Elamipretide HCl

Presentation to the Cardiovascular and Renal Drugs

Advisory Committee

NDA 215244
Stealth BioTherapeutics
October 10, 2024

With us today

Anthony Abbruscato
PharmD
Stealth, VP Clin Dev

David Brown PhD
Stealth, Sr VP
Discovery

Todd Cade, PT, PhD,
FAPTA
Duke

Jim Carr Pharm D
Stealth, Chief Clin
Development

Kathryn Chatfield
MD, PhD
Colorado

Jeff Finman PhD
Cognitive Research
Corp.

Kate McCurdy
Chair, Barth
Syndrome Foundation

Jeffrey Towbin, MD,
MS, FACC, FAAP,
FAHA, FHFSA
Le Bonheur + St Jude

Jim Udelson MD
Tufts

Hilary Vernon
MD, PhD
Johns Hopkins

Janet Wittes PhD

Agenda

Introduction	**Reenie McCarthy** *Chief Executive Officer* *Stealth BioTherapeutics*
Urgency of Unmet Need + Benefit:Risk Tolerance	**Kate McCurdy, MBA** *Chair, Board of Directors* *Barth Syndrome Foundation*
Disease + Natural History Cohort	**Hilary Vernon, MD, PhD** *Professor of Medical Genetics* *Johns Hopkins University School of Medicine*
Safety + Efficacy	**Jim Carr, PharmD** *Chief Clinical Development Officer* *Stealth BioTherapeutics*
Statistical Perspectives	**Janet Wittes, PhD** *Wittes LLC*
Expanded Access Program	**Kathryn Chatfield, MD, PhD** *Associate Professor of Pediatrics-Cardiology* *Director, Cardiac Genetics Clinic, Children's Hospital Colorado*
Closing Remarks	**Reenie McCarthy** *Chief Executive Officer* *Stealth BioTherapeutics*

Introduction

Reenie McCarthy

Chief Executive Officer
Stealth BioTherapeutics

About Stealth BioTherapeutics

Leading Mitochondrial Medicine

Founded to Develop Novel Mitochondrial Targeted Drugs

- *Founded to develop **ELAMIPRETIDE***
  - *Serendipitous discovery*
  - *Targets a previously undruggable target: mitochondria*
- *Other mitochondrial targeted compounds in early development*

For Serious Diseases of Mitochondrial Dysfunction

- ***Barth syndrome***
- *Primary mitochondrial myopathy (PMM; P3)*
- *Dry AMD (P3)*
- *Friedreich's ataxia (FA; preclinical)*
- *ALS (preclinical)*
- *Duchenne muscular dystrophy (DMD; preclinical)*

With High Unmet Medical Need

- ***Fast track: Barth syndrome,**** *PMM,** *dry AMD*
- ***Orphan drug: Barth syndrome,***** *PMM,*** *FA, ALS*
- ***Rare pediatric designation: Barth syndrome***

* *No US approved therapies*
** *US + EMA*

About Barth Syndrome

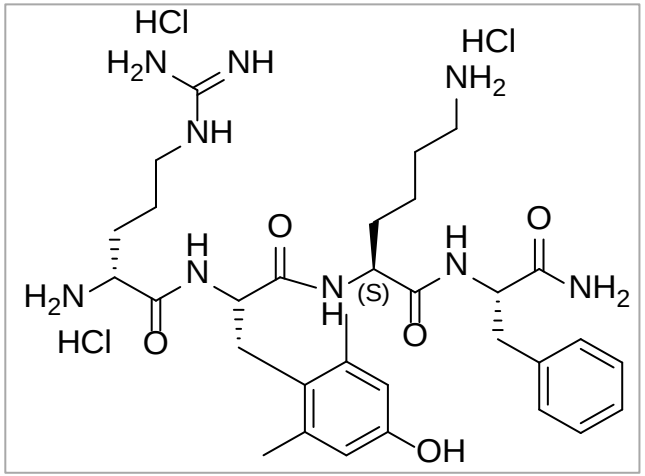
Ultra-rare, Progressively Debilitating, Fatal Mitochondrial Disease

- **Ultra-rare**:
  Affects ~130 US individuals; mostly boys/young men
- **Clinical impact**:
  - Progressive skeletal myopathy -
    exercise intolerance, muscle weakness, debilitating fatigue
  - Progressive and evolving cardiomyopathy -
    ~90% of deaths; 16% transplant rate; phenotype known to undulate between dilation + hypertrophy over lifetime of affected individuals
  - Recurrent infections
  - Growth abnormalities
  - Feeding problems
- **Significantly reduced lifespan**:
  - ~50% of deaths occur by age 1; 85% occur before age 5
  - Puberty is a very high-risk period
  - Most survivors of childhood do not survive their 4th decade

Anzmann et al., "Mitochondrial Dysfunction and Barth Syndrome," in Handbook of Mitochondrial Dysfunction, June 2019; Voice of the Patient Report, 2018

About Elamipretide HCl

Serendipitous discovery by researchers at Weill Cornell



Product Name	Elamipretide HCl
Active Substance	H-D-Arg-2',6'-dimethyl-L-Tyr- L –Lys–Phe-NH2 (elamipretide HCl salt)
Pharmaceutical Form	Solution for injection
Route of Administration	Subcutaneous use
Dose/Dosing Regimen	40 mg administered once daily
Proposed Indication	Treatment of Barth syndrome
Safety	Well-characterized with >400 patient years exposure
Mechanism of Action	Associates with cardiolipin (CL) in the inner mitochondrial membrane to reverse/attenuate mitochondrial dysfunction

Mitochondrial Energy Production + Cardiolipin

Mitochondria are essential for human life, producing 90% of the energy utilized by mammalian cells

Cardiolipin is essential for mitochondrial structure

- The inner mitochondrial membrane (IMM) is folded to create curves, called cristae
- Cardiolipin's conical shape establishes cristae curvature

Cardiolipin is essential for mitochondrial function

- Cardiolipin is necessary for assembly of the protein complexes of the electron transport chain (ETC), which produce cellular energy
- Cardiolipin-mediated cristae curvature organizes the ETC, maximizing energy production + minimizing production of a toxic bioproduct, reactive oxygen species (ROS)

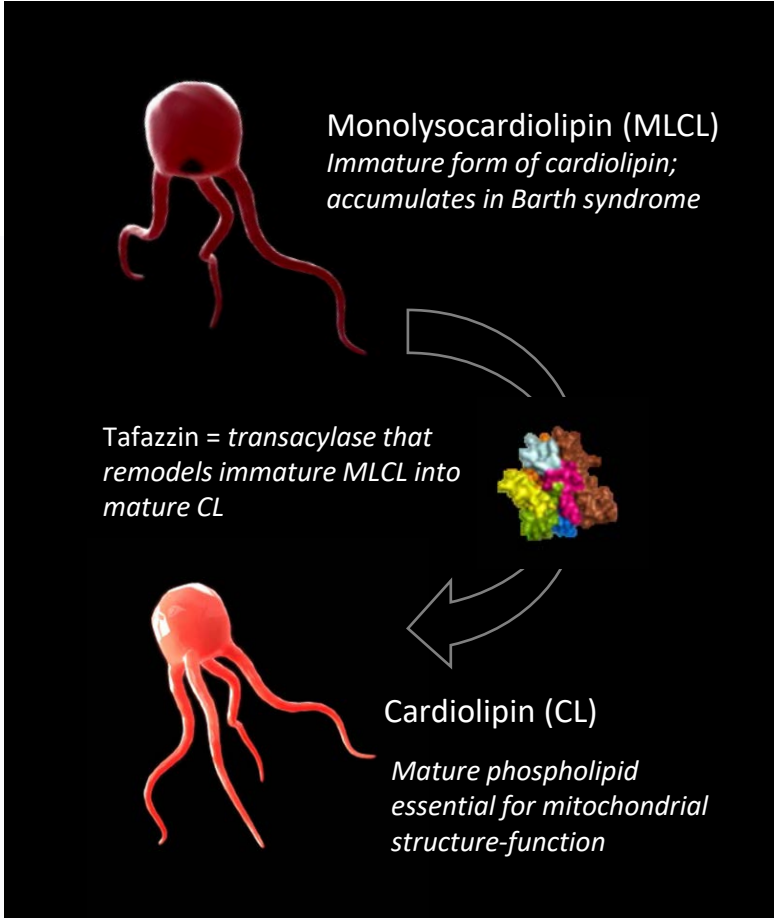
Cardiolipin is essential for human life

Cardiolipin (orange): essential for normal structure + function

Barth syndrome:

a mitochondrial disease of severe cardiolipin deficit

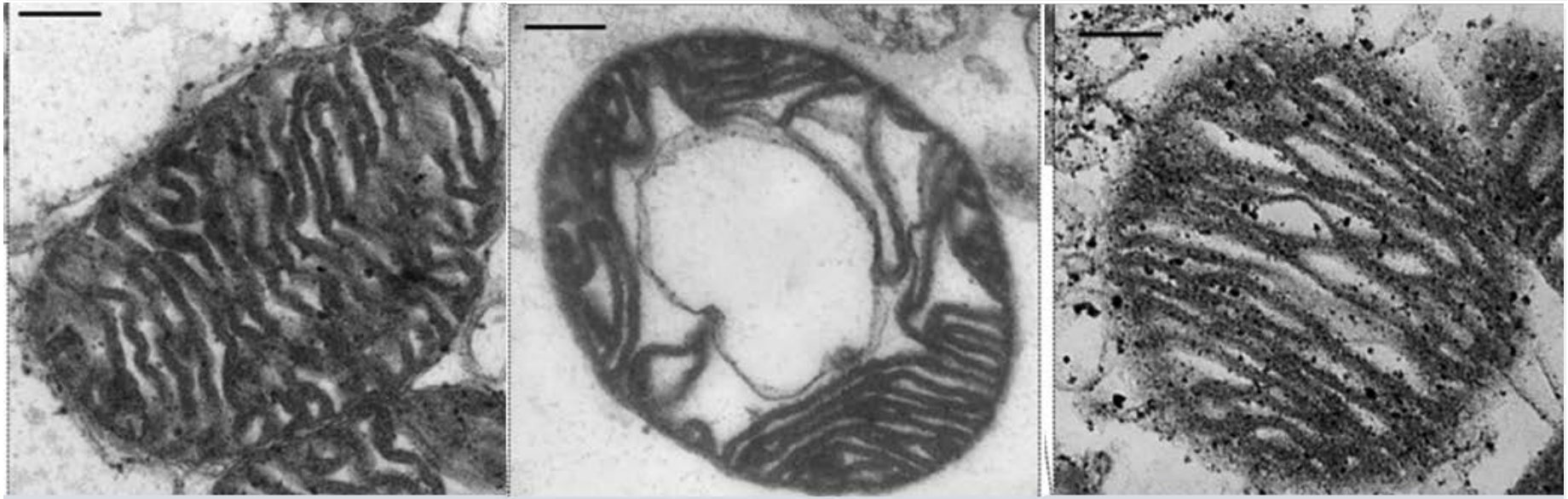
- Caused by mutations in *TAFAZZIN*, an X-linked nuclear gene that encodes for a transacylase also called tafazzin which is involved in cardiolipin assembly
- The resulting tafazzin deficit leads to
  - Elevations in immature MLCL
  - 70% to 95% deficit in mature CL
  - Significantly shortened CL half-life
- As a result, mitochondrial membrane curvature + protein complex organization is disrupted, leading to reduced energy production, increased ROS + symptoms of disease
- The disease can be diagnosed by the ratio of abnormal MLCL to normal CL (MLCL:CL ratio) or genetic testing



Tafazzin (deficient in Barth syndrome) remodels immature MLCL into mature CL

Elamipretide

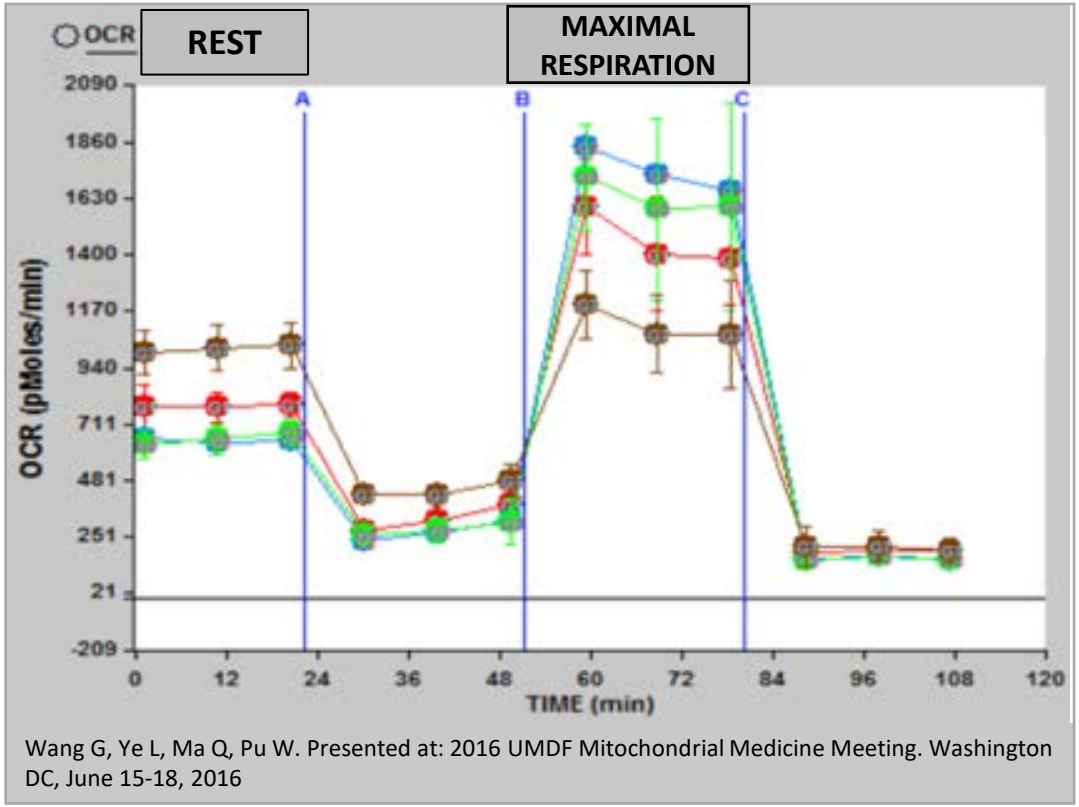
Targets + Protects Cardiolipin



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

Russo et al., 2022, 2024

Elamipretide Improves Mitochondrial Function



Wang G, Ye L, Ma Q, Pu W. Presented at: 2016 UMDF Mitochondrial Medicine Meeting. Washington DC, June 15-18, 2016

Barth syndrome patient-derived cardiomyocytes

Elamipretide + Barth syndrome

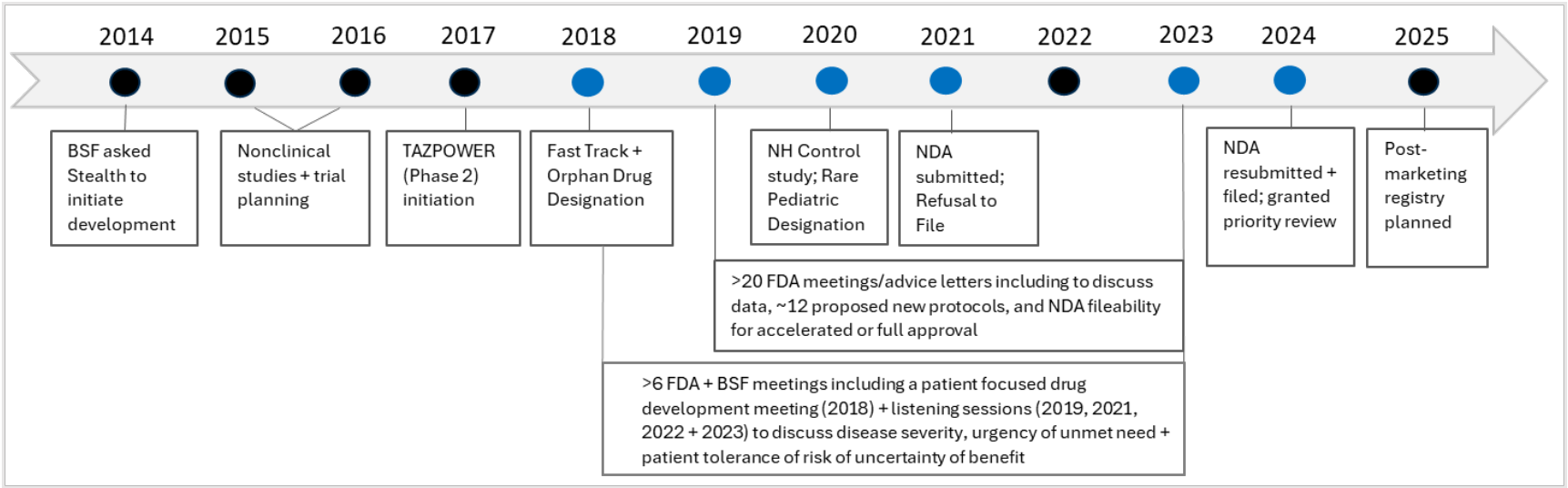
Healthy control

Elamipretide + control

Improvement also observed in TAZ-KD mouse model (Russo et al., 2022, 2024)

Patient-Prompted Development

- First/largest development effort undertaken for Barth syndrome, involving ~half of all evaluable US patients
- Trial design, including endpoint selection, was closely informed by expert clinicians, patients and the FDA
- We had screened most/all eligible US patients for TAZPOWER, so we turned to FDA's 2019 Substantial Evidence Guidance to establish an external control for the TAZPOWER Extension data.
- No other trial designs, including the randomized withdrawal trial mentioned in the FDA's briefing book, were accepted by the FDA, primarily due to powering concerns insurmountable in a disease this rare.



Regulatory Pathways Available

Traditional, or Full Approval

FDA Guidance for Industry, Rare Diseases: Common Issues in Drug Development

"In special circumstances, such as when it may be impractical or unethical, a well-designed and conducted natural history study can provide an external control group for interventional trials" [particularly when] "there is an expected **drug effect** that **is large, self-evident, and temporally closely associated with the intervention**."

