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'Definitely a path forward'

Eyegate combo candidate foiled by placebo performance in cataract patients

By Marie Powers, News Editor

Top-line results from Eyegate Pharmaceuticals Inc.'s phase IIb study of combination drug/device candidate EGP-437 to treat pain and inflammation in patients following cataract surgery hit a familiar stumbling block. Although EGP-437 showed a higher rate of success than vehicle at all time points, the co-primary endpoints of proportion of subjects with an anterior chamber cell (ACC) count of zero at day seven and the proportion of subjects with a pain score of zero at day one did not show statistical significance – largely because the vehicle group outperformed its expected response.

The finding, though disappointing, was instructive for the Waltham, Mass.-based company, which already sees a road forward for the asset in the same indication. To test its thesis, Eyegate plans to repeat the experiment, with a key modification, in another phase II study that may kick off as early as this quarter.

"The fundamental problem that we saw here in cataract surgery is that a large portion of the subjects at 24 hours post-surgery had mild to no inflammation," – specifically, 48 percent to 50 percent of participants in the placebo arm, according to top-line data, explained Stephen From, Eyegate's president and CEO.

"Unfortunately, when we designed this study, we actually randomized immediately after surgery and gave the first iontophoretic treatment, which didn't allow exclusion of mild or noninflamed eyes," he said. "We see that was a big mistake."

EGP-437 incorporates a reformulated topically active corticosteroid, dexamethasone phosphate, delivered into the ocular tissues through the proprietary Eyegate II delivery system. The double-masked, randomized, vehicle-controlled phase IIb trial enrolled 106 subjects at seven U.S. sites to evaluate the safety and efficacy of EGP-437, started immediately after surgery, in patients whose procedures involved implantation of a monofocal posterior chamber intraocular lens, or IOL.

EGP-437 showed numerically better clinical efficacy, defined as an ACC count of zero, throughout the study, especially at day 14 and beyond, and nearly reached statistical significance at day 28. At most time points, more subjects in the EGP-437 arm achieved a pain score of zero compared to control.

For the secondary endpoints, change in mean cell count and in mean pain score, EGP-437 showed statistically significant improvements in both ACC count and pain score, on day seven and day one, respectively.

The EGP-437 arm had a favorable safety profile, with no serious adverse events reported.

Eyegate continues to review the data, which are not yet complete, and From reckons the findings could form the basis for a meeting with the FDA to discuss a pivotal trial design. But the company is opting for a more calculated route.

"I would rather spend a small amount of money right now, making sure our hypothesis is correct, than sitting down with the FDA to move forward into a pivotal based on an educated guess," From told *BioWorld*. The company expects to conduct another phase II study, with patients randomized into the treatment or placebo arms the day following cataract surgery, when the severity of inflammation can be more accurately assessed. The additional trial isn't expected to increase the cost of development materially since the original phase IIb enrolled quickly and sites and other protocols are already in place.

Eyegate also needs to secure buy-in from partner Valeant Pharmaceuticals International Inc., which in 2015 inked an exclusive global licensing agreement for commercial and manufacturing rights to EGP-437. Although financial terms were not disclosed, at the time From characterized the deal as "potentially transformative," with Eyegate set to receive an up-front cash payment along with development and regulatory milestones for an additional indication in uveitis. The company also is eligible for royalties on net sales and additional milestone payments on the achievement of undisclosed sales targets. (See *BioWorld Today*, July 13, 2015.)

The cataract surgery findings for EGP-437 offered a stark reminder of the vagaries of drug development in a therapeutic milieu that is continually evolving. The eye procedure, itself, has improved remarkably over the five-year period since Eyegate began advancing EGP-437 in the indication, From pointed out.

"We're not seeing the same level of inflammation that we used to see," he said, "so it's even more important now to randomize based on severity of inflammation."

'Worth investors' attention in 2018'

That doesn't mean there's not a market for EGP-437 in the indication, added Barbara Wirostko, chief medical officer.

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A former senior medical director at New York-based Pfizer Inc., Wirostko joined Eyegate in conjunction with its March 2016 acquisition of Jade Therapeutics Inc., where she was a co-founder and served as chief scientific officer from the company's inception in 2012.

"There's definitely a path forward," Wirostko told *BioWorld*. "There will always be a need for anti-inflammatories after cataract surgery, but we should begin, perhaps, designing these studies in such a way that we're not including the patients with minimal inflammation who would improve on their own."

