Valerie M. Bowen
2005 Palmer Ave, #1033
Larchmont, NY 10538

May 15, 2025

Re: Docket No. FDA-2023-P-5634

Dear Ms. Bowen:

This letter responds to the citizen petition and attachment you submitted on behalf of the Barth Syndrome Foundation, received by the Food and Drug Administration (FDA, the Agency, or we) on December 21, 2023 (Petition). The Petition requests that the Agency "file [the] [new drug application (NDA)] for elamipretide and [] provide a fair, thorough, equitable review of elamipretide using the advisory committee process."

FDA has carefully considered the information submitted in the Petition and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, the Petition is granted.

I. BACKGROUND

A. Barth Syndrome

Barth syndrome is an x-linked, infantile-onset, cardioskeletal disease caused by defects in the TAZ gene, which encodes tafazzin, a transacylase located in the inner mitochondrial membrane. Tafazzin catalyzes the remodeling of immature to mature cardiolipin, which is an important structural component of the mitochondrial membrane that organizes the super-complexes of the mitochondrial respiratory chain.

Barth syndrome is a rare disease, affecting 1 in 300,000 to 400,000 individuals worldwide. The major clinical characteristics include skeletal myopathy and fatigue, cardiomyopathy (dilated or hypertrophic), pre-pubertal growth delay, neutropenia, prolonged QTc, and arrhythmias. There are currently no approved therapies for Barth syndrome and the main course of management includes treatment of neutropenia with granulocyte-colony stimulating factor (G-CSF), symptomatic management of fatigue and myopathy, and pharmacologic and interventional treatment of cardiac manifestations such as heart failure (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, diuretics, anticoagulants, implantable cardioverter defibrillator, cardiac transplantation).

B. Elamipretide

Because FDA generally cannot disclose data or information contained in an unapproved NDA or abbreviated new drug application (ANDA),[1] our response to this petition is based on information that is publicly available regarding FDA's review of NDA 215244 for elamipretide. On March 22, 2018, Stealth Biotherapeutics Inc. (Stealth) received orphan drug designation for elamipretide, an aromatic cationic tetrapeptide, for the treatment of Barth syndrome.[2] Stealth submitted NDA 215244 for elamipretide for the treatment of Barth syndrome in August 2021.[3] The division refused to file the application because the application had significant deficiencies that could not be promptly resolved, which made the application substantially incomplete.[4] Stealth resubmitted the application on January 29, 2024,[5] and FDA accepted it for review.[6]

A Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting was held on October 10, 2024, to discuss whether the submitted data provide substantial evidence of effectiveness of elamipretide for the treatment of Barth syndrome.[7] The advisory committee discussed whether the evidence from SPIBA-001, A Long-Term Study to Evaluate the Efficacy of Subcutaneous Injections of Elamipretide (MTP-131) Compared to a Retrospective Natural History Control in Patients with Barth Syndrome, or SPIBA-201, Part 2, the open label extension of SPIBA Part 1,[8] along with other evidence (e.g., nonclinical data), showed that elamipretide is effective in the treatment of Barth syndrome.[9] Ten advisory committee members voted that, based on the available evidence, elamipretide is effective in the treatment of Barth syndrome and six voted that, based on the available evidence, elamipretide is not effective in the treatment of Barth syndrome.[10]

In response to the Agency's request, Stealth subsequently submitted additional information to their NDA that constituted a major amendment, extending the user fee goal date for this

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[1] *See* 21 CFR 314.430, 312.130.
[2] FDA's Orphan Drug Designations and Approvals webpage, available at https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm
[3] FDA Cardiovascular and Renal Drugs Advisory Committee briefing document (CRDAC Briefing Document), page 15, Oct. 10, 2024, available at https://www.fda.gov/media/182553/download
[4] FDA's Drug Safety and Availability webpage, *FDA issues refuse-to-file letter for application for Barth syndrome*, Oct. 10, 2021, available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-issues-refuse-file-letter-application-barth-syndrome
[5] CRDAC Briefing Document, page 16.
[6] As noted above, the citizen petition submitted on behalf of Barth Syndrome Foundation was submitted on December 31, 2023. The submission of the petition was after the Agency refused to file the application, but before the resubmission of NDA 215244.
[7] CRDAC Briefing Document, page 8.
[8] SPIBA-201, Part 1, is titled "A Phase 2 Randomized, Double-Blind, Placebo-Controlled Crossover Trial to Evaluate the Safety and Efficacy of Subcutaneous Injections of Elamipretide in Subjects With Genetically Confirmed Barth Syndrome Followed by Open-Label Treatment."
[9] Id. at 9.
[10] FDA Cardiovascular and Renal Drugs Advisory Committee YouTube broadcast, Oct. 10, 2024, available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-10-2024-meeting-cardiovascular-and-renal-drugs-advisory-committee-10102024#event-materials.

application to April 29, 2025.[11] The Agency did not take action on the user fee goal date.[12]

C. Citizen Petition

The citizen petition requests that FDA file the application for elamipretide and provide a "fair, thorough, equitable review of elamipretide using the advisory committee hearing process." (Petition at 1).[13] The petitioner argues that Barth syndrome is an ultra-rare disease and that FDA has not "appropriate[ly] and consistent[ly]" used the flexibility granted by Congress under the Federal Food, Drug, and Cosmetic Act (FD&C Act). (Petition at 1). The petitioner also submitted an attachment to their petition, the Voice of the Patient report, which contains patient testimonials and 19,374 signatures in support of the petition.

