TAZPOWER: Results of a Randomized, Double-Blind, Placebo-Controlled, Crossover and Open-Label Extension Trial of Elamipretide in Barth Syndrome

Hilary Vernon, MD, PhD[1], Brittany DeCroes Hornby, PT, DPT, PCS[2], William Reid Thompson, III, MD[3], Anthony Aiudi, PharmD[4], John J. Jones, PharmD[4], Jim Carr, PharmD[4]

[1]McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine and at the Kennedy Krieger Institute; Director, Barth Syndrome Clinic at Kennedy Krieger Institute, Baltimore, MD; [2]Department of Physical Therapy, Kennedy Krieger Institute; [3]Division of Pediatric Cardiology, Department of Pediatrics, Johns Hopkins University School of Medicine; [4]Stealth BioTherapeutics, Newton, MA

INTRODUCTION

- Barth syndrome (BTHS) is a rare, X-linked infantile-onset disease caused by defects in the TAZ gene that encodes Tafazzin, a transacylase that is responsible for the final remodeling step from immature cardiolipin (MLCL) to mature cardiolipin (L4-CL)
- Tafazzin deficiency results in abnormal MLCL:L4-CL ratio
- Mature CL is critical to normal mitochondrial function and ATP generation
- Clinical presentation of BTHS is typically characterized by cardiomyopathy, skeletal myopathy, neutropenia, and growth abnormalities
- Increasing MLCL:L4-CL is correlated with increasing left ventricular mass, and inversely correlated with the distance walked on the 6MWT
- TAZPOWER is the first clinical trial to evaluate the efficacy/safety of a therapeutic agent in BTHS patients

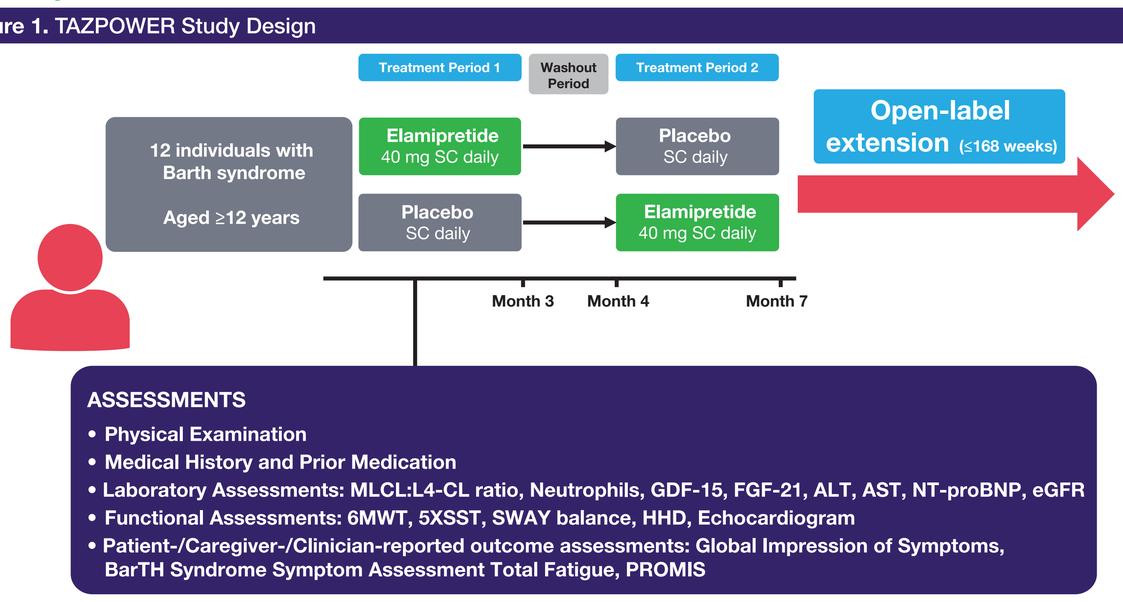
OBJECTIVE

- To measure efficacy through functional and patient-reported outcome assessments and safety/tolerability through adverse events (AEs), clinical data, and laboratory tests
- Subgroup analyses will be conducted to evaluate the potential clinical impact of differences in the immature CL to mature CL (MLCL:L4-CL) ratio

METHODS

Study Design

Figure 1. TAZPOWER Study Design



Key Inclusion Criteria

- Patients ≥12 years of age were required to have genetically confirmed BTHS, to be ambulatory but impaired as assessed by the 6MWT, and on stable medications

Key Exclusion Criteria

- Patients were excluded if they had been hospitalized within 30 days, had uncontrolled hypertension, a history of heart transplantation, or implantation of a cardioverter defibrillator within 3 months or expected implantation during the study

