

‘We’ve exhausted all avenues’: A small biotech may give up on its ultra-rare disease drug over frustration with FDA



Declan Dubuque, 22 months, with his mother, Jamie Dubuque, and father, Jesse Comerford, at home in Rimrock, Ariz.

Jamie Dubuque faces the future with a mixture of gratitude and trepidation.

Her son, Declan, who turns 2 years old in January, survived a life-threatening episode of cardiac arrest that sent him to a hospital emergency room a year ago. But since being diagnosed with an ultra-rare disease, he has been treated with an experimental medicine that has transformed his day-to-day existence.

The toddler has [Barth syndrome](#), which causes an enlarged heart, muscle weakness, and a shortened life expectancy. Although he is now doing well and has avoided the need for a heart transplant, another problem is looming. Declan gets the medicine through a special access program called compassionate use, but the company that developed the drug may soon walk away from the project if it fails to win approval to market its medicine — meaning Declan would lose access to it.

The prospect makes his mother anxious and scared.

“Since he got the drug, he doesn’t complain of pain. We’re chasing after him all day. I can’t keep up with him,” said Dubuque, who lives in Rimrock, Ariz. Without the drug, “it’s possible his heart could take a giant step backwards. I’m aware of the looming cloud over our lives. I wish it away every day. I try not to think about it. My son was given a second chance at life and I’ve never been more grateful for a drug.”

The possibility that Declan may lose access also upsets Reenie McCarthy, the chief executive officer at Stealth BioTherapeutics. The company has spent the past decade developing and testing the drug, called elamipretide, in hopes of convincing the Food and Drug Administration to approve it for a tiny population that numbers no more than 130 to 150 patients around the country.



A photo of Declan in the hospital on his grandfather's phone. Declan has Barth syndrome and is taking elamipretide, a drug produced by Stealth BioTherapeutics that has improved his condition enough that he no longer needs a heart transplant.

CAITLIN O'HARA FOR STAT

But Stealth has had an especially trying time seeking FDA approval for its drug.

The company has been bounced among different agency divisions and, more than once, received conflicting advice about which trial data to submit. To date, Stealth has burned through about \$75 million trying to get its drug approved; last year, its largest investor took the company private after its stock was hammered by the ongoing confusion and disappointments.

<https://www.statnews.com/pharmalot/2023/12/18/barth-syndrome-stealth-biotherapeutics-elamipretide-rare-disease-fda/>

Already rejected two years ago by the FDA, Stealth this month is trying a Hail Mary and will refile its application, but McCarthy is not optimistic.

“We feel we’ve exhausted all avenues with the FDA, and there’s nothing more we can do,” she told us. “We don’t see any path forward. Submitting the application is a last-ditch effort. If the FDA doesn’t approve it, I don’t see any more clinical development work.”

“We’re a small team and have other programs to pursue and we feel like we’re banging our heads against the wall and they keep moving the goalposts... We have to move on.”

Winning FDA approval is never easy, but Stealth’s journey reflects the challenges of getting an ultra-rare disease treatment through what can sometimes be a regulatory maze.



Dubuque prepares meds for Declan.

CAITLIN O'HARA FOR STAT

For Stealth, at least, the path to approval may prove easier in other jurisdictions. The company is still proceeding with plans to win approval in Europe and last May [signed a deal](#) with a U.K. drugmaker to market its medicine in Europe and elsewhere.

“We fully expect that European efforts will continue irrespective of FDA’s decision on this program. For ultra-rare diseases, Europe actually has more consistent and well-defined approval pathways than the U.S.,” McCarthy explained.

Of course, this remains to be seen, but the suggestion is clear: Barth syndrome patients in Europe, the Middle East, and North Africa may eventually gain access to the drug, while patients in the U.S. may not.

Such difficulties are not going unnoticed on Capitol Hill or Wall Street, since patient advocates, lawmakers, and investors are always watching for signs that access and innovation are being impeded.

Hilary Vernon, a physician at the Kennedy Krieger Institute, who runs the only Barth syndrome clinic in the U.S. and has worked with Stealth on its clinical trials, said recently that the story of the Barth syndrome drug and other ultra-rare disease drugs generally is “stalled” at the FDA.

“And the story is stalled because there is no regulatory flexibility and a lack of understanding of the challenges of rare diseases,” she said.

Notably, Vernon made this remark at a press conference held a few weeks ago by a lawmaker who had introduced a bill to create a new pathway for regulatory approval of rare and ultra-rare disease drugs. The bill has generated notice, and the added presence of officials of the Barth Syndrome Foundation, an advocacy group, helped highlight the rollercoaster ride Stealth has taken.

