TAZPOWER Analysis: Elamipretide Significantly Improves Disease Symptomatology versus Natural History Controls in Barth Syndrome

Hilary J. Vernon[1], Ryan Manuel[1], John J. Jones[2], Jim Carr[2], Brittany Hornby[3], William Reid Thompson[4]

[1]Department of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Stealth BioTherapeutics, Inc, Newton, MA; [3]Department of Physical Therapy, Kennedy Krieger, Baltimore MD; [4]Department of Pediatric Cardiology, Taussig Heart Center, Johns Hopkins University School of Medicine, Baltimore, MD

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 is a water-soluble, aromatic-cationic mitochondria-targeting tetrapeptide that readily penetrates and transiently localizes to the inner mitochondrial membrane where it associates with cardiolipin to improve membrane stability, enhance ATP synthesis in several organs (including the heart, kidney, neurons and skeletal muscle), and reduce pathogenic ROS production
- The efficacy and safety of elamipretide were studied in TAZPOWER, which is the first clinical trial to evaluate a therapeutic agent in patients with BTHS
- US Food and Drug Administration guidance supports using natural history controls (NHCs) providing external control groups with matched propensity scores for drug development in interventional, rare-disease studies

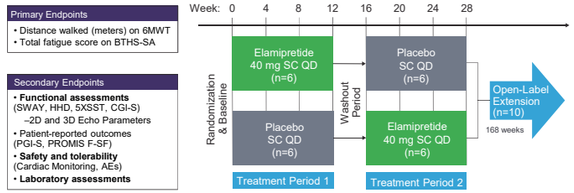
OBJECTIVE

- A NHC cohort with matched propensity scoring was used to assess the effects of elamipretide in the context of the natural history of BTHS through functional and assessments and cardiac parameters

METHODS

- TAZPOWER was a 28-week, randomized, double-blind, placebo-controlled trial followed by an OLE

Figure 1. Study Design



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.

- Effect of elamipretide on BTHS symptoms at OLE week 72 in the TAZPOWER study was compared with NHCs with matched propensity scoring derived from a 9 year-long natural history study that included 82 individuals with BTHS
- Correlation between functional assessments (6-minute Walk Test [6MWT], muscle strength by Hand Held Dynamometry [HHD] Five Times Sit to Stand [5XSST], and SWAY balance) and heart function, and the relationship of stroke volume improvement and stroke volume were evaluated

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

Natural History Controls

- Eligibility of non-trial NHC subject data was confirmed through review of the inclusion criteria
- All subjects who met entry criteria for TAZPOWER were included

Statistical Analysis

- In order to characterize combined evidence associated with multiple endpoints for the comparison of elamipretide therapy in TAZPOWER to the NHC, a patient-level multi-domain resonder index (MDRI) using the primary and secondary clinical endpoints was calculated using a Minimally Clinically Important Difference (MCID) of >10% relative change from baseline
- Analysis of the 6MWT along with the secondary efficacy endpoints (HHD, 5XSST score, SWAY balance), and the MDRI were analyzed with analogous methodology
- Subjects in the TAZPOWER and NHC cohorts were evaluated using a propensity score model to derive the propensity scores and compute stabilized weights based on the propensity scores to balance the TAZPOWER and NHC cohorts and minimize the impact of selection bias on estimates of treatment differences
- Logistic regression was used to compute propensity scores for eligible subjects in the TAZPOWER and NHC cohorts using age, height, and baseline 6MWT distance walked as baseline prognostic covariates

RESULTS

Baseline Prognostic Covariates

- The current analysis includes 8 patients from the TAZPOWER OLE and 19 untreated NHCs
- Baseline prognostic covariates (including age, height, and baseline 6MWT) were comparable between the two populations

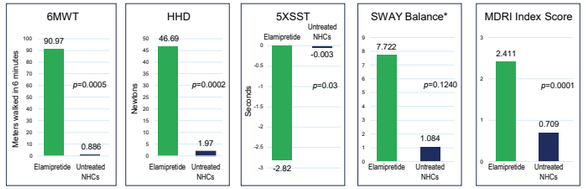
Table 1. Baseline Prognostic Covariates: TAZPOWER Patients and Natural History Controls

	TAZPOWER Patients (n=8)	Natural History Controls (n=19)
Age at Baseline Mean (SD) Range	18.3 (5.02) 12.9–28.7	21.0 (5.46) 12.0–32.6
Height at Baseline Mean (SD) Range	166.6 (12.43) 152.5–180.8	168.6 (14.25) 121.3–186.0
Baseline 6MWT Mean (SD) Range	381.875 (64.1837) 313.00–495.00	394.879 (75.2197) 267.00–536.45