Over 45 therapies have been approved by FDA since 2000 utilizing external controls

Subpart H, Accelerated Approval

- Implemented to speed therapies to patients with serious, rare diseases when experts can reasonably conclude based on findings on biomarkers or intermediate clinical endpoints that a drug is reasonably likely to have the purported effect, which Sponsors must confirm post-marketing
- It is not required, under Subpart H, that surrogate + intermediate clinical endpoint data be generated in a randomized controlled trial
- FDA's concerns about powering the requisite post-marketing confirmatory study in a disease this rare precluded its consideration of this pathway

Key Questions

1. Whether “placebo effect” on a single endpoint, 6MWT, precludes interpretability of the positive NH Control trial + other data generated over 4 years in a large percentage of the evaluable patient population

- **No placebo effect observed on Muscle strength, 5XSST + balance; these functional endpoints should be interpretable**
- 6MWT primary recommended by experts + FDA for primary mitochondrial disease
- Data does not support presumption of “effort bias”
  - 30.1-meter “placebo effect” within pretreatment values; may be due to fatigue of frequent travel (known challenge in this disease) rather than effort bias (physiologically improbable in this disease)
  - Within the variability seen in short-duration heart failure trials
  - Long-term treatment showed durable 3X improvement over placebo, despite no increase in effort (BORG)

2. Whether the totality of the evidence relative to the benefit : risk profile of elamipretide supports a finding of efficacy

- Improvements in how patients' function + feel + in cardiac + molecular biomarkers unidirectionally favor elamipretide, in stark contrast to the expected disease trajectory
- No material safety concerns identified

Evaluation of Efficacy in Serious Ultra-rare Diseases

Evidence 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**.
Food & Drug Act; 21 U.S.C. Sec. 355(d)

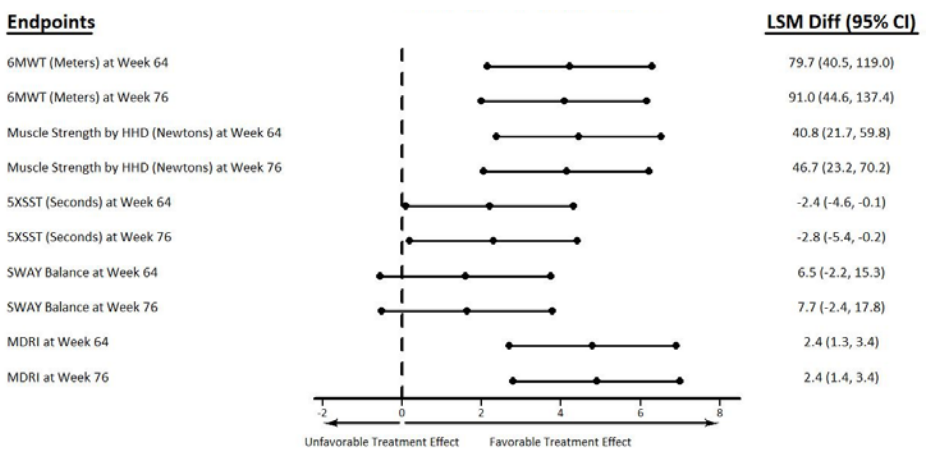
Title 21, Food & Drugs; Subpart E establishes procedures to expedite new therapies to treat life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists…**mandates the broadest flexibility** in applying the statutory standards. Recognizes physicians and patients are generally willing to accept greater **risks** from products that treat life-threatening and severely-debilitating illnesses and that the **benefits** of the drug need to be evaluated in light of the severity of the disease being treated

"I wanted to make sure that you on the committee understand what flexibility you have in addressing the subject… You need to know that the idea of dichotomizing success of studies by a p-value being less than or greater than 0.05 has no basis in law either natural or federal or in regulations and it is barely mentioned in guidance. ***The legal language refers to information that experts would find compelling.*** *Standards applied to rare diseases are clearly not the same as being applied to common diseases."* *Dr Stockbridge's comments to the Entresto Advisory Committee, Dec 15, 2020*

Totality of the Evidence Favors Treatment

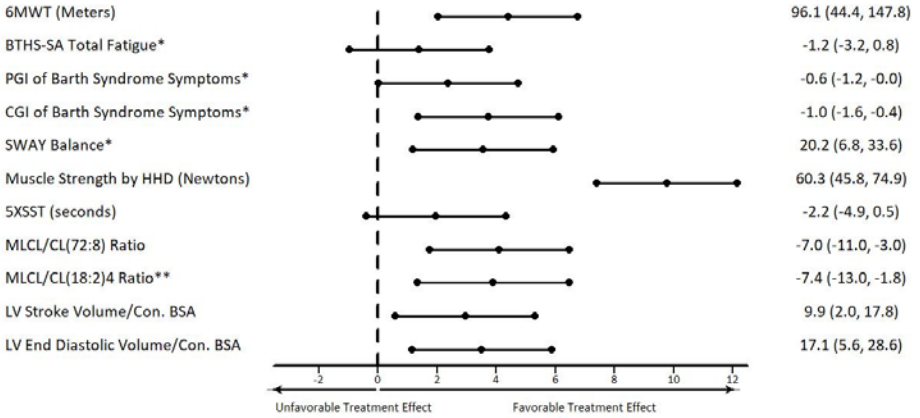
Phase 3 NH Study: All Endpoints Favored Elamipretide

Summary of Treatment Effect



TAZPOWER Extension Study Week 168

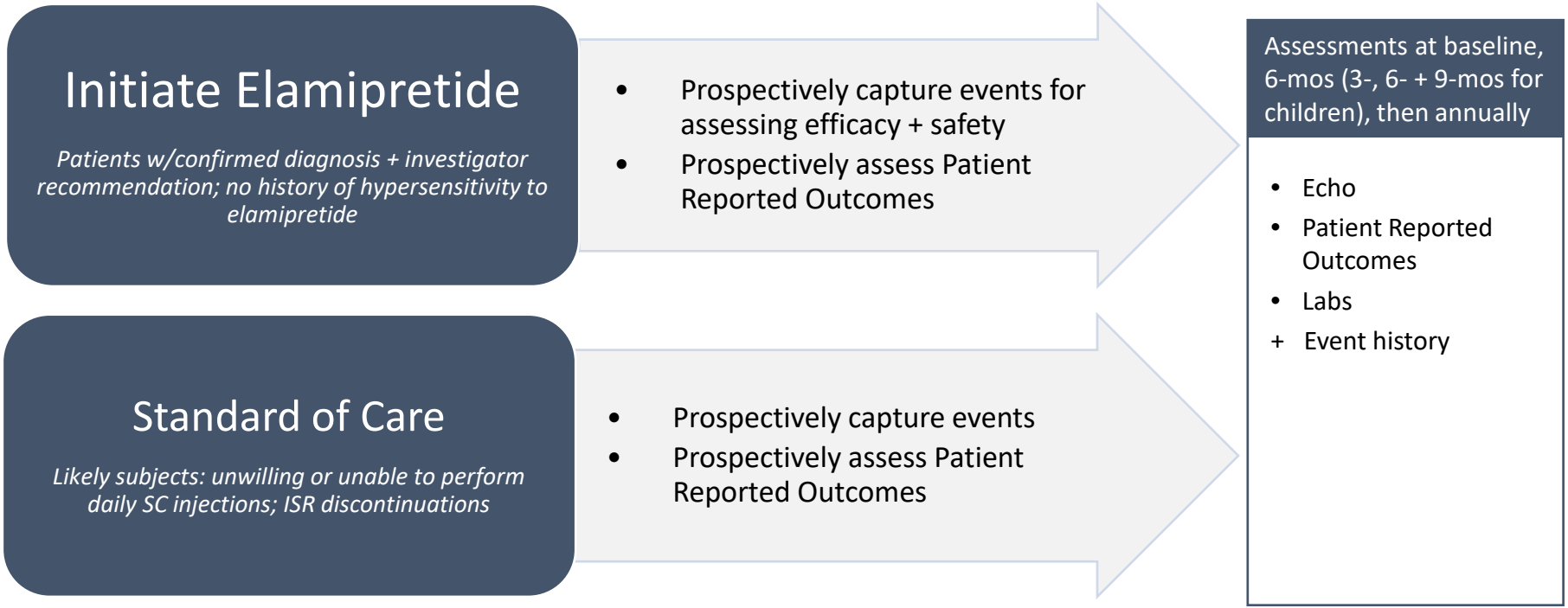
Summary of Treatment Effect Change from Baseline: N=8



*Mean scores were used for the endpoints.

**6 subjects had measurable MLCL/CL(18:2)4 Ratio at Week 168.

Post-marketing Disease Monitoring Program to Assess Safety + Long-term Trends in Outcomes Versus Standard-of-Care



Rationale for Approval of Elamipretide

Urgent Unmet Need

- *Severe, debilitating disease with high pediatric mortality*
- *No other therapies approved or in clinical development*
- *Increasing expanded access demand with requests from 12 US hospitals + 9 foreign countries; FDA has approved every EAP request submitted*

Favorable Safety Profile

✓ *Well-characterized with >400 patient years of exposure + favorable AE profile*

Totality of the Evidence

Assessed Effectiveness Relative to ~50% of the Total Evaluable Patient Population

✓ **Molecular Physiology:** *improvements in abnormal MLCL:CL ratios*

✓ **Function:** *durable + large improvements in*

- *Exercise tolerance*
- *Strength*
- *Balance*

✓ **Feel:** *durable + large improvements reported by patients + clinician (global impression scales); reports[*] of*

- *Improved ability to transfer between classes at school*
- *Ability to work a part-time job*
- *Ability to play with family pets*
- *Recovering more quickly from activities*
- *Cessation of nighttime enuresis*
- *Improved appetite + feeding*

✓ **Cardiac Physiology:** *improvements in left ventricular cardiac parameters*

[*] Patient + Caregiver Perception of Change Protocol evaluated trial experience while still blinded to randomization during 1st 12 weeks of TAZPOWER EXTENSION study

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Urgency of Unmet Need & Risk/Benefit for Patients

Barth Syndrome Foundation®

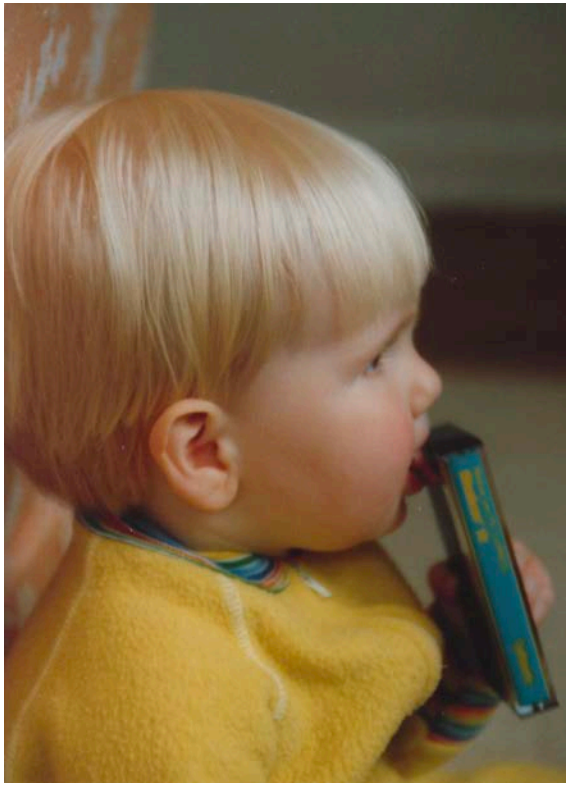
Kate McCurdy, MBA

Co-Founder and Chair of Board of Directors

Mother of Barth Son (Deceased)

Barth Syndrome Foundation

My Wonderful Barth Son, Will

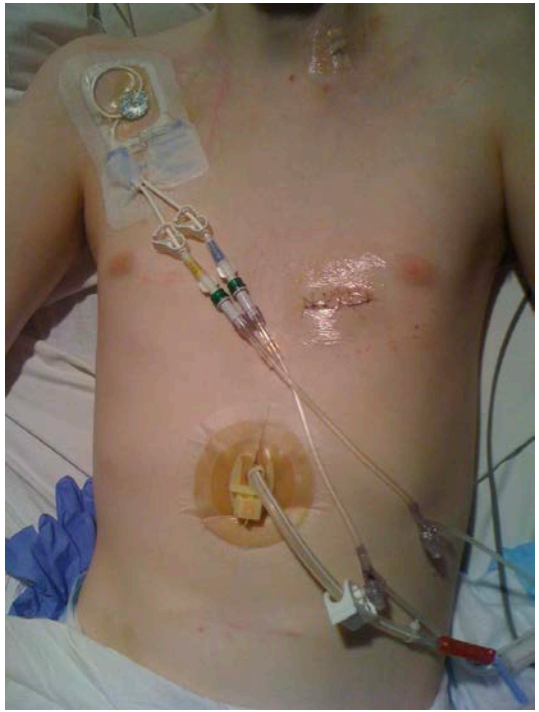


BORN 1986

DIED 2014

BUT Barth individuals look deceptively healthy

Barth Syndrome Foundation®



Summary of Will's Medical History

Barth Syndrome Foundation®

Clinical Issues:

- **Cardiomyopathy** (like 90% of BTHS patients), **with LVNC, led to 2 bouts of heart failure**
- **Neutropenia** (like 85% of BTHS patients)
- **Cardiac arrhythmia** ("risk of a cardiac episode is always present"*)
- **Multiple GI and nutritional issues** (difficulty eating, gagging, nausea, throwing up, diarrhea)
- **Skeletal muscle weakness**
- **Debilitating fatigue** (>80% BTHS patients cite as one of most significant symptoms)
- **Exercise intolerance**
- **Healing problems**
- **Pain** (especially headache, abdominal pain and leg pain)
- **POTS** (postural orthostatic tachycardia syndrome)
- **Various metabolic and endocrine abnormalities**
- **"Barth" delayed growth pattern**

Led to:

- **47 hospitalizations; total of 564 days**
- **57 procedures under anesthesia, including:**
  - **3 implanted defibrillators**
  - **2 gastrostomies**
  - **9 operations to revise scars to aid healing**
  - **1 muscle biopsy**
  - **6 bone marrow aspirations**
  - **1 removal of infected umbilicus**
- **16 central lines**
- **Multiple doctors' appointment every week**
- **Every day** (before his last stay in the hospital)**, took 29 pills, 2 IV medications, 2 subcutaneous injections, TPN thru port-a-cath during day, tube feedings overnight**
- **Many years in school he could attend only part-time and some years for only a handful of days** (50% BTHS had to reduce school or job responsibilities due to BTHS, 25% couldn't go to school or work at all*)
- **Feeling left behind and isolated, not being able to engage in life or contribute**
- **Died at age 28 years**

Barth Syndrome Foundation (BSF)

Founded in 2000, BSF is the only patient organization in world for ultra-rare disease Barth syndrome (BTHS), with 4 international affiliates

Mission: *"Saving lives through education, advances in treatments and finding a cure for Barth syndrome"*

- Registry; R & D grant and contract funding; international scientific, medical & family conferences; family / physician education materials / programs; family support
- Known # living affected individuals (12/31/22)
  - 302 worldwide from 37 countries
  - 129 in US
- BSF is in contact with >90% of affected individuals worldwide

Patient Perspective on Elamipretide

Barth Syndrome Foundation®

- Safe therapy is before you today
- We have seen multidimensional positive trial results AND meaningful effects on the daily lives of all TAZPOWER participants still on drug*
  - *Transformational* reduction in daily symptoms
  - Most go to full day of school or work full-time for the 1st time
  - All have strength and stamina to do household chores and have become significantly more independent enabling more social interaction
  - Recovery time from fatigue is much improved
  - 2 (teenagers) no longer experience overnight enuresis
- EAP cases corroborate life-changing potential

* As informed by discussions with patients, caregivers, and clinicians

Doctor Perspective

~50 medical professionals, a large % of BTHS experts worldwide, asked FDA in 2020 & 2022 to review the data for & in 2024 to approve elamipretide to expedite patient access

Barth Syndrome Foundation®

William T Abraham, MD, FACP, FACC, FAHA, FESC, FRCPE, The Ohio State University, 2022 & 2020	Michael Gewitz, MD, Maria Fareri Children's Hospital at WMC Health, 2024 & 2020	Colin Phoon, MPhil, MD, Hassenfeld Children's Hospital at NYU Langone, 2020
Peter G Barth, MD, PhD, Professor Emeritus, University of Amsterdam, Netherlands, 2024, 2022 & 2020	Amy Goldstein, MD, Children's Hospital of Philadelphia, 2024 & 2020	Robert D. Pitceathly MD, PhD, UCL Queen Sq Inst of Neurology; NHS Highly Specialized Service for Rare Mitochondrial Disorders, 2024
Mary Ann Bonilla, MD, St. Joseph Medical Center, 2020	Barry Greenberg, MD, Professor of Medicine, UCSD, 2022	William Pu, MD, Boston Children's Hospital and Harvard Medical School, 2024 & 2020
Michael Bristow, MD, PhD, University of Colorado, Division of Cardiology, 2024, 2022 & 2020	Richard H. Haas MB, Bchir, MRCP, UCSD Mitochondrial and Metabolic Disease Center, 2024	Stacey Reynolds PhD, OTR/L, FAOTA, Virginia Commonwealth, 2024
Barry Byrne, MD, PhD, University of FL, 2024	Nancy Halnon, MD, UCLA Children's Heart Center, 2024	Hani N. Sabbah, PhD, FACC, FCCP, FHRS, FHFSA, FAHA, Henry Ford Hospital, 2024 & 2022
William Todd Cade, PT, PhD, Duke University School of Medicine, 2024, 2022 & 2020	Grant Hatch, PhD, University of Manitoba, 2024 & 2020	Michael Schlame, MD, New York University, Langone Medical Center, 2024, 2022 & 2020
Charles E Canter, MD, Washington University; St. Louis Childrens, 2024	Majid Hussein, MD, UCLA Children's Heart Center, 2024	Brian Shayota MD, Univ of Utah, 2024
Kathryn Chatfield, MD, PhD, University of Colorado, Anschutz Medical Campus, 2024 & 2022	Michio Hirano, MD, Columbia University, 2024, 2022 & 2020	Brian Stauffer, MD, University of Colorado, Anschutz Medical Campus, 202 & 2022
Maryanne Chrisant, MD, Joe DiMaggio Children's Hospital, 2020	Kan Hor, MD, Nationwide Children's Hospital, 2022	Colin Steward, PhD, FRCP, FRCPCH, Bristol University UK, Founder, NHS Barth Syndrome Service, 2022
Bruce Cohen, MD, Akron Children's Hospital, 2024, 2022 & 2020	John L Jefferies, MD, MPH, FACC, FAHA, FAAP, FHFSA, FESC, University of Tennessee Health Sciences, 2024, 2022 & 2020	Arnold W. Strauss, MD, University of Cincinnati, 2020
Gerald F. Cox, MD, PhD, Boston Children's Hospital, 2024 & 2020	Amel Karaa, MD, Massachusetts General Hospital, Boston, 2024, 2022 & 2020	Carolyn Taylor, MD, Medical University of South Carolina, 2024, 2022 & 2020
Linda Cripe, MD, Nationwide Children's Hospital, 2022	Mary Kay Koenig, MD, McGovern Medical School, 2022	W. Reid Thompson, MD, Johns Hopkins School of Medicine, 2024, 2022 & 2020
Ibrahim Elsharkawi, MD, Mt Sinai, 2024	Jennifer S. Li, MD, Duke, 2024	Jeffrey A. Towbin, MD, MS, Le Bonheur Children's Hospital, 2024
Gregory Enns, MD, Stanford University, 2024 & 2020	Christoph Maack, MD, Director, Head, Wurzburg, Bavaria, Germany, 2022	Jim Udelson, MD, Tufts Medical Center, Boston MA, 2024, 2022 & 2020
Marni J. Falk, MD, Mitochondrial Medicine Frontier Program, CHOP, 2024	Kim McBride, MD, Nationwide Children's Hospital, 2024 & 2022	Hilary Vernon, MD, PhD, Johns Hopkins School of Medicine, 2024, 2022 & 2020
Brian Feingold, MD, MS, FAHA, Professor, Pediatrics University of Pittsburgh, 2024, 2022 & 2020	Shelly Miyamoto, MD, Univ of Colorado, 2024	Jerry Vockley, MD, PhD, University of Pittsburgh, College of Medicine, 2022 & 2020
Jaya Ganesh, MD, Icahn School of Medicine at Mount Sinai, 2020	Laura A. Ortmann, MD, UNMC Medical Director, Cardiovascular Intensive Care Unit, 2024	

Patient Perspective on Any Remaining Risk of Benefit Uncertainty

Barth Syndrome Foundation®

BSF Externally-led PFDD Meeting July 18, 2018

"…most participants stated that as long as [a therapy] did not cause life-threatening side effects, they would try almost any treatment – no matter how inconvenient the route of administration – that would effectively target the underlying cause of the disease and provide them with gains in function and energy to live a fuller life."

