Netarsudil for open-angle glaucoma or ocular hypertension

**LAY SUMMARY**

Glaucoma is a serious condition caused by abnormal pressure within the eye leading to blindness. All glaucoma treatments aim to prevent further damage to sight, but any damage to vision that has already been caused by glaucoma cannot be repaired. Glaucoma can be treated with eye drops, tablets, laser surgery, eye surgery or a combination of these methods.

Netarsudil is a new eye drop to treat patients with glaucoma. It works by reducing the pressure and increasing fluid removal from the eye to prevent further damage to the eye. Netarsudil is taken as an eye drop once a day.

If licensed for use in the UK, it could be a new treatment option for patients with glaucoma which works differently compared to other glaucoma eye drops.

NIHR HSRIC ID: 9615
TARGET GROUP

• Glaucoma or ocular hypertension — open-angle.

TECHNOLOGY

DESCRIPTION

Netarsudil (Rhopressa; AR-13224) inhibits both Rho kinase and the norepinephrine transport protein. The company considers the drug to be a triple-action product, affecting the major pathways involved in the control of intraocular pressure, leading to reduced aqueous humour production, decreased episcleral venous pressure and increased fluid outflow through the trabecular meshwork and the uveoscleral pathway. In phase 3 clinical trials, netarsudil was administered as a 0.02% ophthalmic solution once daily.

Netarsudil does not currently have Marketing Authorisation in the EU for any indication.

Netarsudil is not in clinical trials for any other indication.

INNOVATION and/or ADVANTAGES

If licensed, netarsudil will offer an additional topical treatment option for patients with ocular hypertension or glaucoma, with a different mechanism of action from current available preparations.

DEVELOPER

Aerie Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

Phase III clinical trials.

PATIENT GROUP

BACKGROUND

The glaucomas are a group of optic neuropathies characterised by progressive degeneration of retinal ganglion cells, resulting in a distinct appearance of the optic disc and retinal nerve fibre layer and a concomitant pattern of visual loss. Without adequate treatment, glaucoma can progress to visual disability and eventual blindness. Glaucoma is usually associated with an increase in intraocular pressure (IOP) above the normal value, usually estimated at 21 mmHg; however, surveys show that 20-52% of patients with glaucoma have IOP within the normal range. Ocular hypertension is a term used to describe any situation in which IOP is greater than 21 mmHg, with absence of glaucomatous defects on visual-field testing; and it can last for many years without development of glaucoma.

The overall risk of developing glaucoma increases with the number and strength of risk factors. It increases substantially with the level of IOP elevation and with increasing age. Other strong risk factors include high myopia, diabetes, black ethnicity and a family history of glaucoma.
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glaucoma in a first degree relative\textsuperscript{3,4}. Identifiable gene mutations are implicated but account for only about 5% of cases of adult onset glaucoma\textsuperscript{4}.

Glaucoma is classified into two major categories according to the appearance and obstruction of the drainage pathway at the iridocorneal angle\textsuperscript{4}. Primary open angle glaucoma is the most common type of glaucoma, accounting for over 70% of cases. It is an IOP related optic neuropathy that gives rise to characteristic optic disc changes and visual field loss. In its early stages it affects peripheral visual field only, but as it advances it results in loss of visual acuity and can cause blindness\textsuperscript{4}.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:


**CLINICAL NEED and BURDEN OF DISEASE**

Glaucoma is one of the most common ophthalmic conditions encountered in primary and secondary care\textsuperscript{5}. The World Health Organization estimated that in 2010, glaucoma accounted for 2% of visual impairment and 8% of blindness worldwide\textsuperscript{4}. Disability adjusted life years attributable to glaucoma more than doubled between 1990 and 2010 due to a global increase in the number of older people\textsuperscript{4,6}. Glaucoma is the leading cause of irreversible blindness in the world and the social and economic burden is likely to increase in the future because of longer life expectancy and an ageing population\textsuperscript{2,6}. In the UK, glaucoma is the second most common cause for registration of visual impairment, accounting for 9-12% of registrations in people over the age of 65 years\textsuperscript{4}. Open-angle glaucoma is the most common type of glaucoma; it has an overall prevalence of approximately 2% of people over the age of 40 years and 5% of people over the age of 80 years\textsuperscript{7}.

Ocular hypertension has an overall prevalence of 3-5% of people over the age of 40 years\textsuperscript{8}. Approximately 10% of people with untreated ocular hypertension go on to develop glaucoma\textsuperscript{8}.

In England and Wales, it is estimated that more than 500,000 people have glaucoma\textsuperscript{9}. In 2014-15, there were 21,792 hospital admissions for glaucoma (ICD-10 H40) in England, resulting in 4,804 bed days and 21,964 finished consultant episodes\textsuperscript{10}.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

CURRENT TREATMENT OPTIONS

The management of glaucoma focuses on early recognition and treatments to reduce IOP. Medical, laser, and surgical options are available for lowering IOP. Typically, the patient is started on glaucoma eye drop monotherapy, with extra drops being added as required, so that two or more different types of drug can be used in cases that are difficult to control. If the maximum tolerated treatment regimen is unsuccessful, a laser intervention may be advised or the patient may proceed directly to surgery.

