MMPOWER-2 Open-Label Extension Trial: Long-term Safety and Tolerability of Elamipretide at 12 Months in Patients with Primary Mitochondrial Myopathy

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INTRODUCTION

- Primary mitochondrial myopathies (PMM) are a group of genetic disorders associated with impairment of mitochondrial function, and are most often caused by respiratory chain dysfunction and debilitating skeletal muscle weakness
- Patients with PMM experience muscle weakness, fatigue, and exercise intolerance, which adversely affects physical functioning, activities of daily living, and quality-of-life (QoL)
- Elamipretide is an aromatic-cationic tetrapeptide that readily penetrates cell membranes and transiently localizes to the inner mitochondrial membrane where it associates with cardiolipin to restore cristae architecture and improve ATP production
- The clinical development program for elamipretide includes the MMPOWER-1 and MMPOWER-2 trials, in which treatment with elamipretide demonstrated improvements in associated endpoints for patients with genetically confirmed PMM

OBJECTIVE

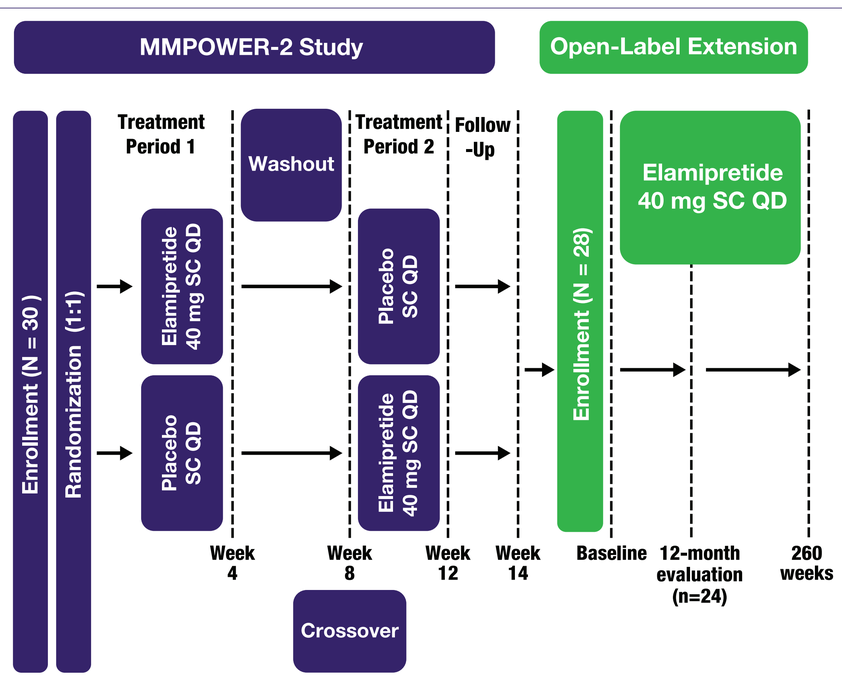
- The primary objective of the open-label extension of MMPOWER-2 (MMPOWER-2 OLE) is to assess the long-term safety and tolerability of a single daily subcutaneous (SC) 40 mg dose of elamipretide in patients with PMM

METHODS

Study Design (Figure 1)

- MMPOWER-2 was a 4-week multicenter, randomized, double-blind, placebo-controlled crossover trial in which patients with genetically confirmed PMM received elamipretide 40 mg or Placebo SC daily
- The current study is a multicenter, 260-week, open-label extension of MMPOWER-2
  - Data presented are a 12-month analysis of elamipretide safety, functional assessment, and QoL data from the OLE

Figure 1. Study Design



Patients

- Key inclusion criteria for OLE
  - Met all inclusion criteria for and enrolled in MMPOWER-2
  - Completed the End-of-Study Visit for MMPOWER-2
  - Determined that the subject can adhere to the trial requirements for the length of the trial
- Key exclusion criteria for OLE
  - Prior or current medical condition that may prevent the subject from safely participating in and/or completing all trial requirements
  - Receipt of any investigational compound and/or participation in another interventional clinical trial within 30 days prior to the OLE baseline visit

