May 12, 2025

Martin A. Makary, MD, MPH
Commissioner
US Food and Drug Administration
White Oak Campus
10903 New Hampshire Ave
Silver Spring, MD 20993

Re: NDA 215244 (elamipretide for the treatment of Barth syndrome)

Dear Dr. Makary:

I am reaching out as a **parent of an affected child, a co-founder and now Board Chair of the Barth Syndrome Foundation, the only advocacy organization in the world (along with our international affiliates) for the ultra-rare, lethal, pediatric, mitochondrial disease, Barth syndrome**. My husband and I know profoundly the serious nature and dire need of this disease, as we lost our wonderful, bright and thoughtful son, Will, to this terrible disease at 28 years old. Despite his many, many hospitalizations, very serious health challenges and vastly reduced quality of life that he endured for his entire life, he was one of the lucky ones because he reached his twenties. A large percentage of Barth patients die in the first few years of life. We and other like-minded parents have been advocating for our sons and their "Barth brothers" ever since we initially met each other.

First, I want to offer my **congratulations on your new and crucially important role**. We, like everyone in our country (and around the world), are counting on you to make a real difference to our collective health.

Second, I have read with great interest your public comments since becoming FDA Commissioner. I am **buoyed by your thoughts regarding improved access to and transparency from FDA leadership**, and I am incredibly encouraged by your ideas regarding rare and, in particular, ultra-rare diseases. **You seem to have a refreshingly pragmatic appreciation of the critical challenges of conducting randomized controlled trials for very small patient populations like ours.**

These issues are especially relevant to our patients and their families, as the **first potential therapy for our disease is in the final stages of FDA review right now (NDA 215244 - elamipretide for the treatment of Barth syndrome)**. In fact, **this review has already gone on for over 13 months (since filing), despite its priority review status.** The first PDUFA date on Jan 29, 2025 was delayed by three months due to additional information and analysis furnished by the sponsor in response to FDA questions, and that was declared to be a major amendment to the NDA. Then, in late April, the FDA let the sponsor know that **the delayed PDUFA date of**

April 29, 2025 would be missed again. But no reasons were given, and no outstanding issues or new requirements were cited, and no timetable for a decision was offered.

Importantly, all agree (including the FDA) that **elamipretide has a very good safety profile**, with over 400 patient years of exposure overall, no serious adverse reactions and really only mild to moderate injection site reactions as side effects in Barth syndrome. Furthermore, the **data supporting its efficacy are strong and many are statistically significant**, and we have personally witnessed the life-changing, and in some cases life-saving, benefits of this treatment. **At the CRDAC advisory committee (Ad Comm) meeting that was held on October 10, 2024, the panel voted 10 to 6 in favor of the drug's effectiveness in Barth syndrome.**

We in the patient community are deeply concerned about the delays we are seeing because we know that **time is of the essence.** Not only have **18% of those with Barth syndrome in the US perished**, but **over 12% of US affected individuals have required a heart transplant during the time this drug has been under development**. In addition, **Stealth BioTherapeutics, the small, privately held pharma company that is the sponsor, is literally coming to the end of its financial ability to continue on**, especially without a new timetable which would allow them to finance their operations while the wait continues. They have endured a hiring freeze for some months already and now are beginning to have to delay payables. The time pressures are serious and very real!

This case is right in line with many ideas you already have spoken about publicly, and **I beseech you to do the right thing (on so many levels) for our ultra-are disease early in your FDA leadership and to encourage the review Division to:**

- Continue to focus on this elamipretide review so that the **already lengthy time delay is minimized**
- **Importantly, inform the sponsor of a new deadline by which a decision will be made;** it is the open-endedness of this that makes it especially difficult for all of us to navigate
- **Approve this life-altering therapy for everyone (without age restriction) suffering from this ultra-rare disease which has no other approved treatments**

