

Tie2 Activation via VE-PTP Inhibition With Razuprotafib as an Adjunct to Latanoprost in Patients With Open Angle Glaucoma or Ocular Hypertension

Mitchell Brigell¹, Barbara Withers¹, Akshay Buch¹, and Kevin G. Peters¹

¹ Aerpio Pharmaceuticals, Cincinnati, OH, USA

Correspondence: Kevin G. Peters, Peters Biopharma Consulting, 9160 Given Road, Cincinnati, OH 45243, USA. e-mail: petersbiopharma@gmail.com

Received: July 22, 2021

Accepted: November 14, 2021

Published: January 6, 2022

Keywords: glaucoma; ocular hypertension; Tie2; VE-PTP; clinical trial

Citation: Brigell M, Withers B, Buch A, Peters KG. Tie2 activation via VE-PTP inhibition with razuprotafib as an adjunct to latanoprost in patients with open angle glaucoma or ocular hypertension. *Transl Vis Sci Technol.* 2022;11(1):7. <https://doi.org/10.1167/tvst.11.1.7>

Purpose: To evaluate the ocular hypotensive efficacy and safety of razuprotafib, a novel Tie2 activator, when used as an adjunct to latanoprost in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Methods: Subjects with OAG or OHT and an unmedicated IOP from ≥ 22 mm Hg to < 36 mm Hg were randomized to one of three treatment arms: razuprotafib every day (QD) + latanoprost; razuprotafib twice daily (BID) + latanoprost; or latanoprost monotherapy. The primary endpoint was change in mean diurnal IOP from baseline at day 28.

Results: A total of 194 subjects were randomized, and 193 (99.5%) completed the study. Razuprotafib BID + latanoprost resulted in a significantly larger reduction in diurnal IOP than latanoprost alone (7.95 ± 0.26 mmHg vs. 7.04 ± 0.26 mm Hg, $P < 0.05$). A smaller improvement was observed after 14 days of treatment (7.62 ± 0.26 mm Hg vs. 7.03 ± 0.26 mm Hg, $P = 0.11$). Razuprotafib QD dosing did not demonstrate additional IOP lowering compared to latanoprost alone. Conjunctival hyperemia on Day 28 increased by 1.1 units on the four-point Efron scale two hours post dose from a baseline value of 0.6 units, and decreased thereafter.

Conclusions: Topical ocular razuprotafib as an adjunct to latanoprost therapy was well tolerated and significantly reduced IOP in patients with OAG/OHT.

Translational Relevance: These data support the IOP lowering efficacy of targeting Tie2 activation in Schlemm's canal in the relevant patient population.

Introduction

Open-angle glaucoma (OAG) is a leading cause of irreversible blindness affecting approximately 44.7 million people worldwide with an estimated prevalence in the United States of 2.7 million in 2011, which is expected to increase to 7.3 million by 2050.¹⁻³ OAG is characterized by optic nerve and neuroretina anomalies and progressive visual field defects. Elevated intraocular pressure (IOP)/ocular hypertension (OHT) is the primary modifiable risk factor and reducing IOP is the only clinical approach shown to slow/prevent vision loss.⁴⁻⁷ Despite the availability of effective IOP lowering drugs, many patients require multiple agents to control IOP that together often fail to achieve a “target” IOP.⁸

Razuprotafib ophthalmic solution is in development as an adjunctive treatment to prostaglandins for treating OAG. Razuprotafib is a novel small molecule which selectively inhibits VE-PTP (vascular endothelial-protein tyrosine phosphatase) and enhances Tie2 (tyrosine kinase with immunoglobulin-like and Epidermal Growth Factor (EGF)-like domains 2) activation and signaling. Angiotensin (Angpt)/Tie2 pathway activation may have therapeutic benefit in patients with OAG and OHT by directly targeting the conventional outflow (CO) pathway. In a recent study, razuprotafib was shown to increase Tie2 activation in endothelium of Schlemm's canal (SC), reduce IOP, and increase outflow facility in mouse eyes.⁹ VE-PTP was localized to SC endothelial cells in human and mouse eyes.⁹⁻¹² Mechanistically, razuprotafib increased the filtration area of SC for aqueous

humor efflux in both wild-type and in Tie2+/- mice.⁹

In previous clinical trials of subcutaneously delivered razuprotafib for the treatment of diabetic eye disease, IOP was lowered by 1 to 1.5 mm Hg in normotensive eyes.⁹ In this article, we report the results of a randomized placebo controlled clinical trial to test the efficacy of 4% razuprotafib ophthalmic solution dosed daily (QD) or two times daily (BID) adjunctive to QD latanoprost in patients with OAG or ocular hypertension (OHT).