BSF Listening Session with FDA March 3, 2021

In general, tolerance for less certainty of treatment especially when possible treatment is deemed safe, including because:

- living with constant uncertainty every day,
- no clinical benefit is ever guaranteed, but Barth patients want option to try,
- need for treatment soon because day-to-day quality of life is very low
- willing to try drug that might improve QOL even if benefit is uncertain or might be at expense of longer life

Urgency of Unmet Need

Barth Syndrome Foundation®

Time is not on the side of our affected individuals

For those who survive past infancy, their future not only remains exceedingly uncertain, but QOL is very low on many dimensions, including crushing fatigue that can lead to isolation and feeling left out of life

Since elamipretide development started in 2014:

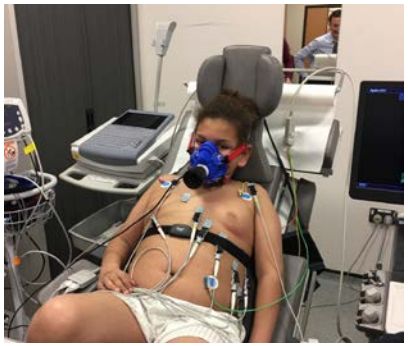
- **18%** of those with Barth syndrome in US have died
- **12%** of US affected individuals have had heart transplant
- **Everyone** who survives lives a life diminished by ravages of this progressive disease

No approved therapies for this universally fatal disease; no other candidates in clinical development

Potential Impact of Your Advice

Barth Syndrome Foundation®

"Much of the effort in evaluating a drug development program goes into avoiding a specific mistake, that is erroneously approving a drug that is not effective. There often is little consideration of another error, which is failing to approve a drug that actually works. ***In devastating diseases, the consequences of this mistake can be extreme, but most of those consequences are borne by patients who traditionally have little say in how the standards are implemented****." Dr. Janet Woodcock*

Barth Syndrome Foundation®

Please remember that behind all the data you will see today are real human beings – our kids

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Disease + Natural History Cohort

Hilary Vernon MD, PhD

Professor of Medical Genetics
Johns Hopkins School of Medicine

Background

- B.A. Biochemistry U Penn
- M.D. Robert Wood Johnson Medical School/UMDNJ
- Ph.D. Rutgers University
- Combined residency in pediatrics and clinical genetics Johns Hopkins
- Fellowship in clinical laboratory biochemical genetics Johns Hopkins University
- Board certified in pediatrics, clinical genetics, and clinical biochemical laboratory genetics
- Joined the faculty at the Kennedy Krieger Institute and at Johns Hopkins University in 2011
- Started Barth Syndrome Clinic at Kennedy-Krieger in 2012

Relevant Disclosures

- Research support from Stealth BioTherapeutics
- Member of the Barth Syndrome Foundation Scientific & Medical Advisory Board

Barth Syndrome Clinic at Kennedy-Krieger Institute at Johns Hopkins

- The only US multidisciplinary clinic - and one of only two worldwide - specializing in Barth syndrome
- Established in 2012
- Collaborative team of experts in metabolism, cardiology, hematology, genetic counseling, physical therapy, + nutrition
- Offers quarterly outpatient clinic for affected individuals
- Over 50 individuals with Barth syndrome – about 40% of US affected individuals - have attended the clinic

Johns Hopkins School of Medicine

McKusick-Nathans Institute of Genetic Medicine

Kennedy Krieger Institute

Identified Need for Natural History Study

Conducted under JHU-approved protocols starting in 2012

- Ultra-rare genetic condition
- Lack of prospective natural history studies
- Lack of clinical targets for measurement of outcomes
- Lack of biomarkers correlating to clinical status
- Limited understanding of genotype/phenotype correlation

Data collection continuing through present

Objective: Define Natural History through Deep Phenotyping

Barth Syndrome Interdisciplinary Clinic

- 12-year observational natural history study
- Infancy through adulthood

Biennial BSF International Meetings

- 12 years of cross-sectional data
- Multi-national cohort of patients

Cardiology (Echo, EKG), Physical Therapy (QoL, 6MWT, HHD), Hematology, Genetics (TAZ genotype, Family History), Collection of Biological specimens (Cell lines, Plasma, Urine)

Tremendous Community Participation

Patients attending outpatient KKI clinics or BSF biennial conferences volunteered for this research

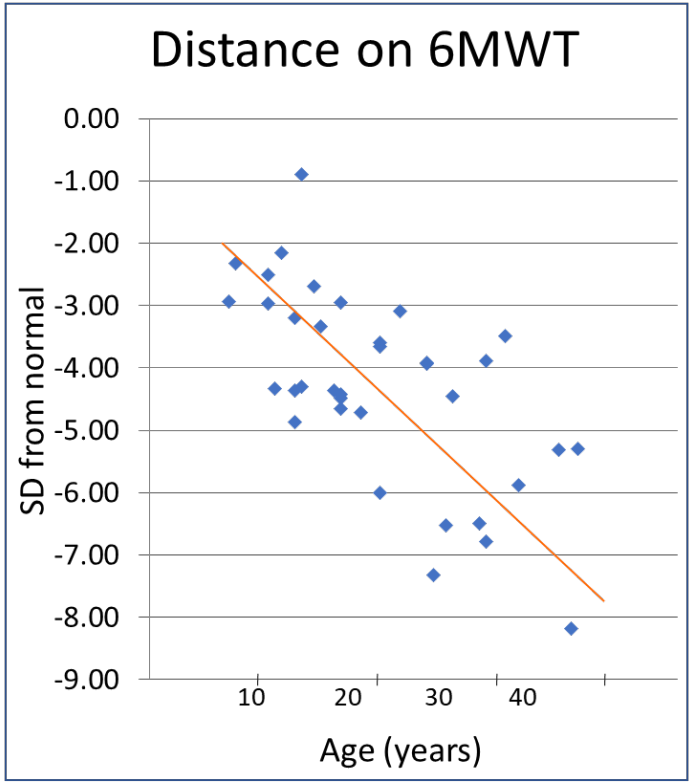
>50% of all US patients

patients registered for participation

- A number of international patients attended at least 1 clinic visit
- ~50% of patients are children <12-years-old
- All subjects old enough to complete functional assessments demonstrated significant impairment, consistent with the disease

Exercise Performance is Abnormal in All Patients with BTHS

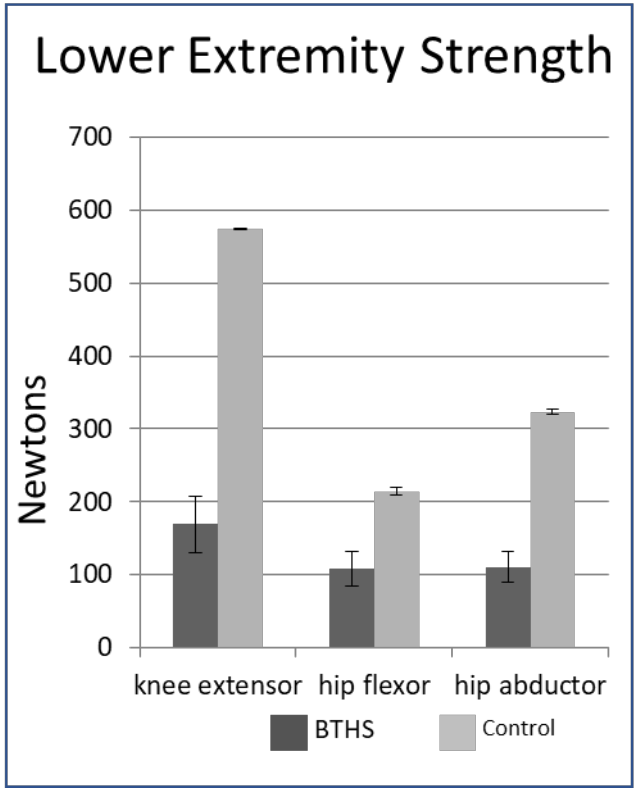
- Older individuals (20 – 32 years) had more fatigue pre-assessment than younger individuals (4 – 19 years)
- The difference between pre- and post-assessment fatigue (measured on BORG scale) was strongly correlated with 6MWT distance for older individuals (r=0.47)



Thompson Genet Med. 2016.

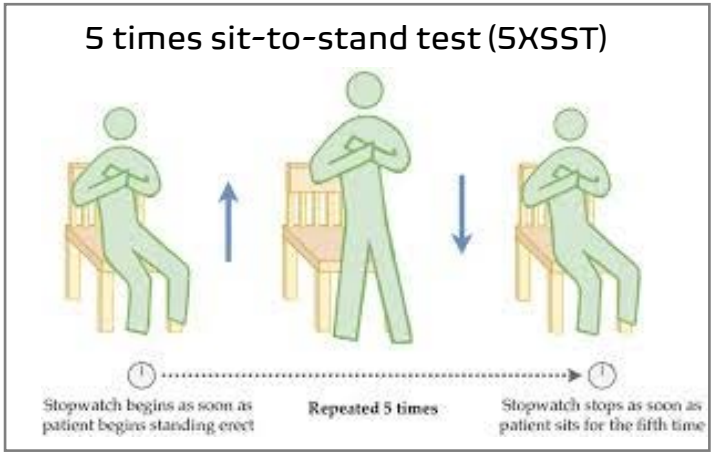
Muscle Strength is Abnormal in All Patients with BTHS

- Older affected individuals (aged 20 – 32 years) had significantly less muscle strength than normative values:
  - Younger affected individuals generated more force relative to their weight than older affected individuals
  - There was a weak positive correlation between strength assessments and 6MWT distance



5XSST and Balance are Impaired in BTHS

- Impaired 5XSST compared to age-matched controls:
  - Affected individuals aged 6 – 19 years needed an average 35% additional time vs. controls to complete 5XSST (p<0.0001)
  - Affected individuals ≥20 years needed an average 42% additional time vs. controls to complete the 5XSST (p=0.04)
- Significantly impaired balance on SWAY application compared to age-matched controls (p=0.003)

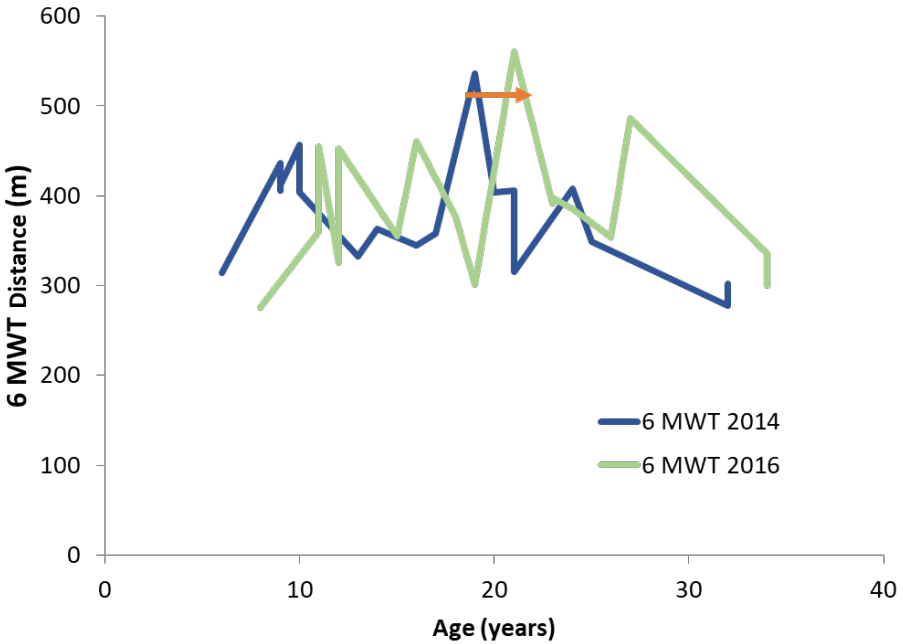


SWAY is an FDA 510(k) cleared balance application

6MWT Statistically Unchanged Over 2-years

- 2014: average distance was 379±63 m (SD)
- 2016: average distance was 387.8 m ± 71 (SD)
- 1 individual had significant worsening, and 1 individual had significant improvement
- Correlated to major health events in the interim

Hornby OJRD. Jan 2019.



Strong Correlation Between Fatigue and Age

Health-related quality of life (HRQoL) questionnaires in children and adults with BTHS and their caregivers showed:

- 33.3% of children aged 2–4 years demonstrated significantly impaired physical functioning
- More severe fatigue are significantly correlated with more impaired HRQoL.
- Fatigue reported across age groups

Fatigue and Quality of Life Worsen with Age

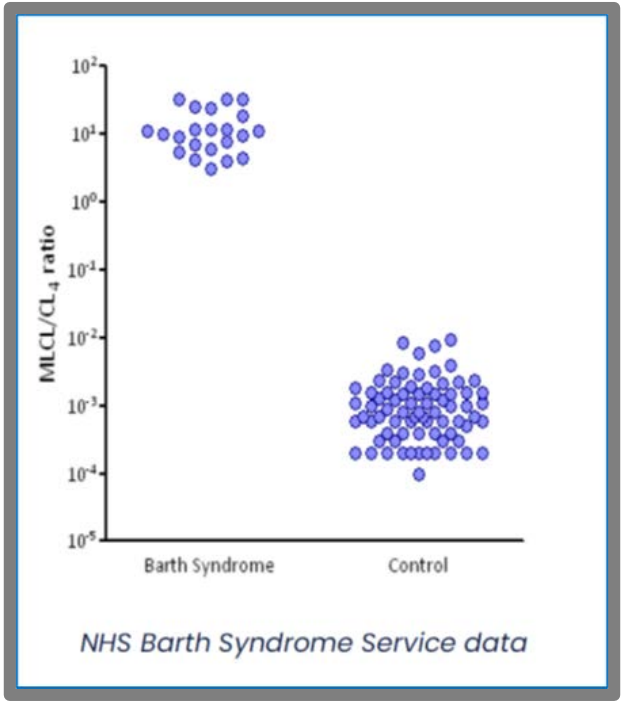
Kim, Ther Ad Rare Dis (2022)

MLCL : CL Biomarker

Diagnostic for Disease

Potential Biomarker of Clinical Status?

- Our study showed the MLCL:CL ratio was **inversely correlated with 6MWT distance** (after correcting for height) (p=0.00014)**, supporting this hypothesis
- Baseline assessments (n=55) show a mean 9.1 (SD 5.89) MLCL:CL (72:8) ratio
- Longitudinal assessments (n=15) show a 6% (SD 23%) average <u>increase</u> in MLCL:CL (72:8) ratio (statistically insignificant), suggesting <u>this ratio does not change over time</u>



NH Study Identified Endpoints for Monitoring and Therapy in Barth Syndrome

Functional Assessments

Severely impaired; do not improve over time

- 6MWT
- Muscle strength by HHD
- 5XSST
- Balance

Quality of Life

Worsens over time

Fatigue and quality of life worsened with age – no disease-specific PRO

Biomarkers

Do not improve over time

Cardiac echo parameters and cardiolipin (MLCL:CL) ratios are correlated with aspects of phenotypic severity and do not improve over time

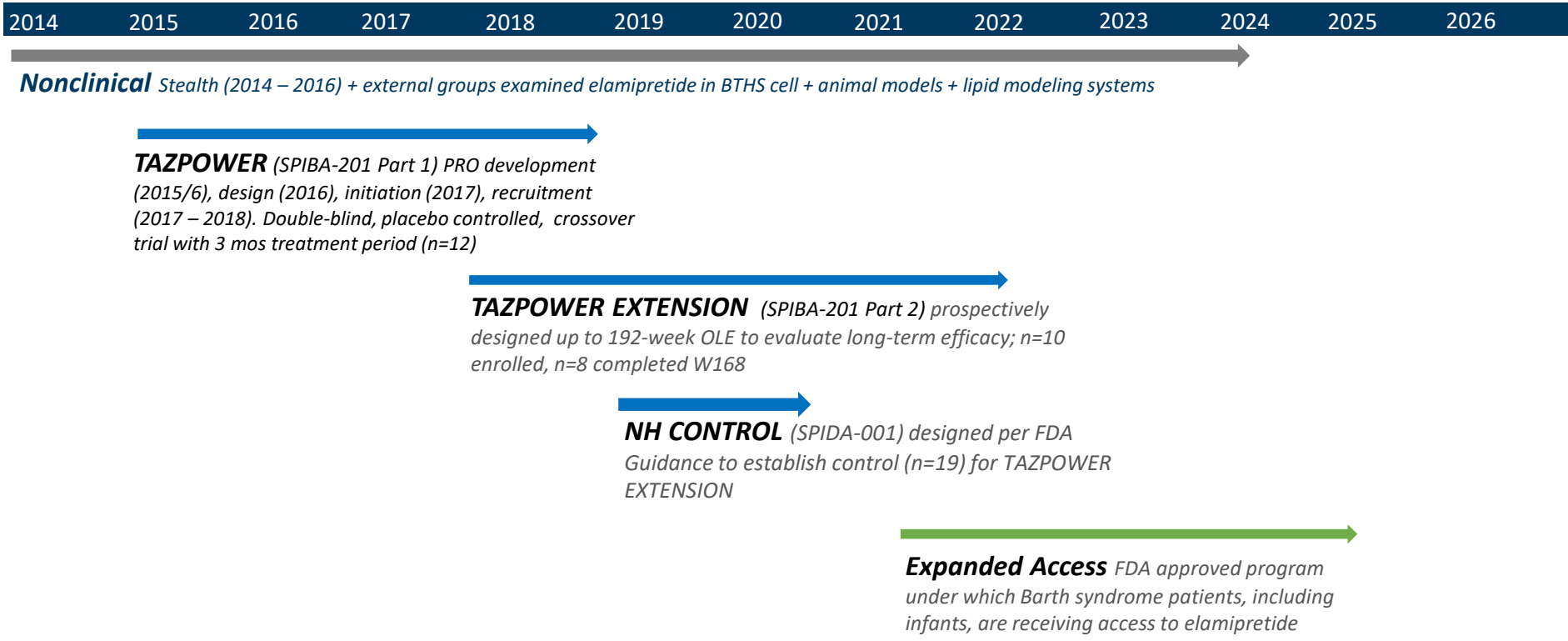
Agenda

Introduction	**Reenie McCarthy** *Chief Executive Officer* *Stealth BioTherapeutics*
Urgency of Unmet Need + Benefit:Risk Tolerance	**Kate McCurdy, MBA** *Chair, Board of Directors* *Barth Syndrome Foundation*
Disease + Natural History Cohort	**Hilary Vernon, MD, PhD** *Professor of Medical Genetics* *Johns Hopkins University School of Medicine*
Safety + Efficacy	**Jim Carr, PharmD** *Chief Clinical Development Officer* *Stealth BioTherapeutics*
Statistical Perspectives	**Janet Wittes, PhD** *Wittes LLC*
Expanded Access Program	**Kathryn Chatfield, MD, PhD** *Associate Professor of Pediatrics-Cardiology* *Director, Cardiac Genetics Clinic, Children's Hospital Colorado*
Closing Remarks	**Reenie McCarthy** *Chief Executive Officer* *Stealth BioTherapeutics*

