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Ultrarare inflection point: stakeholders argue for biomarker-based approvals

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A meeting convened by the Reagan-Udall Foundation for the FDA on qualifying rare disease biomarkers for accelerated approvals could be an inflection point for patients with ultrarare diseases, their families, biotech companies, and FDA.

The workshop, held on Feb. 21, focused on the use of heparan sulfate measured in cerebrospinal fluid (CSF) to support approval of treatments for neuronal mucopolysaccharidoses (MPS), a set of related ultrarare disorders.

Depending on FDA's response to the workshop, it could mark the end of an era of tragic disappointments, alleviating suffering from a set of ultrarare diseases that academic experts believe could have been avoided if FDA had accepted science supporting biomarker-based approvals of treatments for neuronopathic MPS.

It is difficult to overstate the stakes for patients and their families.

Effective therapies would substantially slow, if not halt, the progression of irreversible brain damage.

At least two companies, Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE) and Denali Therapeutics Inc. (NASDAQ:DNLI), have data in hand demonstrating that their investigational therapies produce dramatic reduction of CSF heparan sulfate levels that they believe support approvals to treat the neuronal symptoms of an MPS disorder.

Ultragenyx licensed UX111, a gene therapy for neuronal symptoms of MPS III, also known as Sanfilippo syndrome, from Abeona Therapeutics Inc. (NASDAQ:ABEO).

Denali is developing DNL310, a recombinant protein comprising an antibody fragment against the transferrin receptor fused to iduronate-2-sulfatase, to treat neuronal symptoms of MPS II, Hunter syndrome.

An FDA decision to accept the biomarker as an approvable endpoint could lead to rapid approvals of the Ultragenyx and Denali therapies, and pave the path for approvals of other therapies for neuronal MPS disorders, including an MPS II gene therapy from RegenxBio Inc. (NASDAQ:RGNX).

The impacts of an FDA decision to approve neuronal MPS treatments based on biomarkers would ripple into future generations. It would become possible to establish screening programs to diagnose infants in time to prevent permanent brain damage.

If it is successful, the precedent for drug developers, patient advocates and academic researchers to collaborate on developing consensus about an ultrarare disease biomarker could have a broad impact. Regulatory uncertainty and concerns that FDA will impose infeasible or unethical requirements have put scores of ultrarare disease development programs on hold, despite promising science and urgent unmet needs.

Parents' hope that the workshop will prod FDA to approve neuronal MPS treatments based on a biomarker is tempered by anger and frustration fueled by the conviction that FDA could and should have accepted the biomarker years ago.

Speaking at the Reagan-Udall workshop, parents of children with MPS disorders said the agency's continued rejection of the biomarker and insistence on randomized, controlled trials with clinical endpoints is cruel, unethical and unnecessary.

Academic scientists who have devoted their careers to caring for MPS patients said that progression to irreversible brain damage is inexorable, but the speed of progression to measurable declines is variable. As a result, achieving statistically significant differences between treated and control groups in trials that enroll tens of patients is problematic and can take years, a common theme among severe, progressive diseases.

In contrast, reductions of heparan sulfate in CSF can be detected in months.

Unprecedented cooperation

Emil Kakkis, president and CEO of Ultragenyx, decided to organize a public meeting where neuronal MPS drug developers could present their data alongside academic scientists because several companies were struggling to persuade FDA to accept CSF heparan sulfate as a biomarker, he told BioCentury.

Ultragenyx, Denali and RegenxBio agreed to share data on their unapproved therapies that companies typically treat as proprietary. They each have or will soon have data that could support a biomarker-based review of a neuronal MPS treatment. In the absence of FDA acceptance of the biomarker, they could be three or four years away from submitting marketing applications.

Two companies that have halted neuronal MPS drug development programs, Allievex Corp. and Orchard Therapeutics, a unit of Kyowa Kirin Co. Ltd. (Tokyo:4151), also participated in the workshop.

FDA reviewers, Kakkis told BioCentury, "look at biomarkers like mathematical predictors of a clinical measure. They want to draw a graph that says when the biomarker gets better, the clinical endpoint gets better, and it's a linear proportional relationship."

> **"IF WE DON'T LEAN INTO ACCELERATED APPROVAL, WE ARE GOING TO LEAVE A LOT OF PATIENTS BEHIND."**
>
> PETER MARKS, FDA

Proteinuria, for example, had been in wide clinical use for decades as an indicator of kidney function, with the relationship between the two well-established, before the agency adopted the biomarker as a surrogate endpoint for IgA nephropathy.

"But that's often not how biology works," Kakkis said.

Ultragenyx has reported that its gene therapy leads to a rapid, sustained decrease in CSF heparan sulfate. Patients in the company's trial experienced a 63% reduction in CSF heparan sulfate over a median follow-up of about two years.