Methods

Study Design

This was a phase 2, double masked, randomized, multicenter, parallel-group study. Subjects participated in the study for up to approximately 11 weeks (screening visit, washout period for four to six weeks, two qualification visits [two to seven days apart], and treatment period for 28 days).

To be included in the study, patients were required to be adults with a diagnosis of OAG or OHT (based on IOP, visual fields, and optic nerve cupping) with visual acuity of 0.5 logMAR or better in each eye (20/63 Snellen). Eligible subjects must have been on a stable dose of topical prostaglandin eye drops for at least two weeks before screening with on-treatment IOP \geq 18 mm Hg at screening. After screening, subjects entered a four-week washout period. Post-washout, final IOP at a second qualification visit was required to be \geq 24 mm Hg at 8:00 and \geq 22 mm Hg at 10:00, 12:00, and 16:00 hours.

Eligible subjects were randomized 1:1:1 to razuprotafib ophthalmic solution 4.0% QD (mornings [AM]) and placebo for razuprotafib ophthalmic solution QD (afternoons [PM]) + latanoprost ophthalmic solution 0.005% QD (PM); razuprotafib ophthalmic solution 4.0% BID (AM & PM) + latanoprost ophthalmic solution 0.005% QD (PM); or placebo for razuprotafib ophthalmic solution BID (AM & PM) + latanoprost ophthalmic solution 0.005% QD (PM) for 28 days. Randomization was stratified by mean diurnal IOP (IOP averaged over 08:00, 10:00, 12:00, and 16:00 hours) on qualification visit 2/day -1 (<26 mm Hg vs. \geq 26 mm Hg) in the study eye (qualified eye with highest IOP). A randomization code for treatment allocation was prepared by an independent biostatistician, who was not involved in the day-to-day conduct of the study. Eligible subjects were assigned to one of the three treatment groups using a central interactive web response system. Study

medication kits were allocated via the interactive web response system.

During the treatment period, patients self-administered study medication (razuprotafib ophthalmic solution or placebo for razuprotafib) daily in the AM and PM and also administered latanoprost daily in the PM. Patients dosed each eye by the topical ocular route using dropper bottles to deliver eye drops. Daily AM dose administration of study medication occurred between 07:00 and 10:00 hours and PM dose administration occurred between 19:00 and 22:00 hours. Latanoprost PM dose administration occurred at least five minutes before administration of the PM dose of study medication. Patients began dosing with the AM dose of study medication on the morning of day 1 and concluded dosing after administration of the AM dose of study medication on day 28; there was no PM dose administration on day 28. At study clinic visits conducted on days 14 and 28, subjects administered the AM dose of medication at the clinic after the 08:00 hour ophthalmic assessments had been completed. No ocular medication (other than non-medicated lubricating drops) was allowed during the study.

During the treatment period, subjects were seen in the clinic on days 7, 14 and 28; ocular safety assessments were conducted on all days, and IOP measurements were conducted on days 14 and 28 at the following time points: 08:00, 10:00, 12:00 and 16:00 hours.

At each study visit during the treatment period, multiple ocular safety assessments were conducted including some or all of the following: adverse events, visual acuity, conjunctival hyperemia assessment, objective findings of biomicroscopic examinations (i.e., lids, conjunctiva, cornea, anterior chamber, iris and lens), cup-disc ratio measurements, and dilated ophthalmoscopic examination.

This study was registered on ClinicalTrials.gov (NCT04405245), approved by Alpha Independent Review Board, San Clemente, CA, and all patients provided written informed consent consistent with standards of the Declaration of Helsinki.

IOP Assessment

IOP was measured with a calibrated Goldmann tonometer by a licensed ophthalmologist or optometrist who was masked to the treatment assignment. A separate staff member read the dial setting and recorded the reading. Two consecutive measurements of IOP in each eye were obtained at each time point. If the two measurements differed by >2 mm Hg, a third measurement was obtained. IOP was recorded as the

mean of two measurements or as the median of three measurements.

