKET-2) for netarsudil b.i.d., and 8% (17/208, ROCKET-1) to 10% (27/251, ROCKET-2) for timolol ($P < .0001$for comparison of netarsudil doses to timolol in each study). Conjunctival hyperemia as scored by biomicroscopy in ROCKET-2 was observed at baseline (day 1, 8:00 AM) in 18.3% (138/755) of patients across all groups and was judged by the investigators to be of mild severity in all but 1 patient (moderate). At week 2, 8:00 AM (the first on-treatment visit and approximately 12 hours after last instillation of study medication),

TABLE 6. ROCKET-1: Treatment-Emergent Adverse Events (Safety Population) (Incidence ≥ 3%)

System Organ Class Preferred Term	Netarsudil 0.02% (N = 203) n (%)	Timolol 0.5% (N = 208) n (%)	*P* Value
Eye disorders	137 (67.0)	34 (16.3)	<.0001
Conjunctival hyperaemia	108 (53.2)	17 (8.2)	<.0001
Conjunctival hemorrhage	27 (13.3)	1 (0.5)	<.0001
Erythema of eyelid	12 (5.9)	0	.0002
Vision blurred	11 (5.4)	1 (0.5)	.0027
Corneal deposits	11 (5.4)	0	.0004
Visual acuity reduced	8 (3.9)	3 (1.4)	.1364
Conjunctival vascular disorder	8 (3.9)	1 (0.5)	.0189
Eye irritation	8 (3.9)	1 (0.5)	.0189
Lacrimation increased	8 (3.9)	0	.0033
Conjunctivitis allergic	6 (3.0)	0	.0140
General disorders and administration site conditions	59 (29.1)	57 (27.4)	.7429
Instillation site pain	30 (14.8)	42 (20.2)	.1558
Instillation site erythema	24 (11.8)	4 (1.9)	<.0001
Instillation site discomfort	10 (4.9)	9 (4.3)	.8178
Investigations	22 (10.8)	24 (11.5)	.8763
Vital dye staining cornea present	17 (8.4)	19 (9.1)	.8622
Infections and infestations	14 (6.9)	14 (6.7)	>.9999
Nervous system disorders	6 (3.0)	8 (3.8)	.7871
Gastrointestinal disorders	7 (3.4)	4 (1.9)	.3761
Respiratory, thoracic and mediastinal disorders	6 (3.0)	3 (1.4)	.3331

Adverse events reported for 3.0% or more of subjects in any treatment group.
P values are from Fisher's exact test comparing the distribution of incidence across treatment groups.

conjunctival hyperemia was observed in the study eye of 40.2% (101/251), 43.5% (110/253), and 21.9% (55/251) of patients in the netarsudil q.d., netarsudil b.i.d., and timolol groups, respectively. The biomicroscopy incidence remained at approximately this level throughout the balance of the week 2 visit and through the week 6 and month 3 study visits (Supplemental Table 1; Supplemental Material available at AJO.com). Conjunctival hyperemia as scored by biomicroscopy in ROCKET-1 was observed at baseline in 14.4% (59/411) of patients across both groups and was judged to be of mild severity. At week 2, 8:00 AM, conjunctival hyperemia was seen in 46.8% (95/203) and 13.0% (27/208) of patients in the netarsudil and timolol groups, respectively. The biomicroscopy incidence remained at approximately this level throughout the balance of the week 2 visit, and through the week 6 and month 3 study visits (Supplemental Table 2; Supplemental Material available at AJO.com).

The next most frequent adverse event was conjunctival hemorrhage. In ROCKET-2, conjunctival hemorrhage was reported in 15% (37/251) of netarsudil q.d. patients, 17% (43/253) of netarsudil b.i.d. patients, and no timolol patients. For the most part, investigators described observations as typically unilateral, small microhemorrhages, localized to the limbal area. The onset was variable, and the duration typically 1–3 weeks. When present, 43% (16/37) and 47% (20/43) of the events were considered to be treatment-related for netarsudil q.d. and netarsudil b.i.d., respectively, and 89.2% (33/37) and 86% (37/43) of the events were scored as mild, respectively.

In ROCKET-1, conjunctival hemorrhage was reported in 13.3% (27/203) of netarsudil q.d. patients and 0.5% (1/208) of timolol patients. When present, 51.9% (14/27) of the netarsudil q.d. events and none of the timolol events were considered to be treatment-related, and 96.3% (26/27) and 100% (1/1) of the events were scored as mild, respectively.

