LITERATURE REVIEW

# EFFICACY AND SAFETY OF RHO KINASE INHIBITOR EYEDROPS FOR THE TREATMENT OF OPEN-ANGLE GLAUCOMA AND OCULAR HYPERTENSION: A LITERATURE REVIEW

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## ABSTRACT

***Introduction:*** *Reduction of intraocular pressure (IOP) is the only proven method to treat glaucoma. Studies on aqueous humor dynamics have contributed to our understanding of aqueous outflow mechanisms that have led to the discovery of new drugs from Rho Kinase Inhibitors (RKI).*

***Methods:*** *Literature searching was conducted in four online databases (PubMed, EBSCOhost, ScienceDirect, and Scopus. Search terms included were "Atropine" and "Myopia". Validity was assessed using assessment tool from Cochrane. Efficacy was evaluated using myopia progression in spherical equivalent per year and axial lengthening per year.*

***Results:*** *Sixteen randomized controlled trial studies fulfilled our inclusion criteria and eligibility screening. Overall, atropine shows favorable results in spherical equivalent progression (D/year) compared to control, with SMD = -1.13, 95% CI (-0.58, -1.68). Less axial elongation (mm/year) was observed in atropine group, with SMD = -1.28, 95% CI (-0.18, -2.37). Atropine 0.01% concentration shows overall significantly better myopia progression and axial lengthening compared to control, with SMD = -0.76, 95% CI (-0.08, -1.44) and SMD = -0.63, 95% CI (-0.14, -1.12), respectively. Higher atropine doses showed larger effect sizes with higher occurrence of adverse effects.*

***Conclusion:*** *Atropine eye drops in various doses shows overall effective myopia control in spherical equivalent and axial lengthening. Atropine 0.01% has significant myopia progression inhibition with less adverse effects than higher doses.*

***Keywords:*** *myopia, near-sightedness, atropine, myopic progression*

## INTRODUCTION

Glaucoma is a disease characterized by optic neuropathy with the remodeling of connective tissue of the optic nerve head dan loss of neural tissue associated with the development of several patterns of visual dysfunction.[1] According to Riskesdas 2007, the prevalence of glaucoma in Indonesia was 0.46%. In 2017, the total number of new glaucoma cases as outpatients in Indonesia was 80.548 cases.[2] Primary Open Angle Glaucoma (POAG) is the most common type of glaucoma. In OAG, IOP is the primary and the only treatable risk

factor.[3,4] In OAG, IOP reduction will slow the progression of the disease and reduce the risk of OHT progression to glaucoma. Topical medication for anti-glaucoma is the most common first-line treatment modality.[5]

Many patients need a combination of topical anti-glaucoma medications to achieve their target pressure. Several topical pharmacologic treatment options for lowering IOP include beta-adrenergic antagonists, alpha-2 adrenergic agonists, cholinergic agonists, carbonic anhydrase inhibitors, and prostaglandin analogs (PGAs). Rho kinase inhibitors are the new pharmacotherapies with unique mechanisms of action to reduce IOP.[6,7] Rho kinase is a serine/threonine protein kinase that regulates cytoskeletal activities. The Rho kinase pathway became an area of focus in developing anti-glaucoma medications once it was discovered that pharmacologic manipulation of the cytoskeleton of the eye's outflow pathway could lead to decreased outflow resistance and reduced IOP. Several studies found it has a neuroprotection effect and can reduce fibrosis in glaucoma filtration surgery.[8] Since great potential drugs of this class have been approved for glaucoma treatment, this literature review aims to evaluate the efficacy and safety of two rho kinase inhibitor types for treating OAG and OHT.

## METHODS

Literature search and selection

Literature searching was conducted from four online databases (PubMed, ScienceDirect, Google Scholar, and Springer Link). Search terms included a combination of main keywords: "Open Angle Glaucoma", "Ocular Hypertension", and "Rho Kinase Inhibitors", which provides for Netarsudil (AR-13530), Ripasudil (K-115), and Fixed Combination Netarsudil Latanoprost (FCNL (PG324)). Reference lists of each study were assessed for potentially relevant sources. The search was limited to articles with the human sample, published in English, and available full-text versions. There was no limitation in the year of publication.

Based on search results as described previously, articles were considered eligible to be reviewed if they met the following inclusion criteria: (1) Subjects are patients with OAG or OHT, (2) Using rho kinase inhibitors with concentration that has received approval for widely distributed on the market place (Ripasudil 0.4% ophthalmic solution, Netarsudil 0.02% ophthalmic solution, and Fixed Combinations of Netarsudil 0.02%-Latanoprost 0.005% (FCNL), (3) Primary outcome is IOP reduction from the baseline, (4) Compared to another class of glaucoma medication. The flow chart of literature searching is described in figure 1 below.