Conjunctival Hyperemia Assessment

Conjunctival hyperemia was assessed on days 14 and 28 at pre-dose and two, four, and eight hours post-dose using the five-point Efron bulbar conjunctiva hyperemia scale (0 = Normal, 1 = Trace, 2 = Mild, 3 = Moderate, 4 = Severe). An increase of two or more grades on the hyperemia scale when compared to the lowest score recorded at any previous timepoint for an individual eye was reported as an adverse event. If a subject complained of hyperemia, an adverse event (AE) was recorded regardless of grade on the hyperemia scale.

Statistical Analysis

The planned sample size of 65 subjects per arm completing 28 days of treatment gave 80% power to conclude statistical superiority of razuprotafib (QD or BID) + latanoprost to latanoprost monotherapy assuming a two-sided alpha = 0.05, a true difference in mean diurnal change from baseline IOP of 1.5 mm Hg, a common standard deviation (SD) of 3.5 mm Hg at each time point, and a correlation of 0.60 among time points within a subject's study eye (leading to an SD of the mean diurnal IOP of 3.0 mm Hg). All statistical output was produced with SAS Software, version 9.2 (SAS Inc, Cary, NC, USA). Hypothesis testing, unless otherwise indicated, was performed at a 5% significance level.

Results

Disposition

Between July 2020 and November 2020, a total of 194 patients were randomized and treated; 193 (99.5%) completed the study. One subject in the razuprotafib BID + latanoprost treatment group discontinued study participation due to an adverse event (Fig. 1). The safety and the intent-to-treat populations included all 194 randomized patients. The outcomes of the trial were based on the intent to treat population (all randomized patients with at least one dose of study drug).

Demographics and Baseline Characteristics

The demographics of the study population are shown in Supplementary Table S1 (available at

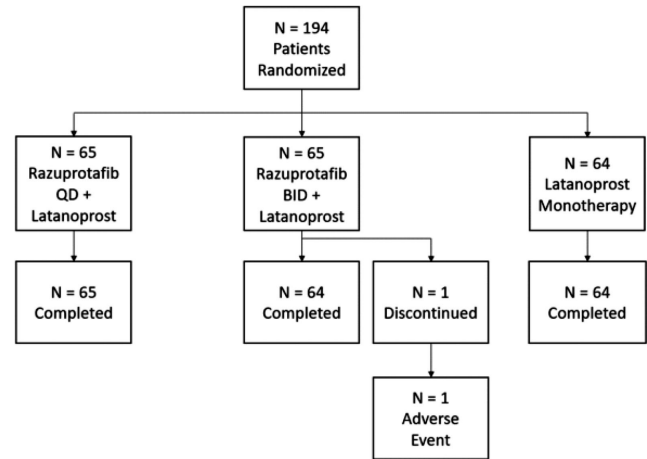


Figure 1. Disposition of patients within the REAL study (Razuprotafib Tie 2 Activation as adjunct to Latanoprost) in patients with OAG or OHT.

www.aaojournal.org). The population was 62% female (n = 120) and had a mean age (\pm standard deviation) of 66.6 ± 10 years (range 34–89 years). The population was 72% white, 27% black, and 1% Asian. Nine percent of patients self-identified as Hispanic. There were no clinically or statistically significant differences among treatment groups.

The baseline characteristics for the study population are shown in Table 1. A similar proportion of subjects in the razuprotafib BID + latanoprost arm and the latanoprost monotherapy arm had a diagnosis of OAG in the study eye (66.2% and 65.6%, respectively); however, the proportion was lower in the razuprotafib QD + latanoprost arm (50.8%). Similarly, corneal thickness at screening was comparable in the study eyes of subjects in the razuprotafib BID + latanoprost arm and the latanoprost monotherapy arms, but slightly lower in the razuprotafib QD + latanoprost arm. The diurnal mean IOP in the study eyes of all three treatment arms was comparable at the screening visit, as was the study eye diurnal mean IOP at baseline (qualification visit 2). There were no clinically or statistically significant differences among treatment groups.

