Elamipretide Effects in Adults with Primary Mitochondrial Myopathy: Phase 2 Double-Blind, Randomized, Placebo-Controlled Crossover Trial (MMPOWER-2)

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INTRODUCTION

• Primary mitochondrial myopathies (PMM) are genetic disorders that impair normal mitochondrial function, primarily affecting skeletal muscle; resulting in: decreased tolerance to physical exercise because of skeletal muscle respiratory chain dysfunction; debilitating muscle weakness, muscle atrophy, limited exercise capacity, and symptoms of fatigue.
• PMM disease progression significantly compromises daily activity performance in the majority of cases.2,3
• Currently, there are no US FDA-approved therapies for PMM.

Figure 1. Restoration of Mitochondrial Bioenergetics

PROTOCOL DESIGN

• Primary objective: To evaluate the effect of 4 weeks of a once daily dose of SC ELAM on the distance walked during the 6MWT.
• Secondary objective: To determine all-cause safety and tolerability during administra
tion of ELAM.

RESULTS

Demographic and Other Baseline Characteristics

Of the 36 eligible, genetically-confirmed participants from MMPOWER-2, 30 were randomized to MMPOWER-2 (Table 1).

Table 1. MMPOWER-2 Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ELAM</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>41.6 (17-69)</td>
<td>48.2 (25-65)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male</td>
<td>20 (66.7)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td>White</td>
<td>13 (43.3)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>165.5 (6.6)</td>
<td>165.9 (6.9)</td>
<td>0.793</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>22.8 (3.5)</td>
<td>22.0 (3.7)</td>
<td>0.649</td>
</tr>
</tbody>
</table>

Efficacy Findings

Functional Assessments

• ELAM resulted in an improvement of 19.8 meters (6MWT - end of treatment period) compared with placebo (95% confidence interval [CI], -2.8, 42.5; p = 0.0023; Figure 5).

CONCLUSIONS

• ELAM patients reported less fatigue during activities as assessed by the PMMSA Total Fatigue During Activities score throughout the treatment period (Figure 7).
• ELAM treatment culminated in a 0.8 point reduction in symptom severity at the end of treatment vs. placebo (95% CI; -1.2, -0.3; p = 0.0018).
• Both scales trended to return to baseline upon discontinuation of ELAM.
• For individual items relating to mitigating symptoms of the individual PMMSA symptoms assessment, ELAM patients vs. placebo had improvements in:
  • Tiredness at rest (p = 0.0033)
  • Muscle weakness at rest (p = 0.0019)
• ELAM participants who walked <450 meters at baseline experienced a greater improvement in 6MWT (vs placebo) than participants who walked ≥450 meters at baseline.
• ELAM treatment was well tolerated by most participants

METHODS

Study Design and Participants

• An initial trial (MMPOWER-1) in genetically-confirmed PMM patients evaluated 3 different daily IV doses of ELAM (0.25, 0.5, and 1.25 mg/kg) for 2 hours for 5 days. High dose ELAM treatment produced improvements in 6MWT.

Figure 2. MMPOWER-2 Primary Endpoint: Change in Distance Walked at Day 5

Figure 3. MMPOWER-2 Study Design

Figure 4. MMPOWER-2 Consort Flow Diagram

Figure 5. MMPOWER-2 Primary Endpoint: Change in Distance Walked Based on Measures of 6MWT

Table 2. Treatment-emergent Adverse Events (AEs) (≥2 Participants)

<table>
<thead>
<tr>
<th>Event (n, %)</th>
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<tbody>
<tr>
<td>Injection site reactions</td>
<td>17 (56.7)</td>
<td>1 (3.3)</td>
<td>0.0033</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>14 (46.7)</td>
<td>2 (6.7)</td>
<td>0.0023</td>
</tr>
<tr>
<td>Pain</td>
<td>6 (20.0)</td>
<td>2 (6.7)</td>
<td>0.297</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>13 (43.3)</td>
<td>2 (6.7)</td>
<td>0.0033</td>
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REFERENCES


Acknowledgments

Patents and their families for their participation, MMPOWER-Acton and the United Mitochondrial Disease Foundation for helping with recruitment. We also thank Harvard Catalist (http://catalyst.harvard.edu) for statistical input and support. Medical writing assistance was provided by Cathy R. Werner, RSC, and Jesel M. Sumanta, PhD. Writing and editorial support for manuscript preparation and production were provided by Clarion Health Communications, LLC and Thelma K. Ryan, PhD (Thelma K. Ryan, PhD, RNA-CT, CHC). Figure 1 artwork was created by Dr. Dean Damato (University of Southern California, Children’s Hospital of Orange County, Orange, CA).}

Safety Evaluation

• Injection site reactions were the most commonly reported AEs with ELAM (81%) (Table 2). Most commonly characterized by erythema (75%), pruritus (47%), pain (20%), urticaria (5%), and edema (10%).
• Seventy percent of patients reported mild injection site reactions such as moderate bruising, discomfort, erythema, indentation, irritation, and/or pain.
• During the trial, there were no serious AEs or deaths reported.

CONCLUSIONS

• ELAM-treated patients showed a 19.8-meter improvement in the 6MWT vs. placebo at the end of a 4-week treatment period.
• Compared to placebo, ELAM participants who walked ≥450 meters at baseline experienced a greater improvement in 6MWT (vs placebo) than participants who walked <450 meters at baseline.
• ELAM treatment resulted in improved Neuro-QoL Fatigue-Short Form scores.
• ELAM participants who walked <450 meters at baseline had a 1.0-point reduction in T-score vs. placebo (95% CI: -1.0, -0.5; p = 0.0115).

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Note: AEs were reported during the treatment period of the crossover trial.ITT: Intention to treat.