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

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INTRODUCTION

- Barth syndrome (BTHS) is a rare, X-linked disease caused by defects in TAZ, the tafazzin encoding gene, responsible for the final remodeling step to mature cardiolipin, critical for mitochondrial function
- The inability to produce mature cardiolipin leads to clinical manifestations of BTHS, including cardiac and skeletal myopathy, neutropenia, and growth abnormalities
- Elamipretide localizes to the inner mitochondrial membrane, where it is believed to associate with cardiolipin, improving membrane stability and ATP production and reducing pathogenic ROS production
- The efficacy and safety of elamipretide are being studied in TAZPOWER, which is the first clinical trial to evaluate a therapeutic agent in patients with BTHS

OBJECTIVE

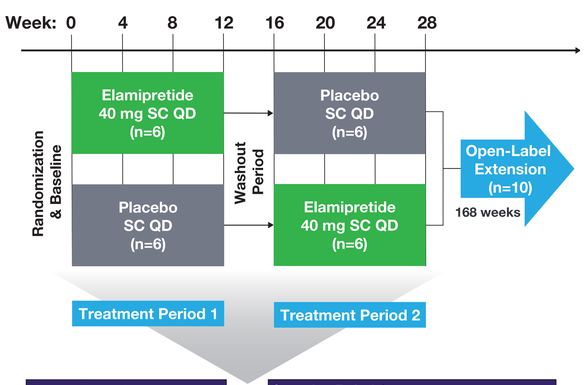
- To measure efficacy through functional, patient-reported outcome (PRO) assessments, and cardiac parameters and safety/tolerability through adverse events (AEs) and laboratory tests

METHODS

Study Design

Figure 1. Study Design

28-week, Randomized, Double-blind, Placebo-controlled Trial Followed by OLE



Primary Endpoints	Secondary Endpoints
• **Distance walked (meters) on 6MWT** • **Total fatigue score on BTHS-SA**	• **Functional assessments** (SWAY, HHD, 5XSST, CGI-S) – 3D Echo Parameters • **Patient-reported outcomes** (PGI-S, PROMIS F-SF) • **Safety and tolerability** (Cardiac Monitoring, AEs) • **Laboratory assessments**

AEs=Adverse Events; BTHS-SA=BarTH Syndrome Symptom Assessment; CGI-S=Clinician Global Impression of Symptom Severity and Change Scale; 5XSST=Five Times Sit-to-Stand Test; HHD=Hand held Dynamometry; PGI-S=Patient Global Impression of Symptom Severity and Change Scale; PROMIS F-SF=Patient-Reported Outcomes Measurement Information System Fatigue-Short Form; 6MWT=6-Minute Walk Test; SWAY=SWAY Application Balance Assessment.

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
  - Body weight >30 kg, eGFR ≥90 mL/min or body weight >40 kg, eGFR ≥60 mL/min at screening

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

RESULTS

Patient Demographics

- A total of 12 patients were randomized into the trial

Table 1. 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
Mean 3D LV End-diastolic Volumes (EDV) (Z-score [SD])	-2.0 (1.34)
Mean Normal Ejection Fraction (% [SD])	60.6 (4.0)

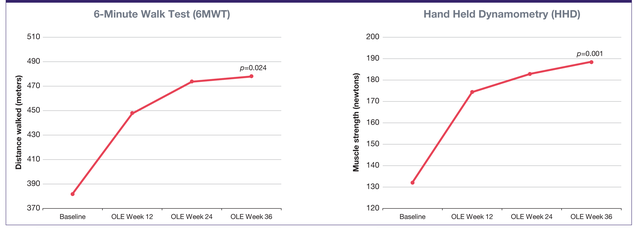
Blinded Trial Results

- 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

Open-label Extension

- A total of 10 patients elected to continue into the TAZPOWER open-label extension (OLE) portion of the trial, which is currently ongoing