Efficacy

After 28 days of dosing, subjects treated with razuprotafib BID adjunctive to latanoprost had a significantly greater reduction in mean diurnal IOP than subjects treated with latanoprost monotherapy (7.95 ± 0.26 mm Hg vs. 7.04 ± 0.26 mm Hg, $P < 0.05$, see Fig. 2A). A smaller improvement was observed after 14 days of treatment that was not statistically significant (7.62 ± 0.26 mm Hg vs. 7.03 ± 0.26 mm Hg, $P = 0.11$). Adjunctive therapy with razuprotafib

Table 1. Baseline Characteristics (ITT Population) of Patients in the Study of Tie 2 Activator (Razuprotafib) as Adjunct to Latanoprost in Patients With OAG or OHT (ITT and Safety Population).

	Razuprotafib QD + Latanoprost (N = 65)	Razuprotafib BID + Latanoprost (N = 65)	Latanoprost Monotherapy (N = 64)
Diagnosis			
OAG - Study Eye	33 (50.8%)	43 (66.2)	42 (65.6)
OHT - Study Eye	32 (49.2%)	22 (33.8)	22 (34.4)
OAG - Fellow Eye	33 (50.8%)	42 (64.6)	42 (65.6)
OHT - Fellow Eye	32 (49.2%)	23 (35.4)	22 (34.4)
Randomization IOP (Study Eye)			
Diurnal Mean <26 mm Hg	49 (75.4%)	49 (75.4)	48 (75.0)
Diurnal Mean ≥26 mm Hg	16 (24.6%)	16 (24.6)	16 (25.0)
Study Eye Screening Corneal Thickness (µm)			
Mean (SD)	544.8 (30.27)	554.0 (28.57)	554.7 (30.58)
Min, Max	483, 609	483, 598	482, 599
Study Eye Screening IOP (mm Hg)			
Mean (SD)	20.34 (1.981)	20.54 (2.283)	20.11 (2.003)
Min, Max	18.0, 26.0	18.0, 27.0	18.0, 26.5
Study Eye Baseline Diurnal Mean IOP (mm Hg)			
Mean (SD)	24.83 (1.559)	25.16 (2.039)	25.11 (1.967)
Min, Max	22.5, 29.5	22.5, 31.8	22.5, 31.0

N in the headers represents the total number of subjects in each treatment group for the population being analyzed. Baseline diurnal mean IOP is defined as the average of 4 IOP values across 8:00-, 10:00-, 12:00-, and 16:00-hour time points at qualification visit 2.

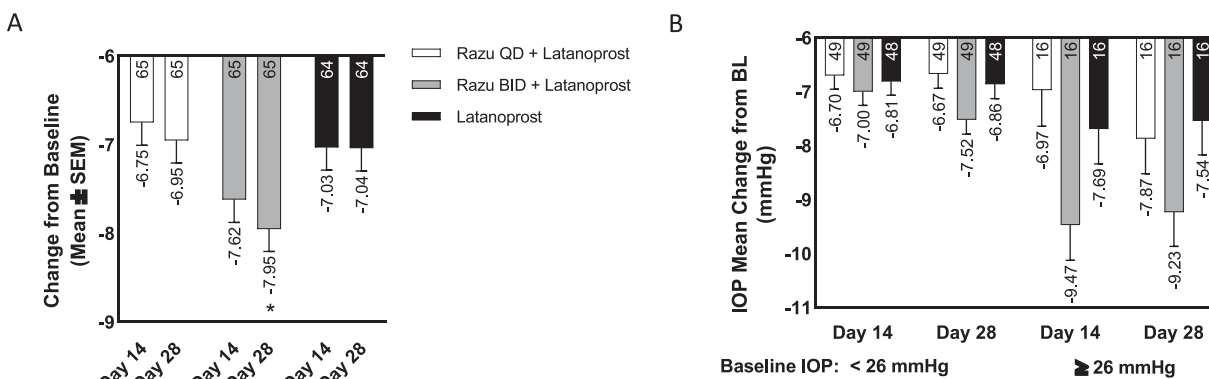


Figure 2. Change in mean diurnal IOP by treatment group after 14 and 28 days of treatment. (A) Overall effect. (B) Subgroups with IOP of <26 mm Hg and ≥26 mm Hg after washout. The numbers below the SEM bars indicate the mean reduction in IOP in each group or subgroup. Numbers at the top of the bars indicate number of patients in each group or subgroup. * $P = 0.01$ versus Latanoprost.