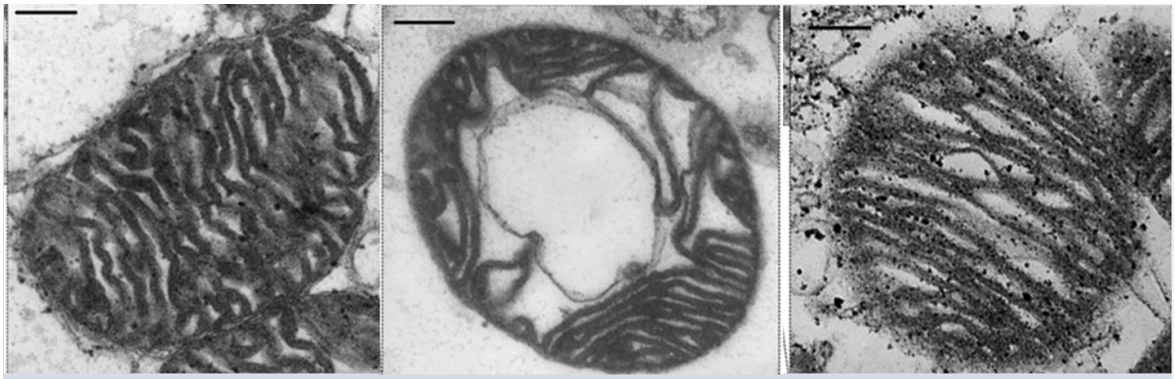
About Barth Syndrome

Barth syndrome is a **life-threatening, ultra-rare, mitochondrial disease** caused by a pathological genetic mutation leading to **severely depleted levels of the mitochondrial phospholipid cardiolipin**, which is essential for human life. **Cardinal symptoms** include cardiomyopathy, neutropenia, skeletal myopathy, truly debilitating fatigue, feeding issues and growth delay, along with an array of other clinical issues. (The two leading causes of death are cardiac failure and/or arrhythmia and sepsis.) **Known living individuals currently number 150 in the U.S.** and fewer than 350 worldwide. This disease **results in death during infancy and childhood much too frequently**, and it is **persistently life-threatening** and is **both significantly and progressively life-limiting and for those who are fortunate enough to survive into the**

adolescent or young adult years. There currently are **no treatments** for our disease, so our patients experience **significant unmet need.**

About Development Of Elamipretide

The development of elamipretide for the treatment of Barth syndrome was initiated at the request of our Foundation and, independently, Dr. Hilary Vernon, who established and continues to run the only dedicated multi-disciplinary center in the US (and one of only two worldwide) at Johns Hopkins, where I know you also were for many years. In 2014, we each **identified elamipretide as having a highly relevant mechanism which targets and stabilizes cardiolipin in disease states**, **as cardiolipin aberrations and deficiencies are the primary defect in Barth syndrome.** The image below is adapted from a Nature publication showing "rescue" of diseased mitochondria in the Barth TAZ KD model to near normal state by the administration of elamipretide, helping to **illustrate the mechanistic plausibility of this treatment that gave us such hope back in 2014.**



Healthy heart mitochondria *Barth (TAZ KD) heart mitochondria* *Barth (TAZ KD) + elamipretide*

Stealth BioTherapeutics (Stealth) decided to conduct clinical trials of elamipretide in Barth syndrome and has included BSF as a partner to offer the patient voice throughout the process. The Barth Syndrome Foundation has held a number of independent meetings directly with the FDA (PFDD, and various listening session), and patient representative(s) have attended every formal sponsor meeting with the FDA since 2019. I have been present myself at each interaction since 2020 and have participated actively in the meeting presentations and discussions. In addition, Stealth shared all the meeting minutes and advice notices prior to its 2024 NDA submission with me in confidence.

Since mid-2019 when Stealth first met with the FDA to discuss trial data, the IND was **shunted between four different CDER Divisions** (DNP, DGIEP, DRDMG and DCN) as the result of reorganizations and reassignments occurring under previous administrations and FDA leadership.

Even more troublesome than this organizational shuffling were the **conflicting views among different Agency reviewers** as to whether additional clinical trials were even possible due to

our disease's incredibly small numbers and the extended duration that would be required to evaluate outcomes even if undertaking a further study were feasible. I personally witnessed the skepticism expressed by Division and Office leadership as to whether new randomized clinical trials were even possible, even as some reviewers continued to request them. Indeed, the former Director of DCN gave a press interview to STAT news in 2022 in which he stated, referring to Barth syndrome, that "…there are places where you can't get there from here. Where do you draw the line? …there's going to be circumstances where there's no path forward." You can imagine the dismay of our ultra-rare and critically ill patient community upon hearing the FDA state that that ours is a condition for which "there's no path forward." Frequently, it was suggested to us that we simply find more patients. When I explained at great length all that we had done to search for more patients but with the addition of very few new ones, I was met with amazement and admiration for the creativity we had used, and no further suggestions were offered. Significant numbers of additional Barth patients simply do not exist.

About Where We Are Today

Our community took great hope in the FDA's decision to file the elamipretide NDA in 2024, ten years after our request that development be initiated. We took great pride in our extensive participation at the Ad Comm meeting in October 2024, where I and many patients and clinicians spoke. And **we celebrated the positive 10 to 6 vote of the Advisory Committee in favor of elamipretide being effective in Barth syndrome.** We also took note of the comments of several dissenters who said that had the question instead been posed as to whether elamipretide should be approved for the treatment of Barth syndrome, they too would have voted favorably, adding to the majority who already did.

