Fixed-dose combination of AR-13324 and latanoprost: a double-masked, 28-day, randomised, controlled study in patients with open-angle glaucoma or ocular hypertension

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ABSTRACT

Background/aims To evaluate the ocular hypotensive efficacy of fixed-dose combinations of the Rho kinase inhibitor and norepinephrine transport inhibitor AR-13324 (0.01% and 0.02%) and latanoprost (PG324 Ophthalmic Solution) relative to the active components AR-13324 0.02% and latanoprost 0.005%, used bilaterally at night.

Methods This was a double-masked, randomised, parallel comparison study in patients with open-angle glaucoma or ocular hypertension. After washout, patients were randomised to one of four treatment arms and treated for 28 days. The primary efficacy variable was mean diurnal intraocular pressure (IOP) at day 29.

Results We randomised 298 patients, of whom 292 (98%) completed the study. Mean unmedicated diurnal IOPs (study eye) was 25.1, 25.1, 26.0 and 25.4 in the PG324 0.01%, PG324 0.02%, latanoprost and AR-13324 0.02% groups, respectively. On day 29, mean diurnal IOP decreased to 17.3, 16.5, 18.4 and 19.1 mm Hg, respectively. For the primary efficacy variable of mean diurnal IOP at day 29, PG324 0.02% met the criterion for statistical superiority relative to both latanoprost and AR-13324 0.02% (p<0.0001), providing additional IOP lowering of 1.9 and 2.6 mm Hg, respectively. PG324 0.01% also met the criterion for superiority. The most frequently reported adverse event was conjunctival hyperaemia with an incidence of 41% (30/73), 40% (29/73), 14% (10/73) and 40% (31/78) in the PG324 0.01%, PG324 0.02%, latanoprost and AR-13324 0.02% groups, respectively.

Conclusions In this short-term study, the fixed-dose combination of AR-13324 0.02% and latanoprost 0.005% in PG324 Ophthalmic Solution provides clinically and statistically superior ocular hypotensive efficacy relative to its individual active components at the same concentrations. The only safety finding of note was transient asymptomatic conjunctival hyperaemia which was typically of mild severity.

Trial registration number NCT02207491.

INTRODUCTION

Raised intraocular pressure (IOP) has been shown to be a significant risk factor for glaucomatous damage and progression by many large controlled studies.¹–³ The goal for treating patients with glaucoma is to lower the IOP to a targeted pressure in order to reduce the risk of further damage to the optic nerve.⁴–⁷

For many glaucoma patients, current glaucoma medications are not sufficiently effective as monotherapy to achieve target IOP. These patients are often prescribed two or more medications, which increases the complexity of the dosing regimen and often leads to decreased patient adherence.⁵ Fixed-dose combination (FDC) products such as timolol plus dorzolamide (Cosopt),⁶ timolol plus brimonidine (Combigan)⁷ and brinzolamide plus brimonidine (Simbrinz)⁸ simplify dosing regimens by providing two medications in a single bottle. However, these products still require at least twice-daily dosing. FDC’s of timolol plus a prostaglandin analogue¹²–¹⁴ are dosed once-daily, but not approved in several major countries, including the USA. The ideal FDC product would provide comparable efficacy as coadministration of two medications with the convenience of a once-daily eye drop regimen to enhance adherence without increased safety risk.

Inhibitors of Rho kinase (RKI) have emerged as a new class of IOP lowering medications that are designed to increase outflow through the trabecular meshwork and are currently being tested in the clinic.¹⁵–¹⁸ Aerie Pharmaceuticals has developed AR-13324, a dual RKI/norepinephrine transport inhibitor. Along with its activity at the trabecular meshwork, AR-13324 also decreases the production of aqueous humour,¹⁹ which may reflect inhibition of norepinephrine transporter. As well, AR-13324 decreases episcleral venous pressure in rabbits.²⁰ AR-13324 has been shown to produce clinically and statistically significant lowering of IOP in patients with once-daily dosing.²¹

PG324 Ophthalmic Solution is a novel FDC of AR-13324 formulated with the prostaglandin analogue latanoprost. The objectives of this study were to evaluate the ocular hypotensive efficacy of PG324 Ophthalmic Solution, 0.01% and 0.02% relative to the active components AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution 0.005%. A secondary objective was to evaluate the ocular and systemic safety of PG324 Ophthalmic Solution, 0.01% and 0.02%.