Cornea verticillata (coded in MedDRA as corneal deposits, and also known as corneal whorls) were seen primarily in the netarsudil groups. In ROCKET-2, cornea verticillata was reported in 9% (22/251) of netarsudil q.d. patients, 15% (37/253) of netarsudil b.i.d. patients, and <1% (1/251) of timolol patients. The onset ranged from 6 to 13 weeks with netarsudil 0.02% q.d., and from 2 to 12 weeks with netarsudil 0.02% b.i.d. In ROCKET-2, dosing continued through 12 months, and follow-up data on resolution is planned for a subsequent report when available. In ROCKET-1, cornea verticillata was reported in 5.4% (11/203) of netarsudil q.d. patients and the onset ranged from 6 to 13 weeks. There was no change in visual acuity in these patients. Upon cessation of dosing, all resolved either during the study or in post-study follow-up,

typically within 13 weeks. In both studies, other common ocular adverse events (>5% incidence) associated with once-daily netarsudil were vision blurred, instillation site pain, instillation site erythema, and erythema of eyelid.

• **OTHER SAFETY MEASURES:** There were no notable differences between treatment groups in either study for visual acuity, pupil diameter, ophthalmoscopy findings, cup-to-disc ratio, visual field, drop comfort, vital signs, or clinical laboratory findings. With respect to systemic safety, there were statistically significant reductions in mean heart rate with timolol (2–3 beats per minute) that were not seen with netarsudil. There was no notable change in blood pressure in any treatment group.

DISCUSSION

WE SOUGHT TO EVALUATE THE SAFETY AND EFFICACY OF netarsudil, a topical investigational drug with novel pharmacology (ROCK inhibition and NET inhibition)[17] and novel aqueous humor dynamic effects[20] in 2 large, active-controlled, double-masked, randomized clinical trials. In both ROCKET-1 and ROCKET-2, netarsudil ophthalmic solution 0.02% dosed q.d. PM produced clinically relevant and statistically significant reductions in mean IOP from baseline at all time points and met the criteria for noninferiority to timolol dosed b.i.d. in patients with maximum baseline IOP < 25 mm Hg (the primary efficacy population in ROCKET-2 and secondary population in ROCKET-1). In ROCKET-2, b.i.d. dosing of netarsudil 0.02% also met the criteria for noninferiority to timolol, but it was not as well tolerated as q.d. dosing, resulting in a higher percentage of discontinuations. In both trials, the reductions in mean IOP obtained with timolol were within the range expected based on historical data in patients with similar baseline IOPs.[26] Thus subsequent clinical studies are using once-daily dosing, as is the submission currently pending for approval with the U.S. Food and Drug Administration.

The finding in ROCKET-1 that netarsudil 0.02% q.d. did not meet the criteria for noninferiority to timolol b.i.d. in the primary efficacy population of patients with maximum baseline IOP < 27 mm Hg was unexpected. In a previous phase 2b study, netarsudil 0.02% produced similar ocular hypotensive effects as latanoprost in patients with baseline IOP ≤ 26 mm Hg.[21] The phase 2b study enrolled patients with baseline IOP up to 35 mm Hg, whereas ROCKET-1 and ROCKET-2 restricted enrollment to patients with baseline IOP < 27 mm Hg.[21] It is possible that reducing the upper limit for baseline IOP in the ROCKET studies did not effectively exclude enrollment of patients with higher baseline IOP, but instead selected for patients with lower IOP on the day of enrollment than was their typical unmedicated IOP level. This hypothesis is being tested in a follow-up phase 3 study, ROCKET-4, which includes subjects with baseline unmedicated IOP from >20 to <30 mm Hg (www.clinicaltrials.gov NCT02558374).

In contrast to previous reports that the absolute ocular hypotensive effect (ie, mm Hg) of timolol and latanoprost was related to baseline IOP,[21,26] netarsudil produced the same IOP-lowering efficacy regardless of baseline IOP in the same study. The apparent ability of netarsudil to maintain similar efficacy across different baseline IOPs may be related its distinct mechanisms for lowering IOP compared to other drug classes.[27]

