MMPOWER-2 Open-Label Extension Trial: 6-Month Treatment Effect on Patients with Baseline 6MWT between 100-450 Meters

Richard Haas,[1] Amy Goldstein,[2] Jerry Vockley,[3] Bruce H Cohen,[4] Amel Karaa[5]

[1]UC San Diego School of Medicine, San Diego, CA; [2]Children's Hospital of Philadelphia, Philadelphia, PA; [3]Children's Hospital of Pittsburgh, Pittsburgh, PA; [4]Akron Children's Hospital, Akron, OH; [5]Massachusetts General Hospital, Boston, MA

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
- 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

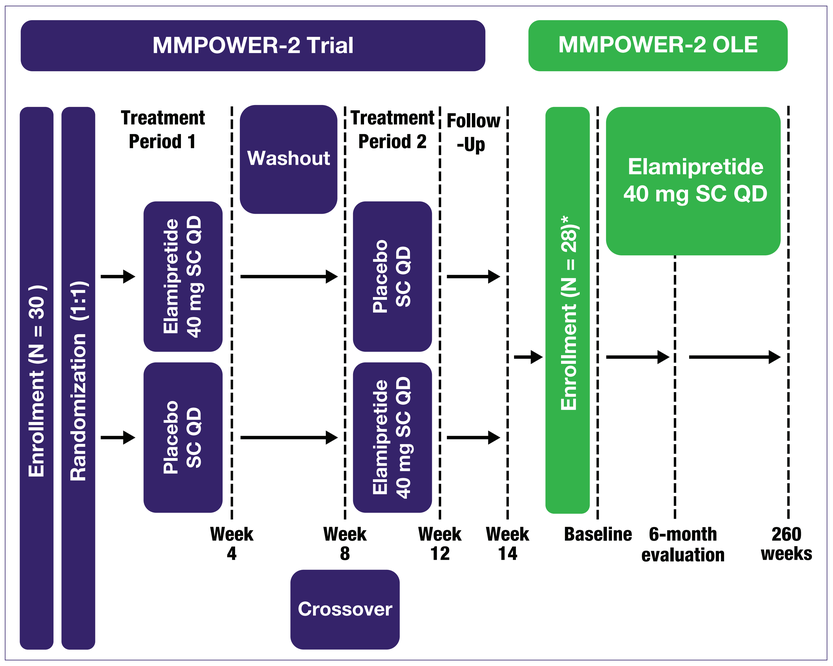
- The primary objective of the open-label extension MMPOWER-2 trial (MMPOWER-2 OLE) is to assess the long-term safety and tolerability of a single daily subcutaneous (SC) 40 mg dose of elamipretide in patients with PMM
- The objective of this post-hoc subgroup analysis is to evaluate the impact of 6 months of continuous elamipretide therapy in patients whose 6-minute walk test (6MWT) results were between 100-450 meters at pre-treatment baseline (elamipretide naïve) before entering into the MMPOWER clinical trial program

METHODS

Study Design

- MMPOWER-2 trial 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 6-month analysis of elamipretide safety, functional assessment, and QoL data from the multicenter, MMPOWER-2 OLE in a subset of patients who met the elamipretide-naïve 6MWT range (100-450 meters) and had a 6-month MMPOWER-2 OLE visit (n=21)
- Natural History data, used as a basis of comparison of available trial endpoints, was obtained from the subset of patients enrolled in the RePOWER Registry, with 6MWT results between 100-450 meters, and subsequently screened for entry into the phase 3 MMPOWER-3 study, both of which are integral parts of the elamipretide clinical development program.

Figure 1. Study Design



*Includes a single patient from MMPOWER-1 who was not randomized into MMPOWER-2.