Data processing

The information extracted from the studies included the authors of each study, the year study was reported, the number of subjects, subjects' mean age, administration methods, the primary endpoint, and adverse effects. Efficacy was evaluated by reported mean change IOP from baseline. Safety was assessed by adverse events experienced during the treatment course.

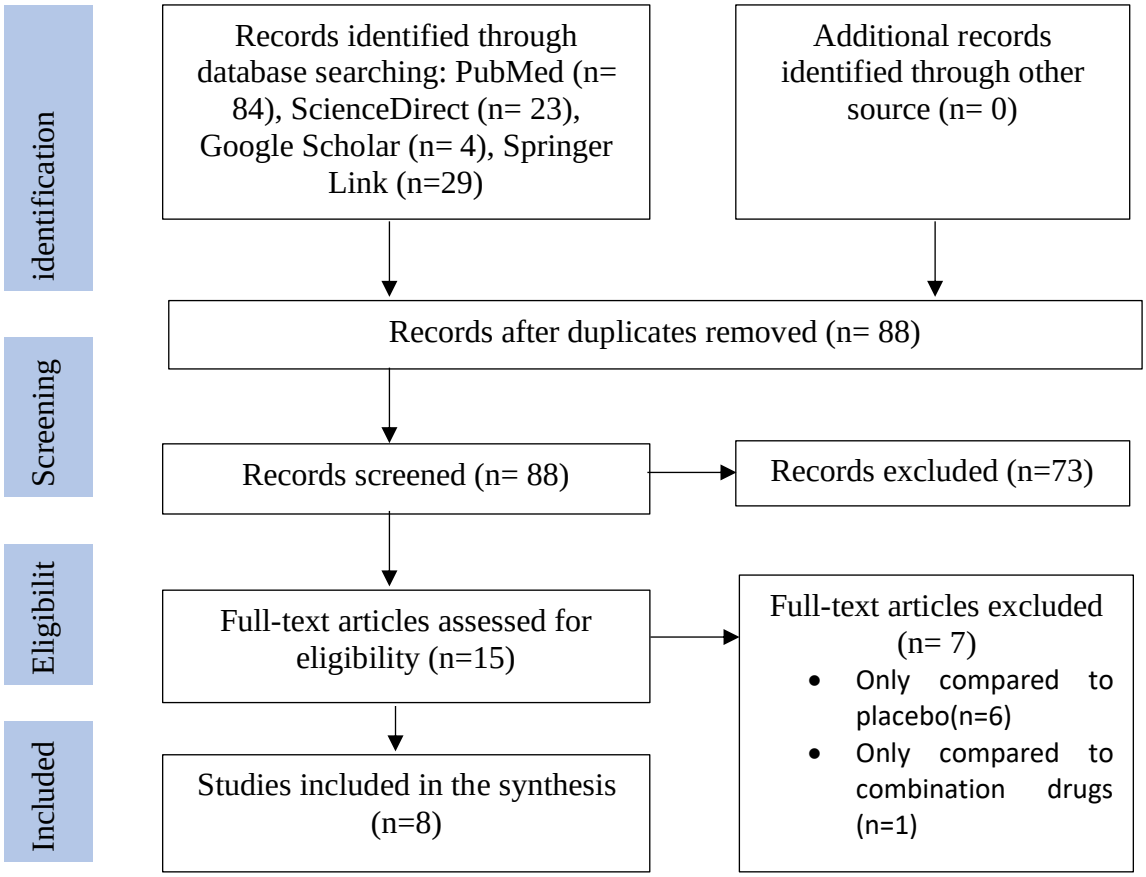


**Figure 1.** A literature search using the PRISMA flow chart

## RESULTS

Eight articles were included in this review and were assessed for their validity using RoB 2 appraisal tool. Validity assessment was summarized using Robvis in figure 2 and figure 3 below.

