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Beyond Luxturna companies vie to become the next ocular gene therapy

By Brian Orelli, Staff Writer

The 2017 FDA approval of Luxturna (voretigene neparvovec-rzyl, Roche Holding AG) spurred a race to create the next gene therapy for the eye. The organ is very amenable to gene therapy given that it's a confined space with post-mitotic cells that has immune privilege and requires substantially smaller amounts of viral vector compared to systemic treatments.

Steve Pakola, chief medical officer, Regenxbio

"I think it's not an accident that Luxturna was the first in vivo gene therapy to achieve approval," Steve Pakola, chief medical officer of Regenxbio Inc., said of the relative ease of treating the eye with gene therapy.

Rockville, Md.-based Regenxbio's most advanced program, RGX-314, is an adeno-associated virus (AAV) 8-based gene therapy that expresses a monoclonal antibody fragment that targets vascular endothelial growth factor (VEGF). The protein is virtually identical to ranibizumab, the active ingredient in Roche Holding AG's Lucentis.

The company recently launched Atmosphere, the first of two pivotal trials testing RGX-314 in patients with wet age-related macular degeneration (AMD). The 300-patient study will compare two dose levels of RGX-314 to Lucentis with a primary endpoint of noninferiority on the change from baseline in Best Corrected Visual Acuity at 54 weeks.

Regenxbio plans to start the second pivotal study comparing RGX-314 to Eylea (aflibercept, Regeneron Pharmaceuticals Inc.) with a similar noninferiority endpoint in the second half of this year.

"We're really going to have an opportunity to learn a lot about our product and take advantage of comparing against the two most well-known and the two most used branded products for treatment of wet AMD," Pakola told *BioWorld*.

Hot on Regenxbio's heels, Adverum Biotechnologies Inc., of Redwood City, Calif., plans to launch its first pivotal study for ADVM-022 in wet AMD in the middle of this year after meeting with the FDA later this quarter. ADVM-022 uses AAV.7m8 to express aflibercept, the VEGF-targeting protein in Eylea.

Adverum plans to test patients who were recently diagnosed with wet AMD. "It will give us the broadest label," Laurent Fischer, CEO at Adverum, told *BioWorld*.

Laurent Fischer, CEO, Adverum Biotechnologies

RGX-314 and ADVM-022 may also end up competing for patients with diabetic macular edema, but development for that indication is behind wet AMD at both companies.

Where to inject

Adverum's AAV.7m8 vector is able to cross a membrane in the eye, which allows for delivery of ADVM-022 via an intravitreal injection, while Regenxbio's pivotal study is studying subretinal injections of RGX-314.

There are some advantages to Regenxbio's approach of subretinal injections, including that the drug gets closer to the target tissue and the subretinal space is immune privileged, so there's little worry about preexisting antibodies against AAV. But subretinal injections require a surgical procedure to perform the injection.

Intravitreal injections avoid the need for surgery, but require steroids to dampen the inflammation caused by the injection.

Regenxbio is exploring a third approach, suprachoroidal injections. "The advantage there is that you're injecting the study drug to a space that's very close to the target tissue," Pakola said. "In both small and large animal models, we get very good transduction and protein expression from our target tissue, the retina, and we see this without inflammation."

The company has already started testing the delivery of suprachoroidal injections in clinical trials for both wet AMD and diabetic retinopathy. Data from the first cohort of patients with wet AMD are expected in the third quarter of 2021.

Master switch

Ocugen Inc. is tackling retinitis pigmentosa (RP), which is caused by mutations in well over 100 mutations. Rather than developing gene therapies to replace each individual mutated gene, the company is developing a gene therapy, OCU-400, which expresses a copy of the nuclear hormone receptor gene, NR2E3. Expression of NR2E3 resets retinal homeostasis,

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Shankar Musunuri, CEO, chairman and co-founder, Ocugen

which stabilized cells and rescued photoreceptor degeneration in five different mouse models of RP.

Malvern, Pa.-based Ocugen is ready to start clinical trials once it is done with preclinical toxicology studies, and it plans to submit an IND for OCU-400 in the second half of this year. The company initially intends to run phase I/II studies in patients with mutations in NR2E3 and RHO.

"Our goal eventually is to get a broad indication," Ocugen Chairman, CEO and co-Founder Shankar Musunuri said. "Obviously we cannot do all 150 genes which affect RP and that only represents 60%. So our goal is if you show safety and efficacy in two to three clinical trials, because of the significant unmet medical need, we believe the agency may give us broad RP with some phase IV commitments obviously."

Ocugen is also developing a gene therapy for dry AMD called OCU-410 which expresses RAR related orphan receptor A (RORA), which can alleviate oxidative stress and inflammation. The company plans to move OCU-410 into clinical development in 2022.