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Tiny biotech says its troubles make case for ultra-rare FDA pathway

Stealth BioTherapeutics has struggled to get a therapy approved for Barth syndrome

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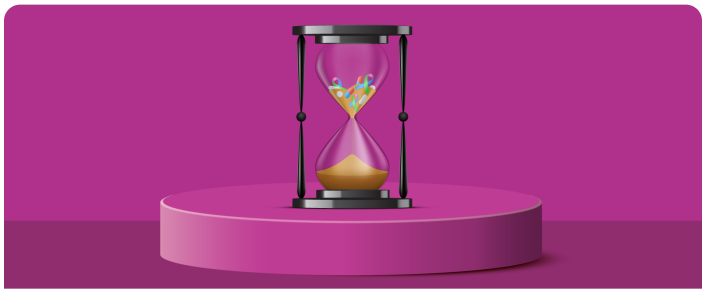

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The struggles of a tiny biotech, Stealth, to develop a therapy for Barth syndrome, a fatal disease that affects about 150 Americans, highlight the regulatory and financial challenges of developing medicines to help patients who have extremely uncommon, serious diseases. These challenges include limited and imperfect data, shifting FDA requirements, and the agency's inability or unwillingness to apply flexibility that has been exercised for other rare disease treatments.

These difficulties are layered on top of the struggle to create a business model for earning a return on a product when the total possible market is in the 10s or 100s of patients.

Stealth BioTherapeutics Inc.'s experience also shows why some patient advocates are calling for FDA to adopt explicit policies to smooth the path to approval for therapies to treat ultra-rare diseases.

Propelled by venture investment and a strong partnership with a tight-knit patient advocacy and medical community, Stealth has been working since 2014 to turn a serendipitous finding in an academic lab into an FDA-approved drug for Barth syndrome. It is on the verge of failure.

Stealth and the Barth Syndrome Foundation, a patient advocacy group, say they are caught in a web of shifting decisions from FDA about the data required to obtain approval. They are frustrated that one of the agency's review divisions has rejected endpoints and trial designs that they believe other divisions have accepted in similar circumstances.

The company and patient advocates also say FDA is requiring a level of statistical rigor and clinical trial sizes that are unattainable given the small number of patients. And they note that agency leaders have intervened to rescue other orphan drug applications with data that fall short of the rigor required for more prevalent diseases.

Stealth's failure would be devastating for patients. "Things are dire," Emily Milligan, executive director of the Barth Syndrome Foundation, told BioCentury.

If Stealth concludes that there is no feasible path toward an approval, patients who are receiving its drug candidate, elamipretide, through an expanded access program may lose access to a therapy that they believe is the only thing standing between them and a painful early death, Milligan said.

She believes that Stealth's inability to gain approval for elamipretide would deter other companies from attempting to develop products to treat a disease that has no approved treatment. The natural history of Barth syndrome is clear: 85% of patients are dead by their fifth birthday. That means that although there are about 150 patients in the U.S., the non-pediatric population is extraordinarily small. The few who survive infancy suffer from devastating health problems that kill most of them in their 20s or 30s. There are about 90 patients in the U.S. over age 12.

"Things are dire."

Emily Milligan, Barth Syndrome Foundation

The company's experience trying to gain approval based on a trial that failed to meet its primary endpoint and open-label follow-up data that it believes demonstrate efficacy — a scenario that has led to approvals for other drugs for rare diseases — shows the lack of clarity about the circumstances in which regulatory flexibility will be applied.

FDA's vague policy of "regulatory flexibility" has been applied idiosyncratically.

Attorneys and regulatory experts with decades of experience cannot predict which applications will receive the kinds of special consideration that have allowed Sarepta Therapeutics Inc. (NASDAQ:SRPT) to obtain accelerated approvals for exon skipping and gene therapy treatments for Duchenne muscular dystrophy and Amylyx Pharmaceuticals Inc. (NASDAQ:AMLX) to obtain approval for a drug to treat amyotrophic lateral sclerosis.

