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Rho kinase inhibitor for primary open-angle glaucoma and ocular hypertension (Review)

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[Intervention Review]

Rho kinase inhibitor for primary open-angle glaucoma and ocular hypertension

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ABSTRACT

Background

Glaucoma is a group of optic neuropathies characterized by progressive degeneration of the retinal ganglion cells, axonal loss and irreversible visual field defects. Glaucoma is classified as primary or secondary, and worldwide, primary glaucoma is a leading cause of irreversible blindness. Several subtypes of glaucoma exist, and primary open-angle glaucoma (POAG) is the most common. The etiology of POAG is unknown, but current treatments aim to reduce intraocular pressure (IOP), thus preventing the onset and progression of the disease. Compared with traditional antiglaucomatous treatments, rho kinase inhibitors (ROKi) have a different pharmacodynamic. ROKi is the only current treatment that effectively lowers IOP by modulating the drainage of aqueous humor through the trabecular meshwork and Schlemm's canal. As ROKi are introduced into the market more widely, it is important to assess the efficacy and potential AEs of the treatment.

Objectives

To compare the efficacy and safety of ROKi with placebo or other glaucoma medication in people diagnosed with open-angle glaucoma (OAG), primary open-angle glaucoma (POAG) or ocular hypertension (OHT).

Search methods

We used standard Cochrane methods and searched databases on 11 December 2020.

Selection criteria

We included randomized clinical trials examining commercially available ROKi-based monotherapy or combination therapy compared with placebo or other IOP-lowering medical treatments in people diagnosed with (P)OAG or OHT. We included trials where ROKi were administered according to official glaucoma guidelines. There were no restrictions regarding type, year or status of the publication.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Two review authors independently screened studies, extracted data, and evaluated risk of bias by using Cochrane's RoB 2 tool.

Main results

We included 17 trials with 4953 participants diagnosed with (P)OAG or OHT. Fifteen were multicenter trials and 15 were masked trials. All participants were aged above 18 years. Trial duration varied from 24 hours to 12 months. Trials were conducted in the USA, Canada and Japan. Sixteen trials were funded by pharmaceutical companies, and one trial provided no information about funding sources. The trials compared ROKi monotherapy (netarsudil or ripasudil) or combination therapy with latanoprost (prostaglandin analog) or timolol (beta-blocker) with placebo, timolol, latanoprost or netarsudil. Reported outcomes were IOP and safety. Meta-analyses were applied to 13 trials (IOP reduction from baseline) and 15 trials (ocular AEs).

Of the trials evaluating IOP, seven were at low risk, three had some concerns, and three were at high risk of bias. Three trials found that netarsudil monotherapy may be superior to placebo (mean difference [MD] 3.11 mmHg, 95% confidence interval [CI] 2.59 to 3.62; I^2 = 0%; 155 participants; low-certainty evidence). Evidence from three trials found that timolol may be superior to netarsudil with an MD of 0.66 mmHg (95% CI 0.41 to 0.91; I^2 = 0%; 1415 participants; low-certainty evidence). Evidence from four trials found that latanoprost may be superior to netarsudil with an MD of 0.97 mmHg (95% CI 0.67 to 1.27; I^2 = 4%; 1283 participants; moderate-certainty evidence).

Evidence from three trials showed that, compared with monotherapy with latanoprost, combination therapy with netarsudil and latanoprost probably led to an additional pooled mean IOP reduction from baseline of 1.64 mmHg (95% CI −2.16 to −1.11; 1114 participants). Evidence from three trials showed that, compared with monotherapy with netarsudil, combination therapy with netarsudil and latanoprost probably led to an additional pooled mean IOP reduction from baseline of 2.66 mmHg (95% CI −2.98 to −2.35; 1132 participants). The certainty of evidence was moderate. One trial showed that, compared with timolol monotherapy, combination therapy with ripasudil and timolol may lead to an IOP reduction from baseline of 0.75 mmHg (95% −1.29 to −CI 0.21; 208 participants). The certainty of evidence was moderate.

Of the trials assessing total ocular AEs, three were at low risk, four had some concerns, and eight were at high risk of bias.

We found very low-certainty evidence that netarsudil may lead to more ocular AEs compared with placebo, with 66 more ocular AEs per 100 person-months (95% CI 28 to 103; I^2 = 86%; 4 trials, 188 participants). We found low-certainty evidence that netarsudil may lead to more ocular AEs compared with latanoprost, with 29 more ocular AEs per 100 person-months (95% CI 17 to 42; I^2 = 95%; 4 trials, 1286 participants).

We found moderate-certainty evidence that, compared with timolol, netarsudil probably led to 21 additional ocular AEs (95% CI 14 to 27; I^2 = 93%; 4 trials, 1678 participants). Data from three trials (1132 participants) showed no evidence of differences in the incidence rate of AEs between combination therapy with netarsudil and latanoprost and netarsudil monotherapy (1 more event per 100 person-months, 95% CI 0 to 3); however, the certainty of evidence was low. Similarly, we found low-certainty evidence that, compared with latanoprost, combination therapy with netarsudil and latanoprost may cause 29 more ocular events per 100 person-months (95% CI 11 to 47; 3 trials, 1116 participants). We found moderate-certainty evidence that, compared with timolol monotherapy, combination therapy with ripasudil and timolol probably causes 35 more ocular events per 100 person-months (95% CI 25 to 45; 1 trial, 208 participants). In all included trials, ROKi was reportedly not associated with any particular serious AEs.

Authors' conclusions

The current evidence suggests that in people diagnosed with OHT or (P)OAG, the hypotensive effect of netarsudil may be inferior to latanoprost and slightly inferior to timolol. Combining netarsudil and latanoprost probably further reduces IOP compared with monotherapy. Netarsudil as mono- or combination therapy may result in more ocular AEs. However, the certainty of evidence was very low or low for all comparisons except timolol. In general, AEs were described as mild, transient, and reversible upon treatment discontinuation. ROKi was not associated with any particular serious AEs. Future trials of sufficient size and follow-up should be conducted to provide reliable information about glaucoma progression, relevant IOP measurements and a detailed description of AEs using similar terminology. This would ensure the robustness and confidence of the results and assess the intermediate- and long-term efficacy and safety of ROKi.

PLAIN LANGUAGE SUMMARY

Rho kinase inhibitors for primary open-angle glaucoma and ocular hypertension

Question

What are the benefits and risks of rho kinase inhibitor eye drops to treat people with either glaucoma or increased eye pressure?

Key messages

Antiglaucomatous eye drops such as latanoprost and timolol may reduce the eye pressure more compared with treatment with a rho kinase inhibitor, but the difference with timolol is small. When combining rho kinase inhibitors with different types of medicine, the eye pressure may be reduced more. People treated with a rho kinase inhibitor experience more adverse events (side effects) compared with other treatments. Future research in this area should focus on reporting disease progression (how the glaucoma gets worse over time).

What is glaucoma?

Glaucoma is a sight-threatening eye disease that can lead to blindness if left untreated. There are different types of glaucoma and the most common is called primary open-angle glaucoma. High eye pressure is a known risk factor for developing glaucoma.

Medical glaucoma treatment

There are different types of eye drops that can be used to treat glaucoma. All medical treatments of glaucoma work by reducing eye pressure. Latanoprost and timolol are two glaucoma medications, and one of the new types of glaucoma medicine is called a rho kinase inhibitor.

What did we want to find out?

We wanted to examine whether the effectiveness and safety of rho kinase inhibitor eye drops were better or worse than other medicines.

What did we do?

We searched for studies that compared:

- rho kinase inhibitor with placebo (a treatment with no therapeutic effect);

- rho kinase inhibitor with other types of glaucoma treatments (latanoprost and timolol).

Search date

We searched medical databases on 11 December 2020.

What did we find?

We found 17 studies examining 4953 people aged at least 18 years diagnosed with primary open-angle glaucoma or high eye pressure and treated with a rho kinase inhibitor. The studies varied in treatment duration from 24 hours to 12 months. They were conducted in the USA, Canada and Japan. Of the studies, 16 were funded by pharmaceutical companies and one did not provide information about potential funding sources. The effect of treatment was evaluated by measuring the eye pressure and assessing the adverse events of treatment.

The studies did not report data disease progression, but they reported data on the lowering of the pressure within the eye and adverse events. Treatment with latanoprost may be better than rho kinase inhibitor. Treatment with timolol may be slightly better than treatment with rho kinase inhibitor. Furthermore, treatment with both rho kinase inhibitor and latanoprost or timolol probably reduces the eye pressure even more. Overall, the studies reported adverse events very differently. More people treated with rho kinase inhibitors may have experienced eye-related adverse events; however, we are not very certain about these findings. There were no serious adverse events reported for treatment with rho kinase inhibitor.

Main limitations of the evidence

The studies did not report all the outcomes that we were interested in. The studies focused on specific outcomes such as eye pressure and adverse events, whereas we wanted to answer other questions as well. The current evidence was based on few studies. Some studies were conducted in a way that may have introduced errors into the results. Studies varied in the way they measured the outcomes and thus may not be comparable to each other.

SUMMARY OF FINDINGS

Summary of findings 1. Rho kinase inhibitor compared to placebo[a]

Population: people with primary open-angle glaucoma or ocular hypertension

Settings: ophthalmology clinics

Intervention: netarsudil 0.02% once per day[a]

Comparison: placebo

Outcomes	Illustrative absolute effect or risk* (95% CI)		Absolute difference (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Assumed effect with placebo	Corresponding effect with netarsudil				
Glaucoma progression at 12 months, measured by additional visual field defects	—	—	—	—	—	Not measured
Difference in mean IOP from baseline at < 6 months	1.20 mmHg (0.62 to 1.77) lower	4.31 mmHg (3.79 to 4.82) lower	**3.11 mmHg** (2.59 to 3.62) lower	155 (3 RCTs)	⊕⊕⊖⊖ **Low**[b,c]	—
Glaucoma progression at 12 months, defined by anatomic (structural) criteria[d]	—	—	—	—	—	Not measured
Patient-reported outcome at the longest follow-up	—	—	—	—	—	Not measured
Mean change in the number of glaucoma medications at the longest follow-up	—	—	—	—	—	Not measured
Need for additional treatment at the longest follow-up	—	—	—	—	—	Not measured
Average number of ocular adverse events at the longest follow-up	60 events per 100 person-months	126 events per 100 person-months (88 to 163)	**66 more events** per 100 person-months (28 to 103)	188 (4 RCTs)	⊕⊖⊖⊖ **Very low**[c,e]	—

CI: confidence interval; **IOP:** intraocular pressure; **RD:** rate difference; **ROKi:** rho kinase inhibitor

*The basis for the **assumed effect** (or risk) is the effect (or risk) in the placebo group across studies. The **corresponding effect (**or risk and its 95% confidence interval) is based on the assumed risk in the comparison group and the difference in the effect (or risk) of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Due to heterogeneity between subgroups, only netarsudil versus placebo is represented in this summary of findings table.
[b]Downgraded one level for risk of bias.
[c]Downgraded one level for imprecision: small sample sizes.
[d]Anatomic criteria may include thinning of neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer, or thinning of the macular ganglion cell layer.
[e]Downgraded two level for high risk of bias in outcome measurement and selective outcome reporting.

Summary of findings 2. Rho kinase inhibitor compared to beta-blocker

Population: people with primary open-angle glaucoma or ocular hypertension

Settings: ophthalmology clinics

Intervention: netarsudil 0.02% once per day

Comparison: timolol 0.5% twice per day

Outcomes	Illustrative absolute effect (or risk) * (95% CI)		Risk difference (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with timolol	Corresponding risk with netarsudil				
Glaucoma progression at 12 months, measured by additional visual field defects	—	—	—	—	—	Not measured
Difference in mean IOP from baseline at < 6 months	4.60 mmHg lower (3.91 to 5.29)	3.94 mmHg lower (3.69 to 4.19)	**0.66 mmHg higher** (0.41 to 0.91)	1415 (3 RCTs)	⊕⊕⊖⊖ **Low**[a]	—
Glaucoma progression at 12 months, defined by anatomic (structural) criteria[b]	—	—	—	—	—	Not measured

Patient-reported outcome at the longest follow-up	—	—	—	—	—	Not measured
Mean change in the number of glaucoma medications at the longest follow-up	—	—	—	—	—	Not measured
Need for additional treatment at the longest follow-up	—	—	—	—	—	Not measured
Number of ocular adverse events at the longest follow-up	9 events per 100 person-months	30 events per 100 person-months (23 to 36)	**21 more events** per 100 person-months (14 to 27)	1678 (4 RCTs)	⊕⊕⊕⊖ **Moderate**[c]	—

BB: beta-blocker; **CI:** confidence interval; **IOP:** intraocular pressure; **RD:** rate difference; **ROKi:** rho kinase inhibitor.
*The basis for the **assumed effect** (or risk) is the effect (or risk) in the Timolol group across studies. The **corresponding effect (**or risk and its 95% confidence interval) is based on the assumed risk in the comparison group and the difference in the effect (or risk) of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded two levels for risk of bias: high risk of bias due to deviation from the intended intervention and missing outcome.
[b]Anatomic criteria may include thinning of neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer, or thinning of the macular ganglion cell layer.
[c]Downgraded one level for risk of bias in incomplete outcome reporting or selective outcome reporting.

Summary of findings 3. Rho kinase inhibitor compared to prostaglandin analog

Population: people with primary open-angle glaucoma or ocular hypertension

Settings: ophthalmology clinics

Intervention: netarsudil 0.02% once per day (4 studies)

Comparison: latanoprost 0.005% twice per day

Outcomes	Illustrative absolute effect (or risk)* (95% CI)		Difference (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	With latanoprost	With netarsudil				

Glaucoma progression at 12 months, measured by additional visual field defects	—	—	—	—	—	Not measured
Difference in mean IOP from baseline at < 6 months	6.44 mmHg lower (6.24 to 6.64)	5.47 mmHg lower (5.18 to 5.76)	**0.97 mmHg higher** (0.67 to 1.27)	1283 (4 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
Glaucoma progression at 12 months, defined by anatomic (structural) criteria[b]	—	—	—	—	—	Not measured
Patient-reported outcome at the longest follow-up	—	—	—	—	—	Not measured
Mean change in the number of glaucoma medications at the longest follow-up	—	—	—	—	—	Not measured
Need for additional treatment at the longest follow-up	—	—	—	—	—	Not measured
Number of ocular adverse events at the longest follow-up	14 events per 100 person-months	43 events per 100 person-months (31 to 56)	**29 more events** per 100 person-months (17 to 42)	1286 (4 RCTs)	⊕⊕⊖⊖ **Low**[c]	—

CI: confidence interval; **IOP:** intraocular pressure; **RD:** rate difference; **ROKi:** rho kinase inhibitor.

*The basis for the **assumed effect** (or risk) is the effect (or risk) in the placebo group across studies. The **corresponding effect (**or risk and its 95% confidence interval) is based on the assumed risk in the comparison group and the difference in the effect (or risk) of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level for risk of bias.
[b]Anatomic criteria may include thinning of neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer, or thinning of the macular ganglion cell layer.
[c]Downgraded two levels for high risk of bias in selective outcome reporting and unclear bias in outcome measurement.

Summary of findings 4. Rho kinase inhibitor and prostaglandin analog compared to prostaglandin analog[a]

Population: people with primary open-angle glaucoma or ocular hypertension

Settings: ophthalmology clinics

Intervention: netarsudil 0.02% + latanoprost 0.005% (FDC) once per day[a]

Comparison: latanoprost 0.005% once per day

Outcomes	Illustrative absolute effect (or risk) * (95% CI)		Difference (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	With latanoprost	With netarsudil + latanoprost (FDC)				
Glaucoma progression at 12 months, measured by additional visual field defects	—	—	—	—	—	Not measured
Difference in mean IOP from baseline at < 6 months	6.62 mmHg (5.67 to 7.57) lower	8.26 mmHg (7.73 to 8.78) lower	**1.64 mmHg** (1.11 to 2.16) lower	1114 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
Glaucoma progression at 12 months, defined by anatomic (structural) criteria[b]	—	—	—	—	—	Not measured
Patient-reported outcome at the longest follow-up	—	—	—	—	—	Not measured
Mean change in the number of glaucoma medications at the longest follow-up	—	—	—	—	—	Not measured
Need for additional treatment at the longest follow-up	—	—	—	—	—	Not measured
Number of ocular adverse events at the longest follow-up	11 events per 100 person-months	37 events per 100 person-months (24 to 51)	**26 more events** per 100 person-months (13 to 40)	1321 (4 RCTs)	⊕⊕⊖⊖ **Low**[c]	—

CI: confidence interval; **FDC:** fixed-dose compound; **IOP:** intraocular pressure; **RD:** rate difference; **ROKi:** rho kinase inhibitor.

*The basis for the **assumed effect** (or risk) is the effect (or risk) in the placebo group across studies. The **corresponding effect (**or risk and its 95% confidence interval) is based on the assumed risk in the comparison group and the difference in the effect (or risk) of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Due to heterogeneity between subgroups, only netarsudil + latanoprost versus latanoprost is represented in this summary of findings table.
[b]Downgraded one level for risk of bias in selective outcome reporting: not all studies reported uncorrected mean changes in diurnal IOP from baseline.
[c]Anatomic criteria may include thinning of neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer, or thinning of the macular ganglion cell layer.
[d]Downgraded two levels for high risk of bias in selective reporting of adverse outcomes.

Summary of findings 5. Rho kinase inhibitor and prostaglandin analog compared to rho kinase inhibitor

Population: people with primary open-angle glaucoma or ocular hypertension

Settings: ophthalmology clinics

Intervention: netarsudil 0.02% + latanoprost 0.005% (FDC) once per day (3 studies)

Comparison: netarsudil 0.02% once per day

Outcomes	Illustrative absolute effect (or risk) * (95% CI)		Difference (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with netarsudil	Corresponding risk with netarsudil + latanoprost (FDC)				
Glaucoma progression at 12 months, measured by additional visual field defects	—	—	—	—	—	Not measured
Difference in mean IOP from baseline at < 6 months	5.47 mmHg (5.23 to 5.70) lower	8.13 mmHg (7.82 to 8.45) lower	**2.66 mmHg** (2.35 to 2.98) lower	1132 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
Glaucoma progression at 12 months, defined by anatomic (structural) criteria[b]	—	—	—	—	—	Not measured
Patient-reported outcome at the longest follow-up	—	—	—	—	—	Not measured
Mean change in the number of glaucoma medications at the longest follow-up	—	—	—	—	—	Not measured
Need for additional treatment at the longest follow-up	—	—	—	—	—	Not measured
Number of ocular adverse events at the longest follow-up	38 events per 100 person-months	39 events per 100 person-months (38 to 41)	**1 more event** per 100 per-	1131 (3 RCTs)	⊕⊕⊖⊖ **Low**[c]	—

						son-months (0 to 3 more)

CI: confidence interval; **FDC:** fixed-dose compound; **IOP:** intraocular pressure; **RD:** rate difference; **ROKi:** rho kinase inhibitor.

*The basis for the **assumed effect** (or risk) is the effect (or risk) in the placebo group across studies. The **corresponding effect (**or risk and its 95% confidence interval) is based on the assumed risk in the comparison group and the difference in the effect (or risk) of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level for risk of bias in selective outcome reporting in some of the included studies.
[b]Anatomic criteria may include thinning of neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer, or thinning of the macular ganglion cell layer.
[c]Downgraded two levels for high risk of bias in selective outcome reporting in all the included studies.

Summary of findings 6. Rho kinase inhibitor and beta-blocker compared to beta-blocker

Population: people with primary open-angle glaucoma or ocular hypertension

Settings: ophthalmology clinics

Intervention: ripasudil 0.4% + timolol 0.5% twice per day (1 study)

Comparison: timolol 0.5% twice per day

Outcomes	Illustrative absolute effect (or risk) * (95% CI)		Risk difference (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with timolol	Corresponding risk with ripasudil + timolol				
Glaucoma progression at 12 months, measured by additional visual field defects	—	—	—	—	—	Not measured
Difference in mean IOP from baseline at < 6 months	1.67 mmHg lower (SD 1.99)	2.42 mmHg (1.88 to 2.96) lower	**0.75 mmHg** (0.21 to 1.29) lower	208 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	—
Glaucoma progression at 12 months, defined by anatomic (structural) criteria[b]	—	—	—	—	—	Not measured

Patient-reported outcome at the longest follow-up	—	—	—	—	—	Not measured
Mean change in the number of glaucoma medications at the longest follow-up	—	—	—	—	—	Not measured
Need for additional treatment at the longest follow-up	—	—	—	—	—	Not measured
Number of ocular adverse events at the longest follow-up	6 events per 100 person-months	41 events per 100 person-months (31 to 51)	**35 more events** per 100 person-months (25 to 45)	208 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	—

BB: beta-blocker; **CI:** confidence interval; **IOP:** intraocular pressure; **RD:** rate difference; **ROKi:** rho kinase inhibitor; **SD:** standard deviation.

*The basis for the **assumed effect** (or risk) is the effect (or risk) in the Timolol group across studies. The **corresponding effect** (or risk and its 95% confidence interval) is based on the assumed risk in the comparison group and the difference in the effect (or risk) of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded one level for imprecision due to small sample size.
[b]Anatomic criteria may include thinning of neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer, or thinning of the macular ganglion cell layer.

BACKGROUND

Description of the condition

Glaucoma is a group of optic neuropathies characterized by progressive degeneration of the retinal ganglion cells, axonal loss and characteristic irreversible visual field defects (Chang 2012; Kolko 2015; Weinreb 2014). Glaucoma is classified as primary or secondary, the latter term describing glaucoma as a complication to another identifiable eye disease, systemic condition or medical treatment. Based on the anatomy of the anterior chamber, primary glaucoma is subclassified as primary open-angle glaucoma (POAG) or angle-closure glaucoma. Based on the intraocular pressure (IOP), POAG is further subclassified as normal-tension glaucoma or high-tension glaucoma (Quigley 2011)

The exact pathogenesis of POAG is unknown. However, several risk factors have been identified including age, gender, familial disposition, ethnicity and IOP (Jonas 2017; Kwon 2009). POAG may be asymptomatic until the late stages of the disease (Weinreb 2014).

Epidemiology

Glaucoma is among the leading causes of irreversible blindness worldwide (Cedrone 2008; Quigley 2006), with an estimated global prevalence of 3.54% (95% confidence interval [CI] 2.09 to 5.82) for people aged 40 to 80 years, which is equivalent to 76.02 million people (Tham 2014). As a result of an increasing elderly population, the number is expected to rise to 111.8 million by 2040 (Tham 2014). Literature concerning the prevalence of ocular hypertension (OHT) is limited, but published studies report a prevalence of OHT between 2.7% (OHT greater than 25 mmHg, for those aged 52 to 82 years) and 3.56% (95% CI 3.12% to 4.06%) (OHT greater than 21 mmHg, for those aged 49 years and older) (Kreuger 1980; Varma 2004).

Glaucoma treatment

Current treatments work by reducing IOP (Mehran 2020), although axon loss and retinal ganglion cell death are only partly addressed by these treatments (Chang 2012). Evidence suggests that lowering IOP reduces the conversion from OHT to glaucoma and additionally slows disease progression in people with glaucoma (Heijl 2002). Thus, treatment initiation and adherence to treatment are vital to avoid significant damage to the ocular structures and impairment of the visual field.

The most common treatment used in preventing glaucoma progression and OHT is daily administration of IOP-lowering eye drops, followed by laser treatment or surgery (Weinreb 2014), although laser treatment is now being advocated as a primary treatment (Gazzard 2019). Marketed conventional antiglaucomatous eye drops generally work by either lowering the production or increasing the outflow of the aqueous humor (AH) (Mehran 2020). Pharmacologically active agents in conventional eye drops include prostaglandin analogs (PA), beta-adrenoceptor antagonists (beta-blockers; BB), carbonic anhydrase inhibitors, alfa-adrenoceptor agonists (alfa-agonists) and cholinergic agonists. They are used as mono- or combination therapy (Conlon 2017). Of these topical treatments, PA is the most effective initial treatment for reducing IOP (Li 2016).

Description of the intervention

Rho kinase inhibitors (ROKi) are generally administered as one eye drop, once or twice per day in the affected eye(s). Once applied, the drugs are effectively absorbed (Isobe 2014; Lin 2018a). Netarsudil (AR-13324) is metabolized to netarsudil-M1 (AR-13503) by esterases, which is a more potent ROKi (Lin 2018a).

ROKi antiglaucomatous eye drops were approved in Japan in 2014 (Garnock-Jones 2014), in the USA by the Food and Drug Administration (FDA) in 2017 (FDA 2017) and in Europe by the European Medicines Agency (EMA) in 2019 (Aerie 2019).

How the intervention might work

Rho kinase (ROCK) is a serine/threonine-protein kinase found downstream of the rho GTPase/ROCK signaling pathway. Currently, two isoenzymes $ROCK_1$ and $ROCK_2$ are identified. Upon activation, ROCK has been shown to regulate actin cytoskeletal dynamics, actomyosin contraction, cell adhesion, cell stiffness, cell morphology and extracellular matrix (ECM) reorganization (Rao 2017). It is evident that ROKis reduce IOP. Moreover, ROKis may possess neuroprotective (Rao 2017), antifibrotic (Rao 2017), as well as cornea protective properties (Okumura 2017). In general, ROKis reduce IOP by increasing the AH outflow through the trabecular (conventional) outflow pathway as a result of decreased contractility of the trabecular meshwork (TM) endothelial cells and the cells of Schlemm's canal (SC) (Braunger 2015; Rao 2017). The ROKi and norepinephrine transporter inhibitor netarsudil may also reduce the episcleral venous pressure (Kazemi 2018; Sit 2021) and the production of AH (Wang 2015).

The increase in AH outflow in response to ROKi application is associated with several factors such as (Rao 2017):

- relaxation of the TM and expansion of the juxtacanalicular network;
- possible increased formation of giant vacuoles in the inner wall of SC;
- widening of SC;
- washout of extracellular material in the TM.

On a cellular level, ROCK inhibition has been shown to inhibit the transdifferentiation of TM cells into a fibrogenic myofibroblast-like phenotype and induce relaxation of TM and SC cells associated with decreased formation of actin stress fibers, focal adhesions and cell–cell interactions. Moreover, ROKis decreases pore formation in SC cells and decreases ECM production of TM and SC cells (Braunger 2015; Rao 2017). Increased drainage resistance in the trabecular pathway is a major cause of elevated IOP in POAG (Gabelt 2005; Lütjen-Drecoll 1999; Stamer 2012). In vivo experiments have established that the rho GTPase/signaling pathway plays an important role in the regulation of IOP through modulation of AH outflow. Several clinical trials, involving healthy as well as people diagnosed with OHT or POAG, have demonstrated that ROKis effectively reduce IOP. Therefore, ROKi-based treatments may prove to be important in the regulation of IOP, and thus prevention of onset and progression of glaucoma.

Why it is important to do this review

ROKis demonstrate different pharmacodynamic properties compared with traditional glaucoma drugs, as they are the only

treatment that effectively reduce IOP through modulation of AH outflow by targeting the TM and SC cells (Tanna 2018). Therefore, ROKi may be an effective alternative or additional treatment, when conventional glaucoma medication is insufficient to prevent glaucoma progression and to control IOP. Adverse effects (AE) of treatment are one of many possible reasons that discourage people from following the prescribed treatment regimen (Wolfram 2019). Adherence to medical treatment is essential to lower IOP effectively and avoid the progression of glaucoma. As ROKi is introduced in the market more widely, it is important to assess the efficacy and potential AEs of this drug.

OBJECTIVES

To compare the efficacy and safety of ROKi with placebo or other glaucoma medication in people diagnosed with open-angle glaucoma (OAG), primary open-angle glaucoma (POAG) or ocular hypertension (OHT).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) comparing monotherapy or combination therapy with ROKi to placebo or other IOP-lowering medical treatments. RCTs were included regardless of type, year or status of publication.

Types of participants

Inclusion criteria

People diagnosed with (P)OAG or OHT, whether previously treated or recently diagnosed, and no prior exposure to ROKis. We applied no restrictions regarding age, gender or geography.

Exclusion criteria

People diagnosed with secondary OAG.

Types of interventions

We included RCTs comparing topical ROKi monotherapy or combination therapy with either placebo or other topical medical glaucoma treatments. The interventions and comparators were required to be administered as prescribed according to official clinical guidelines for the indication of glaucoma.

Types of outcome measures

Primary outcomes

The purpose of IOP-lowering drugs is ultimately to prevent the development and progression of glaucoma. Thus, the primary outcome of this review was glaucoma progression.

- Glaucoma progression, defined as additional visual field defects after at least 12 months of follow-up compared with baseline. Glaucoma progression data were planned to be collected as a dichotomous outcome.

Secondary outcomes

- Difference in mean IOP (mmHg) measured at baseline, compared with IOP at follow-up, as it is the standard surrogate outcome in glaucoma research and known to be associated with glaucoma progression. As ROKis have only recently been approved, we expected most studies to report untreated IOP (after washout) at baseline, as they aimed to investigate the net IOP-lowering effect of ROKi. The expected IOP-lowering effect of a medication is used for decision-making in clinical practice, but IOP may be influenced by other medications or treatments. We collected the change of medicated IOP when available. IOP change was collected as a continuous measure at an early (less than six months) or medium- to long-term (six months or more) follow-up, or both.
- Glaucoma progression, defined by the investigators using valid anatomic (structural) criteria, such as thinning of the neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer, or thinning of the macular ganglion cell layer, after at least 12 months of follow-up compared with baseline.
- Participant-reported outcomes, including quality of life and preferences, medication adherence measured with validated questionnaires comparing the intervention groups at baseline to the longest follow-up (continuous or categorical measure).
- Mean change in the number of glaucoma medications between baseline and the longest follow-up (continuous measure).
- Need for IOP-lowering medications, or additional laser, or surgical treatment measured as the need for additional medications, number of needed medications, laser or surgery at the longest follow-up (dichotomous measure).
- Adverse effects (AE), measured as the severity and number of AE related to the drug (continuous measures) at the longest follow-up. Examples of AEs related to the use of ROKis included conjunctival hyperemia, conjunctival hemorrhage, corneal verticillata and instillation site pain.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision (CEV) information specialist searched the following electronic databases for RCTs and controlled clinical trials. There were no restrictions to language or year of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the CEV Trials Register) in the Cochrane Library (2020, Issue 11) (Appendix 1).
- MEDLINE Ovid (1946 to 11 December 2020) (Appendix 2).
- Embase.com (1947 to 11 December 2020) (Appendix 3).
- PubMed (1948 to 11 December 2020) (Appendix 4).
- Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to 11 December 2020) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 11 December 2020) (Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 11 December 2020) (Appendix 7).

Searching other resources

We searched the reference lists of included studies for additional trials. We did not search conference abstracts for this review, as many eyes and vision conference abstracts are included in Embase, which was accessed as part of the electronic searches.

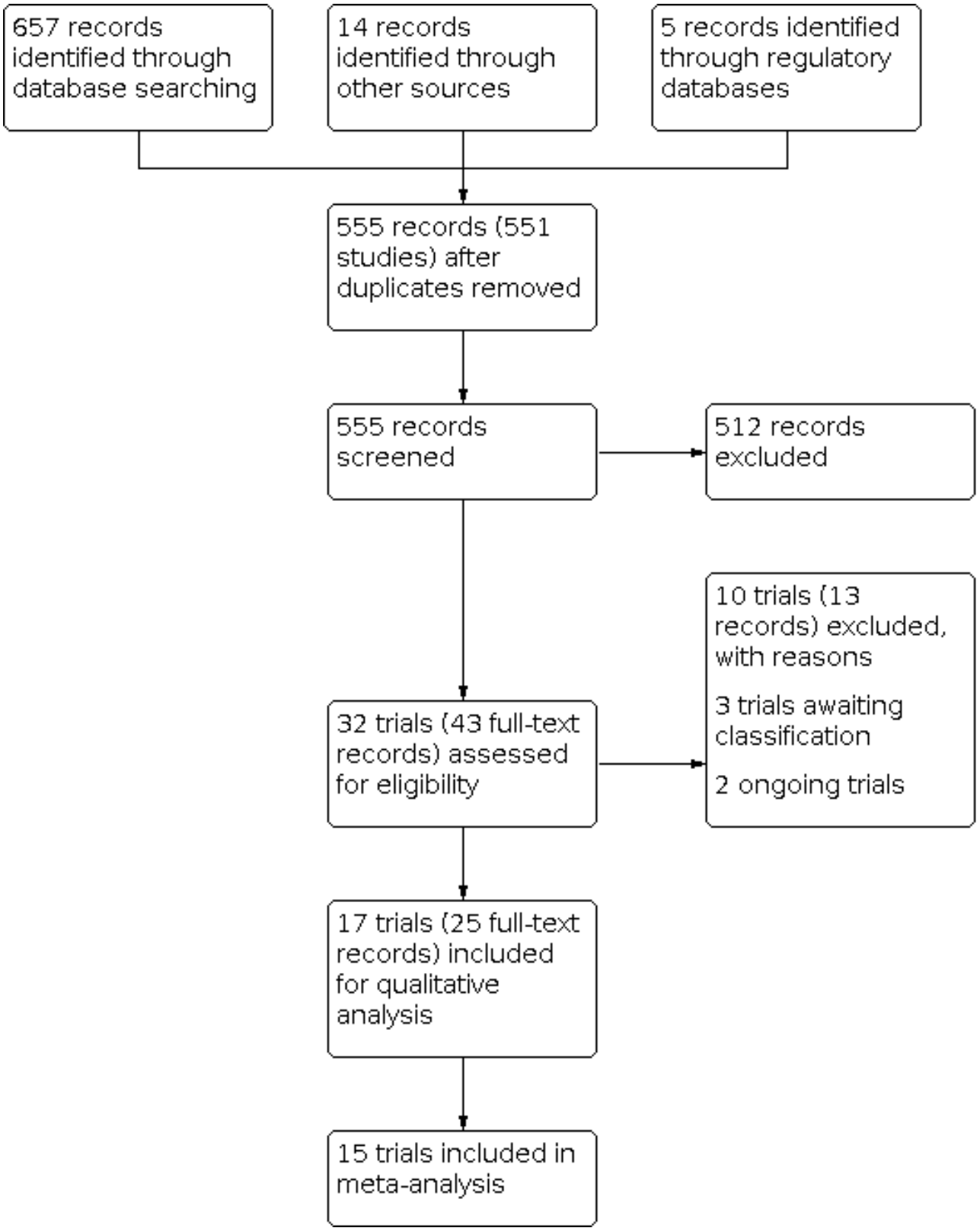
Data collection and analysis

We published the protocol in December 2020 (Freiberg 2020). We collected the data in accordance with the standards and methods provided by Cochrane using Covidence to facilitate independent screening of records and data extraction from study reports by two or more review authors and adjudication after comparisons (Covidence).

Selection of studies

The information specialist from CEV removed duplicates from the search results. Two review authors (JCF and AVS) independently screened each title and abstract of the remaining records and classified it as 'relevant', 'possibly relevant' or 'not relevant'. In case of disagreements, a third review author adjudicated. The two review authors (JCF and AVS) read the full-text reports of the records classified as 'possibly relevant' and 'relevant' and evaluated their final eligibility. We generated a PRISMA flow diagram to illustrate and document the process of identifying eligible studies (see Figure 1; Moher 2009).