Additional Analyses

- Subgroup analyses based on screening MLCL:L4-CL ratio will be conducted with subgroups delineated by the median MLCL:L4-CL ratio
- Patient Perception of Change (PPC) and Caregiver Perception of Change (CPC) Video Assessments
  - A prospectively defined video protocol to collect evidence of clinical meaningfulness to patients

RESULTS

Patient Demographics

- A total of 12 patients were randomized into the trial

Table 1. TAZPOWER Patient Demographics (N=12)

Demographic Variable	Demographic Result
Mean Age (years), (Range)	19.5 (12-35)
Male (n)	12
Race (n) White Multiracial	 11 1
Ethnicity (n) Not Hispanic or Latino Hispanic or Latino	 12 0
Mean Height (cm)	167.3 (150.4-187.7)
Mean Weight (kg)	50.84 (31.4-85.9)
BMI (kg/m^2)	17.6 (13.6-24.4)
Mean 6MWT (meters)	395.5
Mean BTHS-SA Total Fatigue	8.0
Median MLCL:L4-CL ratio	17.3

Efficacy

Blinded Trial Results

- At the end of the double-blind phase of the TAZPOWER trial, statistical significance was not achieved in the ITT population on the primary endpoints. However, a pre-specified analysis of those subjects with lower MLCL:L4-CL ratios showed improvement on several endpoints
- A total of 10 patients elected to continue into the TAZPOWER Open Label Extension portion of the trial, which is currently ongoing

Open-Label Extension Results (OLE)

Table 2. TAZPOWER OLE: Mean Change in 6MWT Distance (meters) from Baseline

Weeks Completed	n	OLE Week 12 Visit	OLE Week 24 Visit	OLE Week 36 Visit
12	10	60.5		
24	7*	58.0	90.0	
36	4	26.0	59.5	76.0

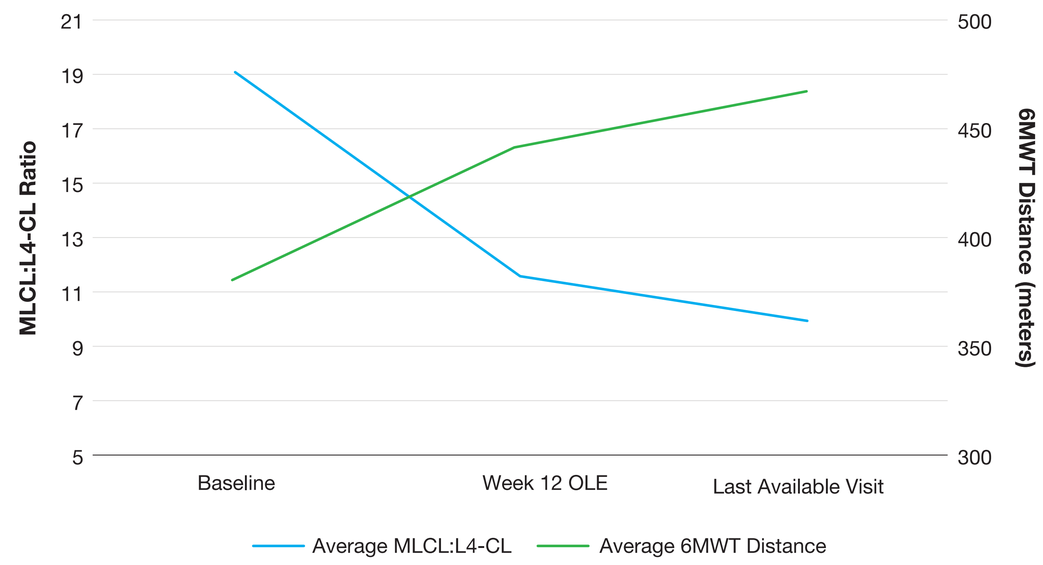
*One subject not included due to cessation of study drug after OLE Week 12 Visit.

Table 3. TAZPOWER OLE: Mean Change in 6MWT by MLCL:L4-CL Ratio Subgroup

Change in 6MWT Distance (meters) from Baseline							
High Ratio Patients (MLCL:L4-CL ≥ 17.3)				Low Ratio Patients (MLCL:L4-CL < 17.3)			
n	Week 12	Week 24	Week 36	n	Week 12	Week 24	Week 36
5	28.2			5	92.8		
4	37.3	59.5		3*	85.7	130.7	
3	33.0	53.0	67.7	1	5.0	79.0	101.0

*One patient excluded due to cessation of treatment after OLE Week 12 Visit.