Denali has reported a greater than 90% mean reduction in CSF heparan sulfate at week 24 of treatment, remaining unchanged at week 104.

Directly correlating the biomarker with clinical benefit is especially difficult in neuronal MPS patients who are not treated until they show obvious symptoms, Kakkis added. "For heparan sulfate, it's exposure during a critical period. Once kids are four or five, even if you reduce heparan sulfate, their cognitive function is poor," and it won't improve.

Stabilization, however, is possible.

"We have kids" who have received the company's gene therapy to treat MPS III "that are older, who are clearly stable, but their cognitive score might not be good," Kakkis said. "They are feeding themselves. They are walking around with family. They're playing. They're going to school. They're teenagers, an age when [untreated MPS patients] are bedridden, and they're not. They're running around, but they don't speak, and so the cognitive scoring doesn't show" a benefit from treatment.

Accelerated approval will be the norm

Products under development to treat neuronal MPS disorders include enzyme replacement therapies that are regulated by FDA's Center for Drug Evaluation and Research (CDER) and gene therapies that are regulated by the Center for Biologics Evaluation and Research (CBER).

Speaking at the Reagan-Udall meeting, CBER Director Peter Marks said the two centers are working to develop a common policy on biomarkers for neuronal MPS disorders.

Marks signaled his strong interest in finding ways to use biomarkers to approve gene therapies for ultrarare diseases. "CBER aims to make 2024 a breakout year addressing key challenges to the development of gene therapies, especially for rare disorders, and reliance on increased use of biomarkers may play a critical role in accomplishing this objective," he said.

Marks added: "If we don't lean into accelerated approval, we are going to leave a lot of patients behind and we may even lead the field to a place where we have more products dropping out of development."

"Accelerated approval," Marks added, "is going to be the norm, I think, for a lot of our initial approvals of gene therapies." CBER granted the first-ever accelerated approval to a gene therapy last year. Micro-dystrophin-expressing treatment Elevidys delandistrogene moxeparvovec from Sarepta Therapeutics Inc. (NASDAQ:SRPT) treats Duchenne muscular dystrophy, a rare, but not ultrarare, progressive neuromuscular disease. Unlike CSF heparan sulfate for neuronal MPS, there is a great deal of debate in the scientific community about whether micro-dystrophin should be accepted as an approvable endpoint for DMD.

Marks played down the differences between CBER and CDER over the use of biomarkers for approving orphan drugs, but Kakkis and Carole Ho, CMO and head of development at Denali, told BioCentury there is a lack of consistency between the two centers, as well as divergence between senior officials and review staff.

If the workshop results in the development of a consistent approach at CDER and CBER to endpoints and clinical trial designs for neuronal MPS disorders, that could be a major step forward.

"CBER has been requiring follow-up until all treated patients are at least five years old," Kakkis told BioCentury. "Since they have to be tested before age two, this results in a multiyear delay."

If CBER requires that Ultragenyx must wait until all 17 patients who have been treated with its gene therapy, UX111, are five years old, the company will not be able to seek approval until 2027, Kakkis said.

Abeona dropped development of the therapy and transferred it to Ultragenyx because CBER reviewers decided that patients would have to be followed for years before a BLA could be submitted. "Abeona could not afford to keep this afloat for that long," Kakkis said.

"I HAVE SEEN TOO MANY DEATHS IN THIS ULTRARARE GROUP THAT ARE NOW PREVENTABLE."

JOSEPH MUENZER, UNIVERSITY OF NORTH CAROLINA

While CBER has informed drug companies that gene therapies could be approved based on single-arm trials, CDER is requiring randomized, double-blind, placebo-controlled studies for enzyme replacement therapies that are intended to treat neuronal MPS.

CDER's requirements are "untenable and unethical," Kakkis said.

Speaking at the Reagan-Udall workshop, John Crowley, incoming president and CEO of BIO, said it is "overwhelmingly clear" that for neuronal MPS disorders CSF heparan "is reasonably likely to predict clinical benefit and should be subject to the accelerated approval pathway."

Crowley, the former CEO of rare disease drug developer Amicus Therapeutics Inc. (NASDAQ:FOLD), also used the workshop as a platform to advocate for the establishment of an FDA center of excellence dedicated to rare diseases, a step the agency has resisted. A center of excellence could "reduce the inconsistencies across CDER and CBER," and bring more resources and enhanced leadership to the regulation of rare diseases, he said.

The situation facing neuronal MPS disorder drug developers is not unanticipated. In 2020, FDA finalized a guidance document providing evidence of effectiveness for slowly progressive, low-prevalence rare diseases with substrate deposition that results from single enzyme defects. This precisely describes neuronal MPS.