Figure 1. Study flow diagram.



Data extraction and management

We collected and organized data following guidance from Chapter 5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2021a). Two review authors (JCF and AVS) independently extracted data from each full-text article, including title; names of authors; study methods; descriptions of participants, interventions and outcomes; study results; and other relevant information (e.g. key conclusions of the study authors, reference to other relevant studies, identification and notes on funding and support, financial disclosures). In cases of disagreements in the data extracted between the two review authors, a third review author adjudicated. Whenever possible, we extracted observed data in preference to statistically corrected data.

In case of missing, incomplete or unclear information, the CEV methodologist contacted study investigators directly to request details. Whenever investigators did not respond within two weeks, the review authors proceeded with the existing information. We exported the collected data to RevMan Web (RevMan Web 2022).

Assessment of risk of bias in included studies

Two review authors (JCF and AVS) independently assessed the risk of bias of included studies using the RoB 2 tool (Sterne 2019), and according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). In case of any disagreement, a third review author adjudicated.

The tool is structured into five domains through which bias may be introduced into outcomes.

- Bias arising from the randomization process.
- Bias due to deviations from intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

We evaluated the risk of bias for every domain as either low risk of bias, some concerns or high risk of bias. The assessment of each domain was guided by signaling questions. The overall assessment of the risk of bias for a given outcome was based on the sum of potential biases in each domain. We considered that a study or trial was at:

- low risk of bias when the study was at low risk of bias for all domains with respect to an outcome;
- some concerns when there was some concern for at least one domain for the specified outcome, but none of the domains was at high risk of bias;
- high risk of bias when at least one domain was judged at high risk of bias, or there were some concerns for multiple domains in a way that substantially lowered confidence in the result.

Measures of treatment effect

We conducted the data analysis using guidance from Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2021). We estimated the mean difference (MD) with 95% CIs for continuous measures and incidence rate difference (RD) with 95% CIs for ocular AEs. We provided a narrative description for sparse or heterogeneous outcome data. When numerical IOP data were not reported in either a registry record or publication, we derived IOP values and standard deviations from graphs (Rohatgi 2021). When mean diurnal IOP was not available, we calculated the mean IOP difference between baseline and follow-up, and imputed a change-from-baseline standard deviation using the correlation coefficient (Higgins 2011).

To quantify the overall risks associated with treatment AEs on the eyes, we categorized the reported number of incidents of similar or clinically related adverse symptoms and signs to prespecified types of ocular AEs (Appendix 8), and then summed the numbers of incidents by type before estimating the incidence rates of total ocular AEs for each treatment group. We estimated standard errors for incidence RDs according to guidance from Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b).

Unit of analysis issues

The participants were the primary unit of analysis. We included one study where participants received different treatments in each eye (Sit 2021). We investigated the impact of this study through a sensitivity analysis.

Dealing with missing data

In case of missing, incomplete or unclear data, the CEV methodologist contacted study investigators directly to request or clarify data. Whenever the investigators did not respond within two weeks, the review authors proceeded with the available data. Furthermore, in cases of substantial quantitative discrepancies between reported data in a full-text publication and trial registry, we contacted the authors to clarify the discrepancies. We conducted analyses using complete cases; we did not impute missing data. Instead, when relevant, we performed sensitivity analyses excluding studies at high risk of bias for missing data.

Assessment of heterogeneity

We assessed clinical or methodological heterogeneity across studies by comparing the study and participant characteristics and risk of bias assessment. We evaluated statistical heterogeneity by observing and analyzing the forest plot and using the I^2 statistic. We interpreted the values of I^2 by applying the following overlapping categories and individual judgment:

- 0% to 40%: may not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

To assess the risk of reporting bias, we compared the outcomes defined in the protocol of the trials with those in the full-text publications from the trials. We included fewer than 10 studies in each analysis, too few to use a funnel plot to assess small-study effects.

Data synthesis

We conducted quantitative synthesis when we had enough similar trials that had reported an outcome to combine their data. This decision was mainly based on the type of comparison. Intervention as a source of clinical heterogeneity and thus statistical heterogeneity were investigated in subgroup analyses.

In cases where we did not have enough comparable studies to conduct a meta-analysis, we provide a narrative summary of data.

We analyzed data using fixed-effect or random-effects statistical models. In cases where we included three or fewer studies, we used a fixed-effect model. If there were more than three studies, the type of statistical model used depended on clinical judgment and the statistical heterogeneity among the included studies. We did not combine data in a meta-analysis when the I^2 statistic was greater than 75% unless effects in the same direction and of similar magnitude were consistent across studies.

Subgroup analysis and investigation of heterogeneity

When there was considerable heterogeneity, we conducted a subgroup analysis based on the type of ROKi intervention. The decision was based on a judgment of the clinical heterogeneity across the included studies as well as the degree of statistical heterogeneity. We used statistical methods provided within Review Manager Web as a tool for formal testing of subgroup differences (RevMan Web 2022).

Sensitivity analysis

When relevant, we re-ran the meta-analyses by excluding studies at high risk of bias and studies that did not correctly manage the unit of analysis issue.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables for each comparison using guidelines in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019). The tables present the key information concerning the certainty of the evidence, the magnitude of the effect of the interventions examined and the sum of available data for the main outcomes. Two review authors independently analyzed the certainty of the evidence using the GRADE approach as high, moderate, low or very low (GRADE Handbook).

We included the following outcomes in the summary of findings tables.

- Glaucoma progression, defined as additional visual field changes after at least 12 months of follow-up compared with baseline.
- Difference in mean IOP from baseline to the longest available follow-up according to the predefined study outcomes.
- Glaucoma progression, defined by the investigators using valid anatomic (structural) criteria after at least 12 months.
- Participant-reported outcomes at the longest available follow-up (short or medium- to long-term, as defined above).
- Mean change in the number of glaucoma medications between baseline and the longest available follow-up (short or medium-to-long term, as defined above).
- Need for IOP-lowering medications, or additional laser, or surgical treatment at the longest available follow-up (short or medium-to-long term, as defined above).
- Number of adverse events at the longest available follow-up.

RESULTS

Description of studies

A detailed description of each included trial is available in the Characteristics of included studies table.

Results of the search

We conducted a search of the electronic databases in December 2020 and identified 676 records (Figure 1). We removed duplicates and screened 555 records corresponding to 551 studies. We excluded 512 records, leaving 43 articles for full-text screening. We excluded 13 full-text articles with reasons, three trials awaited classification (CTRI/2018/04/013091; CTRI/2020/01/022619; NCT03284853), and two trials were ongoing (JapicCTI-194920; UMIN000019017). We included 17 trials in the qualitative synthesis, of which we included 15 trials in one or more meta-analysis.

Included studies

We included 17 RCTs in this review (Aerie 2017; Araie 2021; Asrani 2019 (MERCURY-1); Bacharach 2015; Inoue 2018; Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Lewis 2016; NCT02246764 (ROCKET-3); Peace 2021; Serle 2018 (ROCKET-1); Sit 2021; Tanihara 2013; Tanihara 2015a; Tanihara 2015b; Tanihara 2015c; Walters 2019 (MERCURY-2)).

Thirteen trials were included in the meta-analysis concerning efficacy in IOP reduction (Araie 2021; Asrani 2019 (MERCURY-1); Bacharach 2015; Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Lewis 2016; Peace 2021; Serle 2018 (ROCKET-1); Sit 2021; Tanihara 2013; Tanihara 2015b; Tanihara 2015c; Walters 2019 (MERCURY-2)). Two additional trials were included in the meta-analysis concerning safety defined as 'total ocular AEs', 'conjunctival hyperemia' and 'ocular pain and irritation' (Aerie 2017; NCT02246764 (ROCKET-3)).

Study design

Fifteen trials were multicenter and two were single center (Peace 2021; Sit 2021). One was a cross-over trial (Tanihara 2015a), and the rest were parallel-group studies. Nine trials were in phase 2 and eight trials were in phase 3. Thirteen trials were double-masked according to the publications. According to the trial registry, one trial was triple masked (Aerie 2017), and one trial was quadruple-masked (NCT02246764 (ROCKET-3)). Two trials were open-label (Inoue 2018; Tanihara 2015a).

Participants

The 17 trials randomized 4953 participants. Participants were required to be a minimum of 18 years of age in 10 trials (Aerie 2017; Asrani 2019 (MERCURY-1); Bacharach 2015; Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Lewis 2016; Peace 2021; Serle 2018 (ROCKET-1); Sit 2021; Walters 2019 (MERCURY-2)), a minimum of 19 years of age in one trial (NCT02246764 (ROCKET-3)), and a minimum of 20 years of age in five trials (Araie 2021; Tanihara 2013; Tanihara 2015a; Tanihara 2015b; Tanihara 2015c). Two trials allowed participants to be aged from birth to two years but did not include any participants in this age group (Kahook 2019 (ROCKET-2); Serle 2018 (ROCKET-1)). One trial did not report any restrictions regarding age (Inoue 2018). All participants were diagnosed with POAG, OAG or OHT.

Twelve trials required participants to have a corrected visual acuity equal to or better than +1.0 logMAR on the ETDRS (Early Treatment Diabetic Retinopathy Study) chart equivalent to 20/200 on the Snellen chart or best-corrected visual acuity (BCVA) 0.1 on a Landolt-C Chart (Aerie 2017; Araie 2021; Asrani 2019 (MERCURY-1); Bacharach 2015; Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Lewis 2016; NCT02246764 (ROCKET-3); Peace 2021; Serle 2018 (ROCKET-1); Sit 2021; Walters 2019 (MERCURY-2)). In 15 studies, the trial investigators applied restrictions to unmedicated IOP as an inclusion criterion, whereas three trials did not report sufficient information regarding unmedicated or medicated IOP restrictions (Araie 2021; Inoue 2018; Lewis 2016). One trial included only participants with poorly controlled IOP after three months of treatment with PAs (Inoue 2018). Twelve trials excluded people with pseudoexfoliation or pigment dispersion glaucoma (Aerie 2017; Araie 2021; Asrani 2019 (MERCURY-1); Bacharach 2015; Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Lewis 2016; NCT02246764 (ROCKET-3); Peace 2021; Serle 2018 (ROCKET-1); Sit 2021; Walters 2019 (MERCURY-2)). People who had previously undergone intraocular surgery were excluded from all trials except from one trial, which did not specify any exclusion criteria (Inoue 2018).

Interventions

The 17 trials differed in both interventions and comparisons.

- Netarsudil-based interventions

Twelve trials evaluated the ROKi netarsudil monotherapy; four trials compared netarsudil with placebo (Aerie 2017; Araie 2021; Peace 2021; Sit 2021), four trials compared netarsudil with timolol (Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); NCT02246764 (ROCKET-3); Serle 2018 (ROCKET-1)), and four trials compared netarsudil with latanoprost (Asrani 2019 (MERCURY-1); Bacharach 2015; Lewis 2016; Walters 2019 (MERCURY-2)).

Three trials compared combination therapy of netarsudil and latanoprost with either netarsudil or latanoprost monotherapy (Asrani 2019 (MERCURY-1); Lewis 2016; Walters 2019 (MERCURY-2)).

- Ripasudil-based interventions

Five trials evaluated the ROKi ripasudil; two trials compared ripasudil with placebo (Tanihara 2013; Tanihara 2015a), two trials compared combination therapy of ripasudil and timolol or ripasudil and latanoprost with timolol or latanoprost (Tanihara 2015b; Tanihara 2015c), and one trial compared combination therapy of ripasudil and latanoprost/travoprost/tafluprost with timolol and latanoprost/travoprost/tafluprost (Inoue 2018).

Outcomes

Per protocol (Freiberg 2020), the primary review outcome was glaucoma progression, defined as additional visual field defects quantified after at least 12 months of follow-up from baseline. We also sought to evaluate secondary outcomes, such as changes in mean IOP from baseline; glaucoma progression based on other anatomic or structural criteria defined by the included trials; participant-reported outcomes; documented needs for IOP-lowering medications or surgical treatment; treatment-related adverse events. However, none of the included trials reported outcomes other than 'changes in IOP' and 'ocular adverse events'.

Intraocular pressure

Nine trials reported time point-matched mean IOP at multiple time points during the day at baseline and follow-up or the time point-matched mean IOP change at follow-up compared with baseline, or both (Araie 2021; Asrani 2019 (MERCURY-1); Bacharach 2015; Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Lewis 2016; Peace 2021; Serle 2018 (ROCKET-1); Walters 2019 (MERCURY-2)). Of these, six trials reported the corresponding mean diurnal or nocturnal IOP change at follow-up compared with baseline (Araie 2021; Asrani 2019 (MERCURY-1); Bacharach 2015; Lewis 2016; Peace 2021; Walters 2019 (MERCURY-2)). One trial reported the mean diurnal IOP change but not the single time point measurements (Sit 2021). One trial reported the mean diurnal IOP at follow-up but not the baseline or the change from baseline values (Aerie 2017). Four trials reported the time point-matched adjusted mean IOP change at follow-up compared with baseline (Tanihara 2013; Tanihara 2015a; Tanihara 2015b; Tanihara 2015c). One trial reported single time point mean IOP at baseline and follow-up and the mean IOP change at follow-up compared with baseline. However, the mean single-time point IOP values were based on unspecified, distinct single-time point measures during the day (Inoue 2018).

Safety

All trials evaluated safety in the form of ocular adverse events. The terminology, the degree of detail in the reporting and the reporting threshold varied among the trials.

Overall, the follow-up period varied from 24 hours to 12 months. Further characteristics of the trials are included in the Characteristics of included studies table.

Excluded studies

After full-text screening, we excluded 10 trials, mainly because of ineligible study design. See Characteristics of excluded studies table.

Studies awaiting classification

Three studies are awaiting classification (CTRI/2018/04/013091; CTRI/2020/01/022619; NCT03284853; Characteristics of studies awaiting classification table).

Ongoing studies

Two studies are ongoing (JapicCTI-194920; UMIN000019017; Characteristics of ongoing studies table).

Risk of bias in included studies

We assessed the risk of bias using RoB 2 (Higgins 2021a).

RoB 2 was applied to two critical outcomes: IOP and total ocular AE. Considering IOP, 13 trials were included in the risk of bias assessment (Araie 2021; Asrani 2019 (MERCURY-1); Bacharach 2015; Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Lewis 2016; Peace 2021; Serle 2018 (ROCKET-1); Sit 2021; Tanihara 2013; Tanihara 2015b; Tanihara 2015c; Walters 2019 (MERCURY-2)); two additional trials were included in the risk of bias assessment considering total ocular AEs (Aerie 2017; NCT02246764 (ROCKET-3)).

Domain 1 – randomization process

IOP and ocular AE: of the trials included in the quantitative synthesis, all trials except one (Bacharach 2015) provided sufficient information on the randomization process, the concealment of allocation, and the baseline characteristics of the participants, and thus were judged at low risk of bias.

Domain 2 – deviations from intended interventions

IOP: eight trials reported sufficient information about masking of participants and trial site personnel and methods to avoid deviation from assigned intervention (Araie 2021; Asrani 2019 (MERCURY-1); Bacharach 2015; Lewis 2016; Peace 2021; Tanihara 2015b; Tanihara 2015c; Walters 2019 (MERCURY-2)), thus were judged at low risk of bias. Another two trials were judged as having some concerns due to exclusion of participants after randomization, only including responders of treatment (Sit 2021), and excluding participants who experienced adverse events to treatments, from the analysis (Tanihara 2013). The rest of the trials examined a per-protocol population defined as "subjects without major protocol violation (that was) likely to seriously affect the primary outcome" (Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Serle 2018 (ROCKET-1)) and displayed differential completion rates between the interventions. The trials were thus evaluated as having high risk of bias.

Ocular AEs: all trials provided adequate information on masking and analysis used for effect estimation. We judged all as having low risk of bias in this domain.

Domain 3 – missing outcome data

IOP: 10 trials had no issue of missing outcome data (Araie 2021; Asrani 2019 (MERCURY-1); Bacharach 2015; Lewis 2016; Peace 2021; Sit 2021; Tanihara 2013; Tanihara 2015b; Tanihara 2015c; Walters 2019 (MERCURY-2)). Three trials were judged as having high risk of bias due to the per-protocol analysis based on participants of differential completion rates between the comparison groups. The three studies lacked a detailed description of reasons for excluding participants from analysis, and thus the missing data might have affected the reported outcomes (Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Serle 2018 (ROCKET-1)).

Ocular AEs: all trials had no issue of missing outcome data, and were considered as low risk of bias.

Domain 4 – measurement of the outcome

IOP: all trials provided sufficient information on the method used for outcome measurement, and were judged as having low risk of bias in this domain.

Ocular AEs: 11 trials provided sufficient information on the methods used for measurement of ocular AEs (Aerie 2017; Araie 2021; Asrani 2019 (MERCURY-1); Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); NCT02246764 (ROCKET-3); Serle 2018 (ROCKET-1); Tanihara 2013; Tanihara 2015b; Tanihara 2015c; Walters 2019 (MERCURY-2). The other two trials were judged as prompting some concerns due to limited information available for assessment, lacking a detailed description of how AEs were measured, that is, relying mostly on participant-reported outcomes and thus at risk of being subjective (Bacharach 2015; Lewis 2016). Another two trials were at high risk of bias due to very limited information, with no description or information about how AEs were measured and reported (Peace 2021; Sit 2021).

Domain 5 – selection of the reported result

IOP: all trials reported sufficient information on the prespecified analysis plan/a priori analysis and were considered at low risk of bias.

Ocular AEs: five trials reported all detectable ocular AEs and, thus, were at low risk of bias (Araie 2021; Peace 2021; Sit 2021; Tanihara 2015b; Tanihara 2015c). The remaining trials varied in the degree of under-reporting. Four trials were judged as causing some concerns due to intermediate reporting thresholds (3%) (Kahook 2019 (ROCKET-2); Serle 2018 (ROCKET-1)), or the combination of high reporting thresholds (5%) with low numbers of participants in the treatment arms (40 or fewer) (Aerie 2017; NCT02246764 (ROCKET-3)). Six trials had high (5% or greater) or unknown reporting thresholds resulting in the judgment of having high risk of bias (Asrani 2019 (MERCURY-1); Bacharach 2015; Khouri 2019 (ROCKET-4); Lewis 2016; Tanihara 2013; Walters 2019 (MERCURY-2)).

Overall bias judgment

IOP: seven trials were overall at low risk of bias (Araie 2021; Asrani 2019 (MERCURY-1); Lewis 2016; Peace 2021; Tanihara 2015b; Tanihara 2015c; Walters 2019 (MERCURY-2)), three trials were judged as some concerns (Bacharach 2015; Sit 2021; Tanihara 2013), and three trials were at high risk of bias (Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Serle 2018 (ROCKET-1)).

Ocular AE: three trials were overall at low risk of bias (Araie 2021; Tanihara 2015b; Tanihara 2015c), four trials were overall judged as some concerns (Aerie 2017; Kahook 2019 (ROCKET-2); NCT02246764 (ROCKET-3); Serle 2018 (ROCKET-1)), and eight trials were overall at high risk of bias (Asrani 2019 (MERCURY-1); Bacharach 2015; Khouri 2019 (ROCKET-4); Lewis 2016; Peace 2021; Sit 2021; Tanihara 2013; Walters 2019 (MERCURY-2)).

Effects of interventions

See: **Summary of findings 1** Rho kinase inhibitor compared to placebo[a]; **Summary of findings 2** Rho kinase inhibitor compared to beta-blocker; **Summary of findings 3** Rho kinase inhibitor compared to prostaglandin analog; **Summary of findings 4** Rho kinase inhibitor and prostaglandin analog compared to prostaglandin analog[a]; **Summary of findings 5** Rho kinase inhibitor and prostaglandin analog compared to rho kinase inhibitor; **Summary of findings 6** Rho kinase inhibitor and beta-blocker compared to beta-blocker

It was not possible to include all trials in meta-analyses due to insufficient data (Tanihara 2015a) or non-comparable interventions (Inoue 2018).

Rho kinase inhibitor versus placebo

Primary outcome

Glaucoma progression

None of the trials comparing ROKi versus placebo reported quantifiable data on glaucoma progression such as visual field defects, thinning of the neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer or thinning of the macular ganglion cell layer.

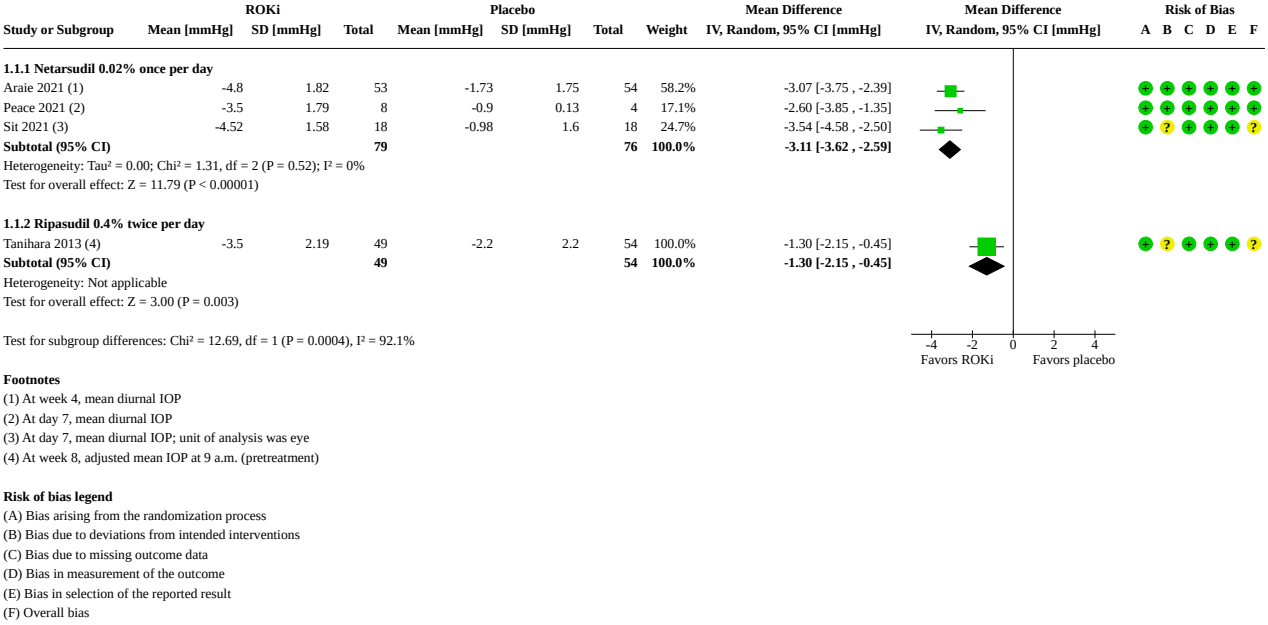
Secondary outcomes

Difference in mean intraocular pressure

Four trials (258 participants) examined the efficacy of ripasudil 0.4% (twice per day, a.m. and p.m.) (Tanihara 2013) and netarsudil 0.02% (once per day, p.m.) (Araie 2021; Peace 2021; Sit 2021) compared with placebo. Due to substantial heterogeneity (I^2 = 92.1%), we did not combine data of netarsudil and ripasudil, neither did we draw any conclusions on ROKi compared with placebo (Analysis 1.1). In a sensitivity analysis that excluded Sit 2021 in which the unit of randomization and analysis was eye and not person, we found no evidence that the heterogeneity was reduced substantially (I^2 = 89.9%; Analysis 1.2).

In an indirect comparison, netarsudil 0.02% reduced IOP from baseline more than ripasudil (netarsudil: MD 3.11 mmHg, 95% CI 2.59 to 3.62; I^2 = 0%; ripasudil: MD 1.30 mmHg, 95% CI 0.45 to 2.15; Figure 2). When excluding Sit 2021, the MD for netarsudil versus placebo was 2.96 mmHg (95% CI 2.37 to 3.56; I^2 = 0%).

Figure 2.



Footnotes
(1) At week 4, mean diurnal IOP
(2) At day 7, mean diurnal IOP
(3) At day 7, mean diurnal IOP; unit of analysis was eye
(4) At week 8, adjusted mean IOP at 9 a.m. (pretreatment)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Overall, we judged the evidence for the estimated MD in IOP reduction from baseline to be low certainty after downgrading one level for risk of bias and one level for imprecision due to small sample sizes (Summary of findings 1).

Glaucoma progression using valid anatomic (structural) criteria

No trials comparing ROKi versus placebo reported glaucoma progression using valid anatomic (structural) criteria.

Participant-reported outcomes

No trials comparing ROKi versus placebo reported participant-reported outcomes.

Mean change in the number of glaucoma medications

No trials comparing ROKi versus placebo reported mean change in the number of glaucoma medications.

Need for intraocular pressure-lowering medications

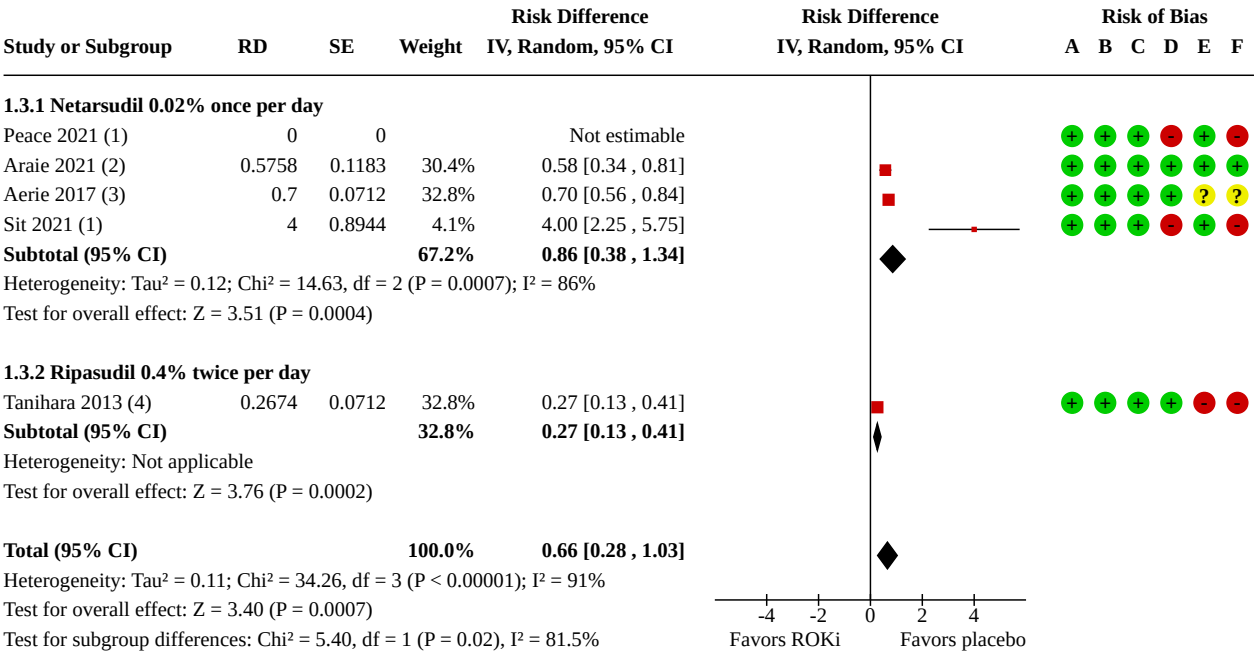
No trials comparing ROKi versus placebo reported need for IOP-lowering medications.

Adverse effects

Five trials (291 participants) examined AEs to treatment comparing either ripasudil 0.4% (twice per day, a.m./p.m.) (Tanihara 2013) or netarsudil 0.02% (once per day, p.m.) to placebo (Aerie 2017; Araie 2021; Peace 2021; Sit 2021).

Ocular adverse events: treatment with netarsudil may lead to an increased rate of ocular AEs compared with placebo, with 66 more ocular AEs per 100 person-months (95% CI 28 to 103; I^2 = 81.5%; Analysis 1.3). We applied a random-effects model though there was substantial heterogeneity within and between the subgroups. Peace 2021 detected no ocular AEs in either of the group, whereas Sit 2021 detected no ocular AEs in the placebo group, which was considered as the major source of the observed heterogeneity (Figure 3). We found no evidence that excluding trials at high risk of bias overall (Peace 2021; Sit 2021) changed the mean incidence RD in ocular AEs (RD 67, 95% CI 55 to 79; I^2 = 0%; Analysis 1.4). Treatment with ripasudil may lead to 27 more events (95% CI 13 to 41) compared with placebo. Overall, the evidence for the estimated difference in incidence rates of ocular AEs was very low certainty after downgrading one level for imprecision due to small sample sizes and two levels for high risk of bias in outcome measurement and selective outcome reporting.

Figure 3.



Footnotes

(1) At day 7 (data from NCT, 5% reporting thereshold)
(2) At day 28 (data from NCT, 0.1% reporting thereshold)
(3) At day 28 (data from NCT, 5% reporting thereshold)
(4) At week 8 (data from article, reporting thereshold unknown)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

In general, treatment with ROKi reported more events of conjunctival hyperemia compared with placebo (Analysis 1.5). There were no events of cornea verticillata, and no evidence of a difference between treatments in terms of ocular pain and irritation (Analysis 1.6). Less than 5% of participants reported serious adverse events (SAEs). For a detailed description, see Appendix 9.

Rho kinase inhibitor versus beta-blocker

Primary outcome

Glaucoma progression

None of the trials comparing ROKi versus BB reported quantifiable data on glaucoma progression such as visual field defects, thinning of the neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer or thinning of the macular ganglion cell layer.

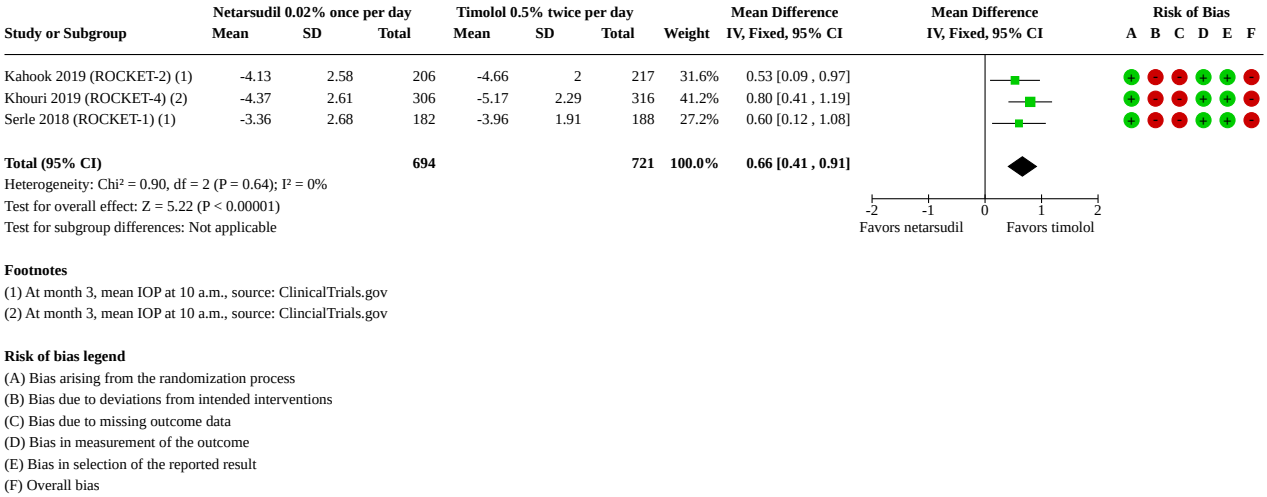
Secondary outcomes

Difference in mean intraocular pressure

Three trials (1415 participants) compared netarsudil 0.02% (once per day, p.m.) with timolol 0.5% (twice per day, a.m. and p.m.) (Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); Serle 2018 (ROCKET-1)).

After three months of treatment, the mean IOP reduction from baseline in the netarsudil group may be slightly smaller compared with timolol (MD 0.66 mmHg, 95% CI 0.41 to 0.91; I^2 = 0%; Analysis 2.1). As all trials were at overall high risk of bias, we did not conduct a sensitivity analysis excluding trials at high risk of bias (Figure 4). Overall, the evidence for the estimated MD in IOP reduction from baseline was low certainty after downgrading two levels for high risk of bias due to deviation from the intended intervention and missing outcome data.

Figure 4.



Footnotes

(1) At month 3, mean IOP at 10 a.m., source: ClinicalTrials.gov
(2) At month 3, mean IOP at 10 a.m., source: ClincialTrials.gov

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Glaucoma progression using valid anatomic (structural) criteria

No trials comparing ROKi versus BB reported glaucoma progression using valid anatomic (structural) criteria.

Participant-reported outcomes

No trials comparing ROKi versus BB reported participant-reported outcomes.

Mean change in the number of glaucoma medications

No trials comparing ROKi versus BB reported mean change in the number of glaucoma medications.

Need for intraocular pressure-lowering medications

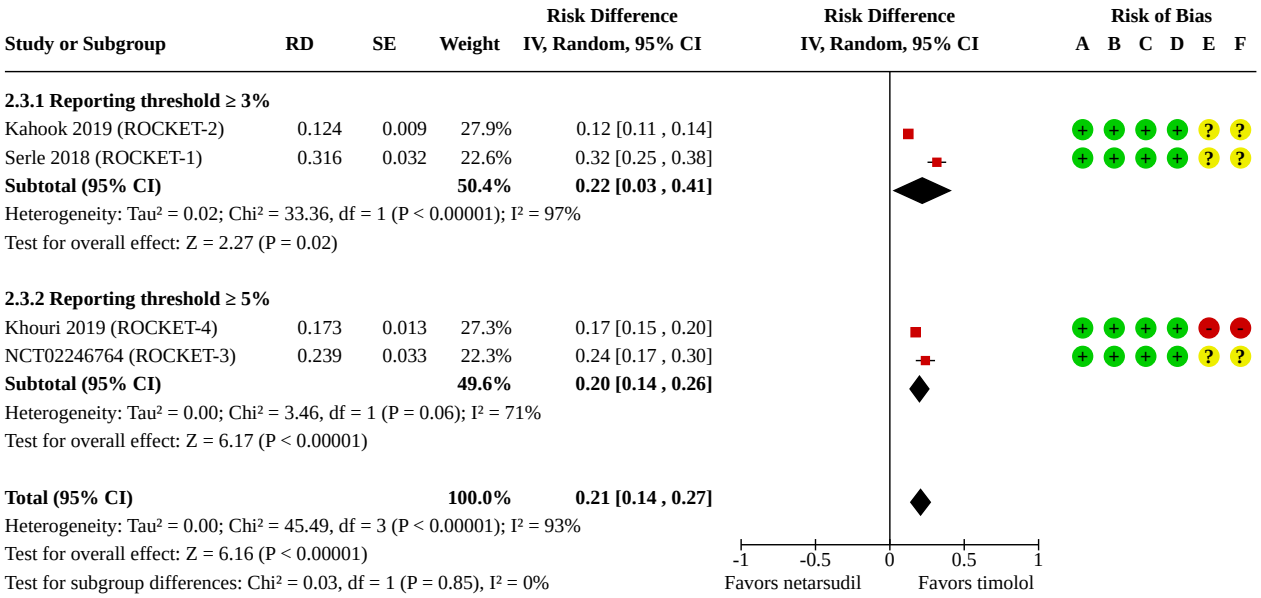
No trials comparing ROKi versus BB reported need for IOP-lowering medications.