Current treatment options include:

- **Topical drug therapies (eye drops):**
  - Prostaglandin analogues to increase outflow—latanoprost; bimatoprost; tafluprost; travoprost.
  - Beta-adrenergic receptor blockers to decrease aqueous production—betaxolol; levobunolol; timolol; carteolol.
  - Alpha-agonists to increase outflow and decrease aqueous production—apraclonidine; brinonidine.
  - Carbonic anhydrase inhibitors to decrease aqueous production—brinzolamide; dorzolamide.
  - Parasympathomimetic to increase outflow—pilocarpine.
- **Oral therapy**—carbonic anhydrase inhibitors. Patients may experience tingling in their fingers and toes, lethargy, and loss of appetite; making it unsuitable for long term treatment but useful for controlling acute increases in pressure or managing raised IOP in the short term while awaiting surgery.
- **Laser treatment**—laser trabeculoplasty is used to open up blocked drainage tubes. Cyclodiode and endocycloide laser of the ciliary body are used for severe glaucoma if standard surgery is not effective.
- **Surgical treatment**—trabeculectomy, which creates a guarded fistula into the wall of the eye to allow a slow egress of aqueous humour into the subconjunctival space.

Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02207491, AR-13324-CS301; AR-13324 vs timolol maleate; phase III.</th>
<th>NCT02207621, AR-13324-CS302; AR-13324 vs timolol maleate; phase III.</th>
<th>NCT02246764, AR-13324-CS303; AR-13324 vs timolol maleate; phase III.</th>
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<tbody>
<tr>
<td>Source of information</td>
<td>Trial registry¹.</td>
<td>Trial registry¹².</td>
<td>Trial registry¹⁴.</td>
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<td>Location</td>
<td>USA.</td>
<td>USA.</td>
<td>USA.</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
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</tbody>
</table>
## Participants

| n=411; 0-2 years of age and 18 years or older; diagnosis of open-angle glaucoma or ocular hypertension; unmedicated IOP>20mmHg and <27mmHg in the study eye at 2 qualification visits, 2-7 days apart, with an IOP >17mmHg and <27mmHg in the same eye at the second visit; corrected visual acuity in each eye +1.0 logMAR or better by Early Treatment Diabetic Retinopathy Study (ETDRS); no pseudoexfoliation or pigment dispersion component of glaucoma; no history of angle closure or narrow angles; no previous laser peripheral iridotomy; no IOP ≥27mmHg in either eye; no use of more than 2 ocular hypotensive medications within 30 days of screening no contraindications to beta-adrenoceptor antagonists; no previous glaucoma intraocular surgery or glaucoma laser procedures in either eye (including laser peripheral iridotomy); no refractive surgery; no ocular trauma within 6 months prior to screening; no ocular surgery or non-refractive laser treatment within 3 months prior to screening; no recent or current ocular infection, inflammation blepharitis, conjunctivitis, and no history of herpes simplex or zoster keratitis; no clinically significant ocular disease in either eye including severe glaucomatous damage; no central corneal thickness >600µm at screening. |
| n=690 (planned); 0-2 years of age and 18 years or older; diagnosis of open-angle glaucoma or ocular hypertension; unmedicated IOP>20mmHg and <27mmHg in the study eye at 2 qualification visits; corrected visual acuity in each eye equivalent to 20/200; no pseudoexfoliation or pigment dispersion component of glaucoma; no history of angle closure or narrow angles; no previous laser peripheral iridotomy; no IOP ≥27mmHg in either eye; no more than 2 ocular hypotensive medications within 30 days of screening; no contraindications to beta-adrenoceptor antagonists; no previous glaucoma intraocular surgery or glaucoma laser procedures in either eye; no refractive surgery; no ocular trauma within 6 months prior to screening; no ocular surgery or non-refractive laser treatment within 3 months prior to screening; no recent or current ocular infection, inflammation blepharitis, conjunctivitis, and no history of herpes simplex or zoster keratitis; no clinically significant ocular disease in either eye including severe glaucomatous damage; no central corneal thickness >600µm at screening. |
| n=240 (planned); 19-99 years of age; diagnosis of open-angle glaucoma or ocular hypertension; unmedicated IOP>20mmHg and <27mmHg in the study eye at 2 qualification visits, 2-7 days apart, with an IOP >17mmHg and <27mmHg in the same eye at the second visit; corrected visual acuity in each eye +1.0 logMAR or better by ETDRS; no pseudoexfoliation or pigment dispersion component of glaucoma; no history of angle closure or narrow angles; no previous laser peripheral iridotomy; no IOP ≥27mmHg in either eye; no more than 2 ocular hypotensive medications within 30 days of screening; no contraindications to beta-adrenoceptor antagonists; no previous glaucoma intraocular surgery or glaucoma laser procedures in either eye; no refractive surgery; no ocular trauma within 6 months prior to screening; no ocular surgery or non-refractive laser treatment within 3 months prior to screening; no recent or current ocular infection, inflammation blepharitis, conjunctivitis, and no history of herpes simplex or zoster keratitis; no clinically significant ocular disease in either eye including severe glaucomatous damage; no central corneal thickness >600µm at screening. |