There were no netarsudil-related systemic safety issues in these studies, in which more than 700 patients were exposed to netarsudil for up to 3 months. There were no ocular serious adverse events judged related to treatment. The most frequent adverse events were ocular: conjunctival hyperemia, conjunctival hemorrhage, and cornea verticillata. Conjunctival hyperemia is an extension of the pharmacology of ROCK inhibitors, which cause vasodilation of blood vessels by inducing relaxation of vascular smooth muscle.[28] While observed in approximately half of the patients treated once daily with netarsudil, for the most part the hyperemia was mild, transient, and self-resolving, with the majority of findings reported by the investigator rather than the patient. Conjunctival hemorrhage was similarly relatively mild and self-resolving, and typically was described by investigators as small petechial hemorrhages. Cornea verticillata was a relatively unexpected finding in this study, because it was not observed in the previous 28-day clinical study of netarsudil.[21] Cornea verticillata was typically scored as mild with no associated decrease in visual function. Indeed, this finding could only be observed at the biomicroscope, and the patients were unaware of the finding. Though additional follow-up is being sought, it appears that the verticillata are self-resolving within several months upon cessation of therapy. Cornea verticillata are associated with many agents, including systemic amiodarone and subconjunctival gentamicin and tobramycin, although not with topical agents.[29]

Although most clinical studies of netarsudil to date have evaluated q.d. dosing, ROCKET-2 included a b.i.d. dosing arm. There was a numerically greater ocular hypotensive effect of up to ~1 mm Hg with b.i.d. netarsudil treatment relative to q.d. treatment. However, b.i.d. dosing was associated with increased frequency of ocular adverse events, as well as a greater rate of discontinuation. Thus, we propose that netarsudil 0.02% dosed q.d. in the evening is the optimal dosing regimen.

In conclusion, netarsudil represents a new class of ocular hypotensive agents. In the 2 large, randomized, double-masked trials reported here, once-daily dosing of netarsudil 0.02% was found to be effective and well tolerated for the treatment of patients with ocular hypertension and open-angle glaucoma. The novel pharmacology and aqueous humor dynamic effects of this molecule suggest it may be a useful addition to the armamentarium of ocular hypotensive medications.

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Supplemental material 1: ROCKET-2: Conjunctival Hyperemia as Observed at Biomicroscopy (Study Eye)

	Netarsudil 0.02% q.d. N=251 n (%)	*Netarsudil 0.02% b.i.d. N=253 n (%)*	*Timolol N=251 n (%)*
Baseline			
16:00 hours	52 (20.7)	42 (16.6)	50 (19.9)
Week 2			
08:00 hours	101 (40.2)	110 (43.5)	55 (21.9)
10:00 hours	104 (41.4)	117 (46.2)	57 (22.7)
16:00 hours	100 (39.8)	115 (45.5)	52 (20.7)
Week 6			
08:00 hours	103 (41.0)	111 (43.9)	50 (19.9)
10:00 hours	105 (41.8)	112 (44.3)	52 (20.7)
16:00 hours	105 (41.8)	110 (43.5)	48 (19.1)
Month 3			
08:00 hours	103 (41.0)	90 (35.6)	44 (17.5)
10:00 hours	107 (42.6)	91 (36.0)	45 (17.9)
16:00 hours	102 (40.6)	90 (35.6)	42 (16.7)

Presented is the incidence of non-zero scores.

Supplemental material 2: ROCKET-1: Conjunctival Hyperemia as Observed at Biomicroscopy (Study Eye)

	Netarsudil 0.02% q.d. N=203 n (%)	*Timolol N=208 n (%)*
Baseline		
16:00 hours	32 (15.8)	25 (12.0)
Week 2		
08:00 hours	95 (46.8)	27 (13.0)
10:00 hours	95 (46.8)	29 (13.9)
16:00 hours	85 (41.9)	23 (11.1)
Week 6		
08:00 hours	100 (49.3)	25 (12.0)
10:00 hours	103(50.7)	28 (13.5)
16:00 hours	94 (46.3)	27 (13.0)
Month 3		
08:00 hours	109 (53.7)	23 (11.1)
10:00 hours	103 (50.7)	23 (11.1)
16:00 hours	95 (46.8)	22 (10.6)

Presented is the incidence of non-zero scores. Month 3 includes early patients who were prematurely discontinued.

