Long-term Safety and Ocular Hypotensive Efficacy Evaluation of Netarsudil Ophthalmic Solution: Rho Kinase Elevated IOP Treatment Trial (ROCKET-2)

MALIK Y. KAHOOK, JANET B. SERLE, FRANCIS S. MAH, TERRY KIM, MICHAEL B. RAIZMAN, THERESA HEAH, NANCY RAMIREZ-DAVIS, CASEY C. KOPCZYNSKI, DALE W. USNER, AND GARY D. NOVACK, FOR THE ROCKET-2 STUDY GROUP

• PURPOSE: To evaluate netarsudil 0.02% ophthalmic solution in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT).
• DESIGN: Double-masked, randomized, multicenter, parallel-group, noninferiority clinical study.
• METHODS: After a washout of all prestudy ocular hypotensive medications, 756 eligible patients with elevated IOP were randomized to receive netarsudil 0.02% once a day (q.d.) (251); netarsudil 0.02% twice a day (b.i.d.) (254); or timolol 0.5% b.i.d. (251) for 12 months, as well as a noninterventional Corneal Observation Study (COS) for patients manifesting cornea verticillata.
• RESULTS: On treatment, mean IOP at 8:00 AM decreased from a baseline IOP of 22.5-22.6 mm Hg to 17.9-18.8 mm Hg, 17.2-18.0 mm Hg, and 17.5-17.9 mm Hg for netarsudil q.d., netarsudil b.i.d., and timolol, respectively, over 12 months. The most frequently reported adverse events (AEs) were ocular, with the most frequent ocular AE being conjunctival hyperemia, with an incidence of 61%, 66%, and 14%, respectively. The next most frequent AEs were corneal deposits (corneal verticillata), with an incidence of 26%, 25%, and 1%, respectively, and conjunctival hemorrhage (typically petechial), with an incidence of 20%, 19%, and 1%, respectively. All 3 AEs were generally scored as mild, with conjunctival hyperemia and/or hemorrhage appearing sporadically during the study. In the observational follow-up component of this study, there was no clinically meaningful impact of corneal verticillata on visual function in affected patients.
• CONCLUSIONS: In this randomized, double-masked trial, once-daily dosing of netarsudil 0.02% was effective, consistently lowering IOP through 12 months, and was tolerated by the majority of patients. (Am J Ophthalmol 2019;200:130–137. © 2019 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 and affects more than 60 million people worldwide.[1,2] Lowering intraocular pressure (IOP) decreases the development and progression of glaucomatous visual field loss.[3–7] Although current ocular hypotensive medications are generally effective at lowering IOP, many patients do not achieve target IOPs.[5,8] Combining current medications with different dosing frequencies can produce complex dosing regimens that contribute to poor patient adherence to prescribed therapy.[9]

In an effort to provide novel pharmacotherapies that can produce effective IOP lowering while providing a convenient, once-daily dosing regimen, Rho kinase (ROCK) inhibitors are being evaluated as a new class of topical agents for the treatment of open-angle glaucoma (OAG) and ocular hypertension (OHT).[10] The most commonly prescribed ocular hypotensive medications reduce IOP by increasing uveoscleral aqueous outflow (prostaglandin analogues) or decreasing aqueous 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 fibrogenic extracellular matrix proteins.[11–15] It is dysfunction of the trabecular outflow pathway that is responsible for elevated IOP in patients with OAG and OHT.[16,17]

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Jan 5, 2019.

From the University of Colorado School of Medicine, Aurora, Colorado, USA (M.Y.K.); Icahn School of Medicine at Mount Sinai, New York, New York, USA (J.B.S.); Scripps Clinic, La Jolla, California, USA (F.S.M.); Duke University School of Medicine, Durham, North Carolina, USA (T.K.); Tufts University School of Medicine, Boston, Massachusetts, USA (M.B.R.); Aerie Pharmaceuticals, Inc, Bedminster, New Jersey, USA (T.H., N.R.-D., C.C.K.); Durham, North Carolina, USA (T.H., N.R.-D., C.C.K.); SDC, Inc, Tempe, Arizona, USA (D.W.U.); PharmaLogic Development, Inc, San Rafael, California, USA (G.D.N.); and Department of Ophthalmology, University of California Davis School of Medicine, Sacramento, California, USA (G.D.N.).