METHODS

Design
This was a double-masked, randomised, parallel comparison study in which patients were randomised to one of four treatment arms: PG324 Ophthalmic Solution, 0.02% or Latanoprost Ophthalmic Solution, 0.02% and AR-13324 formulated with the prostaglandin analogue.
Clinical science

Ophthalmic Solution 0.005%, each dosed once-daily (pm) for 28 days. Patients attended study visits for efficacy and safety measures on days 8, 15, 29 and 30.

Study patients

Individuals were eligible for inclusion if they were adults with a diagnosis of open-angle glaucoma (OAG) or ocular hypertension (OHT) and corrected visual acuity in each eye of +1.0 logMAR or better by Early Treatment Diabetic Retinopathy Study (ETDRS). After washout of ocular hypotensive medication if needed,22 IOP in the study eye was required to be ≥24 mm Hg and <36 mm Hg at two qualification visits (08:00 h), 2–7 days apart, and, at the second qualification visit, IOP was required to be ≥21 mm Hg at 10:00 and 16:00 h in the same eye(s). Excluded from the study were individuals with any of the following characteristics: pseudoexfoliation or pigment dispersion component, history of angle closure or narrow angles. Also excluded were patients with previous glaucoma intraocular surgery, laser or refractive procedures, current infection or inflammation and ocular trauma within 6 months. Women of childbearing potential who were pregnant, nursing, planning a pregnancy or not using a medically acceptable form of birth control were also excluded. The study was approved by governing institutional review boards and all patients gave written informed consent.

Study conduct

Individuals who were potential patients underwent an initial screening visit including measurement of heart rate and blood pressure, and an ophthalmic examination to include ocular inflammation and ocular trauma within 6 months. Women of childbearing potential who were pregnant, nursing, planning a pregnancy or not using a medically acceptable form of birth control were also excluded. The study was approved by governing institutional review boards and all patients gave written informed consent.

Statistics

Several statistical decisions were made a priori. The primary efficacy endpoint was the mean diurnal IOP across patients within a treatment group at day 29. Secondary efficacy endpoints included mean IOP at each post-treatment timepoint, mean change from diurnally adjusted baseline IOP at each timepoint, and percentages of patients achieving prespecified percentage reductions in IOP from baseline to day 29.

With a sample size in each group of 70, the study was estimated to have 90.3% power to detect a difference between PG324 Ophthalmic Solutions, 0.01% or 0.02% and Latanoprost Ophthalmic Solution, 0.005% and 98.9% power to detect a difference between PG324 Ophthalmic Solution, 0.01% or 0.02% and AR-13324 Ophthalmic Solution, 0.02%, in mean diurnal IOP on day 29 assuming a mean difference of −1.5 mm Hg (to latanoprost) and −2.0 mm Hg (to AR-13324), a one-sided α=0.05, and a conservative common SD of 3.0 mm Hg.

The primary population for efficacy was a modified intent-to-treat, defined as all randomised patients who received at least one dose of study medication, had all three baseline IOP measurements (i.e., visit 3, day 1 at 08:00, 10:00 and 16:00 h), and had at least one scheduled post-treatment time-specific IOP measurement.

All statistical output was produced with SAS Software, V9.2.

RESULTS

Disposition and demographics

Of the 332 screened, 298 were randomised, 297 were treated (99.7%) and 292 completed the study (98.0%). Of the six patients who did not complete the study, three were discontinued for adverse events (latanoprost, corneal ulcer at day 8; PG324 0.02%, superficial punctate keratitis at day 4; PG324 0.02%, subconjunctival haemorrhage at day 25), and one each discontinued for withdrawal of consent, disallowed concurrent medication and protocol violation.