II. LEGAL AND REGULATORY AUTHORITY

A. Review of New Drug Applications Under the FD&C Act

FDA's regulation of drug products approved using the NDA or ANDA pathway is governed by the FD&C Act (21 U.S.C. 301 et seq.) and the Agency's implementing regulations codified in Title 21 of the Code of Federal Regulations (CFR). The FD&C Act generally makes it unlawful to market a new drug without first obtaining an approved NDA or ANDA. Before approving an NDA, FDA must determine that the drug product is both safe and effective for use under the conditions prescribed, recommended, or suggested in the drug product's labeling.[14] The demonstration of effectiveness under this standard requires substantial evidence that the drug product will have the effect it purports or is represented to have.[15] Substantial evidence is defined as:

> [E]vidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.[16]

Generally, sponsors should provide evidence of effectiveness in an identified population from

[11] Stealth Press Release, *Stealth BioTherapeutics Announces PDUFA Action Date Extension for Elamipretide to Treat Patients with Barth Syndrome*, Jan. 23, 2025.
[12] Stealth Press Release, *Stealth BioTherapeutics Announces Delay in FDA Action Date for Barth Syndrome Application*, April 29, 2025.
[13] Insomuch as the different parts of the citizen petition use different language in the action requested, this citizen petition response is responding to the request that the Agency file the application for elamipretide and provide a "fair, thorough, equitable review using the advisory committee hearing process."
[14] Section 505(d) of the FD&C Act.
[15] Id. The "substantial evidence" standard refers to both the quality and the quantity of the evidence that the drug will have benefit. See, e.g., draft guidance for industry, "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" (Dec. 2019).
[16] Section 505(d) of the FD&C Act.

adequate and well-controlled clinical investigations.[17] The statute and regulations provide flexibility in how the regulatory standard may be met. FDA "exercise[s] its scientific judgment" in determining the kind and quantity of data an applicant is required to provide for a particular drug to meet the statutory standards.[18]

Additionally, in 1997, Congress amended section 505(d) of the FD&C Act (21 U.S.C. 355(d)) to confirm FDA's interpretation of the statutory requirements, making clear that FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence if FDA determines that such data are sufficient to establish effectiveness.[19] Specifically, Congress added to section 505(d) that:

> If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence.[20]

The finding of substantial evidence of effectiveness is necessary but not sufficient for FDA approval.[21] An approval decision also requires a determination that a drug is safe for its intended use.[22] Because all drugs can have adverse effects, the demonstration of safety requires a benefit-risk assessment that shows that the benefits of the drug outweigh its risks.[23] Broadly speaking, benefit-risk assessment in FDA's drug regulatory context is making an informed judgment as to whether the benefits (with their uncertainties) of the drug outweigh the risks (with their uncertainties and approaches to managing risks) under the conditions of use described in the approved product labeling.[24]

B. Principles and Practices for FDA's Review of NDAs

FDA seeks the highest levels of quality in reviewing submitted applications and making final regulatory decisions. Quality is achieved by applying the fundamental values of accountability, communication, and consistency, and FDA has established policies and processes to ensure that high-quality regulatory decisions are made in a consistent and timely manner.[25] FDA must apply the appropriate statutes and regulations in their review of specific applications, informed by the latest scientific advances and patient perspectives. Critical thinking using current scientific knowledge is an irreplaceable component of NDA review, and the policies and processes governing the review process support this objective. FDA's goal is to ensure the review process

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[17] See 21 CFR 314.126.
[18] 21 CFR 314.105(c); see also 21 CFR 312.80 and 312.84(a).
[19] The Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115).
[20] Section 505(d) of the FD&C Act.
[21] Draft Guidance for Industry, *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*, page 3 (Sept. 2023). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[22] Id.
[23] Id.
[24] Guidance for Industry, *Benefit-Risk Assessment for New Drug and Biological Products*, pages 3-4 (Oct. 2023).
[25] See draft guidance for industry and review staff: *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications* (September 2018).

nimbly adapts to scientific advances in product development, evolving patient perspectives, and any other factors that are relevant to the specific application.

