Dear Advisory Committee Members and members of CRDAC,

We, the undersigned physicians and medical professionals, are specialists knowledgeable about the care of Barth syndrome. Currently, there are no approved treatments specifically for Barth syndrome. This letter is being submitted in support of elamipretide (docket # FDA-2024-N-3969), for which a new drug application is currently under review for the treatment specifically of Barth syndrome.

Barth syndrome (BTHS) is an ultra-rare genetic mitochondrial disease that affects fewer than 150 individuals in the United States. Barth syndrome is a devastating, life-limiting X-linked genetic disease leading, in all known cases, to early death primarily due to cardiomyopathy. Patients do not typically survive past their third decade. While the heart-associated factors of BTHS are life-threatening, affected individuals are plagued by profound and crushing fatigue caused in part by skeletal myopathy that severely limits their ability to participate in life activities such as attending school, holding a full-time job, or engaging in social activities. As individuals age, they suffer from progressive heart failure and associated progressive, debilitating skeletal muscle weakness, exercise intolerance, and fatigue which can impact ambulation and require use of mobility devices.

The BTHS community has suffered greatly and there is an urgent, unmet need for a treatment for this condition. Since 2020, the community has lost >5% of the US population. Individuals with BTHS are at risk for sudden death, particularly during infancy and adolescence. Any medication with the ability to stabilize cardiac function or improve quality of life for this population would be a significant improvement over the currently available treatments. A therapy that has the potential to delay progression or even reverse the trajectory of the disease would greatly impact this community.

The natural history of this condition has been evaluated by several research teams. In particular, left ventricular stroke volume consistently decreases over time (Chowdhury et al., Pediatric Cardiology, 2022) and exercise intolerance is pervasive (Hornby et al., Orphanet, 2019; Thompson et al., Gen Med., 2016) due to decreased mitochondrial respiration (Powers et al., Front Physiol., 2013). As patients age, they do not improve and their quality of life progressively declines.

We have reviewed the published data from SPIBA-001, a Phase 3 Natural History Control trial designed to establish a control for interventional data from SPIBA-201 Part 2, a 192+ week open label extension trial of elamipretide as a potential treatment for BTHS. Data from both these studies have been published and the results are compelling.

- Aside from injection-site reactions, no serious adverse events related to the treatment were reported.
- All functional assessments showed substantial improvement over baseline measurements including the 6-minute walk test (>25% durable improvement), fatigue assessments, muscle strength (>45% durable improvement), SWAY balance assessments and 5x sit-to-stand.
- Left ventricular stroke volume increased 45% over baseline through 168 weeks of elamipretide treatment

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 **far exceeds the variability that would normally be observed in this population** and is directionally consistent across multiple time points assessed, supporting a favorable interpretation of these data.

These changes can be further contextualized clinically by meaningful changes reported by patients in their quality of life. Patients have experienced concrete improvements in their ability to participate in activities of daily living including being able to attend school and continue onto college, maintaining gainful employment, starting new businesses, travel and engaging in normal social activities.

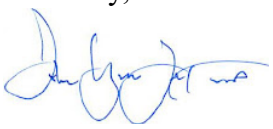
The cardiovascular clinical trialist signatories on this letter are intimately familiar with large trials in heart failure which often contain thousands of participants. While this dataset is comprised of a small number of patients, proportionate to the BTHS community size, the *changes observed are striking*.

- Sustained gains of ~100 meters walked in 6 minutes over a 4-year period in young men presenting who had Class II/III heart failure at baseline is unprecedented.

There is a known placebo effect (~30-meters on the 6-minute walk test) in heart failure trials (Olsson et al., European Heart Journal, 2005). In our clinical judgement, however, that the magnitude of change observed in this dataset far outstrips the typical placebo effect. Because these changes have been sustained for 4+ years, they cannot be attributable solely to hope bias. Moreover, the supportive findings regarding durable improvements in muscle strength and 5X sit to stand, which are extremely challenging assessments for these patients, also debunk any concerns with hope bias.

Given the progressive, life-limiting cardiac and skeletal muscle manifestations for BTHS patients, the considerable unmet need, the elamipretide open label efficacy data and safety, we want to have the opportunity to prescribe elamipretide to our patients with Barth syndrome. As mentioned above, thousands of patients cannot be enrolled in a disease population such as BTHS; these numbers simply do not exist. In conclusion, as medical providers familiar with and in many cases actively treating patients with BTHS, relying upon our best ability and medical judgment of the clinical and basic science data collected to date, we urge FDA to make a fair, equitable and appropriate review for elamipretide.

Sincerely,



John Lynn Jefferies MD, MBA, MPH, FACC, FAHA, FAAP, FHFSA, FRCPE, FESC
Professor, School of Public Health, University of Memphis
Team Cardiologist, Memphis Grizzlies

Additional Signatories

Charles E Canter MD
Professor Pediatrics
Washington University School of Medicine

Jeffrey A. Towbin MD, MS
Tenured Professor and Chief,
Pediatric Cardiology and Executive Co-Director, Heart Institute
Le Bonheur Children's Hospital and the University of Tennessee Health Science Center

Barry J. Byrne MD, PhD
Professor and Associate Chair
University of Florida

Carolyn L Taylor MD
Professor, Pediatric Cardiology
Medical University of South Carolina

Hilary Vernon MD, PhD
Professor of Genetic Medicine and Pediatrics
Johns Hopkins University School of Medicine