The safety population included 297 patients (one patient in the PG324 0.01% group was not considered in the safety population as this patient was randomised but not treated). One additional patient was excluded from the modified Intent to Treat analysis population (one patient in the PG324 0.02% group did not provide IOP data at visits 4, 5 or 6) leaving 296 patients.

The demographics of the study population are shown in Table 1. There were no clinically or statistically significant differences among treatment groups. The population was 59% female (175/298) and had a mean age (±SD) of 64.9±11.6 years (range 26–92). The proportion of patients 65 years of age or greater was 58% (173/298). The population was 79% Caucasian (236/298), 18% African–American (54/298), 2% Asian (7/298) and 0.3% Native American (1/298). Twenty-two per cent (64/298) of patients self-identified as Hispanic. The most frequent iris colour was brown/black (62%, 184/298), followed by blue/grey/green (27%, 79/298) and hazel (12%, 35/298). There were no clinically or statistically significant differences among treatment groups (p≥0.4450).

Mean (±SD) unmedicated diurnal IOP (average of all measurements on day 1, prior to study medication) in the study eye was 25.1±2.3, 25.1±2.4, 26.0±2.8 and 25.4±2.7 mm Hg in the PG324 0.01%, PG324 0.02%, latanoprost and AR-13324 0.02% groups, respectively, with no significant difference among treatments (p=0.1081). In the study eye, mean corneal thickness was 553±30 μm, mean cup:disc ratio was 0.5±0.2 and average mean deviation was −1.5±2.8 dB. Investigator diagnosis of patients was 56% (166/298) as OAG and 44% (132/298) as OHT.

Efficacy

On day 29, mean diurnal IOP decreased to 17.3±2.8, 16.5±2.6, 18.4±2.6 and 19.1±3.2 mm Hg, respectively (figure 1). For the primary efficacy variable of mean diurnal IOP at day 29, PG324 0.02% met the criterion for statistical superiority relative to both latanoprost and AR-13324 0.02%, (p<0.0001), providing additional IOP lowering of 1.9 (90% CI 1.2 to 2.6) and 2.6 mm Hg (90% CI 1.8 to 3.4), respectively. PG324 0.01% also met the criterion for statistical superiority relative to latanoprost and AR-13324 0.02% (additional 1.1 and 1.8 mm Hg.
### Table 1 Demographics (randomised)

<table>
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<th>PG324 0.02% N=73</th>
<th>Latanoprost 0.005% N=73</th>
<th>AR-13324 0.02% N=78</th>
<th>All patients N=298</th>
<th>p Value*</th>
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<td>65.0</td>
<td>67.0</td>
<td>66.0</td>
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<td>(36, 92)</td>
<td>(29, 88)</td>
<td>(30, 86)</td>
<td>(26, 92)</td>
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<td>17 (21.8)</td>
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<td><strong>Ethnicity—n (%)</strong></td>
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<td>59 (80.8)</td>
<td>63 (80.8)</td>
<td>234 (78.5)</td>
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<td>Iris colour—study eye—n (%)</td>
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<td>Blue/Grey/Green</td>
<td>21 (28.4)</td>
<td>24 (32.9)</td>
<td>14 (19.2)</td>
<td>20 (25.6)</td>
<td>79 (26.5)</td>
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Percentages are based on the number of patients (N) in a given treatment group for the population being analysed.

*p Values are from tests of differences across treatment groups and are 2-sided. Fisher’s exact tests were used for the categorical variables and one-way ANOVAs were used for the continuous variables.

p=0.0071 and 0.0002, respectively). Both concentrations of PG324 were also more effective than latanoprost and AR-13324 0.02% at days 8 and 15, with PG324 0.02% providing additional IOP lowering of 2.8 (90% CI 2.0 to 3.6) and 2.6 mm Hg (90% CI 1.7 to 3.5), respectively, and PG324 0.01% providing an additional 2.8 (90% CI 1.9 to 3.7) and 2.9 mm Hg (90% CI 2.0 to 3.8), respectively.