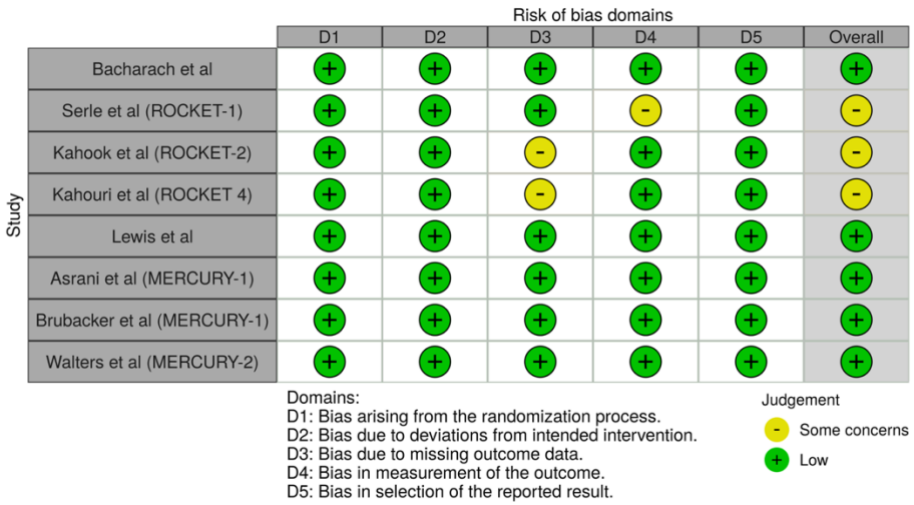


**Figure 2.** Traffic light plots to display overall judgments for all studies.

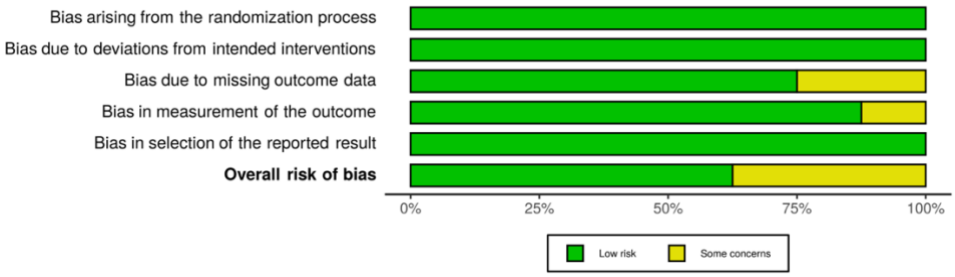


**Figure 3.** Summary plot of overall judgments for all studies.

Overall low risk of bias judgment concluded if the study is judged to be at low risk of bias for all domains. Based on five domains of risk of bias in RoB 2, five of eight studies concluded with a low level of bias. Meanwhile, three studies are judged to raise some concerns due to missing outcome data (2 studies) and due to measurement of the outcome (1 study). However, if at least one domain is judged to raise some concerns, but not at high risk of bias for any field, we can conclude that the overall risk of bias judgment needs some concern.

A total of 8 studies using relevant search terms in various databases are included in this review. All studies are phase III clinical trials that assessed the efficacy and safety of Rho Kinase Inhibitor as an anti-glaucoma treatment. The specific characteristics and methods of each study are shown in Tables 1 and 2. Four RCT studies used Netarsudil, and another four used Fixed Combinations of Netarsudil Latanoprost (FCNL) as the primary intervention. This review divided the samples into two main groups according to anti-glaucoma intervention. The first group consists of the primary Rho Kinase Inhibitor intervention given in the study (Ripasudil, Netarsudil, FDC Netarsudil-Latanoprost 0.005%), and the second is the control group using

former anti-glaucoma agents available (Timolol 0.5% and Latanoprost 0.005%) or its active component (for studies using FDC as primary intervention). Table 3 shows the treatments and follow-up duration in each study.

All studies included in this literature review were conducted to know the efficacy and safety of the ROCK inhibitors. Efficacy in this literature review means a mean reduction from the baseline IOP, and safety profile means both ocular and systemic adverse events related to the treatment.

Bacharach et al[9] study divided subjects into three intervention groups: two groups of Netarsudil with different concentrations (0.01% and 0.02%) and one group of former drug Latanoprost 0.005%. Netarsudil 0.02% was less effective than latanoprost 0.005% by approximately 1 mmHg in these 28 days of study. The IOP reduction in the Netarsudil 0.02% group was 5.7 mmHg compared to 6.8 mmHg in Latanoprost 0.005% group. IOP reduction in the Netarsudil group did not meet the criteria for non-inferiority to latanoprost.