Adverse effects

Four trials (1678 participants) examined the AEs of netarsudil 0.02% (once per day, p.m.) compared with timolol 0.5% (twice per day, a.m./p.m.) (Kahook 2019 (ROCKET-2); Khouri 2019 (ROCKET-4); NCT02246764 (ROCKET-3); Serle 2018 (ROCKET-1); Summary of findings 2).

Total ocular adverse events: treatment with netarsudil probably resulted in a higher rate of ocular AEs compared with timolol, with 21 more ocular AEs per 100 person-months (95% CI 14 to 27; I^2 = 93%; Analysis 2.2). Excluding trials with reporting thresholds of 5% or greater (Khouri 2019 (ROCKET-4); NCT02246764 (ROCKET-3)) did not affect this difference in incidence rates (22 more events per 100 person-months, 95% CI 3 to 41; I^2 = 97%; Figure 5). Additionally, there was no evidence of a difference between subgroups defined by reporting threshold of AEs (Analysis 2.3). Overall, the evidence for the estimated MD in ocular AEs was moderate certainty after downgrading one level for risk of bias due to incomplete outcome reporting or selective outcome reporting.

Figure 5.



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

In general, treatment with ROKi resulted in more events of conjunctival hyperemia (Analysis 2.4) and cornea verticillata compared with timolol. There was no evidence of a difference in terms of ocular pain and irritation (Analysis 2.5). Kahook 2019 (ROCKET-2) reported more than 5% of AEs were serious for both treatments. For a detailed description, see Appendix 9.

Rho kinase inhibitor versus prostaglandin analog

Primary outcome

Glaucoma progression

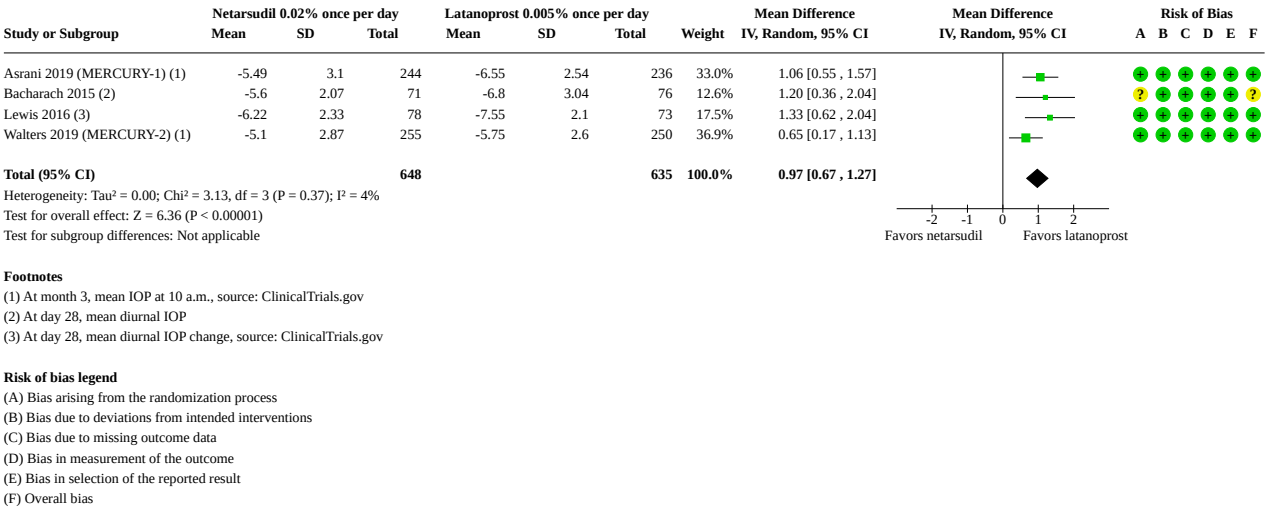
None of the trials comparing ROKi versus PA reported quantifiable data on glaucoma progression such as visual field defects, thinning of the neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer or thinning of the macular ganglion cell layer.

Secondary outcomes

Difference in mean intraocular pressure

Four trials (1283 participants) compared netarsudil 0.02% (once per day, p.m.) and latanoprost 0.005% (once per day, p.m.) (Asrani 2019 (MERCURY-1); Bacharach 2015; Lewis 2016; Walters 2019 (MERCURY-2); Figure 6).

Figure 6.



Footnotes
(1) At month 3, mean IOP at 10 a.m., source: ClinicalTrials.gov
(2) At day 28, mean diurnal IOP
(3) At day 28, mean diurnal IOP change, source: ClinicalTrials.gov

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

After one to three months, latanoprost likely reduced IOP more than netarsudil (MD 0.97 mmHg, 95% CI 0.67 to 1.27; I^2 = 4%; Analysis 3.1). Overall, the evidence for the estimated MD in IOP reduction from baseline was moderate certainty after downgrading one level for risk of bias (Summary of findings 3).

Glaucoma progression using valid anatomic (structural) criteria

No trials comparing ROKi versus PA reported glaucoma progression using valid anatomic (structural) criteria.

Participant-reported outcomes

No trials comparing ROKi versus PA reported participant-reported outcomes

Mean change in the number of glaucoma medications

No trials comparing ROKi versus PA reported mean change in the number of glaucoma medications.

Need for intraocular pressure-lowering medications

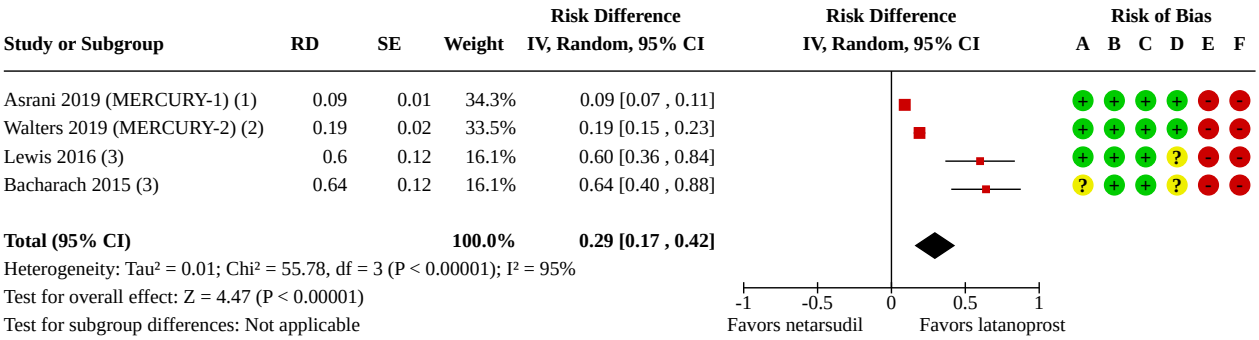
No trials comparing ROKi versus PA reported need for IOP-lowering medications.

Adverse effects

Four trials (1286 participants) examined the AEs of netarsudil 0.02% (once per day, p.m.) and latanoprost 0.005% (once per day, p.m.) (Asrani 2019 (MERCURY-1); Bacharach 2015; Lewis 2016; Walters 2019 (MERCURY-2)).

Total ocular adverse events: netarsudil may lead to more ocular AEs than latanoprost with 29 more ocular AEs per 100 person-months (95% CI 17 to 42; I^2 = 95%; Analysis 3.2). As all trials were at high risk of bias overall, we did not conduct a sensitivity analysis based on the risk of bias judgment (Figure 7). However, the evidence was of low certainty after downgrading it one level for high risk of bias in selective outcome reporting and one level for unclear bias in outcome measurement.

Figure 7.



Footnotes

(1) At month 12 (data from Brubaker 2020, 5% reporting thereshold)
(2) At month 3 (5% reporting thereshold)
(3) At day 28 (5% reporting thereshold)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

In general, compared with latanoprost, treatment with ROKi resulted in slightly more events of conjunctival hyperemia (Analysis 3.3), cornea verticillata and ocular pain and irritation (Analysis 3.4). Asrani 2019 (MERCURY-1) and Lewis 2016 reported that more than 5% of AEs were serious with latanoprost. For a detailed description, see Appendix 9.

Rho kinase inhibitor plus prostaglandin analog versus prostaglandin analog

Primary outcome

Glaucoma progression

None of the trials comparing ROKi plus PA versus PA reported quantifiable data on glaucoma progression such as visual field defects, thinning of the neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer or thinning of the macular ganglion cell layer.

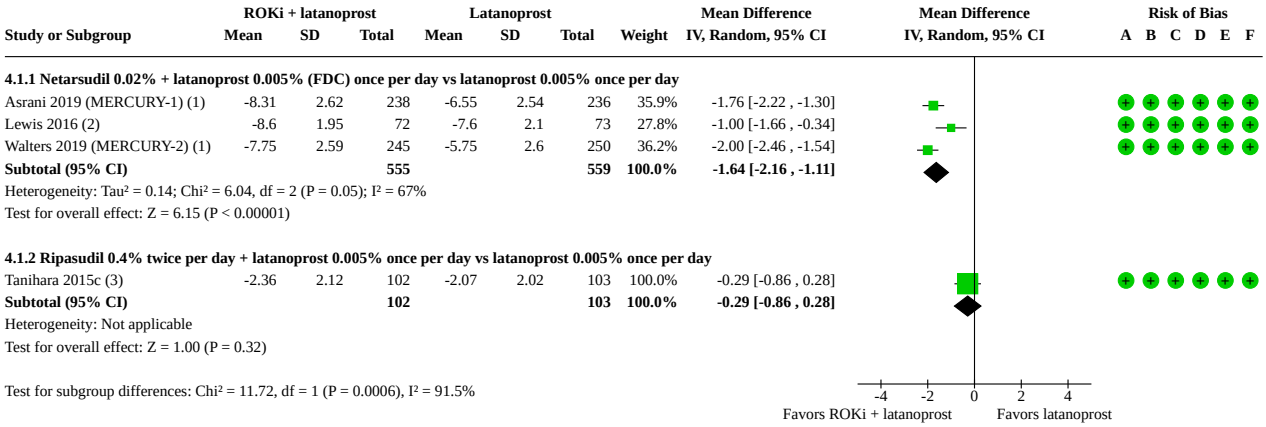
Secondary outcomes

Difference in mean intraocular pressure

Four trials (1319 participants) examined the efficacy of combination therapy with ROKi and PA as either netarsudil 0.02% and latanoprost 0.005% (PG-324) administered once per day (p.m.), or as ripasudil 0.4% (twice per day, a.m. and p.m.) and latanoprost 0.005% (once per day, p.m.) compared with monotherapy with latanoprost 0.005% (once per day, p.m.) (Asrani 2019 (MERCURY-1); Lewis 2016; Tanihara 2015c; Walters 2019 (MERCURY-2)).

The trials were too heterogeneous to draw conclusions on combination therapy with pooled ROKi and latanoprost versus latanoprost (I^2 = 91.5%; Figure 8). Thus, we examined findings from two subgroups based on the type of ROKi (Analysis 4.1). Latanoprost and netarsudil may decrease IOP more than combination therapy with ripasudil and latanoprost. After one to three months of treatment with netarsudil and latanoprost, IOP decreased by an MD of 1.64 mmHg (95% CI 1.11 to 2.16; I^2 = 67%) more than with latanoprost monotherapy. Based on findings from one trial (205 participants), there was no evidence that adding ripasudil to baseline therapy of latanoprost decreased IOP further (MD 0.29 mmHg, 95% CI −0.28 to 0.86).

Figure 8.



Footnotes
(1) At month 3, IOP value at 10 a.m., source: ClinicalTrials.gov
(2) At day 28, mean diurnal IOP, source: ClinicalTrials.gov
(3) At week 8, pretreatment IOP at 9 a.m., extrapolated from graph

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Overall, the evidence for the estimated MD in IOP reduction from baseline was of moderate certainty after downgrading one level for risk of bias in selective outcome reporting as not all studies reported uncorrected mean changes in diurnal IOP from baseline (Summary of findings 4).

Glaucoma progression using valid anatomic (structural) criteria

No trials comparing ROKi plus PA versus PA reported glaucoma progression using valid anatomic (structural) criteria.

Participant-reported outcomes

No trials comparing ROKi plus PA versus PA reported participant-reported outcomes

Mean change in the number of glaucoma medications

No trials comparing ROKi plus PA versus PA reported mean change in the number of glaucoma medications.

Need for intraocular pressure-lowering medications

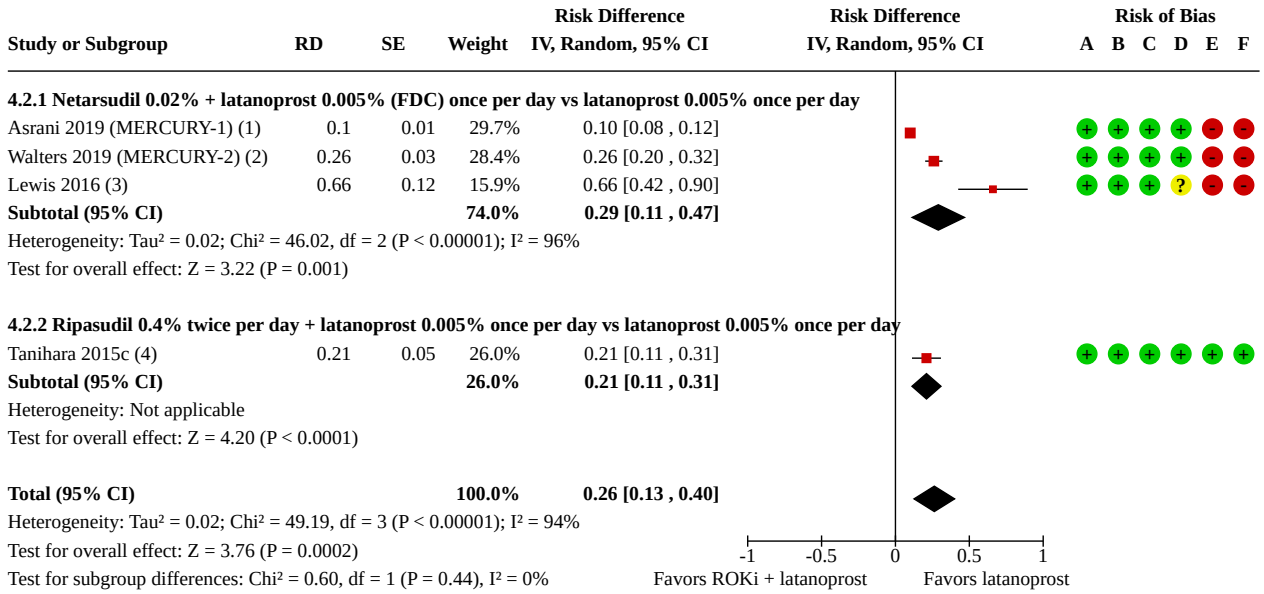
No trials comparing ROKi plus PA versus PA reported need for IOP-lowering medications.

Adverse effects

Four trials (1321 participants) examined the AEs of combination therapy with ROKi and PA as PG-324 0.02% (once per day, p.m.) (fixed-dose compound [FDC] of netarsudil 0.02% and latanoprost 0.005%) or as ripasudil 0.4% (twice per day, a.m./p.m.) combined with latanoprost 0.005% (once per day, p.m.) compared with latanoprost 0.005% (once per day, p.m.) (Asrani 2019 (MERCURY-1); Lewis 2016; Tanihara 2015c; Walters 2019 (MERCURY-2)) (Summary of findings 4).

Total ocular adverse events: the studies were too heterogeneous to combine outcome data. Thus, we evaluated the subgroups based on type of ROKi. Combination of netarsudil and latanoprost may lead to more ocular AEs than latanoprost monotherapy with 29 more events per 100 person-months (95% CI 11 to 47; I^2 = 96%; Analysis 4.2). All trials investigating netarsudil were at high risk of bias, and thus we did not perform a sensitivity analysis. Combination therapy of ripasudil and latanoprost may lead to 21 more ocular AEs per 100 person-months (95% CI 11 to 31) than the latanoprost monotherapy (Figure 9).

Figure 9.



Footnotes

(1) Source: Brubaker 2020, at month 12
(2) At month 3 (5% reporting thereshold)
(3) At day 28 (5% reporting thereshold)
(4) At week 8 (unclear reporting threshold)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

The evidence was uncertain comparing combination therapy of ROKi and latanoprost to latanoprost. Overall, the evidence was of low certainty after downgrading two levels for high risk of bias in selective reporting of adverse outcomes.

In general, treatment with ROKi resulted in more reported events of conjunctival hyperemia (Analysis 4.3) and cornea verticillata. There was no evidence of a difference in terms of ocular pain and irritation (Analysis 4.4). Asrani 2019 (MERCURY-1) and Lewis 2016 reported that more than 5% of AEs were serious with latanoprost. For a detailed description, see Appendix 9.

Rho kinase inhibitor plus prostaglandin analog versus rho kinase inhibitor

Primary outcome

Glaucoma progression

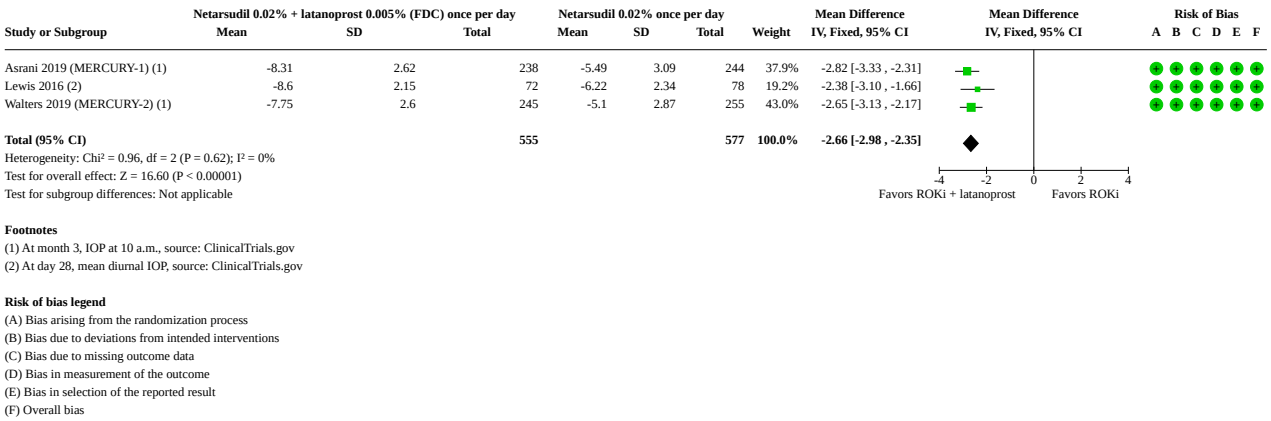
None of the trials comparing ROKi plus PA versus ROKi reported quantifiable data on glaucoma progression such as visual field defects, thinning of the neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer or thinning of the macular ganglion cell layer.

Secondary outcomes

Difference in mean intraocular pressure

Three trials (1132 participants) investigated the efficacy of combination therapy with netarsudil and latanoprost (PG-324 0.02% once per day, p.m.) compared with monotherapy with netarsudil 0.02% (once per day, p.m.) (Asrani 2019 (MERCURY-1); Lewis 2016; Walters 2019 (MERCURY-2); Summary of findings 5). Treatment with netarsudil and latanoprost likely decreased IOP more compared with netarsudil monotherapy (MD 2.66 mmHg, 95% CI 2.35 to 2.98; I^2 = 0%; Analysis 5.1; Figure 10). Overall, the evidence was of moderate certainty after downgrading one level for risk of bias in selective outcome reporting.

Figure 10.



Footnotes
(1) At month 3, IOP at 10 a.m., source: ClinicalTrials.gov
(2) At day 28, mean diurnal IOP, source: ClinicalTrials.gov

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Glaucoma progression using valid anatomic (structural) criteria

No trials comparing ROKi plus PA versus ROKi reported glaucoma progression using valid anatomic (structural) criteria.

Participant-reported outcomes

No trials comparing ROKi plus PA versus ROKi reported participant-reported outcomes.

Mean change in the number of glaucoma medications

No trials comparing ROKi plus PA versus ROKi reported mean change in the number of glaucoma medications.

Need for intraocular pressure-lowering medications

No trials comparing ROKi plus PA versus ROKi reported need for IOP-lowering medications.

Adverse effects

Three trials (1131 participants) investigated the AEs of combination therapy with ROKi and PA as PG-324 0.02% (once per day, p.m.) (FDC of netarsudil 0.02% and latanoprost 0.005%) compared with monotherapy with netarsudil 0.02% (once per day, p.m.) (Asrani 2019 (MERCURY-1); Lewis 2016; Walters 2019 (MERCURY-2)).

Total ocular adverse events: combination therapy may not lead to more ocular AEs than netarsudil monotherapy, with one more ocular AEs per 100 person-months (95% CI 0 to 3; I^2 = 50%) associated with the combination therapy than with the monotherapy (Analysis 5.2). The evidence was low certainty after downgrading two levels for high risk of bias for selective outcome reporting in all included studies.

In general, we found weak evidence of differences between treatments in terms of conjunctival hyperemia (Analysis 5.3) and ocular pain and irritation (Analysis 5.4). Cornea verticillata was reported as an AE of both treatments. Less than 5% of participants reported SAEs. For a detailed description, see Appendix 9.

Rho kinase inhibitor plus beta-blocker versus beta-blocker

Primary outcome

Glaucoma progression

None of the trials comparing ROKi plus BB versus BB reported quantifiable data on glaucoma progression such as visual field defects, thinning of the neuroretinal rim at the optic disk, thinning of the peripapillary retinal nerve fiber layer or thinning of the macular ganglion cell layer.

Secondary outcomes

Difference in mean intraocular pressure

One trial (208 participants) examined the efficacy of combination therapy with ripasudil 0.4% and timolol (twice per day, a.m./p.m.) compared with monotherapy with timolol (twice per day, a.m./p.m.) (Tanihara 2015b).

After two months, treatment with combination therapy of ripasudil and timolol may decrease IOP more than timolol monotherapy (MD 0.75 mmHg, 95% CI 0.21 to 1.29; Analysis 6.1). Overall, the evidence for the estimated MD in IOP reduction from baseline was of moderate certainty after downgrading one level for imprecision due to small sample size (Summary of findings 6).

Glaucoma progression using valid anatomic (structural) criteria

No trials comparing ROKi plus BB versus BB reported glaucoma progression using valid anatomic (structural) criteria.

Participant-reported outcomes

No trials comparing ROKi plus BB versus BB reported participant-reported outcomes.

Mean change in the number of glaucoma medications

No trials comparing ROKi plus BB versus BB reported mean change in the number of glaucoma medications.

Need for intraocular pressure-lowering medications

No trials comparing ROKi plus BB versus BB reported need for IOP-lowering medications.

Adverse effects

One trial (208 participants) examined the AEs of combination therapy with ripasudil 0.4% (twice per day, a.m./p.m.) and timolol 0.5% twice per day (a.m./p.m.) compared with monotherapy with timolol 0.5% (twice per day, a.m./p.m.) (Tanihara 2015b).

Total ocular adverse events: combination therapy with ripasudil and timolol resulted in 35 additional events per 100 person-

months (95% CI 25 to 45) compared with timolol monotherapy (Analysis 6.2). The level of certainty for the single-study estimate was moderate, downgraded one level for imprecision due to small sample size.

Treatment with ripasudil resulted in more events of conjunctival hyperemia compared with timolol (Analysis 6.3). There was weak evidence of RDs between treatments in terms of ocular pain and irritation (Analysis 6.4). Cornea verticillata was not reported. Less than 5% of participants reported SAEs. For a detailed description, see Appendix 9.

DISCUSSION

Summary of main results

In this review, we analyzed findings from 17 trials that evaluated the efficacy and safety of the three marketed ROKi-based drugs; netarsudil 0.02% (once per day, p.m.), ripasudil 0.04% (twice per day, a.m./p.m.) and PG-324 (once per day, p.m.) (FDC of netarsudil 0.02% and latanoprost 0.005%) compared with either placebo, timolol 0.5% (twice per day, a.m./p.m.), latanoprost 0.005% (once per day, p.m.) or netarsudil 0.2% (once per day, p.m.) in people with (P)OAG or OHT.

ROKi was evaluated as mono- and combination therapy, showing that combination therapy with netarsudil and latanoprost may be superior to monotherapy. Furthermore, we found that timolol and latanoprost may be slightly better in reducing IOP in people diagnosed with OHT or POAG. The review focused on commercially available formulations of ROKi.

People treated with ROKi experienced more ocular AEs than those treated with placebo, latanoprost or timolol. In general, AEs were mild, transient and reversible upon treatment discontinuation. ROKi was not associated with any systematically reported SAEs, which were AEs reported to be the primary cause of treatment discontinuation.

Two pharmaceutical companies funded 16 trials: Aerie Pharmaceuticals and Kowa Company. Aerie Pharmaceuticals sponsored trials investigating netarsudil-based interventions, whereas Kowa Company sponsored trials investigating ripasudil-based interventions. Trial findings of industry-controlled and sponsored trials may be influenced by the agenda of the pharmaceutical companies. However, all included trials except Inoue 2018 published the study protocol on either ClinicalTrials.gov or ClinicalTrials.jp before study initiation, which may reduce the influence of funding sources on the analysis and reporting of results. One trial provided no information about funding sources (Inoue 2018).

Overall completeness and applicability of evidence

This review found several trials that investigated the IOP-reducing effect and adverse events of ROKi in people with OHT or POAG, but data on glaucoma progression such as changes in visual field defects are lacking. The included trials reported only two of the prespecified secondary outcomes (IOP reduction and AEs). IOP outcomes were incompletely and variably reported among the trials. Thus, we included both single time point IOP and mean diurnal IOP measurements in the quantitative analyses. The circadian IOP regulation as well as differences in the pharmacodynamic/pharmacokinetic properties of the different interventions may have introduced bias. Thus, single time point IOP may not adequately reflect the actual effect of the different types of ROKi on the mean diurnal IOP. All trials that had investigated ripasudil reported time-matched IOP, whereas trials investigating netarsudil differed between time-matched and mean diurnal IOP. Results from both clinical trials (Peace 2021; Tanihara 2015a) and in vivo experiments (Kaneko 2017; Sturdivant 2016) suggest that netarsudil has a prolonged duration of effect compared with ripasudil, which is reflected in the different recommended dosing frequencies. Therefore, it may be inappropriate to draw conclusions about the efficacy of ripasudil compared with netarsudil in terms of reducing the mean diurnal IOP based on an indirect comparison. Nevertheless, our meta-analyses reflect the variations in drug efficacies at 10 to 12 hours after administration. As ripasudil has a relatively short duration of IOP-lowering effect, the early efficacy of ripasudil may be underestimated.

Cornea verticillate is a well-established AE to treatment with cationic, amphiphilic drugs such as amiodarone or aminoquinolines caused by drug-induced phospholipidosis (Raizman 2017). In most cases, the condition is asymptomatic and reversible. Netarsudil is a cationic and amphiphilic drug (Lin 2018b), and some included trials reported cornea verticillate as an asymptomatic and reversible AE to treatment (Appendix 9).

We addressed treatment safety in the meta-analysis of total ocular AEs; the most frequently reported ocular AEs were conjunctival hyperemia and ocular pain or irritation. There was considerable statistical heterogeneity among the trials, which reflected the clinical and methodological heterogeneity. To compare AEs across trials of different durations, the review team decided to employ incidence rates of reported AEs. This method did not account for temporal associations of occurrence of AE. The incidence rate of short-term AEs thus may underestimate the effects in trials of longer duration.

Most trials reported the number of participants with at least one ocular AE instead of the mean number of ocular AEs per person. The latter was approximated as the sum of each reported ocular AE divided by the number of analyzed participants. This approach may underestimate the actual mean depending on reporting threshold or degree of details when reporting AE. Thus, our estimate reflected the occurrence of AEs among all treated participants and not among participants experiencing AEs.

AEs were inconsistently reported across trials and differed substantially regarding terminology, degree of detail and reporting threshold. To address this problem, we categorized clinically similar or identical AEs to allow the comparison of AEs among trials (Appendix 8). The limitation of this approach was a risk of overestimating the number of specific AEs, especially relevant for categories composed of numerous AEs such as ocular pain and irritation. Furthermore, trials reporting safety outcomes with a low degree of detail and a high reporting threshold would be at risk of being under-represented and vice versa. The AEs categorized as ocular pain or irritation included both acute AEs upon instillation and more long-term AEs that could lead to discontinuation of medication.

When addressing SAEs, some trials applied a standardized terminology (i.e. Medical Dictionary for Regulatory Activities, MedDRA) with strict definitions, whereas others provided limited

or no information about the definition of SAEs. The review team decided to apply the FDA's definition of SAE (FDA 2016). Thus, AEs that met the FDA criteria were classified as SAEs independently of the classification used in trial reports. Furthermore, when no degree of severity or qualitative description of a given AE was provided, the AE evaluation was classified based on the potential severity (e.g. unspecified asthma would be considered as an SAE). This approach may have overestimated the number of SAEs reported.

Quality of the evidence

We evaluated the confidence in the estimates of the effects using the GRADE approach (GRADE Handbook).

None of the studies investigated our primary outcome of disease progression. We were able to assess only two of the six prespecified secondary outcomes. Most trials evaluated the short-term effects of ROKi (less than six months of treatment), and thus we were unable to evaluate the long-term effects of treatment with ROKi. The assessment and reporting of AEs varied substantially among the trials. The trials included in the analyses were heterogeneous and thus difficult to compare. As the quantitative analyses included fewer than 10 studies, the risk of publication bias was not assessed employing funnel plots. Our judgments of certainty of evidence ranged from very low to moderate, depending upon the outcome and comparison of intervention arms.

Limitations to the trials were mainly insufficient reporting on study design, differences in methods of measuring and reporting the outcomes, and differences in descriptive terminology. The short duration of the included trials did not permit meaningful analysis of the comparative effectiveness of ROKi on glaucoma progression. Thus, advocates of ROKi must design and conduct trials with longer follow-up of treatment and observation, and measurement of outcomes that focus on changes in visual field and morphology associated with glaucoma in order to provide convincing data regarding their effectiveness and safety.

Potential biases in the review process

We followed the *Cochrane Handbook for Systematic Reviews of Interventions* and guidelines to conduct a systematic review. We applied a broad search strategy to ensure that all relevant papers were included in this review. Two review authors independently extracted data and assessed risk of bias; we also followed the prespecified methods of meta-analysis and investigations of subgroup differences. To our knowledge, there should be no bias in the review process with respect to trial selection and analysis of available data. The primary bias is the short follow-up of participants in individual trials so that intermediate- and long-term effects of ROKi on IOP and glaucoma progression could not be examined, a factor beyond the control of the review authors. Thus, those effects remain unknown.

Agreements and disagreements with other studies or reviews

Since treatment with ROKi is newly introduced in the USA and Europe (USA in 2017 [FDA 2017] and Europe in 2019 [Aerie 2019]), the number of reviews that have examined this treatment is limited. Other reviews have included trials and data for the same trials that we did. To our knowledge, this is the first systematic review to assess both the efficacy and safety of ROKi.

Tanna 2018 and Mehran 2020 concluded that monotherapy with ROKi was not superior to the traditional antiglaucomatous eye drops. However, they suggested that people could benefit from combination therapy with ROKi, as ROKi primarily acts on the outflow resistance of the AH. The two reviews found that the incidence of AEs was higher for ROKi compared with other treatments. Moura-Coelho 2019 agreed that the efficacy and safety of ROKis were convincing and could be used to gain an additive IOP-reducing effect from combination therapy. This conclusion supports our finding that the greatest reduction of IOP was in the trials of ROKi and latanoprost combination therapy.

The IOP-lowering effect of ROKi depends on the responsiveness/functionality of the TM. It may be hypothesized that ROKi would be more effective in early disease stages of POAG or other subtypes of glaucoma in the absence of, perhaps, irreversible TM/SC cellular dysfunction or structural damage. Likewise, the efficacy of ROKi may to some extent depend on the anatomy of the iridocorneal angle. If overactivity of rho GTPase/ROCK signaling pathway is a causal factor of OHT/increased TM resistance, ROKis may prove to be the preferred drugs compared with other glaucoma medications in some subtypes of glaucoma/OHT such as glucocorticoid-induced glaucoma/OHT (Li 2021b). However, the amount of data from interventional trials is limited, and the current evidence is inconclusive regarding the preventive effect of ROKi on topical corticosteroid-induced OHT (Price 2021).

Preclinical data from in vivo animal models indicate that ROKi expresses neuroprotective properties (promoting axonal outgrow, survival of retinal ganglia cells and increasing blood flow to the optic disk) (Rao 2017). Whether these effects can be translated into humans is unknown. Furthermore, it is questionable whether persistent topical administration will lead to sufficient intravitreal concentrations of ROKi to promote meaningful clinical effects in the glaucomatous retina.

AUTHORS' CONCLUSIONS

Implications for practice

Rho kinase inhibitors (ROKis) are currently prescribed to reduce intraocular pressure (IOP) in people with open-angle glaucoma (OAG) or ocular hypertension (OHT). With reservations because of the limited amount and quality of clinical evidence, the results from our review suggest that ROKi monotherapy (netarsudil 0.02% once per day or ripasudil 0.4% twice per day) reduces IOP in people diagnosed with OAG or OHT, but treatment with ROKi may be inferior compared with monotherapy with timolol 0.5% twice per day or latanoprost 0.005% once per day. Furthermore, combining ROKi (netarsudil 0.02% once per day or ripasudil 0.4%) with either latanoprost 0.005% or timolol 0.5% twice per day probably results in additional IOP reduction compared with monotherapy (netarsudil 0.02% once per day, latanoprost 0.005% once per day or timolol 0.5% twice per day). In terms of adverse events (AEs), ROKi monotherapy and combination therapy may increase the rate of ocular AEs compared with latanoprost and timolol monotherapy. However, the certainty of evidence was low or very low for all comparisons except with timolol (moderate-certainty evidence).

Implications for research

This review highlights the need for additional comparable trials investigating the efficacy and safety of ROKi in people with OAG

and OHT in order to evaluate their effectiveness and safety in routine clinical care. Even though the review included 17 trials, the trials were too heterogeneous to include in a reasonable, collective meta-analysis. Future trials should be sufficiently large and follow participants for a sufficiently long time to provide reliable information about glaucoma progression, relevant outcome measurements of IOP and a detailed description of AEs to treatment using similar terminology in order to ensure the robustness and confidence of the found results.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aerie 2017

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 42 participants **Number of participants (eyes) randomized per group:** placebo: 15, netarsudil 0.02%: 15, netarsudil 0.04%: 12 participants **Total number of participants (eyes) lost to follow-up:** 1 participant lost to follow-up, 2 participants excluded from analysis **Number of participants (eyes) lost to follow-up per group:** placebo: 1, netarsudil 0.02%: 1, netarsudil 0.04%: 0 participants **Power calculation and sample size consideration reported:** yes **Planned length of follow-up:** 28 days **Actual length of follow-up:** 28 days **How missing outcome data were handled:** Monte Carlo Markov Chain multiple imputation techniques **Was the trial single/double/triple-masked:** triple-masked (NCT), double-masked (protocol)

Aerie 2017 *(Continued)*

Was the trial an equivalence/superiority/non-inferiority study: superiority

Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: mITT

Duration of washout for each drug class before interventions began: 4 weeks (prostaglandins and BBs); 2 weeks (adrenergic agonists); 5 days (muscarinic agonists, carbon anhydrase inhibitors)

Participants

Baseline characteristics

Placebo

- *Female, n (%)*: 8 (66.7%)
- *Age, mean*: 65.6 (SD 14.98) years
- *Age ≥ 65 years, n (%)*: 6 (50%)
- *Number of participants randomized*: 12
- *Number of participants analyzed*: 12

Netarsudil 0.02%, once per day (p.m.)

