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PRODUCT DEVELOPMENT | REPRINT FROM MAY 09, 2024

Kate raises the bar for DMD gene therapy

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As patients and the biopharma industry await an FDA decision on full approval of the first gene therapy to reach the market for Duchenne muscular dystrophy, new data from Kate Therapeutics bolsters the central thesis of many gene therapy start-ups: that engineering AAV vectors to be more targeted will dramatically improve on first-generation products.

On Friday, Kate Therapeutics Inc. co-founder and CSO Sharif Tabebordbar will present preclinical data from the company's lead internal development candidate, KT809, during a plenary session at the American Society of Gene & Cell Therapy (ASGCT), which runs through May 11.

The data will showcase the transduction efficiency of the Duchenne muscular dystrophy (DMD) gene therapy candidate in skeletal muscle and heart tissue, in both mice and non-human primates. The experiments take a step beyond what others have reported by directly comparing Kate's vector to a surrogate of Elevidys delandistrogene moxeparvovec, the approved AAV gene therapy from Sarepta Therapeutics Inc. (NASDAQ:SRPT).

The Elevidys surrogate uses the same vector, promoter and microdystrophin sequence as the marketed product, but includes a tag at the end of the protein sequence that allows detection by immunofluorescence.

Ahead of the presentation, Kate told BioCentury that KT809 led to a greater increase in microdystrophin expression in skeletal and heart muscle than treatment with the Elevidys surrogate.

Tabebordbar said that there was no published information on protein expression from approved gene therapies in non-human primates, "so we basically had to do the experiments ourselves and inject the compound at a clinical dose in cyno macaques and see what expression looks like."

Kate found the Elevidys surrogate produced "a reasonable amount of protein expression in mice," in both skeletal muscle and heart, he said, but "very low levels of transgene protein expression, almost undetectable," in the heart of non-human primates.

In contrast, Tabebordbar said the company observed "near physiological" expression levels of the protein in macaques treated with KT809. "We can basically transduce 100% of skeletal muscle fibers in cyno macaques and 80-90% of cardiomyocytes."

KT809 was delivered at 4x1013 vg/kg, while the Elevidys surrogate was delivered at the approved dose of 1.33x1014 vg/kg.

Kevin Forrest, co-founder, president and CEO of the biotech, told BioCentury that microdystrophin expression in the heart is an important differentiator.

"While this disease is largely considered a skeletal muscle disease, one of the major organs that causes mortality in these boys is the heart," he said. "Not expressing the therapeutic in the appropriate tissue, specifically the heart, is really concerning."

KT809 also showed a different liver accumulation profile. Kate's liver de-targeted vector led to 27x fewer copies of the vector's genome in the liver than the Elevidys surrogate.

Liver toxicity is the major dose-limiting factor for AAV gene therapies. Because the vectors naturally accumulate in the liver, it's difficult to reach effective levels in non-hepatic tissues without toxic liver exposure — especially when the target tissue is large, as is the case for skeletal muscle.

Selective liver de-targeting is difficult to achieve. "The major issue is that you also reduce on-target transduction," said Tabebordbar. When you de-target AAV vectors, "you don't transduce the liver, but you also don't transduce the muscles."

Kate believes it has a solution in its MyoAAV-LD vectors, which it found through generating and screening a library of millions of AAV variants. The company launched last June with a $51 million series A round co-led by Westlake Village BioPartners and Versant Ventures. Its capsid engineering platform was developed by Tabebordbar and licensed from the Broad Institute of MIT and Harvard.

Kate has not yet disclosed a timeline for starting clinical trials. The company's next steps include performing longer non-human primate studies. That means key questions could take years to be answered, such as whether the expression data in animals will translate to humans and be sufficient to drive clearer functional benefits than those demonstrated by Elevidys. The Sarepta therapy was granted accelerated approval based on increased microdystrophin expression. In its confirmatory trial, Elevidys missed the primary functional endpoint but produced modest improvements in secondary endpoints.

A rare best-in-class opportunity?

Although functional outcomes data aren't available, Kate's protein expression data help make the case for vector engineering as a path to differentiated products, which is critical, as the bar for differentiation is high for rare disease gene therapies — an arena where the standard biopharma paradigm of continually improving on the first drugs in a class faces challenges.

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Because the body mounts an immune response against AAV vectors, patients can at this time only be treated with one AAV therapy. If that product doesn't work, there's no opportunity to switch to a more effective gene therapy that gets approved later. The consequence for companies developing rare disease gene therapies is that the first-in-class product shrinks the already small market. And patients are confronted with the difficult decision of taking an available drug or waiting for a better product that may or may not get developed.

An analysis conducted by BioCentury last year found companies often drop AAV programs for rare diseases when a first-in-class program nears the market. But, so far, that hasn't been the case for DMD.

The market opportunity for next-generation AAV therapies is influenced both by the rarity of the specific indication and the efficacy of the first approved therapy. DMD is among the more prevalent rare diseases, and Elevidys faces an efficacy controversy as safety concerns rise for the next-most advanced therapy, fordadistrogene movaparvovec from Pfizer Inc. (NYSE:PFE).

Forrest believes a commercial opportunity exists for another gene therapy in DMD. He acknowledged that "in gene therapy, it's a unique market where the first to market really matters." However, because dystrophin is a large gene, he said, "you often get mutations in this gene and every year, unfortunately for the patients, there is a large incident population."

Other companies seem to agree.

Behind Elevidys and Phase III candidate fordadistrogene movaparvovec, at least three others are in the clinic and five companies have disclosed preclinical programs.

In an ideal world, DMD patients and their families would have the opportunity to compare treatment options and select the one with the best safety and efficacy profile for them. For the youngest DMD patients, who are most likely to benefit from a gene therapy, there is a particular urgency for additional treatment options.

Elevidys is indicated for 4- and 5-year-olds. Pfizer is studying fordadistrogene movaparvovec in patients as young as 2 years

old, but is investigating a death in its Phase II study in 2- and 3-year-olds.

FDA is considering an expanded label for Elevidys that would help create access for older patients. The argument for the expansion is that although patients are less likely to receive major functional gains after they lose the ability to walk, they lose little in trying.

Forrest believes a heart-targeted gene therapy will be critical at the later diseases stages, and he cautioned that "taking a drug that doesn't express in the heart will potentially preclude you from taking something that does."

"For a lot of the older patients in this population, they've lost the ability to walk, but what really affects those patients as you get older, in addition to cardiorespiratory issues, is cardiomyopathy," he said.

Kate plans to pursue parallel accelerated paths to the clinic for KT809 and its second internal program, a gene therapy to treat facioscapulohumeral muscular dystrophy, an indication for which nothing is approved.

Sarepta did not respond to a request for comment.

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