In the U.S., a rare disease is defined as any condition that afflicts 200,000 people or fewer. There are an estimated 7,000 such diseases, according to the FDA. But there is no legal or regulatory bright line to distinguish ultra-rare diseases, other than an informal rule of thumb that such diseases affect one patient per 50,000 people, or

<https://www.statnews.com/pharmalot/2023/12/18/barth-syndrome-stealth-biotherapeutics-elamipretide-rare-disease-fda/>

fewer than 20 patients in a population of 1 million people. That arbitrary definition works out to about 6,000 patients in the U.S.

As a result, companies seeking to develop a drug for a tiny population must search for as many patients as possible in order to gather sufficient evidence on safety and effectiveness to satisfy FDA medical reviewers and division heads. This can be quite difficult when the pool of patients is miniscule, as is the case with Barth syndrome and the Stealth drug.

Consider that over the last few years no fewer than four FDA divisions were, at different times, handed responsibility for overseeing the Stealth marketing application, which is an unusually high number. Moreover, these transfers occurred after a mid-stage trial was already completed, which is rather late in the development of a drug to make such changes.

Adding to the confusion, the Division of Cardiology and Nephrology — which has been working with Stealth since late 2020 — agreed to review its application based on certain data, then changed course and asked the company to run another clinical trial. At the request of patient advocates, the company sought FDA approval anyway, and the agency refused to review the submitted application.

Last year, the same division indicated that data showing the Stealth drug improved heart function could be used to win accelerated approval, an FDA designation for a medicine that appears to meet an unmet medical need but will require follow-up trials to provide the proof. But this past June, the division did an about-face and decided the data did not support such an approval.

In response to questions about the Stealth drug, specifically, the spokeswoman wrote “the FDA generally cannot confirm or deny the existence of a pending product application or discuss the status of a pending application.” Beyond that, we were told to contact Stealth. So we asked McCarthy to provide more details.

During the process, McCarthy said the company attempted to follow up with alternate protocols for running another trial but got nowhere. At various times, the FDA insisted on larger sets of trial data — essentially, a request for more evidence that the drug can be effective — even though finding a sufficient number of eligible patients had become very difficult, according to the company.

The agency also sent mixed signals about using a [natural history trial](#), which tracks the progression of a disease. Stealth compared that trial data with results of an uncontrolled study, after its [original trial](#) failed to meet its endpoints. Together, these showed patient symptoms improved from the time they started on the drug, and also improved when compared to patients who were not on the drug in the natural history study

But two FDA divisions declined to review the natural history control data, despite prior assurances that objective evidence showing the effect of a drug, such as on heart function, would make it possible to interpret such data, McCarthy said. Moreover, in 2019, the agency had [issued guidance](#) for pharmaceutical companies considering the use of natural history studies for winning approval.

The FDA, McCarthy contended, never got comfortable with the small number of patients proposed for clinical work, since there are only 130 to 150 in the U.S. and

fewer than 250 worldwide. Organizing a trial would require multiple clinical sites in different countries. Meanwhile, about 15% of patients had heart transplants, so they would be ineligible.

“They’re still not willing to review the data and want another pre-approval trial and never signed off on any protocols we’ve given them,” said McCarthy, who added the company could file an appeal if the FDA again rejects its application.

But the agency is “very conservative, for the most part,” she continued. “It’s hard to rely on the FDA and its use of regulatory flexibility, because it’s quixotic and inconsistent. And that makes it hard to make investment decisions based on regulatory flexibility, because it’s not applied consistently. I wouldn’t develop an ultra-rare disease drug now. I think it’s really, really risky.”

To some, the frustration and confusion that Stealth encountered is hardly unusual for a company trying to bring medicines for treating ultra-rare diseases to the public. Some experts say a key issue can be traced to the vagaries of the FDA, where different division heads and shifting personnel can lead to different requirements and decisions for seemingly similar drugs and clinical trial work.

Indeed, the FDA may appear to be a monolithic bureaucracy to outsiders but is, in fact, a collection of divisions and departments that do not always operate in the same way or apply the same standards exactly alike.

“Different approval standards across FDA centers, offices and divisions is an often shifting, sometimes puzzling, black box posing a unique challenge for biopharma

<https://www.statnews.com/pharmalot/2023/12/18/barth-syndrome-stealth-biotherapeutics-elamipretide-rare-disease-fda/>

specialists and generalists with biotech exposure,” the pharmaceutical and biotech analysts at TD Cowen, an investment firm, wrote in a lengthy report last fall about agency review practices.

“FDA approval of a drug is not solely dependent on clinical data generated and how it stacks up against FDA guidance, but also the organizational psychology of the division in which it undergoes review,” they wrote. “The movement of leadership within the FDA invariably influences the reviews and regulatory decisions. Hence, ‘who’ the drug applications go to matters just as much as ‘which’ division reviews it.”