- *Female, n (%)*: 10 (71.4%)
- *Age, mean*: 61.1 (SD 20.32) years
- *Age ≥ 65 years, n (%)*: 6 (42.9%)
- *Number of participants randomized*: 14
- *Number of participants analyzed*: 14

Netarsudil 0.04%, once per day (p.m.)

- *Female, n (%)*: 11 (78.6%)
- *Age, mean*: 60.9 (SD 12.12) years
- *Age ≥ 65 years, n (%)*: 6 (42.9%)
- *Number of participants randomized*: 14
- *Number of participants analyzed*: 14

Overall

- *Female, n (%)*: 29 (72.5%)
- *Age, mean*: 62.4 (SD 15.95) years
- *Age ≥ 65 years, n (%)*: 18 (45%)
- *Number of participants randomized*: 40
- *Number of participants analyzed*: 40

Inclusion criteria: aged ≥ 18 years; of Japanese ethnicity within the second generation defined as (a) first generation born in Japan, immigrated to US and (b) second generation – parents are first generation and the patient was born in US as an American citizen; diagnosis of OAG or OHT in both eyes; medicated IOP ≥ 15 mmHg and < 30 mmHg in both eyes at screening OAG eyes, unmedicated IOP ≥ 15 mmHg and < 35 mmHg at 2 qualification visits at 8 a.m., 10 a.m. and 4 p.m.; OHT eyes, unmedicated IOP ≥ 22 mmHg and < 35 mmHg at 8 a.m., 10 a.m. and 4 p.m.; best corrected visual acuity + 1.0 logMAR or better by ETDRS in each eye; able to give signed informed consent and follow instructions

Exclusion criteria: clinically significant ocular disease; pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma or narrow angles; IOP ≥ 35 mmHg in either eye; ocular hyperemia score of moderate (+2) at qualification visit #2; previous glaucoma intraocular surgery; refractive surgery in either eye; ocular injury within 6 months prior to screening or ocular surgery or non-refractive laser treatment within 3 months prior to screening; recent or current ocular infection or inflammation in either eye; use of ocular medication in either eye of any type within 30 days of screening and throughout the study; mean central corneal thickness > 620 µm in either eye; any abnormality preventing reliable applanation tonometry of either eye; known hypersensitivity to benzalkonium chloride or excipients of netarsudil ophthalmic solution; clinically significant abnormalities in screening laboratory tests; clinically significant systemic disease that might interfere with the study; participated in any investigational study within 30 days prior to screening; systemic medication that

Aerie 2017 *(Continued)*

	could have a substantial effect on IOP within 30 days prior to screening or anticipated during the study; women of child-bearing potential who are pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable form of birth control **Pretreatment:** no formal comparison results reported
Interventions	• Placebo • Netarsudil 0.02%, once per day (p.m.) • Netarsudil 0.04%, once per day (p.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)** • Mean diurnal IOP at week 4 **Other outcomes reported (time points assessed and reported)** • Extent of exposure in days • Mean diurnal IOP at days 8 and 15 • Mean change from baseline in mean diurnal IOP at each post-treatment visit • Mean IOP at each post-treatment time point • Mean change from diurnally adjusted baseline IOP at each post-treatment time point • Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point • Percentages of participants achieving prespecified mean, mean change and percent mean change in mean diurnal IOP levels • Adverse events
Identification	**Sponsorship source:** Aerie Pharmaceuticals **Country:** USA **Setting:** 40 locations **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT03310580 **Phase of trial:** phase 2 **Current publication reported findings from > 1 trial:** no **Year publication accepted:** 2019 (results posted) **Year study initiation (participants screening, enrollment and treatment):** 2017
Notes	Other study ID: AR-13324-CS205

Araie 2021

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 215 participants

Araie 2021 *(Continued)*

Number of participants (eyes) randomized per group: placebo: 55, netarsudil 0.01%: 54, netarsudil 0.02%: 51, netarsudil 0.04%: 55 participants

Total number of participants (eyes) lost to follow-up: 8 participants

Number of participants (eyes) lost to follow-up per group: placebo: 1, netarsudil 0.01%: 1, netarsudil 0.02%: 5, netarsudil 0.04%: 1 participant

Power calculation and sample size consideration reported: yes

Planned length of follow-up: 4 weeks

Actual length of follow-up: 4 weeks

How missing outcome data were handled: Monte Carlo Markov chain multiple imputation techniques

Was the trial single/double/triple-masked: double-masked

Based on the study hypothesis, was the trial an equivalence/superiority/non-inferiority study: superiority

Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: ITT

Duration of washout for each drug class before interventions began: 5 days for muscarinic agonists or carbonic anhydrase inhibitors; 2 weeks for adrenergic agonists; 4 weeks for prostaglandins or BBs; 6 weeks for ROKi

Participants

Baseline characteristics

Placebo, once per day (8–10 p.m.)

- *Female, n (%)*: 31 (56.4%)
- *Age, mean*: 64.6 (SD 12.6) years
- *Age ≥ 65 years, n (%)*: 32 (58.2%)
- *POAG, n (%)*: 40 (72.7%)
- *Number of participants randomized*: 55
- *Number of participants analyzed*: 55

AR-13324 (netarsudil), 0.01%, once per day (8–10 p.m.)

- *Female, n (%)*: 36 (65.5%)
- *Age, mean*: 62.7 (SD 14.6) years
- *Age ≥ 65 years, n (%)*: 33 (60%)
- *POAG, n (%)*: 39 (70.9%)
- *Number of participants randomized*: 55
- *Number of participants analyzed*: 55

AR-13324 (netarsudil), 0.02%, once per day (8–10 p.m.)

- *Female, n (%)*: 29 (53.7%)
- *Age, mean*: 64.1 (SD 12.2) years
- *Age ≥ 65 years, n (%)*: 31 (57.4%)
- *POAG, n (%)*: 39 (72.2%)
- *Number of participants randomized*: 54
- *Number of participants analyzed*: 54

AR-13324 (netarsudil), 0.04%, once per day (8–10 p.m.)

- *Female, n (%)*: 27 (52.9%)
- *Age, mean*: 62 (SD 13.6) years
- *Age ≥ 65 years, n (%)*: 23 (45.1%)

Araie 2021 *(Continued)*

- *POAG, n (%)*: 35 (68.6%)
- *Number of participants randomized*: 51
- *Number of participants analyzed*: 51

Overall

- *Female, n (%)*: 123 (57.2%)
- *Age, mean*: 63.4 (SD 13.2) years
- *Age ≥ 65 years, n (%)*: 119 (55.3%)
- *POAG, n (%)*: 153 (71.2%)
- *Number of participants randomized*: 215
- *Number of participants analyzed*: 215

Inclusion criteria: aged ≥ 20 years; diagnosis of OAG or OHT in both eyes (OAG in 1 eye and OHT in the fellow eye was acceptable); BCVA ≥ 0.1 in decimal unit using Landolt-C chart or its equivalent; willing to give signed informed consent and following study instructions

Exclusion criteria: clinically significant ocular diseases; pseudoexfoliation or pigment dispersion component glaucoma, history of narrow angle closure glaucoma or narrow angles; previous glaucoma intraocular surgery; refractive surgery in either eye; ocular trauma; ocular infection or inflammation; known hypersensitivity to benzalkonium chloride or excipient of netarsudil ophthalmic solution; cannot demonstrate proper delivery of the eye drop; clinically significant abnormalities in screen laboratory tests; clinically significant systemic disease; participation in any investigational study within 30 days of screening; women of child-bearing potential who were pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable form of birth control

Pretreatment characteristics between groups: no significant differences

Interventions	• Placebo, once per day (8–10 p.m.) • Netarsudil (AR-13324), 0.01%, once per day (8–10 p.m.) • Netarsudil (AR-13324), 0.02%, once per day (8–10 p.m.) • Netarsudil (AR-13324), 0.04%, once per day (8–10 p.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)** • Mean diurnal IOP at week 4 (averages of IOP at 9 a.m., 11 a.m., 4 p.m.) **Other outcomes reported (time points assessed and reported)** • Mean diurnal IOP at weeks 1 and 2 • Mean, mean change and mean percentage change in IOP at each post-treatment time point (9 a.m., 11 a.m., 4 p.m.) at each post-treatment visit • Percentage of participants achieving prespecified mean diurnal IOP • Adverse events
Identification	**Sponsorship source:** Aerie Pharmaceuticals **Country:** Japan **Setting:** multicenter, 25 locations **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT03844945 **Phase of the trial (phase 2/phase 3/unclear):** phase 2 **Current publication reported findings from > 1 trial:** no **Year of publication accepted:** 2021

Araie 2021 *(Continued)*

	Year of study initiation (participants screening, enrollment and treatment): 2019
Notes	A netarsudil dose-finding trial (phase 2)

Asrani 2019 (MERCURY-1)

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 718 participants **Number of participants (eyes) randomized per group:** netarsudil: 244, FDC: 238, latanoprost: 236 participants **Number of participants (eyes) lost to follow-up per group:** netarsudil: 43, FDC: 37, latanoprost: 13 participants **Total number of participants (eyes) lost to follow-up:** 93 participants **Power calculation and sample size consideration reported:** yes **Planned length of follow-up:** 3 months for efficacy; 12 months for safety **Actual length of follow-up:** 3 months for efficacy; safety outcomes at 12 months were reported separately (Brubaker 2020) **How missing outcome data were handled:** Markov Chain Monte Carlo multiple imputation techniques **Was the trial single/double/triple-masked:** double-masked **Based on the study hypothesis, was the trial an equivalence/superiority/non-inferiority study:** superiority **Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis:** ITT **Duration of washout for each drug class before interventions began:** 4 weeks for PAs and BBs, 2 weeks for adrenergic agonists, and 5 days for muscarinic agonists and carbonic anhydrase inhibitors
Participants	**Baseline characteristics** Netarsudil 0.02%, once per day (p.m.) • *Female, n (%)*: 136 (55.7%) • *Age ≥ 65 years, n (%)*: 137 (56.1%) • *POAG, n (%)*: 186 (76.2%) • *Time since diagnosis to study entry, mean*: 337.6 (SD 350.2) weeks • *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 183 (75.0%) • *Duration on current ocular hypotensive therapy, mean*: 176.8 (SD 196.2) weeks • *Number of participants randomized*: 244 • *Number of participants analyzed*: 244 Latanoprost 0.005%, once per day (p.m.) • *Female, n (%)*: 136 (57.6%)

Asrani 2019 (MERCURY-1) *(Continued)*

- *Age ≥ 65 years, n (%)*: 141 (59.7%)
- *POAG, n (%)*: 180 (76.3%)
- *Time since diagnosis to study entry, mean*: 336.5 (SD 356.6) weeks
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 165 (69.9%)
- *Duration on current ocular hypotensive therapy, mean*: 186.1 (SD 227.8) weeks
- *Number of participants randomized*: 236
- *Number of participants analyzed*: 236

Netarsudil 0.02%/latanoprost 0.005% (FDC), once per day (p.m.)

- *Female, n (%)*: 134 (56.3%)
- *Age ≥ 65 years, n (%)*: 129 (54.2%)
- *POAG, n (%)*: 174 (73.1%)
- *Time since diagnosis to study entry, mean*: 403.0 (SD 451.7) weeks
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 182 (76.5%)
- *Duration on current ocular hypotensive therapy, mean*: 180.9 (SD 240.7) weeks
- *Number of participants randomized*: 238
- *Number of participants analyzed*: 238

Overall

- *Female, n (%)*: 406 (56.5%)
- *Age ≥ 65 years, n (%)*: 407 (56.7%)
- *POAG, n (%)*: 540 (75.2%)
- *Time since diagnosis to study entry, mean*: 359.0 (SD 389.6) weeks
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 530 (73.8%)
- *Duration on current ocular hypotensive therapy, mean*: 181.1 (SD 221.8) weeks
- *Number of participants randomized*: 718
- *Number of participants analyzed*: 718

Inclusion criteria: bilateral OAG or OHT and were aged ≥ 18 years with unmedicated IOP > 20 and < 36 mmHg in both eyes at 8 a.m. at 2 qualification visits (2–7 days apart) and > 17 and < 36 mmHg in both eyes at 10 a.m. and 4 p.m. at the second qualification visit. Patients using ocular hypotensive medications were required to undergo washout before study entry: 4 weeks for PAs and BBs, 2 weeks for adrenergic agonists, and 5 days for muscarinic agonists and carbonic anhydrase inhibitors. BCVA in each eye was +1.0 logMAR or better by ETDRS measurement

Exclusion criteria: treated with > 2 ocular hypotensive medications within 30 days of screening; pseudoexfoliation or pigment dispersion glaucoma; history of iridocorneal angle closure or narrow angles (including previous peripheral iridotomy); previous glaucoma incisional or laser surgery; previous refractive surgery; central corneal thickness > 620 mm; known hypersensitivity or contraindications to netarsudil or latanoprost (or their excipients); with clinically significant ocular disease other than glaucoma in either eye or systemic disease that might interfere with the study; women of child-bearing potential who were pregnant, breast-feeding, planning a pregnancy, or not using a medically acceptable form of birth control

Pretreatment differences between groups: baseline demographics were similar across treatment groups

Other description of the overall study population at baseline: in total, 55.3% (397/718) receiving prostaglandin monotherapy, 7.0% (50/718) other monotherapy and 11.6% (83/718) combination therapy

Interventions	• Netarsudil 0.02%, once per day (p.m.) • Latanoprost 0.005%, once per day (p.m.) • Netarsudil 0.02%/latanoprost 0.005% (FDC), once per day (p.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)**

Asrani 2019 (MERCURY-1) *(Continued)*

- IOP at 2 weeks, 6 weeks, 3 months

Other outcomes reported (time points assessed and reported)

- Safety outcomes measures: ocular and systemic adverse events during the 12-month treatment period

Identification	**Sponsorship source:** funding/support: the MERCURY-1 study was sponsored by Aerie Pharmaceuticals, Inc., who participated in the design and conduct of the study; the collection, management, analysis and interpretation of data; and the preparation, review and approval of the manuscript. **Country:** USA **Setting:** 56 active sites in 21 states **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT02558400 **Current publication reported findings from > 1 trial:** no **Phase of the trial (phase 2/phase 3/unclear):** phase 3 **Year of study initiation (participants screening, enrollment and treatment):** 2017 **Year of publication accepted:** 2019
Notes	

Bacharach 2015

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 224 participants **Number of participants (eyes) randomized per group:** netarsudil 0.01%: 75, netarsudil 0.02%: 72, latanoprost: 77 participants **Total number of participants (eyes) lost to follow-up:** 1 participant **Number of participants (eyes) lost to follow-up per group:** netarsudil 0.01%: 1, netarsudil 0.02%: 0, latanoprost: 0 participant **Power calculation and sample size consideration reported:** yes **Planned length of follow-up:** 28 days (+ day 29 and day 30) **Actual length of follow-up:** 28 days (+ day 29 and day 30) **How missing outcome data were handled:** unclear **Was the trial single/double/triple-masked:** quadruple-masked (NCT), double-masked (article) **Was the trial an equivalence/superiority/non-inferiority study:** non-inferiority study **Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis:** mITT

Bacharach 2015 *(Continued)*

Duration of washout for each drug class before interventions began: prostaglandins: 4 weeks; BBs: 4 weeks; adrenergic agonists (including alfa-agonists such as brimonidine and apraclonidine): 2 weeks; muscarinic agonists (e.g. pilocarpine), carbonic anhydrase inhibitors (topical or oral): 5 days

Participants	**Baseline characteristics** Netarsudil 0.01%, once per day (10–11 p.m.) • *Female, n (%)*: 42 (56%) • *Age, mean*: 63.5 (SD 11.54) years • *Age ≥ 65 years, n (%)*: 39 (52%) • *Number of participants randomized*: 75 • *Number of participants analyzed*: 74 Netarsudil 0.02%, once per day (10–11 p.m.) • *Female, n (%)*: 45 (62.5%) • *Age, mean*: 66.3 (SD 10.25) years • *Age ≥ 65 years, n (%)*: 45 (62.5%) • *Number of participants randomized*: 72 • *Number of participants analyzed*: 71 Latanoprost 0.005%, once per day (10–11 p.m.) • *Female, n (%)*: 45(58.4%) • *Age, mean*: 65.7 (SD 11.82) years • *Age ≥ 65 years, n (%)*: 41 (53.2%) • *Number of participants randomized*: 77 • *Number of participants analyzed*: 76 Overall • *Female, n (%)*: 132 (58.9%) • *Age, mean*: 65.1 (SD 11.26) years • *Age ≥ 65 years, n (%)*: 125 (56%) • *POAG, n (%)*: 134 (60%) • *Number of participants randomized*: 224 • *Number of participants analyzed*: 221 **Inclusion criteria:** aged ≥ 18 years; diagnosis of OAG or OHT; unmedicated (post-washout) IOP ≥ 24 mmHg at 2 eligibility visits (8 hours), 2–7 days apart, and ≥ 22 mmHg at 10 a.m. and 4 p.m. at second qualification visit; if only 1 eye met the IOP criteria it must have been the same eye that met the criteria at all the qualification time points; corrected visual acuity in each eye +1.0 logMAR or better by ETDRS in each eye (equivalent to 20/200); able and willing to give signed informed consent and follow study instructions **Exclusion criteria:** glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure or narrow angles. Note: previous laser peripheral iridotomy was NOT acceptable; IOP > 36 mmHg known hypersensitivity to any component of the formulation (benzalkonium chloride, etc.), or to topical anesthetics; previous glaucoma intraocular surgery or glaucoma laser procedures in study eye(s) (e.g. laser trabeculoplasty); refractive surgery in study eye(s) (e.g. radial keratotomy, photorefractive keratectomy, laser eye surgery, etc.); ocular trauma within past 6 months, or ocular surgery or laser treatment within the past 3 months prior to screening; evidence of ocular infection, inflammation, clinically significant blepharitis or conjunctivitis at screening (visit 0), or history of herpes simplex keratitis; ocular medication of any type within 30 days of visit 0, except for (a) ocular hypotensive medications (which must have been washed out according to the provided schedule), (b) lid scrubs (which may have been used prior to, but not after visit 0) or (c) lubricating drops for dry eye (which may have been used throughout the study); clinically significant ocular disease (e.g. uveitis, severe keratoconjunctivitis sicca) which might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for 1 month is not judged safe (i.e. cup–disk ratio > 0.8);

Bacharach 2015 *(Continued)*

	central corneal thickness > 600 µm; any abnormality preventing reliable applanation tonometry of either eye. Systemic: clinically significant abnormalities (as determined by the treating physician) in laboratory tests at screening; known hypersensitivity or contraindication to latanoprost; clinically significant systemic disease (e.g. myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study; participation in any investigational study within 30 days prior to screening; changes of systemic medication that could have a substantial effect on IOP within 30 days prior to screening, or anticipated during the study; due to the current status of the preclinical safety program, women of child-bearing potential who were pregnant, breast-feeding, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman was considered of child-bearing potential unless she was 1 year postmenopausal or three months postsurgical sterilization. All females of child-bearing potential must have had a negative urine pregnancy test result at the screening examination and must not have intended to become pregnant during the study **Pretreatment differences between groups:** no significant differences (Table 3) **Other description of the overall study population at baseline:** none
Interventions	• Netarsudil 0.01%, once per day (10–11 p.m.) • Netarsudil 0.02%, once per day (10–11 p.m.) • Latanoprost 0.005%, once per day (10–11 p.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)** • Mean diurnal IOP **Other outcomes reported (time points assessed and reported)** • Adverse events • Extent of exposure to intervention and control treatment
Identification	**Sponsorship source:** Aerie Pharmaceuticals, Inc. **Country:** USA **Setting:** 22 private practice ophthalmology clinics **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT01731002 **Phase of the trial:** phase 2b **Current publication reported findings from > 1 trial:** no **Year of publication accepted:** 2014 **Year of study initiation (participants screening, enrollment and treatment):** 2012
Notes	3 severe adverse events were judged not to be related to treatment: 1 pneumonia (latanoprost), 1 influenza and syncope (latanoprost), 1 death from leukemia (netarsudil 0.01%)

Inoue 2018

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant

Inoue 2018 *(Continued)*

Total number of participants (eyes) randomized: 51 participants

Number of participants (eyes) randomized per group: added group: 25, switched group: 26 participants

Total number of participants (eyes) lost to follow-up: 5 participants

Number of participants (eyes) lost to follow-up per group: added group: 4, switched group: 1 participants

Power calculation and sample size consideration reported: yes

Planned length of follow-up: 3 months

Actual length of follow-up: 3 months

How missing outcome data were handled: exclusion from the analysis

Was the trial single/double/triple-masked: open-label

Was the trial an equivalence/superiority/non-inferiority study: unclear

Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: mITT

Duration of washout for each drug class before interventions began: not reported

Participants

Baseline characteristics

Ripasudil 0.4% twice per day + latanoprost 0.005%/travoprost 0.004%/tafluprost 0.005% once per day (added group)

- *Female, n (%)*: 18 (69%)
- *Age, mean*: 69.7 (SD 8.4) years
- *POAG, n (%)*: 13 (50%)
- *Normal tension glaucoma, n (%)*: 13 (50%)
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 25 (100%)
- *Duration on current ocular hypotensive therapy, mean*: 84.2 (SD 55.3) months
- *Number of participants randomized*: 26
- *Number of participants analyzed*: 25

Timolol 0.5% + latanoprost 0.005%/travoprost 0.004%/tafluprost 0.005% FDC, once per day (switched group)

- *Female, n (%)*: 18 (72%)
- *Age, mean*: 64.7 (SD 11.6) years
- *POAG, n (%)*: 18 (72%)
- *Normal tension glaucoma, n (%)*: 7 (28%)
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 26 (100%)
- *Duration on current ocular hypotensive therapy, mean*: 110.2 (SD 46.8) months
- *Number of participants randomized*: 25
- *Number of participants analyzed*: 21

Overall

- *Female, n (%)*: 36 (71%)
- *Age, mean*: 67.2 (SD 10.3) years
- *POAG, n (%)*: 31 (61%)
- *Normal tension glaucoma, n (%)*: 20 (39%)
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 51 (100%)
- *Duration on current ocular hypotensive therapy, mean*: 96.9 (SD 52.5) months

Inoue 2018 *(Continued)*

	• *Number of participants randomized*: 51 • *Number of participants analyzed*: 46 **Inclusion criteria:** POAG with insufficient IOP control while taking PA monotherapy insufficient IOP reduction after > 3 months of treatment (mean treatment duration, 96.9 [SD 52.5] months; range 3–198 months) with latanoprost (40 eyes), travoprost (7 eyes), or tafluprost (4 eyes) **Exclusion criteria:** not reported **Pretreatment:** at baseline, no significant between-group differences were found **Other description of the overall study population at baseline:** not reported
Interventions	• Added group: ripasudil 0.4% twice per day + latanoprost 0.005%/travoprost 0.004%/tafluprost 0.005% once per day • Switched group: timolol 0.5% + latanoprost 0.005%/travoprost 0.004%/tafluprost 0.005% FDC, once per day
Outcomes	**Primary outcome reported (time points assessed and reported)** • IOP reduction from baseline after 3 months of treatment **Other outcomes reported (time points assessed and reported)** • IOP reduction from baseline between the treatment groups at 1 month • Adverse events
Identification	**Sponsorship source:** no sponsorship source reported. Conflicts of interest: K Inoue, none; K Ishida, none; G Tomita, none. **Country:** Japan **Setting:** Inouye Eye Hospital (Tokyo, Japan) **Online trial registration site:** not reported **Trial registration #:** not reported **Phase of the trial (phase 2/phase 3/unclear):** unclear **Current publication reported findings from > 1 trial:** no **Year of publication accepted:** 2018 **Year of study initiation (participants screening, enrollment and treatment):** 2015
Notes	

Kahook 2019 (ROCKET-2)

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 756 participants

Kahook 2019 (ROCKET-2) *(Continued)*

Number of participants (eyes) randomized per group: netarsudil 0.02% once per day: 251, netarsudil 0.02% twice per day: 254, timolol: 251 participants

Total number of participants (eyes) lost to follow-up: 124 participants

Number of participants (eyes) lost to follow-up per group: netarsudil 0.02% once per day: 46, netarsudil 0.02% twice per day: 101, timolol: 14 participants

Power calculation and sample size consideration reported: yes

Planned length of follow-up: primary outcome at 3 months; safety outcomes at 12 months

Actual length of follow-up: primary outcome at 3 months; safety outcomes at 12 months

How missing outcome data were handled: unclear

Was the trial single/double/triple-masked: double-masked (article), quadruple-masked (NCT)

Was the trial an equivalence/superiority/non-inferiority study: non-inferiority

Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: NCT: the PP population included all participants who did not have a major protocol violation likely to seriously affect the primary outcome of the study

Duration of washout for each drug class before interventions began: 28 days for BBs, prostaglandins and the dorzolamide-timolol fixed combination; 14 days for alfa- and alfa/beta-agonists, 5 days for miotics and oral or topical carbonic anhydrase inhibitors, and 3 days if participants were receiving no IOP-lowering therapy

Participants

Baseline characteristics

Netarsudil 0.02%, once per day (p.m.)

- *Female, n (%)*: 148 (59%)
- *Age, mean*: 65.3 (SD 11.48) years
- *Age ≥ 65 years, n (%)*: 140 (55.8%)
- *POAG, n (%)*: 167 (66.5%)
- *Number of participants randomized*: 251
- *Number of participants analyzed*: 205; 114 (IOP < 25 mmHg)

Netarsudil 0.02%, twice per day

- *Female, n (%)*: 165 (65)
- *Age, mean*: 64.1 (SD 12.46) years
- *Age ≥ 65 years, n (%)*: 128 (50.4%)
- *POAG, n (%)*: 158 (62.2%)
- *Number of participants randomized*: 254
- *Number of participants analyzed*: 153; 88 (IOP < 25 mmHg)

Timolol 0.5%, twice per day

- *Female, n (%)*: 150 (59.8%)
- *Age, mean*: 63 (SD 11.81) years
- *Age ≥ 65 years, n (%)*: 120 (47.8%)
- *POAG, n (%)*: 171 (68.1)
- *Number of participants randomized*: 251
- *Number of participants analyzed*: 237; 139 (IOP < 25 mmHg)

Overall

- *Female, n (%)*: 463 (61.2%)

Kahook 2019 (ROCKET-2) *(Continued)*

- *Age, mean*: 64.1 (SD 11.95) years
- *Age ≥ 65 years, n (%)*: 388 (51.3%)
- *POAG, n (%)*: 496 (65.6%)
- *Number of participants randomized*: 756
- *Number of participants analyzed*: 595; 341 (IOP < 25 mmHg)

Inclusion criteria: 0–2 years of age and ≥ 18 years; diagnosis of OAG or OHT; unmedicated (post-washout) IOP > 20 mmHg and < 27 mmHg in the study eye at 2 qualification visits; corrected visual acuity in each eye equivalent to 20/200; able and willing to give signed informed consent (parent or guardian consent for children) and follow study instructions

Exclusion criteria: glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure, or narrow angles. Note: previous laser peripheral iridotomy is NOT acceptable; IOP ≥ 27 mmHg (unmedicated) in both eyes or use of > 2 ocular hypotensive medications within 30 days of screening. Note: fixed dose combinations count as 2 medications; known hypersensitivity to any component of the formulations to be used (benzalkonium chloride, etc.), to topical anesthetics or BBs; previous glaucoma intraocular surgery or glaucoma laser procedures in either eye; refractive surgery in either eye; ocular trauma in either eye within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening; recent or current evidence of ocular infection or inflammation in either eye; current evidence of clinically significant blepharitis, conjunctivitis or a history of herpes simplex or zoster keratitis at screening in either eye; ocular medication in either eye of any type within 30 days of screening; clinically significant ocular disease in either eye (e.g. corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for 1 month is not judged safe; central corneal thickness in either eye > 600 µm at screening; any abnormality in either eye preventing reliable applanation tonometry of either eye. Systemic: clinically relevant abnormalities (as determined by the investigator) in laboratory tests at screening which may impact the study; known hypersensitivity or contraindication to BBs (e.g. chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third-degree heart block or congestive heart failure; severe diabetes); clinically significant systemic disease (e.g. uncontrolled diabetes, myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study; participation in any investigational study within 30 days prior to screening; changes of systemic medication that could have an effect on IOP within 30 days prior to screening, or anticipated during the study; women of child-bearing potential who are pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable form of birth control. An adult woman was considered of child-bearing potential unless she was 1 year postmenopausal or 3 months postsurgical sterilization. All females of child-bearing potential must have had a negative urine pregnancy test result at the screening examination and must not have intended to become pregnant during the study

Pretreatment characteristics between groups: no statistically significant differences in demographics between treatment groups

Other description of the overall study population at baseline: not reported

Interventions	• Netarsudil 0.02%, once per day (p.m.) • Netarsudil 0.02%, twice per day • Timolol 0.5%, twice per day
Outcomes	**Primary outcome reported (time points assessed and reported)** • Mean IOP at 8 a.m., 10 a.m., and 4 p.m. at week 2, week 6 and month 3 in the PP population with IOP < 25 mmHg at all baseline time points **Other outcomes reported (time points assessed and reported)** • Extent of exposure • Ocular and systemic safety
Identification	**Sponsorship source:** Aerie Pharmaceuticals **Country:** USA

Kahook 2019 (ROCKET-2) *(Continued)*

	Setting: multicenter (62 clinical trial sites) **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT02207621 **Phase of the trial (phase 2/phase 3/unclear):** phase 3 **Current publication reported findings from > 1 trial:** no **Year of publication accepted:** 2019 **Year of study initiation (participants screening, enrollment and treatment):** 2014
Notes	Primary efficacy data of ROCKET-2 at 3 months were reported in Serle 2018; safety data of ROCKET-2 at 12 months in Kahook 2019.

Khouri 2019 (ROCKET-4)

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 708 participants **Number of participants (eyes) randomized per group:** netarsudil: 351, timolol: 357 participants **Total number of participants (eyes) lost to follow-up:** 86 participants **Number of participants (eyes) lost to follow-up per group:** netarsudil: 45, timolol: 41 participants **Power calculation and sample size consideration reported:** yes **Planned length of follow-up:** 6 months **Actual length of follow-up:** 6 months **How missing outcome data were handled:** exclusion of participants **Was the trial single/double/triple-masked:** double-masked (article), quadruple-masked (NCT) **Was the trial an equivalence/superiority/non-inferiority study:** non-inferiority **Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis:** PP **Duration of washout for each drug class before interventions began:** 4 weeks for participants using PAs or BBs prior to study entry, 2 weeks for those using adrenergic agonists, and 5 days for those using muscarinic agonists or topical carbonic anhydrase inhibitors
Participants	**Baseline characteristics** Netarsudil 0.02%, once per day (p.m.) • *Female, n (%)*: 208 (59.3%) • *Age, mean*: 64.1 (SD 11.6) years • *Age ≥ 65 years, n (%)*: 186 (53%) • *POAG, n (%)*: 223 (63.5%) • *Time since diagnosis to study entry, mean*: 364.1 (SD 367.3) weeks

Khouri 2019 (ROCKET-4) *(Continued)*

- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 221 (63.0%)
- *Number of participants randomized*: 351
- *Number of participants analyzed*: 186 (IOP < 25 mmHg)

Timolol 0.5%, twice per day

- *Female, n (%)*: 237 (66.4%)
- *Age, mean*: 64.5 (SD 11) years
- *Age ≥ 65 years, n (%)*: 193 (54.1%)
- *POAG, n (%)*: 244 (68.3%)
- *Time since diagnosis to study entry, mean*: 344.2 (SD 341.1) weeks
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 222 (62.2%)
- *Number of participants randomized*: 357
- *Number of participants analyzed*: 186 (IOP < 25 mmHg)

Overall

- *Female, n (%)*: 445 (62.9)
- *Age, mean*: 64.3 (SD 11.25) years
- *Age ≥ 65 years, n (%)*: 379 (53.5%)
- *POAG, n (%)*: 467 (66.0%)
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 443 (62.6%)
- *Number of participants randomized*: 708
- *Number of participants analyzed*: 372 (IOP < 25 mmHg)

Inclusion criteria: aged ≥ 18 years; diagnosis of OAG or OHT in both eyes; post-washout IOP > 20 mmHg and < 30 mmHg in 1 or both eyes at 2 qualification visits; corrected visual acuity equivalent to 20/200; able to give informed consent and follow study instructions

Exclusion criteria: clinically significant ocular disease; pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure or narrow angles; unmedicated IOP ≥ 30 mmHg; use of > 2 ocular hypotensive medications within 30 days of screening; known hypersensitivity to any component of the formulation; previous glaucoma surgery or refractive surgery; ocular trauma within 6 months prior to screening; any ocular surgery or non-refractive laser treatment within 3 months prior to screening; recent or current ocular infection or inflammation in either eye; used ocular medication in either eye of any type within 30 days of screening; mean central corneal thickness > 620 µm at screening; any abnormality preventing reliable applanation tonometry of either eye; clinically significant abnormalities in laboratory tests at screening; known hypersensitivity or contraindication to BBs; clinically significant systemic disease; participation in any investigational study within 60 days prior to screening; used any systemic medication that could have a substantial effect in IOP within 30 days prior to screening; women who are pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable form of birth control

Pretreatment differences between groups: baseline demographics of randomized participants were similar between the 2 treatment groups

Other description of the overall study population at baseline: not reported

Interventions	• Netarsudil 0.02%, once per day (p.m.) • Timolol 0.5%, twice per day
Outcomes	**Primary outcome reported (time points assessed and reported)** • Mean IOP at 8 a.m., 10 a.m., and 4 p.m. at week 2, week 6 and month 3 in participants with baseline IOP < 25 mmHg **Other outcomes reported (time points assessed and reported)** • Mean IOP at 8 a.m., 10 a.m., and 4 p.m. at week 2, week 6 and month 3 was also examined in participants with baseline IOP < 27 mmHg and in the overall study population (baseline IOP < 30 mmHg)

Khouri 2019 (ROCKET-4) *(Continued)*

- Systemic and ocular safety

Identification	**Sponsorship source:** Aerie Pharmaceuticals **Country:** USA **Setting:** 52 activity sites **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT02558374 **Phase of the trial (phase 2/phase 3/unclear):** phase 3 **Current publication reported findings from > 1 trial:** no **Year of publication accepted:** 2019 **Year of study initiation (participants screening, enrollment and treatment):** 2015
Notes	ROCKET-4; the citation links to a prior conference abstract whereas the full text was published in Khouri 2019 with a different title.