Safety + Efficacy

Jim Carr, PharmD
Chief Clinical Development Officer
Stealth BioTherapeutics

Barth Syndrome Development Program



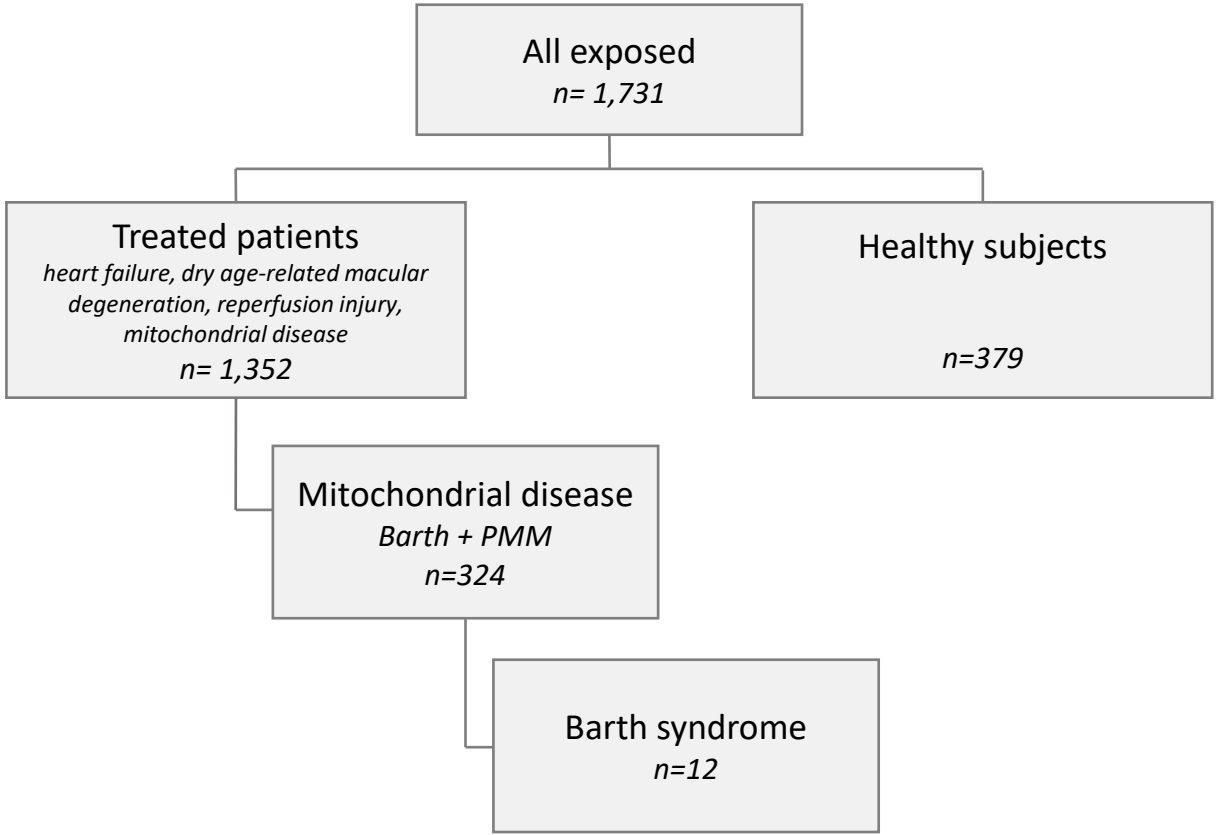
TAZPOWER

Adverse events (AE) in two or more subjects

System Organ Class Preferred Term	ELAM 40 mg n (%)	Placebo n (%)
At least one Treatment Emergent Adverse Event (TEAE)	12 (100.0)	10 (83.3)
General disorders and administration site conditions	12 (100.0)	8 (66.7)
Injection site erythema	12 (100.0)	3 (25.0)
Injection site pain	9 (75.0)	5 (41.7)
Injection site induration	8 (66.7)	2 (16.7)
Injection site pruritus	8 (66.7)	2 (16.7)
Injection site bruising	3 (25.0)	0
Injection site urticaria	3 (25.0)	0
Medical device site irritation	2 (16.7)	1 (8.3)
Nervous system disorders	3 (25.0)	5 (41.7)
Headache	1 (8.3)	3 (25.0)
Gastrointestinal disorders	1 (8.3)	4 (33.3)
Aphthous ulcer	0	2 (16.7)
Infections and infestations	4 (33.3)	3 (25.0)
Bronchitis	2 (16.7)	1 (8.3)
Injury, poisoning, and procedural complications	2 (16.7)	3 (25.0)
Ligament sprain	2 (16.7)	1 (8.3)

Integrated Summary of Safety

- *>1,700 subjects*
- *>400 patient years*



ALL EXPOSED ADVERSE EVENTS

Summary of the Most Common Related TEAEs in ≥2% of Subjects in the All Exposed Population by System Organ Class and Preferred Term – SC or IV Administration

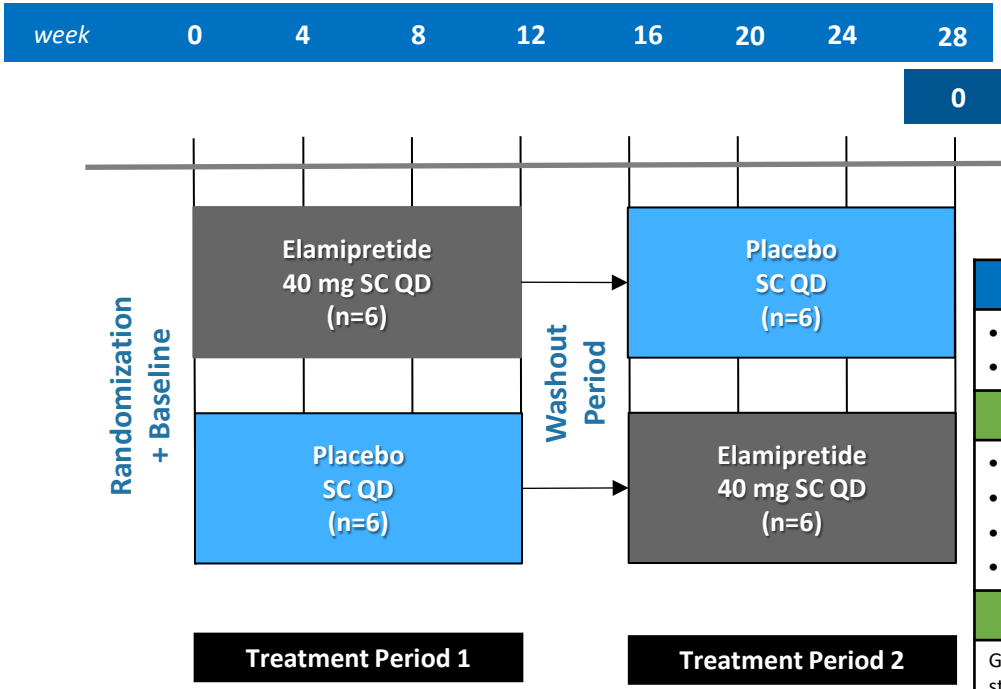
Safety Population	All Exposed		
Total Daily Dose	Placebo	40 mg	Any Dose
Number of subjects	724	528	1673
At Least 1 TEAE	139 (19.2)	432 (81.8)	630 (37.7)
Blood and lymphatic system disorders			
Eosinophilia	0	11 (2.1)	11 (0.7)
General disorders and administration site conditions			
Injection site bruising	24 (3.3)	63 (11.9)	87 (5.2)
Injection site erythema	36 (5.0)	310 (58.7)	365 (21.8)
Injection site hemorrhage	11 (1.5)	35 (6.6)	46 (2.7)
Injection site induration	12 (1.7)	137 (25.9)	155 (9.3)
Injection site mass	4 (0.6)	39 (7.4)	43 (2.6)
Injection site nodule	2 (0.3)	22(4.2)	25 (1.5)
Injection site pain	32 (4.4)	185 (35.0)	237 (14.2)
Injection site pruritis	16 (2.2)	329 (62.3)	380 (22.7)
Injection site rash	1 (0.1)	12 (2.3)	13 (0.8)
Injection site swelling	7 (1.0)	128 (24.2)	165 (9.9)
Injection site urticaria	0	59 (11.2)	59 (3.5)
Investigations			
Eosinophil count increased	0	26 (4.9)	27 (1.6)
Nervous system disorders			
Dizziness	5 (0.7)	11 (2.1)	17 (1.0)
Headache	12 (1.7)	13 (2.5)	36 (2.2)

ALL EXPOSED ADVERSE EVENTS

Serious Adverse Events in ≥1% of Subjects in the All Exposed Population at Any Dose in Any Study by System Organ Class and Preferred Term – SC or IV Administration

Safety Population	All Exposed n (%)		
TDD	Placebo	40 mg	Any Dose
Number of subjects	724	528	1673
At least 1 TESAE	51 (7.0)	55 (10.4)	150 (9.0)
Cardiac disorders	**30 (4.1)**	**4 (0.8)**	**58 (3.5)**
Cardiac failure	16 (2.2)	0	22 (1.3)
Gastrointestinal disorders	**3 (0.4)**	**8 (1.5)**	**11 (0.7)**
Infections and infestations	**5 (0.7)**	**15 (2.8)**	**29 (1.7)**
Nervous system disorders	**3 (0.4)**	**7 (1.3)**	**12 (0.7)**

TAZPOWER (SPIBA-201 P1)



-------Double-blind, placebo-controlled crossover study-------

TAZPOWER EXTENSION

(SPIBA-201 P2)

Primary Endpoints

- **Distance walked (meters) on 6MWT**
- **Total fatigue score on BTHS-SA**

Secondary Endpoints

- **Functional assessments** (SWAY, HHD, 5XSST)
- **Physician- + Patient-reported outcomes** (CGI-S, PGI-S)
- **Cardiac Monitoring**
- **Safety + tolerability** (AEs, Laboratory Assessments)

Key Inclusion Criteria

Genetically-confirmed BTHS---Male sex---Age ≥12 years---Ambulatory but impaired during 6MWT---On stable medications---Weight >30 kg, eGFR ≥90 mL/min or weight >40 kg, eGFR ≥60 mL/min at screening

----------Baseline-controlled extension study----------

TAZPOWER

Patient demographics + clinical characteristics

Demographic/Characteristic	Patients Enrolled (N=12)
Mean Age, years (Range)	19.5 (12-35)
Male Sex, n	12
Race (n) White Multiracial	 11 1
Mean Height, cm (Range)	167.3 (150.4-187.7)
Mean Weight, kg (Range)	50.8 (31.4-85.9)
Mean BMI, kg/m^2 (Range)	17.6 (13.6-24.4)
Mean 6MWT, meters	405.35
Mean BTHS-SA Total Fatigue	7.56

16 subjects were screened; 12 met inclusion criteria + were enrolled

TAZPOWER

Functional endpoints

- *No effect of elamipretide observed over 3-months*
- *Only endpoint that showed placebo effect was 6MWT*

	Elamipretide (n=12)		Placebo (n=12)	
Endpoint	**Predose Elam**	**W12**	**Predose Plac**	**W12**
6MWT (meters) Mean (SD)	400.1 (55.07)	443.1 (65.43)	412.6 (60.16)	443.9 (77.10)
Muscle strength by HHD (newtons) Mean (SD)	131.24 (29.90)	135.93 (52.28)	123.10 (24.68)	129.25 (34.24)
5XSST (seconds) Mean (SD)	12.97 (3.34)	14.02 (5.45)	13.71 (5.31)	13.75 (6.10)
SWAY Balance (1-100 scale) Mean (SD)	70.75 (19.72)	78.70 (15.16)	68.82 (24.75)	71.35 (20.25)

Discussion of Effort on 6MWT

- FDA attributes the ~60-meter mean change in 6/12 subjects on placebo in first treatment period to potential effort bias
- 6MWT fluctuations did not exceed screening values, assessed pre-randomization without expectational bias, suggesting this was likely an artifact of trial design not varying levels of effort
  - 1st clinical trial in this disease
  - Intensive visit schedule/travel schedule + associated fatigue/poor recovery may have resulted in “bad days” per fatigue scores (7-day average)
- No “placebo effect” on other functional endpoints

Changes did not exceed screening values; likely due to fatigue not “effort bias”

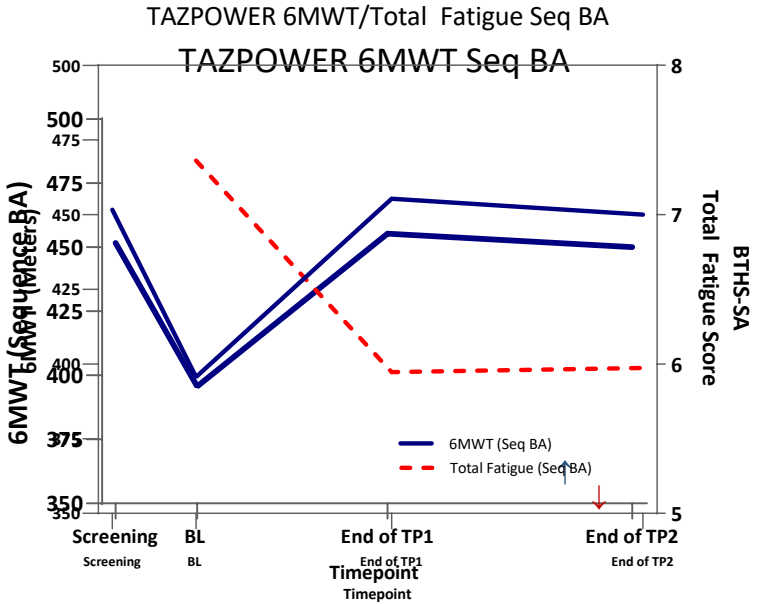
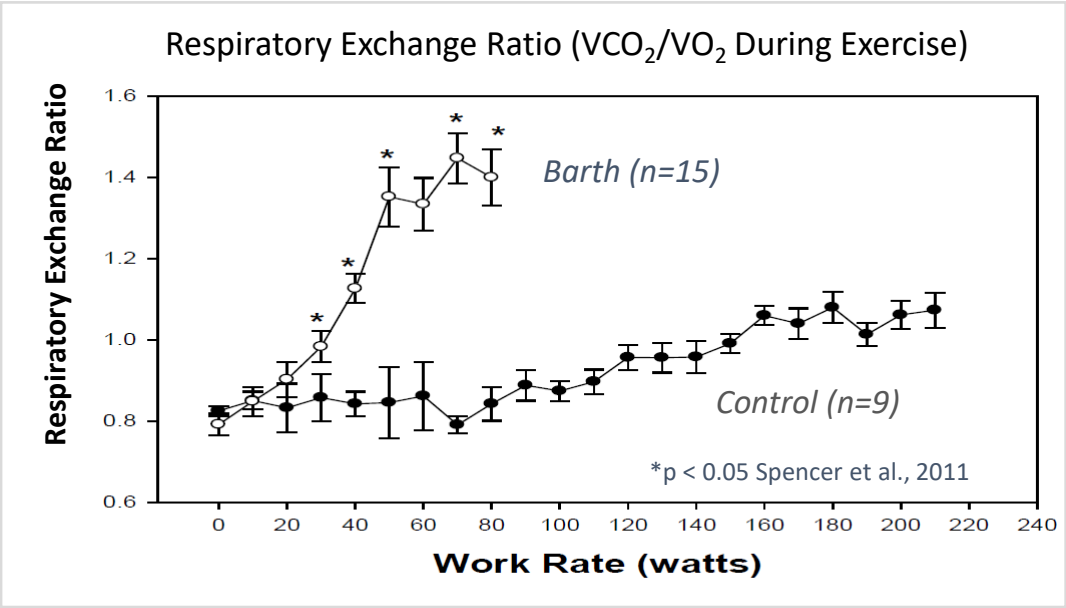


Figure shows BA randomization sequence (n=6) featured in FDA briefing book; prespecified analysis compared all subjects on elamipretide vs. all subjects on placebo (n=12 each)

↑↓ *Direction of positive change*

Effort-dependent Improvement is Improbable



Endurance Exercise Training Study:

only modest improvement in exercise endurance

- 12-week, supervised individualized endurance exercise training study (cycle ergometer for 30-45' 3X/week) in Barth syndrome subjects (23 ± 5 years, n = 4)
- Peak oxygen consumption modestly (~5%) improved in three of four participants

Cade et al., Endurance Exercise Training in Young Adults with Barth Syndrome: A Pilot Study. JIMD Rep. 2017

TAZPOWER Conclusions

- TAZPOWER showed no significant findings on functional endpoints after 3 months of treatment
  - Principal Investigator reported improvements on CGI-C (impression of change) + case-study notes
  - Data from PCPC protocol capturing patients' + caregivers' perspectives of change during TAZPOWER demonstrated perceived benefit; see www.stealthbt.com/poc or scan →
- Apparent disconnect between patient/clinician/caregiver perception of benefit and functional endpoints
- Emerging clinical data in other indications supported longer-term treatment (PMM + dry AMD)

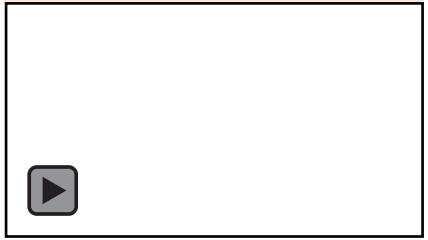
Steps Taken to Maximize OLE Data

- TAZPOWER Extension was ongoing to characterize long-term effect of elamipretide on TAZPOWER endpoints
- Most/all eligible US patients screened for TAZPOWER; another randomized controlled trial posed feasibility challenges
- FDA's Jan 2019 Guidance on Rare Diseases: Common Issues in Drug Development, provided that *"In special circumstances, such as when it may be impractical or unethical, a well-designed and conducted natural history study can provide an external control group for interventional trials"*
- We designed the NH Control study closely following the Guidance to maximize interpretability of the TAZPOWER Extension study data

Time Course to Improvements

Hours/Days → *Days/Weeks* → *Weeks/Months* → *Months/Year*

HOURS
Improvements in **respiration** in explanted human heart tissue (Colorado Cardiac Transplant Program)



DAYS/WEEKS
Restoration of **healthy gene expression + cardiac/ mitochondrial protein turnover** in BTHS cell models (JHU)

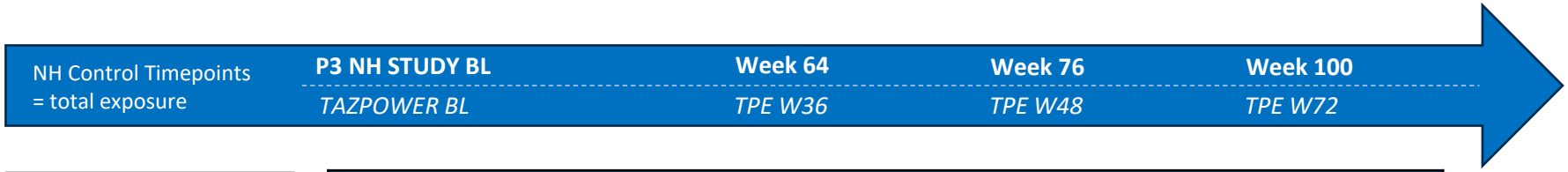
WEEKS/MONTHS
Improved MLCL:CL ratio

MONTHS/YEARS
Myocardial + skeletal muscle remodeling + improved end organ function observed

HN Sabbah, Heart Failure Reviews, 2022

Phase 3 NH CONTROL Study

Designed + conducted to establish an external control for the TAZPOWER EXTENSION data



TAZPOWER EXTENSION Subjects at W36 (n=8)

NH Control (n=19)

Primary Endpoints

- **Distance walked (meters) on 6MWT at Week 64**
- **Distance walked (meters) on 6MWT at Week 76**

Secondary Endpoints ***no hierarchical ranking specified***

- **Muscle Strength by HHD at Weeks 64 + 76**
- **5XSST at Weeks 64 + 76**
- **SWAY Balance at Weeks 64 + 76**
- **MDRI at Weeks 64 + 76**

Key Inclusion/Exclusion Criteria

TAZPOWER EXTENSION participants with values at W36; sensitivity analyses included all TAZPOWER participants

NH cohort participants age ≥12-years-old, transplant-free, with at least 2 6MWT data points. TAZPOWER participants excluded as controls

Abbreviations: TPE = TAZPOWER EXTENSION Study

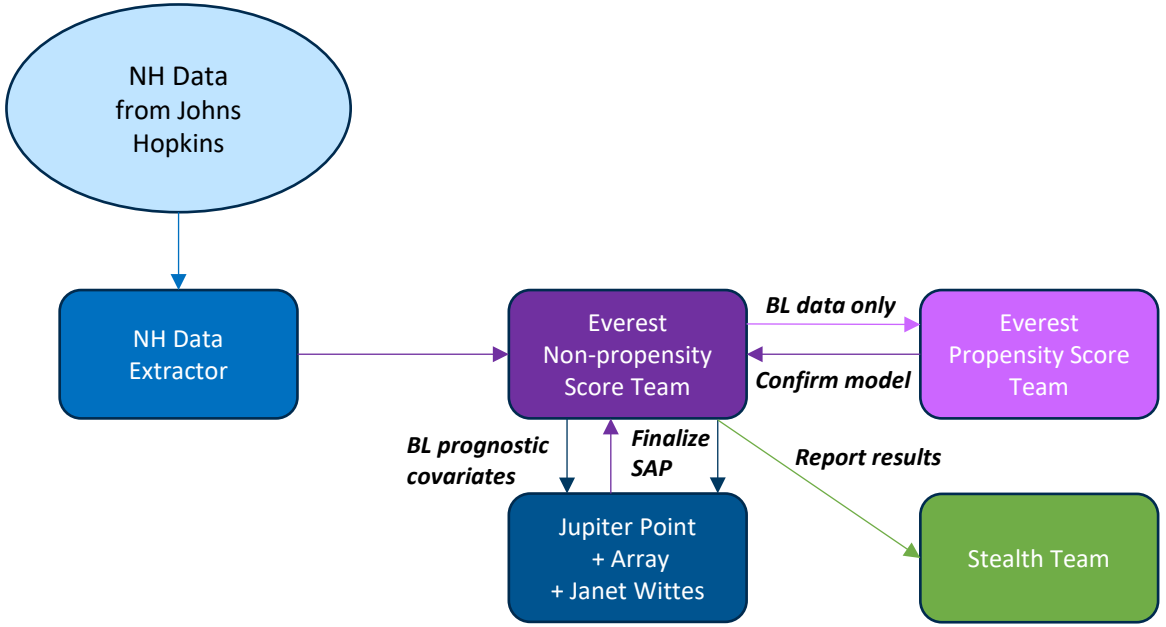
Rigorous data handling + blinding charters implemented to minimize potential for bias