Across the nine on-treatment timepoints, mean IOP decreased to 16.0–18.4, 15.6–17.0, 17.7–19.6 and 17.9–20.3 mm Hg (SD: 2.8–4.3) in the PG324 0.01%, PG324 0.02%, latanoprost and AR-13324 0.02% groups, respectively, resulting in mean differences in favour of PG324 0.02% of 1.6–3.2 mm Hg versus latanoprost and 1.7–3.4 mm Hg versus AR-13324 (all p<0.001, figure 2). ANCOVA was used to adjust for the higher unmedicated baseline IOP in the latanoprost group and produced differences in the change from baseline least square means in favour of PG324 0.02% of 1.4–2.9 mm Hg versus latanoprost and 1.6–3.3 mm Hg versus AR-13324 (p≤0.006). On day 30 at 08:00 h, 36 h after the last dose (off-treatment), mean IOP was 20.3, 19.6, 21.9 and 21.0 mm Hg in the PG324 0.01%, PG324 0.02%, latanoprost and AR-13324 0.02% groups, respectively. Ocular hypotensive efficacy was observed 36 h after the last dose, as evidenced by mean IOP on day 30 still being several mm Hg below mean unmedicated baseline IOP (figure 2).

At day 29, the proportion of patients with mean diurnal IOP of ≤18 mm Hg was 63% (46/73), 69% (47/72), 47% (34/73) and 39% (30/78) in the PG324 0.01%, PG324 0.02%, latanoprost and AR-13324 0.02% groups, respectively (p=0.0105 for PG324 0.02% vs latanoprost, figure 3).

### Safety

The most frequently reported adverse event was conjunctival hyperaemia with an incidence of 41% (30/73), 40% (29/73), 14% (10/73) and 40% (31/78) in the PG324 0.01%, PG324 0.02%, latanoprost and AR-13324 0.02% groups, respectively. The severity of conjunctival hyperaemia was mild in most of the patients (93% (28/30), 76% (22/29), 100% (10/10) and 84% (26/31), respectively). Also reported was instillation site erythema (16% (12/73), 19% (14/73), 1% (1/73) and 22% (17/78)) and instillation site pain (7% (5/73), 11% (8/73), 3% (2/73) and 5% (4/78)), respectively. There were 11 patients with conjunctival haemorrhage of varying severity, one in the PG324 0.01% group (sight-threatening), five in the PG324 0.02% group (four mild, one moderate), none in the latanoprost group and five in the AR-13324 0.02% group (four mild, one moderate, table 2).

Five patients had study medication discontinued for adverse events (three in the PG324 0.02% group, one in the latanoprost group and one in the AR-13324 0.02% group).

There were five serious adverse events in three patients (all in the latanoprost group), none of which was judged related to treatment: one patient with a corneal ulcer, one patient with a perforated colon and two episodes of diverticulitis and one patient with acute cholecystitis. There was no evidence of...
treatment-related effects on visual acuity, clinical laboratory or haematology values, heart rate or blood pressure.

Biomicroscopy
At baseline (day 1, 08:00 h), 4% (11/297) of patients across all groups had conjunctival hyperaemia of mild severity. On day 8, 08:00 h (the first on-treatment visit and approximately 12 h after instillation), conjunctival hyperaemia (mild or moderate) was seen in 41% (30/73), 49% (36/73), 8% (6/73) and 35% (27/78) in the PG324 0.01%, PG324 0.02%, latanoprost and AR-13324 treatment groups, respectively. This rate remained at approximately this level or lower throughout the 28 days of treatment. At day 29, 08:00 h, the rate was 32% (23/73), 44% (32/73), 10% (7/73) and 29% (23/78), respectively. The hyperaemia for PG324 and AR-13324 was transient and self-limiting, in that at day 30, 08:00 h (approximately 36 h after last instillation), the rate had reduced to 14% (10/73), 25% (18/73), 5% (4/73) and 19% (15/78), respectively.

