Dear Dr. Stockbridge,

We, the undersigned physicians, are specialists knowledgeable about the care of Barth syndrome, an ultra-rare genetic mitochondrial disease that affects fewer than 130 individuals in the United States.

Barth syndrome is a devastating X-linked genetic disease leading, in all known cases, to early death which is usually (>90% of cases) attributable to cardiomyopathy. Patients do not typically survive past their third decade of life. During their truncated lifespan, these young men are severely limited in their activities of daily living by progressive heart failure and associated progressive debilitating skeletal muscle weakness, exercise intolerance and fatigue. All patients with Barth syndrome are at a high risk of sudden death, with particularly high-risk periods in infancy and adolescence. For those patients who survive these high-risk periods, the progressive nature of the disease increasingly limits their strength and exercise tolerance, in many cases leading to loss of ambulation and self-care capabilities and very commonly restricting their ability to attend school, maintain gainful employment, and engage in normal social activities.

The unmet need in Barth syndrome is immediate, severe, and urgent. Time is of the essence in identifying a therapy to stabilize cardiac function and improve exercise tolerance to improve the quality of life for these young patients and hopefully to delay an otherwise inevitable progression to early mortality. A therapy that has the potential to delay progression or alter the natural trajectory of the disease would be of tremendous benefit.

The natural history of Barth syndrome is well-characterized. Longitudinal studies of cardiac function demonstrate a progressive decline in left ventricular stroke volume (Chowdhury et al., Pediatric Cardiology, 2022) with consistently poor exercise tolerance (Hornby et al., Orphanet, 2019; Thompson et al., Gen Med., 2016). Physiologically, the severe mitochondrial dysfunction characterizing this disease significantly limits mitochondrial respiratory capacity and therefore diminishes exercise capacity (Powers et al., Front Physiol., 2013), such that patients are not expected to be able to meaningfully increase their exercise tolerance.

The Barth Syndrome Foundation has shared with us the data from the SPIBA-201 clinical trial and open-label extension, the first clinical trial ever conducted in Barth syndrome in which the investigational product, elamipretide, was assessed as a potential treatment. Although the trial did not show statistically significant changes in the prespecified primary endpoints during the short (3-months of therapy) double-blind placebo-controlled treatment period, early signals of efficacy emerged during that time-period. After almost 4 years of total exposure in the open-label extension portion of the trial, we understand that improvements have been observed in how patients' function, how patients feel, and how patients' hearts are working.

- Improvements were observed across multiple functional endpoints assessing exercise tolerance and skeletal muscle function, which are known to decline in the natural course of the disease.
- Patients and the clinician reported that patients are feeling better as measured by outcome assessments of symptoms and quality of life.

- Improvements in objective measures of cardiac function were observed (assessed by echocardiography) – contrary to what is expected in the natural course of the disease.

Importantly, from the cardiologists signatory to this letter, the significant and large improvements in left ventricular stroke volume index support a view that elamipretide has contributed to cardiac structural remodeling in this patient population. For drugs known to have this effect, the typical time-course to early observation of the effect is typically 6-9 months, which is consistent with the trajectory of early improvements observed in this trial beginning around week 36 of the open-label extension. The magnitude of the effect observed – more than 40% mean improvement in stroke volume from baseline – is well above the normal variability of echocardiographic assessments and is moreover directionally consistent across multiple time points assessed, supporting a favorable interpretation of these data. All patients who remained on therapy in open-label extension demonstrated meaningful improvements in exercise tolerance and/or cardiac function also supports a favorable interpretation. Moreover, the overall correlations observed between increased left ventricular volumes and assessments of submaximal exercise tolerance support a conclusion that these changes have translated into clinical benefit for these patients.

Many of us are cardiovascular clinical trialists familiar with large trials in heart failure which necessarily comprise thousands of patients to be adequately powered to achieve statistically significant outcomes. The changes observed in this very small data set of cardiomyopathic patients, albeit during an open label treatment arm, are impressive. An almost 100-meter mean improvement in distance walked in 6 minutes sustained over a 4-year period in young men presenting at baseline with a level of impairment akin to septuagenarians with Class II/III heart failure is generally unprecedented for patients with this clinical presentation. We are all familiar with the well-characterized placebo effect (typically around 30-meters on the 6-minute walk test) exhibited across multiple heart failure trials (Olsson et al., European Heart Journal, 2005). In our clinical judgement and based on our collective knowledge of this disease, it is unimaginable that a change of the magnitude observed in this dataset, which far outstrips the typical placebo effect and was maintained over 4-years, could be attributable solely to hope bias.

Most importantly, these patients, their caregivers, and their doctor have characterized the meaningfulness of these improvements relative to how they feel and function on a day-to-day basis. The feedback collected via patient, caregiver and clinician reported outcome assessments, clinician medical records, the patient and caregiver perception of change interview protocol, and testimonials offered to the Barth community at the Patient Focused Drug Development meeting in 2018 and during weekly webinars hosted by the Barth community in 2020, is consistent and compelling – patients have experienced tangible and sustained improvement in their ability to participate in activities of daily living including being able to attend school, maintaining gainful employment, and engaging in normal social activities. We understand that the principal investigator has assessed many of these patients as having no signs or symptoms of Barth syndrome during multiple recent clinic visits – a finding that is wholly unprecedented in this severe genetic disease.

The safety profile of elamipretide in Barth syndrome appears to be acceptable. Most adverse events were injection site-related and characterized as mild or moderate in severity, and there were no Suspected Unexpected Serious Adverse Reactions. This is consistent with the safety profile of elamipretide as observed during what we understand to be over 100-patient years of exposure collected to date. As physicians, we view the potential benefit afforded by elamipretide relative to the favorable safety profile exhibited to date as supporting a decision to make this drug immediately available to patients and prescribing physicians.

Given the progressive cardiac and skeletal muscle manifestations during adolescence for Barth syndrome patients and the considerable unmet need, we want to have the current opportunity to prescribe elamipretide to our patients with Barth syndrome while more definitive efficacy studies, if these are deemed required, are conducted. The young men affected by Barth syndrome do not have years to wait for the sponsor to enroll, conduct and read out upon a second clinical trial which, given the ultra-rare nature of this disease, would be highly likely to remain underpowered to generate more conclusive efficacy signals. As mentioned above, in the realm of heart failure, we would normally expect that many hundreds if not thousands of patients would be required to observe any significant changes in cardiac function and exercise capacity. These numbers simply do not exist in this ultra-rare disease that affects fewer than 250 individuals worldwide. In our minds, it is not an acceptable answer to expect patients affected by this ultra-rare life-limiting disease to wait for many more years to gain access to a therapy which presents minimal safety risks and appears, based on multiple lines of evidence collected to date, to offer meaningful benefit.

In conclusion, as doctors familiar with and in many cases actively treating patients with Barth syndrome, relying upon our best ability and medical judgment of the clinical and basic science data collected to date, we ask that you encourage the sponsor to submit a new drug application for elamipretide for the treatment of Barth syndrome and that you undertake to promptly review that application.

Sincerely,

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The Ohio State University

cc: Dr. Robert Califf
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Dr. Peter Stein
Dr. Hylton Joffe
Dr. Lisa Yanoff
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