Study Assessments

- Safety and tolerability
  - Primary safety and tolerability measures for adverse events (AEs), including serious adverse events (SAEs), assessed for severity (mild/moderate/severe) and causal relationship to elamipretide
- Trends over time for additional assessments
  - Six Minute Walk Test (6MWT)
    - Distance walked
  - Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)
    - The PMMSA was created, in accordance with FDA guidance on Patient-Reported Outcome Measures, to assess the severity of 10 of the most common symptoms of PMM using the following 4-point scale: (1) not at all, (2) mild, (3) moderate, and (4) severe. The PMMSA Total Fatigue score, a prespecified fatigue subscale, assessed tiredness and muscle weakness at rest and during activities
  - Neuro-QoL Fatigue questionnaire
    - Neuro-QoL is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults and children living with neurological conditions. The Fatigue questionnaire measures sensations ranging from tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that decreases the patient's capacity for physical, functional, social, and mental activities
  - EQ-5D
    - A standardized instrument developed by the EuroQoL Group as a measure of health-related QoL that can be used in a wide range of health conditions and treatments. EQ-5D is one of the most commonly used generic health status measurements, providing solid validity and reliability. The 5 domains of the EQ-5D are scored using a 5-point scale: (1) no problem, (2) slight problem, (3) moderate problem, (4) severe problem, (5) unable/extreme
      - Individual Domain Scores
      - Problem to No Problem Transition

RESULTS

Patients

Table 1. Summary of Patient Characteristics

Patient Characteristic	Value
Average age (years)	50.3
Age range (years)	19.2 – 66.1
Gender	Male = 3 (12.5%) Female = 21 (87.5%)
Race	White = 23 (95.8%) Other/Multiple = 1 (4.2%)

Safety and Tolerability

- The safety profile of elamipretide in this trial was consistent with the results obtained from previous trials in patients with PMM
- Overall, SC elamipretide therapy was well tolerated, with most adverse events reported to be of mild severity
- Ten SAEs were reported in 6 subjects
  - All SAEs were deemed to be unrelated or unlikely related to elamipretide
- Injection site reactions were the most commonly reported AEs with elamipretide, the majority of which were mild
- There were 4 discontinuations to date, only 1 of which was related to an AE (report of eczema)

Table 2. Adverse Events

Adverse Event	Number of Subjects Reporting (%)
At least one adverse event	28 (100.0)*
Injection site pruritus	21 (75.0)
Injection site erythema	17 (60.7)
Injection site urticaria	13 (46.4)
Injection site mass	11 (39.3)
Injection site pain	9 (32.1)
Injection site rash	4 (14.3)
Injection site bruising	3 (10.7)
Injection site swelling	3 (10.7)
Fall	8 (28.6)
Fatigue	5 (17.9)
Dizziness postural	3 (10.7)
Blood lactic acid increased	4 (14.3)
Eosinophil count increased	3 (10.7)

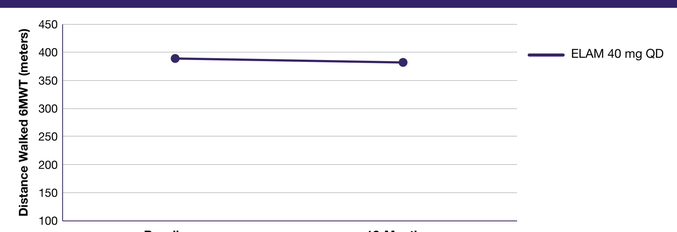
Adverse Event (cont.)	Number of Subjects Reporting (%)
Headache	7 (25.0)
Pain in extremity	4 (14.3)
Abdominal pain	3 (10.7)
Chest pain	3 (10.7)
Arthralgia	3 (10.7)
Back pain	3 (10.7)
Migraine	3 (10.7)
Neuralgia	3 (10.7)
Nasopharyngitis	6 (21.4)
Vomiting	5 (17.9)
Sinusitis	4 (14.3)
Upper respiratory tract infection	4 (14.3)
Gastroenteritis viral	3 (10.7)
Urinary tract infection	3 (10.7)
Cough	3 (10.7)

*N of 28 includes total study population of 24 patients included in the efficacy analysis and 4 patients who withdrew before the 12-month assessment.