Methods

- NH Data Sources:
  - Barth Syndrome Foundation International Conference
  - Multidisciplinary Barth Syndrome Clinic at JHU
- Propensity Scores:
  - Multiple models explored using only BL; selected model with best fit
  - Propensity scores + stabilized weights utilized to minimize impact of selection bias
- Analysis methods:
  - Linear regression used to estimate value of an endpoint at timepoints of interest
  - For each subject, a regression line was fitted using all available endpoint data, starting with BL
  - Interpolated value was used for comparison between elamipretide + NH control groups using a mixed model of repeated measures

Firewalls to Minimize Bias

- Utilized multiple blinded, firewalled statistical teams + rigorous data flow restrictions to minimize bias
- Prognostic match team had access only to baseline data
- Stealth team did not have access to NH database prior to study completion



Concept Statistical Analysis Plan, v1.0, 1/15/2020; Data Blinding Charter, v3.0, 1/15/2020; Protocol = SPIBA-001 Protocol v3.0, 1/15/2020; Supplemental Statistical Analysis Plan, v2.0, 5/8/2020

Patient Demographics + Clinical Characteristics

Variable	Elamipretide-treated TRTS (N = 8)	NH control UNTS (N = 19)
Age		
Mean (SD)	18.3 (5.02)	21.0 (5.46)
Min, Max	12.9, 28.7	12.0, 32.6
Height		
Mean (SD)	166.6 (12.43)	168.6 (14.25)
Min, Max	152.5, 180.8	121.3, 186.0
6MWT		
Mean (SD)	381.88 (64.18)	394.88 (75.22)
Min, Max	313.0, 495.0	267.0, 536.45
Muscle strength (HHD)		
Mean (SD)	132.10 (26.47)	151.79 (52.30)
Min, Max	79.62, 159.24	53.38, 241.76
5XSST		
Mean (SD)	12.89 (2.86)	11.18 (3.03)
Min, Max	9.18, 16.65	5.50, 15.88
SWAY Balance		
Mean (SD)	70.90 (19.51)	68.66 (20.72)
Min, Max	45.40, 90.30	17.27, 97.10

Included all eligible NH subjects ≥12-years-old with longitudinal data to minimize potential bias

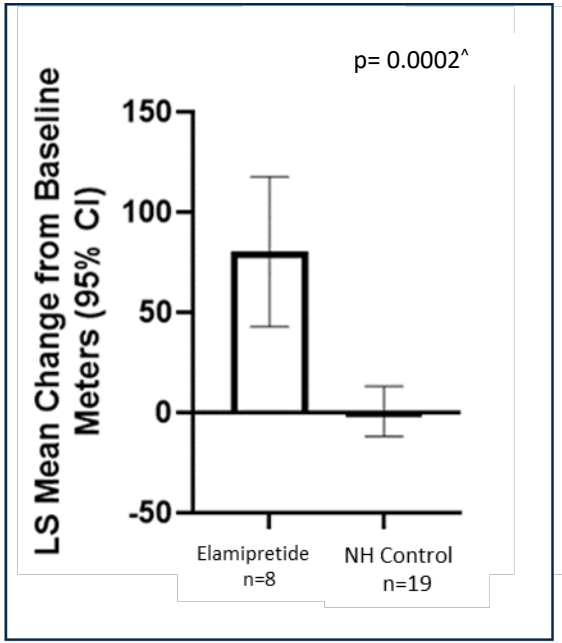
Highly comparable baseline characteristics between cohorts

Six-minute Walk Test ↑

- Chosen as primary to minimize bias (i.e., same as TAZPOWER)
- Strong rationale in this disease because depends on both cardiac and muscle function
- Impaired at BL (mean 381.88m elam, 394.88m NH) versus predicted values (637m)
- Clinically meaningful change reported to be 25m (PMM) to 35m (COPD)

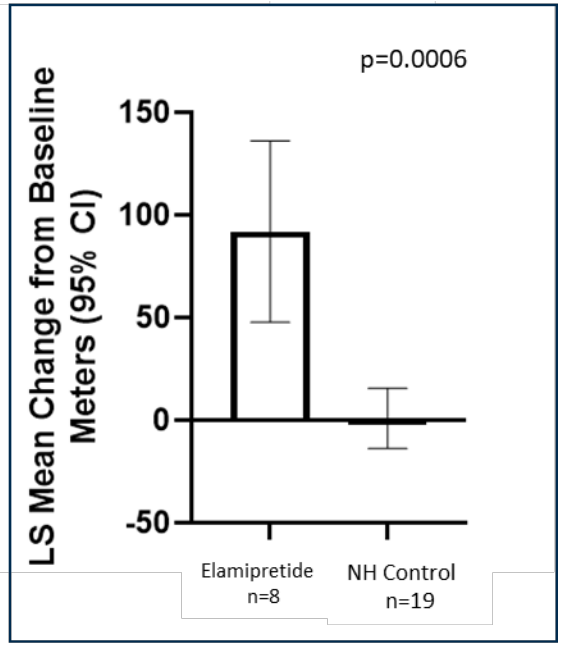
m=meters

6MWT Change from BL at Week 64



W64 = W36 of TAZPOWER EXTENSION

6MWT Change from BL at Week 76



W76 = W48 of TAZPOWER EXTENSION

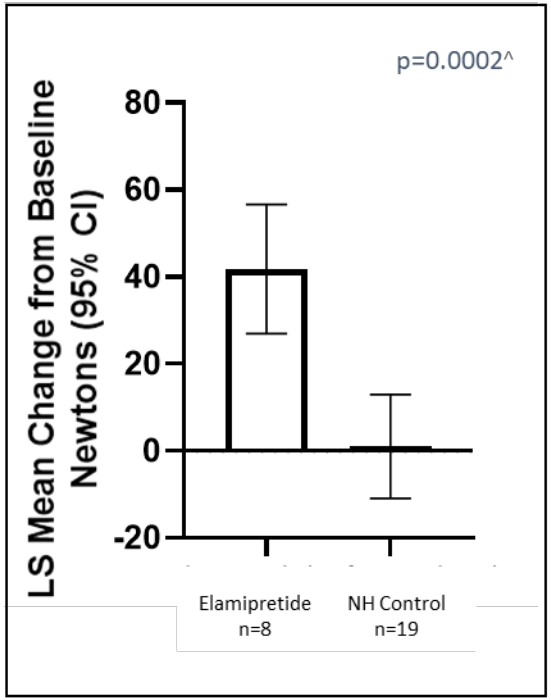
^p≤0.025 is significant with Bonferroni correction

↑↓ = direction of positive change

Muscle Strength ↑

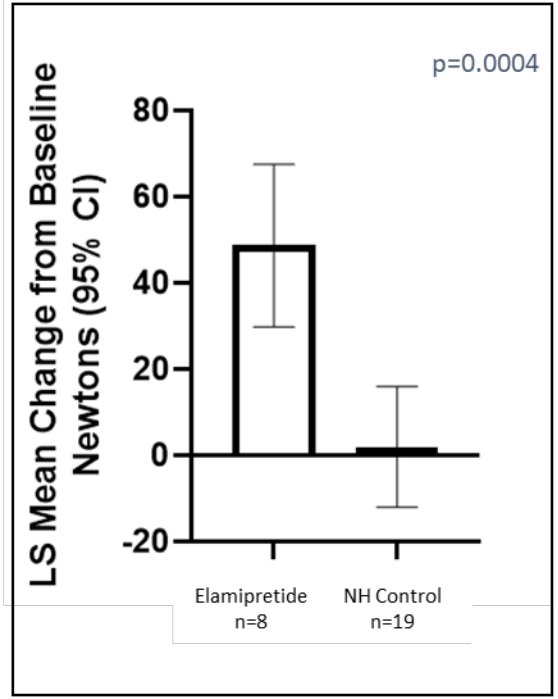
- Impaired at BL (mean 132.09n elam, 151.79n NH) versus predicted values (202.5n)
- Clinically meaningful change reported to be 9n (~2 pounds) in DMD
- Directionally positive changes on 5XSST and Balance are supportive of this finding

Muscle Strength at Week 64



W64 = W36 of TAZPOWER EXTENSION

Muscle Strength at Week 76



W76 = W48 of TAZPOWER EXTENSION

n=newtons; 1n = 0.22 pound

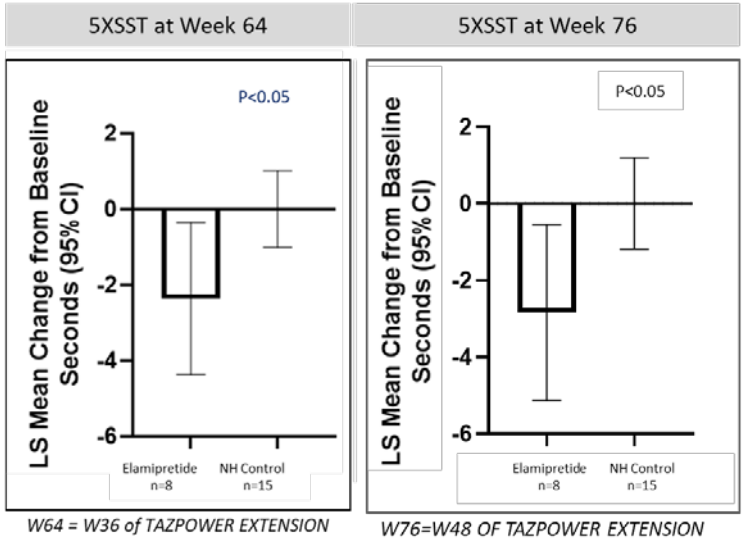
^p≤0.00625 is significant with Bonferroni correction

5XSST ↓

- Physically demanding test of core muscle strength measures how many seconds it takes to rise from/return to seated position 5X in rapid succession
- Impaired at BL (mean 12.89s elam, 11.18s NH) versus 6.5s predicted
- Clinically meaningful change reported to be -0.76s for stroke, -1.7s for COPD

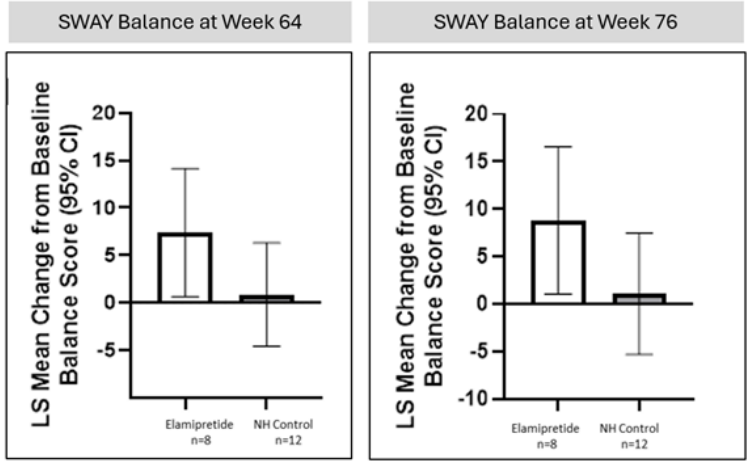
SWAY Balance ↑

- Mobile app measures balance utilizing 5 stances (feet together, tandem right foot forward, tandem left foot forward, single leg right foot, single leg left foot) to compute a composite score from 0 to 100 (higher = better postural stability)
- Impaired at BL (mean 70.9 elam, 68.66 NH) versus 84.98 predicted



W64 = W36 of TAZPOWER EXTENSION

W76=W48 OF TAZPOWER EXTENSION



W64 = W36 of TAZPOWER EXTENSION

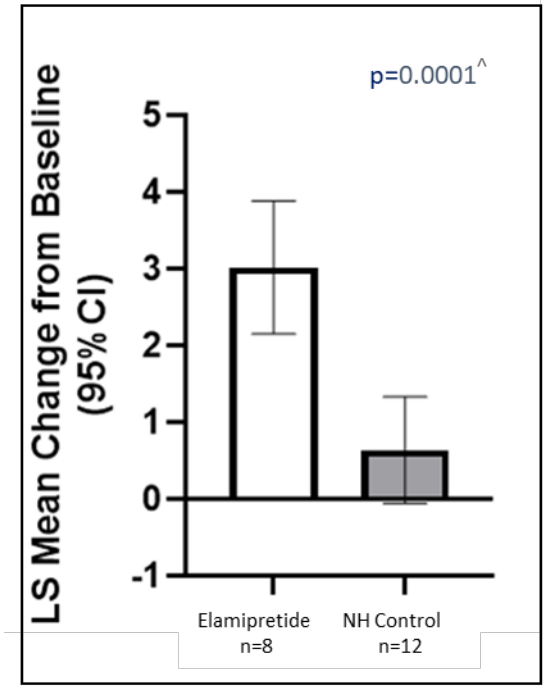
W76=W48 OF TAZPOWER EXTENSION

s=seconds

Multi-domain Responder Index ↑

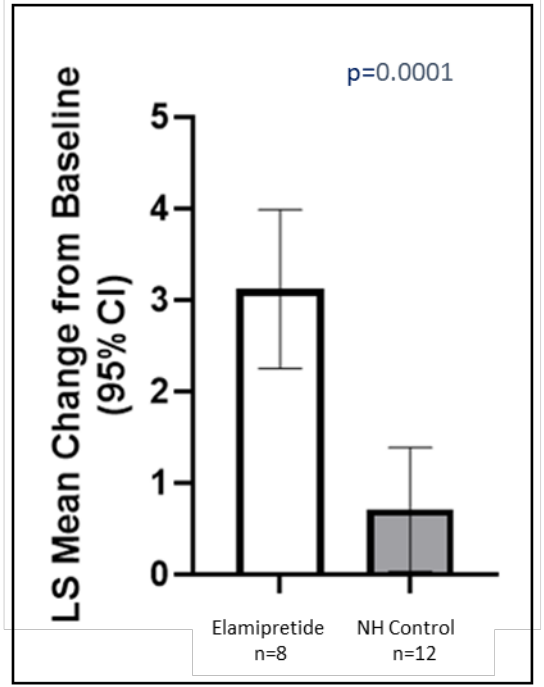
- Assesses health across multiple relevant assessments for complex, multisystem, chronic, rare diseases
- Prespecified 10% as clinically important change for each endpoint (6MWT, muscle strength, 5XSST, balance)
- 9-point scale from -4 (subjects declined by ≥10% on all 4 domains) to 4 (subjects improved by ≥10% on all domains)

MDRI at Week 64



W64 = W36 of TAZPOWER EXTENSION

MDRI at Week 76



W78 = W48 of TAZPOWER EXTENSION

^p≤0.00625 is significant with Bonferroni correction

Sensitivity Analyses Confirm Findings

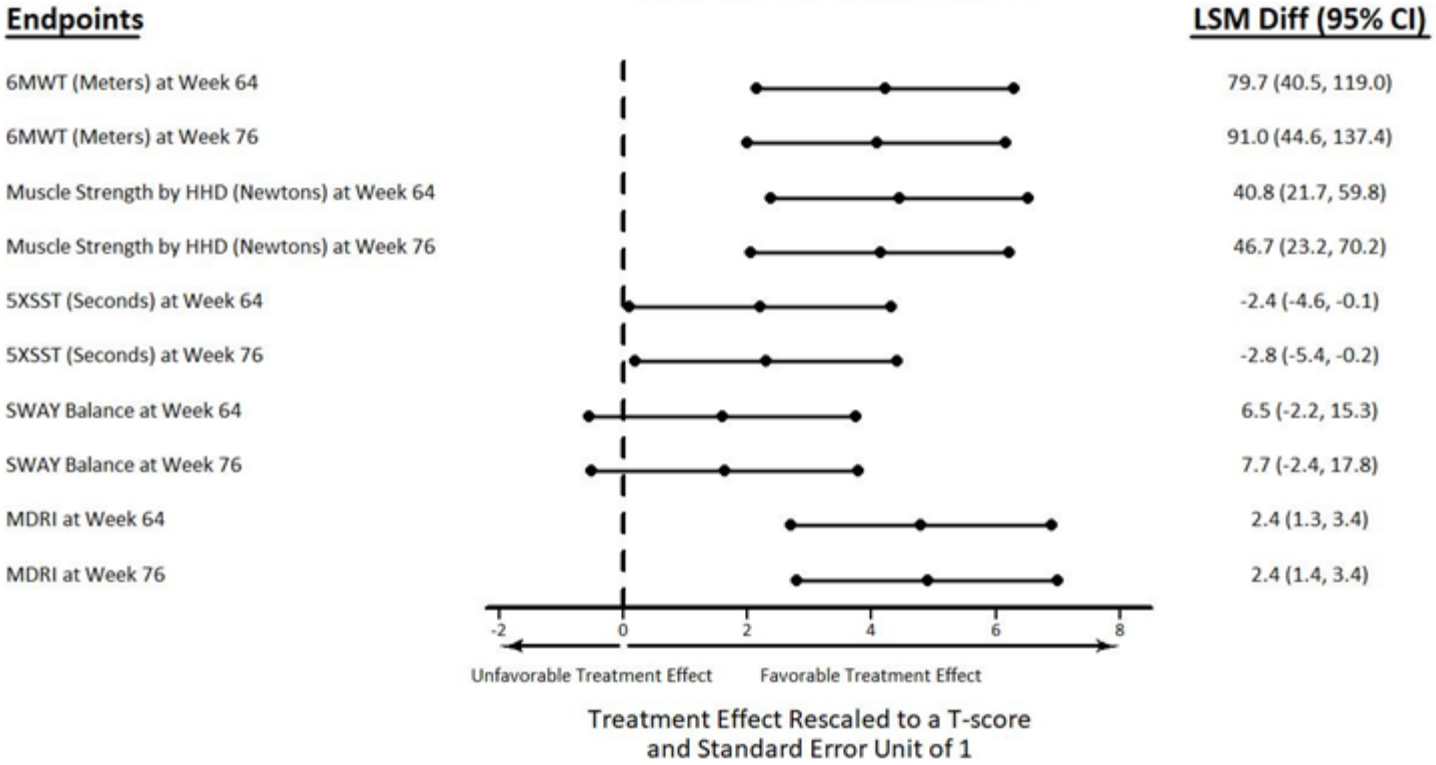
- *Conducted to "pressure test" the data, i.e., to confirm that a different or no propensity model, different patient variables or different timepoints would not change study conclusions*
- *Prespecified; jackknife and W100 conducted in response to FDA request*
- *All analyses for 6MWT confirmatory with p<0.001; similar findings for all other endpoints*

- ✓ Utilized alternative propensity model
- ✓ Replicated main analysis using unweighted propensity scores
- ✓ Removed the largest responder for each functional endpoint (jackknife resampling)
- ✓ Included 4 elamipretide-treated subjects who discontinued from/did not continue into TAZPOWER Extension
- ✓ Assessed additional timepoints (including W100 at FDA request)

