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A new paradigm for ultra-rare diseases

Emil Kakkis thinks acceptance of biomarkers as endpoints, use of an EUA standard, and rigorous outcomes data collection would unleash treatments

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Most patients with very rare diseases have no effective treatment options and, based on the current trajectory of drug development, have little reason to expect help any time soon. Emil Kakkis, president and CEO of Ultragenyx, contends that systematically implementing three sets of policies could dramatically improve the situation.

Changing the kinds of endpoints that can support accelerated approvals, applying the Emergency Use Authorization approval standard, and establishing systems for the collection of robust, comprehensive long-term outcomes data would unleash a flood of drug development for ultra-rare monogenetic disorders, he believes.

As an academic clinician, founder of Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), former CMO of BioMarin Pharmaceutical Inc. (NASDAQ:BMRN) and board member at two patient advocacy organizations, Kakkis has seen what works – and what doesn't work – when it comes to developing drugs for rare diseases.

Kakkis defines an ultra-rare condition as one that is diagnosed in 2,000 or fewer people in the U.S. About 85% of the over 6,000 identified rare diseases have a prevalence of less than one in a million; most manifest in children, and many are the result of single-gene defects.

For ultra-rare diseases with a clear etiology, Kakkis proposes expanding the outcomes used to assess benefit, from the current definition that requires an observable improvement in the way a patient feels, functions or survives, to include treating the underlying cause of disease.

"FDA looks at biomarkers as a mathematically associated measure, like a blood test, that's mathematically associated with a clinical endpoint, one-to-one," Kakkis said. "You draw a graph and they show one predicts the other. That's their mindset."

"Treating the underlying cause of disease is treating the disease."

Emil Kakkis, Ultragenyx

Kakkis argues that a different kind of biomarker is appropriate for ultra-rare monogenetic diseases. "I'm talking about biomarkers that are scientifically based, meaning we know that they're a measure of the source of the underlying disease. Like the lysosomal diseases, where it's a stored material that builds up, phenylketonuria, PKU, where its phenylalanine levels, and in arginase deficiency where it is arginine levels."

He contends that FDA should accept biomarkers that show effects on biological causes of these kinds of diseases as the basis for accelerated approvals of ultra-rare disease treatments. The treatment paradigm should embrace the idea that "treating the underlying cause of disease is treating the disease," he said.

Sponsors would have to provide pathophysiologic and pharmacological data, including from animal models, to establish that the magnitude of effect and distribution of the drug to the site of action is sufficient.

Direct and primary disease-based biomarkers are as predictive of benefit for rare genetic diseases as the biomarkers used for HIV and HCV, according to Kakkis.

Too many drug development programs have run out of funding, or haven't been launched, because small biotechs couldn't afford to spend five years or longer to demonstrate the correlation between a putative surrogate endpoint and clinical benefit, Kakkis told BioCentury. This is especially true in diseases with long progression times, and for diseases with highly variable symptoms.

The COVID-19 experience was a vivid demonstration of FDA's Emergency Use Authorization pathway, which allows for approvals of medical products in emergencies when the known and potential benefits outweigh the potential risks and there are no adequate, approved and available alternatives.

This is the appropriate standard for drugs to treat ultra-rare diseases, rather than the traditional "substantial evidence of effectiveness" standard, according to Kakkis.

To ensure that outcomes data are collected, approvals for treatments for ultra-rare diseases would be contingent on the implementation of a disease monitoring program. The programs would be partnerships between drug manufacturers and physician groups that monitor patients with a specific disease, regardless of the treatment they are receiving, for ten years.

Data from the programs would be available to regulators and academic researchers.