There are two reasons why FDA reviewers have been reluctant to apply this guidance to neuronal MPS, Ho told BioCentury. The agency is concerned about the quality of assays for CSF heparan sulfate, and FDA reviewers "feel that they don't understand what is downstream of the substrate accumulation that leads to neuronal loss and damage and subsequently clinical endpoints."

FDA reviewers, she added, "feel that there is data from past programs that don't show a correlation between clinical outcomes and the substrate reduction, and because of that, I think there are a number of people who are reluctant to now use their own guidance because they actually think they have

data that is in contrary to the assumption that the reduction in substrate will lead to clinical outcomes."

Those concerns, Ho said, do not reflect the current state of the science.

A mountain of evidence

Academic researchers and industry scientists presented a mountain of evidence at the Reagan-Udall workshop, some decades-old and some hot off the press, indicating that reduction in CSF heparan sulfate is reasonably likely to predict clinical benefit, which is the legal criteria for an accelerated approval endpoint.

Although the discussion focused on accelerated approval, the data presented seemed to fulfill the requirements for full approval. Similarly, although the title of the workshop was "Qualifying Biomarkers to Support Rare Disease Regulatory Pathways," formal qualification is not a prerequisite for FDA to approve a medicine based on a biomarker.

Joseph Muenzer, a professor at the University of North Carolina who has treated and studied MPS for four decades, made the case that the accumulation of heparan sulfate in the brain is not merely a marker of disease progression, it is the cause of neuronal MPS disorders.

"I have seen too many deaths in this ultrarare group that are now preventable" with drugs that have been shown to normalize CSF heparan sulfate but haven't been approved, Muenzer said. These children "continue to suffer and die prematurely because of the lack of regulatory flexibility."

Muenzer described attributes of neuronal MPS disorders, such as their heterogeneous progression rates, that make trials with clinical endpoints challenging. "Because of the slow and variable disease course, it may take four to six years or more to observe the effects of a successful intervention."

While measurements of CSF heparan sulfate were previously unreliable, Maria Fuller, a professor and clinical scientist specializing in biochemical genetics within genetics and molecular pathology at the University of Adelaide, presented data at the workshop showing that CSF heparan sulfate can be accurately measured using mass spectrometry.

Patricia Dickson, a professor and director, genetics and genomic medicine, in the Department of Pediatrics at Washington University School of Medicine in St. Louis, presented new data from animal studies that show that CSF heparan sulfate originates in the brain, and thus is a marker of brain concentrations.

Her experiments indicate that measurements of serum heparan sulfate do not reflect levels in the brain and that a gene therapy that reduced CSF heparan sulfate had no effect on serum concentrations of heparan sulfate.

This explains why MPS therapies that do not cross the blood-brain barrier improve somatic symptoms but do not prevent brain damage.

> **"YOU CAN RINSE AND REPEAT THAT FOR EVERY NEUROLOGIC MPS DISEASE."**
>
> CARA O'NEILL, CURE SANFILIPPO FOUNDATION

'Rinse and repeat'

Speaking at the Reagan-Udall workshop, parents of children living with neuronal MPS disorders expressed extreme frustration with FDA. The agency's failure to accept CSF heparan sulfate as an approval endpoint, its requirements for placebo-controlled trials, and demands for large, statistically significant improvements in cognitive function are creating insurmountable barriers, they said.

Cara O'Neill, a pediatrician who is CSO of the Cure Sanfilippo Foundation, and the mother of a girl with MPS III, described a recurring nightmare. Companies believe they can create a treatment. They engage with FDA and are excited and invest in a development program. Then, the agency moves the goalposts, "timelines are drawn out, costs go through the roof, and companies end up shelving the program or go bankrupt."

O'Neill added: "You can rinse and repeat that for every neurologic MPS disease."

While this pattern is repeating, "our kids go from singing the ABCs to stuttering to silence," which is interrupted by "frequent periods of screaming and distress we live with every day."

At least eight development programs for MPS III have been halted in recent years and the status of a ninth is uncertain, according to the Cure Sanfilippo Foundation.

O'Neill challenged FDA officials who require trials in which patients with neuronal MPS are randomized to therapies that reduce CSF heparan sulfate or a control group to consider the parents' perspective. She asked if they would be willing to enroll their child who is at a period of maximum cognitive vulnerability "in a study where they will be allowed to develop irreversible brain injury."

Families of children with MPS disorders are not always steeped in the science, O'Neill said, but "they know that heparan sulfate in excess is the problem, it is the disease, what

defines it, what was used to make the diagnosis, and what drives the pathology."