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

0002-9394
https://doi.org/10.1016/j.ajo.2019.01.003

Netarsudil (previously AR-13324) is a potent ROCK inhibitor and also an inhibitor of the norepinephrine transporter.[18,19] In preclinical models, netarsudil has been shown to lower IOP through 3 effects on aqueous humor dynamics: (1) increases trabecular outflow facility, (2) decreases production of aqueous humor,[14] and (3) decreases episcleral venous pressure.[20] 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.[21] In a 28-day phase 2, randomized, double-masked, study, netarsudil ophthalmic solution 0.02% produced clinically significant reductions in mean diurnal IOP. In a prespecified subset analysis of patients with baseline IOPs ≤26 mm Hg, netarsudil 0.02% and latanoprost were similarly effective.[22]

Results from the first 3 months of the 12-month Phase 3 ROCKET-2 study were recently published.[23] In this report, we extend the previous findings to include the long-term results from the 12-month ROCKET-2 study. Netarsudil ophthalmic solution 0.02% was approved for clinical use by the U.S. Food and Drug Administration (FDA) in December 2017.

METHODS

• **STUDY DESIGN:** ROCKET-2 was a 12-month, double-masked, randomized, multicenter, parallel-group study that compared netarsudil ophthalmic solution 0.02% (netarsudil) to timolol maleate ophthalmic solution 0.5% (timolol) in patients with OAG or OHT. Netarsudil was dosed once a day (q.d.) PM or twice a day (b.i.d.). Timolol was dosed b.i.d. The studies were conducted in accordance with Good Clinical Practices Guidelines and adhered to the Declaration of Helsinki, and written informed consent was obtained from all subjects. A list of investigators and sites that participated in these studies is provided in the Addendum (Supplemental Material available at AJO.com). ROCKET-2 is registered with clinicaltrials.gov as NCT02207621.

Eligible patients were randomized by a computer-generated method to receive netarsudil or timolol in both eyes. Patients and designated 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. Patients were scheduled to attend a total of 9 study visits: a Screening Visit, Qualification Visit #1, Qualification Visit #2/Day 1 (baseline), Week 2, Week 6, Month 3, Month 6, Month 9, and Month 12. Examinations included IOP measurements (8:00 AM, 10:00 AM, and 4:00 PM), best-corrected visual acuity (BCVA) by Early Treatment of Diabetic Retinopathy Study (ETDRS) charts,[24] biomicroscopy, and assessment of adverse events (AE). Diurnal IOP measurements (8:00 AM, 10:00 AM, and 4:00 PM) were performed at baseline, Week 2, Week 6, and Month 3; IOP was measured at 8:00 AM only at Month 6, Month 9, and Month 12. Dilated ophthalmoscopy and static automated visual fields were performed at Screening, Month 3, and Month 12.

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 obtained. IOP was to be recorded as the mean of 2 measurements or as the median of 3 measurements.[25] 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).

At the completion of the Month 12 visit and netarsudil treatment, a subset of netarsudil-treated patients with the finding of cornea verticillata were eligible to enroll in a noninterventional Corneal Observation Study (COS, AR-13324-OBS01) to assess the potential impact of cornea verticillata on visual function. The first study visit occurred within 2 weeks of completing the Month 12 visit, and subsequent COS visits occurred monthly for 3 months and bimonthly thereafter until cornea verticillata had resolved (grade 0) or stabilized (≥1 year after netarsudil cessation without worsening). Cornea verticillata grading[26] and BCVA were performed at all COS visits. At the Week 2 and final COS visits, a Visual Function Index (VF-14) questionnaire[27] and the Pelli-Robson contrast sensitivity[28,29] test were performed.

• **PATIENTS:** Eligible patients were adults (18 years of age or greater) or, to meet FDA law, children aged 0-2 years with a diagnosis of bilateral OAG or OHT. Unmedicated IOP (after washout if required)[30] 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, unmedicated IOP was 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 and those 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 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 eye drop instillation.[31]

• **STATISTICS:** As previously reported, the primary efficacy outcome 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 (PP) population with IOP <25 mm Hg at all baseline time points.[23]

Power calculations and definition of noninferiority margin are provided in the previous report.[23] Assessment of safety and tolerability was based on patient reports in response to open-ended questions (eg, "how are you feeling") and ophthalmic and systemic examinations. AEs were coded using the Medical Dictionary for Regulatory Activities (Versions 17.0-19.0). The safety population included all randomized patients who received at least 1 dose of study medication.

Analyses were conducted using SAS (SAS Institute, Cary, North Carolina, USA), version 9.2 or higher. Statistical significance was $P \leq .05$, 2-tailed, with no adjustment for multiplicity.