James E. Udelson MD
Chief, Division of Cardiology, Tufts Medical Center Professor of Medicine and Radiology
Tufts University School of Medicine

Majid Husain MD
Assistant Clinical Professor, Pediatric Cardiology
UCLA Mattel Children's Hospital, David Geffen School of Medicine

Michael Bristow MD, PhD
Professor of Medicine (Cardiology)
University of Colorado, Aurora and Boulder

Nancy Halnon MD
Clinical Professor, Pediatrics
Department of Pediatrics,
Pediatric Cardiology,
UCLA David Geffen School of Medicine and Mattel Children's Hospital

Kim L McBride MD
Professor and Department Head,
Department of Medical Genetics,
Cumming School of Medicine, University of Calgary

Grant M Hatch PhD
Professor Emeritus
University of Manitoba

Laura A Ortmann MD
Associate Professor, Director of Cardiac Critical Care
University of Nebraska Medical Center

William Todd Cade PT, PhD
Professor & Division Chief
Doctor of Physical Therapy Division
Duke University School of Medicine

Brian L. Stauffer MD
Professor, Medicine/Cardiology
University of Colorado, Anschutz Medical Campus

Robert D S Pitceathly MD, PhD
Professor Department of Neuromuscular Diseases
UCL Queen Square Institute of Neurology, London, UK; NHS Highly Specialised Service for Rare Mitochondrial Disorders, Queen Square Centre for Neuromuscular Diseases, The National Hospital for Neurology and Neurosurgery, London, UK

Christoph Maack MD
Professor Doctor
Comprehensive Heart Failure Center, University Clinic Wuerzburg, Germany

Marni J. Falk MD
Professor and Executive Director of Mitochondrial Medicine Frontier Program
Division of Human Genetics, Department of Pediatrics
Children's Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine

Shelley Miyamoto MD
Professor, Pediatrics
University of Colorado Anschutz Medical Campus and Children's Hospital Colorado

Gregory Mark Enns MB, ChB
Professor of Pediatrics
Stanford University

Kathryn C. Chatfield MD, PhD
Associate Professor of Pediatrics
University of Colorado Anschutz Medical Campus

W. Reid Thompson MD
Associate Professor of Pediatrics
Johns Hopkins University School of Medicine and Kennedy Krieger Institute, Division of Pediatric Cardiology

William Pu MD
Associate Chief of Cardiolgy for Basic and Translational Research Affairs
Department of Cardiology
Boston Children's Hospital, Harvard Medical School

Amel Karaa MD
Director of the Mitochondrial Disease Program
Massachusetts General Hospital

Michael Gewitz MD, FAAP,FACC,FAHA
Exec. Director, Maria Fareri Children's Hospital at WMCHealth, Professor of Pediatrics
NY Medical College WMCHealth System; NY Medical College of Touro University

Ibrahim Elsharkawi MD
Doctor in the Department of Genetics and Genomics and Pediatrics
Mount Sinai

Gerald F Cox MD, PhD
Staff Physician in Genetics Boston Children's Hospital
Owner, Gerald Cox Rare Care Consulting, LLC
Instructor in Pediatrics, Harvard Medical School

Jennifer S. Li MD
Beverly C. Morgan Distinguished Professor of Pediatrics
Duke University

Brian Feingold MD, MS, FAHA
Professor, Pediatrics and Clinical and Translational Research; Medical Director Heart Failure/Heart TransplantationUniversity of Pittsburgh / UPMC Children's Hospital of Pittsburgh

Brian Shayota MD
Medical Geneticist
University of Utah

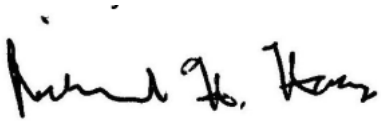
Bruce H. Cohen MD, FAAN, FCNS
Professor of Pediatrics, Northeast Ohio Medical University and Director of the NeuroDevelopmental Science Center
Akron Children's Hospital and Northeast Ohio Medical University

Peter G. Barth MD, PhD
Emeritus Professor Pediatric Neurology
University of Amsterdam, Netherlands
Prof. Emeritus Pediatric Neurology, Fac of Medicine, University of Amsterdam, Netherlands

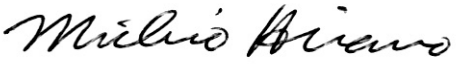
Stacey Reynolds PhD, OTR/L, FAOTA
Professor, Department of Occupational Therapy
Virginia Commonwealth University

Amy Goldstein MD
Professor of Clinical Pediatrics; Clinic Director of the Mitochondrial Medicine Program
Perelman School of Medicine of the University of Pennsylvania, Children's Hospital of Philadelphia

Michael Schlame MD
Professor of Anesthesiology & Cell Biology, Director of Cardiothoracic Anesthesia
New York University Langone Medical Center, New York



Richard H. Haas MB, BChir, MRCP
Professor of Neurosciences and Pediatrics, Co-Director UCSD Mitochondrial and Metabolic Disease Center, Director North American Mitochondrial Disease Consortium Education Core
University of California San Diego, La Jolla, CA



Michio Hirano MD
Lucy G. Moses Professor
Columbia University Irving Medical Center
New York

Hani N. Sabbah PhD, FACC, FCCP, FHRS, FHFSA, FAHA
Professor of Medicine
Wayne State University
Professor of Medicine, Research
Michigan State University
Director of Cardiovascular Research
Henry Ford Health
Henry Ford Hospital