An interventional clinical trial to evaluate the role of elamipretide in individuals with Barth Syndrome

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Disclosures

• Dr. Vernon has disclosed a financial relationship with Stealth BioTherapeutics
  – Funding for the SPIBA clinical trial program in Barth Syndrome
Barth Syndrome: A Rare, X-Linked Disorder

- Caused by pathogenic variants in tafazzin (TAZ)
- Acyltransferase
  - Final step in production of mature cardiolipin
  - Defects in TAZ lead to accumulation of monolysocardiolipin (MLCL) and reduction in remodeled, mature cardiolipin (CL)
Cardiolipin: A mitochondrial phospholipid with many roles

- Located on the inner mitochondrial membrane (IMM)
  - maintaining mitochondrial structure
  - organizing IMM protein complexes
  - apoptosis

- Abnormalities implicated in multiple diseases
  - Diabetes, obesity, heart disease
  - BTHS: Only known Mendelian disorder of CL metabolism

BTHS Mitochondria
- Loss of IMM organization
- Decrease in respiratory supercomplex formation
- Inefficient electron flow and ATP generation

Healthy Mitochondria
- IMM well organized
- Respiratory supercomplexes intact
- Efficient electron flow and ATP generation

Barth Syndrome: Clinical features

- 1 in every 300,000–400,000 births
  - Presents during infancy/early childhood
  - 50% of deaths <1y of life
  - Life expectancy is foreshortened for many
- Cardiac disease
  - Dilated cardiomyopathy +/- hypertrophic component
  - Left Ventricular non-compaction
  - Waxing and waning severity of cardiac dysfunction
- Intermittent Neutropenia
- Skeletal muscle weakness
- Growth abnormalities

Obstacles for developing therapeutics in BTHS

- Ultra-rare genetic condition
- Lack of prospective natural history studies
  - Small cohorts
- Difficulty with clinical targets for measurement of outcome
  - waxing and waning of cardiac function and neutropenia
  - quantitative measurements often in the normal range
- No biomarkers correlating to clinical status
- No known genotype/phenotype correlation

Defining the BTHS phenotype: Multidimensional cross sectional clinical study

- Define phenotypic spectrum of disease and look for correlations between quantitative data across 34 individuals with BTHS
  - Cardiac size and function
  - Skeletal muscle strength
  - Endurance (6 minute walk test)
  - Quality of life
  - MLCL/CL
  - Metabolomics analysis
    - identify further discriminating biochemical features

Defining the BTHS phenotype

**Cardiolipin Ratio**

**Lower Extremity Strength**

**6MMWT Distance**
MLCL:CL Ratio Linked to Morbidity

- Regression analysis performed to identify relationships between metabolite measurements and quantitative clinical outcomes

<table>
<thead>
<tr>
<th>MLCL:CL Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inversely correlates with distance walked on the 6MWT ( (P=0.00014) )</td>
</tr>
<tr>
<td>• Increasing ratio correlates with increasing LVM ( (P=0.0374) )</td>
</tr>
</tbody>
</table>

6MWT and LVM serve as independent clinical markers for therapeutic monitoring
2-year longitudinal follow up study of 6MWT in 18 subjects

- 2014: average distance was 379±63 m (SD)
- 2016: average distance was 387.8 m ± 71 (SD)
- 1 individual had significant worsening, and 1 individual had significant improvement
  - Correlated to major health events in the interim time period

6MWT is statistically unchanged across the study population in a 2 year follow up study.

Hornby et al. Orphanet J Rare Dis. 2019 Jan 22;14(1):37
Elamipretide purported mechanism of action

Elamipretide is believed to diffuse across cell membranes and bind to cardiolipin in IMM

By binding to cardiolipin in the inner mitochondrial membrane (IMM), elamipretide is believed to stabilize cristae architecture and electron transport chain (ETC) structure during oxidative stress.
TAZPOWER: Elamipretide in Patients With Barth Syndrome

Double-Blind Trial Results
&
Open-Label Extension Trial Results @ Week 36
TAZPOWER Study Design
12-Week Pivotal Trial Followed by Open Label Extension

**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 Fatigue)
- Safety and tolerability
- Laboratory assessments (MLCL:L4-CL ratio)

**Key Inclusion Criteria**
- Genetically confirmed BTHS
- Males age ≥12 y
- Ambulatory and impaired during 6MWT
- On stable medication for 30 d prior to baseline visit