To this end, FDA has implemented several operational principles to ensure effective, efficient, and thorough review of NDAs, which result in high-quality regulatory decisions.[26] First, FDA works to facilitate a well-designed and executed product development phase to ensure that high-quality NDAs are submitted. The Agency seeks to maintain a well-managed and collaborative review process, which helps to accommodate and adequately consider events and findings. During the review of an NDA, FDA tries to promptly communicate significant review issues to the applicant. Finally, FDA seeks to provide clear and concise documentation of the scientific review and regulatory decision to ensure a thorough and informative record of its regulatory action.

C. Rare Diseases

The development of drugs costs sponsors millions of dollars in research, clinical trials, and other activities necessary to develop, obtain approval for, and market a new drug. For many diseases that affect only a small number of individuals, the chances of recovering development costs through treatment sales are small. Thus, sponsors may have little economic incentive to invest in the development of treatments for rare diseases. Additionally, many rare diseases are serious conditions with no approved treatments, leaving substantial unmet medical need for patients.

To help address this, in 1983, Congress passed the Orphan Drug Act (Pub. L. No. 97-414, 96 Stat. 2049 (1983)), which amends the FD&C Act, adding certain provisions regarding drugs for rare diseases or conditions. The act is intended to encourage the development of drugs for such diseases or conditions (referred to as orphan drugs), for example, by reducing development costs and providing financial incentives.[27] Section 526(a)(2)(A) of the FD&C Act (21 U.S.C. 360(bb)) defines a rare disease or condition, in part, as a disease or condition that "affects less than 200,000 persons in the United States."[28] Most rare diseases, however, affect far fewer people. The sponsor of an orphan drug (a drug intended for use in a rare disease or condition)[29] may be eligible for orphan-drug designation and certain financial incentives intended to help

[26] CDER's review process is described in the CDER 21st Century Review Process Desk Reference Guide, available at *https://www.fda.gov/media/78941/download*. Additional detail on specific processes (e.g., meetings, advisory committees) can be found on the Good Review Practices (GRP) website, available at *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/good-review-practices-grps*.

[27] See section 1(b) of the Orphan Drug Act. Pub. L. No. 97-414, 96 Stat. 2049 (1983) ("The Congress finds that— … (5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and (6) it is in the public interest to provide such changes and incentives for the development of orphan drugs.")

[28] In addition, section 526(a)(2)(B) of the FD&C Act also defines a rare disease or condition as any disease or condition that "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

[29] See 21 CFR 316.3(b)(10).

make developing drugs for small numbers of patients financially viable.[30]

FDA recognizes that rare diseases are highly diverse with varying prevalence, rates of progression, and degrees of heterogeneity that can affect both clinical manifestations and disease courses even within a condition. Further complexity is added depending on what is known about a disease's natural history and pathophysiology. As such, no one program can be designed exactly like another. FDA is committed to supporting sponsors in creating successful drug development programs that address the challenges posed by each disease and encourages sponsors to engage early with the Agency to discuss their drug development program.

III. DISCUSSION

Stealth resubmitted NDA 215244 for elamipretide for the treatment of Barth syndrome on January 29, 2024, and FDA subsequently accepted it for review.[31] The CRDAC held an advisory committee meeting on October 10, 2024.[32] As such, the petitioner's request that FDA file the application for elamipretide and hold an advisory committee meeting to ensure a "fair, thorough, equitable review" of the application are granted.

FDA remains committed to engaging with the Barth syndrome patient community and Stealth on the efforts to develop safe and effective therapies for patients with Barth syndrome. As discussed above, FDA's statutes and regulations provide flexibility in how the regulatory standard for substantial evidence of effectiveness can be met. FDA exercises its scientific judgment in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs. In doing so, FDA must make informed judgments regarding the data submitted in an application and whether the benefits of the drug outweigh the risks. This review also considers whether all applicable requirements have been met. A "fair, thorough, equitable review" of an application is not (and should not be) designed to yield a particular outcome. In its review of all applications, including NDA 215244 for elamipretide, FDA follows established policies and practices to ensure high-quality regulatory decisions are made in a consistent manner.

Your Petition therefore is granted. FDA has filed the NDA and consulted an advisory committee on this application. Your Petition is also granted insofar as FDA conducts a "fair, thorough, equitable review" of all applications.

[30] Incentives associated with orphan-drug designation include a tax credit for 25 percent of qualified clinical trial costs, exemption from fees under the Prescription Drug User Fee Act, and potential eligibility for a 7-year period of market exclusivity. See Public Law 97-414 (1983), as amended.
[31] CRDAC Briefing Document, page 16.
[32] 89 FR 72846 (Sept. 6, 2024).

IV. CONCLUSION

For the reasons explained above, your Petition is granted.

Sincerely,

Jacqueline A. Corrigan-curay -S

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Date: 2025.05.15 13:17:46 -04'00'

Jacqueline Corrigan-Curay, J.D., M.D.
Acting Director
Center for Drug Evaluation and Research