Lewis 2016

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 298 participants **Number of participants (eyes) randomized per group:** netarsudil 0.01%/latanoprost 0.005%: 74; netarsudil 0.02%/latanoprost 0.005%: 73; latanoprost 0.005%: 73; netarsudil 0.02%: 78 participants **Total number of participants (eyes) lost to follow-up:** 2 participants **Number of participants (eyes) lost to follow-up per group:** netarsudil 0.01%/latanoprost 0.005%: 1; netarsudil 0.02%/latanoprost 0.005%: 1; latanoprost 0.005%: 0; netarsudil 0.02%: 0 participant **Power calculation and sample size consideration reported:** yes **Planned length of follow-up:** 28 days **Actual length of follow-up:** 28 days **How missing outcome data were handled:** exclusion **Was the trial single/double/triple-masked:** double-masked **Was the trial an equivalence/superiority/non-inferiority study:** superiority **Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis:** mITT **Duration of washout for each drug class before interventions began:** 28 days for BB, prostaglandins and the dorzolamide-timolol fixed combination; 14 days for alfa- and alfa/beta-agonists, 5 days for miotics and oral or topical carbonic anhydrase inhibitors, and 3 days if participants were receiving no IOP-lowering therapy (based on Lewis 2016).

Lewis 2016 *(Continued)*

Participants	**Baseline characteristics** Netarsudil 0.01%/latanoprost 0.005% (PG-324), once per day • *Female, n (%)*: 47 (63.5%) • *Age, mean*: 65.4 (SD 11.26) years • *Age ≥ 65 years, n (%)*: 45 (60.8%) • *Number of participants randomized*: 74 • *Number of participants analyzed*: 73 Netarsudil 0.02%/latanoprost 0.005% (PG-324), once per day • *Female, n (%)*: 39 (53.4%) • *Age, mean*: 64.2 (SD 11.07) years • *Age ≥ 65 years, n (%)*: 38 (52.1%) • *Number of participants randomized*: 73 • *Number of participants analyzed*: 72 Latanoprost 0.005%, once per day • *Female, n (%)*: 46 (63%) • *Age, mean*: 65.1 (SD 12.8) years • *Age ≥ 65 years, n (%)*: 45 (61.6%) • *Number of participants randomized*: 73 • *Number of participants analyzed*: 73 Netarsudil 0.02%, once per day • *Female, n (%)*: 43 (55.1%) • *Age, mean*: 64.8 (SD 11.28) years • *Age ≥ 65 years, n (%)*: 45 (57.7%) • *Number of participants randomized*: 78 • *Number of participants analyzed*: 78 Overall • *Female, n (%)*: 175 (58.7%) • *Age, mean*: 64.9 (SD 11.57) years • *Age ≥ 65 years, n (%)*: 173 (58.1%) • *Number of participants randomized*: 298 • *Number of participants analyzed*: 296 **Inclusion criteria:** aged ≥ 18 years; diagnosis of OAG or OHT; corrected visual acuity in each eye equivalent to 20/200 or better; able and willing to give signed informed consent and follow study instructions **Exclusion criteria:** ophthalmic: glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure, or narrow angles; IOP >36 mmHg; known hypersensitivity to any component of the formulation, latanoprost or to topical anesthetics; previous glaucoma intraocular surgery or glaucoma laser procedures in study eye(s); refractive surgery in study eye(s); ocular trauma within the 6 months prior to screening, or ocular surgery or laser treatment within the 3 months prior to screening; evidence of ocular infection and inflammation; clinically significant ocular disease, which might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for 1 month is not judged safe; central corneal thickness > 600 µm; any abnormality preventing reliable applanation tonometry of either eye. Systemic: clinically significant abnormalities (as determined by the investigator) in laboratory tests at screening; clinically significant systemic disease; participation in any investigational study within 30 days prior to screening; changes in systemic medication; women of child-bearing potential who were pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable form of birth control

Lewis 2016 *(Continued)*

	Pretreatment characteristics between groups: no clinically or statistically significant differences among treatment groups (Table 1, Lewis 2016) **Other description of the overall study population at baseline:** the population was 79% Caucasian (236/298), 18% African–American (54/298), 2% Asian (7/298) and 0.3% Native American (1/298). 22% (64/298) of participants self-identified as Hispanic. The most frequent iris color was brown/black (62%, 184/298), followed by blue/grey/green (27%, 79/298) and hazel (12%, 35/298)
Interventions	• Netarsudil 0.01%/latanoprost 0.005% (PG-324), once per day • Netarsudil 0.02%/latanoprost 0.005% (PG-324), once per day • Latanoprost 0.005%, once per day • Netarsudil 0.02%, once per day
Outcomes	**Primary outcome reported (time points assessed and reported)** • Mean diurnal IOP **Other outcomes reported (time points assessed and reported)** • Mean IOP at each post-treatment time point • Mean change from diurnally adjusted baseline IOP at each time point • Percentages of participants achieving prespecified percentage reductions in IOP from baseline to day 29 • Systemic and ocular safety
Identification	**Sponsorship source:** Aerie Pharmaceuticals **Country:** USA **Setting:** multicenter, 23 study locations **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT02057575 **Phase of the trial:** phase 2 **Current publication reported findings from > 1 trial:** no **Year of publication accepted:** 2015 **Year of study initiation (participants screening, enrollment and treatment):** 2014
Notes	

NCT02246764 (ROCKET-3)

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 93 participants **Number of participants (eyes) randomized per group:** netarsudil 0.02% once per day: 34; netarsudil 0.02% twice per day: 36; timolol: 23 participants

NCT02246764 (ROCKET-3) *(Continued)*

Total number of participants (eyes) lost to follow-up: 0

Number of participants (eyes) lost to follow-up per group: netarsudil 0.02% once per day: 0; netarsudil 0.02% twice per day: 0; timolol: 0 participants

Power calculation and sample size consideration reported: no

Planned length of follow-up: 12 months

Actual length of follow-up: 12 months

How missing outcome data were handled: unclear

Was the trial single/double/triple-masked: quadruple-masked (NCT)

Was the trial an equivalence/superiority/non-inferiority study: unclear

Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: ITT

Duration of washout for each drug class before interventions began: ≥ 4 weeks for participants using PAs or BBs before study entry, ≥ 2 weeks for those using α-agonists, and ≥ 5 days for those using muscarinic agonists or carbonic anhydrase inhibitors

Participants

Baseline characteristics

Netarsudil 0.02%, once per day

- *Female, n (%)*: 18 (52.9%)
- *Age, mean*: 64.6 (SD 7.73) years
- *Number of participants randomized*: 34
- *Number of participants analyzed*: 34

Netarsudil 0.02%, twice per day

- *Female, n (%)*: 18 (50%)
- *Age, mean*: 64.4 (SD 7.84) years
- *Number of participants randomized*: 36
- *Number of participants analyzed*: 36

Timolol 0.5%, twice per day

- *Female, n (%)*: 8 (34.8%)
- *Age, mean*: 61.9 (SD 12.52) years
- *Number of participants randomized*: 23
- *Number of participants analyzed*: 23

Overall

- *Female, n (%)*: 44 (47.3%)
- *Age, mean*: 63.8 (SD 9.14) years
- *Age ≥ 65 years, n (%)*:
- *Number of participants randomized*: 93
- *Number of participants analyzed*: 93

Inclusion criteria: aged ≥ 19 years; diagnosis of OAG or OHT; unmedicated (post-washout) IOP > 20 mmHg and < 27 mmHg in the study eye at 2 qualification visits (8 a.m.), 2–7 days apart. At second qualification visit, IOP > 17 mmHg and < 27 mmHg at 10 a.m. and 4 p.m.(in the same eye); corrected visual acuity in each eye +1.0 logMAR or better by ETDRS in each eye (equivalent to 20/200); able and willing to give signed informed consent and follow study instructions

Excluded criteria: glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure, or narrow angles. Note: previous laser peripheral iridotomy is NOT acceptable; IOP ≥ 27 mmHg

NCT02246764 (ROCKET-3) *(Continued)*

	(unmedicated) in both eyes or use of > 2 ocular hypotensive medications within 30 days of screening. Note: fixed dose combinations count as 2 medications; known hypersensitivity to any component of the formulations to be used (benzalkonium chloride, etc.), to topical anesthetics or BBs; previous glaucoma intraocular surgery or glaucoma laser procedures in either eye; refractive surgery in either eye; ocular trauma in either eye within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening; recent or current evidence of ocular infection or inflammation in either eye; current evidence of clinically significant blepharitis, conjunctivitis or a history of herpes simplex or zoster keratitis at screening in either eye; ocular medication in either eye of any type within 30 days of screening; clinically significant ocular disease in either eye (e.g. corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for 1 month is not judged safe; central corneal thickness in either eye > 600 µm at screening; any abnormality in either eye preventing reliable applanation tonometry of either eye. Systemic: clinically relevant abnormalities (as determined by the investigator) in laboratory tests at screening which may impact the study; known hypersensitivity or contraindication to BBs (e.g. chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third-degree heart block or congestive heart failure; severe diabetes); clinically significant systemic disease (e.g. uncontrolled diabetes, myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study; participation in any investigational study within 30 days prior to screening; changes of systemic medication that could have an effect on IOP within 30 days prior to screening, or anticipated during the study; women of child-bearing potential who are pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable form of birth control. An adult woman was considered of child-bearing potential unless she was 1 year postmenopausal or 3 months postsurgical sterilization. All females of child-bearing potential must have had a negative urine pregnancy test result at the screening examination and must not have intended to become pregnant during the study **Pretreatment characteristics between groups:** no formal comparison results were shown **Other description of the overall study population at baseline:** not reported
Interventions	• Netarsudil 0.02%, once per day • Netarsudil 0.02%, twice per day • Timolol 0.5%, twice per day
Outcomes	**Primary outcome reported (time points assessed and reported)** • Extend of exposure **Other outcomes reported (time points assessed and reported)** • Adverse events at 12 months • Ocular and systemic safety • Visual acuity at 12 months • Ophthalmologist evaluation using biomicroscope and ophthalmoscope using scoring system
Identification	**Sponsorship source:** Aerie Pharmaceuticals **Country:** USA **Setting:** multicenter **Comments:** ROCKET-3 (a safety trial); data extracted based on the NCT record; early termination due to slow recruitment **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT02246764 **Phase of the trial (phase 2/phase 3/unclear):** phase 3 **Current publication reported findings from > 1 trial:** yes

NCT02246764 (ROCKET-3) *(Continued)*

Year of publication accepted: 2018 (reported)

Year of study initiation (participants screening, enrollment and treatment): 2014

Notes

Peace 2021

Study characteristics

Methods

Study design: randomized controlled trial

Study grouping: parallel group

Unit of randomization: participant

Total number of participants (eyes) randomized: 12 participants

Number of participants (eyes) randomized per group: placebo: 8, netarsudil 0.02%: 4 participants

Total number of participants (eyes) lost to follow-up: 0 participants

Number of participants (eyes) lost to follow-up per group: placebo: 0, netarsudil 0.02%: 0 participants

Power calculation and sample size consideration reported: yes

Planned length of follow-up: 7 days

Actual length of follow-up: 7 days

How missing outcome data were handled: unclear

Was the trial single/double/triple-masked: double-masked (article), quadruple-masked (NCT)

Was the trial an equivalence/superiority/non-inferiority study: superiority

Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: ITT

Duration of washout for each drug class before interventions began: 4 weeks for PAs and BBs; 2 weeks for adrenergic agonists (including alfa-agonists); or 5 days for muscarinic agonists and carbonic anhydrase inhibitors (topical or oral formulations)

Participants

Baseline characteristics

Placebo

- *Female, n (%)*: 2 (50%)
- *Age, mean*: 64.5 (SD 5.07) years
- *Age ≥ 65 years, n (%)*: 3 (75%)
- *POAG, n (%)*: 3 (75%)
- *Time since diagnosis to study entry, mean*: 447.8 (SD 265.05) weeks
- *Duration on current ocular hypotensive therapy, mean*: 48.3 (SD 50.91) weeks
- *Number of participants randomized*: 4
- *Number of participants analyzed*: 4

Netarsudil 0.02%, once per day (8-10 p.m.)

- *Female, n (%)*: 4 (50%)
- *Age, mean*: 64.4 (SD 10.23) years

Peace 2021 *(Continued)*

- *Age ≥ 65 years, n (%)*: 5 (62.5)
- *POAG, n (%)*: 8 (100%)
- *Time since diagnosis to study entry, mean*: 356.4 (SD 342.39) weeks
- *Duration on current ocular hypotensive therapy, mean*: 71.3 (SD 141.95) weeks
- *Number of participants randomized*: 8
- *Number of participants analyzed*: 8

Overall

- *Female, n (%)*: 6 (50%)
- *Age, mean*: 64.4 (SD 8.58) years
- *Age ≥ 65 years, n (%)*: 8 (66.7%)
- *POAG, n (%)*: 11 (91.7%)
- *Time since diagnosis to study entry, mean*: 386.8 (SD 309.49) weeks
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 10 (83.3%)
- *Duration on current ocular hypotensive therapy, mean*: 62.1 (SD 110.45) weeks
- *Number of participants randomized*: 12
- *Number of participants analyzed*: 12

Inclusion criteria: aged ≥ 18 years; ocular hypertension or OAG in both eyes; unmedicated IOP > 17 mmHg in 1 or both eyes and < 30 mmHg in both eyes; corrected visual acuity in each eye equivalent to 20/200 or better; able and willing to give signed informed consent and follow study instructions

Exclusion criteria: glaucoma with pseudoexfoliation or pigment dispersion component, history of angle closure, narrow angles; IOP ≥ 30 mmHg; use of ocular medications within 30 days; known hypersensitivity to any component of the test formulations or to medications used routinely during a clinical eye examination; previous eye surgery (other than cataract); ocular trauma within 6 months; clinically significant ocular disease that might interfere with the study; central corneal thickness > 620 µm

Pretreatment characteristics between groups: no statistical comparisons reported (Table 2)

Other description of the overall study population at baseline: women and men were equally distributed in each treatment group, there were more participants aged ≥ 65 years (66.7%) than < 65 years (33.3%), and a higher percentage of participants were black or African American (75.0%) than any other race (25.0%)

Interventions	• Placebo • Netarsudil 0.02%, once per day (8–10 p.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)** • Mean change from baseline in mean nocturnal IOP (defined as mean of 4 nocturnal time points: 9 p.m., 0 midnight, 3 a.m. and 6 a.m.) at day 8/day 9 **Other outcomes reported (time points assessed and reported)** • Mean change from baseline in mean diurnal IOP (defined as mean of 4 diurnal time points: 9 a.m., 12 noon, 3 p.m., 6 p.m.) at day 8/day 9 • Mean change from baseline in mean 24-hour IOP (defined as the mean of all 8 time points) at day 8/day 9 • Mean change from baseline IOP at each post-treatment time point at day 8/day 9 • Mean IOP at each post-treatment time point at day 8/day 9 • Systemic and ocular safety
Identification	**Sponsorship source:** Aerie pharmaceuticals **Country:** USA **Setting:** single-center

Peace 2021 *(Continued)*

Comments: IOP data: mean nocturnal IOP from NCT report; cup–disc ratio

Online trial registration site: ClinicalTrials.gov

Trial registration #: NCT02874846

Phase of the trial (phase 2/phase 3/unclear): phase 2

Current publication reported findings from > 1 trial: no

Year of publication accepted: 2020

Year of study initiation (participants screening, enrollment and treatment): 2016

Notes

Serle 2018 (ROCKET-1)

Study characteristics

Methods

Study design: randomized controlled trial

Study grouping: parallel group

Unit of randomization: participant

Total number of participants (eyes) randomized: 411 participants

Number of participants (eyes) randomized per group: netarsudil: 202, timolol: 209 participants

Total number of participants (eyes) lost to follow-up: 1 participant

Number of participants (eyes) lost to follow-up per group: netarsudil: 0, timolol: 1 participant

Power calculation and sample size consideration reported: yes

Planned length of follow-up: 3 months

Actual length of follow-up: 3 months

How missing outcome data were handled: unclear

Was the trial single/double/triple-masked: double-masked (article), quadruple-masked (NCT)

Was the trial an equivalence/superiority/non-inferiority study: non-inferiority

Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: PP

Duration of washout for each drug class before interventions began: 28 days for BBs, prostaglandins and the dorzolamide-timolol fixed combination; 14 days for alfa- and alfa/beta-agonists, 5 days for miotics and oral or topical carbonic anhydrase inhibitors, and 3 days if participants were receiving no IOP-lowering therapy (based on Serle 2018).

Participants

Baseline characteristics

Netarsudil 0.02%, once per day (p.m.)

- *Female, n (%)*: 114 (56.4)
- *Age, mean*: 65.8 (SD 11.65) years
- *Age ≥ 65 years, n (%)*: 124 (61.4%)
- *POAG, n (%)*: 134 (66.3%)
- *Number of participants randomized*: 202

Serle 2018 (ROCKET-1) *(Continued)*

- *Number of participants analyzed*: 157 (IOP < 27 mmHg)

Timolol 0.5%, twice per day

- *Female, n (%)*: 136 (65.1%)
- *Age, mean*: 64.2 (SD 11.34) years
- *Age ≥ 65 years, n (%)*: 113 (54.1%)
- *POAG, n (%)*: 136 (65.1%)
- *Number of participants randomized*: 209
- *Number of participants analyzed*: 181 (IOP < 27 mmHg)

Overall

- *Female, n (%)*: 250 (60.8%)
- *Age, mean*: 65 (SD 11.5) years
- *Age ≥ 65 years, n (%)*: 237 (57.7%)
- *POAG, n (%)*: 270 (65.7%)
- *Number of participants randomized*: 411
- *Number of participants analyzed*: 338 (IOP < 27 mmHg)

Inclusion criteria: aged 0–2 years or ≥ 18 years; diagnosis of OAG or OHT; unmedicated (post-washout) IOP > 20 mmHg and < 27 mmHg in the study eye at 2 qualification visits; corrected visual acuity in each eye equivalent to 20/200; able and willing to give signed informed consent (parent or guardian consent for children) and follow study instructions

Exclusion criteria: glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure, or narrow angles. Note: previous laser peripheral iridotomy was NOT acceptable; IOP ≥ 27 mmHg (unmedicated) in both eyes (individuals who are excluded for this criterion were not allowed to attempt requalification), or use of > 2 ocular hypotensive medications within 30 days of screening. Note: fixed-dose combinations count as 2 medications; known hypersensitivity to any component of the formulations to be used (benzalkonium chloride, etc.), to topical anesthetics or BBs; previous glaucoma intraocular surgery or glaucoma laser procedures in either eye; refractive surgery in either eye; ocular trauma in either eye within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening; recent or current evidence of ocular infection or inflammation in either eye; current evidence of clinically significant blepharitis, conjunctivitis or history of herpes simplex or zoster keratitis at screening in either eye; ocular medication in either eye of any type within 30 days of screening; clinically significant ocular disease in either eye (e.g. corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for 1 month is not judged safe; central corneal thickness in either eye > 600 µm at screening; any abnormality in either eye preventing reliable applanation tonometry of either eye. Systemic: clinically relevant abnormalities (as determined by the investigator) in laboratory tests at screening which may impact the study; known hypersensitivity or contraindication to BBs (e.g. chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second- or third-degree heart block or congestive heart failure; severe diabetes); clinically significant systemic disease (e.g. uncontrolled diabetes, myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study; participation in any investigational study within 30 days prior to screening; changes of systemic medication that could have an effect on IOP within 30 days prior to screening, or anticipated during the study; women of child-bearing potential who were pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable form of birth control. An adult woman was considered of child-bearing potential unless she was 1 year postmenopausal or 3 months postsurgical sterilization. All females of child-bearing potential must have had a negative urine pregnancy test result at the screening examination and must not have intended to become pregnant during the study

Pretreatment characteristics between groups: no statistical differences (Table 2, Serle 2018)

Other description of the overall study population at baseline: the only characteristic that was statistically significantly different between treatment groups was iris color

Interventions	• Netarsudil 0.02%, once per day (p.m.)

Serle 2018 (ROCKET-1) *(Continued)*

	• Timolol 0.5%, twice per day
Outcomes	**Primary outcome reported (time points assessed and reported)** • Mean IOP at the following time points: 8:00 a.m., 10:00 a.m., and 4:00 p.m. at week 2, week 6, and month 3 visits **Other outcomes reported (time points assessed and reported)** • Safety
Identification	**Sponsorship source:** Aerie Pharmaceuticals **Country:** USA **Setting:** multicenter **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT02207491 **Phase of the trial (phase 2/phase 3/unclear):** phase 3 **Current publication reported findings from > 1 trial:** yes **Year of publication accepted:** 2017 **Year of study initiation (participants screening, enrollment and treatment):** 2014
Notes	ROCKET-1 trial results; primary outcome in participants whose baseline IOP < 27 mmHg (PP analysis)

Sit 2021

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** eyes **Total number of participants (eyes) randomized:** 40 eyes **Number of participants (eyes) randomized per group:** placebo: 20, netarsudil: 20 eyes **Total number of participants (eyes) lost to follow-up:** 4 eyes **Number of participants (eyes) lost to follow-up per group:** placebo: 2, netarsudil: 2 eyes **Power calculation and sample size consideration reported:** yes (analysis plan and published study protocol) **Planned length of follow-up:** 7 days **Actual length of follow-up:** 7 days **How missing outcome data were handled:** missing data were not imputed **Was the trial single/double/triple-masked:** double-masked **Was the trial an equivalence/superiority/non-inferiority study:** superiority **Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis:** mITT

Sit 2021 *(Continued)*

	Duration of washout for each drug class before interventions began: ≥ 4 weeks for prostaglandins and BBs, 2 weeks for alfa-agonists and 5 days for muscarinic agonists and carbonic anhydrase inhibitors
Participants	**Baseline characteristics** Overall • *Female, n (%)*: 14 (70%) • *Age, mean*: 63 (SD 12.5) years • *Age ≥ 65 years, n (%)*: 11 (55%) • *POAG, n (%)*: 5 (25%) • *Number of eyes randomized*: 40 • *Number of eyes analyzed*: 36 **Inclusion criteria:** aged ≥ 18 years; diagnosis of POAG or OHT in both eyes; unmedicated IOP > 20 mmHg and < 30 mmHg in both eyes at first qualification visit; BCVA equivalent to 20/200 Snellen or better; able to give informed consent and follow study instructions **Excluded criteria:** clinically significant ocular disease; pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles; IOP ≥ 30 mmHg in either eye; difference in IOP between eyes > 4 mmHg at qualification visit; use of > 2 ocular hypotensive medications within 30 days of screening; known hypersensitivity to any component of the formulation; previous glaucoma surgery or refractive surgery; keratorefractive surgery in either eye; report of ocular injury in either eye within the 6 months prior to screening or ocular or non-refractive surgery within 3 months prior to screening; recent or current ocular infection or inflammation in either eye; use of ocular medication in either eye of any type within 30 days of screening; mean central corneal thickness > 620 µm in either eye; any abnormality preventing reliable applanation tonometry of either eye; lack of suitable episcleral vein prior to performing episcleral venus pressure measurement (applicable to 1 site only). Systemic: clinically significant abnormalities within 6 weeks prior to screening; clinically significant systemic disease; participation in any investigational study within 60 days prior to screening; use of systemic medication that could have an effect on IOP within 30 days prior to screening; women of child-bearing potential who were pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable form of birth control **Pretreatment differences between groups:** irrelevant for within-person study
Interventions	• Placebo, once per day (8–10 a.m.) • Netarsudil 0.02% once per day (8–10 a.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)** • Change in mean diurnal trabecular outflow facility on day 8 compared with baseline (day 1) defined as the mean of facility measurements at 1 p.m. and 4 p.m. **Other outcomes reported (time points assessed and reported)** • Effect of study drug on IOP and episcleral venus pressure compared with vehicle • Ocular and systemic safety
Identification	**Sponsorship source:** Aerie Pharmaceuticals **Country:** USA **Setting:** multicenter, 2 clinical sites **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT03233308 **Phase of the trial (phase 2/phase 3/unclear):** phase 2

Sit 2021 *(Continued)*

	Current publication reported findings from > 1 trial: no
	Year of publication accepted: 2021
	Year of study initiation (participants screening, enrollment and treatment): 2017
Notes	Within-person study

Tanihara 2013

Study characteristics	
Methods	**Study design:** randomized controlled trial
	Study grouping: parallel group
	Unit of randomization: participant
	Total number of participants (eyes) randomized: 2010 participants
	Number of participants (eyes) randomized per group: placebo: 54; ripasudil 0.1%: 53; ripasudil 0.2%: 54; ripasudil 0.4%: 49 participants
	Total number of participants (eyes) lost to follow-up: 7 participants
	Number of participants (eyes) lost to follow-up per group: placebo: 2; ripasudil 0.1%: 3; ripasudil 0.2%: 2; ripasudil 0.4%: 0 participants
	Power calculation and sample size consideration reported: yes
	Planned length of follow-up: 8 weeks
	Actual length of follow-up: 8 weeks
	How missing outcome data were handled: exclusion
	Was the trial single/double/triple-masked: double-masked
	Was the trial an equivalence/superiority/non-inferiority study: superiority
	Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: mITT
	Duration of washout for each drug class before interventions began: 4 weeks for prostaglandin and sympatholytic, 2 weeks for other antiglaucoma medication
Participants	**Baseline characteristics**
	Placebo, twice per day (9 a.m., 9 p.m.)
	• *Female, n (%)*: 33 (61%) • *Age, mean*: 63 (SD 14) years • *POAG, n (%)*: 25 (46%) • *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 29 (54%) • *Number of participants randomized*: 54 • *Number of participants analyzed*: 52
	Ripasudil 0.1%, twice per day (9 a.m., 9 p.m.)
	• *Female, n (%)*: 26 (49%) • *Age, mean*: 58 (SD 14) years • *POAG, n (%)*: 20 (38%)

Tanihara 2013 *(Continued)*

- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 29 (55%)
- *Number of participants randomized*: 53
- *Number of participants analyzed*: 50

Ripasudil 0.2%, twice per day (9 a.m., 9 p.m.)

- *Female, n (%)*: 35 (65%)
- *Age, mean*: 59 (SD 15) years
- *POAG, n (%)*: 22 (41%)
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 31 (57%)
- *Number of participants randomized*: 54
- *Number of participants analyzed*: 52

Ripasudil 0.4%, twice per day (9 a.m., 9 p.m.)

- *Female, n (%)*: 29 (59%)
- *Age, mean*: 58 (SD 17) years
- *POAG, n (%)*: 20 (41%)
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 32 (65%)
- *Number of participants randomized*: 49
- *Number of participants analyzed*: 49

Overall

- *Female, n (%)*: 123 (59%)
- *Age, mean*: 60 (SD 15)
- *POAG, n (%)*: 87 (41%)
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 121 (58%)
- *Number of participants randomized*: 210
- *Number of participants analyzed*: 203

Inclusion criteria: men or women (excluding women of child-bearing potential who were pregnant, breast-feeding or planning a pregnancy) with POAG or OHT; aged ≥ 20 years; untreated IOP (after washout) ≥ 21 mmHg and IOP differences were within 3 mmHg in ≥ 1 eye at 2 eligibility visits (9 a.m.), 2–14 days apart; untreated IOP was < 35 mmHg in both eyes

Exclusion criteria: people with narrow angles defined as grade 2 or less of the Shaffer classification by gonioscopy or who had undergone ocular surgery (other than cataract surgery > 1 year ago, retinal laser treatment and yttrium–aluminum–garnet laser posterior capsulotomy > 90 days ago, and eyelid surgery > 120 days ago); severe visual field defects or with a corrected visual acuity of worse than 0.3 (decimal fraction) in either eye

During the trial, participants were prohibited from receiving other IOP-lowering agents, receiving any ophthalmic agents (excluding artificial tears) or steroids, wearing contact lenses and changing dosages of any systemic medications that may affect IOP

Pretreatment characteristics between groups: no statistical comparisons are provided in Table 1 of-Tanihara 2013

Other description of the overall study population at baseline: none

Interventions	• Placebo, twice per day (9 a.m., 9 p.m.) • Ripasudil 0.1%, twice per day (9 a.m., 9 p.m.) • Ripasudil 0.2%, twice per day (9 a.m., 9 p.m.) • Ripasudil 0.4%, twice per day (9 a.m., 9 p.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)** • Changes in IOP at the last visit from the baseline at time-matched points

Tanihara 2013 *(Continued)*

	Other outcomes reported (time points assessed and reported) • Adverse events
Identification	**Sponsorship source:** Kowa company, Ltd **Country:** Japan **Setting:** multicenter, 29 clinical centers **Online trial registration site:** www.clinicaltrials.jp **Trial registration #:** JAPIC101015 **Phase of the trial (phase 2/phase 3/unclear):** phase 2a **Current publication reported findings from > 1 trial:** no **Year of publication accepted:** 2013 **Year of study initiation (participants screening, enrollment and treatment):** 2010
Notes	Adverse events that lead to withdrawal from the trial were iron-deficiency anemia (1 in placebo group), retinal tear (1 in placebo group), fracture of the femoral neck (1 in 0.1% group), asthma (in 0.2% and 0.4% groups), photophobia (in 0.1% group)

Tanihara 2015a

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** cross-over **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 28 participants **Number of participants (eyes) randomized per group:** 28 participants **Total number of participants (eyes) lost to follow-up:** 0 participants **Number of participants (eyes) lost to follow-up per group:** 0 participants **Power calculation and sample size consideration reported:** no **Planned length of follow-up:** 24 hours **Actual length of follow-up:** 24 hours **How missing outcome data were handled:** NA **Was the trial single/double/triple-masked:** open-label **Was the trial an equivalence/superiority/non-inferiority study:** equivalence **Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis:** ITT **Duration of washout for each drug class before interventions began:** 4 weeks for prostaglandin and BBs; 2 weeks for other IOP-lowering agents; 5–30 days between cross-over periods
Participants	**Baseline characteristics**

Tanihara 2015a *(Continued)*

	Group C • *Female, n (%)*: 14 (50%) • *Age, mean*: 47 (SD 12) years • *POAG, n (%)*: 7 (25%) • *Number of participants randomized*: 8 **Inclusion criteria:** Japanese men or non-pregnant women diagnosed with POAG or OHT, aged 20–64 years; untreated or post-washout IOP levels ≥ 21 mmHg in 1 or both eyes at the screening visit **Exclusion criteria:** people with ocular disease (other than POAG or OHT) or ocular surgery (other than eyelid surgery performed < 120 days prior to screening); severe visual field defects or with a corrected visual acuity of worse than decimal visual acuity 0.3 (commensurate with 0.5 logMAR); people with IOP ≥ 30 mmHg excluded in terms of safety concerns During the study, participants were prohibited from receiving other IOP-lowering medications, any ophthalmic medications or steroids, wearing contact lenses and changing dosages of any systemic medications **Pretreatment characteristics between groups:** not relevant
Interventions	**Intervention characteristics** • Placebo, twice per day (9 a.m. and 9 p.m.) • K115 (ripasudil) 0.2%, twice per day (9 a.m. and 9 p.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)** • IOP reduction **Other outcomes reported (time points assessed and reported)** • Safety (ophthalmologic findings and physiologic parameters)
Identification	**Sponsorship source:** sponsored by Kowa Company, Ltd, Nagoya, Japan. Sponsor participated in study design, conducting the study, data collection, data management, data analysis, review and approval of the manuscript **Country:** Japan **Setting:** 3 clinical pharmacology facilities **Online trial registration site:** www.clinicaltrials.jp **Trial registration #:** study no. 090708 **Phase of the trial (phase 2/phase 3/unclear):** phase 2 **Current publication reported findings from > 1 trial:** no **Year of publication accepted:** 2014 **Year of study initiation (participants screening, enrollment and treatment):** 2009
Notes	A phase 2, cross-over, 3-arm trial of ripasudil 0.2%, 0.4% vs placebo. Only data from group C in dosing period 1 (placebo) and 2 (0.2%) are eligible for inclusion.