<H1>Appendix. List of Study Group Investigators and Sites

ROCKET-2 Study Group

- Louis M Alpern, MD
  (The Cataract & Glaucoma Center, El Paso, Texas)
- Jason Bacharach, MD
  (North Bay Eye Associates, Petaluma, California)
- Howard Barnebey, MD
  (Specialty Eye Care Center, Bellevue, Washington)
- Robert Benza, MD
  (Apex Eye, Cincinnati, Ohio)
- Ramon A. Berenguer, MD
  (Florida Medical Center & Research, Inc, Miami, Florida)
- John W. Boyle, IV, MD
  (Gulf Eye Associates, Metairie, Louisiana)
- James D. Branch, MD
  (Winston-Salem, North Carolina)
- David C. Brown, MD
  (Eye Centers of Florida, Ft Myers, Florida)
- Donald L. Budenz, MD and Scott Lawrence, MD
  (University of North Carolina, Chapel Hill, North Carolina)
- William C. Christie, MD
  (Scott & Christie & Associates, PC, Cranberry Township, Pennsylvania)
- Crandall, James, MD
  (Asheville Eye Associates, Hendersonville, North Carolina)
- Bradley S. Daines, MD
  (Reliant Medical Group, Inc, Worcester, Massachusetts)
- Douglas G. Day, MD
  (Coastal Research Associates, LLC, Roswell, Georgia)
- Michael J. Depenbusch, MD
  (Arizona Eye Center, Chandler, Arizona)
- El-Roy D. Dixon, MD
  (Dixon Eye Care, Albany, Georgia)
- Harvey B. DuBiner, MD
  (Clayton Medical Center, Morrow, Georgia)
- Eran Duzman, MD
  (Lakeside Vision Center, Irvine, California)
- Gregory A. Eippert, MD
  (Ophthalmic Physicians, Inc, Mentor, Ohio)
- Sherif M. El-Harazi, MD
  (Lugene Eye Institute, Glendale, California)
- Richard M. Evans, MD
  (Medical Center Ophthalmology Associates, San Antonio, Texas)
- Victor H. Gonzalez, MD
  (Valley Retina Institute, Harlingen, Texas)

- Raj K. Goyal, MD
  (Chicago Eye Specialists, Chicago, Illinois)
- Thomas Graul, MD
  (Eye Surgical Associates, Lincoln, Nebraska)
- William L Haynes., MD
  (Asheville Eye Associates, Asheville, North Carolina)
- Gary S. Hirshfield, MD
  (Hirshfield Eye Associates, Fresh Meadows, New York)
- Kandon K. Kamae, MD
  (Spokane Eye Clinical Research, Spokane, Washington)
- Joshua Kim, MD
  (Center for Sight, Venice, Florida)
- Bradley Kwapiszeski, MD
  (Heart of America Eye Care, Shawnee Mission, Kansas)
- Hamed Bazargan Lari, MD
  (Summit Medical Group, Berkeley Heights, New Jersey)
- Adam G. LePosa, OD
  (Baltimore, Maryland)
- Norman Levy, MD
  (Florida Ophthalmic Institute, Gainesville, Florida)
- Christopher Lin, MD
  (Shasta Eye Medical Group, Inc, Redding, California)
- John Linn, MD
  (Eye Specialty Group, Memphis, Tennessee)
- Andrew G. Logan, MD
  (Logan Ophthalmic Research, Tamarac, Florida)
- Jeffrey R. Lozier, MD
  (Arch Health Partners, Poway, California)
- Donald L. McCormack, MD
  (Boulder Medical Center, Boulder, Colorado)
- Eugene B. McLaurin, MD
  (Total Eye Care, Memphis, Tennessee)
- Edward Meier, MD
  (Eye Care Associates of Greater Cincinnati, Apex Eye, Mason, Ohio)
- Eydie Miller-Ellis, MD
  (University of Pennsylvania Scheie Eye Institute, Philadelphia, Pennsylvania)
- Thomas K. Mundorf, MD
  (Mundorf Eye Center, Charlotte, North Carolina)
- Rebecca Reid Breckenridge Murphy, MD
  (Upstate Pharmaceutical Research, Anderson, South Carolina)
- Vicky C. Pai, MD
  (Foothill Eye Institute, Pasadena, California)
- James H Peace, MD
  (United Medical Research Institute, Inglewood, California)
- Anthony Realini, MD, MPH

(West Virginia University Eye Institute, Morgantown, West Virginia)
- Kenneth Sall, MD
  (Sall Research Medical Center, Artesia, California)
- Elizabeth D. Sharpe, MD
  (Glaucoma Consultants & Center for Eye Research, Mt. Pleasant, South Carolina)
- Steven M. Silverstein, MD
  (Silverstein Eye Centers, Kansas City, Missouri)
- Blake G. Simmons, OD
  (St. Luke's Eye Care & Laser Center, Colorado Springs, Colorado)
- Steve T. Simmons, MD
  (Glaucoma Consultants of the Capital Region, Slingerlands, New York)
- Stacy Smith, MD
  (Salt Lake City, Utah)
- Stephen Smith, MD
  (Eye Associates of Fort Myers, Fort Meyers, Florida)
- Robert J. Smyth-Medina, MD
  (North Valley Eye Medical Group, Inc, Mission Hills, California)
- Robert Stamper, MD
  (University of California, San Francisco, Department of Ophthalmology, Glaucoma Clinic, San Francisco, California
- Richard T. Sturm, MD
  (Ophthalmic Consultants of Long Island, Lynbrook, New York)
- Matthew J. Swanic, MD
  (Las Vegas Eye Institute, Las Vegas, Nevada)
- Michael E. Tepedino, MD
  (Cornerstone Eye Care, High Point, North Carolina)
- Julie Tsai, MD
  (San Antonio, Texas)
- Vishteh Armin, MD
  (Havana Research Institute, LLC, Burbank, California)
- Thomas R. Walters, MD
  (Texan Eye, Austin, Texas)
- Mark J. Weiss, MD
  (Tulsa, Oklahoma)
- David L. Wirta, MD
  (Eye Research Foundation, Newport Beach, California)
- Darrell WuDunn, MD, PhD
  (Indiana University-Eugene & Marilyn Glick Eye Institute, Indianapolis, Minnesota)