Results Uniformly Favor Treatment

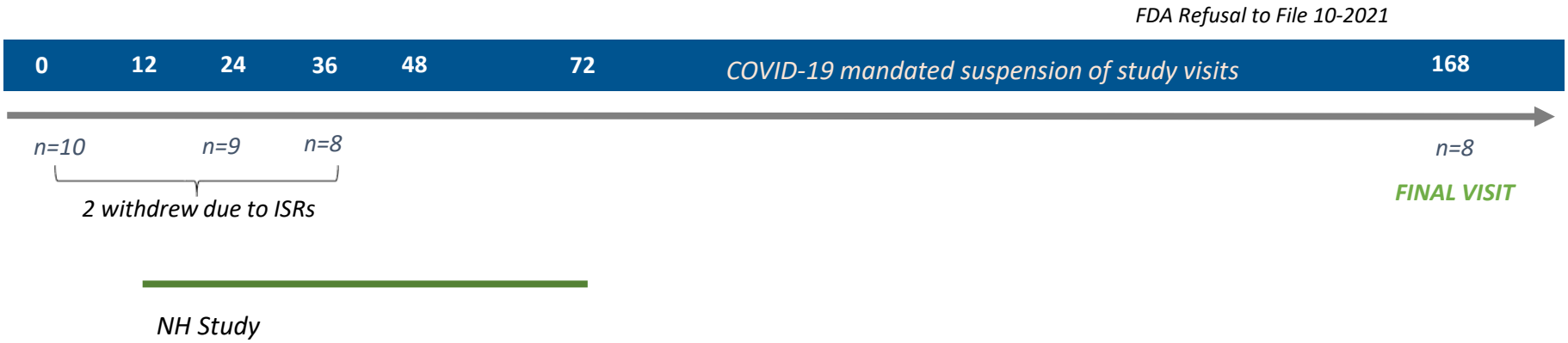
Phase 3 NH Study: All Endpoints Favored Elamipretide

Summary of Treatment Effect

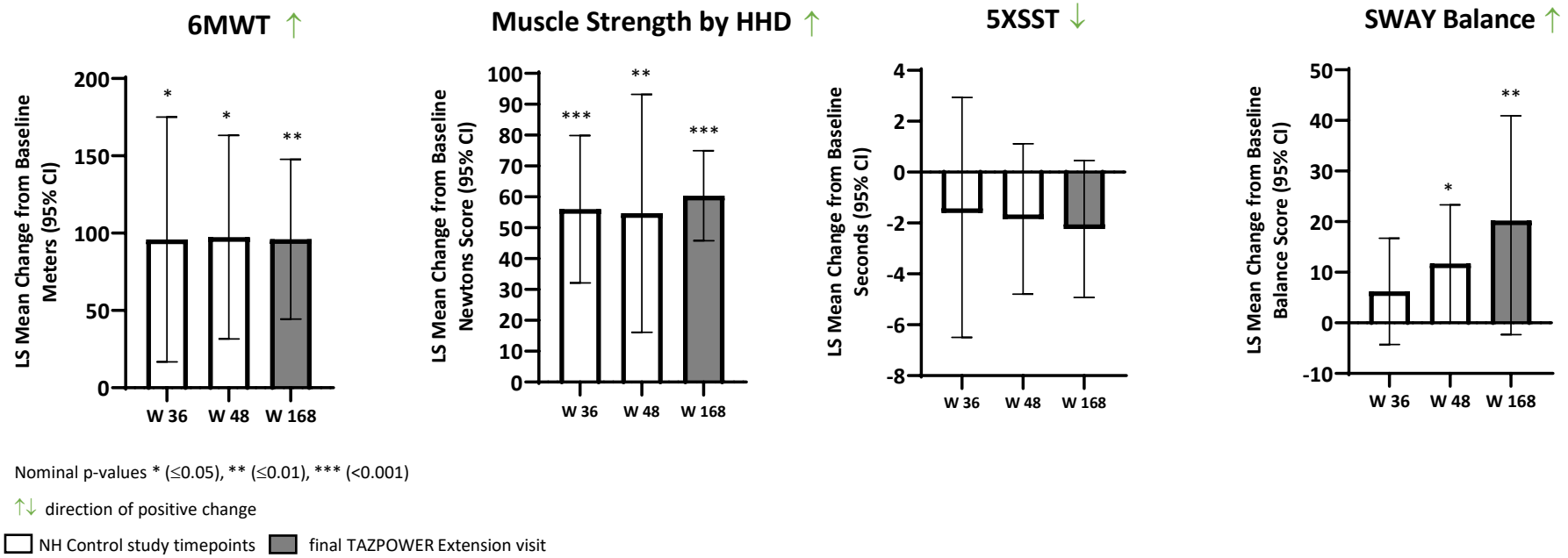


TAZPOWER EXTENSION

(SPIBA-201 P2)



Durable Functional Improvements



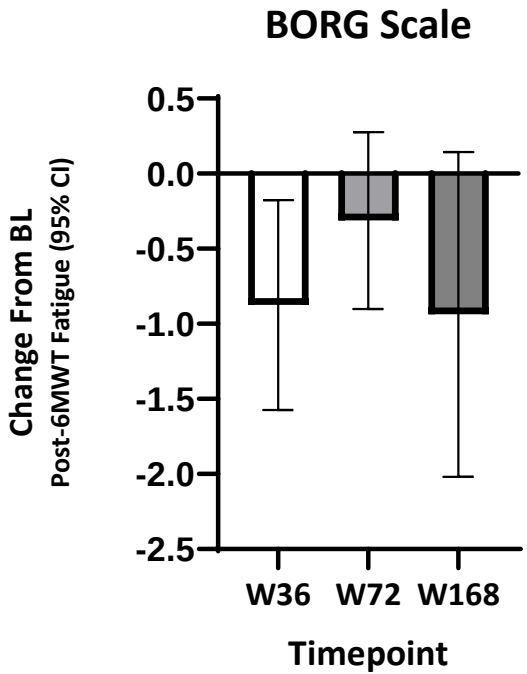
Nominal p-values * (≤0.05), ** (≤0.01), *** (<0.001)

↑↓ direction of positive change

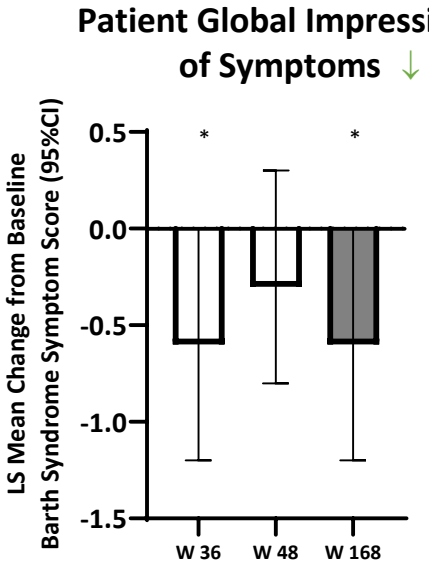
NH Control study timepoints final TAZPOWER Extension visit

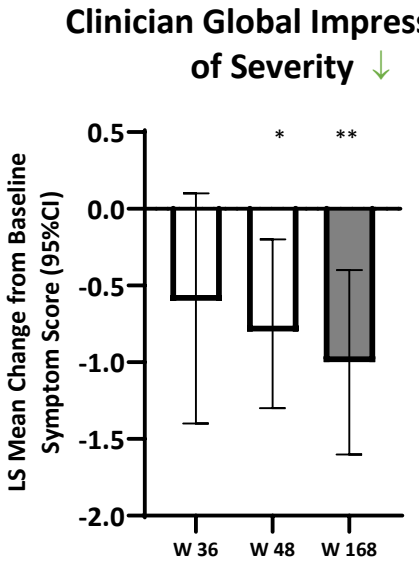
Post-exertional Fatigue ↓

- Assessed pre- and post-exertional fatigue on 0-10 scale
- Despite increase in walk distance, fatigue did not increase (trend to decrease)



Durable Symptom Improvements ↓





Nominal p-values * (≤0.05), ** (≤0.01)

↑↓ direction of positive change

Functional Improvements Exceed "Placebo Effect"

- 6MWT is only functional endpoint on which any "placebo response," which was within observed pretreatment values, was observed during TAZPOWER
- On all endpoints, long-term therapy in TAZPOWER Extension overcame placebo response with improvements wholly unpredicted by NH of disease

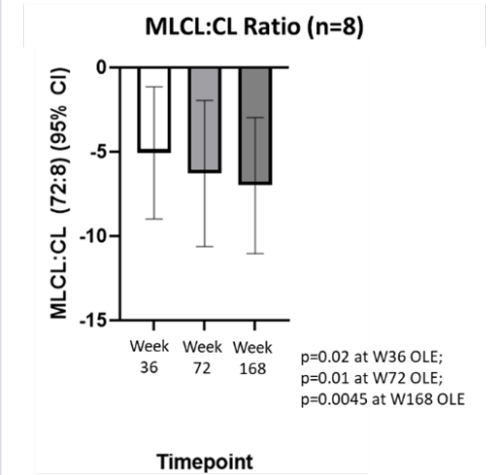
TAZPOWER Extension changes versus TAZPOWER placebo effect (n=8)

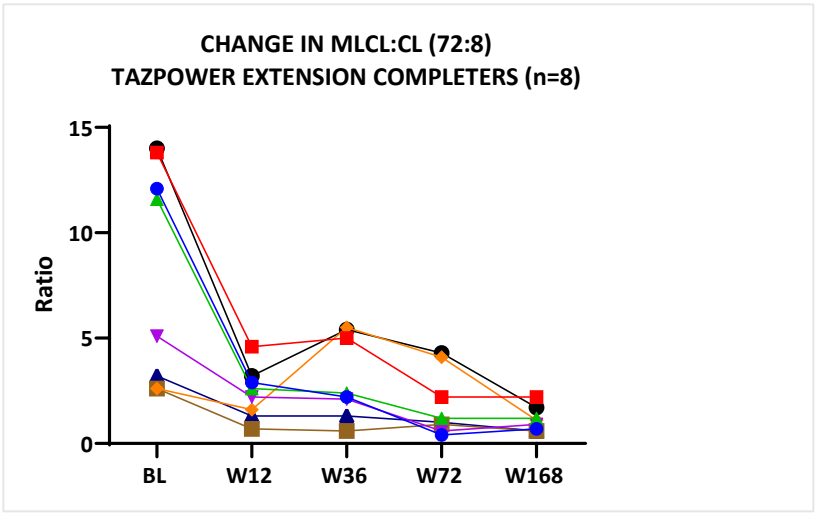
Endpoint	Δ 6MWT ↑		Δ SWAY ↑		Δ Muscle HHD ↑		Δ 5XSST ↓	
Treatment Timepoint	Placebo TAZPOWER	Elam W168	Placebo TAZPOWER	Elam W168	Placebo TAZPOWER	Elam W168	Placebo TAZPOWER	Elam W168
Mean	31.3	96.1	-0.9	20.2	2.3	60.3	-0.2	-2.2

↑↓ denotes direction of positive change
Δ denotes change from BL

Cardiolipin Ratios ↓

- Molecular abnormality associated with disease severity
- No change observed in natural course of disease





MLCL:CL (72:8) ratio shown; Error bars are confidence intervals

Nominally significant improvements observed by W12 (p<0.001), after 24-weeks of drug exposure, corresponding to time course for functional improvements. This molecular abnormality has been associated with disease severity

Unexpected Discovery of Intermediate Cardiac Phenotype

Observed changes in LV volumes prompted further interrogation of BL cardiac parameters

9 of 12 TAZPOWER subjects were diagnosed with cardiomyopathy in their first 18-months of life

Parameter*	**Unit**	**TAZPOWER BL** Mean (SD)
(3D) LV EDV z-score		-2.07 (1.36)
(3D) LV ESV z-score		-1.84 (0.97)
(3D) LV SV z-score		-1.93 (1.52)
(2D) LV mass z-score		-0.37 (0.90)
(3D) LV EF	%	61.12 (4.19)
(2D) GLS triplane	%	-19.82 (1.69)
HS-Troponin 1	ug/L	0.01 (0.007)
NT pro-BNP	pmol/L	12.18 (6.27)

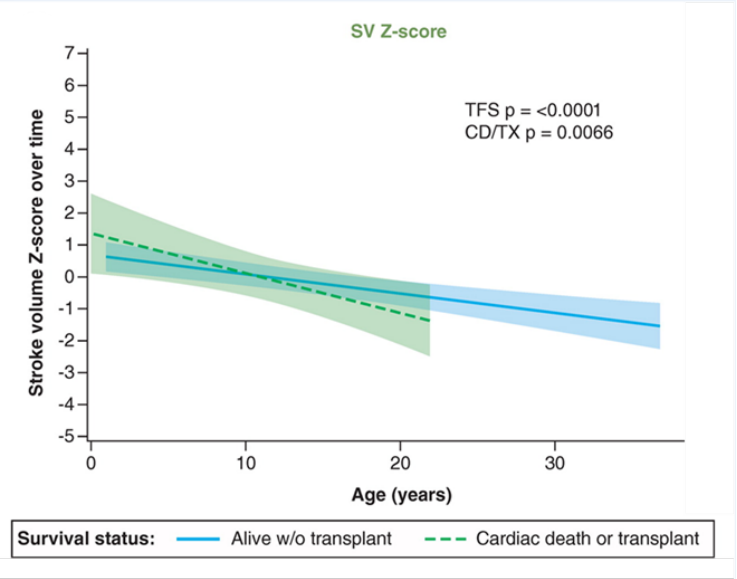
* NOTE: LV volume analysis n=12; all other parameters shown are n=10 TAZPOWER Extension participants

Hypertrophic-like Cardiac Phenotype

Common to Mitochondrial Cardiomyopathies

*"Mitochondrial cardiomyopathy most frequently causes non-obstructive hypertrophic cardiomyopathy and heart failure with preserved ejection fraction. Usually, late in the course of the condition, ventricular dilatation with reduced ejection fraction, leading to dilated cardiomyopathy, may occur."^*

- Barth syndrome cardiomyopathy is known to be undulating; ventricular dilatation can occur early (infancy) or late in the disease
- Survivors of early childhood may undergo hypertrophic remodeling, potentially to facilitate glycolysis
- Longitudinal analysis of n=44 BTHS subjects followed up to 15 years shows progressive + significant decline in LV volumes + internal diameter with age, with associated significant decline in LV SV, LV global longitudinal strain, right ventricular fractional area of change + septal E:e but no change in LVEF + LV fractional shortening

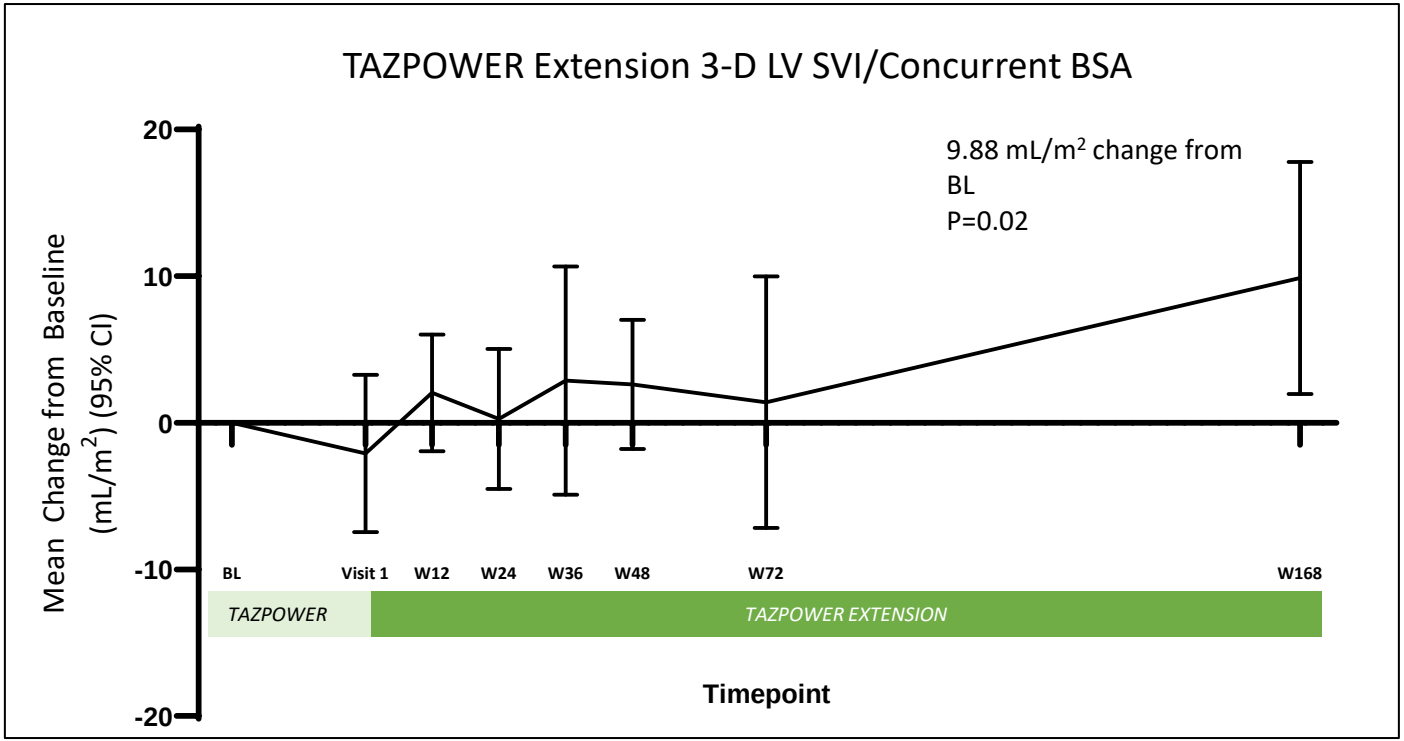


Sabbah, 2023; Chowdhury, 2022

^ Eugene Braunwald, Mitochondrial cardiomyopathy: a fertile field for research, European Heart Journal, Volume 44, Issue 26, 7 July 2023, Pages 2361–2362, https://doi.org/10.1093/eurheartj/ehad177

LV SVI ↑

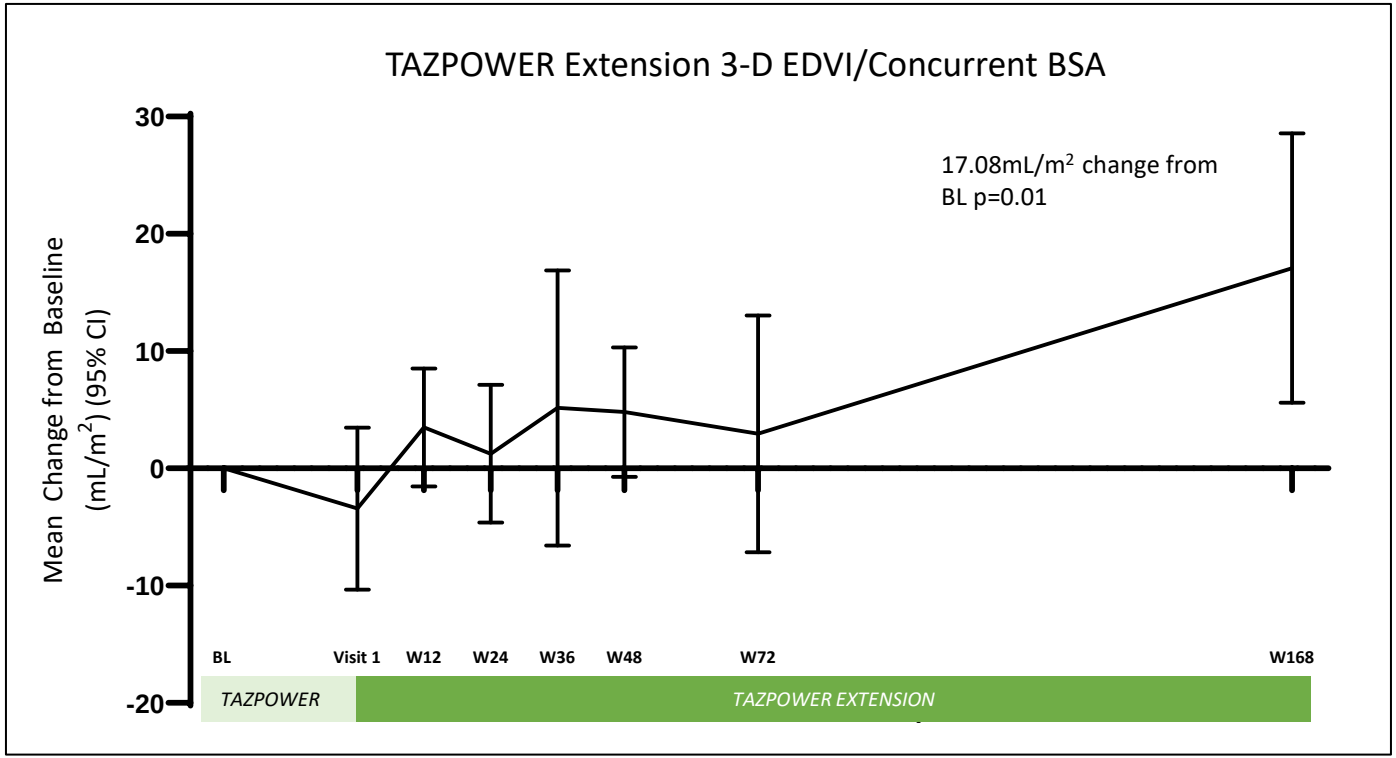
- ✓ Z-scores normalized *(BL -1.93; W168 -0.89)*
- ✓ Durable signal at W96 + W192 for 3 subjects who completed those visits
- ✓ Positive slope of change observed by W36
- ✓ Independent echo overread (Tufts) confirmed signal
- ✓ Contrary to NH which predicts continued decline



