June XX
2025

The Honorable Martin A. Makary M.D., M.P.H.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

Dear Commissioner Makary:

We are writing to you today to respectfully request your prompt attention to the review and final approval process for elamipretide–a first of its kind, experimental medication aimed at treating Barth Syndrome.

As you may be aware, elamipretide is the first and only treatment in clinical development for Barth syndrome, an ultra-rare, lethal, progressive genetic disorder with no known cure or FDA-approved treatment options. Barth syndrome is characterized by symptoms including severe and debilitating muscle weakness, exercise intolerance and fatigue, cardiomyopathy and cardiac dysfunction commonly leading to premature death, recurrent infections, feeding issues, and delayed growth. Those affected have a shortened life expectancy, with 85 percent of early deaths occurring by age five and most survivors of early childhood passing away before their forties.

Despite the exceedingly rare nature of Barth syndrome (1:1,000,000 male births), which impacts fewer than 150 known individuals in the United States, we are aware of three families in the state of Colorado who have children living with Barth syndrome. We would like to highlight a 6 month old baby named Gilbert who has had the ability to access elamipretide through expanded access. Gilbert was born in heart failure, requiring intensive care at Children's Hospital Colorado for 80 days. He was diagnosed with Barth syndrome when he was 16 days old and was able to start elamipretide at 28 days of life. Before elamipretide took its full effect, Gilbert barely had the energy to eat more than a 20 mL bottle and he would have to take frequent breaks throughout the feed. He was in the 0.2 percentile for weight and he required a nasal feeding tube. Today, after over 150 days on elamipretide, Gilbert is in the 44.1 percentile for weight. He is able to breastfeed—something he didn't have the strength for before-–and he has plenty of energy to play with his sisters.

We respectfully request the FDA provide our offices with clarity around elamipretide's review pathway moving forward. Gilbert's story and other reports across the country demonstrate the profound and meaningful benefits in the lives of some of our state and country's most vulnerable individuals, those impacted by ultra-rare diseases with no treatment options. Given the early-onset nature of this disease, as well as the successful research conducted on the effectiveness of this treatment, approval by the FDA for elamipretide must be of paramount importance. We strongly urge your fair and prompt consideration of elamipretide at the earliest opportunity that aligns with the safety guidelines and processes of the FDA.

In accordance with all existing rules, regulations, and ethical guidelines, we appreciate your

urgent consideration and your continued engagement with our respective staff.

Thank you for your attention to this important matter.

Sincerely,

Here are the questions that we are asking offices to ask on our behalf.

1. Explain the dissonance with the AdComm vote and the CRL. Especially when in FDA response to the citizen petition stated the review would be conducted using the Advisory Committee process.

2. Why was traditional approval denied for elamipretide, the first ever therapy for Barth syndrome with the Advisory Committee Process which traditionally approves 97% of drug applications for initial therapies?

3. This decision is out of alignment with the Commissioner's messaging on fast-tracking approvals for rare diseases, explain the rationale.

4. Why did the FDA elect not to approve elamipretide through traditional means?

5. Why has this path forward through the Accelerated Approval pathway just being offered now when it has been denied previously? Given the delays that we have encountered thus far, what assurances are there that this pathway won't require the company to submit yet another full application, delaying full approval for years?

6. The FDA's recent response to a reporter featuring a Wisconsin Barth syndrome family was "The FDA bases approval decisions on whether an application submitted to FDA for approval of the drug show that it is safe and effective for use under the conditions in its proposed labeling. This includes a benefit-risk assessment based on the totality of the data presented in each application."

7. Where is the totality of the evidence if the patients' testimonials from the AdComm are glaringly absent from the CRL?

8. Where is the voice of the patient from our Tolerance of Risk without known benefit session with the FDA?

9. What is the path forward for babies with Barth syndrome? Hence the reason we are asking for broad labeling for the drug as a treatment for Barth syndrome.

10. What if any consideration is given to patient access to drugs approved through Accelerated Approval which are not recognized by BCBS as FDA approved drugs?

11. Is broad labeling which would include access for babies being considered by the FDA?