Figure 2. Association Between MLCL:L4-CL Ratio and 6MWT



- In the ongoing OLE study, data demonstrate an association between mean reductions in MLCL:L4-CL ratio and mean improvements in 6MWT, suggesting a physiologic basis to observed functional improvements
  - Mean improvement of -7.4 (-38.7%, *P*=0.03) from baseline was observed at OLE week 12 visit
  - Using a last observation carried forward method, a mean improvement of -9.4 (-47.3%, *p*=0.02) from baseline was observed at the last available visit (n=10)

Table 4. TAZPOWER OLE: Mean Change in BTHS-SA Fatigue Score by MLCL:L4-CL Ratio Subgroup

Change in BTHS-SA Fatigue Score From Baseline							
High Ratio Patients (MLCL:L4-CL ≥ 17.3)				Low Ratio Patients (MLCL:L4-CL < 17.3)			
n	Week 12	Week 24	Week 36	n	Week 12	Week 24	Week 36
5	-1.1			5	-2.0		
4	-1.6	-0.6		3*	-2.8	-1.8	
3	-1.7	-1.0	-1.0	1	-3.3	-3.3	-3.3

*One patient excluded due to cessation of treatment after OLE Week Visit.

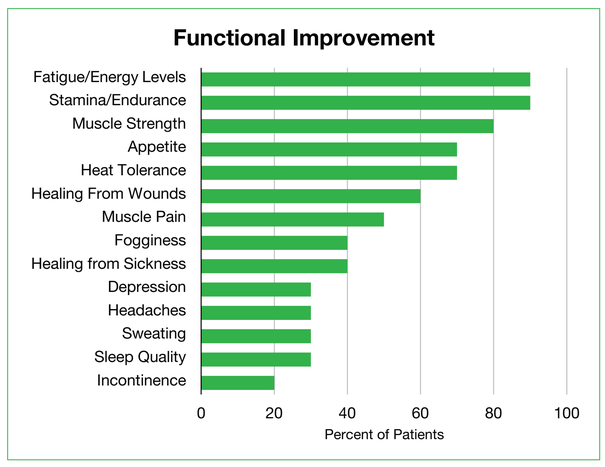
Safety and Tolerability

Table 5. TAZPOWER: Treatment-Emergent Adverse Events

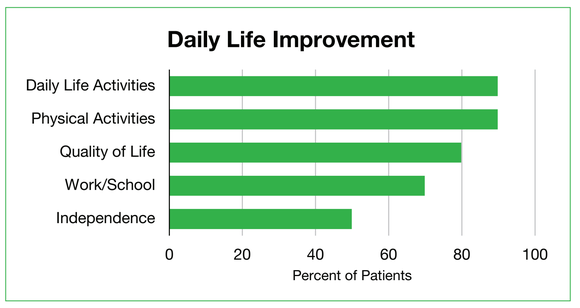
Blinded Trial Adverse Events, N (%)		
System Organ Class Preferred Term	Elamipretide (n=12)	Placebo (n=12)
At Least 1 TEAE	12 (100)	10 (83.3)
General Disorders and Administration Site Conditions	12 (100)	8 (66.7)
Nervous System Disorders	3 (25)	5 (41.7)
Gastrointestinal Disorders	1 (8.3)	4 (33.3)
Infections and Infestations	4 (33.3)	3 (25)
Injury, Poisoning, and Procedural Complications	2 (16.7)	3 (25)

Open-label Extension Adverse Events, N (%)				
System Organ Class Preferred Term	Elamipretide (n=10)	Mild	Moderate	Severe
At Least 1 TEAE	9 (90)	9 (90)	8 (80)	1 (10)
General Disorders and Administration Site Conditions	5 (50)	4 (40)	4 (40)	0 (0)
Nervous System Disorders	4 (40)	2 (20)	2 (20)	0 (0)
Injury, Poisoning, and Procedural Complications	3 (30)	2 (20)	1 (10)	1 (10)
Respiratory, Thoracic, and Mediastinal Disorders	2 (20)	2 (20)	1 (10)	0 (0)

Figure 3. Patient Perception of Change (PPC) and Caregiver Perceptions of Change (CPC) Video Assessments



- Represents improvements reported by participating subjects (and/or their caregivers) (n=9)



Data on file. Stealth BioTherapeutics; 2019.

CONCLUSIONS

- Blinded Phase of the TAZPOWER Trial
  - Statistical significance was not achieved in the ITT population on the primary endpoints
  - Elamipretide provided clinically meaningful improvements in individual functional and patient-reported outcome measures
  - Elamipretide was generally safe and well tolerated. Most adverse events were mild to moderate in severity. The most commonly reported adverse events include injection site reactions
- Open-Label Extension Phase of the TAZPOWER Trial
  - Continued therapy with elamipretide produced favorable reductions in the MLCL:L4-CL ratio
  - Continued therapy with elamipretide produced favorable improvements in functional and patient reported outcomes
  - Safety and tolerability of elamipretide was consistent with blinded phase observations
- An association between mean reductions in MLCL:L4-CL ratio and mean improvements in 6MWT suggests a physiologic basis to observed improvements in functional assessments
  - Patient and/or caregiver video results provide evidence of clinically meaningful improvements with elamipretide therapy

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