RESULTS

• **DISPOSITION AND DEMOGRAPHICS:** *Prestudy Characteristics*. A total of 756 patients were enrolled. The demographics for the safety population were previously reported.[23] In brief, the population had a mean age in the mid 60s, was predominantly female, and was approximately three fourths white and one fourth African American. There were no statistically significant differences in demographics between treatment groups. Although eligible for enrollment, no patients 0-2 years of age were enrolled. At the time of prestudy 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 randomized to the netarsudil b.i.d. treatment group did not receive study medication.

Disposition. In the original report at 3 months, 82% (205/251), 60% (153/254), and 94% (237/251) of patients in the netarsudil q.d., netarsudil b.i.d., and timolol b.i.d. groups, respectively, completed the first 3 months. The proportion of patients discontinuing prior to 3 months owing to an adverse event was 12% (31/251), 30% (77/254), and 1% (2/251), respectively.[23] For the entire 12 months 58% (146/251), 34% (86/254), and 81% (204/251) of patients in the netarsudil q.d., netarsudil b.i.d., and timolol groups, respectively, completed the study. The proportion of patients discontinuing owing to an adverse event was 28% (71/251), 52% (132/254), and 6% (15/251), respectively.

• **INTRAOCULAR PRESSURE:** The 3-month primary efficacy analysis for ROCKET-2 was previously reported and demonstrated that both netarsudil q.d. and b.i.d. met the prespecified criteria for noninferiority to timolol.[1] Following the Month 3 visit, IOPs were measured at the Months 6, 9, and 12 visits at 8:00 AM only. Therefore, long-term ocular hypotensive efficacy of netarsudil ophthalmic solution 0.02% was evaluated using mean IOP measured at 8:00 AM from Week 2 to Month 12 in the primary efficacy population (PP population with maximum baseline IOP <25 mm Hg). Mean IOP at baseline at 8:00 AM was 22.5-22.6 mm Hg. Mean IOP at 8:00 AM ranged from 17.9 to 18.8 mm Hg and from 17.2 to 18.0 mm Hg for netarsudil dosed q.d. and b.i.d., respectively, and from 17.5 to 17.9 mm Hg for timolol, thereby demonstrating persistence of ocular hypotensive efficacy of netarsudil (Table 1). There was little evidence of tolerance (reduction in ocular hypotensive efficacy) in any treatment group over the 12 months of the study (Table 1).

• **ADVERSE EVENTS:** AEs in patients treated with once-daily netarsudil were predominantly nonserious and generally mild in intensity, whereas twice-daily dosing resulted in a higher proportion of AEs with moderate intensity. The incidence of ocular AEs over 12 months was 83% (209/251) in the netarsudil q.d. group, 88% (222/253) in the netarsudil b.i.d. group, and 49% (124/251) in the timolol group. The most frequent AEs recorded over 12 months of treatment are shown in Table 2.

The most frequently reported ocular adverse event was conjunctival hyperemia, with an incidence of 61% (152/251) for netarsudil q.d., 66% (168/253) for netarsudil b.i.d., and 14% (35/251) for timolol. For netarsudil, the severity of these findings was mostly mild (q.d.: 75%, 114/152; b.i.d.: 61%, 102/168). For timolol, the severity was also mostly mild (89%, 31/35). The onset of conjunctival hyperemia in netarsudil-treated groups was relatively early, with approximately 50%-60% of the first occurrence within the first 24 days of the study. Conjunctival hyperemia was also assessed at the biomicroscope by the investigators at regularly scheduled visits. From a mean baseline of 0.2 (0-to-3-unit scale) in all groups, the mean conjunctival hyperemia score in the study eye at each on-treatment study visit ranged from 0.5 to 0.7 in the netarsudil q.d. group and from 0.6 to 0.8 in the netarsudil b.i.d. group and remained at the baseline score of 0.2 in the timolol group. The incidence of conjunctival hyperemia leading to discontinuation of study drug was 12% (31/251), 24%

TABLE 1. ROCKET-2: Mean Intraocular Pressure (mm Hg) by Visit: Primary Efficacy Population[a]

