BIOPHARMADIVE

First Duchenne gene therapy approved by FDA for young children

The approval of Elevidys is a milestone for research into the progressive and deadly disease, and raises the stakes of an ongoing trial that could prove how well it works.

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Courtesy of Sarepta

The Food and Drug Administration on Thursday approved the first gene therapy for Duchenne muscular dystrophy, a milestone in treatment for the deadly disease and a calculated gamble the medicine can slow its unrelenting progression.

The regulator granted the treatment, called Elevidys and developed by biotechnology company Sarepta Therapeutics, an “accelerated” clearance, meaning its benefit must be confirmed in further testing. Its use is limited to Duchenne patients who are 4 or 5 years of age, can still walk, and don’t have genetic mutations that might blunt the treatment’s effects or raise its safety risks.

The approval is narrower than Sarepta originally sought, due to limitations in the data the company submitted to regulators. Sarepta estimates that, in any given year, there are about 400 children aged 4 or 5 years old with Duchenne in the U.S., according to a company spokesperson.

The agency based its decision on the therapy's ability to help patients make a tiny protein, dubbed microdystrophin, that the FDA deems "reasonably likely" to result in a health benefit.

Sarepta must prove that's the case with an ongoing late-stage clinical trial expected to deliver results by the end of the year. If successful, that trial would support a full approval of Elevidys and could allow Sarepta to expand the FDA's restrictions to include older children. However, if negative, Celia Witten, the acting director of the FDA office that reviewed Sarepta's therapy, said last month the regulator could remove the drug from market.

In a statement Thursday, the FDA reiterated that position, noting that it would review data from the trial quickly to decide whether any action, like a revised label or market withdrawal, would be required.

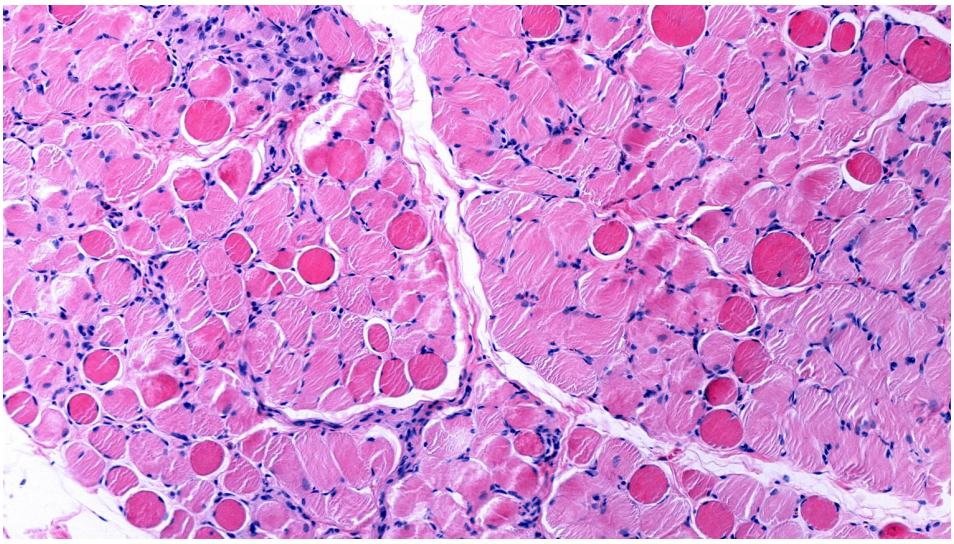
"The approval of Elevidys is a watershed moment for the treatment of Duchenne," said CEO Doug Ingram, in a statement. If the Phase 3 study "confirms the benefits seen in our prior trials, Sarepta will move rapidly to submit a[n application] supplement to expand the approved label as broadly as good science permits," he added.

Though the current approval is relatively narrow in scope and the therapy isn't a cure, many patient advocates and families see Elevidys as a significant step forward in treatment for a disease that's frustrated drug developers for decades.

"Even 10 years ago, there wasn't anything in the works like there is today," said Susan Finazzo, whose two young sons have Duchenne, in a recent interview. "This gives us hope."

"It means a lot for the field and really opens up things," added Jerry Mendell, director of gene therapy research at Nationwide Children's Hospital and a co-inventor of Sarepta's treatment, prior to the approval.

