TAZPOWER: Study Design of a Randomized, Double-Blind, Placebo-Controlled Crossover and Extension Trial of Elamipretide in Subjects with Barth Syndrome and Baseline Characteristics

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

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

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

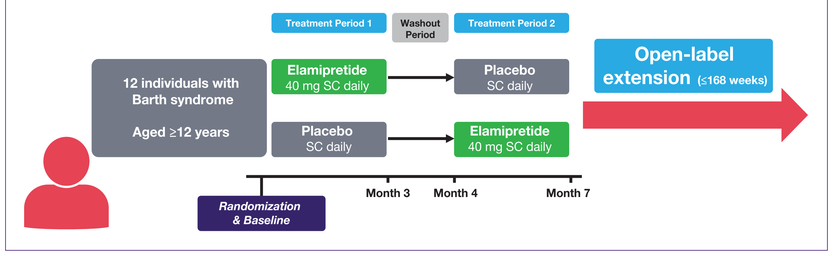
OBJECTIVE

- To measure efficacy through functional and patient-reported outcome assessments, exploratory biomarkers, 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. Study Design and Baseline Assessments



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

Baseline Assessments

- Functional assessments conducted at baseline included:
  - **6-Minute Walk Test (6MWT)** is a functional-based test of exercise performance that measures the distance (meters) an individual is able to walk over a total of 6 minutes
  - **Five Times Sit-to-Stand Test (5XSST)** assesses functional lower extremity strength, transitional movements, balance, and fall risk by measuring time (seconds) it takes a patient to stand from and return to a seated position, repeated 5 times
  - **SWAY Application Balance Assessment** provides an average of the deflections reported during 5 stances and ranges from 0 to 100, with higher scores indicating better balance
  - **Hand held dynamometry (HHD)** is an assessment of muscle strength (newtons) of both knee extensors reporting an average of 2 attempts for each extremity
  - **Echocardiogram** documenting cardiac structural and functional parameters
- Patient-/caregiver-/clinician-reported outcome assessments included:
  - **Global Impression of Symptom Severity and Change Scales** rate overall assessment of symptoms related to BTHS on a 5-point scaled question scored 0 to 4 (0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Very Severe) and Global Impression of Change scales rate changes in symptoms related to BTHS on a 7-point scaled question score -3 to 3 (-3=Very much Worse; -2=Moderately Worse; -1=A Little Worse, 0=No Change, 1=A Little Better, 2=Moderately Better, 3=Very much Better)
    - **CGI** - Clinician Global Impression of Symptom Severity and Change
    - **PGI** - Patient Global Impression of Symptom Severity and Change
    - **CaGI** - Caregiver Global Impression of Symptom Severity and Change
  - **BarTH Syndrome Symptom Assessment (BTHS-SA)**, which is an age-appropriate, daily patient-reported outcome that was created, in accordance with FDA guidance on Patient-Reported Outcome Measures, to assess the severity of the most common symptoms of BTHS using a 5-point scale (1=Not at All, 2=Mild, 3=Moderate, 4=Severe, 5=Very Severe). The BTHS-SA scores are the average of the daily scores over the 7 consecutive days immediately prior to a visit
    - **BTHS-SA Total Fatigue** score, a pre-specified fatigue subscale that assessed a subset of 3 symptoms: tiredness at rest, tiredness during activities, and muscle weakness during activities
  - **PROMIS Short Form Fatigue** used to evaluate self-reported symptoms of tiredness to debilitating sense of exhaustion
    - **PROMIS Fatigue - Short Form 8a** consists of 8 questions and has a possible raw score from 8 to 40. Each question is scored 1 to 5 (1=Not at All/Never, 2=A Little Bit/Rarely, 3=Somewhat/Sometimes, 4=Quite a Bit/Often, and 5=Very Much/Always)
    - **PROMIS Pediatric Fatigue - Short Form 10a** consists of 10 questions and has a possible raw score from 0 to 40. Each question is scored 0 to 4 (0=Never, 1=Almost Never, 2=Sometimes, 3=Often, 4=Almost Always)
    - Both the **PROMIS Fatigue - Short Form 8a** and **PROMIS Pediatric Fatigue - Short Form 10a** raw scores are converted to T-scores (with a T = 50 indicating average function compared to the reference population and a standard deviation of 10). T-scores from both assessments were reported together and considered a single secondary endpoint irrespective of age group
- Exploratory biomarkers
  - 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

Subgroup Analyses

- Subgroup analyses based on screening MLCL:L4-CL ratio will be conducted with subgroups delineated by the median MLCL:L4-CL ratio

RESULTS

Patient Demographics

Table 1. Patient Demographics (N=12)