ROCKET-1 Study Group
- Sanjay Asrani, MD
  (Duke Eye Center, Durham, North Carolina)
- Jason Bacharach MD
  (North Bay Eye Associates, Petaluma, California)
- David Belyea, MD

(George Washington University, Washington, DC)

- Michael S. Berlin, MD
  (Glaucoma Institute of Beverly Hills, Los Angeles, California)
- Jacob W. Brubaker, MD
  (Grutzmacher, Lewis & Sierra, Sacramento, California)
- Leonard R. Cacioppo, MD
  (Hernando Eye Institute, Brooksville, Florida)
- Eric A. Cohn, DO
  (Avail Clinical Research, LLC, DeLand, Florida)
- David L. Cooke, MD
  (Great Lakes Eye Care, Saint Joseph, Michigan)
- Harvey B. DuBiner, MD
  (Clayton Medical Center, Morrow, Georgia)
- Sherif M. El-Harazi, MD, MPH
  (Lugene Eye Institute, Glendale, California)
- Richard Evans, MD
  (Medical Center Ophthalmology Associates, San Antonio, Texas)
- Carl T. Hartman, MD
  (Southern California Eye Physicians & Assoc, Long Beach, California)
- Gary W. Jerkins, MD
  (Nashville Vision Associates, Nashville, Tennessee)
- Karen L. Klugo, MD
  (Apex Eye, Cincinnati, Ohio)
- Michael S. Korenfeld, MD
  (Comprehensive Eye Care, Washington, Missouri)
- Bradley Kwapizeski, MD
  (Heart of America Eye Care, P.A., Shawnee Mission, Kansas)
- Eugene B. McLaurin, MD
  (Total Eye Care, Memphis, Tennessee)
- Jonathan S. Myers, MD
  (Wills Eye Institute, Philadelphia, Pennsylvania)
- Constance Okeke, MD
  (Virginia Eye Consultants, Norfolk, Virginia)
- James H. Peace, MD
  (United Medical Research Institute, Inglewood, California)
- Eugene E. Protzko, MD
  (Seidenberg Protzko Eye Associates, Havre de Grace, Maryland)
- Ned M. Reinstein, MD
  (Reinstein Eye Associates, Tulsa, Oklahoma)
- Robert Ritch, MD
  (Glaucoma Associates of New York, New York, New York)
- Mark S. Rubin, MD
  (International Eye Associates, Ormond Beach, Florida)
- Robert M. Saltzmann, MD
  (Charlotte Eye Ear Nose & Throat Associates, Charlotte, North Carolina)

- Howard I. Schenker, MD
  (Rochester Ophthalmology Group , Rochester, New York)
- Philip Lee Shettle, DO
  (Shettle Eye Research, Inc, Largo, Florida)
- Scott Smetana, MD
  (Eye Associates of Colorado Springs, Colorado Springs, Colorado)
- Richard T. Sturm, MD
  (Ophthalmic Consultants of Long Island, Lynbrook, New York)
- Gregory M. Sulkowski, MD
  (Taustine Eye Center, Louisville, Kentucky)
- Julie Tsai, MD
  (San Antonio, Texas)
- Carl Tubbs, MD
  (Specialty Eye Care, Parker, Colorado)
- Farrell C. Tyson, MD
  (Argus Research at Cape Coral Eye Center, Cape Coral, Florida)
- Thasarat S. Vajaranant, MD
  (University of Illinois, Chicago, Illinois)
- David L. Wirta, MD
  (Eye Research Foundation Newport Beach, California)
- Peter Wollan, MD
  (Eye Physicians of Austin, Austin, Texas)
- Todd E. Woodruff, MD
  (The Glaucoma Center, Inc, Akron, Ohio)