	Mean IOP			Netarsudil q.d.–Timolol (95% C.I.)		Netarsudil b.i.d.–Timolol (95% CI)	
	Netarsudil q.d. (N = 129)	Netarsudil b.i.d. (N = 132)	Timolol (N = 142)	Mean Difference	95% CI	Mean Difference	95% CI
Baseline							
8:00 AM	22.54 (n = 129)	22.55 (n = 132)	22.54 (N=142)	0.00	(−0.25, 0.25)	0.01	(−0.24, 0.26)
10:00 AM	21.29 (n = 129)	21.27 (n = 132)	21.27 (N=142)	0.02	(−0.37, 0.41)	−0.01	(−0.40, 0.38)
4:00 PM	20.43 (n = 129)	20.56 (n =132)	20.71 (n = 142)	−0.28	(−0.71, 0.14)	−0.15	(−0.58, 0.29)
Day 15							
8:00 AM	18.07 (n = 127)	17.21 (n = 127)	17.69 (n = 142)	0.37	(−0.25, 0.99)	−0.48	(−1.19, 0.22)
10:00 AM	16.72 (n = 126)	16.35 (n = 120)	16.93 (n = 141)	−0.21	(−0.82, 0.41)	−0.57	(−1.24, 0.09)
4:00 PM	16.68 (n = 126)	15.65 (n = 118)	16.83 (n = 141)	−0.15	(−0.75, 0.46)	−1.18	(−1.82, −0.54)
Day 43							
8:00 AM	17.95 (n = 122)	17.64 (n = 111)	17.46 (n = 141)	0.49	(−0.13, 1.12)	0.17	(−0.51, 0.86)
10:00 AM	16.95 (n = 120)	16.28 (n = 106)	16.63 (n = 141)	0.32	(−0.31, 0.95)	−0.34	(−1.02, 0.33)
4:00 PM	17.00 (n = 120)	15.75 (n = 106)	16.60 (n = 141)	0.40	(−0.22, 1.02)	−0.85	(−1.53, −0.17)
Day 90							
8:00 AM	18.24 (n = 116)	17.58 (n = 91)	17.47 (n = 140)	0.77	(0.03, 1.50)	0.11	(−0.64, 0.86)
10:00 AM	17.03 (n = 114)	16.94 (n = 88)	16.92 (n = 140)	0.10	(−0.59, 0.80)	0.02	(−0.72, 0.77)
4:00 PM	17.13 (n = 114)	16.51 (n = 88)	16.95 (n = 139)	0.18	(−0.55, 0.91)	−0.44	(−1.16, 0.27)
Month 6							
8:00 AM	17.92 (n = 105)	17.71 (n = 69)	17.86 (n = 135)	0.07	(−0.68, 0.81)	−0.15	(−0.97, 0.68)
Month 9							
8:00 AM	18.16 (n = 91)	17.15 (n = 59)	17.47 (n = 125)	0.69	(−0.13, 1.51)	−0.32	(−1.22, 0.59)
Month 12							
8:00 AM	18.80 (n = 86)	17.96 (n = 56)	17.55 (n = 124)	1.25	(0.25, 2.26)	0.41	(−0.54, 1.36)

b.i.d. = twice a day; CI = confidence interval; q.d. = 4 times a day.

Difference from timolol 0.5% 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.