While there are debates about whether those approvals should have been granted, there can be no doubt that patients and drug developers deserve to know if the rationale behind them and other drugs that were approved based on regulatory flexibility can be extrapolated to other types of rare diseases.

FDA told BioCentury it is precluded by law from commenting on existing or potential applications, including Stealth's.

It is possible that Stealth and the Barth Syndrome Foundation have misinterpreted FDA's actions and statements, or that the agency's handling of elamipretide is being driven by factors the company and patient advocates are unaware of.

It is clear, however, that senior FDA officials have intervened in similar situations to enable approvals, and that agency officials at some of the divisions of the Center for Drug Evaluation and Research (CDER) have interpreted their mandate to exercise regulatory flexibility for rare conditions in ways that would have allowed at least for a review of the data supporting the safety and efficacy of elamipretide for Barth syndrome.

Data that the Barth Syndrome Foundation and physicians who specialize in treating the disease believe demonstrate the safety and efficacy of elamipretide may turn out to be illusory, but they contend that the risks are minimal in the context of a uniformly fatal disease, with no approved therapy.

The Barth syndrome community is not alone in believing that FDA has failed to afford it the regulatory flexibility that has been extended to developers of therapies for other rare conditions. Academic researchers working to develop therapies for Prader–Willi syndrome, for example, have recently made the same argument.

The case for ultra-rare

Milligan and Stealth's CEO, Reenie McCarthy, attribute elamipretide's travails to shifting and inconsistent demands from FDA, including encouraging the company to submit an NDA, backtracking two weeks before the planned submission, and then refusing to accept the submission.

The foundation and the company also contend that CDER's Division of Cardiology and Nephrology (DCN) has refused to consider endpoints and trial designs that other divisions have accepted as the basis for accelerated approvals of therapies for ultra-rare conditions. And they say DCN has requested that the company conduct trials that would be impossible to conduct given the very small number of patients.

For Stealth, time is running out to resolve differences with FDA.

The company is close to seeking approval of elamipretide for a different indication, primary mitochondrial myopathy caused by nuclear DNA mutations, which affects adults.

Approval in that indication would make it impossible for Stealth to obtain a rare pediatric priority review voucher for Barth syndrome because the incentive is available only if the therapy's first approval is for a rare disease that affects children.

If it cannot receive a priority review voucher, which could be sold for about $100 million, it will not be possible to convince investors that Stealth can earn a sufficient return to justify continuing its pursuit of a Barth Syndrome indication, McCarthy said. In 2022, Morningside Venture Investments, the company's largest investor, and J Wood Capital took Stealth private "after a pretty rough reaction to the Barth stops and starts via the public market," she told BioCentury.

"It is incomprehensible to us that comparable standards for regulatory flexibility have not been considered for our indication."
Emily Milligan, Barth Syndrome Foundation

Stealth's FDA journey for Barth syndrome has spanned eight years and four different review divisions, and has been marked by a request for randomized-withdrawal data the company was concerned was unethical, and completion of a new natural history study that FDA subsequently determined was uninterpretable. The company received a refuse-to-file (RTF) letter after it decided to submit an NDA, despite FDA's warning that the data might not support a review or approval.

Although elamipretide failed to meet the primary endpoints in the blinded portion of its Phase II/III trial, the therapy produced several statistically significant efficacy signals in the study's open-label extension, as well as when compared to a natural history control group.

The Barth community believes that Stealth "has been subjected unfairly to a different and higher standard," Milligan told BioCentury. She cited FDA's acceptance of natural history control data as the primary basis of approval of Brineura cerliponase alfa from BioMarin Pharmaceutical Inc. (NASDAQ:BMRN) for a specific form of Batten disease, and as essential confirmatory evidence for approval of Skyclarys omaveloxolone from Reata Pharmaceuticals Inc. (NASDAQ:RETA) for Friedreich's ataxia.

Brineura was approved based on a single-arm open label clinical trial with an extension (n=24) that was compared with a natural historical control group (n=42). Like elamipretide, it did not meet the prespecified primary endpoint at a prespecified time point.