Serle et al[10], Kahook et al[11], and Khouri et al[9] conducted ROCKET-1, ROCKET-2, and ROCKET-4, respectively. ROCKET studies compared the efficacy and safety of Netarsudil to Timolol 0.5%. ROCKET-1 and ROCKET-4 studies had three months follow-up duration for efficacy. Meanwhile, the ROCKET-2 study had 12 months. All groups in these ROCKET studies produced statistically mean reduction from the baseline IOP. In the ROCKET-1 study, the mean decrease from baseline IOP was 3.3 – 5.0 mmHg for Netarsudil 0.02% and 3.7 – 5.1 mmHg for Timolol 0.5%. However, Netarsudil 0.02% did not meet the criteria for non-inferiority to Timolol 0.5% because the upper limit of 2-sided 95% CI for the difference between Netarsudil and Timolol was greater than 1.5 mmHg at 3 of the 9-time points when the analysis included all subjects with maximum baseline IOP < 27 mmHg. Serle et al[10], in the ROCKET-1 study, then added a new analysis with a reduction of the baseline IOP into < 25 mmHg. The result was that Netarsudil 0.05% meets the criteria for non-inferiority to Timolol 0.5%.

ROCKET 2 study compared Netarsudil 0.02% q.d and b.i.d, to Timolol 0.5%. The result showed that Netarsudil 0.02% q.d and b.i.d made statistically significant IOP reduction from the baseline (3.74 mmHg, 4.59 mmHg, 4.99 mmHg, respectively). In the noninferiority study, the ROCKET-2 study had a similar result as the ROCKET-1 study. Subjects in the ROCKET-2 study were POAG patients with baseline IOP < 25 mmHg. The study showed that only Netarsudil 0.05% q.d meet the criteria for non-inferiority to Timolol 0.5%.

ROCKET-4 study had a similar treatment and follow-up duration with ROCKET-1 but with a different baseline IOP in the inclusion criteria. In ROCKET 4, the baseline IOP in the

inclusion criteria was 20 to 30 mmHg. In the sub-analysis of subjects with baseline IOP ≤ 25 mmHg and ≤ 27 mmHg, Netarsudil 0.05% met the criteria for non-inferiority compared with timolol 0.5%.

Lewis et al[12] conducted a study with four groups of intervention. This study aims to evaluate the efficacy of two FDC drugs consisting of Netarsudil 0.01% - Latanoprost 0.005% and Netarsudil 0.02% - Latanoprost 0.005%, compared to each of their active component (Latanoprost 0.005% and Netarsudil 0.02%). The follow-up duration was 28 days. The result showed that the FDC of Netarsudil 0.02% - Latanoprost 0.005% met the criteria for statistical superiority over its active component alone, providing additional IOP lowering 1.9 mmHg (CI95% 1.2 – 2.6) than Latanoprost 0.005% and 2.6 mmHg (CI95% 1.8 – 3.4) than Netarsudil 0.02%. The FDC with Netarsudil 0.02% had a more significant IOP reduction than FDC with Netarsudil 0.01%.

MERCURY studies investigated the efficacy and safety of FDC Netarsudil 0.02%-Latanoprost 0.005% compared to each of its active components (Netarsudil 0.02% and Latanoprost 0.005%). Two studies presented data from the MERCURY-1 trial. Asrani et al[13] presented three months' endpoint analysis from the MERCURY-1 trial. Meanwhile, Brubaker et al[14] presented 12 months endpoint analysis. In these two studies, FDC Netarsudil 0.02%-Latanoprost 0.005% showed statistical superiority every month compared to Netarsudil 0.02% and Latanoprost 0.005%. The proportion of the subjects that achieved mean IOP ≤18 mmHg in 12 months follow-up was 81.6% in the FDC group; meanwhile, in the Latanoprost group was 65.5%, and in the Netarsudil group was 57.4%. 60.8% of subjects in the FDC group for 12 months MERCURY-1 study had an IOP reduction of more than 30% from the baseline. The number of percentages with an IOP reduction of more than 30% from the baseline in the Latanoprost 0.005% group was 33.5%, and in the Netarsudil 0.02% was only 33.1%. The MERCURY-2 study, which has three months of follow-up, had the same result as MERCURY-1.

The three most common adverse events almost in all studies of Netarsudil 0.02% were conjunctival hyperemia, cornea verticillate, and conjunctival hemorrhage. Conjunctival hyperemia occurred almost in more than 50% of subjects in every study. Meanwhile, in the latanoprost 0.005% group only less than 20%, and in Timolol 0.5% group less than 9%. No study showed systemic adverse events of Netarsudil 0.02%, including changes in blood pressure and heart rate. All studies used FDC Netarsudil 0.02%-Latanoprost 0.005% as the primary treatment reported no new adverse events except that have been observed previously in Netarsudil 0.02% and Latanoprost 0.005%. The details are summarized in table 6.