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

System Organ Class and Preferred Term	Netarsudil .02% q.d. (N = 251) n (%)	Netarsudil .02% b.i.d. (N = 253) n (%)	Timolol .5% b.i.d. (N = 251) n (%)	*P* Value
Eye disorders	198 (78.9)	215 (85.0)	86 (34.3)	<.0001/<.0001
Conjunctival hyperemia	152 (6.6)	168 (66.4)	35 (13.9)	<.0001/<.0001
Cornea verticillata	64 (25.5)	64 (25.3)	2 (0.8)	<.0001/<.0001
Conjunctival hemorrhage	49 (19.5)	49 (19.4)	2 (0.8)	<.0001/<.0001
Vision blurred	27 (1.8)	44 (17.4)	7 (2.8)	.0005/<.0001
Lacrimation increased	19 (7.6)	25 (9.9)	0	<.0001/<.0001
Visual acuity reduced	22 (8.8)	22 (8.7)	6 (2.4)	.0029/.0029
Eye pruritus	14 (5.6)	20 (7.9)	3 (1.2)	.0113/.0004
Conjunctival edema	8 (3.2)	19 (7.5)	0	.0074/<.0001
Erythema of eyelid	14 (5.6)	12 (4.7)	2 (0.8)	.0036/.0118
Eye irritation	11 (4.4)	13 (5.1)	8 (3.2)	.6411/.3731
Punctate keratitis	12 (4.8)	12 (4.7)	5 (2.0)	.1366/.1367
Eyelid edema	11 (4.4)	12 (4.7)	3 (1.2)	.0540/.0326
Eye pain	10 (4.0)	11 (4.3)	8 (3.2)	.8111/.6412
Foreign body sensation in eyes	7 (2.8)	14 (5.5)	1 (0.4)	.0681/.0008
Conjunctivitis allergic	6 (2.4)	11 (4.3)	1 (0.4)	.1224/.0058
Photophobia	5 (2.0)	8 (3.2)	1 (0.4)	.2159/.0374
Blepharitis	4 (1.6)	8 (3.2)	1 (0.4)	.3725/.0374
Corneal opacity	1 (0.4)	11 (4.3)	0	>.9999/.0009
Eye discharge	4 (1.6)	8 (3.2)	3 (1.2)	>.9999/.2214
General disorders and administration site	68 (27.1)	78 (3.8)	53 (21.1)	.1439/.0147
Instillation site pain	45 (17.9)	45 (17.8)	41 (16.3)	.7225/.7228
Instillation site erythema	14 (5.6)	32 (12.6)	5 (2.0)	.0586/<.0001
Instillation site discomfort	9 (3.6)	7 (2.8)	5 (2.0)	.4173/.7717
Infections and infestations	28 (11.2)	37 (14.6)	29 (11.6)	>.9999/.3557
Conjunctivitis	6 (2.4)	8 (3.2)	3 (1.2)	.5038/.2214
Upper respiratory tract infection	5 (2.0)	9 (3.6)	7 (2.8)	.7717/.8005
Investigations	36 (14.3)	28 (11.1)	24 (9.6)	.1296/.6609
Vital dye staining cornea present	14 (5.6)	17 (6.7)	14 (5.6)	.9999/.7115
Nervous system disorders	16 (6.4)	18 (7.1)	17 (6.8)	>.9999/>.9999
Headache	6 (2.4)	10 (4.0)	9 (3.6)	.6017/>.9999
Skin and subcutaneous tissue disorders	13 (5.2)	15 (5.9)	7 (2.8)	.2534/.1253
Injury, poisoning, and procedural complications	13 (5.2)	6 (2.4)	11 (4.4)	.8348/.2284
Metabolism and nutrition disorders	7 (2.8)	9 (3.6)	11 (4.4)	.4725/.6561
Respiratory, thoracic, and mediastinal disorders	10 (4.0)	6 (2.4)	14 (5.6)	.5312/.0717
Musculoskeletal and connective tissue disorders	12 (4.8)	3 (1.2)	17 (6.8)	.4447/.0012
Gastrointestinal disorders	2 (0.8)	10 (4.0)	9 (3.6)	.0625/>.9999
Cardiac disorders	9 (3.6)	2 (0.8)	7 (2.8)	.8004/.1052

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

Adverse events reported for 3.0% or more of subjects in any treatment group. *P* values, expressed as p1/p2, are from Fisher exact test comparing the distribution of incidence between netarsudil q.d. vs timolol b.i.d. (p1) and netarsudil b.i.d. vs timolol b.i.d. (p2).

(60/253), and 0% for netarsudil q.d., netarsudil b.i.d., and timolol, respectively.

The next most frequent adverse event was corneal deposits (also known as cornea verticillata), with an incidence of 26% (64/251) for netarsudil q.d., 25% (64/253) for netarsudil b.i.d., and 1% (2/251) for timolol. Cornea verticillata in the netarsudil groups were predominantly bilateral, asymptomatic, and of mild severity, with mean onset times of 172.9 (range 40-396) days and 127.1 (range 14-363) days for the netarsudil 0.02% q.d. and b.i.d. groups, respectively. The incidence of corneal deposits leading to discontinuation of study drug was 5% (13/251), 10%

(24/253), and 0% for netarsudil q.d., netarsudil b.i.d., and timolol, respectively.

Of the 130 patients who developed cornea verticillata, 45 patients were eligible to participate in the COS. Of these, 26 patients experienced resolution of cornea verticillata prior to study start. Cornea verticillata resolved in all patients except 3, in whom it improved but did not resolve by the final study visit; further follow-up demonstrated resolution in all but 1 eye of 1 patient, which improved and stabilized. The mean time to corneal deposit resolution or stabilization from last dose of study drug was 341.2 days (median = 314.5 days). There was no clinically meaningful change in the visual function assessment (visual acuity, contrast sensitivity, and VF-14 questionnaire) from the start of the COS to resolution/stabilization of the corneal verticillata.

The third most frequent adverse event was conjunctival hemorrhage. Conjunctival hemorrhage was reported in 100 patients: 20% (49/251) of netarsudil q.d. patients, 19% (49/253) of netarsudil b.i.d. patients, and 1% (2/251) of 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. The incidence of conjunctival hemorrhage leading to discontinuation of study drug was 2% (6/251), 4% (9/253), and 0% for netarsudil q.d., netarsudil b.i.d., and timolol, respectively.