Skyclarys was approved based "on an effort-dependent/subjective endpoint (the mFARS scale) based in part on a post-hoc comparison of open-label data to natural history controls," Milligan said in an email.

"For us, this same type of information is not even being accepted as a threshold for a full NDA review, much less drug approval," Milligan said. "It is incomprehensible to us that comparable standards for regulatory flexibility have not been considered for our indication (and in our Division), and we are chagrined by the perceived inconsistencies across FDA drug review processes."

To rare disease public policy advocates, Stealth's experience shows the need for a well-defined regulatory pathway, created through statute or administratively, for the review and approval of therapies for ultra-rare disorders.

They believe that companies such as Stealth that are trying to create therapies for little-known conditions are subject to inconsistent and often unattainable standards, while those working on diseases that have caught the attention of the public and top FDA officials have been afforded a great deal of regulatory flexibility.

FDA should create explicit criteria regarding the quantity and type of evidence required to approve therapies for ultra-rare diseases, Frank Sasinowski, chair of the EveryLife Foundation for Rare Diseases, told BioCentury.

"The standard," he said, "shouldn't be one adequate and well-controlled trial with confirmatory evidence because you can't do an adequate and well-controlled trial" for a medicine intended for an extremely small population.

Sasinowski, a director at the law firm Hyman, Phelps & McNamara who represents Stealth, proposes defining ultra-rare as a disease or condition affecting 2,000 or fewer U.S. citizens. The Orphan Drug Act defines rare diseases in the U.S. as those that affect 200,000 or fewer people.

Stealth's McCarthy and the Barth Syndrome Foundation's Milligan told BioCentury that their experience points to the need for different criteria for evaluating drugs to treat diseases that affect very small numbers of people.

Emil Kakkis, president and CEO of Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), also supports the establishment of evidentiary standards for ultra-rare disorders that take into account the difficulty of meeting conventional approval requirements. Kakkis is a former board member of the EveryLife Foundation and of the National Organization for Rare Disorders.

A clear delineation of ultra-rare disease and of standards FDA will apply to treatment candidates for those diseases would put guardrails around the notion of regulatory flexibility, Sasinowski said. It would, for example, make it clear that the amount of uncertainty FDA would accept for a treatment intended for a population of a few hundred patients may not be acceptable for rare diseases that affect 20,000 or 200,000 patients.

Clock ticking

After being passed from CDER's Division of Neurology to the Division of Gastroenterology and Inborn Error Products, which was then reorganized into the Division of Rare Diseases and Medical Genetics (DRDMG), Stealth's elamipretide finally landed at the Division of Cardiology and Nephrology.

According to Stealth, in February 2021 the DCN advised the company to submit an NDA based on evidence the company had collected.

In March, the company told officials at the division that they planned to submit an NDA in two weeks. In response, FDA officials said that the agreement to review the application has been reviewed by a committee of senior CDER officials that concluded that the data were insufficient and FDA might not be willing to review the NDA.

Stealth submitted an NDA in August, and in October, it received the RTF letter.

Since the winter of 2021, Stealth has had a series of interactions with FDA regarding the possibility of resubmitting its NDA and seeking accelerated approval. According to the company, the agency's responses have been inconsistent with advice it had provided previously.

In June 2023, the division told Stealth that approval would only be possible if it conducted a new placebo-controlled trial.

The company and the Barth Syndrome Foundation say that this requirement is impossible to fulfill because there are not enough eligible adolescent or adult patients to enroll a trial.

In any case, the company cannot justify the investment, given the lack of clarity about the regulatory requirements and the possibility that elamipretide will become ineligible for a priority review voucher, McCarthy said.

The only hope for getting elamipretide approved, she said, is for FDA to drop its requirement for a new study and agree to review an NDA that the company could submit in the coming months. "If we get an RTF, we are done," McCarthy said.