## Schedule

<p>| Randomised to AR-13324 0.02% ophthalmic solution once daily; or timolol maleate 0.5% ophthalmic solution once daily. The duration of treatment has not been reported. |
| Randomised to AR-13324 ophthalmic solution once daily; or AR-13324 twice daily; or timolol maleate ophthalmic solution twice daily. The dosage and duration of treatment have not been reported. |
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<tr>
<th>Follow-up</th>
<th>Primary outcome/s</th>
<th>Secondary outcome/s</th>
<th>Key results</th>
<th>Adverse effects (AEs)</th>
<th>Expected reporting date</th>
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<tr>
<td>Not reported.</td>
<td>IOP.</td>
<td>Ocular safety.</td>
<td>Not reported.</td>
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<td>Not reported.</td>
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<tr>
<td>Not reported.</td>
<td>Safety; visual acuity using ETDRS; evaluation of anterior and posterior segment.</td>
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<th>Design</th>
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<tr>
<td>NCT01528787; AR-13324-CS201; AR-13324 vs placebo; phase II.</td>
<td>Aerie Pharmaceuticals.</td>
<td>Complete.</td>
<td>Trial registry</td>
<td>USA.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
</tbody>
</table>

<p>| Participants | n=700 (planned); 18 years and older; diagnosis of open-angle glaucoma or ocular hypertension; unmedicated IOP≥20mmHg and &lt;30mm Hg in the study eye at 2 qualification visits; corrected visual acuity in each eye equivalent to 20/200; no pseudoexfoliation or pigment dispersion component of glaucoma; no history of angle closure or narrow angles; no IOP ≥30mmHg in both eyes; no more than 2 hypotensive ocular medications within 30 days of screening; no contraindications to beta-adrenoceptor antagonists; no previous glaucoma intraocular surgery or glaucoma laser procedures in either eye (including laser peripheral iridotomy); no refractive surgery; no ocular trauma within 6 months prior to screening; no ocular surgery or non-refractive laser treatment |
| n=224; 18 years and older; diagnosis of open-angle glaucoma or ocular hypertension; unmedicated IOP≥24mmHg in the study eye at 2 qualification visits, 2-7days apart, with an IOP ≥22mmHg in the same eye at the second visit; corrected visual acuity in each eye +1.0 logMAR or better by ETDRS; no pseudoexfoliation or pigment dispersion component of glaucoma; no history of angle closure or narrow angles; no IOP &gt;36mmHg in both eyes; no more than 2 ocular hypotensive medications within 30 days of screening; no previous glaucoma intraocular surgery or glaucoma laser procedures in either eye (including laser peripheral iridotomy); no refractive surgery; no ocular trauma within 6 months prior to screening; no ocular surgery or non-refractive laser treatment |
| n=85; 18 years and older; diagnosis of open-angle glaucoma or ocular hypertension; unmedicated IOP≥24mmHg in the study eye at 2 qualification visits, 2-7days apart, with an IOP ≥21mmHg in the same eye at the second visit; corrected visual acuity in each eye +1.0 logMAR or better by ETDRS; no pseudoexfoliation or pigment dispersion component of glaucoma; no history of angle closure or narrow angles; no IOP &gt;36mmHg in both eyes; no more than 2 ocular hypotensive medications within 30 days of screening; no previous glaucoma intraocular surgery or glaucoma laser procedures in either eye (including laser peripheral iridotomy); no refractive surgery; no ocular trauma within 6 months prior to screening; no ocular surgery or non-refractive laser treatment |</p>
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<th>Horizon Scanning Research &amp; Intelligence Centre</th>
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<td>within 3 months prior to screening; no recent or current ocular infection or inflammation; no mean corneal thickness &gt;620µm at screening.</td>
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<tr>
<td>Adverse effects (AEs)</td>
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</table>
Expected reporting date | Estimated study completion date is reported as November 2016. | - | Not reported.

ESTIMATED COST and IMPACT

COST

The cost of netarsudil is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Other
- Reduced symptoms or disability
- No impact identified

Impact on Health and Social Care Services
- Increased use of existing services
- Re-organisation of existing services
- Other
- Decreased use of existing services
- Need for new services
- None identified

Impact on Costs and Other Resource Use
- Increased drug treatment costs
- Other increase in costs
- Other: uncertain unit cost compared to existing alternative medications.
- Reduced drug treatment costs
- Other reduction in costs
- None identified

Other Issues
- Clinical uncertainty or other research question identified
- None identified

REFERENCES