Indexed to concurrent BSA post-hoc at FDA request; pre-specified analysis indexed to BL BSA.
n=10 BL, Visit 1, W12; n=9 W24; n=8 W36-168

LV EDVI ↑

- ✓ Z-scores normalized *(BL -1.59; W168 –0.46)*
- ✓ Durable signal at W96 + W192 for 3 subjects who completed those visits
- ✓ Positive slope of change observed by W36
- ✓ Independent echo overread (Tufts) confirmed signal
- ✓ Contrary to NH which predicts continued decline



n=10 at BL, Visit 1, W12; n=9 W24; n=8 W36-168
Indexing to concurrent BSA, z-score analysis + scrambled echo overreads conducted post-hoc at FDA request

Improved LV Structure + Function

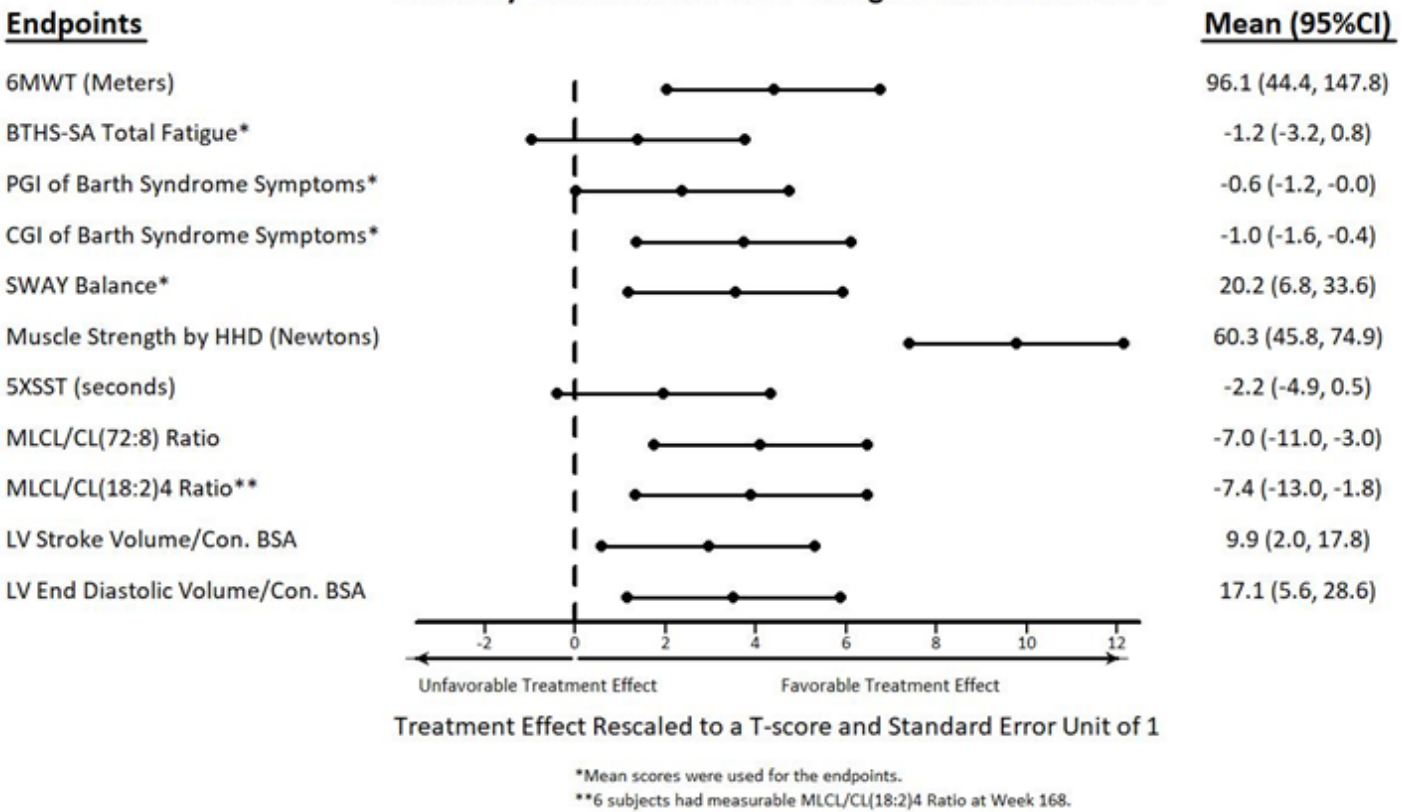
Parameter*	Unit	TAZPOWER BL Mean (SD)	TAZPOWER Extension W168 Mean (SD)
(3D) LV EDV z-score		-2.07 (1.36)	-1.16 (2.16)
(3D) LV ESV z-score		-1.84 (0.97)	-1.20 (1.74)
(3D) LV SV z-score		-1.93 (1.52)	-0.86 (0.53)
(2D) LV mass z-score		-0.37 (0.90)	-0.10 (0.59)
(3D) LV EF	%	61.12 (4.19)	61.9 (3.40)
(2D) GLS triplane	%	-19.82 (1.69)	-18.99 (2.03)
HS-Troponin 1	ug/L	0.01 (0.007)	0.009 (0.00)
NT pro-BNP	pmol/L	12.18 (6.27)	15.96 (15.28)

* NOTE: LV volume analysis n=12 at BL, n=2 at TAZPOWER final visit, n=2 at early termination visit, n=8 at TAZPOWER Extension W168; all other parameters shown are n=10 at BL, n=8 at W168

Results Uniformly Favor Treatment

TAZPOWER Extension Study Week 168

Summary of Treatment Effect Change from Baseline: N=8



Treatment Effect Rescaled to a T-score and Standard Error Unit of 1

*Mean scores were used for the endpoints.
**6 subjects had measurable MLCL/CL(18:2)4 Ratio at Week 168.

Data Support a Finding of Efficacy

- **Molecular improvements** in pathognomonic abnormal cardiolipin ratio
- **Functional improvements** in endurance + strength were large, clinically meaningful + durable
- **Patient + clinician reported improvements** in severity of disease symptoms support the meaningfulness of functional improvements
- **Cardiac improvements** in LV volumes likely contributed to functional recovery
- In all respects, these findings go against the well-established + well-understood trajectory of this disease

Agenda

Introduction	**Reenie McCarthy** *Chief Executive Officer* *Stealth BioTherapeutics*
Urgency of Unmet Need + Benefit:Risk Tolerance	**Kate McCurdy, MBA** *Chair, Board of Directors* *Barth Syndrome Foundation*
Disease + Natural History Cohort	**Hilary Vernon, MD, PhD** *Professor of Medical Genetics* *Johns Hopkins University School of Medicine*
Safety + Efficacy	**Jim Carr, PharmD** *Chief Clinical Development Officer* *Stealth BioTherapeutics*
Statistical Perspectives	**Janet Wittes, PhD** *Wittes LLC*
Expanded Access Program	**Kathryn Chatfield, MD, PhD** *Associate Professor of Pediatrics-Cardiology* *Director, Cardiac Genetics Clinic, Children's Hospital Colorado*
Closing Remarks	**Reenie McCarthy** *Chief Executive Officer* *Stealth BioTherapeutics*

Statistical Perspectives

Janet Wittes, PhD

Disclosure

Consultant for Stealth BioTherapeutics

Statistical Principles Affecting Study Design for Rare Cardiac Conditions- CVCT 2022

Used Barth syndrome as the main example for the question: “how do you study this type of disease?”

- For an ultra-rare disease our choices are:
  - randomized controlled study with low power
    - check EACH observation before you unblind
  - historical control; higher power, but potential bias
    - use models (but prespecify)
  - other designs (crossover, n of one)

Key consideration in designing historical control trials is minimizing risk of bias

Strategies to Reduce Bias

Comparison of contemporaneous datasets - no change in standard of care

- NH data collected 2012-2019; interventional data collected 2017-2019

Consistency in data collection team and methods

- In both natural history (NH) and interventional study, same
  - Investigator
  - Physiotherapist
  - Standardized protocol to conduct all assessments
    - All functional tests from the NH database were assessed as endpoints

Firewalled analysis teams

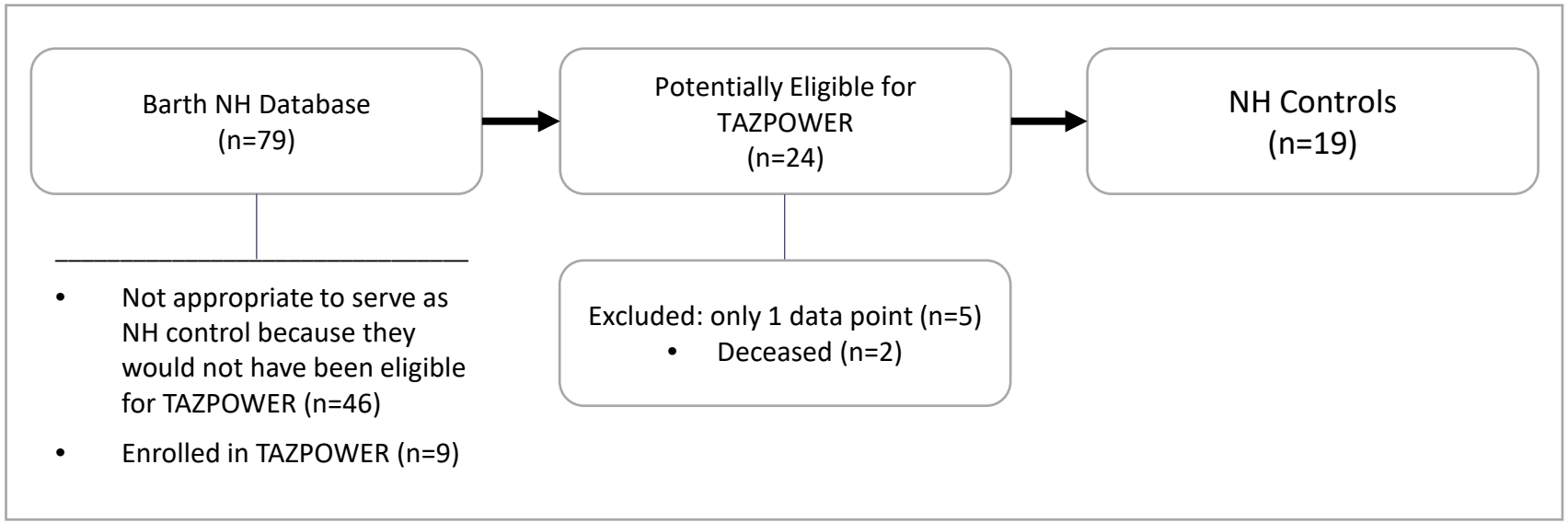
- Team building propensity model had no access to post-baseline data
- Team developing the SAP had no access to NH data

Clear inclusion criteria to reduce selection bias

Sensitivity analyses

- Aggressive kicking the tires

Natural History Controls Similar to Treated Patients



The natural history controls comprise a high percentage of patients who could have been used for comparison to the treated population

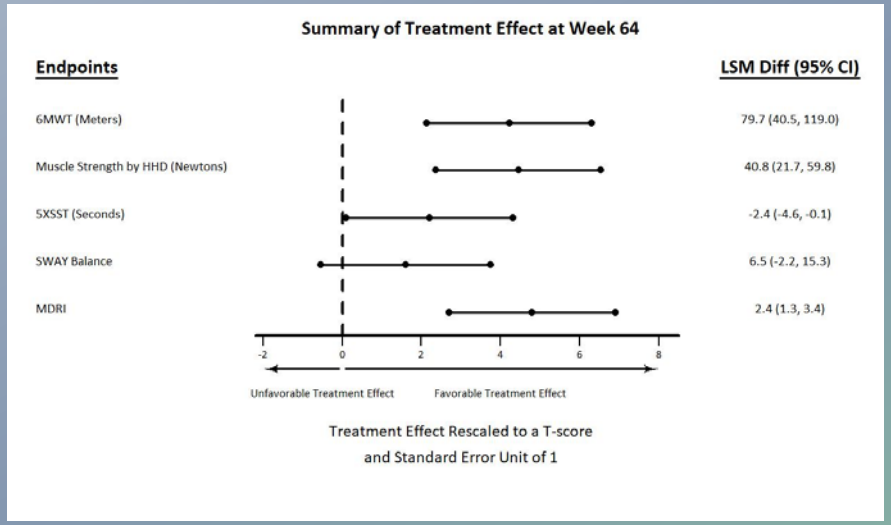
Treated and untreated have similar baseline characteristics

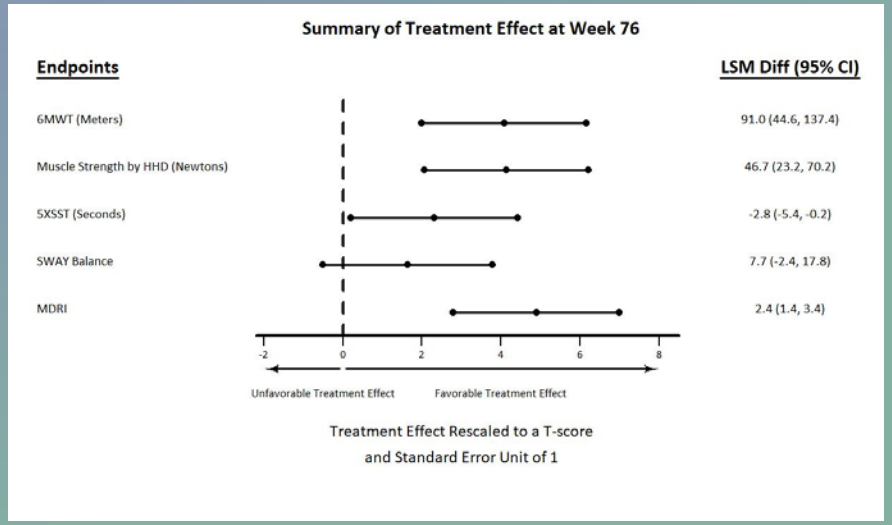
Every Statistical Analysis Shows a Similar Story

Many sensitivity analyses support the conclusions

- ✓ Explored various propensity models
- ✓ Performed jackknife resampling to exclude the subject with the most favorable treatment response on each functional endpoint
- ✓ Assessed additional timepoints (i.e., Week 40, Week 52, and Week 100)
- ✓ Analyses using actual vs interpolated data- increases estimated effects at primary timepoints
- ✓ Analysis of 6MWT using screening AND actual values for treated cohort shows smaller but statistically significant benefit of elamipretide vs. natural history controls

Concordance of Evidence





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Expanded Access Program

Kathryn Chatfield, MD, PhD

Associate Professor of Pediatrics-Cardiology

Director, Cardiac Genetics Clinic, Children's Hospital Colorado

Background

- MD/PhD Dartmouth Medical School/Dartmouth College, PhD in Pharmacology/Toxicology
- Combined residency in pediatrics and clinical genetics, Children's Hospital of Philadelphia, Instructor appointment at University of Pennsylvania
- Fellowship in pediatric cardiology at University of Colorado School of Medicine/ Children's Hospital Colorado
- Board Certified in Pediatrics, Pediatric Cardiology (ABP) and Clinical Genetics (ABMGG)
- Joined faculty at University of Colorado Anschutz Medical Campus in 2013
- Started the Cardiovascular Genetics program at Children's Hospital Colorado
- Staff Attending physician on the Advanced Heart Failure and Heart Transplant service, Children's Hospital Colorado (Advanced heart failure includes management of patients on ventricular assist devices)

Relevant Disclosures

- NIH funded, study of metabolic alterations in pediatric forms of heart failure.
- Previously funded by the Barth Syndrome Foundation
- Referred two TAZPOWER participants to Dr. Vernon, JHU for trial screening/participation
- Research support from Stealth BioTherapeutics.
- Compensated by Stealth BioTherapeutics for time and travel incurred for this meeting

Experience with Dilated Cardiomyopathy in Expanded Access Program

- Cardiomyopathy in Barth syndrome is attributable to mitochondrial dysfunction. No matter how the structure and function of the heart remodels and adjusts to address that dysfunction, and this can be an undulating process in Barth syndrome, the underlying pathology is a mitochondrial pathology due to severe cardiolipin deficit
- Cardiomyopathy has an undulating course in Barth syndrome. Severe dilated cardiomyopathy may be observed in both infancy and adulthood. For survivors, the heart appears to compensate with hypertrophic remodeling, which may reverse abruptly at any time in life due to metabolic stress
- The TAZPOWER and TAZPOWER Extension studies enrolled children and young men ≥12-years-old. Recognizing the high unmet need also affecting younger children, we highlight several case study reports regarding the utility of elamipretide for the treatment of pediatric onset dilated cardiomyopathy in Barth syndrome.