Sarepta priced its therapy, a one-time infusion meant to last years, at $3.2 million, making it one of the most expensive medicines in the world.



An illustration of necrotic muscle fiber in Duchenne muscular dystrophy.
Jose Luis Calvo Martin, Jose Enrique Garcia-Maurino Muzquiz via Getty Images

Duchenne is caused by inherited mutations in the largest known human gene, one responsible for building a protein, dystrophin, that protects muscle tissue from damage by its repeated contraction and relaxation. Without it, the muscles of those with the condition, almost exclusively boys, slowly waste away. People with Duchenne usually lose the ability to walk in their teens and die from heart or lung weakness around age 30.

Many patients rely on steroids to slow the disease, but at the cost of side effects like weight gain, behavioral changes and growth defects. Some can get “exon skippers,” including three drugs sold by Sarepta, which are thought to modestly delay progression.

Patients as well as Duchenne physicians and researchers are hoping gene therapy can work better, such as by more clearly halting or possibly even turning back the disease.

Sarepta's treatment is the result of decades of research into Duchenne and its underlying genetics. Like other gene therapies in clinical development, it delivers into the body's cells DNA encoding the microdystrophin protein, which is designed to imitate a form of dystrophin found in people with a milder type of muscular dystrophy known as Becker.

Clinical testing has shown Sarepta's therapy can produce a large amount of this protein, far above what experts believe is needed to benefit patients. Some participants in Sarepta's main study are also performing better on certain functional tests than historical data suggests they would otherwise, which experts and advocates take as proof Sarepta's treatment works.

"What we're seeing is stabilization of a disease that we've never been able to stabilize before," said John Brandsema, a pediatric neurologist at the Children's Hospital of Philadelphia, prior to the approval. "That is a tremendous achievement."

Tim Revell, the father of two boys with Duchenne, said he and others expect Elevidys can help their sons, and that its benefits can last. "We're hoping and praying" it "can help the older boys live, and the younger boys keep walking," Revell said in a recent interview.

Sarepta hasn't proven it can. The only placebo-controlled test to produce results so far did not show the therapy meaningfully improved function. In their review, FDA scientists were skeptical of the treatment, as were some members of an advisory panel the regulator convened last month.

Though a majority voted to recommend an approval, a number of the panelists worried about the FDA clearing a potentially ineffective drug, as there's a chance people who receive it couldn't

receive another, similar type of gene therapy later on. Treatment was also linked in a few cases to serious liver damage.

“While the risks are low, there was no evidence of benefit,” said Lisa Lee, a panelist and associate vice president for research and innovation at Virginia Tech, at the May meeting. “Without some data showing benefit, we’re basically asking families to shut off any future short- or mid-term possibilities for treatment.” Lee voted against recommending the therapy’s approval.

Still, Duchenne patients are certain to progress without treatment, putting pressure on the FDA to act quickly. “Time is muscle,” said Jennifer Handt, the parent of a boy with Duchenne, wrote in a recent email.

Some top officials within the FDA have advocated for flexibility in exactly these types of situations. At a meeting held by a nonprofit group in March, Peter Marks, head of the FDA office that reviews gene therapies, spoke of the urgency to expedite new genetic medicines for rare and life-threatening diseases.

“We can’t be so careful about our approvals under accelerated approval that we prevent potentially life-saving therapies from getting to market in a timely manner,” Marks said then.

The same month, he had reportedly pushed the agency to schedule the May advisory meeting for Sarepta’s treatment, after learning agency scientists were leaning toward a rejection, according to Stat News.

The FDA ultimately chose a compromise of sorts. It delayed its decision by a month, using the time to narrow its initial approval to a younger group of boys who an after-the-fact analysis of the company’s study results suggested might benefit the most.

An approval now, rather than after Sarepta's ongoing Phase 3 study reads out at the end of this year, means eligible patients, their families and physicians can consider Elevidys sooner. But it leaves those who are older potentially without a chance to receive the treatment, as they may not meet any expanded criteria the FDA later clears.

"We're pretty hopeful the Phase 3 will read out positively," Pat Furlong, CEO of advocacy group Parent Project Muscular Dystrophy, said in a recent interview. "To be honest, I don't think we have the appetite to think differently at this moment."

Editor's note: This story has been updated to include Elevidys' list price.