Starting Stealth

Elamipretide started out as a research tool. Hazel Szeto, a pharmacologist at Weill Cornell Medical College, was looking for compounds that bind to opioid receptors. She found one that did something quite different: it penetrated cells, targeted mitochondria, increasing adenosine triphosphate (ATP) production and decreasing production of reactive oxygen species.

In 2006, with backing from Morningside Venture, Szeto founded Stealth, licensed elamipretide from Cornell, and started research multiple indications, including heart failure, ophthalmic diseases and neuromuscular diseases.

In 2014, the Barth Syndrome Foundation asked Stealth to consider developing elamipretide for their disease, based in part on its effect on cardiolipin, a major component of the mitochondria inner membrane that is disrupted by the mutations that cause Barth syndrome. By binding cardiolipin, elamipretide helps restore the structure and organization of the membrane needed to support ATP production.

In May 2017, researchers at Johns Hopkins University, one of only two multidisciplinary centers in the world treating Barth syndrome, started the Phase II/III TAZPOWER trial of elamipretide, which was designed with and sponsored by Stealth.

The 28-week double-blind, placebo-controlled crossover study enrolled 12 patients, which comprised the entire population available for a study, and was followed by 168-week open-label treatment extension. The primary endpoints were improvement on the six-minute walk test (6MWT) and improvement on a BTHS Symptom Assessment (BTHS-SA) scale.

In November 2018, Stealth learned that neither primary endpoint had been met in the blinded portion of the trial. However, researchers saw what they believed were important improvements in function in the 10 patients who remained in the open-label extension. At 36 weeks, these included a 96-meter improvement in the 6MWT (p = 0.024), a significant improvement in BTHS-SA (-2.1 points, p=0.031), and improvements in secondary endpoints including knee extensor strength, patient global impression of symptoms, and some cardiac parameters.

In April 2019, Stealth met with Billy Dunn, who at the time headed CDER's Division of Neurology, to discuss submitting an application for elamipretide to treat Barth syndrome. According to the company, Dunn said more data would be required, and suggested that it conduct a randomized withdrawal trial of the eight patients remaining in the open-label extension. Stealth had concerns about this suggestion, including about the statistical power of such a small study to demonstrate benefit, as well as ethical concerns about the impact of withdrawal on the health of patients in the absence of rescue medication.

"If we get an RTF, we are done."
Reenie McCarthy, Stealth BioTherapeutics

At that meeting, Dunn informed Stealth that responsibility for its IND was being transferred to the Division of Gastroenterology and Inborn Error Products (DGIEP). In the fall 2019, DGIEP was reorganized into the Division of Rare Diseases and Medical Genetics (DRDMG).

Stealth conducted a natural history control study comprised of 19 propensity score matched subjects with Barth syndrome. According to the company, patients who received elamipretide for up to one year had a mean improvement of greater than 80 meters on their six-minute walk test, versus less than one meter for subjects in the natural history group evaluated over the same period.

Those improvements were durable for patients who remained on therapy, according to Stealth. "In the open-label extension, we were seeing more than 25% improvements in exercise tolerance, improvements in strength, improvements in balance, and those continue to be durable essentially over a four-year open-label extension period," McCarthy said.

At a meeting in April 2020 and a written response in July, FDA's rare diseases division staff told Stealth that natural history control data were uninterpretable for effort-dependent endpoints such as 6MWT and said improvements in cardiac function were not robust enough to interpret, McCarthy told BioCentury.

The Barth Syndrome Foundation has held an externally led patient-focused drug development meeting to provide FDA patient and family perspectives on the disease, and has met with FDA staff to discuss the community's willingness to tolerate the risk that elamipretide may not live up to expectations.

The foundation submitted a petition to FDA in September 2020 urging it to approve Stealth's NDA on an urgent basis. Signatures on the petition included 67 of the 225 individuals living with Barth worldwide, 877 parents and family members of Barth patients, living and deceased, as well as scientists, healthcare providers and community advocates.

In addition, the foundation has organized two letters from key opinion leaders, including clinicians who treat Barth syndrome patients, urging FDA to review Stealth's application.