QD dosing did not demonstrate additional IOP lowering compared to latanoprost alone. In a planned subgroup analysis, subjects with mean diurnal IOPs of ≥26 mm Hg after washout showed a greater reduction of IOP with adjunctive razuprotafib BID therapy than those with washout IOPs <26 mm Hg. For the subgroup with higher washout IOPs, razuprotafib BID provided an additional 1.79 ± 0.92 mm Hg reduction in mean diurnal IOP compared to latanoprost

after 14 days of treatment and an incremental benefit of 1.68 ± 0.89 mm Hg after 28 days of treatment (Fig. 2B).

IOP results for individual time points by treatment group are shown in Figure 3. After the washout of prostaglandin therapy there was an approximately 6 mm increase in IOP compared to the screening value. The effect of adjunctive razuprotafib began by seven days of treatment and increased over time to reach

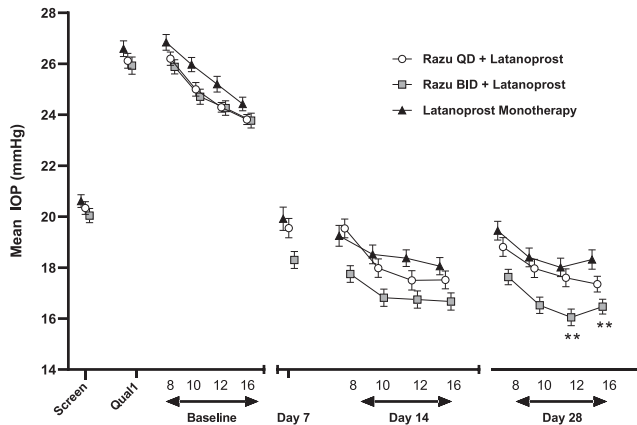


Figure 3. Mean IOP by time point and treatment group. The numbers 8, 10, 12, and 16 on the x-axis refer to the individual post-dose time points, 8:00 (pre-dose), 10:00, 12:00, and 16:00 hours, respectively, comprising the diurnal IOP at baseline, day 14, and day 28. Only a single IOP measurement was taken at screening, qualification 1, and day 7 visits.

statistical significance for the razuprotafib BID group compared to latanoprost monotherapy at the 12:00 and 16:00 hour time points on day 28.

Safety

There were no deaths or other serious adverse events reported in the study. A single subject in the study experienced an ocular adverse event (conjunctival hyperemia) leading to discontinuation of treatment (razuprotafib BID + latanoprost) and ultimately study discontinuation.

Adverse events for the safety population are shown in Supplementary Tables S2 and S3 (available at www.aaojournal.org). The most common adverse events in

the study (occurring in >5% on any treatment arm) were conjunctival hyperemia, dysgeusia and instillation site pain (Table 2). There were no adverse events considered severe in intensity and the majority of events reported were considered mild in intensity (91% mild). A significantly greater percentage of subjects in the razuprotafib QD + latanoprost and razuprotafib BID + latanoprost treatment arms had conjunctival hyperemia compared with the latanoprost monotherapy arm (40.0% vs. 14.1%, $P = 0.0014$, and 60.0% vs. 14.1%, $P < 0.0001$, respectively). It is important to note that of the 74 subjects reporting 114 adverse events of conjunctival hyperemia, 89 events were triggered by a ≥ 2 grade increase on the Efron five-point scale, and only 25 events were due to a subject complaint. The mean hyperemia score in the razuprotafib BID + latanoprost treatment group increased by 1.1 units two hours post dose from a baseline value of 0.6 units, and decreased steadily thereafter (Fig. 4).

Additionally, a greater percentage of subjects in the razuprotafib BID + latanoprost treatment arm reported dysgeusia compared with subjects in the latanoprost monotherapy arm (12.3% vs. 1.6%; $P = 0.0327$). Importantly, there were no other significant non-ocular AEs reported.