The analysts devised a grading scheme for each division and determined that the Division of Cardiology and Nephrology, on a scale of 1 to 5, received a 2, which signals inflexibility and rarely exerting discretion. This division “has typically erred on the side of conservatism, most often reviewing and making decisions by the rulebook,” the analysts wrote.

And while the FDA has trumpeted its accelerated approval pathway, experts contend the agency sometimes continues to struggle with the program, because not all drugs prove to be as useful as initially thought. Moreover, the FDA lacks the means — and institutional memory — to sufficiently weigh unusual and unique circumstances, a group of experts [wrote in a paper](#) in the Annals of Internal Medicine.

The FDA spokeswoman wrote that, in general, the agency “remains committed to our goal of facilitating the development of safe, effective drugs that have the potential to meaningfully impact rare diseases, including very rare diseases. While we work to bring these treatments to patients as quickly and efficiently as possible, we must

ensure drugs meet the FDA's rigorous approval standards through thorough and comprehensive review of the evidence presented.

“We still face unique challenges in the development of treatments for rare diseases, such as small patient populations which limit the number of people available to participate in clinical trials. The FDA applies flexibility in these situations to address particular challenges posed by each disease, while upholding our regulatory standards.”

She added the agency does have “several tools” to speed reviews for life-threatening conditions for which there are treatments.

But not everyone is convinced these tools are sufficient. To fix the shortcomings — real and perceived — Sen. Mike Braun (R-Ind.) introduced a bill to jumpstart the FDA approval process for rare and ultra-rare disease drugs. Called the [Promising Pathways Act](#), the bill would allow for a two-year provisional approval for drugs that demonstrate substantial safety and indicate early signs of effectiveness.

A drug company could request additional two-year periods, up to eight years, and meanwhile provide substantiated surrogate endpoints and real-world data — gleaned from patient registries — to prove effectiveness. From there, the FDA could grant full approval. As with the accelerated approval program, the purpose is to speed access to people with terminal illnesses as quickly as possible.

“In many cases, patients don't have enough time to wait and this would provide a format to address those situations,” Braun told us. Stealth, he added, is “a great

<https://www.statnews.com/pharmalot/2023/12/18/barth-syndrome-stealth-biotherapeutics-elamipretide-rare-disease-fda/>

example of why we need to get moving on it. This is designed for a company that doesn't have the legs to hold out for the standard amount of time [for FDA approval], especially if its drug is showing good results. It would be a loss, otherwise.”



Dubuque plays with Declan at home.

CAITLIN O'HARA FOR STAT

Not everyone is convinced the legislation is workable. At an October Senate hearing to discuss the bill, Holly Fernandez-Lynch, an assistant professor of medical ethics and law at the University of Pennsylvania, testified it sets a low bar because the notion of a provisional approval might weaken standards. She also maintained patient registries are limited and the bill fails to define such key terms as “relevant early evidence.”

<https://www.statnews.com/pharmalot/2023/12/18/barth-syndrome-stealth-biotherapeutics-elamipretide-rare-disease-fda/>

Not surprisingly, though, the legislation is backed by several patient advocacy groups that often agitate for faster regulatory approval of medicines for different diseases where treatments are lacking. Among them is the Barth Syndrome Foundation, which nearly a decade ago had solicited Stealth to develop its drug and has pushed FDA officials to approve it.

Nonetheless, the legislation is unlikely to become law fast enough to alter the fate of the Stealth drug. And this concerns Amy Goldstein, who is a physician with the Division of Human Genetics at Children's Hospital of Philadelphia, where she diagnosed Declan with Barth syndrome earlier this year and has continued to arrange for the drug to be made available to him.

"This drug helped his heart revert back to normal. This has been a very dramatic story," she said. "The FDA literally let us save his life when they approved compassionate use, but now they won't look at the data to save more than 120 other lives. I know the FDA has a job to do, but this is a lifesaving medication."

As for Dubuque, she is trying to remain optimistic.

"I'm just living every day with him and cherishing it," she said. "It couldn't have gone any better. We continue to receive great news from the doctors. He's thriving. But if the drug is not approved, it will be very detrimental not just to us, but everyone else in the future with this disease."

<https://www.statnews.com/pharmalot/2023/12/18/barth-syndrome-stealth-biotherapeutics-elamipretide-rare-disease-fda/>

About the Author



Ed Silverman

Pharmalot Columnist, Senior Writer

Ed Silverman covers the pharmaceutical industry.

✉ ed.silverman@statnews.com

🐦 [@Pharmalot](https://twitter.com/Pharmalot)