Quality-of-Life and Functional Assessments Quality-of-Life

- 6-Minute Walk Test (**Figure 2**)
  - Patients maintained their level of functional capacity at 12 months (n=23*)

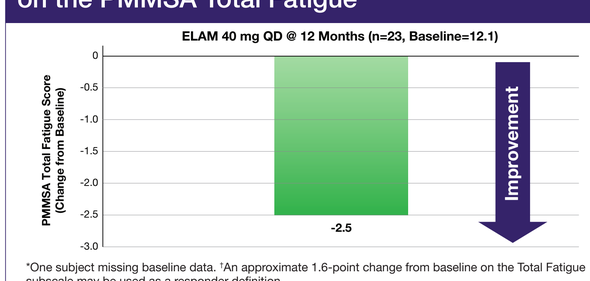
Figure 2. Change from Baseline in 6 Minute Walk Test



*Testing was terminated in one patient prior to 6 minutes due to "pain in bilateral lower extremities and numbness"

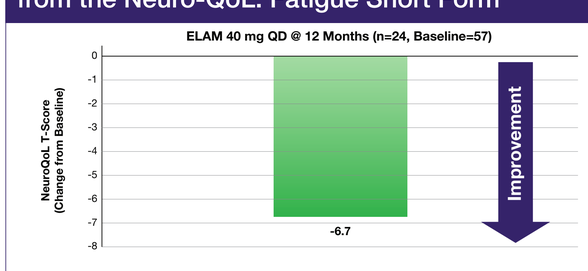
- PMMSA Total Fatigue Score (**Figure 3**)
  - Patients continued to improve on their self-reported total fatigue score during the additional 12 months of elamipretide treatment (n=23)*†
- Neuro-QoL Fatigue Short Form (**Figure 4**)
  - Patients continued to improve their Neuro-QoL Fatigue Short Form T-score during the additional 12 months of elamipretide treatment (n=24)

Figure 3. Change from Baseline in Mean Scores on the PMMSA Total Fatigue



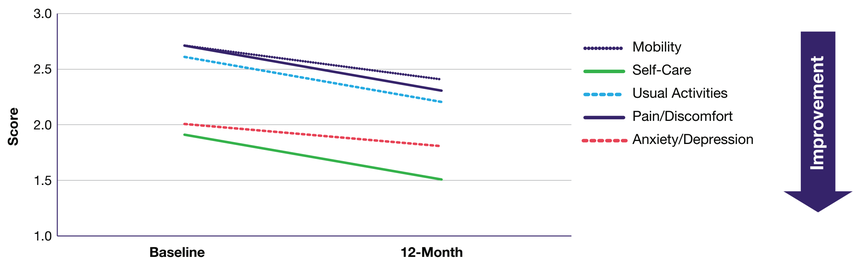
*One subject missing baseline data. †An approximate 1.6-point change from baseline on the Total Fatigue subscale may be used as a responder definition.