Other adverse events seen at ≥3% incidence associated with once-daily netarsudil were instillation site pain, blurred vision, increased lacrimation, reduced visual acuity, eye pruritus, and erythema of the eyelid. More patients in the netarsudil groups compared to the timolol group experienced a 3-line ETDRS worsening in visual acuity in the study eye at 1 or more visits: 6% (16/251) of netarsudil q.d. patients, 8% (19/253) of netarsudil b.i.d. patients, and 4% (9/251) of timolol patients. However, visual acuity worsening was predominately monocular, was observed at sporadic visits, and, for most patients, resolved.

• **OTHER SAFETY MEASURES:** There were no notable differences between treatment groups for pupil diameter, ophthalmoscopy findings, cup-to-disc ratio, visual field, drop comfort, vital signs, or clinical laboratory findings. Mean corneal endothelial cell density in the study eye of patients in the netarsudil q.d., netarsudil b.i.d., and timolol groups was 2480, 2447, and 2455 cells/mm^2, respectively, at baseline and 2489, 2450, and 2451 cells/mm^2, respectively, at day 90. Values were similar in the netarsudil q.d. and b.i.d. groups relative to timolol at both baseline and day 90. Similar values were reported in the fellow eyes at baseline and at day 90. With respect to systemic safety, there were changes in mean heart rate with timolol (-1.6 to -2.7 beats/min) that were statistically significant at all visits ($P < .0001$ to $P < .0068$). In contrast, there was no statistically significant change in mean heart rate at any study visit in the netarsudil b.i.d. group, and the netarsudil q.d. group had only 1 visit with a statistically significant change in mean heart rate (-1.3 beats/min, $P = .0281$).

DISCUSSION

IN THE PREVIOUS REPORT OF 3-MONTH RESULTS FROM THE ROCKET-1 and ROCKET-2 studies,[23] netarsudil 0.02% dosed q.d. PM or b.i.d. effectively and safely lowered IOP in patients with OAG or OHT. Both dosing regimens 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 this report of the 12-month results from ROCKET-2, netarsudil maintained stable hypotensive efficacy through the full 12 months of dosing.

Netarsudil 0.02% administered q.d. PM was safe, was tolerated by the majority of patients, and is the recommended dosing frequency.[23] This is the dose approved by the FDA. As previously reported, netarsudil 0.02% administered b.i.d. was not as well tolerated as q.d. dosing, resulting in a greater number of discontinuations. There was a relatively low incidence of discontinuation in the timolol group, which may be expected given that subjects with contraindications or a history of adverse reactions to β-adrenoceptor antagonist therapy were excluded from the study. Despite these exclusion criteria, statistically significant reductions in heart rate were recorded at each on-treatment visit in the timolol group through 12 months.

There were no netarsudil-related systemic safety issues identified with longer-term dosing in ROCKET-2 and no new adverse events. As was reported in the 3-month safety analysis, the most frequent adverse events were conjunctival hyperemia, conjunctival hemorrhage, and cornea verticillata. The findings of conjunctival hyperemia and conjunctival hemorrhage were generally mild and transient as originally reported, but the incidence of each finding increased somewhat owing to the longer study duration and increased number of examinations. Cornea verticillata was also typically scored as mild; however, this finding persisted in affected individuals for the duration of treatment. The majority of cornea verticillata findings occurred after 3 months of treatment, with a mean time to onset of approximately 6 months for q.d. PM dosing. As originally reported, this finding could only be observed at the biomicroscope and had no effect on visual function during treatment.[23] For most patients, cornea verticillata were self-resolving within several months after cessation of therapy. The observational extension component (COS) of

this study further demonstrated no clinically meaningful impact of cornea verticillata on visual function.

A variety of drugs that are both cationic and amphiphilic are known to induce cornea verticillata, which arise owing to the lysosomal accumulation of phospholipids within corneal epithelial cells through a process called phospholipidosis.[32] Cornea verticillata have been associated with many agents, including systemic amiodarone and nonsteroidal anti-inflammatory drugs, and ocular gentamicin and tobramycin.[33] Netarsudil is a cationic amphiphilic drug and the developer has shown that netarsudil (although not its active metabolite, AR-13503) can induce phospholipidosis in Chinese hamster ovary cells, suggesting that the etiology of the netarsudil-induced corneal verticillata is phospholipidosis.[34] It is probably unrelated to the on-target pharmacology of this molecule. It is unusual for cornea verticillata to result in reduction of visual acuity or ocular symptoms, and the deposits typically resolve with discontinuation of the drug.[35]

In conclusion, in this randomized, double-masked trial, once-daily dosing of netarsudil 0.02% was found to be effective, consistently lowering IOP through 12 months, and was tolerated by the majority of patients with open-angle glaucoma and ocular hypertension. The novel pharmacology and distinct aqueous humor dynamic effects of this molecule suggest it may have utility as a first-line treatment option and as an adjunct to the other classes of compounds used to treat glaucoma.