## DISCUSSION

This literature review included Ripasudil 0.4%, Netarsudil 0.02%, and FCNL in the literature search. However, no study compared Ripasudil 0.4% with another class of glaucoma medications included. A study by Tanihara et al[15] compared IOP lowering effects of Ripasudil 0.4% as monotherapy and as an additive therapy to prostaglandin analogs, β-blockers, and the FDC of prostaglandin analog-β-blockers. Other studies compared Ripasudil in different concentrations or as an additional drug to another class of glaucoma medications. Therefore, these studies did not meet our inclusion criteria.

All four studies with Netarsudil 0.02% as the primary treatment included in this literature review achieved significant IOP reduction from the baseline. Only one study by Bacharach et al[16] used latanoprost 0.005% (prostaglandin analog) as a comparator. Meanwhile, the others used timolol 0.2%. Latanoprost is more efficacious than Timolol in lowering IOP. Therefore, the new medications should be compared with latanoprost. However, there is no regulation to compare the new medicine with the most superior efficacy drug. Even in one study using Prostaglandin Analog as a comparator by Bacharach et al., the result showed that Netarsudil 0.02% didn't meet the criteria for non-inferiority to latanoprost 0.005%. However, Bacharach et al. analyzed a subgroup of baseline IOP ≤ 26 mmHg. From this subgroup, Netarsudil met the criteria of non-inferiority compared to Latanoprost 0.005%. Meanwhile, in subgroup > 26 mmHg, Latanoprost tends to achieve higher IOP reduction.[7,16,17]

Even though rho kinase inhibitor is a new class of IOP lowering medication that has a mechanism to increase outflow through the trabecular meshwork, decrease the production of aqueous humor, and reduce episcleral venous pressure, for many glaucoma patients are not sufficiently effective as monotherapy to achieve target IOP. The patients still need two or more medications. Fixed dose combination (FDC) can reduce the complexity of multi drugs usage, simplify the dosing regimens, and are expected to increase patient adherence.[12] Study by Bacharach et al.[16] showed the superiority of latanoprost for glaucoma treatment to reduce IOP than Netarsudil 0.02%. Latanoprost is also the most superior lowering IOP agent for glaucoma patients. There is no FDC combining latanoprost and other anti-glaucoma agents dosed once daily. A fixed Combination of Netarsudil Latanoprost (FCNL) is a novel FDC of rho kinase inhibitor with a once-daily dosage. Four FCNL (Netarsudil 0.02%-latanoprost 0.05%) studies included in this review met the criteria for statistical superiority over the comparators.[12-18]

In the Advanced Glaucoma Intervention Study VII report, patients with advanced disease who maintained IOP below 18 mmHg by medical or surgical intervention will have a reduction in visual field defect progression, and below 14 mmHg will have no disease

progression during the study period.[19] In Mercury-1, 82% of patients in the FCNL group achieved IOP below 18 mmHg in 3 months and 81.6% in 12 months, meanwhile in the Latanoprost group, only 69.1% and 65.5% and the Netarsudil 0.02% group only 53.5% and 57.4% in 3 months and 12 months respectively. At the end of the Mercury-1 study, 27.2% of patients had already achieved IOP below 14 mmHg in the FCNL group. Meanwhile, in Latanoprost only 11.8% and in Netarsudil only 16.2%. This data showed the superiority of FCNL compared to its individual active components in reducing the risk of glaucomatous disease progression. The Mercury-1 results showed similarity with Mercury-2 results. Therefore the superiority of IOP reduction from the FCNL group was consistent and can be considered for additional treatment of advanced glaucoma patients.[13-18]

Almost all studies included in this review reported conjunctival hyperemia, cornea verticillate, and corneal hemorrhages as the most common adverse events from ROCK inhibitors. The mechanism of conjunctival hyperemia induced by ROCK inhibitors hypothesize to be related to the ability of ROCK inhibitors to make smooth muscle relaxation and the resultant dilatation of the blood vessels. However, only a few patients discontinued the trials due to conjunctival hyperemia alone because it's usually only transient; the severity was mild to moderate, the severity not increasing with continued dosing, and more commonly reported from physical examination, not by patient's complaint. Corneal verticillate is a benign lipid deposit in corneal epithelium form through phospholipidosis which occurs when cationic amphiphilic drugs are complex with lysosomal phospholipids. Corneal verticillate has been reported as an ocular adverse event of ROCK inhibitors. It's usually bilateral, mild to moderate, asymptomatic with no impact on visual acuity, and resolved after treatment cessation. Conjunctival hemorrhage, usually only small petechial hemorrhages, is an adverse effect of ROCK inhibitors with mild to moderate severity. It usually didn't have an impact on visual acuity and self-resolving.[16 -18]

