Ocugen Heads Toward Phase III In Dry Eye With Potential Benefits Over Older Drugs

By Joseph Haas
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Executive Summary
Biotech hopes to counter established Restasis and Xiidra in dry eye with a combination of two approved ophthalmology eye drops, offering quicker onset of action, tolerability and strong efficacy

Ocugen Inc. says it is ready to take its combination product OCU310 into Phase III after unveiling top-line Phase II data demonstrating tolerability of the two-drug combo. Promising trends for signs and symptoms of the disease could wind up as advantages on the market, should they hold up in Phase III.

The Malvern, Pa.-based firm revealed March 20 that OCU310, a twice-daily eye drop composed of the alpha 2 adrenergic receptor agonist brimonidine tartrate 0.2% and the corticosteroid loteprednol acetate 0.2%, met the primary endpoint of tolerability after 12 weeks of treatment against control groups of brimonidine alone or placebo. Brimonidine is approved as an eye drop for glaucoma under the brand name Alphagan (Allergan PLC), while loteprednol (Bausch & Lomb Inc.'s Lotemax) is approved to treat eye irritation. Loteprednol also is the active ingredient in Kala Pharmaceuticals Inc.'s Phase III dry eye candidate KPI-121 0.25% - the company also has KPI-121 1% (proposed brand name Inveltys) under review at US FDA for post-ocular surgery pain and inflammation with an Aug. 28 action date.

The Ocugen Phase II study was not sufficiently powered to demonstrate efficacy, but the company said the combo showed promise in exploratory endpoints, assessing symptom relief with the Symptom Assessment Questionnaire in Dry Eye (SANDE) instrument and effect on signs of dry eye using two staining tests.

"Overall these are early, encouraging results from a small Phase II study," Datamonitor Healthcare analyst David Dahan said. "Without any quantitative details released, it appears there were numerical improvements in both signs and symptoms of dry eye, but we will have to wait for Phase III results to know if these improvements are statistically significant."

Ocugen plans to begin a Phase III program for OCU310 during the third quarter, but first will need to finalize a protocol with the US FDA and raise additional funding, CEO Shankar Musunuri said in an interview. Several companies are developing candidates to compete with Allergan's Restasis (cyclosporine ophthalmic emulsion) and Shire PLC's Xiidra (lifitegrast), the only approved drug therapies for dry eye, with Kala, Sun Pharmaceutical Industries Ltd. and Mimetogen Pharmaceuticals Inc. already

in Phase III. (Also see "In Dry Eye, A Variety Of Mechanisms Pursue Established Therapies" - Scrip, 15 Jan, 2018.)

Ocugen will introduce a proprietary nano-emulsion formulation of OCU310 in Phase III, Musunuri said, and it also hopes to further differentiate the product in comparison to the two approved dry eye drugs, which themselves have to battle for market share against generic, over-the-counter products. (Also see "Allergan, Shire Battle In Dry Eye As Generics Advance" - Scrip, 15 Jan, 2018.)

"Based on input from KOLs and talking to the market, one of the things that people look for is when you get dry eye is rapid onset of relief. Currently marketed products take some time to work," the exec told Scrip.

Ocugen is betting that brimonidine's multi-modal mechanism of action as a vasoconstrictor, a CGRP peptide blocker and its abilities to clear leukocytes and provide analgesic benefit, combined with loteprednol's anti-inflammatory action, will be complementary and offer currently unsatisfied dry eye patients a desirable set of therapeutic benefits.

"We're trying not only to have a long-term efficacy effect so the patients are getting more relief from dry eye disease, but we also want to have rapid onset," Shankar continued. "That is very important for a lot of these patients because it takes several weeks for a drug to work and then it can become a compliance issue."

Tolerability Findings Key To Advancing Combo Product

The Phase II data showed that using a visual analog scale, tolerability for OCU310 and placebo were similar for all post-baseline doctor visits through week 12 of treatment. Adverse event rates also were low and similar to placebo – all important issues since OCU310 is a combination product that theoretically could present drug-drug interaction issues, Shankar said. The company's strategy is to use the 505(b)(2) regulatory pathway for OCU310 since both drug components have previously obtained FDA approval.

To demonstrate efficacy with a dry eye therapy candidate, a sponsor must demonstrate the ability to provide benefit on both a sign and a symptom of the disease. Using the SANDE patient-assessment tool, Ocugen found that OCU310 improved the frequency and severity of eye dryness and irritation from baseline compared to placebo. For signs of dry eye disease, Ocugen used lissamine green staining to assess conjunctival and corneal smoothness compared to baseline after 12 weeks of treatment. Both tests showed greater improvement compared to placebo over 12 weeks.

Ocugen will use the SANDE instrument for its symptomology endpoint in Phase III but is still determining how to proceed on a sign endpoint, Chief Medical Officer Daniel Jorgensen told Scrip.

"Basically, the data were strong for both," he noted. "We feel pretty good about either one of them. Because of the type of staining, from a practical standpoint it might be easier in the clinic to have conjunctiva as the actual endpoint, and maybe cornea as secondary endpoint. We haven't determined that yet, but it will be one of the two." On either measure, staining indicates whether treatment is making the eye surface smoother and less irritated, he added.

Ocugen previously raised $15m over a pair of private financings but said last year that it would need additional funds to advance OCU310, as well as its lead candidate OCU300, a brimonidine formulation

for graft-versus-host disease, through pivotal Phase III studies. [See Deal] While Ocugen is still working to schedule a type C meeting with FDA to design the Phase III program for OCU310, it expects it will need to conduct two Phase III studies of 500 patients or more each, Musunuri said

The firm is currently raising a crossover financing to fund the Phase III trials for both candidates and also is investigating the possibility of a partnership for OCU310, the CEO said. It already raised an additional $5m from existing investors and expects to complete the crossover financing in time to launch the dry eye Phase III program during the third quarter, he added.