A finding from the cataract study that, as a clinician, Wirostko found particularly valuable was that "we did not need anyone to be rescued after day 14 in our active arm," she said. "So not only did we see an effect with our product after three administrations, but we also saw an extended duration of effect. We had patients continue to improve between day 14 and day 28 in the active arm."

That finding reinforced the confidence of Eyegate's key opinion leaders that the drug is working, according to From.

"We saw the divergence in the delta get larger at every single visit, from day zero to day 28," he said. In contrast, no additional resolutions occurred in the placebo arm between day 14 and day 28 – a period when rescues continued to occur in the placebo arm.

In the meantime, "in no way whatsoever does this jeopardize what we think is happening with the uveitis study," From emphasized, referencing the multicenter, randomized, double-blind phase III effort that continues to test EGP-437 compared to prednisolone acetate ophthalmic suspension (1 percent) in individuals with non-infectious anterior segment uveitis, defined as an ACC count of >/= 11 cells.

Although the cataract surgery and uveitis studies both focus on treatment of inflammation, targeting similar tissues, "one indication is caused by a traumatic event while the other is more autoimmune, so the etiology is a little different," From said. By definition, patients with uveitis require a certain level of inflammation to be randomized into the study. Additionally, the uveitis study, against standard of care, is designed to show noninferiority, compared to the cataract surgery trial, which pitted EGP-437 against placebo in a superiority design.

Unlike the cataract surgery trial, enrollment in the uveitis study has been "incredibly slow," From acknowledged, although Eyegate hopes to report top-line data in the third quarter and remains optimistic about an NDA filing this year.

Although design of the phase III uveitis effort isn't measurably different from earlier studies, Eyegate has been forced to compete with other therapies and candidates – sometimes with lower enrollment thresholds – at the sites. The company is seeking to enroll 250 individuals with uveitis across 60 U.S. sites. The primary outcome measure is the proportion of patients with an ACC count of zero at day 14, according to Cortellis Clinical Trials Intelligence.

"Uveitis is a little stricter on the inclusion/exclusion than cataracts, and there are many different etiologies here," From pointed out. "In many cases, we don't even know why patients are getting uveitis, and it's a small population to begin with, which makes the indication much tougher to enroll."

Eyegate reported in December that the study was 75 percent enrolled, triggering a milestone payment from Valeant.

Eyegate also has a platform based on a cross-linked thiolated carboxymethyl hyaluronic acid, or CMHA-S, a modified form of the natural polymer hyaluronic acid, or HA. Formulated as an ocular bandage gel (OBD), the agent provides hydration and healing when applied to the ocular surface. The company is advancing the candidate to treat ocular surface injuries, including wounds from photorefractive keratectomy, or PRK, surgery and superficial punctate keratitis, or dry eye, with plans to move it into the clinic this quarter.

In a note issued in November following the American Academy of Ophthalmology 2017 annual meeting, H.C. Wainwright analyst Raghuram Selvaraju observed that, "Importantly, the FDA has permitted OBG to be developed under the de novo 510(k) pathway for regulatory clearance. We believe the development for the dry eye indication under a device pathway could be quicker, cheaper and easier for meeting the efficacy endpoint. Therefore, this product candidate is worth investors' attention in 2018."

It's been a tough stretch for companies pursuing eye therapies. In August, Ophthotech Corp. closed the book on its anti-platelet-derived growth factor therapy, Fovista (pegpleranib), following failure in wet age-related macular degeneration (AMD), turning to its complement 5 inhibitor Zimura (avacincaptad pegol) in eye diseases and planning to shop for additional assets. (See *BioWorld*, Aug. 15, 2017.)

Last month, two trials of KPI-121 0.25 percent – a therapy that uses the mucus-penetrating particle technology developed by Kala Pharmaceuticals Inc. to enhance delivery of loteprednol etabonate into target tissue – produced mixed results vs. placebo in dry eye and dented the company's shares (NASDAQ:KALA). (See *BioWorld,* Jan. 8, 2018.)

The same day, Ohr Pharmaceutical Inc., of New York, took an even bigger hit after unveiling top-line data showing that the phase III Mako study did not meet its primary endpoint of visual acuity gain in a test of topical squalamine – discovered in the tissues of the dogfish shark – when combined with monthly Lucentis (ranibizumab, Roche Holding AG) in wet AMD.

On Monday, Eyegate's shares (NASDAQ:EYEG) plunged amid a broad collapse in the markets, closing at 60 cents for a loss of 42 cents, or 41.3 percent. ♦

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