In FCNL studies, no new adverse events were reported that were not previously reported in Netarsudil and Latanoprost studies.[12-18] FCNL safety profile through month 12 showed similar to Netarsudil alone.[14] All studies in this review showed more ocular adverse events in ROCK inhibitors than its comparators (Timolol 0.2% and Latanoprost 0.005%). The relatively low rate of adverse events in ROCK inhibitors' comparators is due to the study enrollment criteria, which usually included patients who had previously been treated with Timolol 0.2% or Latanoprost 0.005% and excluded patients with contraindications to or have a history of adverse reactions to Timolol 0.2% or Latanoprost 0.005%[16-18]

## CONCLUSION

Netarsudil 0.02% (one of the ROCK inhibitors) proved inferior to Latanoprost 0.005% as a lowering IOP agent in glaucoma patients, even though not inferior to Timolol 0.5%. For OAG and OHT patients, Netarsudil 0.02% may not be used as a first-line IOP lowering agent. It can be an option as a second-line drug when a first line is ineffective. ROCK inhibitors are likely to have their greatest utility as adjunctive agents. Because their mechanism of action lowers aqueous humor outflow resistance, they should be additive to agents that act on the aqueous inflow or unconventional outflow.

Although it still needs longer-term follow-up data, FCNL can be an option to lower the IOP because of its clinical and statistically superior ocular hypotensive effect compared to its individual active components. FCNL also has a once-daily dosing regimen that potentially promotes adherence in long-term glaucoma treatment. Both Netarsudil 0.02% and FCNL have tolerable ocular adverse events. No new adverse events were found in FCNL that have not been observed previously in its active component.

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Table 4. Characteristics of studies with monotherapy Rho Kinase Inhibitor as the primary intervention

| No | Author | Year | Study Design | Evidence Level | Phase | Intervention | Sample Size | Subjects |
|---|---|---|---|---|---|---|---|---|
| 1. | Bacharach et al[16] | 2015 | Randomized, double mask, clinical trial | II | III | • Netarsudil 0.01%<br>• Netarsudil 0.02% q.d.<br>• Latanoprost 0.005% | 221 (224) | OAG, OHT |
| 2. | Serle et al[10] (ROCKET-1) | 2017 | Randomized, double mask, clinical trial | II | III | • Netarsudil 0.02% q.d.<br>• Timolol 0.5% | 367 (411) | OAG, OHT |
| 3 | Kahook et al[11] (ROCKET-2) | 2019 | Randomized, double mask, clinical trial | II | III | • Netarsudil 0.02% q.d.<br>• Netarsudil 0.02% b.i.d.<br>• Timolol 0.5% | 436 (756) | OAG, OHT |
| 4 | Khouri et al[9] (ROCKET-4) | 2019 | Randomized, double mask, clinical trial | II | III | • Netarsudil 0.02% q.d.<br>• timolol 0.5% | 557 (708) | OAG, OHT |

Table 5. Characteristics of studies with FCNL as the primary intervention

| No | Author | Year | Study Design | Evidence Level | Phase | Intervention | Sample Size | Subjects |
|---|---|---|---|---|---|---|---|---|
| 1. | Lewis, RA[12] | 2016 | Randomized, double mask, clinical trial | II | III | • FDC Netarsudil 0.01% -Latanprost 0.005%<br>• FDC Netarsudil 0.02% -Latanprost 0.005%<br>• Netarsudil 0.02%<br>• Latanoprost 0.005% | 292 (297) | OAG, OHT |
| 2. | Asrani et al (MERCURY-1)[13] | 2019 | Randomized, double mask, clinical trial | II | III | • FDC Netarsudil 0.02% -Latanprost 0.005%<br>• Netarsudil 0.02%<br>• Latanoprost 0.005% | 625 (718) | OAG, OHT |
| 3. | Brubaker et al (MERCURY-1)[14] | 2020 | Randomized, double mask, clinical trial | II | III | • FDC Netarsudil 0.02% -Latanprost 0.005%<br>• Netarsudil 0.02%<br>• Latanoprost 0.005% | 510 (718) | OAG, OHT |
| 4. | Walters et al (MERCURY-2) [18] | 2019 | Randomized, double mask, clinical trial | II | III | • FDC Netarsudil 0.02% -Latanprost 0.005%<br>• Netarsudil 0.02%<br>• Latanoprost 0.005% | 685 (750) | OAG, OHT |