FUNDING/SUPPORT: THIS RESEARCH WAS SPONSORED BY AERIE PHARMACEUTICALS (BEDMINSTER, NEW JERSEY, USA). FINANcial Disclosures: Malik Y. Kahook is a consultant to New World Medical, Alcon, Allergan, Equinox, and IanTech Medical, and receives patent royalties from New World Medical, Alcon, Johnson and Johnson Vision, IanTech Medical, and Aurea Medical. Janet B. Serle is a consultant to Aerie, Auventx, Bausch + Lomb, Gedeon Richter, and Inotek; receives financial support from Aerie, Allergan, and Ocular Therapeutix; and has a personal financial interest in Aerie. Francis S. Mah is a consultant to Abbott Medical Optics Inc, Aerie, Alcon Laboratories, Inc, Allergan, Bausch + Lomb, CoDa/Ocunexus, ForeSight, NovaBay, Ocular Science, Ocular Therapeutix, PolyActiva, Shire, Slack Publishing, Sun Pharma, Sydnexis, and TearLab; receives research support from Abbott Medical Optics Inc, Alcon Laboratories,Inc, Allergan, and Bausch + Lomb; receives nonremunerative compensation from Abbott Medical Optics Inc, Alcon Laboratories, Inc, Allergan, and Ocular Therapeutix; and owns stock in Ocular Science. Terry Kim serves as consultant for Aerie Pharmaceuticals, Alcon/Novartis, Allergan/Actavis, Avedro, Avellino Labs, Bausch + Lomb/Valeant, Blephex, CoDa/Ocunexus Therapeutics, Kala Pharmaceuticals, NovaBay Pharmaceuticals, Ocular Therapeutix, Omeros, Powervision, Presbyopia Therapies, Shire, Sightlife Surgical Inc, Silk Technologies, Simple Contacts, TearLab, and TearScience. Michael B. Raizman is a consultant to Aerie, Alcon, Arch Therapeutics, Avedro, EyeGate, Kala, Ocular Therapeutix, Psivida, Seattle Genetics, Shire, Stealth, Sun, TearLab, and Vertex, and has a financial interest in Avedro, and EyeGate. Theresa Heah, Nancy Ramirez-Davis, and Casey C. Kopczynski are employees of and stockholders in Aerie Pharmaceuticals. Dale W. Usner is an employee of SDC, a contractor to Aerie. Gary D. Novack is a consultant to Aerie and numerous other pharmaceutical and medical device firms. All authors attest that they meet the current ICMJE criteria for authorship.

Other Acknowledgments: The authors acknowledge the technical input of Pedram Hamrah, MD, New England Eye Center of Tufts Medical Center, Boston, Massachusetts, USA, and Christopher J. Rapuano, MD, Wills Eye Hospital, Philadelphia, Pennsylvania, USA.

The 3-month portion of this report was previously published in the *American Journal of Ophthalmology*[23] and presented at the American Glaucoma Society (March 2016, Ft Lauderdale, Florida, USA; March 2017, Coronado, California, USA), the Association for Research in Vision and Ophthalmology (May 2016, Seattle, Washington, USA), and the European Glaucoma Society (June 2016, Prague, Czech Republic), with portions published in *Glaucoma Today* 2016;14(2):43-45, *Cataract & Refractive Surgery Today* 2016;16(6):35-37, and *Advanced Ocular Care* 2016;7(6):44-46. The 12-month part of this manuscript was presented at the Association for Research in Vision and Ophthalmology (May 2018, Honolulu Hawaii, USA; Serle JB, Kahook MY, Lewis RA, et al. Long-term safety and ocular hypotensive efficacy of netarsudil ophthalmic solution: The ROCKET-2 Study. *Invest Ophthalmol Vis Sci* 2018;59:ARVO E-Abstract 1242).