Figure 4. Change from Baseline in Mean T-scores from the Neuro-QoL: Fatigue Short Form



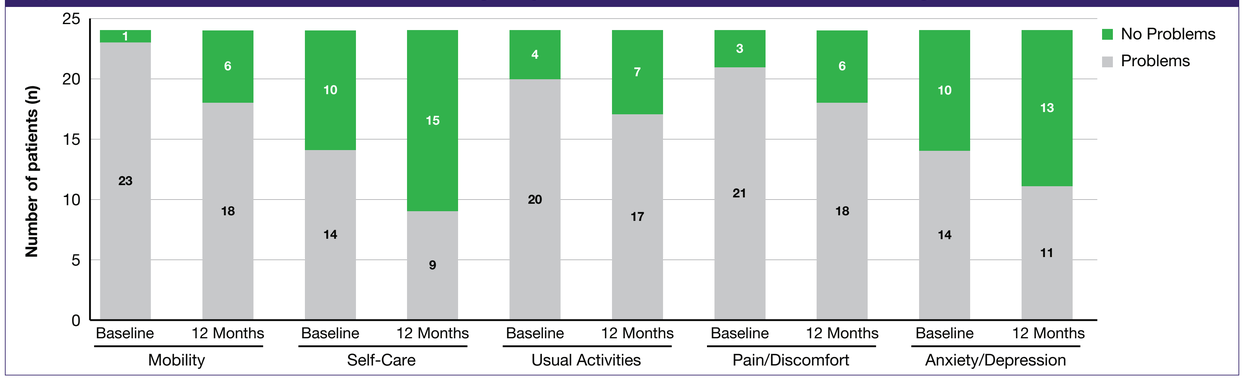
- EQ-5D: Individual Domain Scores (**Figure 5a**)
  - Patients continued to improve all EQ-5D Individual Domain scores (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) during the additional 12 months of elamipretide treatment (n=24)

Figure 4a. Change from Baseline in EQ-5D Individual Domain Scores



- EQ-5D: Problem to No Problem Transition (**Figure 5b**)
  - Patients shift from reporting any level of "problem" to reporting "no problem" scores (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) during the additional 12 months of elamipretide treatment (n=24)

Figure 5b. Patients Shift from Reporting Any Level of "Problem" to Reporting "No Problem"



CONCLUSIONS

- Patients receiving continued therapy with elamipretide demonstrated a favorable effect over the duration of the additional 12-month observation period in the current OLE study
- Injection site reactions were the most commonly reported AE with elamipretide, the rates of which were consistent with those observed in previous clinical trials
- Daily SC elamipretide therapy appears to be well tolerated with only 1 patient discontinuing therapy due to an adverse reaction
- Patients were able to maintain their distance walked on the 6MWT throughout the elamipretide treatment period
- Treatment with elamipretide resulted in improvements in all patient-reported outcome and QoL assessments

Disclosures*

Amel Karaa: received research grant, reimbursement for travel, and consulting payments from Stealth BT, Sanofi Genzyme, and Shire; received research grant and reimbursement for travel from Protalix and REATA; received consulting payments from MitoBridge; and is on the medical advisory board of MitoAction and on the scientific and medical advisory board of the United Mitochondrial Disease Foundation, is a board member of Rare New England and the Mitochondrial Medicine Society, and is an investigator in the North American Mitochondrial Disease Consortium.

Amy Goldstein: received research grant, reimbursement for travel, and consulting payments from Stealth BT; is on the scientific and medical advisory board of the United Mitochondrial Disease Foundation, DSMB at the University of Pittsburgh, and the editorial boards for the Journal of Child Neurology and Pediatric Neurology; and is a consultant for Biomarin, an investigator in the North American Mitochondrial Disease Consortium, and the president of the Mitochondrial Medicine Society.

Richard Haas: received research grant, reimbursement for travel, and consulting payments from Stealth BT; is on the scientific and medical advisory board of the United Mitochondrial Disease Foundation and the advisory board for MitoBridge; received clinical trial funding from Edison Pharmaceuticals, Stealth BioTherapeutics, Horizon Pharma (previously Raptor), and Sarepta; and received grant funding through the FDA Orphan Products Clinical Trials Grants Program (previously Orphan Products Grants; #1RO1FD004147) and the NIH (U54 NS078059).

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*All payments from Stealth BT were directly pertaining to travel for investigator meetings and the conduct of this clinical trial. As part of the trial, the investigators and coordinators have also received a mini iPad to conduct trial procedures.

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