Tanihara 2015b

Study characteristics	

Tanihara 2015b *(Continued)*

Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 208 participants **Number of participants (eyes) randomized per group:** timolol: 104, ripasudil + timolol: 104 participants **Total number of participants (eyes) lost to follow-up:** 6 participants **Number of participants (eyes) lost to follow-up per group:** timolol: 4, ripasudil + timolol: 2 participants **Power calculation and sample size consideration reported:** yes **Planned length of follow-up:** 8 weeks **Actual length of follow-up:** 8 weeks **How missing outcome data were handled:** unclear **Was the trial single/double/triple-masked:** double-masked **Was the trial an equivalence/superiority/non-inferiority study:** equivalence **Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis:** ITT **Duration of washout for each drug class before interventions began:** none but a 4-week of run-in period with the intervention medication was applied
Participants	**Baseline characteristics** Timolol 0.5%, twice per day (9 a.m. and 9 p.m.) • *Female, n (%)*: 51 (49%) • *Age, mean*: 60 (SD 13) years • *POAG, n (%)*: 48 (46.2%) • *Number of participants randomized*: 104 • *Number of participants analyzed*: 104 Ripasudil 0.4% + timolol 0.5% (FDC), twice per day (9 a.m. and 9 p.m.) • *Female, n (%)*: 52 (50%) • *Age, mean*: 62 (SD 12) years • *POAG, n (%)*: 50 (48.1%) • *Number of participants randomized*: 104 • *Number of participants analyzed*: 104 Overall • *Female, n (%)*: 103 (49.5%) • *Age, mean*: 61 (SD 12.5) years • *POAG, n (%)*: 98 (47.1%) • *Number of participants randomized*: 208 • *Number of participants analyzed*: 208 **Inclusion criteria:** men or women with POAG or OHT; aged ≥ 20 years; IOP after run-in periods (treated with timolol, 0.5%, twice per day or latanoprost, 0.005%, once per day for ≥ 4 weeks) ≥ 18 mmHg, IOP

Tanihara 2015b *(Continued)*

	difference within 3 mmHg in ≥ 1 eye at 2 eligibility visits (9 a.m.) 2–14 days apart, and treated IOP < 35 mmHg in both eyes **Exclusion criteria:** people with narrow angles defined as grade 2 or less by the Shaffer classification by gonioscopy or who had undergone ocular surgery (other than cataract surgery > 1 year ago, retinal laser treatment or neodymium-doped yttrium aluminum garnet laser posterior capsulotomy > 90 days ago, and eyelid surgery > 120 days ago) in either eye; severe visual field defects or a corrected visual acuity of worse than 20/70 in either eye **Pretreatment characteristics between groups:** no significant differences in table 1 of Tanihara 2015b
Interventions	• Timolol 0.5%, twice per day (9 a.m. and 9 p.m.) • Ripasudil 0.4% + timolol 0.5% (FDC), twice per day (9 a.m. and 9 p.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)** • Changes in IOP at weeks 4, 6 and 8 from baseline (week 0) at time-matched points (9 a.m. and 11 a.m.) **Other outcomes reported (time points assessed and reported)** • Changes in IOP before instillation and 2 hours after instillation at weeks 2, 4, 6 and 8 • Safety: adverse events, adverse drug reactions, ophthalmologic findings except IOP, blood pressure, pulse rate, and hematologic and biochemical tests
Identification	**Sponsorship source:** Kowa Company **Country:** Japan **Setting:** multicenter (29 Japanese clinical centers) **Online trial registration site:** www.clinicaltrials.jp **Trial registration #:** JAPIC111701 **Phase of the trial (phase 2/phase 3/unclear):** phase 3 **Current publication reported findings from > 1 trial:** yes **Year of publication accepted:** 2015 **Year of study initiation (participants screening, enrollment and treatment):** 2011
Notes	Data extracted for K-115 (ripasudil) + timolol vs placebo + timolol

Tanihara 2015c

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 205 participants **Number of participants (eyes) randomized per group:** placebo + latanoprost: 103, ripasudil + latanoprost: 102 participants **Total number of participants (eyes) lost to follow-up:** 9 participants

Tanihara 2015c *(Continued)*

Number of participants (eyes) lost to follow-up per group: placebo + latanoprost: 6, ripasudil + latanoprost: 3 participants

Power calculation and sample size consideration reported: yes

Planned length of follow-up: 8 weeks

Actual length of follow-up: 8 weeks

How missing outcome data were handled: unclear

Was the trial single/double/triple-masked: double-masked

Was the trial an equivalence/superiority/non-inferiority study: equivalence

Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: ITT

Duration of washout for each drug class before interventions began: none but a 4-week run-in period for latanoprost was applied

Participants	**Baseline characteristics** Placebo, twice per day (9 a.m. and 9 p.m.) + latanoprost 0.005%, once per day • *Female, n (%)*: 50 (48.5%) • *Age, mean*: 63 (SD 10) years • *POAG, n (%)*: 64 (62.1%) • *Number of participants randomized*: 103 • *Number of participants analyzed*: 103 Ripasudil 0.4%, twice per day (9 a.m. and 9 p.m.) + latanoprost 0.005%, once per day • *Female, n (%)*: 55 (53.9%) • *Age, mean*: 64 (SD 10) years • *POAG, n (%)*: 62 (60.8%) • *Number of participants randomized*: 102 • *Number of participants analyzed*: 102 Overall • *Female, n (%)*: 105 (51.2%) • *Age, mean*: 63.5 (SD 10.0) years • *POAG, n (%)*: 126 (61.5%) • *Number of participants randomized*: 205 • *Number of participants analyzed*: 205 **Inclusion criteria:** men or women with POAG or OHT; aged ≥ 20 years; IOP after run-in periods (treated with timolol, 0.5% twice per day or latanoprost, 0.005%, once per day for ≥ 4 weeks) of ≥ 18 mmHg; IOP difference within 3 mmHg in ≥ 1 eye at 2 eligibility visits (9 a.m.) 2–14 days apart, and treated IOP < 35 mmHg in both eyes **Exclusion criteria:** people with narrow angles defined as grade 2 or less by the Shaffer classification by gonioscopy or who had undergone ocular surgery (other than cataract surgery > 1 year ago, retinal laser treatment or neodymium-doped yttrium aluminum garnet laser posterior capsulotomy > 90 days ago, and eyelid surgery > 120 days ago) in either eye; severe visual field defects or a corrected visual acuity of worse than 20/70 in either eye **Pretreatment characteristics between groups:** no significant differences in Table 1 of Tanihara 2015c **Other description of the overall study population at baseline:** NA
Interventions	• Placebo, twice per day (9 a.m. and 9 p.m.) + latanoprost 0.005%, once per day

Tanihara 2015c *(Continued)*

	• Ripasudil 0.4%, twice per day (9 a.m. and 9 p.m.) + latanoprost 0.005%, once per day
Outcomes	**Primary outcome reported (time points assessed and reported)** • Changes in IOP at weeks 4, 6 and 8 from baseline (week 0) at time-matched points (9 a.m. and 11 a.m.) **Other outcomes reported (time points assessed and reported)** • Changes in IOP before instillation and 2 hours after instillation at weeks 2, 4, 6 and 8 • Safety: adverse events, adverse drug reactions, ophthalmologic findings except IOP, blood pressure, pulse rate, and hematologic and biochemical tests
Identification	**Sponsorship source:** Kowa Company **Country:** Japan **Setting:** multicenter (29 Japanese clinical centers) **Online trial registration site:** www.clinicaltrials.jp **Trial registration #:** JAPIC111700 **Phase of the trial (phase 2/phase 3/unclear):** phase 3 **Current publication reported findings from > 1 trial:** yes **Year of publication accepted:** 2015 **Year of study initiation (participants screening, enrollment and treatment):** 2011
Notes	Data extracted for K-115 (ripasudil) + latanoprost vs placebo + latanoprost

Walters 2019 (MERCURY-2)

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study grouping:** parallel group **Unit of randomization:** participant **Total number of participants (eyes) randomized:** 750 participants **Number of participants (eyes) randomized per group:** netarsudil: 245, latanoprost: 255, netarsudil/latanoprost: 250 participants **Total number of participants (eyes) lost to follow-up:** 3 participants **Number of participants (eyes) lost to follow-up per group:** netarsudil: 1, latanoprost: 0, netarsudil/latanoprost: 2 participants **Power calculation and sample size consideration reported:** yes **Planned length of follow-up:** 3 months **Actual length of follow-up:** 3 months **How missing outcome data were handled:** missing data were imputed using Markov Chain Monte Carlo multiple imputation techniques **Was the trial single/double/triple-masked:** double-masked

Walters 2019 (MERCURY-2) *(Continued)*

Was the trial an equivalence/superiority/non-inferiority study: superiority

Extracted outcome results were based on ITT/mITT/CC/PP/PT analysis: ITT

Duration of washout for each drug class before interventions began: 4 weeks for PAs or BBs, 2 weeks for adrenergic agonists and 5 days for muscarinic agonists or carbonic anhydrase inhibitors

Participants

Baseline characteristics

Netarsudil 0.02%, once per day (p.m.)

- *Female, n (%)*: 153 (60%)
- *Age, mean*: 64.5 (SD 10.58) years
- *Age ≥ 65 years, n (%)*: 146 (57.3%)
- *POAG, n (%)*: 187 (73.3%)
- *Time since diagnosis to study entry, mean*: 339.7 (SD 360.49) weeks
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 161 (63.1%)
- *Duration on current ocular hypotensive therapy, mean*: 138.7 (SD 197.94) weeks
- *Number of participants randomized*: 255
- *Number of participants analyzed*: 228

Latanoprost 0.005%, once per day (p.m.)

- *Female, n (%)*: 144 (57.6%)
- *Age, mean*: 64.3 (SD 11.41) years
- *Age ≥ 65 years, n (%)*: 138 (55.2%)
- *POAG, n (%)*: 171 (68.4%)
- *Time since diagnosis to study entry, mean*: 360 (SD 380.51) weeks
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 167 (66.8%)
- *Duration on current ocular hypotensive therapy, mean*: 146 (SD 211.98) weeks
- *Number of participants randomized*: 250
- *Number of participants analyzed*: 236

Netarsudil 0.02%/latanoprost 0.005% (FDC), once per day (p.m.)

- *Female, n (%)*: 152 (62%)
- *Age, mean*: 64.2 (SD 11.81) years
- *Age ≥ 65 years, n (%)*: 127 (51.8%)
- *POAG, n (%)*: 172 (70.2%)
- *Time since diagnosis to study entry, mean*: 317.5 (SD 325.84) weeks
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 159 (64.9%)
- *Duration on current ocular hypotensive therapy, mean*: 158.8 (SD 227.23) weeks
- *Number of participants randomized*: 245
- *Number of participants analyzed*: 228

Overall

- *Female, n (%)*: 449 (59.9%)
- *Age, mean*: 64.3 (SD 11.26) years
- *Age ≥ 65 years, n (%)*: 411 (54.8%)
- *POAG, n (%)*: 530 (70.67%)
- *Time since diagnosis to study entry, mean*: 339.2 (SD 187.1)
- *Receiving a glaucoma medication within 30 days of baseline screening, n (%)*: 487 (64.9%)
- *Duration on current ocular hypotensive therapy, mean*: 147.7 (SD 212.4) weeks
- *Number of participants randomized*: 750
- *Number of participants analyzed*: 692

Walters 2019 (MERCURY-2) *(Continued)*

	Inclusion criteria: ≥ 18 years (≥ 19 years in Canada); diagnosis of OAG or OHT in both eyes; unmedicated IOP > 20 mmHg and < 36 mmHg in both eyes at 2 qualification visits; BCVA equivalent to 20/200 Snellen or better; able to give informed consent and follow study instructions **Excluded criteria:** clinically significant ocular disease; pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure or narrow angles; unmedicated IOP ≥ 36 mmHg in either eye or use of > 2 ocular hypotensive medications within 30 days of screening; known hypersensitivity to any component of the formulation or latanoprost; previous glaucoma surgery or refractive surgery; ocular trauma within 6 months prior to screening; any ocular surgery or non-refractive laser treatment within 3 months prior to screening; recent or current ocular infection or inflammation in either eye; use of ocular medication in either eye of any type within 30 days of screening and throughout of the study; mean central corneal thickness > 620 µm at screening in either eye; any abnormality preventing reliable applanation tonometry of either eye. Systemic: clinically significant abnormalities in laboratory tests at screening; clinically significant systemic diseases; participation in any investigational study within 60 days prior to screening; systemic medication that could have had a substantial effect on IOP within 30 days prior to screening, or anticipated to be used during the study; women of child-bearing potential who were pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable form of birth control **Pretreatment characteristics between groups:** baseline demographics similar across the 3 treatment arms (Table 1 of Walters 2019 (MERCURY-2)) **Other description of the overall study population at baseline:** 91.3% of participants completed 3 months of treatment (netarsudil: 90.2%, latanoprost: 89.4%, netarsudil/latanoprost: 94.4%)
Interventions	• Netarsudil 0.02%, once per day (p.m.) • Latanoprost 0.005%, once per day (p.m.) • Netarsudil 0.02%/latanoprost 0.005% (FDC), once per day (p.m.)
Outcomes	**Primary outcome reported (time points assessed and reported)** • Mean IOP at 8 a.m., 10 a.m., and 4 p.m. at week 2, week 6 and month 3 **Other outcomes reported (time points assessed and reported)** • Mean diurnal IOP, mean change and mean percent change from diurnally adjusted (time-consistent) baseline IOP, and percentages of participants achieving prespecified thresholds for mean, mean change and mean percent change in mean diurnal IOP • Ocular and systemic adverse events during the 3-month treatment period
Identification	**Sponsorship source:** Aerie Pharmaceuticals **Country:** USA and Canada **Setting:** 60 active sites **Online trial registration site:** ClinicalTrials.gov **Trial registration #:** NCT02674854 **Phase of the trial (phase 2/phase 3/unclear):** phase 3 **Current publication reported findings from > 1 trial:** no **Year of publication accepted:** 2019 **Year of study initiation (participants screening, enrollment and treatment):** 2016
Notes	IOP data were extracted from ClinicalTrials.gov

BB: beta-blocker; BCVA: best-corrected visual acuity; CC: complete case; ETDRS: Early Treatment Diabetic Retinopathy Study; FDC: fixed-dose compound; IOP: intraocular pressure; ITT: intention to treat; mITT: modified intention to treat; OAG: open-angle glaucoma; OHT:

ocular hypertension; PA: prostaglandin analog; POAG: primary open-angle glaucoma; PP: per protocol; PT: per treatment; ROKi: Rho kinase inhibitor; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dubiner 2014	Ineligible study design: dose-finding study
Inazaki 2017	Ineligible study design: observational study
Komizo 2019	Ineligible study design: observational study
Kopczynski 2018	Ineligible study design: review article
NCT02173223	Ineligible study population: people with uncontrolled advanced glaucoma with prior failed trabeculectomy or tube shunt
NCT03808688	Ineligible study design: observational study
Sakamoto 2019	Ineligible study design: observational study
Tanihara 2016	Ineligible study design: observational study
UMIN000026228	Ineligible study design: observational study
Weiss 2013	Ineligible intervention: not the dosage of interest

Characteristics of studies awaiting classification *[ordered by study ID]*

CTRI/2018/04/013091

Methods	Randomized, parallel group, active controlled trial Method of generating randomization sequence: computer-generated randomization Method of allocation concealment: sequentially numbered, sealed, opaque envelopes Masking: participant and investigator (double-masked)
Participants	**Inclusion criteria:** people with IOP 22–30 mmHg at time of screening in any 1 eye. In case both eyes are affected then the eye fulfilling the criteria will be considered for the evaluations. If both eyes fulfill the criteria, then the right eye will be considered for the study; voluntary willingness of person to give written informed consent prior to participation in trial **Exclusion criteria:** women who are not using an effective means of birth control or who are pregnant or breast-feeding; any severe or advanced cases of glaucoma; Shaffer angle grade < 2 in either eye (range, 0 [complete or partial closure] to 3 [wide open angle, > 20]), as measured by gonioscopy; people who are blind or have a single eye; severe central visual field loss in either eye measured by perimetry; cup–disk ratio > 0.80; scheduled to undergo eye surgery during the study; history of/current chronic, recurrent or severe inflammatory eye disease (e.g. scleritis, uveitis, herpes keratitis) or current other severe ocular pathology (including severe dry eye) that would affect the conduct of the study; history of ocular trauma or any other intraocular surgery within the past 6 months in either eye; current/history of ocular infection or inflammation within the past 3 months as determined by patient history or eye examination, or both
Interventions	• Ripasudil hydrochloride hydrate eye drops 0.4% w/v: 1 drop in the affected eye twice per day for 90 days

CTRI/2018/04/013091 *(Continued)*

	• Timolol maleate eye drops 0.5% w/v: 1 drop into the affected eye twice per day for 90 days
Outcomes	**Primary outcome** • Mean reduction in IOP from baseline to end of study visit. Time point: day 0 and day 90 **Secondary outcome** • Mean reduction in the phasing of IOP from baseline to end of study visit. Time point: day 0 and day 90
Notes	Phase 3; date completed: 12 June 2018

CTRI/2020/01/022619

Methods	Randomized, parallel group, active controlled trial Method of generating randomization sequence: computer-generated randomization Method of allocation concealment: sequentially numbered, sealed, opaque envelopes Masking: participant and investigator (double-masked)
Participants	**Inclusion criteria:** men and women aged 18–65 years; newly diagnosed primary open-angle glaucoma/ocular hypertension in 1 or both eyes confirmed by Goldmann applanation tonometry; IOP 22–27 mmHg at time of screening in any 1 eye. In case both the eyes of a single subject are affected then the eye fulfilling the criteria will be considered for the evaluations. If both eyes are fulfilling the criteria, then the right eye will be considered for the study; visual acuity ≥ 6/60; willingness to give written informed consent prior to participation in trial **Exclusion criteria:** any of the following. Ophthalmic: any severe or advanced cases of glaucoma; Shaffer angle grade ≤ 2 in either eye, as measured by gonioscopy; with pseudoexfoliation or pigment dispersion component glaucoma; blind or have 1 eye; severe central visual field loss in either eye measured by perimetry; cup–disk ratio > 0.80; current or history within 3 months prior to baseline of significant ocular disease, e.g. corneal edema, uveitis, ocular infection or ocular trauma in either eye; current corneal abnormalities that would prevent accurate IOP readings with the Goldmann applanation tonometer; history of any ocular surgery in either eye (e.g. peripheral iridotomy, glaucoma incisional or laser surgery, refractive surgery) or are planning to undergo any ocular surgery during the study period; central corneal thickness > 600 mm in either eye; history of clinically relevant or progressive retinal disease such as retinal degeneration, diabetic retinopathy or retinal detachment; contact lens user; contraindication or hypersensitivity to any component of study medication; history of chronic use of any ocular medication; local administration of corticosteroids injections in the eye. Others: use within 1 month prior to baseline of systemic corticosteroid or high-dose salicylate therapy or oral carbonic anhydrase inhibitor; pregnant, breast-feeding or planning a pregnancy; of child-bearing potential who do not agree to utilize an adequate form of birth control; history of CVS, hepatic, psychiatric, cancer or renal diseases that could be considered significant for enrollment in the study; history of bronchial asthma, bronchial hyper-reactivity or severe COPD that would preclude the safe administration of a topical beta-blocker; people receiving high-dose (> 1 g per day) salicylate, topical as well as oral beta-blockers, alpha agonists and blockers, angiotensin-converting enzyme inhibitors and calcium channel blockers, systemic administration of corticosteroids or immunosuppressive agents; participation in any clinical study within 30 days prior to entry into the study; unwilling to comply with the study protocol and does not provide written informed consent to participation; with type 1 and uncontrolled type 2 diabetes mellitus (i.e. defined as glycosylated hemoglobin > 7%)
Interventions	• Netarsudil ophthalmic solution 0.02% w/v: 1 drop in affected eye twice per day for 90 days • Timolol maleate eye drops 0.5% w/v: 1 drop in affected eye twice per day for 90 days

CTRI/2020/01/022619 *(Continued)*

Outcomes	**Primary outcome** • Mean reduction in IOP at end of 12 weeks of treatment compared to baseline at 9 a.m., 11 a.m. and 5 p.m.; time point: day 0 and day 84 **Secondary outcomes** • Mean reduction in IOP at end of 4 weeks of treatment compared to baseline; mean reduction in IOP at end of 8 weeks of treatment compared to baseline; assessment of safety (comparison of incidence of treatment-emergent adverse event) and change in ophthalmological parameters; assessment of tolerability of investigational product based on incidence of adverse events and serious adverse events; changes in laboratory values; time point: days 0, 28 and 56
Notes	Phase 3

NCT03284853

Methods	Randomized parallel trial Masking: participant, care provider, investigator (triple-masked)
Participants	**Inclusion criteria:** aged ≥ 18 years; diagnosis of open-angle glaucoma or ocular hypertension; participants insufficiently controlled or considered in need for combination therapy; medicated IOP ≥ 17 mmHg and < 28 mmHg in both eyes at screening visit; unmedicated (post-washout) IOP > 20 mmHg in 1 or both eyes and < 36 mmHg in both eyes at 2 qualification visits. At second qualification visit to have IOP > 17 mmHg in 1 or both eyes and < 36 mmHg in both eyes. If only 1 eye qualifies at second qualification visit it MUST be the same eye qualified on the first visit (this will be known as the study eye); best corrected visual acuity +1.0 logMAR or better; willing and able to give informed consent and follow instructions; women must be either of non-child-bearing potential, or women with child-bearing potential and men with reproductive potential must be willing to practice acceptable methods of birth control during study; women of child-bearing potential must have a negative urine pregnancy test within 7 days of first dose of study treatment and agree to use highly effective birth control from time of randomization and for 3 months after last dose of study medication; men with a female partner of child-bearing potential must have either had a prior vasectomy or agree to use effective birth control from time of randomization and for 3 months following the last dose of study medication; in France, a person will be eligible for inclusion only if either affiliated to or as a beneficiary of a social security number **Exclusion criteria:** ophthalmic: clinically significant ocular disease which might interfere with interpretation of the study results, including people with glaucomatous damage so severe that washout of ocular hypotensive medication for ≥ 4 weeks would not be judged as safe; pseudoexfoliation or pigment dispersion glaucoma, history of narrow angles or angle closure glaucoma. Previous laser peripheral iridotomy is not permitted; IOP (note: fixed-dose combinations, for the purpose of this exclusion criterion count as 1 medication); however, people currently taking 2 fixed-dose combination products are excluded; treatment-naïve people; prior treatment with GANFORT topical eye drops, where person's IOP did not achieve target IOP and was considered a failure or an insufficient response; currently (prior to screening visit) being treated with GANFORT; known hypersensitivity to any component of the investigational formulations to be used; previous glaucoma intraocular surgery; refractive surgery in either eye; ocular trauma within 6 months prior to screening, or ocular surgery or non-refractive laser treatment within 3 months prior to screening; recent or current evidence of ocular infection or inflammation in either eye; use of ocular medication in either eye within 30 days of screening and throughout the study except for permitted ocular medication (which must be the same medication for 30 days prior to screening) as prescribed by the investigator; mean central corneal thickness > 620 µm at screening; any abnormality preventing reliable Goldmann applanation tonometry of either eye. Systemic: clinically significant abnormalities in laboratory tests at screening; known hypersensitivity or contraindication to GANFORT and to beta-blockers; clinically significant systemic disease that might interfere with the study; participation in any investigational study within 30 days prior to screening; systemic medication (includ-

NCT03284853 *(Continued)*

	ing corticosteroids) that could have a substantial effect on IOP which HAVE NOT been maintained at a consistent dose and regimen within 30 days prior to screening, and are anticipated to change in dose or regimen (or both) during the study; use of topical steroids containing medications on the face or in or around the eyes; women of child-bearing potential who are pregnant, breast-feeding, planning a pregnancy or not using a medically acceptable and highly effective form of birth control; vulnerable people such as minors, adults under legal protection or unable to express their consent; people deprived of liberty or people subject to psychiatric care
Interventions	• Netarsudil 0.02%/latanoprost 0.005% PG-324 ophthalmic solution; 1 drop per day to each eye for 180 days • GANFORT (bimatoprost 0.03%/timolol 0.5%) ophthalmic solution; 1 drop per day to each eye for 180 days
Outcomes	**Primary outcome** • Mean diurnal IOP by Goldmann applanation tonometry at day 90 **Secondary outcomes** • Assessment of anterior segment tissues by slit lamp biomicroscopy at 6 months • Assessment of posterior segment tissues by dilated ophthalmoscopy at 6 months • Systemic safety of vital signs (heart rate) at 6 months • Systemic safety of vital signs (blood pressure/systolic diastolic at 6 months • Systemic safety clinical laboratory assessments (hematology and clinical chemistry) at 6 months • Assessment of IOP at 6 months
Notes	Phase 3; date completed: 6 November 2020; results submitted to ClinicalTrials.gov on 5 November 2021

COPD: chronic obstructive pulmonary disease; CVS: cardiovascular surgical; IOP: intraocular pressure.

Characteristics of ongoing studies *[ordered by study ID]*

JapicCTI-194920

Study name	A comparison study on WP-1303 and ripasudil ophthalmic solution in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OH)
Methods	Study type: interventional Study design: multicenter, randomized, single-masked, parallel-group
Participants	**Inclusion criteria:** men and women with POAG or OHT; IOP < 35 mmHg for both eyes; 1 eye is ≥ 21 mmHg; aged > 20 years **Exclusion criteria:** visual acuity < 0.3; presence of active eye disease (e.g. uveitis, ocular infection, severe dry eye); pregnant or lactating women or women who desire to be pregnant; people judged inappropriate to participate in the study by investigator or subinvestigator
Interventions	• WP-1303 • Ripasudil hydrochloride hydrate
Outcomes	**Primary outcomes** • Efficacy: IOP • Safety: adverse event and adverse drug reaction **Secondary outcome**

JapicCTI-194920 *(Continued)*	
	• Efficacy: IOP
Starting date	6 September 2019
Contact information	Wakamoto Pharmaceutical Co., Ltd. Clinical Development. Address: 2-2, Nihonnbashi Honcho 2-chome, Chuo-ku Tokyo. Telephone: +81-3-3279-0370
Notes	Study terminated on 25 December 2019.

UMIN000019017	
Study name	Efficacy of Rho-kinase inhibitor ophthalmic solution on bleb formation after trabeculectomy, a randomized parallel study
Methods	Basic design: parallel Randomization: randomized Randomization unit: participants Masking: open-label
Participants	**Inclusion criteria:** men and women who have trabeculectomy as the therapy of open-angle glaucoma which is not sufficiently controlled; age ≥ 20 years **Key exclusion criteria:** people who had intraocular surgeries within 6 months; IOP unable to be measured by Goldmann applanation tonometer; conjunctival surgeries (including glaucoma surgeries); allergy to the ingredients of Rho-kinase inhibitor ophthalmic solution; used Rho-kinase inhibitor ophthalmic solution before surgery; pregnant or breast-feeding; people unsuitable for study according to doctor.
Interventions	• Ripasudil 0.4% ophthalmic solution twice per day for 3 months • No treatment
Outcomes	**Primary outcomes** • Transition of IOP for 12 months after surgery • Bleb scoring at 6 months after surgery
Starting date	1 November 2015 (no longer recruiting); last follow-up date: 30 September 2022
Contact information	okumic@hiroshima-u.ac.jp
Notes	Study enrolled 112 participants; results of the study were unpublished.

IOP: intraocular pressure; OHT: ocular hypertension; POAG: primary open-angle glaucoma.

RISK OF BIAS

Legend: Low risk of bias High risk of bias Some concerns

Risk of bias for analysis 1.1 Mean intraocular pressure (IOP) changes from baseline

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Netarsudil 0.02% once per day						
Araie 2021	✓	✓	✓	✓	✓	✓
Peace 2021	✓	✓	✓	✓	✓	✓
Sit 2021	✓	~	✓	✓	✓	~
Subgroup 1.1.2 Ripasudil 0.4% twice per day						
Tanihara 2013	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.2 Mean IOP changes from baseline: sensitivity analysis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.2.1 Netarsudil 0.02% once per day						
Araie 2021	✓	✓	✓	✓	✓	✓
Peace 2021	✓	✓	✓	✓	✓	✓
Subgroup 1.2.2 Ripasudil 0.4% twice per day						
Tanihara 2013	✓	~	✓	✓	✓	~

Risk of bias for analysis 2.1 Mean IOP changes from baseline

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Kahook 2019 (ROCKET-2)	✓	✗	✗	✓	✓	✗
Khouri 2019 (ROCKET-4)	✓	✗	✗	✓	✓	✗
Serle 2018 (ROCKET-1)	✓	✗	✗	✓	✓	✗

Risk of bias for analysis 3.1 Mean IOP changes from baseline (mmHg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Asrani 2019 (MERCURY-1)	✓	✓	✓	✓	✓	✓
Bacharach 2015	~	✓	✓	✓	✓	~
Lewis 2016	✓	✓	✓	✓	✓	✓
Walters 2019 (MERCURY-2)	✓	✓	✓	✓	✓	✓

DATA AND ANALYSES

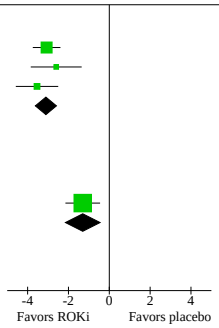
Comparison 1. Rho kinase inhibitor versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mean intraocular pressure (IOP) changes from baseline	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 Netarsudil 0.02% once per day	3	155	Mean Difference (IV, Random, 95% CI)	-3.11 [-3.62, -2.59]
1.1.2 Ripasudil 0.4% twice per day	1	103	Mean Difference (IV, Random, 95% CI)	-1.30 [-2.15, -0.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Mean IOP changes from baseline: sensitivity analysis	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Netarsudil 0.02% once per day	2	119	Mean Difference (IV, Fixed, 95% CI)	-2.96 [-3.56, -2.37]
1.2.2 Ripasudil 0.4% twice per day	1	103	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-2.15, -0.45]
1.3 Total ocular adverse events (per person-month) – incidence risk difference	5		Risk Difference (IV, Random, 95% CI)	0.66 [0.28, 1.03]
1.3.1 Netarsudil 0.02% once per day	4		Risk Difference (IV, Random, 95% CI)	0.86 [0.38, 1.34]
1.3.2 Ripasudil 0.4% twice per day	1		Risk Difference (IV, Random, 95% CI)	0.27 [0.13, 0.41]
1.4 Total ocular adverse events (per person-month): sensitivity analysis	2		Risk Difference (IV, Random, 95% CI)	0.67 [0.55, 0.79]
1.5 Conjunctival hyperemia as adverse event (per person-month)*	5		Risk Difference (IV, Random, 95% CI)	0.46 [0.19, 0.73]
1.5.1 Ripasudil 0.4% twice per day	1		Risk Difference (IV, Random, 95% CI)	0.26 [0.14, 0.38]
1.5.2 Netarsudil 0.02% once per day	4		Risk Difference (IV, Random, 95% CI)	0.79 [0.16, 1.42]
1.6 Ocular pain or irritation as adverse event (per person-month)*	5		Risk Difference (IV, Random, 95% CI)	0.04 [-0.07, 0.15]
1.6.1 Ripasudil 0.4% twice per day	1		Risk Difference (IV, Random, 95% CI)	0.01 [-0.05, 0.07]
1.6.2 Netarsudil 0.02% once per day	4		Risk Difference (IV, Random, 95% CI)	0.08 [-0.14, 0.30]

Analysis 1.1. Comparison 1: Rho kinase inhibitor versus placebo, Outcome 1: Mean intraocular pressure (IOP) changes from baseline

Study or Subgroup	ROKi Mean [mmHg]	ROKi SD [mmHg]	ROKi Total	Placebo Mean [mmHg]	Placebo SD [mmHg]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [mmHg]	Risk of Bias A B C D E F
1.1.1 Netarsudil 0.02% once per day									
Araie 2021 (1)	-4.8	1.82	53	-1.73	1.75	54	58.2%	-3.07 [-3.75 , -2.39]	+ + + + + +
Peace 2021 (2)	-3.5	1.79	8	-0.9	0.13	4	17.1%	-2.60 [-3.85 , -1.35]	+ + + + + +
Sit 2021 (3)	-4.52	1.58	18	-0.98	1.6	18	24.7%	-3.54 [-4.58 , -2.50]	+ ? + + + ?
Subtotal (95% CI)			**79**			**76**	**100.0%**	**-3.11 [-3.62 , -2.59]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 2 (P = 0.52); I² = 0%									
Test for overall effect: Z = 11.79 (P < 0.00001)									
1.1.2 Ripasudil 0.4% twice per day									
Tanihara 2013 (4)	-3.5	2.19	49	-2.2	2.2	54	100.0%	-1.30 [-2.15 , -0.45]	+ ? + + + ?
Subtotal (95% CI)			**49**			**54**	**100.0%**	**-1.30 [-2.15 , -0.45]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.00 (P = 0.003)									
Test for subgroup differences: Chi² = 12.69, df = 1 (P = 0.0004), I² = 92.1%									

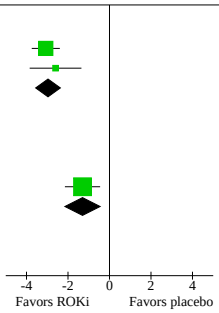


Footnotes
(1) At week 4, mean diurnal IOP
(2) At day 7, mean diurnal IOP
(3) At day 7, mean diurnal IOP; unit of analysis was eye
(4) At week 8, adjusted mean IOP at 9 a.m. (pretreatment)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Rho kinase inhibitor versus placebo, Outcome 2: Mean IOP changes from baseline: sensitivity analysis

Study or Subgroup	ROKi Mean [mmHg]	ROKi SD [mmHg]	ROKi Total	Placebo Mean [mmHg]	Placebo SD [mmHg]	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI [mmHg]	Risk of Bias A B C D E F
1.2.1 Netarsudil 0.02% once per day									
Araie 2021 (1)	-4.8	1.82	53	-1.73	1.75	54	77.2%	-3.07 [-3.75 , -2.39]	+ + + + + +
Peace 2021 (2)	-3.5	1.79	8	-0.9	0.13	4	22.8%	-2.60 [-3.85 , -1.35]	+ + + + + +
Subtotal (95% CI)			**61**			**58**	**100.0%**	**-2.96 [-3.56 , -2.37]**	
Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%									
Test for overall effect: Z = 9.76 (P < 0.00001)									
1.2.2 Ripasudil 0.4% twice per day									
Tanihara 2013 (3)	-3.5	2.19	49	-2.2	2.2	54	100.0%	-1.30 [-2.15 , -0.45]	+ ? + + + ?
Subtotal (95% CI)			**49**			**54**	**100.0%**	**-1.30 [-2.15 , -0.45]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.00 (P = 0.003)									
Test for subgroup differences: Chi² = 9.89, df = 1 (P = 0.002), I² = 89.9%									

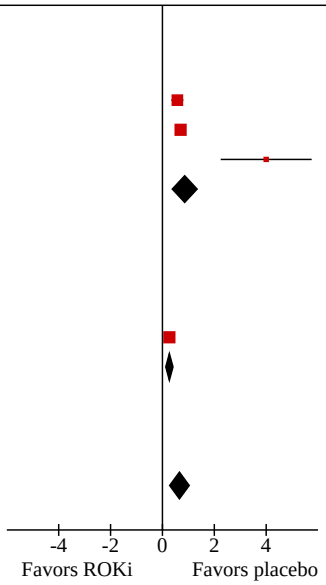


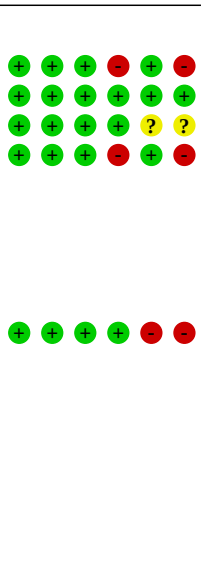
Footnotes
(1) At week 4, mean diurnal IOP
(2) At day 7, mean diurnal IOP
(3) At week 8, adjusted mean IOP at 9 a.m. (pretreatment)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Rho kinase inhibitor versus placebo, Outcome 3: Total ocular adverse events (per person-month) – incidence risk difference

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
1.3.1 Netarsudil 0.02% once per day				
Peace 2021 (1)	0	0		Not estimable
Araie 2021 (2)	0.5758	0.1183	30.4%	0.58 [0.34 , 0.81]
Aerie 2017 (3)	0.7	0.0712	32.8%	0.70 [0.56 , 0.84]
Sit 2021 (1)	4	0.8944	4.1%	4.00 [2.25 , 5.75]
Subtotal (95% CI)			**67.2%**	**0.86 [0.38 , 1.34]**
Heterogeneity: Tau² = 0.12; Chi² = 14.63, df = 2 (P = 0.0007); I² = 86%				
Test for overall effect: Z = 3.51 (P = 0.0004)				
1.3.2 Ripasudil 0.4% twice per day				
Tanihara 2013 (4)	0.2674	0.0712	32.8%	0.27 [0.13 , 0.41]
Subtotal (95% CI)			**32.8%**	**0.27 [0.13 , 0.41]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.76 (P = 0.0002)				
Total (95% CI)			**100.0%**	**0.66 [0.28 , 1.03]**
Heterogeneity: Tau² = 0.11; Chi² = 34.26, df = 3 (P < 0.00001); I² = 91%				
Test for overall effect: Z = 3.40 (P = 0.0007)				
Test for subgroup differences: Chi² = 5.40, df = 1 (P = 0.02), I² = 81.5%				





Footnotes

(1) At day 7 (data from NCT, 5% reporting thereshold)
(2) At day 28 (data from NCT, 0.1% reporting thereshold)
(3) At day 28 (data from NCT, 5% reporting thereshold)
(4) At week 8 (data from article, reporting thereshold unknown)

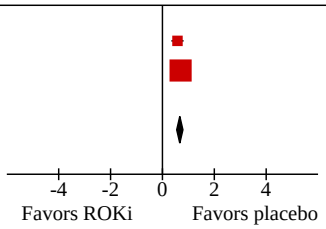
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Rho kinase inhibitor versus placebo, Outcome 4: Total ocular adverse events (per person-month): sensitivity analysis

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
Araie 2021 (1)	0.58	0.12	25.4%	0.58 [0.34 , 0.82]
Aerie 2017 (2)	0.7	0.07	74.6%	0.70 [0.56 , 0.84]
Total (95% CI)			**100.0%**	**0.67 [0.55 , 0.79]**

Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 11.07 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes

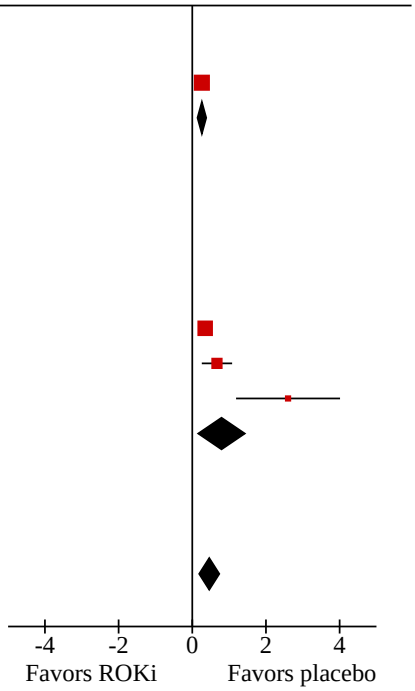
(1) At day 28 (data from NCT, 0.1% reporting thereshold)
(2) At day 28 (data from NCT, 5% reporting thereshold)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Rho kinase inhibitor versus placebo, Outcome 5: Conjunctival hyperemia as adverse event (per person-month)*

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
1.5.1 Ripasudil 0.4% twice per day				
Tanihara 2013 (1)	0.26	0.06	38.6%	0.26 [0.14 , 0.38]
Subtotal (95% CI)			**38.6%**	**0.26 [0.14 , 0.38]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.33 (P < 0.0001)				
1.5.2 Netarsudil 0.02% once per day				
Peace 2021 (2)	0	0		Not estimable
Araie 2021 (3)	0.35	0.08	36.6%	0.35 [0.19 , 0.51]
Aerie 2017 (3)	0.67	0.21	21.3%	0.67 [0.26 , 1.08]
Sit 2021 (2)	2.6	0.72	3.4%	2.60 [1.19 , 4.01]
Subtotal (95% CI)			**61.4%**	**0.79 [0.16 , 1.42]**
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 11.34$, df = 2 (P = 0.003); $I^2 = 82\%$				
Test for overall effect: Z = 2.47 (P = 0.01)				
Total (95% CI)			**100.0%**	**0.46 [0.19 , 0.73]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 13.95$, df = 3 (P = 0.003); $I^2 = 78\%$				
Test for overall effect: Z = 3.31 (P = 0.0009)				
Test for subgroup differences: $Chi^2 = 2.66$, df = 1 (P = 0.10), $I^2 = 62.4\%$				



Footnotes

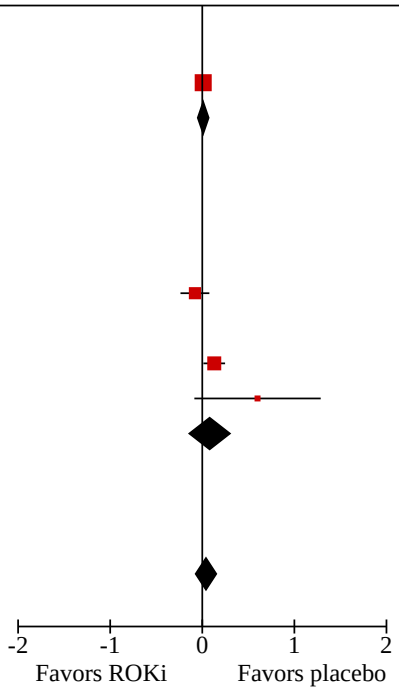
(1) At week 8, 9 a.m.