Table 6. Treatment of Each Study

| No | Author | Dosage of main intervention | Group* 2 | | Group* 3 | | Group* 4 | | Follow-up Duration |
|---|---|---|---|---|---|---|---|---|---|
| **Primary intervention: Netarsudil 0.02%** | | | | | | | | | |
| 1 | Bacharach et al[16] | 1x/day | Latanoprost 0.005% | 1x/day | - | | - | | 28 days |
| 2 | Serle et al (ROCKET-1)[10] | 1x/day | Timolol 0.5% | 2x/day | - | | - | | 3 months |
| 3 | Kahook et al (ROCKET-2)[11] | 1x/day | Timolol 0.5% | 2x/day | Netarsudil 0.02% | 2x/day | | | 12 months |
| 4 | Khouri et al (ROCKET-4)[9] | 1x/day | Timolol 0.5% | 2x/day | - | | - | | 3 months (efficacy) 6 months (safety) |
| **Primary intervention: FCNL (Netarsudil 0.02%/Latanoprost 0.005%)** | | | | | | | | | |
| 1 | Lewis et al[12] | 1x/day | Latanoprost 0.005% | 1x/day | Netarsudil 0.02% | 1x/day | FDC netarsudil 0.01% / latanoprost 0.005% | 1x/day | 28 days |
| 2 | Asrani et al (MERCURY-1)[13] | 1x/day | Latanoprost 0.005% | 1x/day | Netarsudil 0.02% | 1x/day | - | | 3 months |
| 3 | Brubacker et al (MERCURY-1)[14] | 1x/day | Latanoprost 0.005% | 1x/day | Netarsudil 0.02% | 1x/day | - | | 12 months |
| 4 | Walters et al (MERCURY-2)[18] | 1x/day | Latanoprost 0.005% | 1x/day | Netarsudil 0.02% | 1x/day | - | - | 3 months |

*Groups 2-4 present data from comparator of primary intervention of each study.

Table 7. Baseline characteristics

| No | Author | Mean Age (SD) Group* | | | | Gender (M/F) Group* | | | | Previous Treatments (n(%)) Group* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| **Primary intervention: Netarsudil 0.02%** | | | | | | | | | | | | | |
| 1 | Bacharach et al[16] | 65.1 (11.3) | 65.1 (11.3) | | | 79/132 | 79/132 | | | **No data** | | | |
| 2 | Serle et al (ROCKET-1)[10] | 65.8 (11.65) | 64.2 (11.34) | | | 88/114 | 73/136 | | | 172 (85) | 195 (93) | 367 (83) | |
| 3 | Kahook et al (ROCKET-2)[11] | 65.3 (11.48) | 64.1 (12.46) | 63.0 (11.80) | | 103/148 | 89/165 | 101/150 | | 172 (85) | 195 (93) | 367 (83) | |
| 4 | Khouri et al (ROCKET-4)[9] | 64.1 (11.6) | 64.5 (11.0) | | | 143/208 | 120/237 | | | 221 (63) | 222 (62.2) | | |
| **Primary intervention: FCNL (Netarsudil 0.02%/Latanoprost 0.005%)** | | | | | | | | | | | | | |
| 1 | Lewis et al[12] | 65.4 (11.26) | 64.2 (73) | 65.1 (12.80) | 64.8 (11.28) | 27/47 | 34/39 | 27/46 | 35/43 | **No data** | | | |
| 2 | Asrani et al (MERCURY-1)[13] | <65$^{th}$: 109 patients >65$^{th}$: 129 patients | <65$^{th}$: 95 patients >65$^{th}$: 141 patients | <65$^{th}$: 107 patients >65$^{th}$: 137 patients | | 104/134 | 100/136 | 108/136 | | 182 (76.5) | 165 (69.1) | 183 (75) | |
| 3 | Brubacker et al (MERCURY-1)[14] | 64.4 (11.33) | 65.4 (10.98) | 64.6 (10.97) | | 104/134 | 100/136 | 108/236 | | 184 (77.3) | 167 (71.8) | 186 (76.2) | |
| 4 | Walters et al (MERCURY-2)[18] | 64.2 (11.81) | 64.3 (11.41) | 64.5 (10.58) | | 93/152 | 102/153 | 106/144 | | 159 (64.9) | 167 (66.8) | 161 (63.1) | |

* Group 1 presents data from the primary intervention given in each study (Netarsudil 0.02% or FDC Netarsudil 0.02%-Latanoprost 0.005%); meanwhile, groups 2-4 present data from comparator treatments of each study.

