TAZPOWER: Biomarker Cardiolipin Ratios and Clinical Symptom Severity from a Randomized, Double-Blind, Placebo-Controlled, Crossover and Open-Label Extension Trial of Elamipretide in Barth Syndrome

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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)
- 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
- In preclinical studies, elamipretide stabilized L4-CL, reduced oxidative stress, improved ATP generation, and increased TAZ gene expression
- The efficacy and safety of elamipretide are being studied in TAZPOWER, which is the first clinical trial to evaluate the efficacy/safety of a therapeutic agent in patients with BTHS

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 conducted to evaluate the potential clinical impact of differences in the MLCL:L4-CL ratio and to determine the effect of elamipretide therapy on MLCL:L4-CL ratios and efficacy assessments in patients with genetically-confirmed BTHS

METHODS

Study Design

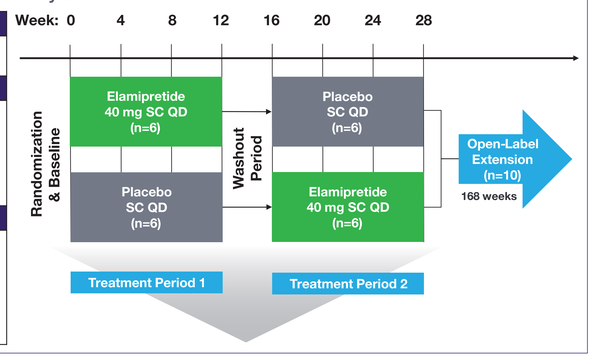
Figure 1. TAZPOWER Study Design

12-Week Pivotal Trial Followed by OLE

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

Secondary Endpoints
- **Functional assessments** (SWAY, HHD, 5XSST, CGI-S)
- **Patient-reported outcomes** (PGI-S, PROMIS F-SF)
- **Safety and tolerability**
- **Laboratory assessments** (MLCL:L4-CL ratio)

Inclusion Criteria
- Genetically confirmed BTHS
- Males age ≥12 y
- Body weight >30 kg, eGFR ≥90 mL/min or body weight >40 kg, eGFR ≥60 mL/min at screening
- Ambulatory and impaired during 6MWT
- On stable medication for 30 d prior to baseline visit



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 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

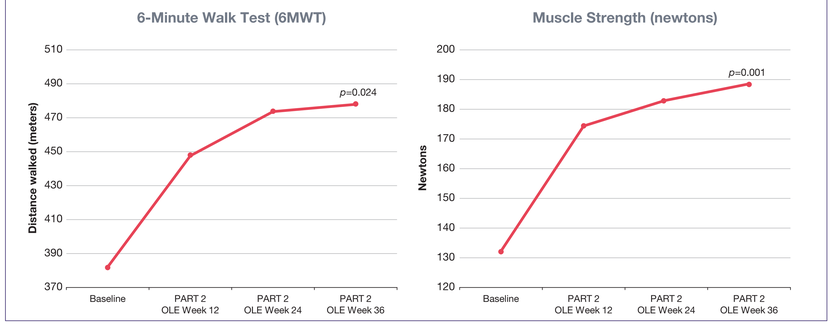
Table 1. TAZPOWER Patient Demographics (N=12)

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)	50.8 (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

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 (OLE) portion of the trial, which is currently ongoing

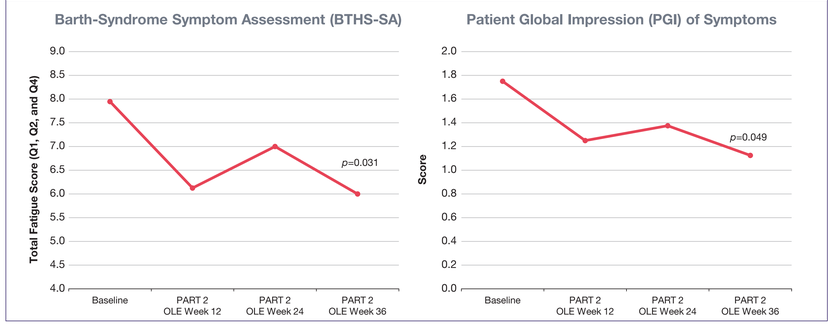
Figure 2. Functional Assessments



Change in 6MWT Distance (meters) From Baseline			
n	Week 12	Week 24	Week 36
8	66.0 m	92.0 m	95.9 m

Change in Muscle Strength (newtons) From Baseline			
n	Week 12	Week 24	Week 36
8	42.0	50.6	56.0