Discussion

The results of this study show that topical ocular administration of the Tie2 activator razuprotafib, as an adjunct to standard of care latanoprost, was well tolerated and significantly reduced IOP in patients with glaucoma. This confirms and extends results in

Table 2. Most Common Treatment-Emergent Adverse Events*

Preferred Term (PT)	Razuprotafib QD + Latanoprost (N = 65)	Razuprotafib BID + Latanoprost (N = 65)	Latanoprost Monotherapy (N = 64)	P Value†
Any treatment-emergent AE	30 (46.2%)	43 (66.2%)	19 (29.7%)	
Conjunctival hyperemia	26 (40.0%)	39 (60.0%)	9 (14.1%)	0.0014/<0.0001
Dysgeusia	3 (4.6%)	8 (12.3%)	1 (1.6%)	0.6191/0.0327
Instillation site pain	0	2 (3.1%)	4 (6.3%)	0.0577/0.4401

N in the headers represents the total number of subjects in each treatment group for the population being analyzed. Percentages are based on N in each treatment group unless otherwise noted. Adverse events are coded using MedDRA Version 23.0. Subjects having more than one AE within a PT are counted only once for that PT. SOCs and PTs within SOCs are listed in alphabetical order.

*Reported in >5% of Subjects in Any Treatment Group) in the Study of Tie 2 Activator (Razuprotafib) as adjunct to Latanoprost in Patients with OAG or OHT (Safety Population)

†P values expressed as p1/p2 are from Fisher’s exact test comparing the incidence between razuprotafib QD + latanoprost and razuprotafib BID + latanoprost versus latanoprost monotherapy.

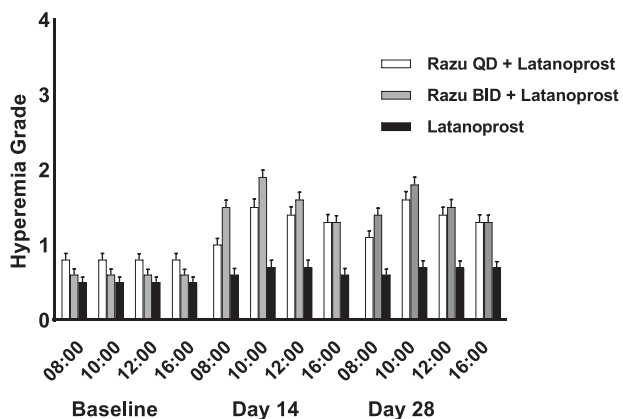


Figure 4. Mean worst eye conjunctival hyperemia grade at Baseline and Days 14 and 28 using the five-point Efron bulbar conjunctiva hyperemia scale (0 = Normal, 1 = Trace, 2 = Mild, 3 = Moderate, 4 = Severe).

two consecutive clinical trials assessing subcutaneous administration of razuprotafib for the treatment of diabetic retinopathy, where significant IOP reduction was observed in ocular normotensive patients.⁹ In the current trial, adjunctive topical ocular razuprotafib BID dosing was more effective than QD dosing with increasing IOP lowering effect in both the QD and BID group between day 14 and day 28, reaching statistical significance at 28 days in the BID group. Moreover, the adjunctive IOP lowering effect was larger in patients with baseline IOP ≥ 26 mm Hg. The time- and pressure-dependence of IOP lowering are consistent with razuprotafib's proposed mechanism of action to increase conventional outflow facility by targeting Schlemm's canal function and repair.⁹

Supporting the proposed mechanism, mouse and human genetic data have established a role for the Tie2 pathway in the development and maintenance of Schlemm's canal.¹³⁻¹⁸ Importantly, human genetic studies show that both Tie2 and Angpt1 loss-of-function variants associate with risk of congenital glaucoma, and single-nucleotide polymorphisms in the Angpt1 promoter region significantly associate with ocular hypertension and OAG risk.¹⁸⁻²¹ The molecular target of razuprotafib, VE-PTP, is expressed by SC endothelium in mice and humans, and topical ocular administration of razuprotafib in mice increased Tie2 activation, enhanced SC filtration area, and increased outflow facility, resulting in reduced IOP.⁹⁻¹² As a genetic correlate to the studies with razuprotafib, the developmental defect of SC size in Tie2^{+/-} mice could be partially compensated by removing one VE-PTP allele in double hemizygous mice.¹⁶ Importantly, SC luminal area is smaller, and outflow facility is lower in glaucomatous eyes compared to age-matched controls.²²⁻²⁴ Taken together, these findings

further support Tie2 activation with razuprotafib as a potential disease modifying approach to treating OAG mediated by the anatomical remodeling effects on Schlemm's canal. Moreover, because razuprotafib works by increasing conventional outflow, it represents an ideal adjuvant therapy to standard of care prostaglandins that reduce IOP primarily via a secondary outflow route known as the uveoscleral or unconventional outflow pathway.²⁵

Overall, razuprotafib was well tolerated, with mostly mild hyperemia as the main adverse effect. The hyperemia is likely due to the vasodilator effect of activating endothelial nitric oxide synthase downstream of Tie2 activation.^{26,27} The hyperemia was transient, peaked within two hours of dosing, and was not associated with other adverse events such as conjunctival pain or hemorrhage. Other than mild dysgeusia, no clinically significant non-ocular adverse events were noted.