Forcing drug companies to conduct clinical trials rather than allowing biomarker-based approvals is unethical, Muenzer and O'Neill said.

O'Neill also expressed concern that if FDA continues to require randomized, placebo-controlled trials with clinical endpoints, companies will halt their development programs. "We have safety information, a valid biomarker and treatments right here that are about to be lost."

Heather Lau, Ultragenyx's executive director, global clinical development, said at the workshop that the heparan sulfate CSF readout is rapid, whereas "clinical outcomes assessing neurodevelopment in a therapeutic trial for neuronal MPS may take years to be fully realized and the magnitude and type of clinical benefit may be different depending on age of intervention."

Parents told the workshop that while treating infants and children before they experience irreversible brain damage is optimal, there is enormous benefit to stabilizing disease in older children who have already experienced brain damage.

Approval of treatments for neuronal MPS disorders also would break a Catch-22. Screening of newborns, which would make it possible to dramatically alter the natural history of the disease, transforming the lives of patients and producing strong clinical data, won't be deployed until there is an approved treatment. In the absence of screening, children are typically diagnosed when they are too old to prevent the onset of neuronal symptoms that make it difficult to demonstrate a large treatment effect.

Three therapies

Ultragenyx reports that it has demonstrated a mean reduction in heparan sulfate of over 50% two years after treatment in an intent-to-treat analysis of 17 patients.

"Our plan is to say we have enough data to support approval," Kakkis told BioCentury, "and that we would follow these kids for five to 10 years."

FDA should accept heparan sulfate in CSF as an endpoint for full approval, he added. "The measurement is the disease cause and not a surrogate, and therefore it should be a standard approval. However, I think we should impart the rigor of a very long-term study to look at clinical outcomes, first to confirm the benefit, but secondly because we want to know what the limitations are, to set the stage for the next guy to come up with something better."

Denali also believes the data it has collected could support approval.

> **"IF FDA LEANS INTO BIOMARKERS THE WAY IT SHOULD, I EXPECT A COUPLE DOZEN THERAPIES WITHIN A COUPLE OF YEARS TO BE ABLE TO GET APPROVED."**
>
> EMIL KAKKIS, ULTRAGENYX

Data from a Phase I/II trial demonstrate that Denali's enzyme replacement therapy for MPS II, Hunter syndrome, has "reached the asymptote of biology correction," Ho told BioCentury. "We normalize the CSF heparan sulfate levels with our IV administered therapy that has an ability to penetrate blood-brain barrier."

In addition to normalizing CSF heparan sulfate in every MPS patient who has been treated, "we reduce the neurofilament by 61% and that decrease starts on a mean basis shortly after six months," Ho said. "That tells us is that this reduction in CSF heparan sulfate is resulting in a reduction of a biomarker of neuronal axonal damage, that the normalization is resulting in a biomarker reduction that's really reflecting brain health."

So far, Denali has not persuaded reviewers at CDER. They have informed the company that because Denali's data are not from a randomized trial with a clinical endpoint, it cannot support approval, Ho said.

As a result, Denali is conducting a Phase II/III trial with patients randomized to receive either its enzyme replacement therapy or Elaprase idursulfase from Takeda Pharmaceutical Co. Ltd. (Tokyo:4502; NYSE:TAK), which has been approved to treat MPS II. Elaprase treats somatic symptoms but does not prevent brain damage, so patients on the control arm are certain to experience irreversible harm.

Denali expects to complete enrollment this year, it will take two years to complete the trial and then some time to analyze it and submit a marketing application, Ho said.

If FDA shifts its thinking on CSF heparan sulfate and grants Denali accelerated approval based on evidence it has already acquired, the ongoing trial could fulfill requirements for confirmation of clinical benefit.

Unlocking ultrarare disease therapies

Looking beyond MPS, Kakkis seized on Marks' commitment to using accelerated approval to bring gene therapies to patients with rare diseases. "His legacy will be defined in the next couple of years," Kakkis said. "If he wants a legacy that

he brought gene therapy to multiple diseases and changed the future of rare disease medicine, he has that opportunity in front of him."

Failure to accept biomarkers will whittle the gene therapy industry "to be only a few players in a few larger market diseases," according to Kakkis. "All of these rare diseases that we could have treated will be left to family foundations scraping bits of money" and trying to create gene therapies.

Creating a precedent for biomarker-based approvals of rare diseases would "bring money back into the space," he said. "Right now, everyone's running away because of the regulatory uncertainty and demands for impossible randomized trials." The demands make ultrarare drug development impossible because they are so costly that companies cannot recover their development costs, according to Kakkis.

On the other hand, "if FDA leans into biomarkers the way it should, I expect a couple dozen therapies within a couple of years to be able to get approved," Kakkis said.

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