(2) At day 7

(3) At day 28

Analysis 1.6. Comparison 1: Rho kinase inhibitor versus placebo, Outcome 6: Ocular pain or irritation as adverse event (per person-month)*

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
1.6.1 Ripasudil 0.4% twice per day				
Tanihara 2013 (1)	0.01	0.03	41.9%	0.01 [-0.05 , 0.07]
Subtotal (95% CI)			**41.9%**	**0.01 [-0.05 , 0.07]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.33 (P = 0.74)				
1.6.2 Netarsudil 0.02% once per day				
Aerie 2017 (2)	-0.08	0.08	24.5%	-0.08 [-0.24 , 0.08]
Peace 2021 (3)	0	0		Not estimable
Araie 2021 (2)	0.13	0.06	31.1%	0.13 [0.01 , 0.25]
Sit 2021 (3)	0.6	0.35	2.5%	0.60 [-0.09 , 1.29]
Subtotal (95% CI)			**58.1%**	**0.08 [-0.14 , 0.30]**
Heterogeneity: Tau² = 0.02; Chi² = 6.80, df = 2 (P = 0.03); I² = 71%				
Test for overall effect: Z = 0.71 (P = 0.48)				
Total (95% CI)			**100.0%**	**0.04 [-0.07 , 0.15]**
Heterogeneity: Tau² = 0.01; Chi² = 7.73, df = 3 (P = 0.05); I² = 61%				
Test for overall effect: Z = 0.70 (P = 0.48)				
Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%				



Footnotes

(1) At week 8, 9 a.m

(2) At day 28

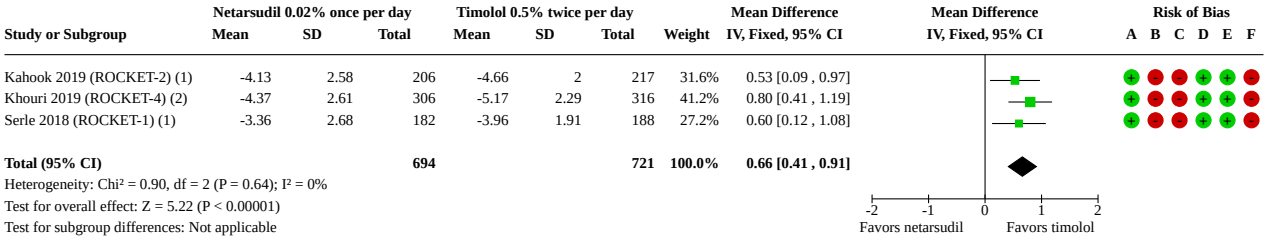
(3) At day 7

Comparison 2. Rho kinase inhibitor versus beta-blocker

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mean IOP changes from baseline	3	1415	Mean Difference (IV, Fixed, 95% CI)	0.66 [0.41, 0.91]
2.2 Total ocular adverse events (per person-month) – incidence risk difference	4		Risk Difference (IV, Random, 95% CI)	0.21 [0.14, 0.27]
2.3 Total ocular adverse events (per person-month) – subgroup analysis by levels of reporting threshold	4		Risk Difference (IV, Random, 95% CI)	0.21 [0.14, 0.27]
2.3.1 Reporting threshold ≥ 3%	2		Risk Difference (IV, Random, 95% CI)	0.22 [0.03, 0.41]
2.3.2 Reporting threshold ≥ 5%	2		Risk Difference (IV, Random, 95% CI)	0.20 [0.14, 0.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Conjunctival hyperemia as adverse event (per person-month)*	4		Risk Difference (IV, Random, 95% CI)	0.07 [0.04, 0.11]
2.5 Ocular pain or irritation as adverse event (per person-month)*	4		Risk Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.02]

Analysis 2.1. Comparison 2: Rho kinase inhibitor versus beta-blocker, Outcome 1: Mean IOP changes from baseline



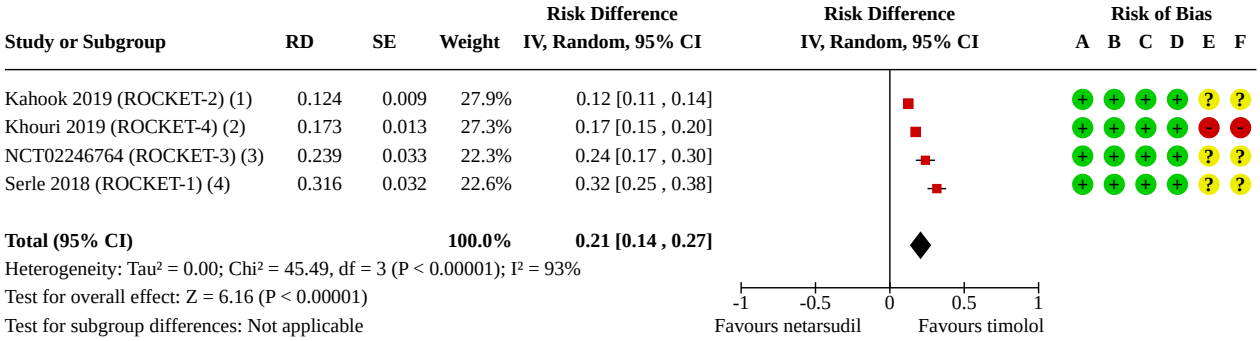
Footnotes

(1) At month 3, mean IOP at 10 a.m., source: ClinicalTrials.gov
(2) At month 3, mean IOP at 10 a.m., source: ClincialTrials.gov

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Rho kinase inhibitor versus beta-blocker, Outcome 2: Total ocular adverse events (per person-month) – incidence risk difference



Footnotes

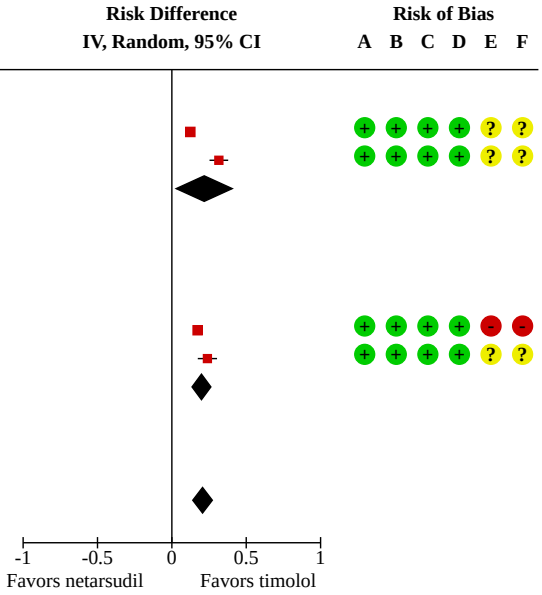
(1) At month 12 (data from article, 3% reporting threshold)
(2) At month 6 (data from article, 5% reporting threshold)
(3) At month 12 (data from NCT, 5% reporting threshold)
(4) At month 3 (data from article, 3% reporting threshold)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Rho kinase inhibitor versus beta-blocker, Outcome 3: Total ocular adverse events (per person-month) – subgroup analysis by levels of reporting threshold

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
2.3.1 Reporting threshold ≥ 3%				
Kahook 2019 (ROCKET-2)	0.124	0.009	27.9%	0.12 [0.11 , 0.14]
Serle 2018 (ROCKET-1)	0.316	0.032	22.6%	0.32 [0.25 , 0.38]
Subtotal (95% CI)			**50.4%**	**0.22 [0.03 , 0.41]**
Heterogeneity: Tau² = 0.02; Chi² = 33.36, df = 1 (P < 0.00001); I² = 97%				
Test for overall effect: Z = 2.27 (P = 0.02)				
2.3.2 Reporting threshold ≥ 5%				
Khouri 2019 (ROCKET-4)	0.173	0.013	27.3%	0.17 [0.15 , 0.20]
NCT02246764 (ROCKET-3)	0.239	0.033	22.3%	0.24 [0.17 , 0.30]
Subtotal (95% CI)			**49.6%**	**0.20 [0.14 , 0.26]**
Heterogeneity: Tau² = 0.00; Chi² = 3.46, df = 1 (P = 0.06); I² = 71%				
Test for overall effect: Z = 6.17 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.21 [0.14 , 0.27]**
Heterogeneity: Tau² = 0.00; Chi² = 45.49, df = 3 (P < 0.00001); I² = 93%				
Test for overall effect: Z = 6.16 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%				

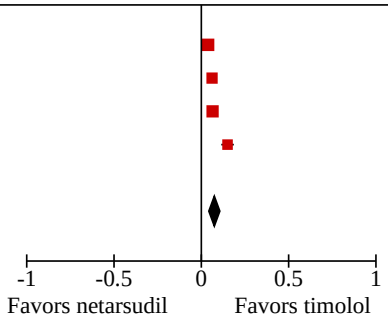


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Rho kinase inhibitor versus beta-blocker, Outcome 4: Conjunctival hyperemia as adverse event (per person-month)*

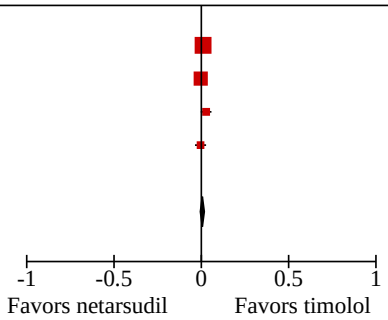
Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
Kahook 2019 (ROCKET-2)	0.0388	0.0045	28.1%	0.04 [0.03 , 0.05]
NCT02246764 (ROCKET-3)	0.0614	0.0139	23.6%	0.06 [0.03 , 0.09]
Khouri 2019 (ROCKET-4)	0.0644	0.0067	27.4%	0.06 [0.05 , 0.08]
Serle 2018 (ROCKET-1)	0.1501	0.0183	20.9%	0.15 [0.11 , 0.19]
Total (95% CI)			**100.0%**	**0.07 [0.04 , 0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 41.21, df = 3 (P < 0.00001); I² = 93%				
Test for overall effect: Z = 4.64 (P < 0.00001)				
Test for subgroup differences: Not applicable				



Analysis 2.5. Comparison 2: Rho kinase inhibitor versus beta-blocker, Outcome 5: Ocular pain or irritation as adverse event (per person-month)*

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
Kahook 2019 (ROCKET-2)	0.01	0.0042	44.6%	0.01 [0.00 , 0.02]
Khouri 2019 (ROCKET-4)	-0.0035	0.0062	34.6%	-0.00 [-0.02 , 0.01]
NCT02246764 (ROCKET-3)	0.0274	0.0156	10.7%	0.03 [-0.00 , 0.06]
Serle 2018 (ROCKET-1)	-0.0045	0.0162	10.1%	-0.00 [-0.04 , 0.03]
Total (95% CI)			**100.0%**	**0.01 [-0.01 , 0.02]**

Heterogeneity: Tau² = 0.00; Chi² = 5.55, df = 3 (P = 0.14); I² = 46%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable



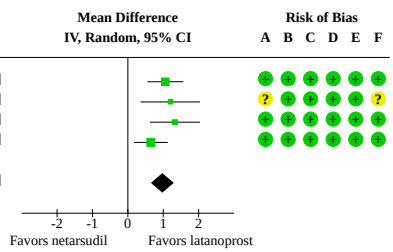
Comparison 3. Rho kinase inhibitor versus prostaglandin analog

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mean IOP changes from baseline (mmHg)	4	1283	Mean Difference (IV, Random, 95% CI)	0.97 [0.67, 1.27]
3.2 Total ocular adverse events (per person-month) – incidence rate difference	4		Risk Difference (IV, Random, 95% CI)	0.29 [0.17, 0.42]
3.3 Conjunctival hyperemia as adverse event (per person-month)*	4		Risk Difference (IV, Random, 95% CI)	0.11 [0.03, 0.19]
3.4 Ocular pain or irritation as adverse event (per person-month)*	4		Risk Difference (IV, Random, 95% CI)	0.02 [0.01, 0.03]

Analysis 3.1. Comparison 3: Rho kinase inhibitor versus prostaglandin analog, Outcome 1: Mean IOP changes from baseline (mmHg)

Study or Subgroup	Netarsudil 0.02% once per day Mean	SD	Total	Latanoprost 0.005% once per day Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Asrani 2019 (MERCURY-1) (1)	-5.49	3.1	244	-6.55	2.54	236	33.0%	1.06 [0.55 , 1.57]
Bacharach 2015 (2)	-5.6	2.07	71	-6.8	3.04	76	12.6%	1.20 [0.36 , 2.04]
Lewis 2016 (3)	-6.22	2.33	78	-7.55	2.1	73	17.5%	1.33 [0.62 , 2.04]
Walters 2019 (MERCURY-2) (1)	-5.1	2.87	255	-5.75	2.6	250	36.9%	0.65 [0.17 , 1.13]
Total (95% CI)			**648**			**635**	**100.0%**	**0.97 [0.67 , 1.27]**

Heterogeneity: Tau² = 0.00; Chi² = 3.13, df = 3 (P = 0.37); I² = 4%
Test for overall effect: Z = 6.36 (P < 0.00001)
Test for subgroup differences: Not applicable



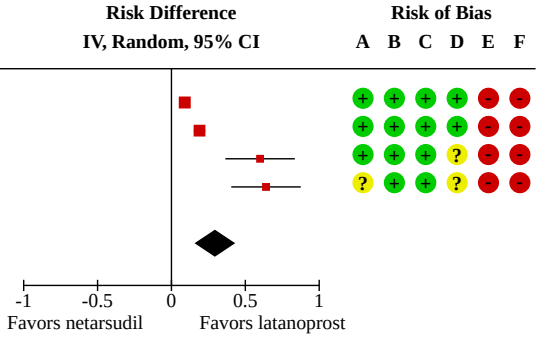
Footnotes
(1) At month 3, mean IOP at 10 a.m., source: ClinicalTrials.gov
(2) At day 28, mean diurnal IOP
(3) At day 28, mean diurnal IOP change, source: ClinicalTrials.gov

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.2. Comparison 3: Rho kinase inhibitor versus prostaglandin analog, Outcome 2: Total ocular adverse events (per person-month) – incidence rate difference

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
Asrani 2019 (MERCURY-1) (1)	0.09	0.01	34.3%	0.09 [0.07 , 0.11]
Walters 2019 (MERCURY-2) (2)	0.19	0.02	33.5%	0.19 [0.15 , 0.23]
Lewis 2016 (3)	0.6	0.12	16.1%	0.60 [0.36 , 0.84]
Bacharach 2015 (3)	0.64	0.12	16.1%	0.64 [0.40 , 0.88]
Total (95% CI)			**100.0%**	**0.29 [0.17 , 0.42]**

Heterogeneity: Tau² = 0.01; Chi² = 55.78, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.47 (P < 0.00001)
Test for subgroup differences: Not applicable



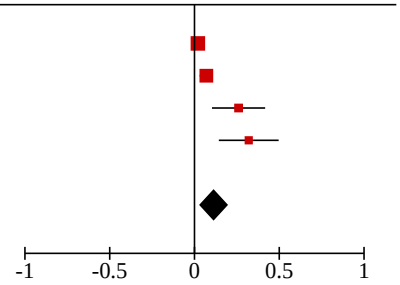
Footnotes
(1) At month 12 (data from Brubaker 2020, 5% reporting thereshold)
(2) At month 3 (5% reporting thereshold)
(3) At day 28 (5% reporting thereshold)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.3. Comparison 3: Rho kinase inhibitor versus prostaglandin analog, Outcome 3: Conjunctival hyperemia as adverse event (per person-month)*

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
Asrani 2019 (MERCURY-1) (1)	0.02	0.005	37.4%	0.02 [0.01 , 0.03]
Walters 2019 (MERCURY-2) (2)	0.07	0.02	34.4%	0.07 [0.03 , 0.11]
Lewis 2016 (3)	0.26	0.08	15.1%	0.26 [0.10 , 0.42]
Bacharach 2015	0.32	0.09	13.0%	0.32 [0.14 , 0.50]
Total (95% CI)			**100.0%**	**0.11 [0.03 , 0.19]**

Heterogeneity: Tau² = 0.00; Chi² = 25.43, df = 3 (P < 0.0001); I² = 88%
Test for overall effect: Z = 2.80 (P = 0.005)
Test for subgroup differences: Not applicable

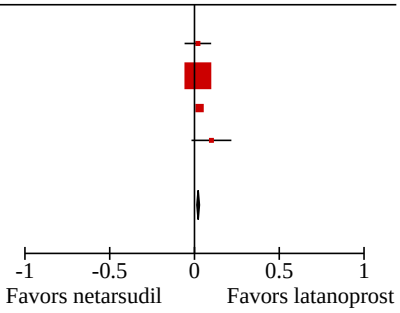


Footnotes
(1) Source: Brubaker 2020, at month 12
(2) At month 3
(3) At day 28

Analysis 3.4. Comparison 3: Rho kinase inhibitor versus prostaglandin analog, Outcome 4: Ocular pain or irritation as adverse event (per person-month)*

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
Lewis 2016 (1)	0.02	0.04	0.9%	0.02 [-0.06 , 0.10]
Asrani 2019 (MERCURY-1) (2)	0.02	0.004	85.1%	0.02 [0.01 , 0.03]
Walters 2019 (MERCURY-2) (3)	0.03	0.01	13.6%	0.03 [0.01 , 0.05]
Bacharach 2015	0.1	0.06	0.4%	0.10 [-0.02 , 0.22]
Total (95% CI)			**100.0%**	**0.02 [0.01 , 0.03]**

Heterogeneity: Tau² = 0.00; Chi² = 2.57, df = 3 (P = 0.46); I² = 0%
Test for overall effect: Z = 5.87 (P < 0.00001)
Test for subgroup differences: Not applicable



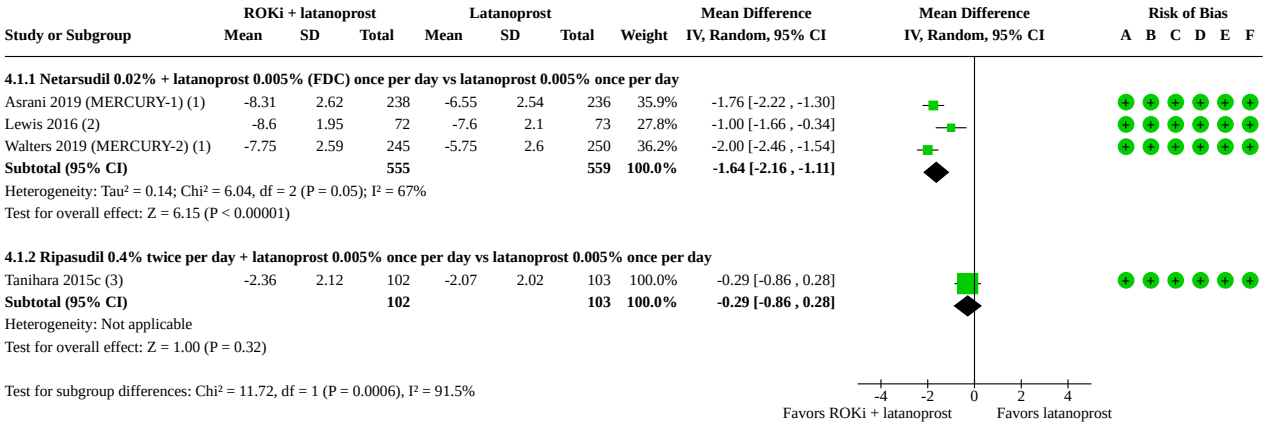
Footnotes
(1) At day 28
(2) Source: Brubaker 2020, at month 12
(3) At month 3

Comparison 4. Rho kinase inhibitor + prostaglandin analog versus prostaglandin analog

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Mean IOP changes from baseline	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1.1 Netarsudil 0.02% + latanoprost 0.005% (FDC) once per day vs latanoprost 0.005% once per day	3	1114	Mean Difference (IV, Random, 95% CI)	-1.64 [-2.16, -1.11]
4.1.2 Ripasudil 0.4% twice per day + latanoprost 0.005% once per day vs latanoprost 0.005% once per day	1	205	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.86, 0.28]
4.2 Total ocular adverse events (per person-month) – incidence rate difference	4		Risk Difference (IV, Random, 95% CI)	0.26 [0.13, 0.40]
4.2.1 Netarsudil 0.02% + latanoprost 0.005% (FDC) once per day vs latanoprost 0.005% once per day	3		Risk Difference (IV, Random, 95% CI)	0.29 [0.11, 0.47]
4.2.2 Ripasudil 0.4% twice per day + latanoprost 0.005% once per day vs latanoprost 0.005% once per day	1		Risk Difference (IV, Random, 95% CI)	0.21 [0.11, 0.31]
4.3 Conjunctival hyperemia as adverse event (per person-month)*	4		Risk Difference (IV, Random, 95% CI)	0.15 [0.03, 0.27]
4.3.1 Netarsudil 0.02% + latanoprost 0.005% (FDC) once per day vs latanoprost 0.005% once per day	3		Risk Difference (IV, Random, 95% CI)	0.10 [0.00, 0.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3.2 Ripasudil 0.4% twice per day + latanoprost 0.005% once per day vs latanoprost 0.005% once per day	1		Risk Difference (IV, Random, 95% CI)	0.24 [0.16, 0.32]
4.4 Ocular pain or irritation as adverse event (per person-month)*	4		Risk Difference (IV, Random, 95% CI)	0.03 [-0.00, 0.07]
4.4.1 Netarsudil 0.02% + latanoprost 0.005% (FDC) once per day vs latanoprost 0.005% once per day	3		Risk Difference (IV, Random, 95% CI)	0.05 [0.01, 0.09]
4.4.2 Ripasudil 0.4% twice per day + latanoprost 0.005% once per day vs latanoprost 0.005% once per day	1		Risk Difference (IV, Random, 95% CI)	-0.02 [-0.06, 0.02]

Analysis 4.1. Comparison 4: Rho kinase inhibitor + prostaglandin analog versus prostaglandin analog, Outcome 1: Mean IOP changes from baseline



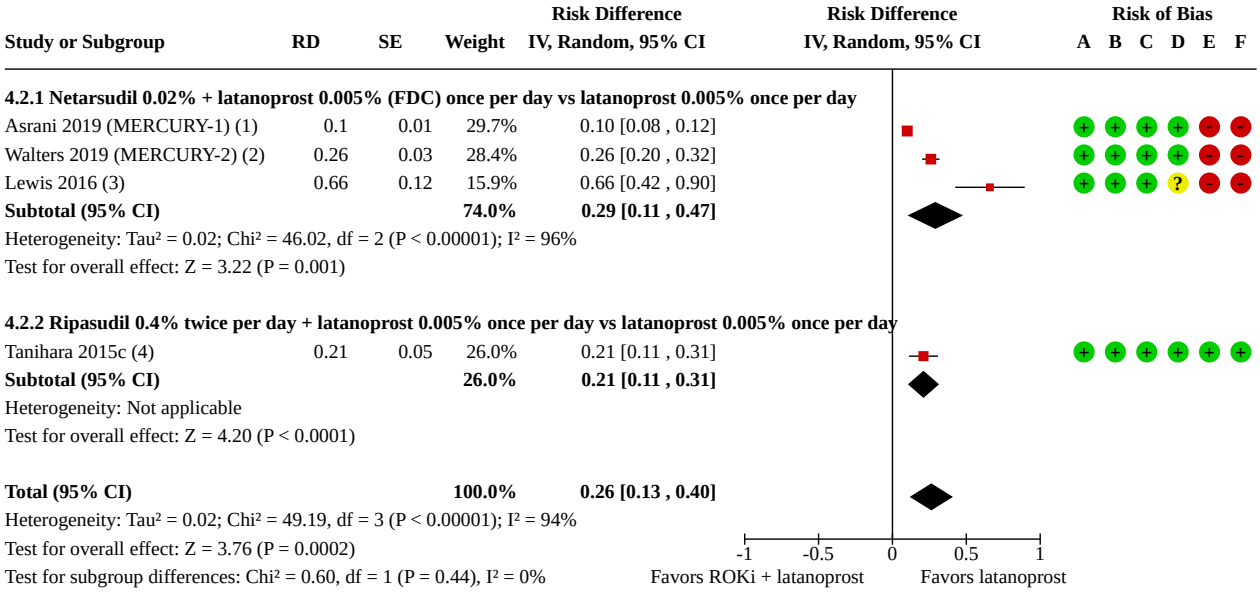
Footnotes

(1) At month 3, IOP value at 10 a.m., source: ClinicalTrials.gov
(2) At day 28, mean diurnal IOP, source: ClinicalTrials.gov
(3) At week 8, pretreatment IOP at 9 a.m., extrapolated from graph

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.2. Comparison 4: Rho kinase inhibitor + prostaglandin analog versus prostaglandin analog, Outcome 2: Total ocular adverse events (per person-month) – incidence rate difference



Footnotes

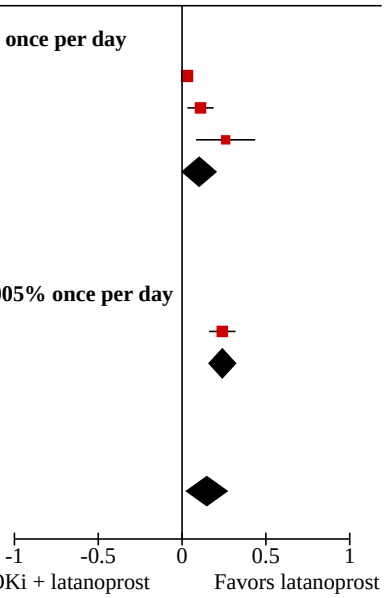
(1) Source: Brubaker 2020, at month 12
(2) At month 3 (5% reporting thereshold)
(3) At day 28 (5% reporting thereshold)
(4) At week 8 (unclear reporting threshold)

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.3. Comparison 4: Rho kinase inhibitor + prostaglandin analog versus prostaglandin analog, Outcome 3: Conjunctival hyperemia as adverse event (per person-month)*

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
4.3.1 Netarsudil 0.02% + latanoprost 0.005% (FDC) once per day vs latanoprost 0.005% once per day				
Asrani 2019 (MERCURY-1) (1)	0.03	0.005	29.5%	0.03 [0.02 , 0.04]
Walters 2019 (MERCURY-2) (2)	0.11	0.04	26.2%	0.11 [0.03 , 0.19]
Lewis 2016 (3)	0.26	0.09	18.0%	0.26 [0.08 , 0.44]
Subtotal (95% CI)			**73.8%**	**0.10 [0.00 , 0.20]**
Heterogeneity: Tau² = 0.01; Chi² = 10.38, df = 2 (P = 0.006); I² = 81%				
Test for overall effect: Z = 2.00 (P = 0.05)				
4.3.2 Ripasudil 0.4% twice per day + latanoprost 0.005% once per day vs latanoprost 0.005% once per day				
Tanihara 2015c (4)	0.24	0.04	26.2%	0.24 [0.16 , 0.32]
Subtotal (95% CI)			**26.2%**	**0.24 [0.16 , 0.32]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 6.00 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.15 [0.03 , 0.27]**
Heterogeneity: Tau² = 0.01; Chi² = 37.03, df = 3 (P < 0.00001); I² = 92%				
Test for overall effect: Z = 2.41 (P = 0.02)				
Test for subgroup differences: Chi² = 4.54, df = 1 (P = 0.03), I² = 78.0%				



Footnotes

(1) Source: Brubaker 2020, at month 12

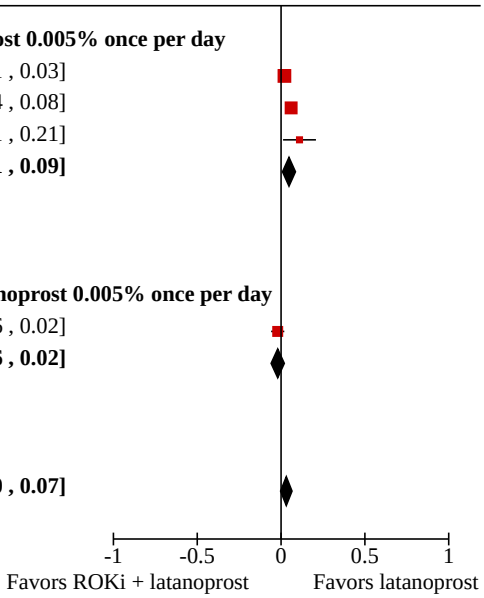
(2) At month 3

(3) At day 28

(4) At week 8

Analysis 4.4. Comparison 4: Rho kinase inhibitor + prostaglandin analog versus prostaglandin analog, Outcome 4: Ocular pain or irritation as adverse event (per person-month)*

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Random, 95% CI
4.4.1 Netarsudil 0.02% + latanoprost 0.005% (FDC) once per day vs latanoprost 0.005% once per day				
Asrani 2019 (MERCURY-1) (1)	0.02	0.004	35.0%	0.02 [0.01 , 0.03]
Walters 2019 (MERCURY-2) (2)	0.06	0.01	31.9%	0.06 [0.04 , 0.08]
Lewis 2016 (3)	0.11	0.05	9.0%	0.11 [0.01 , 0.21]
Subtotal (95% CI)			**75.8%**	**0.05 [0.01 , 0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 16.63, df = 2 (P = 0.0002); I² = 88%				
Test for overall effect: Z = 2.41 (P = 0.02)				
4.4.2 Ripasudil 0.4% twice per day + latanoprost 0.005% once per day vs latanoprost 0.005% once per day				
Tanihara 2015c (4)	-0.02	0.02	24.2%	-0.02 [-0.06 , 0.02]
Subtotal (95% CI)			**24.2%**	**-0.02 [-0.06 , 0.02]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.00 (P = 0.32)				
Total (95% CI)			**100.0%**	**0.03 [-0.00 , 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 21.74, df = 3 (P < 0.0001); I² = 86%				
Test for overall effect: Z = 1.80 (P = 0.07)				
Test for subgroup differences: Chi² = 5.77, df = 1 (P = 0.02), I² = 82.7%				



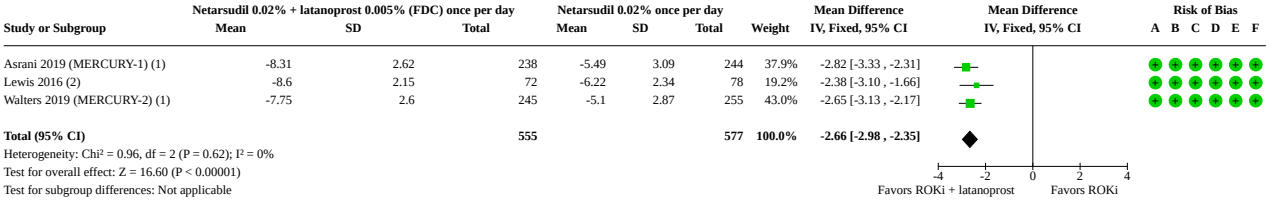
Footnotes

(1) Source: Brubaker 2020, at month 12
(2) At month 3
(3) At day 28
(4) At week 8

Comparison 5. Rho kinase inhibitor + prostaglandin analog versus Rho kinase inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Mean IOP changes from baseline	3	1132	Mean Difference (IV, Fixed, 95% CI)	-2.66 [-2.98, -2.35]
5.2 Total ocular adverse events (per person-month) – incidence rate difference	3		Risk Difference (IV, Fixed, 95% CI)	0.01 [-0.00, 0.03]
5.3 Conjunctival hyperemia as adverse event (per person-month)*	3		Risk Difference (IV, Fixed, 95% CI)	0.01 [0.00, 0.02]
5.4 Ocular pain or irritation as adverse event (per person-month)*	3		Risk Difference (IV, Fixed, 95% CI)	0.00 [-0.00, 0.01]