The main limitation of this study was the short duration of treatment. The time dependent trend of IOP lowering after one month of treatment supports the proposed MOA involving increased conventional outflow via the remodeling of Schlemm's canal and suggests that a longer study may have resulted in a larger IOP lowering effect. Another limitation of this study was study entry based on a relatively low post-washout IOP (≥ 24 mm Hg at 8:00 and ≥ 22 mm Hg at 10:00, 12:00, and 16:00 hours). A conventional outflow targeted agent would be expected to have a larger IOP lowering effect in patients with higher baseline IOP as illustrated by the larger IOP lowering effect of razuprotafib in patients with baseline IOP ≥ 26 mm Hg. Based on these considerations, a longer study including patients with higher post-washout IOP or basing entry on IOP after a prostaglandin run-in period may have resulted in a larger IOP lowering effect.

Netarsudil, another conventional outflow targeted therapy available as a once-daily fixed-dose combination with latanoprost (Rocklatan), yields a ~ 1.5 mm Hg reduction in IOP compared to latanoprost alone.^{28,29} However, unlike razuprotafib, the IOP lowering effect of netarsudil appears to be larger in patients with IOP ≤ 25 mm Hg and the IOP lowering effect appears to wane over time. The differences between razuprotafib and netarsudil could be due to the specific component of conventional outflow targeted, Schlemm's canal remodeling versus episcleral venous pressure, respectively. In particular, the reduced performance of netarsudil in patients with highly elevated IOP could be secondary to severe outflow limitation proximal to the episcleral veins (i.e., Schlemm's canal or the trabecular meshwork). Thus combining razuprotafib or possibly Vizulta (latanoprostene bunod), a once daily nitric

oxide donating prostaglandin that targets the trabecular meshwork, with netarsudil could be optimal for patients with advanced disease.³⁰ Nonetheless, continued requirement of BID dosing of razuprotafib would represent a relative disadvantage for patient convenience due to additional dosing frequency and decreased potential of creating a “one bottle” drug. Thus further assessment of both BID and QD dosing over a longer duration in patients with higher baseline IOP will inform the potential for razuprotafib as a Schlemm’s canal targeted OHT/OAG therapy.

Acknowledgments

Supported by Aerpio Pharmaceuticals, Inc.

Disclosure: **M. Brigell**, Aerpio (C, I); **B. Withers**, Aerpio (E, I); **A. Buch**, Aerpio (E, I); **K.G. Peters**, Aerpio (E, I)