The Barth syndrome community has participated in two different trials for potential therapies for our disease – this one for elamipretide and another one for bezafibrate conducted in the UK. Our patients in each were equally hopeful for positive results. But the drug being studied in the UK simply did not offer benefit, and our patients truthfully admitted that they did not find that the drug worked for them. But that is NOT the experience those in the elamipretide trial have had. Why are we so passionate about this program? Because **we have seen that this drug works and has made very meaningful differences in the lives of those who have been fortunate enough to be able to try it – infants, children, teenagers, and young adults alike.**

The following statement by Dr. Stacey Reynolds, an Occupational Therapist and Professor and Director of Research at Virginia Commonwealth University who has been conducting research on fatigue and other related issues of daily living within the Barth syndrome community for 14 years, stands out to me as encapsulating the experience and perspectives of our community and the medical professionals familiar with our exceedingly rare disease:

> *"Since members of the community have been taking elamipretide, I have seen things for the first time ever, I've seen babies with Barth syndrome hitting their developmental and*

weight milestones. I'm hearing about adolescents who do not regress during puberty and I'm seeing adult men who are on elamipretide who are working full-time jobs. ***This is something that has never even been a possibility for this community.****"*

In addition, case studies have been published of infants and toddlers who have gained access to elamipretide through emergency access and seen unprecedented improvements. As one example, below is a passage from a letter by Dr. Amy C. Goldstein published in Genetics in Medicine about an 11-month old Barth syndrome patient who had a history of gross motor delay and feeding issues but who suddenly became very ill with rhinovirus, enterovirus infections and showed a severely dilated left ventricle and an ejection fraction of <25%. He had to be resuscitated and intubated and was transferred to Children's Hospital of Philadelphia's ICU where he was put on ECMO (which was later changed to a Berlin Heart, a left ventricular assist device). He was determined to have Barth syndrome and quickly was started on elamipretide through the emergency access program and listed for heart transplant. Five months later, he had a much improved ejection fraction of 54% and could be transferred to a hospital nearer home where, after a total of about 6 months of support, his left ventricular assist device was explanted and he was sent home. When the letter was written, this child was 23 months old and his mother stated that he was "crawling, standing, walking with assistance and babbling" and his most recent ejection fraction at that time was 67%.

"To our knowledge, no BTHS [Barth syndrome] patients who required LVADS [left ventricular assist devices] have been explanted to date and all needed OTH [orthotopic heart transplantation] after LVAD. The findings in our case report suggest that, although the LVAD and SOC HF [standard of care heart failure] therapies likely contributed to improvement and maintenance in cardiac function, respectively, elamipretide therapy may have maintained the improvement in LV [left ventricular] function after removal of the LVAD by increasing the maximal rate of ATP synthesis and normalizing mitochondrial function ***providing promise for elamipretide as an effective targeted therapy for BTHS patients.****"*

This is life-saving and profound. We continue to hear from our community about success stories in the most dire of circumstances, in which critically ill infants receive emergency access to elamipretide and, despite the well-documented odds, stabilize and in some cases thrive. Because of what we all have witnessed with our own eyes and have heard about from those we know well, our patients are talking to their doctors about this drug. As a result, **about 20% of our US patient population is currently receiving drug through expanded access.**

Since the Ad Comm meeting, and despite the two PDUFA delays. we are aware that the FDA review team **active review has been ongoing, and we are immensely grateful for the Agency's continued efforts despite understandable resourcing constraints following the recent restructuring.**

Our Hope In You

As I have implored Dr. Hylton Joffe to do in my recent letters, we hope that the Agency will reach a favorable determination on the elamipretide NDA, as any other result does not reflect the evidence and thus would be truly devastating for our community. I also have urged Dr. Joffe to strongly consider a label without any age restriction, given the riveting testimony from caregivers and doctors of desperately sick very young children whose lives have been saved by this drug.

This all seems to be aligned with your thoughts of allowing ultra-rare disease patients, facing very serious conditions and with no other approved therapies, to be able to try a drug with a scientifically plausible mechanism and at least one promising trial (especially if it also has a very good safety record, which elamipretide undeniably does). We all know that existing standard regulatory approaches do not work well for tiny populations, and regulatory flexibility is appropriate and justified in situations of very high unmet need and extremely small populations, just like this one. We are asking that you **look to Barth syndrome to showcase your refreshingly pragmatic approach to the regulatory paradigms appropriate for ultra-rare diseases.**

If you would find it helpful, I and some of our families whose lives have been vastly improved by elamipretide would be honored to meet with you (in person or on Zoom) to elaborate on our situation and offer our personal stories about the challenges that face those in our small community. We certainly appreciate the many constraints on your time as you seek to implement important and impactful reforms, however, so I wanted to write this lengthy letter with the basics in case a meeting is not possible.

We have been lifted up with hope listening to your thoughts on how to approach ultra-rare diseases. We hope that the pain, loss and tremendous anxiety we in Barth syndrome community have experienced over the past five years while elamipretide NDAs have been under consideration and have languished within the Agency can help inform the power of your vision and the desperate need of communities like ours that it become the new reality.

Thank you in advance for your consideration.

With optimism,

Kate McCurdy

Kate McCurdy
Mother of Barth Son (Deceased)
Co-founder and Board Chair
Barth Syndrome Foundation
www.barthsyndrome.org