• At the end of the double-blind phase, statistical significance was not achieved on the primary endpoints
• Elamipretide provided clinically meaningful improvements in individual functional and patient-reported outcome measures
• Differential effect observed in patients with MLCL:L4-CL ratio below the median value of 17.3
## Safety: Adverse Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Elamipretide 40 mg (N=12) n (%)</th>
<th>Placebo (N=12) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At Least One Adverse Events</strong></td>
<td>12 (100.0)</td>
<td>10 (83.3)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphthous ulcer</td>
<td>0</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td><strong>General disorders and administrative site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>12 (100.0)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>9 (75.0)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Injection site induration</td>
<td>8 (66.7)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>8 (66.7)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>3 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Injection site urticaria</td>
<td>3 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Medical device site irritation</td>
<td>2 (16.7)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2 (16.7)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>1 (8.3)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Pharyngitis streptococcal</td>
<td>1 (8.3)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ligament sprain</td>
<td>2 (16.7)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (8.3)</td>
<td>3 (25.0)</td>
</tr>
</tbody>
</table>

Patient Transition into Open-Label Extension

Week: 0 4 8 12 16 20 24 28

Elamipretide 40 mg SC QD (n=6)

Placebo SC QD (n=6)

Open-Label Extension up to 168 weeks

10 of 12 patients elected to continue in OLE
All 10 patients have OLE week 12 assessments
8 of 10 patients have OLE week 24, 36, and 48 assessments

Assessments

- Distance walked (meters) on 6MWT
- Total fatigue score on BTHS-SA
- Functional assessments (SWAY, HHD, 5XSST, CGI-S)
- Patient-reported outcomes (PGI-S, PROMIS F-SF)
- Safety and tolerability
- Laboratory assessments (MLCL:L4-CL ratio)

Efficacy in OLE: Functional Assessments

### 6-Minute Walk Test (6MWT)

<table>
<thead>
<tr>
<th></th>
<th>Part 2 OLE Week 12</th>
<th>Part 2 OLE Week 24</th>
<th>Part 2 OLE Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>370.0</td>
<td>390.0</td>
<td>410.0</td>
</tr>
<tr>
<td>Week 12</td>
<td>430.0 (±75.23)</td>
<td>450.0 (±74.03)</td>
<td>470.0 (±94.61)</td>
</tr>
<tr>
<td>Week 24</td>
<td>490.0</td>
<td>510.0</td>
<td></td>
</tr>
<tr>
<td>Week 36</td>
<td>530.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**p = 0.024**

### Muscle Strength (newtons)

<table>
<thead>
<tr>
<th></th>
<th>Part 2 OLE Week 12</th>
<th>Part 2 OLE Week 24</th>
<th>Part 2 OLE Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>120.0</td>
<td>130.0</td>
<td>140.0</td>
</tr>
<tr>
<td>Week 12</td>
<td>162.0 (±30.33)</td>
<td>170.0 (±32.47)</td>
<td>180.0 (±28.56)</td>
</tr>
<tr>
<td>Week 24</td>
<td>190.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 36</td>
<td>200.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**p = 0.001**

Data on file.

Stealth BioTherapeutics.
Efficacy in OLE: Patient-Reported Symptom Assessments

Barth-Syndrome Symptom Assessment (BTHS-SA)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PART 2 OLE Week 12</th>
<th>PART 2 OLE Week 24</th>
<th>PART 2 OLE Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Fatigue Score (Q1, Q2, and Q4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change in BTHS-SA From Baseline

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in BTHS-SA</td>
<td>-1.8 (±1.93)</td>
<td>-1.1 (±1.53)</td>
<td>-2.1 (±2.18)</td>
</tr>
</tbody>
</table>

\( p = 0.031 \)

Patient Global Impression (PGI) of Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PART 2 OLE Week 12</th>
<th>PART 2 OLE Week 24</th>
<th>PART 2 OLE Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change in PGI of Symptoms From Baseline

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in PGI of Symptoms</td>
<td>-0.5 (±0.93)</td>
<td>-0.4 (±0.52)</td>
<td>-0.6 (±0.74)</td>
</tr>
</tbody>
</table>

\( p = 0.049 \)

Efficacy in OLE: Symptom Assessments

**PROMIS Short Form Fatigue**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PART 2 OLE Week 12</th>
<th>PART 2 OLE Week 24</th>
<th>PART 2 OLE Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-score</td>
<td>60.0</td>
<td>51.0</td>
<td>46.0</td>
<td>42.0</td>
</tr>
</tbody>
</table>