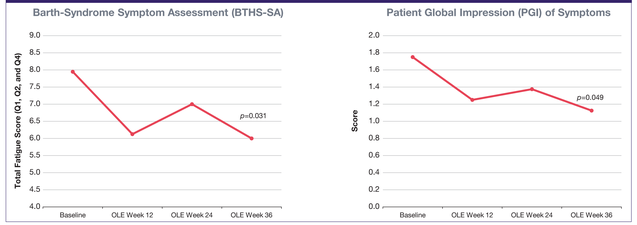
Figure 2. Functional Assessments



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 HHD Muscle Strength (newtons) from Baseline			
n	Week 12	Week 24	Week 36
8	42.0	50.6	56.0

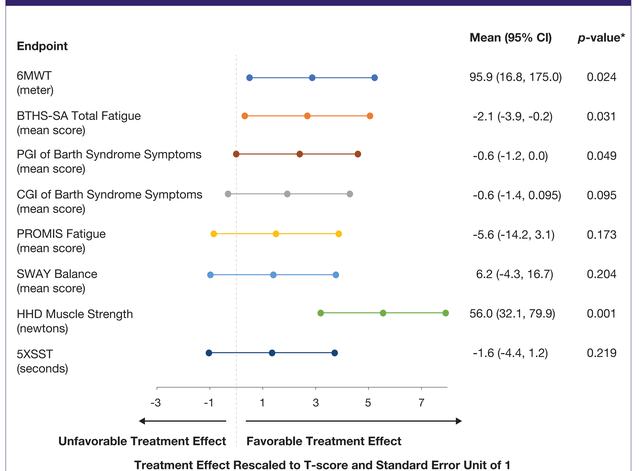
Figure 3. Patient-reported Outcomes Assessments



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

Change in PGI-S from Baseline			
n	Week 12	Week 24	Week 36
8	-0.5	-0.4	-0.6

Figure 4. Summary of Treatment Effect Changes from Baseline to Week 36 OLE (n=8)

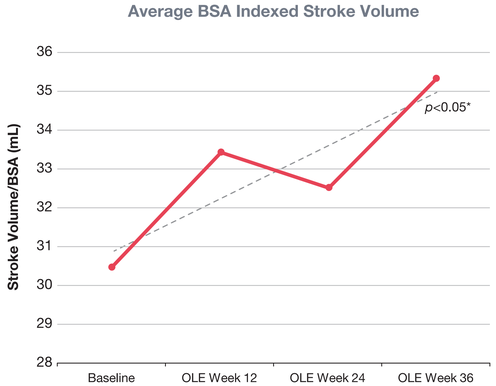


*p-values represent a t-test for matched pairs, comparing mean at baseline to mean at Week 36 OLE.

Cardiac Findings

- Baseline to OLE week 36 cardiac findings demonstrated improvements in the indexed stroke volume (4.8mL, $p<0.05$)

Figure 5. Cardiac Assessment



*Average of estimated slopes via linear regression

Safety and Tolerability

- There were 91 TEAEs reported, with 1 serious AE deemed not related to elamipretide; injection site reactions occurred in 100% of patients while on elamipretide

Table 2. 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

CONCLUSIONS

- TAZPOWER is the first clinical trial to evaluate the tolerability and efficacy of a potential therapeutic agent in patients with BTHS
- 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 PROs
  - Elamipretide was generally well tolerated; most adverse events were mild to moderate in severity, with the most commonly reported adverse events including injection site reactions
- Open-Label Extension Phase of the TAZPOWER Trial
  - At 36-week OLE, elamipretide therapy was associated with improvements in 6MWT, BTHS-SA Total Fatigue Score, and PRO assessments
  - Safety and tolerability of elamipretide was consistent with blinded phase observations
- Cardiac Findings at Open-Label Extension
  - Cardiac findings at 36-week OLE showed a statistically significant improvement in indexed stroke volume

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