REFERENCES

1. Alward WL. Medical management of glaucoma. *N Engl J Med* 1998;339(18):1298–1307.
2. Casson RJ, Chidlow G, Wood JP, Crowston JG, Goldberg I. Definition of glaucoma: clinical and experimental concepts. *Clin Exp Ophthalmol* 2012;40(4):341–349.
3. 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.
4. 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.
5. Kass MA, Heuer DK, Higginbotham EJ, et al. Ocular Hypertension Treatment Study Group: 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.
6. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001;108(11):1943–1953.
7. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet* 2015;385(9975):1295–1304.
8. European Glaucoma Society. Terminology and Guidelines for Glaucoma. 4th ed. Savona, Italy: PubliComm; 2014.
9. Robin AL, Novack GD, Covert DW, Crockett RS, Marcic TS. Adherence in glaucoma: objective measurements of once-daily and adjunctive medication use. *Am J Ophthalmol* 2007;144(4):533–540.
10. Kopczynski CC, Epstein DL. Emerging trabecular outflow drugs. *J Ocul Pharmacol Ther* 2014;30(2-3):85–87.

11. Tian B, Kaufman PL. Effects of the Rho kinase inhibitor Y-27632 and the phosphatase inhibitor calyculin A on outflow facility in monkeys. *Exp Eye Res* 2005;80(2):215–225.
12. Tokushige H, Inatani M, Nemoto S, et al. Effects of topical administration of Y-39983, a selective rho-associated protein kinase inhibitor, on ocular tissues in rabbits and monkeys. *Invest Ophthalmol Vis Sci* 2007;48(7):3216–3222.
13. Honjo M, Inatani M, Kido N, et al. Effects of protein kinase inhibitor, HA1077, on intraocular pressure and outflow facility in rabbit eyes. *Arch Ophthalmol* 2001;119(8):1171–1178.
14. Wang R-F, 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.
15. 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.
16. Grant WM. Clinical tonography. *Trans Am Acad Ophthalmol Otolaryngol* 1951;55:774–781.
17. Stamer WD, Acott TS. Current understanding of conventional outflow dysfunction in glaucoma. *Curr Opin Ophthalmol* 2012;23(2):135–143.
18. Sturdivant JM, Royalty SM, Lin CW, et al. Discovery of the ROCK inhibitor netarsudil for the treatment of open-angle glaucoma. *Bioorg Med Chem Lett* 2016;26(10):2475–2480.
19. 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.
20. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure in Dutch Belted rabbits. *J Ocul Pharmacol Ther* 2015;31(3):146–151.
21. 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.
22. Bacharach J, Dubiner HB, Levy B, Kopczynski CC, Novack GD, AR-13324-CS202 Study Group. Double-masked, randomized, dose-response study of AR-13324 vs. latanoprost in patients with elevated intraocular pressure. *Ophthalmology* 2015;122(2):302–307.
23. 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: Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). *Am J Ophthalmol* 2018; 186:116–127.
24. Ferris FL III, Sperduto RD. Standardized illumination for visual acuity testing in clinical research. *Am J Ophthalmol* 1982; 94:97–98.
25. Sherwood MB, Craven ER, Chou C, et al. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. *Arch Ophthalmol* 2006;124(9):1230–1238.
26. Orlando RG, Dangel ME, Schaal SF. Clinical experience and grading of amiodarone keratopathy. *Ophthalmology* 1984; 91(10):1184–1187.
27. Steinberg EP, Bass EB, Luthra R, et al. Variation in ophthalmic testing before cataract surgery. Results of a national survey of ophthalmologists [see comments]. *Arch Ophthalmol* 1994;112(7):896–902.
28. Pelli DG, Robson JG, Wilkins AJ. The design of a new letter chart for measuring contrast sensitivity. *Clin Vis Sci* 1988;2187–2199.
29. Elliott DB, Bullimore MA, Bailey IL. Improving the reliability of the Pelli-Robson contrast sensitivity test. *Clin Vis Sci* 1991;6(6):471–475.
30. 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.
31. Stone JL, Robin AL, Novack GD, Covert D, Cagle GD. An objective evaluation of eye-drop instillation in glaucoma patients. *Arch Ophthalmol* 2009;127(6):732–736.
32. Hollander DA, Aldave AJ. Drug-induced corneal complications. *Curr Opin Ophthalmol* 2004;15(6):541–548.
33. Raizman MB, Hamrah P, Holland EJ, et al. Drug-induced corneal epithelial changes. *Surv Ophthalmol* 2017;62(3): 286–301.
34. Lin C-W, Foley BE, Carbajal KS, Kopczynski CC. Evaluation of the Potential of AR-13324 and AR-13503 to Induce Phospholipidosis. Honolulu, HI: Association for Research in Vision and Ophthalmology; 2018.
35. Mantyjarvi M, Tuppurainen K, Ikaheimo K. Ocular side effects of amiodarone. *Surv Ophthalmol* 1998;42(4):360–366.