References

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121:2081–2090.
2. Vajaranant TS, Wu S, Torres M, Varma RA. 40-year forecast of the demographic shift in primary open-angle glaucoma in the United States. *Invest Ophthalmol Vis Sci*. 2012;53:2464–2466.
3. Vajaranant TS, Wu S, Torres M, Varma R. The changing face of primary open-angle glaucoma in the United States: demographic and geographic changes from 2011 to 2050. *Am J Ophthalmol*. 2012;154:303–314.e303.
4. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:714–720; discussion 829–730.
5. Heijl A, Leske MC, Bengtsson B, Hyman L, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2002;120:1268–1279.
6. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701–713; discussion 829–730.
7. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114:1965–1972.
8. Aptel F, Aryal-Charles N, Giraud JM, et al. Progression of visual field in patients with primary open-angle glaucoma - ProgF study 1. *Acta Ophthalmol*. 2015;93:e615–620.
9. Li G, Nottebaum AF, Brigell M, et al. A small molecule inhibitor of VE-PTP activates Tie2 in Schlemm’s canal increasing outflow facility and reducing intraocular pressure. *Invest Ophthalmol Vis Sci*. 2020;61:12.
10. He L, Vanlandewijck M, Mäe MA, et al. Single-cell RNA sequencing of mouse brain and lung vascular and vessel-associated cell types. *Sci Data*. 2018;5:180160.
11. Patel G, Fury W, Yang H, et al. Molecular taxonomy of human ocular outflow tissues defined by single-cell transcriptomics. *Proc Natl Acad Sci USA*. 2020;117:12856–12867.
12. van Zyl T, Yan W, McAdams A, et al. Cell atlas of aqueous humor outflow pathways in eyes of humans and four model species provides insight into glaucoma pathogenesis. *Proc Natl Acad Sci USA*. 2020;117:10339–10349.
13. Bernier-Latmani J, Petrova TV. All TIEd up: mechanisms of Schlemm’s canal maintenance. *J Clin Invest*. 2017;127:3594–3597.
14. Kim J, Park DY, Bae H, et al. Impaired angiotensin/Tie2 signaling compromises Schlemm’s canal integrity and induces glaucoma. *J Clin Invest*. 2017;127:3877–3896.
15. Souma T, Tompson SW, Thomson BR, et al. Angiotensin receptor TEK mutations underlie primary congenital glaucoma with variable expressivity. *J Clin Invest*. 2016;126:2575–2587.
16. Thomson BR, Carota IA, Souma T, Soman S, Vestweber D, Quaggin SE. Targeting the vascular-specific phosphatase PTPRB protects against retinal ganglion cell loss in a pre-clinical model of glaucoma. *Elife*. 2019;8:e48474.
17. Thomson BR, Heinen S, Jeansson M, et al. A lymphatic defect causes ocular hypertension and glaucoma in mice. *J Clin Invest*. 2014;124:4320–4324.
18. Thomson BR, Souma T, Tompson SW, et al. Angiotensin-1 is required for Schlemm’s canal development in mice and humans. *J Clin Invest*. 2017;127:4421–4436.
19. Choquet H, Thai KK, Yin J, et al. A large multi-ethnic genome-wide association study identifies novel genetic loci for intraocular pressure. *Nat Commun*. 2017;8:2108.

20. Kabra M, Zhang W, Rathi S, et al. Angiopoietin receptor TEK interacts with CYP1B1 in primary congenital glaucoma. *Hum Genet.* 2017;136:941–949.
21. Khawaja AP, Bailey JN, Wareham NJ, et al. Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma. *Nat Genet.* 2018;50:778–782.
22. Hann CR, Vercnocke AJ, Bentley MD, Jorgensen SM, Fautsch MP. Anatomic changes in Schlemm's canal and collector channels in normal and primary open-angle glaucoma eyes using low and high perfusion pressures. *Invest Ophthalmol Vis Sci.* 2014;55:5834–5841.
23. Yan X, Mu L, Chen Z, Zhu Y, Song Y, Zhang H. Schlemm's canal and trabecular meshwork in eyes with primary open angle glaucoma: a comparative study using high-frequency ultrasound biomicroscopy. *PLoS One.* 2016;11:e0145824.
24. Allingham RR, de Kater AW, Ethier CR. Schlemm's canal and primary open angle glaucoma: correlation between Schlemm's canal dimensions and outflow facility. *Exp Eye Res.* 1996;62:101–109.
25. Johnson M, McLaren JW, Overby DR. Unconventional aqueous humor outflow: a review. *Exp Eye Res.* 2017;158:94–111.
26. Shen J, Frye M, Lee BL, et al. Targeting VE-PTP activates TIE2 and stabilizes the ocular vasculature. *J Clin Invest.* 2014;124:4564–4576.
27. Siragusa M, Oliveira Justo AF, Malacarne PF, et al. VE-PTP inhibition elicits eNOS phosphorylation to blunt endothelial dysfunction and hypertension in diabetes. *Cardiovasc Res.* 2021;117:1546–1556.
28. 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.
29. Weinreb RN, Liebmann JM, Martin KR, Kaufman PL, Vittitow JL. Latanoprostene bunod 0.024% in subjects with open-angle glaucoma or ocular hypertension: pooled phase 3 study findings. *J Glaucoma.* 2018;27:7–15.
30. Asrani S, Bacharach J, Holland E, et al. Fixed-dose combination of netarsudil and latanoprost in ocular hypertension and open-angle glaucoma: pooled efficacy/safety analysis of phase 3 MERCURY-1 and -2. *Adv Ther.* 2020;37:1620–1631.