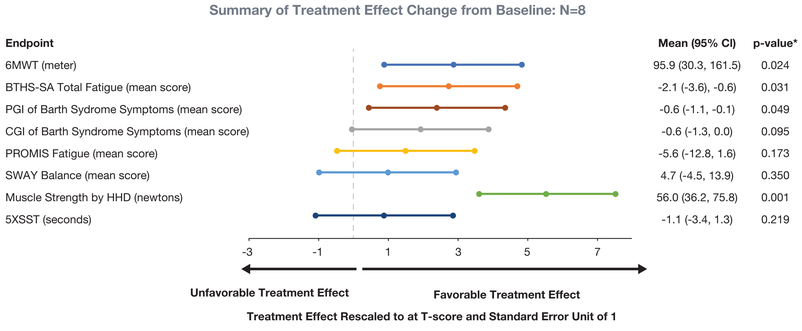
Figure 3. Patient Reported Assessments



Change in BTHS-SA From Baseline			
n	Week 12	Week 24	Week 36
8	-1.8	-1.1	-2.1

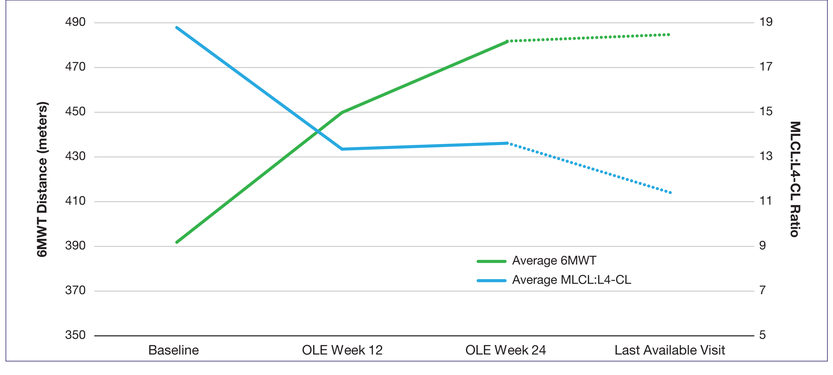
Change in BTHS-SA From Baseline			
n	Week 12	Week 24	Week 36
8	-0.5	-0.4	-0.6

Figure 4. Summary of Treatment Effect Changes



*p-values represent a t-test for matched pairs, comparing mean at Week 36 in Part 2 of SPIBA-201.

Figure 5. Potentially Disease-Modifying Improvements in Cardiolipin Ratio



Change in 6MWT & MLCL:L4-CL Ratio From Baseline				
n	Assessment	Week 12	Week 24	Last Available Visit
7*	6MWT	58.0	90.0	93.0
7*	MLCL:L4-CL	-5.4	-5.1	-7.4

* MLCL:L4-CL data available for 7 of 8 subjects at OLE Week 24

- 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

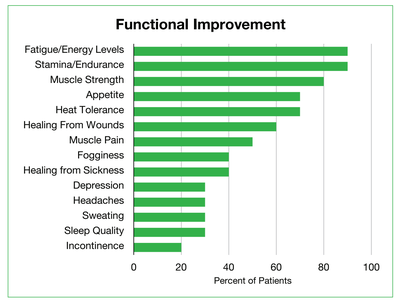
Safety and Tolerability

Table 2. TAZPOWER: Treatment-Emergent Adverse Events

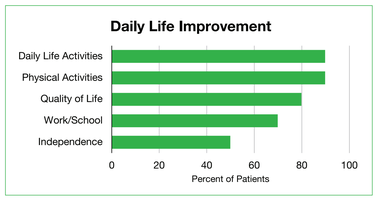
Blinded Trial Adverse Events, N (%)		
System Organ Class Preferred Term	Elamipretide 40 mg (N=12) n (%)	Placebo (N=12) n (%)
At Least 1 TEAE	12 (100.0)	10 (83.3)
General disorders		
Aphthous ulcer	0	2 (16.7)
General disorders and administrative site conditions		
Injection site erythema	12 (100.0)	3 (25.0)
Injection site pain	9 (75.0)	4 (33.3)
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)
Infections and infestations		
Bronchitis	2 (16.7)	1 (8.3)
Viral upper respiratory tract infection	1 (8.3)	2 (16.7)
Pharyngitis streptococcal	1 (8.3)	2 (16.7)
Injury, poisoning and procedural complications		
Ligament sprain	2 (16.7)	1 (8.3)
Nervous system disorders		
Headache	1 (8.3)	3 (25.0)

Open-Label Extension Adverse Events, n (%)				
Preferred Terms	Elamipretide (n=10)	Mild	Moderate	Severe
General disorders and administration site conditions				
Injection site erythema	8	8 (80)	1 (10)	0
Injection site pain	7	7 (70)	0	0
Injection site pruritus	7	7 (70)	1 (10)	0
Injection site induration	5	5 (50)	0	0
Nervous system disorders				
Dizziness	4	2 (20)	2 (20)	0
Headache	3	3 (30)	0	0
Musculoskeletal and connective tissue disorders				
Arthralgia	2	1 (10)	1 (10)	0
Pain in extremity	2	2 (20)	0	0
Respiratory, thoracic and mediastinal disorders				
Cough	2	0	2 (20)	0
Oropharyngeal pain	2	2 (20)	0	0
Infections and infestations				
Ear infection	2	1 (10)	1 (10)	0
Gingivitis	2	1 (10)	1 (10)	0
Injury, poisoning and procedural complications				
Joint dislocation	2	1 (10)	0	1 (10)
Muscle strain	2	2 (20)	0	0
Gastrointestinal disorders				
Nausea	2	2 (20)	0	0

Figure 6. 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)



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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