**Clinician Global Impression (CGI) of Symptoms**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PART 2 OLE Week 12</th>
<th>PART 2 OLE Week 24</th>
<th>PART 2 OLE Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>0.0</td>
<td>0.4</td>
<td>0.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

- Change in PROMIS T-Score From Baseline:
  - Week 12: -6.5 (±9.44)
  - Week 24: -3.8 (±6.29)
  - Week 36: -5.6 (±10.38)
  - p = 0.173

- Change in CGI of Symptoms From Baseline:
  - Week 12: 0.0
  - Week 24: -0.3 (±0.46)
  - Week 24: -0.9 (±0.83)
  - Week 36: -0.6 (±0.92)
  - p = 0.095
Efficacy in OLE: Functional Assessments

5-Times Sit-to-Stand (5XSST) [seconds]

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>-0.6 (±3.31)</td>
<td>-2.0 (±2.83)</td>
<td>-1.1 (±3.35)</td>
</tr>
</tbody>
</table>

p = 0.219

SWAY Balance Score

<table>
<thead>
<tr>
<th></th>
<th>Part 2 OLE Week 12</th>
<th>Part 2 OLE Week 24</th>
<th>Part 2 OLE Week 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance Score</td>
<td>85.0 (±15.72)</td>
<td>70.0 (±7.70)</td>
<td>65.0 (±13.25)</td>
</tr>
</tbody>
</table>

p = 0.350

Data on file.

Stealth BioTherapeutics.
### Summary of Treatment Effects: OLE Week 36

#### SPIBA-201 Part 2 Week 36
Summary of Treatment Effect Change from Baseline: N=8

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Mean (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT (meter)</td>
<td>95.9 (30.3, 161.5)</td>
<td>0.024</td>
</tr>
<tr>
<td>BTHS-SA Total Fatigue (mean score)</td>
<td>-2.1 (-3.6, -0.6)</td>
<td>0.031</td>
</tr>
<tr>
<td>PGI of Barth Syndrome Symptoms (mean score)</td>
<td>-0.6 (-1.1, -0.1)</td>
<td>0.049</td>
</tr>
<tr>
<td>CGI of Barth Syndrome Symptoms (mean score)</td>
<td>-0.6 (-1.3, 0.0)</td>
<td>0.095</td>
</tr>
<tr>
<td>PROMIS Fatigue (mean score)</td>
<td>-5.6 (-12.8, 1.6)</td>
<td>0.173</td>
</tr>
<tr>
<td>SWAY Balance (mean score)</td>
<td>4.7 (-4.5, 13.9)</td>
<td>0.350</td>
</tr>
<tr>
<td>Muscle Strength by HHD (Newtons)</td>
<td>56.0 (36.2, 75.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>5XSST (seconds)</td>
<td>-1.1 (-3.4, 1.3)</td>
<td>0.219</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>Unfavorable Treatment Effect</th>
<th>Favorable Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint</td>
<td>Treatment Effect Rescaled to a T-score and Standard Error Unit of 1</td>
<td>Treatment Effect Rescaled to a T-score and Standard Error Unit of 1</td>
</tr>
</tbody>
</table>

* p-values represent a t-test for matched pairs, comparing mean at baseline to mean at Week 36 in Part 2 of SPIBA-201.
Additional outcome: Increased cardiac stroke volume
Summary of observations

SPIBA 201, the first interventional clinical trial in Barth Syndrome

- 12-week double-blind phase
  - Statistical significance was not achieved on primary endpoints
  - However, subjects with lower MLCL:L4-CL ratios showed improvement compared to baseline on several endpoints

- Open Label Extension
  - Clinically significant improvements were observed in functional and PRO endpoints compared to baseline
  - Cardiac function data is suggestive of additional clinical benefit

- Elamipretide was generally well tolerated.
  - Most adverse events were mild to moderate in severity.
  - The most commonly reported adverse events include injection site reactions
BTHS: An example of advancing therapeutic development in a rare disease

• Thorough phenotyping
  – Cross sectional and longitudinal
  – Multidimensional
• Selection of quantitative endpoints
• Identification of potentially therapeutic compound
• Rational clinical trial design
  – Overcome limits of small participant pool
• Community engagement
Acknowledgements

Brittany Hornby, DPT
Reid Thompson, MD
Ryan Manuel, BS

And most importantly, the study participants and their families