Ocugen Eyes Broad Retinitis Pigmentosa Indication With One Gene Therapy
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By Joseph Haas

Ocugen's shares finished the trading day on 28 August at $0.40 per share, compared to a 52-week high of $17.40. That downturn in market capitalization likely reflects the wager the company placed on switching to a gene therapy approach as well as its recent decision to shutter older pipeline assets focused on dry eye disease (OCU310) and ocular graft-versus-host disease (OCU300). (Also see “Ocugen Heads Toward Phase III In Dry Eye With Potential Benefits Over Older Drugs” - Scrip, 20 Mar, 2018.)

The earlier-stage gene therapy programs are based on intellectual property related to targeted delivery and expression of certain nuclear hormone receptors (NHRs) that are naturally expressed in retinal tissue, which was licensed from Harvard University in 2017.

Addressing All Of RP’s Underlying Mutations

CEO Shankar Musunuri, also the firm’s chairman and co-founder, is focused on the potential of OCU400 to address a broad base of retinitis pigmentosa (RP) patients, a disease that has no marketed therapy. While Roche Holding AG and Spark Therapeutics, Inc. are attempting to develop their gene therapy Luxturna (voretigene neparvovec) – currently approved to treat Leber’s congenital amaurosis – for patients with RPE65-mutant retinitis pigmentosa, that drug would treat about 600 patients in the US.

Ocugen already had US Food and Drug Administration orphan drug designations for

A public company since its reverse merger with Histogen, Inc. in April 2019, Ocugen Inc. has not walked the smoothest path, but it thinks it can offer significant benefit to retinitis pigmentosa patients with a gene therapy candidate, OCU400, that might be applicable to most or all patients with a disease characterized by more than 150 genetic mutations.

But the Philadelphia-area firm must stay ahead of its financial challenges to bring that lead program and two other gene therapy candidates into the clinic. Despite reaching the public market last year, Ocugen of late has used the at-the-market process to raise equity financing, bringing in $15.4m in June to increase its financial runway through the first quarter of 2021. (Also see “Deal Watch: Gilead To Use Insitro’s AI/Functional Genomics Tech For NASH Targets” - Scrip, 17 Apr, 2019) However, the company does not expect to advance OCU400 into clinical development until the third quarter of next year, so it has more fundraising to do.
OCU400 to treat RP caused by NR2E3 and CEP290 mutations and in recent weeks got additional orphan designations for the PDE6 and Rhodopsin (RHO) mutations.

Because each of these products employs a vector of the human NR2E3 gene, in essence each therapy is the same product, Musunuri explained. “Once we complete all of the manufacturing, it’s the same product [for the various mutations].”

“We have initiated GLP toxicology studies and GMP manufacturing”, Musunuri said. “This time next year, we’ll file an [investigational new drug (IND) application] and initiate two Phase I/II trials.”

Chinese vaccine specialist CanSino Biologics Inc. is doing the manufacturing scale-up to produce 200 liters of OCU400, the CEO said, so Ocugen will have access to the same amount of the therapy for clinical trials as it will need for commercializing the product, if approved.

“Manufacturing is critical for gene therapy products and minimizing any regulatory risks about product consistency issues is key,” he said. “So, scaling this process, even for Phase I/II at a commercial scale, will really help us in the future from the chemistry, manufacturing and controls and manufacturing side. We are going to minimize our risk going forward, because it’s the same scale as when we go commercial.”

**Strategy For Quick Move Into Phase III**

The initial Phase I/II trials of OCU400, which are expected to take about a year to complete, will test the therapy in patients with RP caused by NR2E3 and RHO mutations. Ocugen then hopes to be able to take safety data and efficacy signals from those two studies to the FDA, to ultimately get approval to initiate three Phase III studies, in the same two populations plus RP caused by CEP290 mutations, Musunuri explained. All the manufacturing and preclinical data performed early on should be usable as OCU400 moves into later-stage testing in multiple mutations, he noted.

“Typically, in Phase I/II, you do efficacy monitoring, you don’t pick the primary endpoints, you call them exploratory endpoints,” the exec explained. “So, let’s say you monitor four or five exploratory endpoints, and based on a specific population and disease, you pick one, you discuss that with FDA and finalize that as a primary endpoint, then you finalize your Phase III protocol and move on to Phase III.”

The goal is to have Phase III data from three parallel trials in 2025 and take that package to regulatory
agencies for accelerated approval because each population studied is an orphan population. “Once we demonstrate safety and efficacy in three different diseases and populations, we’ll be able to make a good case with FDA or [the European Medicines Agency] for a broad retinitis pigmentosa indication, with some Phase IV commitments,” Musunuri said.

Retinitis pigmentosa is potentially a significant commercial opportunity, with about 100,000 total patients in the US and an estimated 1.5 million patients worldwide, he added. Ocugen thinks OCU400 might be appropriate for all or most of those patients because it is based on addressing nuclear hormone genes that regulate multiple functions in the retina. If successful, the company's gene therapy will address much of the disease population with one product, whereas other companies may need to develop individual therapies to address each separate mutation causing RP, he asserted.

Beyond its manufacturing partnership with CanSino, Ocugen is holding off on seeking development or commercial partners for now. Partners likely will be more interested in OCU400 after Ocugen has some clinical data in hand, making 2022 the optimal time to seek a partner, Musunuri said.

Beyond OCU400, Ocugen also has in preclinical development OCU410, a RORA gene-targeted therapy expected to enter clinical development in 2022 for dry age-related macular degeneration (AMD), an unmet medical need with an estimated 9 million to 10 million US patients. The company is also developing OCU200, an integrin-targeting biologic for diabetic macular edema, diabetic retinopathy and wet AMD. That candidate also is on track to enter the clinic in 2022, the company said.