The Effects of Netarsudil Ophthalmic Solution on Aqueous Humor Dynamics in Humans

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PURPOSE

• Netarsudil is a once-daily, fixed-dose regimen (ROCK) and norepinephrine transporter (NET) inhibitor that was specifically designed for the treatment of patients with glaucoma or ocular hypertension.1

• Netarsudil has been shown to reduce intraocular pressure (IOP) in animal studies by:1

  - Increasing aqueous humor outflow facility through the trabecular meshwork
  - Lowering episcleral venous pressure (EVP, via inhibition of ROCK)
  - Decreasing aqueous humor production (possibly via inhibition of NET)

In this study (NCT02406287), we assessed the effect of netarsudil on aqueous humor dynamics in humans.

METHODS

Study design

• Randomized, double-masked phase 1 study
• 11 healthy subjects
• 18 years of age or older
• IOP 14–21 mmHg monthly

Day 1 (baseline)

• Measured IOP, EVP, and aqueous humor flow rate
• Calculated uncontrolled outflow
• Treated every morning for 7 days
• Study: netarsudil 0.02%
• Controlled eye vehicle

Day 8:

• Measured IOP, EVP, aqueous humor flow rate
• Calculated uncontrolled outflow
• Safety
  - Adverse events, visual acuity, biomicroscopy examination
  - Statistics analysis
  - Variables after treatment were compared to baseline using paired t-tests (2-sided 95% and 95% confidence intervals where applicable)

Aqueous humor dynamics

• Outflow facility: by custom digital Schiotz tonography2
• IOP: 4-minute recording
• Outflow facility determined using Grant equation3

Aqueous humor flow rate: by fluorophotometry4

• 2 fluorescent fluorophores topicaly at 2:00 am
• Fluorescein concentration in cornea and anterior chamber measured by scanning fluorophotometry5 at 8:00 am, 10:00 am, and 12:00 pm

Aqueous humor flow rate calculated by fluorescein clearance6

Episcleral venous pressure: by automated episcleral venogrammetry (Figure 1)

• Inflatable bulb placed over eye
• Collapse of vessel recorded by a video camera as pressure inside the bulb increased
• Applied pressure at initiation of collapse accepted as venous pressure

Uncontrolled (unvascularized) outflow rate: calculated by using the modified Goldmann equation

\[ \text{U} = \frac{\text{Q} - \text{C} \times 0.2}{\text{P}} \]

where

- U = uncontrolled outflow rate
- Q = aqueous humor flow rate
- C = venous outflow pressure
- IOP = intraocular pressure

RESULTS

Table 1. Disposition and baseline characteristics

<table>
<thead>
<tr>
<th>All Subjects, N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of randomized subjects*</td>
<td>11 (100.0)</td>
</tr>
<tr>
<td>Study completion</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td>Discontinued study</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Gender</td>
<td>Black/African American 1 (9.1)</td>
</tr>
<tr>
<td>Race</td>
<td>Hispanic/Latin 1 (9.1)</td>
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<tr>
<td>Sex</td>
<td>Male 1 (9.1)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>White 10 (90.9)</td>
</tr>
<tr>
<td>Age (SD, years)</td>
<td>49.6 ± 13.8 (21–64)</td>
</tr>
</tbody>
</table>

Safety

• All subjects reported ocular treatment-emergent adverse events (TEAEs) in the netarsudil-treated eye.
• Ocular treatment-emergent adverse events (TEAEs) included:
  - One subject reported mild dry eye.

Table 1. Disposition and baseline characteristics

- No significant change in calculated uveoscleral outflow rate.
- No significant change in calculated episcleral venous pressure.

Differences in IOP, EVP, and outflow facility vs baseline and vs placebo reached statistical significance.

CONCLUSIONS

• Once-daily dosing of netarsudil ophthalmic solution 0.02% lowered IOP in a phase 1 study, consistent with previous reports.1

• The primary IOP-lowering mechanism was an increase in outflow facility (trabecular outflow).

• A statistically significant decrease in EVP from baseline was also observed.

• Changes in aqueous humor flow and uncontrolled outflow did not achieve statistical significance.

• Mild, transient conjunctival hyperemia observed after AM dosing is consistent with the pharmacology of the major and minor reports.1,11

• Netarsudil ophthalmic solution 0.02% is a novel potential option that reduces IOP in humans by a unique combination of mechanisms.

REFERENCES


DISCLOSURE

The authors would like to thank Melissa Bartol of the Mayo Clinic, Aquous Humor Dynamics Laboratory and Swetha Meenakshi of Aerie Pharmaceuticals, Inc. for their assistance.

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SUPPORT