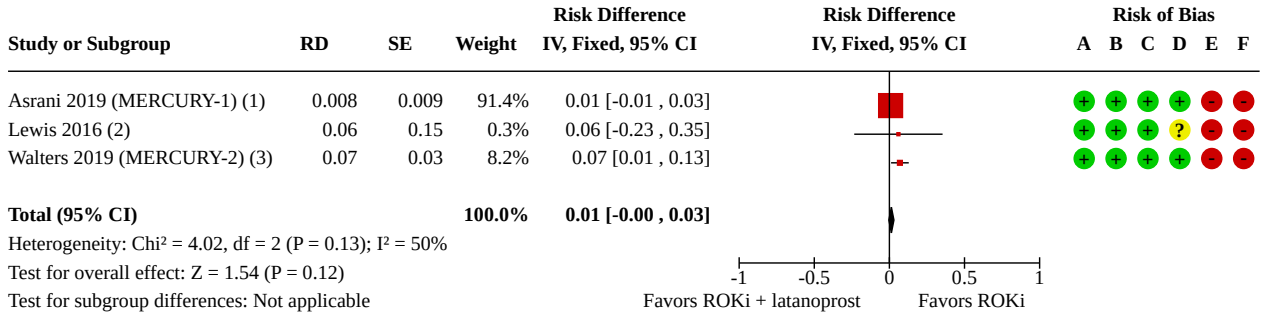
Analysis 5.1. Comparison 5: Rho kinase inhibitor + prostaglandin analog versus Rho kinase inhibitor, Outcome 1: Mean IOP changes from baseline



Footnotes
(1) At month 3, IOP at 10 a.m., source: ClinicalTrials.gov
(2) At day 28, mean diurnal IOP, source: ClinicalTrials.gov

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.2. Comparison 5: Rho kinase inhibitor + prostaglandin analog versus Rho kinase inhibitor, Outcome 2: Total ocular adverse events (per person-month) – incidence rate difference



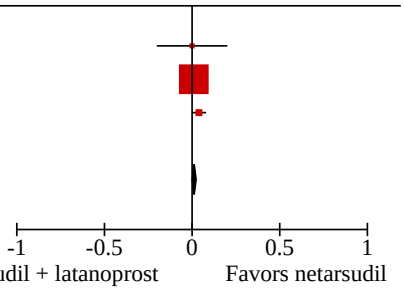
Footnotes
(1) At month 12 (data from Brubaker 2020, 5% reporting thereshold)
(2) At day 28 (data from article, 5% reporting thereshold)
(3) At month 3 (data from article, 5% reporting thereshold)

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.3. Comparison 5: Rho kinase inhibitor + prostaglandin analog versus Rho kinase inhibitor, Outcome 3: Conjunctival hyperemia as adverse event (per person-month)*

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Fixed, 95% CI
Lewis 2016 (1)	-0.0002	0.1027	0.3%	-0.00 [-0.20 , 0.20]
Asrani 2019 (MERCURY-1) (2)	0.0097	0.0058	92.5%	0.01 [-0.00 , 0.02]
Walters 2019 (MERCURY-2) (3)	0.0392	0.0208	7.2%	0.04 [-0.00 , 0.08]
Total (95% CI)			**100.0%**	**0.01 [0.00 , 0.02]**

Heterogeneity: Chi² = 1.88, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 2.11 (P = 0.03)
Test for subgroup differences: Not applicable

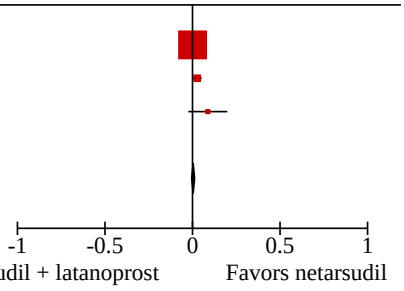


Footnotes
(1) At day 28 (data from article, 5% reporting thereshold)
(2) At month 12 (data from Brubaker 2020, 5% reporting thereshold)
(3) At month 3 (data from article, 5% reporting thereshold)

Analysis 5.4. Comparison 5: Rho kinase inhibitor + prostaglandin analog versus Rho kinase inhibitor, Outcome 4: Ocular pain or irritation as adverse event (per person-month)*

Study or Subgroup	RD	SE	Weight	Risk Difference IV, Fixed, 95% CI
Asrani 2019 (MERCURY-1) (1)	0.0006	0.0044	89.5%	0.00 [-0.01 , 0.01]
Walters 2019 (MERCURY-2) (2)	0.0269	0.0132	9.9%	0.03 [0.00 , 0.05]
Lewis 2016 (3)	0.0875	0.0569	0.5%	0.09 [-0.02 , 0.20]
Total (95% CI)			**100.0%**	**0.00 [-0.00 , 0.01]**

Heterogeneity: Chi² = 5.75, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



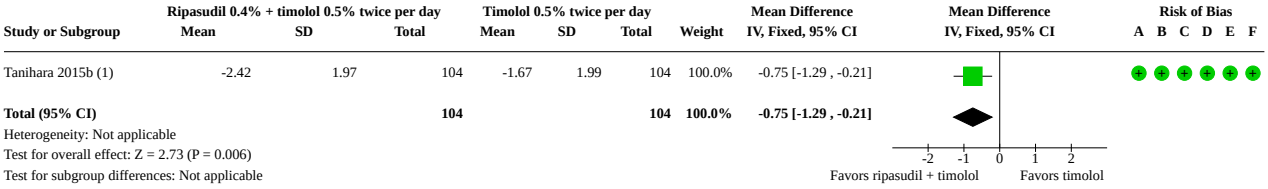
Footnotes
(1) At month 12 (data from Brubaker 2020, 5% reporting thereshold)
(2) At month 3 (data from article, 5% reporting thereshold)
(3) At day 28 (data from article, 5% reporting thereshold)

Comparison 6. Rho kinase inhibitor + beta-blocker versus beta-blocker

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Mean IOP changes from baseline	1	208	Mean Difference (IV, Fixed, 95% CI)	-0.75 [-1.29, -0.21]
6.2 Total ocular adverse events (per person-month) – incidence rate difference	1		Risk Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Conjunctival hyperemia as adverse event (per person-month)	1		Risk Difference (IV, Fixed, 95% CI)	Subtotals only
6.4 Ocular pain or irritation as adverse event (per person-month)	1		Risk Difference (IV, Fixed, 95% CI)	Subtotals only

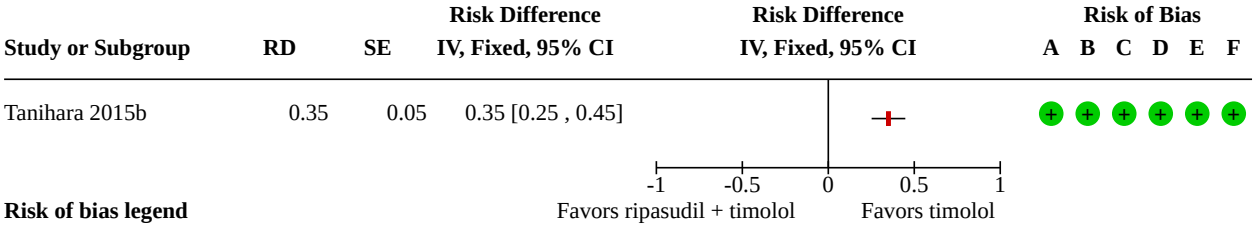
Analysis 6.1. Comparison 6: Rho kinase inhibitor + beta-blocker versus beta-blocker, Outcome 1: Mean IOP changes from baseline



Footnotes
(1) At week 8, pretreatment (change at 9 a.m., extrapolated from graph)

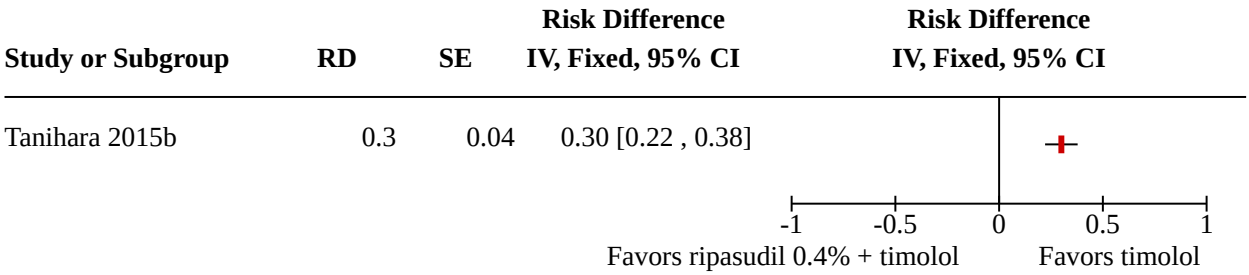
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.2. Comparison 6: Rho kinase inhibitor + beta-blocker versus beta-blocker, Outcome 2: Total ocular adverse events (per person-month) – incidence rate difference

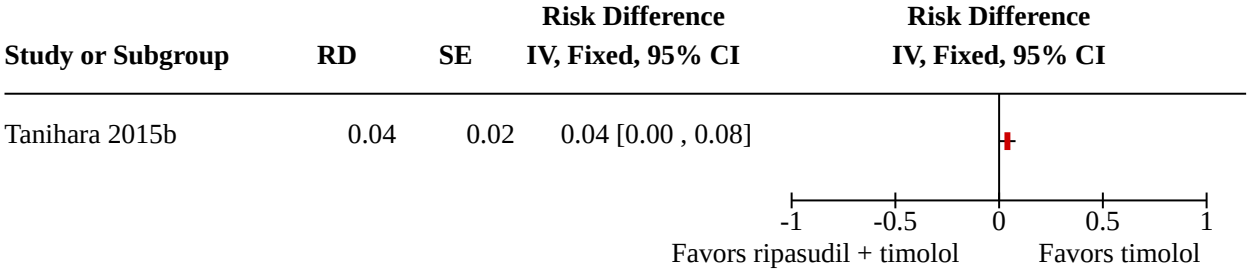


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.3. Comparison 6: Rho kinase inhibitor + beta-blocker versus beta-blocker, Outcome 3: Conjunctival hyperemia as adverse event (per person-month)



Analysis 6.4. Comparison 6: Rho kinase inhibitor + beta-blocker versus beta-blocker, Outcome 4: Ocular pain or irritation as adverse event (per person-month)



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma] explode all trees
#2 MeSH descriptor: [Ocular Hypertension] explode all trees
#3 MeSH descriptor: [Intraocular Pressure] explode all trees
#4 glaucom*
#5 (POAG or OHT)
#6 (ocular or intra*ocular) near/3 (hypertension* or tension* or pressur*)
#7 IOP
#8 {or #1-#7}
#9 MeSH descriptor: [rho-Associated Kinases] explode all trees
#10 ROCK OR ROK OR ROKalpha OR "rho associated" OR p160ROCK
#11 (rho near/3 kinase*) OR (rhoA near/3 kinase*)
#12 (protein* near/3 kinase*)
#13 {or #9-#12}
#14 #8 AND #13

Appendix 2. MEDLINE Ovid search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Glaucoma/
13. exp Ocular Hypertension/
14. exp Intraocular Pressure/
15. glaucom*.tw.
16. (POAG or OHT).tw.
17. ((ocular* or intra*ocular) adj3 (hypertension* or tension* or pressur*)).tw.
18. IOP.tw.
19. or/12-18
20. exp rho-Associated Kinases/
21. (ROCK or ROK or ROKalpha or "rho associated" OR p160ROCK).tw.
22. ((rho adj3 kinase*) or (rhoA adj3 kinase*)).tw.
23. (protein* adj3 kinase*).tw.
24. or/20-23
25. 19 and 24
26. 11 and 25

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'glaucoma'/exp
#34 'intraocular pressure'/exp
#35 'intraocular pressure abnormality'/de
#36 'intraocular hypertension'/exp
#37 glaucom*:ab,ti,kw
#38 (POAG OR OHT):ab,ti,kw
#39 ((intra*ocular OR ocular*) NEAR/3 (hypertension* OR tension* OR pressur*)):ab,ti,kw
#40 iop:ab,ti,kw

#41 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#42 'rho kinase'/exp
#43 rock:ab,ti,kw OR rok:ab,ti,kw OR rokalpha:ab,ti,kw OR 'rho associated':ab,ti,kw OR 'rhoa associated':ab,ti,kw OR p160ROCK:ab,ti,kw
#44 ((rho NEAR/3 kinase*):ab,ti,kw) OR ((rhoa NEAR/3 kinase*):ab,ti,kw)
#45 (protein* NEAR/3 kinase*):ab,ti,kw
#46 #42 OR #43 OR #44 OR #45
#47 #41 AND #46
#48 #32 AND #47

Appendix 4. PubMed search strategy

1. ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
2. glaucom*[tw]
3. POAG[tw] OR OHT[tw]
4. ((ocular*[tw] OR "intra ocular"[tw]) AND (hypertension*[tw] OR tension*[tw] OR pressur*[tw]))
5. IOP[tw]
6. #2 OR #3 OR #4 OR #5
7. (ROCK[tw] OR ROK[tw] OR ROKalpha[tw] OR "rho associated"[tw] OR p160ROCK[tw])
8. ((rho[tw] AND kinase*[tw]) OR (rhoA[tw] AND kinase*[tw]))
9. (protein*[tw] AND kinase*[tw])
10. #7 OR #8 OR #9
11. #6 AND #10
12. #1 AND #11
13. Medline[sb]
14. #12 NOT #13

Appendix 5. LILACS search strategy

(MH:C11.525$ OR glaucom$ OR "Ocular Hypertension" OR "Hipertensión Ocular" OR "Hipertensão Ocular" OR MH:G14.440$ OR ((intraocular OR "intra-ocular" OR ocular$) AND (hypertension$ OR tension$ OR pressur$)) OR "Presión Intraocular" OR "Pressão Intraocular" OR IOP OR MH:E04.540.450$ OR MH:E04.540.825.249$ OR POAG OR OHT) AND (MH:D08.811.913.696.620.682.700.814$ OR MH:D12.644.360.590$ OR MH:D12.776.476.595$ OR ROCK OR ROK OR ROKalpha OR "rho associated" OR p160ROCK OR RhoA OR (rho AND kinase$) OR (protein$ AND kinase$) OR "Quinasas Asociadas a rho" OR "Quinases Associadas a rho")

Appendix 6. ClinicalTrials.gov search strategy

(glaucoma OR hypertension OR intraocular pressure OR POAG OR IOP) AND ("rho associated" OR "Rho kinase" OR ROCK OR ROK OR ROKalpha OR "rhoA associated" OR p160ROCK OR "Protein Kinase")

Appendix 7. WHO ICTRP search strategy

glaucoma AND rho OR glaucoma AND rhoA OR glaucoma AND ROCK OR glaucoma AND ROK OR glaucoma AND RokAlpha OR glaucoma AND "protein kinase" OR glaucoma AND p160ROCK OR hypertension AND rho OR hypertension AND rhoA OR hypertension AND ROCK OR hypertension AND ROK OR hypertension AND RokAlpha OR hypertension AND "protein kinase" OR hypertension AND p160ROCK OR "intraocular pressure" AND rho OR "intraocular pressure" AND rhoA OR "intraocular pressure" AND ROCK OR "intraocular pressure" AND ROK OR "intraocular pressure" AND RokAlpha OR "intraocular pressure" AND "protein kinase" OR "intraocular pressure" AND p160ROCK

Appendix 8. Pooling of adverse events

Category	Event 1	Event 2	Event 3	Event 4	Event 5	Event 6	Event 7	Event 8
Conjunctival hyperemia	Conjunctival hyperemia	—	—	—	—	—	—	—
Ocular hyperemia	Ocular hyperemia	—	—	—	—	—	—	—
Ocular pain and irritation	Instillation foreign body sensation	Instillation pain	Instillation discomfort	Foreign body sensation	Ophthalmalgia	Ocular irritation	Eye pain	Eye pruritus
Cornea verticillata	Cornea verticillata	Corneal deposits	Corneal opacity	—	—	—	—	—
Increased lacrimation	Increased lacrimation	Eye discharge	—	—	—	—	—	—
Punctate keratitis	Punctate keratitis	Corneal erosion	Vital dye staining of cornea	—	—	—	—	—
Visual AE	Blurred vision	Visual acuity reduced	Eyesight deterioration	—	—	—	—	—
Allergy	Conjunctivitis allergic	Conjunctival follicles	—	—	—	—	—	—
Edema	Eye swelling	Conjunctival edema	Eyelid edema	—	—	—	—	—
Iritis	Photophobia	Iritis	—	—	—	—	—	—

Appendix 9. Detailed overview of specific adverse events

Adverse effects

ROKi versus placebo

Conjunctival hyperemia: after two months, treatment with ripasudil led to an increased rate of conjunctival hyperemia, with an incidence rate difference (IRD) of 26 more events per 100 person-months (95% confidence interval [CI] 14 to 38). Treatment with netarsudil yielded 79 more events per 100 person-months (95% CI 16 to 142) than placebo. In combination, treatment with ROKi resulted in 46 more events per 100 person-months (95% CI 19 to 73; I^2 = 62.4%). We found no evidence of a difference between subgroups defined by the type of ROKi (P = 0.10; Analysis 1.5).

Araie 2021 found a mean conjunctival hyperemia score (0 to 3: 0 = none, 1 = mild, 2 = moderate, 3 = severe) evaluated by biomicroscopic examination of 0.2 for netarsudil and 0 for placebo at 4-week follow-up compared to a mean baseline score of 0 for both interventions. The mean conjunctival hyperemia score remained relatively constant across week 1, 2 and 4. Sit 2021 evaluated 9/13 events as mild and 4/13 events as moderate in the netarsudil group. Tanihara 2013 evaluated all events of conjunctival hyperemia in the ripasudil group (32/32) and the placebo group (7/7) as mild. Thirty events in the ripasudil group and five events in the placebo group resolved spontaneously within 12 hours or less after application.

Ocular pain and irritation: we found no evidence of a difference between treatments in terms of ocular pain and irritation (IRD 4 more events per 100 person-months, 95% CI −7 to 15; I^2 = 61%). Neither did we find any evidence of differences between subgroups based on the type of ROKi (Analysis 1.6). Araie 2021 evaluated all events as mild, whereas Sit 2021 reported 1/3 events as mild and 2/3 events as moderate in the netarsudil group.

Cornea verticillata: none of the studies reported any events of cornea verticillata.

Serious adverse events (SAE): Araie 2021 reported one SAE (1.9%) (corneal abrasion) in the netarsudil group and no SAEs in the placebo group. Peace 2021, Aerie 2017, and Sit 2021 reported no SAEs in all treatment groups. Tanihara 2013 reported no SAEs with ripasudil and two SAEs (3.7%; iron-deficiency anemia and retinal tear) with placebo. None of the SAEs were attributed to treatment with ROKi.

ROKi versus beta-blocker

Conjunctival hyperemia: after three to 12 months, treatment with netarsudil led to 7 more events of conjunctival hyperemia per 100 person-months (95% CI 4 to 11; I^2 = 93%) compared to timolol (Analysis 2.4).

Kahook 2019 (ROCKET-2) reported a mean conjunctival hyperemia score (0 to 3 scale) of 0.5 to 0.7 for netarsudil compared to 0.2 for timolol (baseline values of 0.2 for both interventions). Similarly, Khouri 2019 (ROCKET-4) reported a mean conjunctival hyperemia score (0 to 3 scale) of 0.7 for netarsudil and 0.2 for timolol (baseline of 0.2 for both interventions) at six months' follow-up. The mean hyperemia score remained constant across the six months of the study for both treatments. Serle 2018 (ROCKET-1) described all events of conjunctival hyperemia as mild. The hyperemia was described as primarily transient/intermittent by Kahook 2019 (ROCKET-2) and Khouri 2019 (ROCKET-4).

Ocular pain and irritation: we found no evidence of a difference between treatments in terms of ocular pain and irritation (IRD 1 more events per 100 person-months (95% CI −1 to 2; I^2 = 46%; Analysis 2.5).

Cornea verticillata: at 12 months' follow-up, Kahook 2019 (ROCKET-2) detected 65 events (25.49%) of cornea verticillata with netarsudil compared to two events (0.8%) with timolol. At 6 months' follow-up, Khouri 2019 (ROCKET-4) reported 86 (24.5%) events in the netarsudil group and 0 events in the timolol group. At 12 months' follow-up, NCT02246764 (ROCKET-3) reported 18 (52.94%) events in the netarsudil group and 0 events in the timolol group. At 3 months' follow-up, Serle 2018 (ROCKET-1) detected 11 (5.42%) events in the netarsudil group and no events in the timolol group. Kahook 2019 (ROCKET-2) reported a mean time to onset of 172.9 days (range 40 to 396 days) and a mean time to resolution of 341.2 days after treatment discontinuation. All but one participant had complete resolution, in which cornea verticillata improved and stabilized. Khouri 2019 (ROCKET-4) reported a mean time to onset of 109.2 days (range 30 to 183) and a mean time to resolution of 87.3 days (range 0 to 264). Serle 2018 (ROCKET-1) reported a range of six to 13 weeks until onset, and complete resolution typically within 13 weeks. The severity was predominantly described as mild without influencing the visual function (i.e. visual acuity, contrast sensitivity).

SAEs: Kahook 2019 (ROCKET-2) reported 22 SAE (8.76%; 8 cardiac disorders, 1 cholelithiasis, 1 cellulitis, 1 postoperative Ileus, 1 fluid overload, 1 back pain, 1 osteoarthritis, 4 neoplasms, 2 central nervous system disorders, 1 pulmonary artery stenosis and 1 accelerated hypertension) with netarsudil and 18 SAEs (7.17%; 1 cardiac disorder, 1 cataract, 1 gastric ulcer perforation, 1 cholecystitis, 3 infections/infestations, 4 injuries, 1 prostate-specific antigen increased, 1 synovial cyst, 1 carotid artery stenosis, 2 renal and urinary disorder, 1 pulmonary embolism and 1 peripheral artery occlusion) with timolol. Khouri 2019 (ROCKET-4) reported 11 SAE (3. 13%; 2 cardiac disorder, 2 gastrointestinal (GI) disorders, 3 neoplasms, 1 central nervous system disorder, 1 renal and urinary disorder, 1 cervical dysplasia, and 1 pneumonia aspiration) with netarsudil and 12 SAE (3.36%; 3 cardiac disorders, 1 GI disorder, 1 pneumonia, 2 injuries, 2 neoplasms, 2 central nervous system disorders and 1 metal status change) with timolol. NCT02246764 (ROCKET-3) reported no SAE with netarsudil compared to one SAE (4.35%; breast cancer) with timolol. Serle 2018 (ROCKET-1) reported three SAE (1.48%; 1 cardiac disorder, 1 hypertension, 1

prostate cancer) with netarsudil compared to six SAE (2.88%; 1 cardiac disorder, 1 pneumonia, 2 nervous system disorders, 1 reproductive and breast disorder, and 1 acute respiratory failure) with timolol.

ROKi versus prostaglandin analog

Conjunctival hyperemia: treatment with netarsudil yielded a pooled mean excess of 11 events of conjunctival hyperemia per 100 person-months (95% CI 3 to 19; I^2 = 88%) compared to latanoprost (Analysis 3.3). At 12 months' follow-up, Asrani 2019 (MERCURY-1) reported a mean conjunctival hyperemia score of 0.6 for netarsudil compared to 0.3 for latanoprost (0 to 3 scale, baseline 0.2 for both interventions). Walters 2019 (MERCURY-2) reported a mean conjunctival hyperemia score of 0.5 for netarsudil and 0.2 for latanoprost (0 to 3 scale, baseline of 0.1 for both outcomes). The mean hyperemia score remained relatively constant during study conduct (Asrani 2019 (MERCURY-1); Walters 2019 (MERCURY-2)).

Ocular pain and irritation: treatment with netarsudil resulted in a pooled mean excess of 2 events of ocular pain and irritation per 100 person-months (95% CI 1 to 3; I^2 = 0%) compared to treatment with latanoprost (Analysis 3.4).

Cornea verticillata: after 12 months of treatment, Asrani 2019 (MERCURY-1) reported 33 events (13;58%) of cornea verticillata in the netarsudil group and no events in the latanoprost group. All cases were asymptomatic and predominantly judged as mild. The mean time to onset was 216.6 days, whereas the mean time to resolution was 86.4 days after treatment discontinuation. After three months of treatment, Walters 2019 (MERCURY-2) found 25 events (9.8%) with netarsudil compared to no events with latanoprost. All cases were asymptomatic and predominantly judged as mild.

SAEs: Asrani 2019 (MERCURY-1) reported 11 SAEs (4.52%; 1 cardiac disorder, 2 GI disorders, 1 cellulitis, 1 hypoglycemia, 2 neoplasms, 1 spontaneous abortion, 1 bronchitis chronic and 2 vascular disorders) with netarsudil monotherapy compared to 14 SAEs (5.91%; 2 cardiac disorder, 1 GI disorders, 1 sepsis, 2 injuries, 1 osteoarthritis, 3 neoplasms, 2 nervous system disorders, 1 pulmonary embolism and 1 deep vein thrombosis) with latanoprost. Bacharach 2015 reported no SAEs with netarsudil compared to two SAEs (2.6%; 1 pneumonia and 1 fall) with latanoprost. Lewis 2016 reported no SAEs with netarsudil compared to four SAEs (5.48%; 1 ulcerative keratitis, and 3 gastrointestinal/hepatobiliary disorders) with latanoprost. Walters 2019 (MERCURY-2) reported seven SAE (2.75%; 4 cardiac disorder, 1 bronchitis, 1 central nervous system disorder and 1 pulmonary embolism) with netarsudil compared to five SAEs (1.99%; 1 cardiac disorder, 1 retinal detachment, 1 cholecystitis acute and 2 infections) with latanoprost.

ROKi plus prostaglandin analog versus prostaglandin analog

Conjunctival hyperemia: combination therapy with ripasudil and latanoprost caused on average an additional 24 events per 100 person-months (95% CI 16 to 32) compared to latanoprost monotherapy, whereas combination therapy with netarsudil and latanoprost resulted in a pooled mean excess of 10 events per 100 person-months (95% CI 0 to 20; I^2 = 81%) compared to latanoprost monotherapy (Analysis 4.3). Overall, combination therapy with ROKi and latanoprost led to more events compared to latanoprost monotherapy, with an IRD of 15 more events per 100 person-months (95% CI 3 to 27; I^2 = 92%). We found no evidence of a difference between subgroups defined by the type of ROKi (I^2 = 78%).

Asrani 2019 (MERCURY-1) found a mean conjunctival hyperemia score of 0.6 for combination therapy with netarsudil and latanoprost compared to 0.3 for latanoprost (0 to 3 scale, baseline 0.2 for both interventions). Walters 2019 (MERCURY-2) reported a mean conjunctival hyperemia score of 0.7 for combination therapy with netarsudil and latanoprost compared to 0.2 for latanoprost (baseline values of 0.2 for netarsudil/latanoprost and 0.1 for latanoprost). The mean hyperemia score remained relatively constant during study conducts (Asrani 2019 (MERCURY-1); Walters 2019 (MERCURY-2)).

Ocular pain and irritation: we found weak evidence of a minor difference between treatments in terms of ocular pain and irritation, with an IRD of 3 events per 100 person-months (95% CI 0 to 7; I^2 = 86%), with the combination of netarsudil and latanoprost associated with more excess AEs than the latanoprost monotherapy group (Analysis 4.4).

Cornea verticillata: after 12 months of treatment, Asrani 2019 (MERCURY-1) reported 42 events (17.65%) of cornea verticillata with combination therapy of netarsudil and latanoprost compared to no events with latanoprost, whereas Walters 2019 (MERCURY-2) reported 32 events (13.11%) with combination therapy of netarsudil and latanoprost compared to no events with latanoprost at three months' follow-up. Cases were asymptomatic and predominantly judged as mild (Asrani 2019 (MERCURY-1); Walters 2019 (MERCURY-2)). Mean onset was 180.6 days after initiation, while mean time to resolution after treatment discontinuation was 48.7 days (Asrani 2019 (MERCURY-1)).

SAEs: Asrani 2019 (MERCURY-1) reported six SAEs (2.52%; 1 anemia, 1 GI disorder, 1 cholecystitis, 1 pneumonia, 1 neoplasm and 1 central nervous system disorder) with combination therapy compared to 14 SAEs (5.91%) with latanoprost (see detailed description above). Lewis 2016 reported no SAEs with combination therapy and four SAEs (5.48%) with latanoprost (see detailed description above). Tanihara 2015c reported three SAEs (2.94%) (1 otitis media and 2 visual field defects) with ripasudil plus latanoprost and five SAEs (1.99%) (2 cataract, 2 otitis media and 1 visual field defect) with latanoprost. Walters 2019 (MERCURY-2) reported three SAEs (2.94%) (2 cardiac disorders and 1 mental status change) with combination therapy compared to five SAEs (4.85%) with latanoprost (see detailed description above).

ROKi plus prostaglandin analog versus rho kinase inhibitor

Conjunctival hyperemia: we found no evidence of a difference between treatments in terms of conjunctival hyperemia (IRD 1 more event per 100 person-months, 95% CI 0 to 2; I^2 = 0%; Analysis 5.3). Asrani 2019 (MERCURY-1) found a mean conjunctival hyperemia score of 0.6 for both combination therapy with netarsudil and latanoprost and netarsudil monotherapy (0 to 3 scale, baseline 0.2 for both interventions).

Walters 2019 (MERCURY-2) reported a mean conjunctival hyperemia score of 0.7 for combination therapy with netarsudil and latanoprost compared to 0.5 for netarsudil monotherapy (0 to 3 scale, baseline values of 0.2 for combination therapy and 0.1 for netarsudil monotherapy). The mean hyperemia score remained relatively constant during study conducts (Asrani 2019 (MERCURY-1); Walters 2019 (MERCURY-2)).

Ocular pain and irritation: we found no evidence of a difference between treatments in terms of ocular pain and irritation (IRD 0 per 100 person-months (95% CI 0 to 1; I^2 = 65%; Analysis 5.4).

Cornea verticillata: Asrani 2019 (MERCURY-1) reported 42 events (17.65%) of cornea verticillata with combination therapy of netarsudil and latanoprost compared to 33 events (13.58%) with netarsudil, whereas Walters 2019 (MERCURY-2) reported 32 events (13.11%) with combination therapy of netarsudil and latanoprost compared to 25 events (9.8%) with netarsudil. Asrani 2019 (MERCURY-1) reported a mean onset of 180.6 days after initiation and mean time to resolution after discontinuation of 48.7 days for combination therapy. Considering netarsudil monotherapy, the mean time until onset was 216.6 days, whereas the mean time until resolution was 86.4 days after treatment discontinuation.

SAEs: Asrani 2019 (MERCURY-1) reported six SAEs (2.52%) with combination therapy compared to 11 SAEs (4.53%) with netarsudil monotherapy. Lewis 2016 reported no SAE for both combination therapy and monotherapy with netarsudil. Walters 2019 (MERCURY-2) reported three SAEs (1.23%) with combination therapy compared to seven SAEs (2.75%) with monotherapy (see detailed description above).

ROKi plus beta-blocker versus beta-blocker

Conjunctival hyperemia: on average combination therapy with ripasudil and timolol resulted in 30 more events of conjunctival hyperemia per 100 person-months (95% CI 22 to 38) compared to timolol monotherapy (Analysis 6.3). The severity of conjunctival hyperemia was not examined.

Ocular pain and irritation: we found no evidence of a difference between treatments in terms of ocular pain and irritation (IRD 4 more events per 100 person-months, 95% CI 0 to 8; Analysis 6.4).

Cornea verticillata: the trial did not investigate events of cornea verticillata.

SAEs: Tanihara 2015b reported one SAE (0.96%; visual field defect) with combination therapy and four SAEs (4.81%; 2 spinal osteoarthritis, 1 asthma and 1 cholelithiasis) with timolol.

HISTORY

Protocol first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

JCF, AVS, NK, MK, AA and GV designed, drafted, and wrote the protocol. All authors approved the final protocol.

JCF and AVS carried out the searches, assessed inclusion of publications and extracted data.

JCF and AVS drafted the review.

MK, AA and GV commented on the draft, and JCF adjusted the final draft accordingly.

JVF, AVS, MK, AA and GV approved the published version of the review.

DECLARATIONS OF INTEREST

JCF: none.

AVS: none.

MK is on the advisory board or is a consultant for AbbVie, Thea Pharmaceuticals and Santen. Collaborations are not related to this current review.

AA: none.

GV: none known. Dr Virgili is a member of the editorial team and was not involved in the editorial processes.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Eye Institute, National Institutes of Health, USA

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- Queen's University Belfast, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of participants

Normal-tension glaucoma was considered as a subgroup of POAG. As some studies had open-angle glaucoma (OAG) and not primary open-angle glaucoma (POAG) as inclusion criteria, the review team decided to include studies both investigating OAG and POAG. This was not clearly stated in the protocol.

Types of interventions

Various trials evaluated different non-clinically prescribed doses of marketed ROKis as well as non-marketed ROKis such as AR-12286, SNJ-1656, AMA0076 and WP-1303. However, due to the modest amount and heterogeneous nature of the clinical evidence, the review team decided not to evaluate the effects of non-therapeutic doses of commercial as well as non-commercial ROKis.

Outcomes

We specified in the protocol that we would collect adverse effects (AEs) as measured in dichotomous measures at the longest follow-up. However, with the variable lengths of follow-up across studies, we decided to calculate incidence rates of AEs by averaging the numbers of adverse events reported over the relevant person-periods exposed to the treatment (in 100 person-months). The protocol also specified that we would collect ocular AEs related to the intervention drug. Yet some studies did not clarify whether the reported ocular AEs were considered related or unrelated to the intervention drug. Thus, the numbers extracted for analysis were for all ocular AEs and for studies that did not report whether it was directly related to the intervention drug. Furthermore, if a given AE was classified as an ocular AE or serious AE by the review team, the AE would be regarded as so independently of the statement of the trial investigators.

Measures of treatment effect

For categorical data with dichotomous measures, the protocol specified that the treatment effect would be estimated using risk ratios (RR) with 95% CIs. This was only relevant for AE data. As the studies varied in follow-up period, we calculated the AE incidence RDs with 95% CIs instead. None of the included studies reported continuous measures obtained from different measurement tools.

Unit of analysis issues

None of the eligible studies reported data for both eyes of participants treated with the same intervention. Hence, no estimates that accounted for the between-eye correlation were made. Of the eligible studies, only one reported data from participants receiving different interventions in each eye (Sit 2021). Therefore, the review team decided not to access the within-person effect as otherwise stated in the protocol. Rather, we performed a sensitivity analysis to evaluate the single study effect (Analysis 1.2).

Subgroup analysis and investigation of heterogeneity

We did not perform a subgroup analysis based on population, as the included studies either did not include both subgroups or did not clearly distinguish between OAG and OHT. We performed a subgroup analysis based on the different types of ROKis.

We did not evaluate responses of the highest and lowest dose of non-therapeutic doses of ROKi due to limited data.

Reporting of outcomes

For the secondary outcomes 'change in IOP from baseline', the protocol stated that data from the longest available follow-up would be reported. However, it should be specified that 'the longest available follow-up' is the follow-up period prespecified for the primary and secondary outcomes in the included studies, since the studies were specifically designed for these time points. This was not clearly described in the protocol.

In the protocol, we stated that the outcomes 'change in IOP from baseline' and 'number of adverse events' should be reported at short (less than six months) or medium-to-long term (six months or more). However, very few of the included studies reported medium-to-long term outcomes. Thus, the review team decided not to report these outcomes based on short- and medium- to long-term considerations.

INDEX TERMS

Medical Subject Headings (MeSH)

*Glaucoma, Open-Angle [drug therapy]; *Ocular Hypertension [drug therapy]; Randomized Controlled Trials as Topic; *rho-Associated Kinases [antagonists & inhibitors] [therapeutic use]; Treatment Outcome

MeSH check words

Humans