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The FDA Returns to Its Bad Habits

The agency may nix a new treatment for a debilitating orphan disease.

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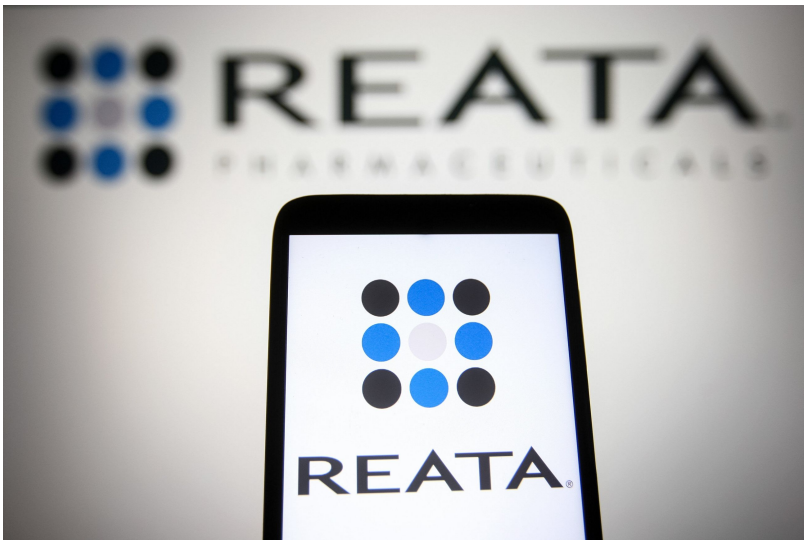

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Drug treatments for debilitating diseases are advancing rapidly, but the Food and Drug Administration isn't moving with as much alacrity. Witness how the agency has slow-rolled its review of a breakthrough treatment for a rare degenerative nervous system disorder.

Friedreich's Ataxia (FA) stems from a genetic mutation that causes a deficiency of the protein frataxin, which is critical to metabolic function. The progressive disease usually develops in children and results in difficulty walking, slurred speech, hearing and vision loss and shortness of breath. About 5,000 patients in the U.S. are afflicted with the disease, and most die in their 30s of heart problems. There is no approved treatment, only medications to manage symptoms such as diabetes.

Enter Reata Pharmaceuticals, which has developed a drug called omaveloxolone that has shown the ability to slow and even reverse patient decline. A randomized controlled trial with 103 patients showed that those receiving the drug showed statistically significant improvement as rated by physicians compared to a placebo group after 48 weeks of

treatment. The difference was the equivalent of about two years of progression. Patients who received the drug also demonstrated improved ability to complete daily activities.

Yet FDA staff deemed the results "not exceptionally persuasive." The agency traditionally requires a statistical measure called the p-value—the probability of obtaining a result by chance—to be less than 0.01 to approve a drug based on a single study. Reata's p-value was 0.014, which means there was a 1.4% chance that its positive result was a fluke. That's still small.

Obtaining an even smaller p-value would require a larger trial, which is difficult for an orphan disease like FA. The small number of FA patients are scattered across the U.S., and most can't visit clinics for regular check-ins. Reata nonetheless obliged the FDA's requests for more evidence by extending its trial by 72 weeks.

The sequel study demonstrated that patients who had received the drug maintained improvements over two-and-a-half years, and earlier treatment appeared to provide a greater benefit. A third study comparing patients who received the treatment with those who followed the natural course of the disease found the drug slowed progression by 55%.

Yet FDA staff were still unsatisfied. They quibbled that some patients in Reata's extension trial didn't show up for periodic check-ins. This was because of the pandemic. So after filing for drug approval last spring, Reata submitted mountains of more data in response to the FDA's criticisms. The FDA has until Feb. 28 to issue a decision.

FDA neuroscience chief Billy Dunn caught political flak for overruling an advisory committee and agency statisticians on Biogen's Alzheimer's drug Aduhelm. He has advocated for more regulatory flexibility on experimental drugs that treat degenerative diseases. But many in the agency and the public-health world disagree.

FDA officials sometimes act as if their delays don't have real-world costs. Many FA patients could have benefited from omaveloxolone in the more than three years since Reata announced its positive trial results. The FDA showed with Covid vaccines that it can move fast in an emergency, and diseases like FA are dire emergencies for people who suffer from them.

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