Figure 1  Mean±SEM. Diurnal intraocular pressure (mm Hg, modified Intent to Treat analysis population).

Figure 2  Mean±SEM. Intraocular pressure (mm Hg, modified Intent to Treat analysis population).
DISCUSSION

For the primary efficacy variable of mean diurnal IOP at day 29, PG324 0.02% met the criterion for statistical superiority relative to both latanoprost and AR-13324 0.02% (p<0.0001). PG324 0.02% produced greater IOP reductions than PG324 0.01%, although 0.01% also met the criterion for statistical superiority relative to latanoprost and AR-13324 0.02% (p=0.0071 and 0.002). The statistical superiority of PG324 0.02% to each of its active components was seen at the first on-treatment visit at day 8, and remained relatively constant through day 29.

Furthermore on day 30, approximately 36 h after the last dose, both PG324 formulations, as well as AR-13324 alone, maintained lower IOPs than latanoprost alone.

Both concentrations of PG324 were well tolerated. The most frequently reported adverse event was conjunctival hyperaemia with an incidence of 41% and 40% for 0.01% and 0.02%, respectively. For the most part, the events were mild and transient. The presumed mechanism of the hyperaemia is relaxation of vascular smooth muscle.27 The incidence of hyperaemia adverse events for AR-13324 alone was 40%, indicating that the addition of latanoprost to AR-13324 in PG324 neither increased nor decreased the incidence of hyperaemia. There was a low incidence (1.4%–6.8%) of mild to moderate conjunctival haemorrhage among patients treated with PG324 or AR-13324. The mechanistic cause of this finding is unknown, but it is possible that vasodilation may sensitise some individuals to known...
triggers of conjunctival haemorrhage, such as coughing, sneezing and eye rubbing.

The ocular hypotensive effect of both positive controls, latanoprost and AR-13324 was similar to previous studies, supporting the validity of the current study. All four treatments provided statistically (p<0.0001) and clinically significant (6.2 to 9.1 mm Hg) decreases in mean diurnal IOP from unmedicated baseline. PG324 0.02% produced mean IOPs of 15.6–17 mm Hg across all timepoints compared to mean IOPs of 17.7–19.6 mm Hg produced by latanoprost. This corresponded to differences in IOP of 1.6–3.2 mm Hg in favour of PG324 0.02%. Furthermore, the greater IOP-lowering effect for PG324 persisted 36 h after the last dose with a difference of 2.2 mm Hg in favour of PG324 on day 30. The additivity of these two agents, ~2 mm Hg, was at least as great as other FDCs approved in the USA, Europe and/or Japan. Thus, we conclude that additivity of the present FDC is clinically significant. As this study was only 1 month in duration, the clinical utility of PG324 as a once-daily FDC therapy will require evaluation in a study of longer duration.

In conclusion, the FDC of AR-13324 0.02% and latanoprost 0.005% in PG324 Ophthalmic Solution 0.02% provides clinically and statistically superior ocular hypotensive efficacy relative to its individual active components at the same concentrations. The only safety finding of note was transient asymptomatic conjunctival hyperaemia which was typically of mild severity.

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Collaborators

Contributors
RAL, BL, NR, CCK, DWU and GDN: providing conception and design, data analysis and interpretation, reviewing the manuscript.

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Competing interests
BL and CCK and NR are employees of, and stockholders in Aerie Pharmaceuticals, Inc. GDN is a consultant for Aerie Pharmaceuticals, Inc. RAL is a consultant for Aerie Pharmaceuticals, Inc. and several other ophthalmic pharmaceutical and medical device companies, and a stockholder in Aerie Pharmaceuticals, Inc.

Ethics approval
Schulman Associates.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data sharing statement
This research is part of the development of AR-13324 by Aerie Pharmaceuticals, Inc.

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