Elamipretide Expanded Access Case Studies

Limited data may be derived from expanded access, pointing to the utility of a post-marketing registry

Newborn at Nationwide Children's with heart gallop, lactic acidosis and EF of ~20% unresponsive to medical management and diagnosed genetically with Barth syndrome. Elamipretide initiated at 3-weeks-old with EF unimproved on maximal medical therapy. With elamipretide, filgrastim, sacubitril/valsartan, carvedilol, and spironolactone, EF gradually improved to 45-55% and by 4-months the child was meeting developmental milestones. At 5.5-months, the child died with autopsy listing the cause of death as undetermined with other significant conditions: Barth syndrome, unsafe sleep environment, and Klebsiella pneumoniae bacteremia.[1]
11-mos-old male admitted to CHOP; EF <25%. ECMO and VAD instrumentation utilized. Elamipretide administered by hospital day 15 on top of standard of care. Heart function improved to extent VAD was explanted with native heart intact.[2]
Newborn at Mt Sinai; EF 19%. Elamipretide administered by 6-days-old on top of standard of care. After 72 days, improvements in clinical and cardiac parameters observed. At 4-months, EF stable in 40s and observed developmental progress; downgraded to 1b on transplant list. [3] The patient's EF is now 68%.
1-day-old male admitted to Children's Nebraska; EF 20%. Intubated and evaluated for LVAD and transplant. Elamipretide administered by 34-days-old on top of standard of care. At 6-mos and now post-discharge, LV within normal size and functioning normally. [4]
2-week-old male admitted to UCLA NICU. Team was concerned child would not survive wait to transplant. Administered elamipretide around 1-month-old on top of standard of care. Transplanted around 4-mos old and expected to be discharged on elamipretide. [5]

[1] Koenig et al., Use of Elamipretide in patients assigned treatment in the compassionate use program: Case series in pediatric patients with rare orphan diseases, JIMD Rep., Jan 2023;
[2] Goldstein et al., Expanded-Access Use of Elamipretide In a Critically Ill Patient with Barth Syndrome: A Case Report, Genetics in Medicine Open, 2024;
[3] Letter from Ibrahmi Elsharkawi, MD, Mt Sinai, to Robert Califf, MD and Aliza Thompson, MD (August 2024);
[4] Letter from Laura Ortmann, MD, Children's Nebraska, to Robert Califf, MD and Patrizia Cavazzoni, MD (September 2024);
[5] Letter from Nancy Halnon, MD to Patrizia Cavazzoni (September 6, 2024)

Elamipretide Case Study 2: VAD Explantation

- ~14% of affected individuals receive at least one heart transplant,[1] 29% of these utilize a ventricular assist device (VAD)and 5% utilize extracorporeal membrane oxygenation (ECMO)[2]
- There are no other known cases of myocardial recovery in children affected with Barth syndrome supported with a durable VAD
- A systematic review on the incidence of myocardial recovery in children with all indications supported with a durable VAD shows an overall incidence of 8.7% recovery
  (Rohde et al., Eur J Cardiothorac Surg. 2023 Aug 1)

[1] Clarke, S.L., Bowron, A., Gonzalez, I.L. et al. Barth syndrome. Orphanet J Rare Dis 8, 23 (2013). https://doi.org/10.1186/1750-1172-8-23
[2] Favorable outcomes after heart transplantation in Barth syndrome Li, Yu et al., The Journal of Heart and Lung Transplantation, Volume 40, Issue 10, 1191 - 1198

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Closing Remarks

Reenie McCarthy
Chief Executive Officer
Stealth BioTherapeutics

Supports Favorable Benefit:Risk Determination

✓ **Safety**

- No material safety concerns identified
- FDA consistently approves expanded access for the most vulnerable of patients

✓ **Efficacy**

- Molecular physiology: Significant improvements in abnormal cardiolipin ratios central to disease pathology
- Function: Large + durable improvements in exercise tolerance, muscle strength + balance
- Feel: Patients + the clinician reported significant lessening of severity of symptoms; patients + their caregivers reported meaningful improvements in activities of daily living
- Cardiac physiology: Improvements in LV volumes which were associated with functional improvements

REGULATORY STANDARD

- Requires *broadest flexibility*
- Recognizes physicians + patients are willing to accept greater risks
- Recognizes that the benefits of a drug need to be evaluated in light of the severity of the disease being treated
- Refers to information that experts would find compelling

Title 21 Food and Drugs Subpart E

Recap of Statistical Concerns and Further Insights

Statistical Concerns	Further Insights
Selection Bias in the NH Cohort	• NH control cohort uses nearly all patients who could have enrolled in TAZPOWER • No evidence the excluded 5 patients who had no longitudinal data were doing better (2 passed away)
Placebo response for 6MWT	• Appears to be associated with increased fatigue; post-baseline values do not exceed screening values • Analyses using screening 6MWT values preserves clinically relevant benefit and is statistically significant • No placebo effect on other functional endpoints
Propensity score model development process	• Propensity score development team had no access to longitudinal data • Followed a pre-specified process that protected against bias
Imputation	• Observed values tend to be higher than interpolated for TAZPOWER subjects • In the NH cohort, the average trend is flat • Analysis at week 100, using actual data for both groups, confirms the effect

Questions for Your Consideration

TAZPOWER Extension (SPIBA-201 Part 2)

Improvements from BL on all domains

- ✓ 6MWT - >25% improved from BL
  - *Improved from both screening + BL*
- ✓ Muscle strength - >45% improved from BL
- ✓ 5XSST – directionally improved
- ✓ SWAY balance - >45% improved from BL
- ✓ Echocardiography – z-scores normalized
- ✓ BTHS-Total Fatigue – directionally improved
- ✓ PGI-S - improved
- ✓ CGI-S - improved

NH Control study (SPIBA-001)

Improvements unexpected in NH

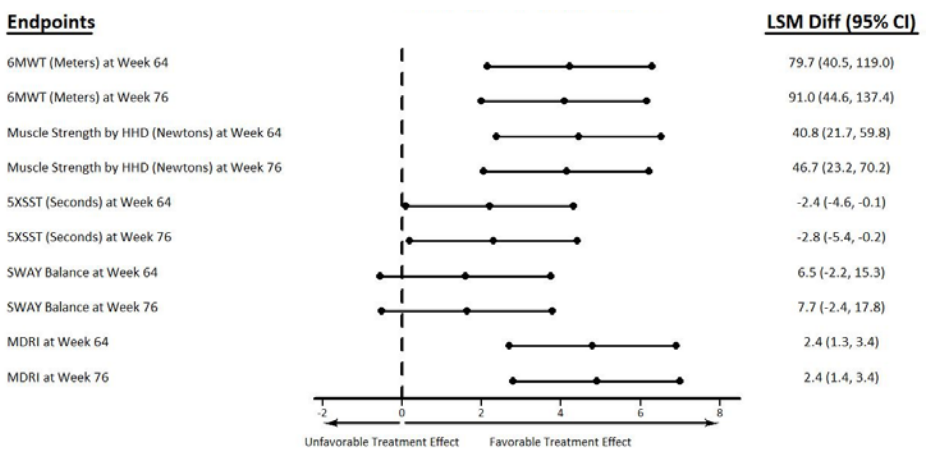
- ✓ 6MWT - >90% improved vs NH controls
- ✓ Muscle strength - >90% improved vs NH controls
- ✓ 5XSST - improved
- ✓ SWAY balance - directionally improved
- ✓ MDRI - >80% improved vs NH controls
- ✓ Echocardiography – supportive of TAZPOWER Extension findings

✓ *Consistent with findings in nPMM + across nonclinical models*

Totality of the Evidence Favors Treatment

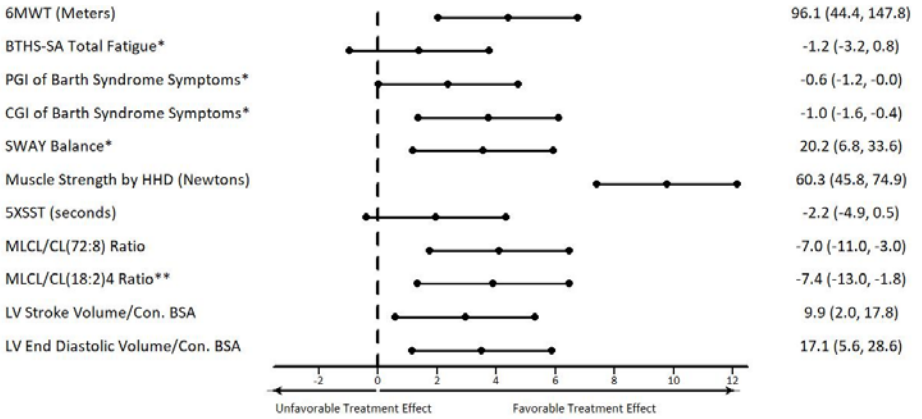
Phase 3 NH Study: All Endpoints Favored Elamipretide

Summary of Treatment Effect



TAZPOWER Extension Study Week 168

Summary of Treatment Effect Change from Baseline: N=8



*Mean scores were used for the endpoints.

**6 subjects had measurable MLCL/CL(18:2)4 Ratio at Week 168.

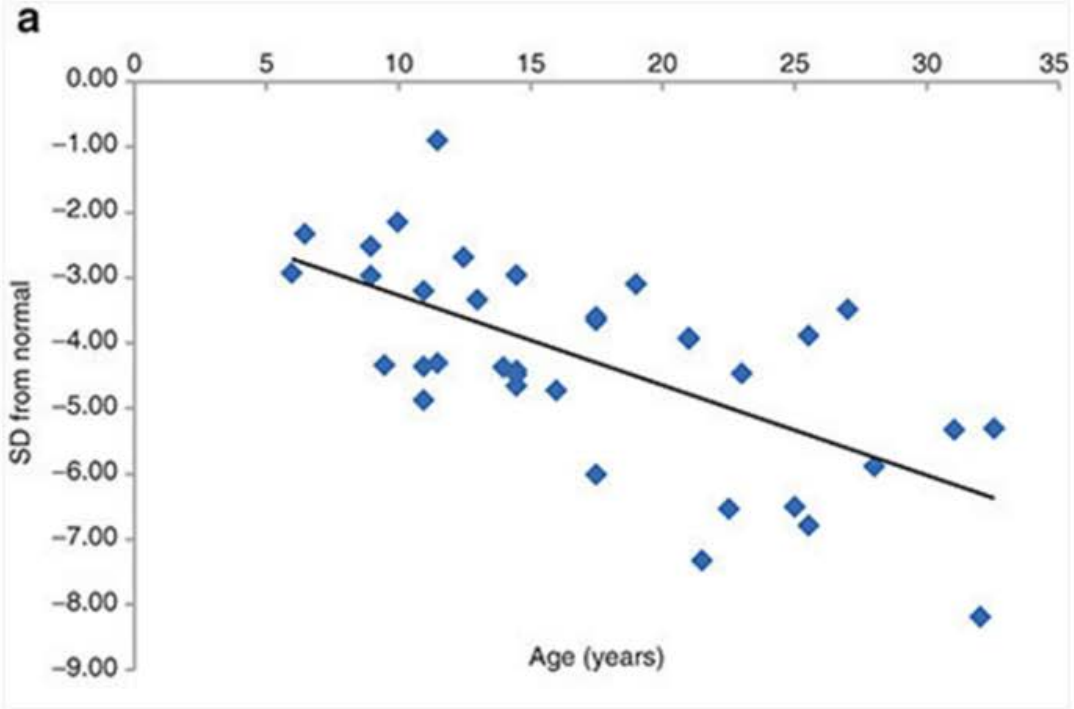
The Need for an Approved Therapy is Urgent Now

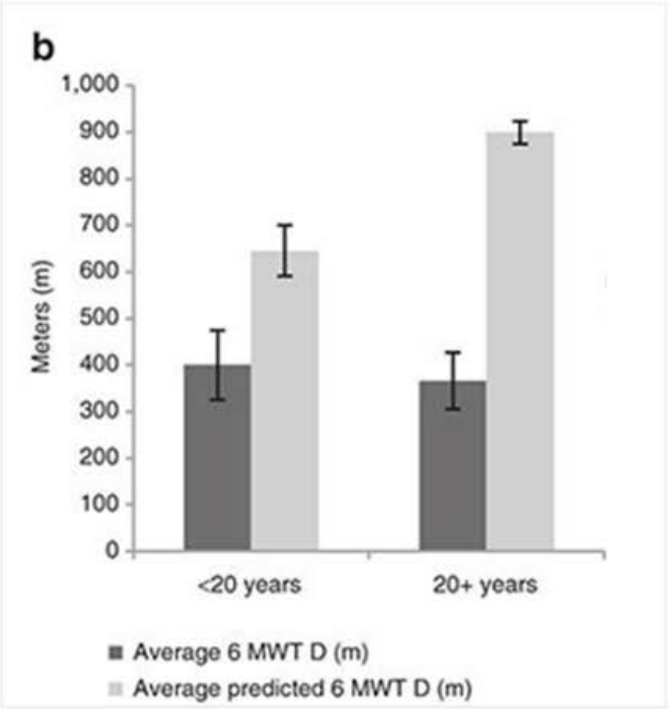
- Children + young men are leading lives significantly limited by this devastating disease.
- There are no therapies approved or even in clinical development for Barth syndrome. Given the ultra-rare nature of the disease, it would take many years to recruit + conduct additional studies even if other potential therapies were available + even assuming powering considerations will not preclude investigation. We have committed to further research through a proposed post-marketing Disease Monitoring Program.
- We ask you to conclude that, based on the totality of the evidence we have shared, the benefit of elamipretide outweighs the risks, supporting approval of elamipretide for Barth syndrome.

Thank you

Backup Slides Shown

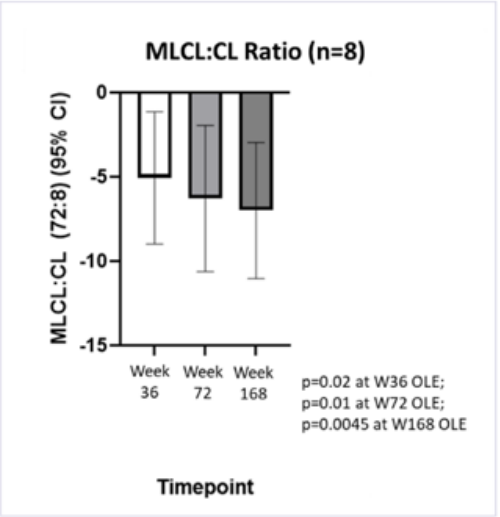
Figure 7: Barth Syndrome (a) 6MWT Standard Deviation from Normal Controls and (b) Average 6MWT Distance versus Predicted Distance

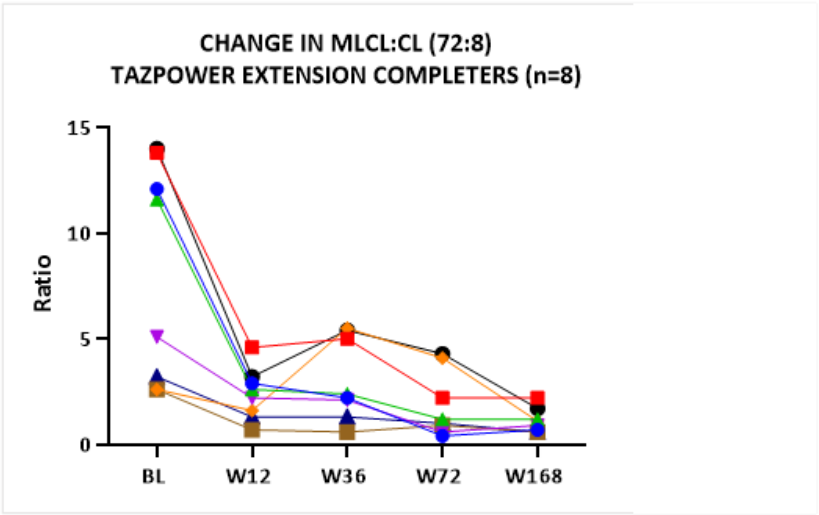




Cardiolipin Ratios ↓

- Molecular abnormality associated with disease severity
- No change observed in natural course of disease



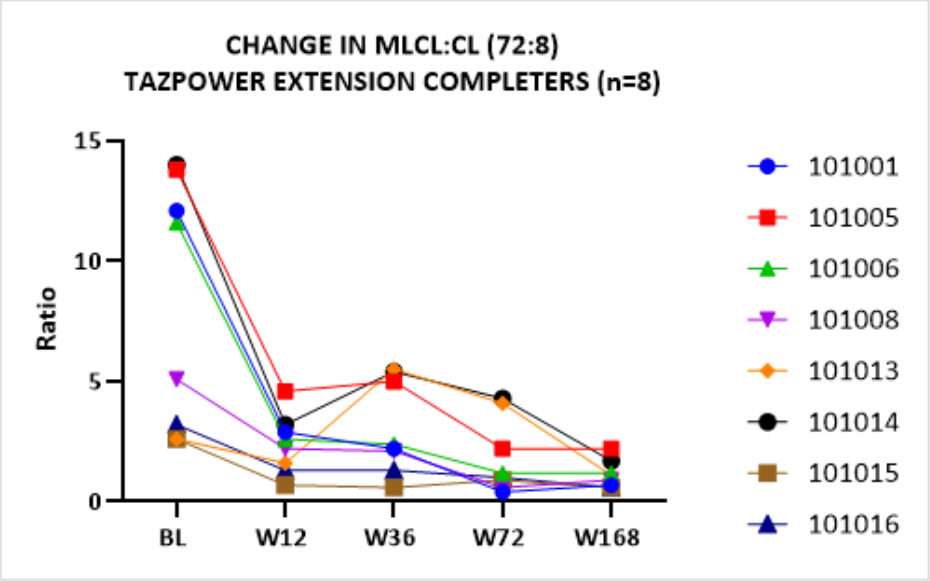


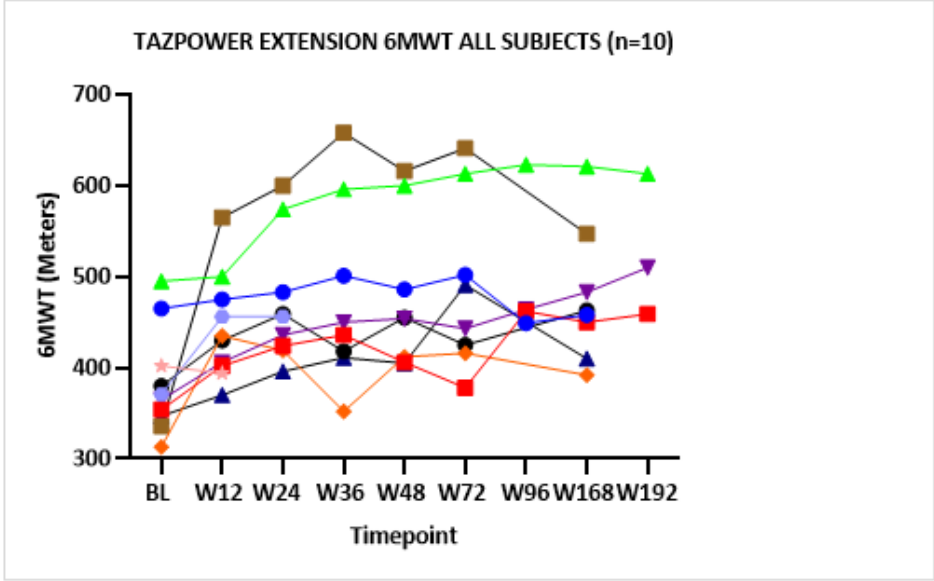
MLCL:CL (72:8) ratio shown; Error bars are confidence intervals

Nominally significant improvements observed by W12 (p<0.001), after 24-weeks of drug exposure, corresponding to time course for functional improvements. This molecular abnormality has been associated with disease severity

Changes Observed After 24-weeks Exposure to Drug

(W12 of TAZPOWER Extension + 12 weeks exposure during TAZPOWER)





6MWT Change from Baseline at Week 100 using only Actual Data

Time Point[1]	Treatment Cohort	
	TRTS	**UNTS[2]**
	(N=8)	**(N=15)**
Baseline		
Mean (SD)	381.9 (64.18)	389.7 (72.70)
Week 100[2]		
Mean (SD)	488.6 (94.50)	380.3 (67.05)
Change from Baseline at Week 100		
Mean (SD)	106.8 (90.38)	-9.5 (47.05)
LS Mean (SE)[3]	107.3 (24.29)	-9.7 (17.55)
95% CI	56.09, 158.59	
LSM Diff (SE)[3]	117.1 (30.43)	
95% CI	52.92, 181.35	
p-value	0.0013	

6MWT Change from Screening at Week 100 using Only Actual Data

Table 6. Total Distance Walked (m) in 6MWT and Change from Screening Based on Observed Values (NH Evaluable Set; Sensitivity Analysis 5)

Time Point[1]	Treatment Cohort	
	TRTS (N=8)	UNTS[2] (N=15)
Screening		
Mean (SD)	435.0 (59.83)	389.7 (72.70)
Week 100[2]		
Mean (SD)	488.6 (94.50)	380.3 (67.05)
Change from Screening at Week 100		
Mean (SD)	53.6 (83.15)	-9.5 (47.05)
LS Mean (SE)[3]	61.4 (24.23)	-13.6 (17.28)
95% CI	10.24, 112.48	-50.06, 22.86
LSM Diff (SE)[3]	75.0 (30.79)	
95% CI	10.0, 139.9	
p-value	0.0262	

SPIBA-201 6MWT by Sequence