Product Discovery & Development

RhoKing glaucoma

By Erin McCallister
Senior Writer

Although its AR-12286 is not the most advanced Rho kinase inhibitor in the increasingly crowded glaucoma space, **Aerie Pharmaceuticals Inc.** believes the compound's potency and specificity will allow it to compete. Last week, the biotech announced top line data from a Phase IIa trial in which AR-12286 showed a favorable effect on intraocular pressure.

In the U.S. double-blind study in 88 patients, patients were given AR-12286 or sham eye drop once in the morning, once at night, or twice a day. Each dosing regime was administered for one week for a total of three weeks. Intraocular pressure (IOP) was measured for each dosing regime. No serious side effects were reported.

The maximum change in mean intraocular pressure (IOP) from baseline was 28% for the 0.25% solution of AR-12286 dosed twice daily. The company has not disclosed the p-value, but said the mean change from baseline was statistically significant for all dose arms.

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> **Tom van Haarlem, Aerie Pharmaceuticals**

According to President and CEO Tom van Haarlem, the results are consistent with those seen for other glaucoma medications, including Xalatan latanoprost from **Pfizer Inc.** According to Xalatan's label, once-daily dosing of the prostaglandin analog results in a 25-32% mean change in IOP from baseline.

Aerie co-founder David Epstein told BioCentury the highest dose of once-daily AR-12286 also resulted in sustained 24-hour pressure lowering. Epstein is also chairman of the department of ophthalmology at **Duke University School of Medicine**.

The compound met the primary endpoints of safety and tolerability. Mild to moderate, transient hyperemia (eye redness) was seen in a minority of patients.

According to van Haarlem, tolerability has been a major stumbling block for Rho kinase inhibitors, which are associated with vasodilation, resulting in redness. He also said the potency of most experimental compounds requires at least twice-daily dosing, which can exacerbate the redness.

Based on the Phase IIa results, Aerie believes AR-12286 may be sufficiently potent to allow once-daily dosing while reducing redness.

"For patients that experience redness, it usually disappears within one or two hours. If they use [AR-12286] once a day at bed time, the patient won't notice the redness," Epstein said.

van Haarlem noted AR-12286 also may be more specific than other compounds in development. "Though we don't know for sure, this specificity could play a role in how these compounds actually work in the clinic," he told BioCentury.

Aerie conducted specificity testing of AR-12286 against RKI983, a Rho kinase inhibitor from **Novartis AG** and **Senju Pharmaceutical Co. Ltd.**, and found that AR-12286 hit five off-target kinases, while the Senju compound hit 25.

According to clinicaltrials.gov, RKI983 is in a clinical trial vs. Xalatan in patients with primary open angle glaucoma or ocular hypertension.

Several other companies have conducted clinical trials of Rho kinase inhibitors in glaucoma, but also have not yet released detailed data.

Inspire Pharmaceuticals Inc. reported top-line results in September from a Phase I trial of INS117548 showing the compound demonstrated "mild" IOP-lowering effects in 84 randomized patients.

According to clinicaltrials.gov, **Santen Pharmaceutical Co. Ltd.** started Phase I/II testing of its DE-104 compound in March.

van Haarlem expects AR-12286 could be used as an alternative to prostaglandins and beta blockers or as a complementary treatment.

"We hope to offer a third, completely different mechanism to be combined with the others available, which will increase the opportunities for the ophthalmology community," he said.

In glaucoma, the eye's drainage system breaks down, causing a build-up of aqueous humor that leads to IOP, vision loss and eventual blindness.

Marketed prostaglandin analogs work by increasing drainage via the scleral pathway. Generic beta blockers also are used to reduce IOP by slowing down aqueous humor production.

In contrast, Rho kinase inhibitors work in the cytoskeleton to relax the trabecular meshwork, through which the majority of drainage occurs.

Aerie hopes to present full data from the Phase IIa trial at the **Association for Research in Vision Ophthalmology** (ARVO) conference in May 2010. In the meantime, the company is finalizing its Phase IIb protocol, with plans to start the trial in February 2010. The study will include once-daily dosing of AR-12286 as a monotherapy. A second Phase IIb trial will study AR-12286 in combination with Xalatan.

The biotech also has a dual-acting compound in preclinical testing for glaucoma: AR-13165 inhibits Rho kinase and a second undisclosed target.

COMPANIES AND INSTITUTIONS MENTIONED

Aerie Pharmaceuticals Inc., Bridgewater, N.J.
Association for Research in Vision Ophthalmology, Rockville, Md.
Duke University School of Medicine, Durham, N.C.
Inspire Pharmaceuticals Inc. (NASDAQ:ISPH), Durham, N.C.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Santen Pharmaceutical Co. Ltd. (Tokyo:4536; Osaka:4536), Osaka, Japan
Senju Pharmaceutical Co. Ltd., Osaka, Japan