| No | Author | Mean Baseline IOP (mmHg) Group* | | | | Mean Post-Treatment IOP (mmHg / %) Group* | | | | Mean Reduction from Baseline (mmHg / %) Group* | | | | p value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | |
| **Main intervention: Netarsudil 0.02%** | | | | | | | | | | | | | | |
| 1 | Bacharach et al[16] | 25.8 | 25.6 | 25.5 | | 20.1 | 20.0 | 18.7 | | 5.5 | 5.7 | 6.8 | | P<0.001 |
| 2 | Serle et al (ROCKET-1)[10] | 23.42 | 23.37 | | | 19.81 | 18.47 | | | 3.61 | 4.8 | | | P<0.0001 |
| 3 | Kahook et al[11] (ROCKET-2) | 22.54 | 22.55 | 22.54 | | 18.80 | 17.96 | 17.55 | | 3.74 | 4.59 | 4.99 | | P<0.0001 |
| 4 | Khouri et al (ROCKET-4)[9] | 20.69 | 20.69 | | | 16.73 | 16.80 | | | 3.88 | 3.89 | | | P<0.0001 |
| **Main intervention: FCNL (Netarsudil 0.02%/Latanoprost 0.005%)** | | | | | | | | | | | | | | |
| 1 | Lewis et al[12] | 25.1 (2.3) | 25.1 (2.4) | 26.0 (2.8) | 25.4 (2.7) | 17.3 (2.8) | 16.5 (2.6) | 18.4 (2.6) | 19.2 (3.2) | 7.8 | 8.6 | 7.6 | 6.3 | P<0.0001 |
| 2 | Asrani et al (MERCURY-1)[13] | | 23.5 | 23.7 | | 18.1 | 17.1 | 15.6 | | -33.7% (-35.4, -32.1) | -27.6% (-28.9, -26.2) | -22.8% (-24.5, -21.2) | | P<0.0001 |
| 3 | Brubacker et al (MERCURY-1)[14] | 23.7 | 23.5 | 23.6 | | 16.2 | 17.6 | 17.9 | | 7.5 | 5.9 | 5.7 | | P<0.0001 |
| 4 | Walters et al (MERCURY-2)[18] | 23.5 | 23.5 | 23.6 | | 15.9 | 17.5 | 18.6 | | 7.6 | 6.0 | 5.0 | | P<0.0001 |

Table 8. Primary Endpoint

* Group 1 presents data from the primary intervention given in each study (Netarsudil 0.02% or FDC Netarsudil 0.02%-Latanoprost 0.005%); meanwhile, groups 2-4 present data from comparator treatments of each study.

Table 9. Adverse events of Rho Kinase Inhibitor

| Author | Intervention | Adverse Events |
|---|---|---|
| Bacharach et al[16] | Netarsudil 0,02% | Conjunctival/ocular hyperemia, increased lacrimation, subconjunctival hemorrhage, foreign body sensation |
| Serle et al (ROCKET-1)[10] | Netarsudil 0.02% | Conjunctival hyperemia, conjunctival hemorrhage, cornea verticillate, instillation site pain, erythema of the eyelid, reduced visual acuity. |
| Kahook et al (ROCKET-2)[11] | Netarsudil 0.02% | Conjunctival hyperemia, cornea verticillate, conjunctival hemorrhage, instillation site pain, lacrimation, erythema of the eyelid, reduced visual acuity, pruritus. |
| Khouri et al (ROCKET-4)[9] | Netarsudil 0,02% | Conjunctival hyperemia, cornea verticillate, conjunctival hemorrhage, increased lacrimation, erythema of the eyelid, blurred vision. |
| Lewis et al[12] | FDC netarsudil 0.02% - latanoprost 0.005% | Conjunctival hyperemia, conjunctival hemorrhage, increased lacrimation, eye pruritus, instillation site erythema, instillation site pain |
| Asrani et al (MERCURY-1)[13] | FDC netarsudil 0.02% - latanoprost 0.005% | Conjunctival hyperemia, conjunctival hemorrhage, conjunctival verticillate, eye pruritus, instillation site pain, increased lacrimation |
| Brubacker et al (MERCURY-1)[14] | FDC netarsudil 0.02% - latanoprost 0.005% | Conjunctival hyperemia, conjunctival hemorrhage, conjunctival verticillate, eye pruritus, instillation site pain. |
| Walters et al (MERCURY-2)[18] | FDC netarsudil 0.02% - latanoprost 0.005% | Conjunctival hyperemia, conjunctival verticillate, conjunctival hemorrhage, corneal disorder, instillation site pain and discomfort. |