Demographic Variable	Total Population Mean (Range)	Pediatric 12 to 17 years Mean (Range)	Adult ≥18 years Mean (Range)
Age (years)	19.5 (12-35)	14.9 (12-17)	28.8 (21-35)
Male (n)	12	8	4
Race (n)			
White	11	7	4
Multiracial	1	1	0
Ethnicity (n)			
Not Hispanic or Latino	12	8	4
Hispanic or Latino	0	0	0
Height (cm)	167.3 (150.4-187.7)	160.2 (150.4-180.0)	181.5 (172.7-187.7)
Weight (kg)	50.84 (31.4-85.9)	41.3 (31.4-74.5)	69.9 (63.8-85.9)
BMI (kg/m^2)	17.6 (13.6-24.4)	15.8 (13.6-23.0)	21.2 (18.7-24.4)

Baseline Patient Characteristics

- Vital signs, including ECG parameters, were within normal limits
- Average laboratory values (eGRF, ALT, and AST) were within normal limits at baseline, indicating normal liver and renal function

NOTE: 2 pediatric patients had ALT levels of 30 U/L and 33 U/L, respectively (reference range 9-24 U/L)

Baseline Comorbid Medical Diagnoses and Concomitant Medications

- Most commonly reported comorbid medical diagnoses reported in ≥50% of patients at baseline included cardiomyopathy (66.6%), neutropenia (58.3%), and hypotonia (50%)
- At baseline, the % ejection fraction was within normal limits for all patients
- 91.6% (n=11) patients reported taking at least 1 concomitant prescription medication at baseline

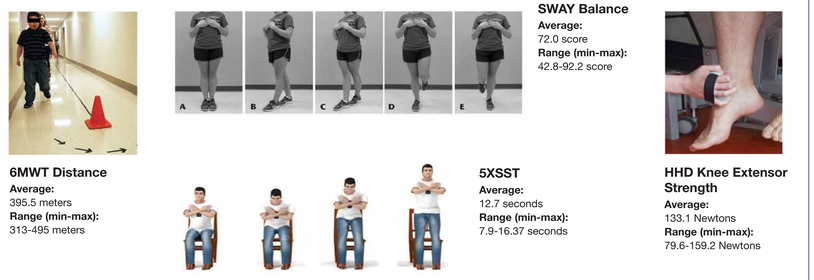
Table 2. Selected Concomitant Prescription Medications at Baseline

Indication for Use	Prescription Medication	Number of Patients Reporting Use at Baseline
Cardioprotection: Cardiomyopathy/Heart Failure	ACE inhibitor (various)	5
	Digoxin	4
	Carvedilol/Metoprolol	4
	Losartan	1
	Spironolactone	1
Neutropenia/Infection Prevention	Filgrastim	7
	TMP/SMX	1
	Amoxicillin	1
BTHS "Tonic"/ Mitochondrial Function	Citrulline	4
	Arginine	2
	CoQ10	2
	Levocarnitine	1

Baseline Functional Assessments

- Baseline functional assessments demonstrated impairment in the BTHS patient population (**Figure 2**)
  - Average 6MWT score was significantly lower than the average reported in healthy subjects (659±62 m)
  - Average SWAY balance score was lower than reported in healthy subjects (86.9 ±14.37)
  - Average 5XSST score was higher that the average reported in healthy subjects (11.4 sec)

Figure 2. Baseline Functional Assessments (N=12)*



6MWT Distance
Average: 395.5 meters
Range (min-max): 313-495 meters

SWAY Balance
Average: 72.0 score
Range (min-max): 42.8-92.2 score

5XSST
Average: 12.7 seconds
Range (min-max): 7.9-16.37 seconds

HHD Knee Extensor Strength
Average: 133.1 Newtons
Range (min-max): 79.6-159.2 Newtons

*n=11 for the 5XSST (1 participant could not attempt the 5XSST due to leg weakness)

Table 3. Patient-/Caregiver-/Clinician-reported Outcome Assessments (N=12)

Outcome Assessment	Average Score	Range (Min-Max)
BTHS-SA Total Fatigue	8.0	5.9-10
Global Impression of Symptom Severity scale		
CGI	2.4	2-3
PGI	2.8	2-4
CaGI	2.3	1-3
PROMIS Fatigue T-Score	63.6	52.5-74.4*

*T-score of 50=average fatigue of the general US population

Table 4. Individual Patient Screening MLCL:L4-CL Ratio*

Subject ID	Screening Ratio	Subject ID	Screening Ratio
101-001	23.0	101-008	35.4
101-003	32.7	101-010	22.8
101-004	15.6	101-013	11.2
101-005	29.4	101-014	18.4
101-006	16.2	101-015	2.3
101-007	4.4	101-016	6.7

*Median 17.3

CONCLUSIONS

- Patients enrolled in the TAZPOWER clinical trial have comorbidities that are well managed with current standards for cardiac and hematologic care
- The inclusion and exclusion criteria for the TAZPOWER trial precluded participation of patients with more severe medical histories
- Functional test results, Global Impression questionnaire results, and exploratory biomarkers findings indicate an additional disease burden that remains unaddressed by current therapy
- TAZPOWER is the first clinical trial specifically designed to evaluate a therapeutic agent, elamipretide, in the treatment of patients with BTHS

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