Natural History Comparison

- At OLE Week 72, elamipretide patients (n=8) showed greater mean improvements from baseline versus prognostically matched NHCs (n=19)
- Subjects treated with elamipretide in TAZPOWER showed a significant increase from baseline in the mean distance walked based on the 6MWT, mean muscle strength by HHD, and 5XSST compared with NHCs at OLE Week 76 (p=0.0005)
- While not statistically significant, subjects treated with elamipretide in TAZPOWER showed improvement from baseline in the SWAY Balance Assessment scores at Week 72 compared with untreated NHCs
- Statistically significant differences in MDRI were observed for subjects treated with elamipretide at OLE Week 76 compared with untreated NHCs (p=0.0001)

Figure 2. Change from Baseline to OLE Week 76 for Elamipretide Compared with Untreated Natural History Controls

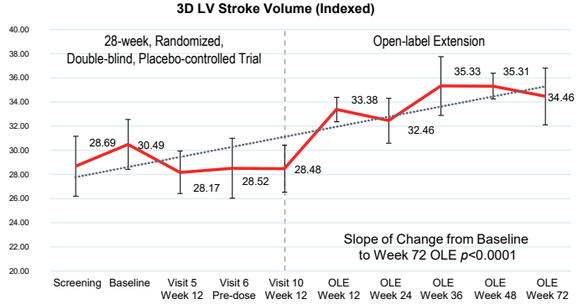


*OLE Week 72.

Cardiac Findings

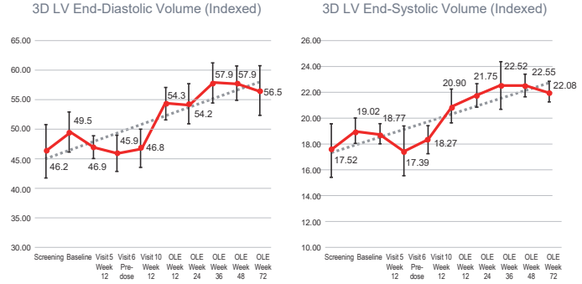
- Correlations between resting stroke volume and 6MWT strengthening were seen with long-term OLE therapy (OLE Week 72 r=0.52)
- Data through TAZPOWER OLE Week 72 show sustained significant improvement in the slope of change from baseline for left ventricular stroke volume (p<0.0001)
- NHC analysis confirmed that these improvements (+1.92 mL at OLE Week 72) are not expected in the natural course of disease, in which stroke volume is expected to decline (-4.8 mL) over a comparable time period (p=0.002)

Figure 3. 3D Left Ventricular (LV) Stroke Volume (Indexed to Baseline BSA)



- Data through TAZPOWER OLE Week 72 show sustained significant improvement in left ventricular end diastolic (p<0.0001) and end systolic (p=0.0002) volumes

Figure 4. 3D Left Ventricular (LV) End-Diastolic and End-Systolic Volumes (Indexed to Baseline BSA) through TAZPOWER OLE Week 76



- At baseline, the mean LV end diastolic volume (SD) was lower for the TAZPOWER elamipretide patients at 46.09 (8.511) compared with the untreated NHCs at 54.41 (18.490)
- Mean post-baseline LV end-diastolic volume (SD) increased for the TAZPOWER elamipretide patients at 48.22 (6.869) mL and decreased for the untreated NHCs at 53.48 (12.964) mL
- The LS mean in LV end-diastolic volume observed for elamipretide TAZPOWER patients and untreated NHCs was 2.08 and -2.66, respectively; however, the LS mean difference was not significant

CONCLUSIONS

- TAZPOWER is the first clinical trial to evaluate the efficacy and tolerability of a potential therapeutic agent for patients in BTHS
- At baseline, ELAM-treated (n=8) and NHC BTHS patients (n=19) with similar between-group prognostic covariates (age, height, baseline 6MWT score) performed poorly on functional assessment (6MWT), with pathologic exercise symptoms of heart failure
- A treatment benefit of long-term elamipretide therapy was observed in subjects with genetically-confirmed BTHS, as shown by the statistically significant improvements from baseline in functional endpoints for subjects who received elamipretide treatment, compared to NHC who did not receive elamipretide treatment
- Long-term elamipretide-treated subjects showed increases in the slope of change from baseline in average indexed stroke volume, which may coincide with observed improvements in functional domain outcomes
- This analysis demonstrates the power of longitudinal natural history data in ultra-rare diseases in evaluating and validating clinical trial outcomes

Disclosures: The authors declare no conflict of interest.
Study Funding: Trial funded by Stealth BioTherapeutics, Newton, MA
Medical writing assistance was provided by James A. Shiffer, RPh, Write On Time Medical Communications, LLC

Disclosure Slide

Financial Disclosure for:

Hilary J. Vernon[1], Ryan Manuel[1], John J. Jones[2], Jim Carr[2], Brittany Hornby[3], William Reid Thompson[4]

[1]Department of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Stealth BioTherapeutics, Inc, Newton, MA; [3]Department of Physical Therapy, Kennedy Krieger, Baltimore MD; [4]Department of Pediatric Cardiology, Taussig Heart Center, Johns Hopkins University School of Medicine, Baltimore, MD

We have nothing to disclose

Disclosure Slide

Financial Disclosure for:

Name

Title

Xxx Company

Consultant/Consulting fee