Patients

- Key inclusion criteria for MMPOWER-2 OLE
  - Subject completed the end-of-study visit in MMPOWER-1 and/or MMPOWER-2 (if enrolled in both trials, the end-of-study visits in both trials must have been completed)
  - Investigator determined that subject can, and subject agrees to, adhere to the trial requirements for the length of the trial including self-administration (by subject or trained caregiver) of study drug
- Key exclusion criteria for MMPOWER-2 OLE
  - Subject has received any investigational compound (excluding elamipretide) and/or has participated in another interventional clinical trial within 30 days prior to the MMPOWER-2 OLE baseline visit (excluding MMPOWER-2) or is concurrently enrolled in any non-interventional research of any type to be judged to be scientifically or medically incompatible with the trial as deemed by the investigator
  - Subject experienced an adverse reaction attributed to study drug resulting in permanent discontinuation of study drug in the MMPOWER-1 or MMPOWER-2 trials
  - Subject has undergone an inpatient hospitalization within the 1 month prior to the MMPOWER-2 OLE baseline visit Study Assessments
- 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
- Efficacy assessments analyzed for this cohort included change in the 6MWT, Primary Mitochondrial Myopathy Symptom Assessment (PMMSA) Total Fatigue score, Neuro-QoL Short Form Fatigue, and EQ-5D
  - **6MWT:** measures distance walked in meters
  - **PMSSA:** assesses 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:** 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:** measures health-related QoL for 5 domains (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) on 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

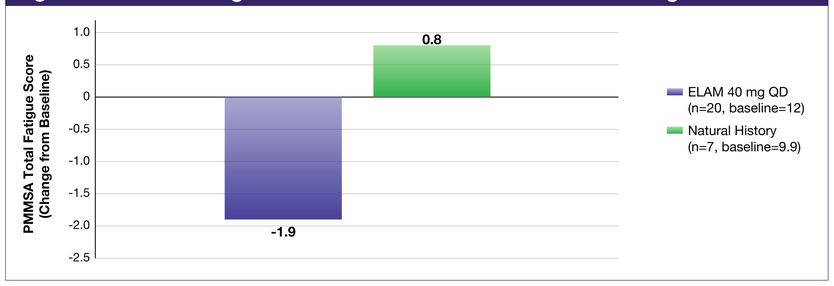
Table 1. Summary of Patient Characteristics

Patient Characteristic	Value
Average age (years)	48.5
Age range (years)	19.2 – 66.1
Gender	Male = 2 (9.5%) Female = 19 (90.5%)
Race	White = 20 (95.2%) Other/Multiple = 1 (4.8%)

Functional Assessments and Quality-of-Life

- Distance walked in the 6MWT was maintained throughout the 6 month observation period for the patients treated daily with 40 mg SC elamipretide (n=21). Patients in the Natural History group experienced an average reduction of 18 meters at the 6 month assessment.

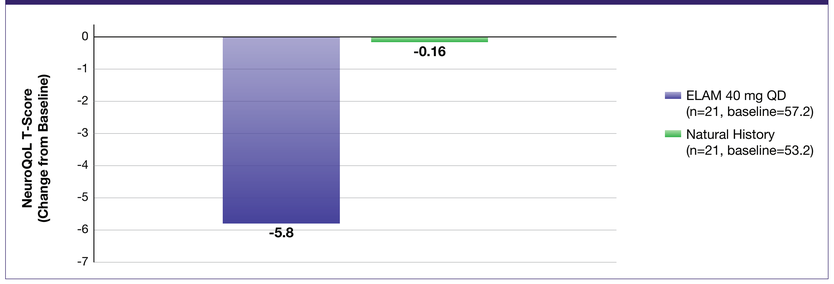
Figure 2. Mean Change from Baseline on the PMMSA Total Fatigue



*One subject missing baseline data. †An approximate 1.6-point change is considered to be clinically meaningful.

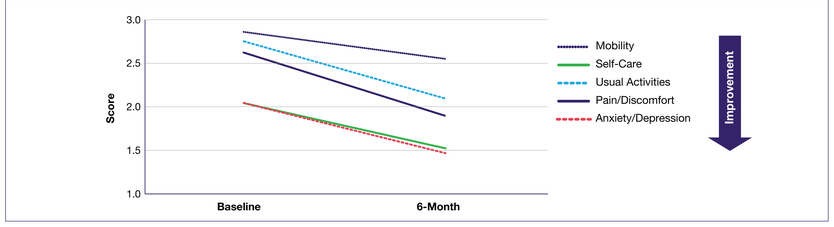
- Patients continued to improve their Neuro-QoL Fatigue Short Form T-score during the additional 6 months of elamipretide treatment (n=21)

Figure 3. Mean Change from Baseline in T-scores from the Neuro-QoL Fatigue Short Form



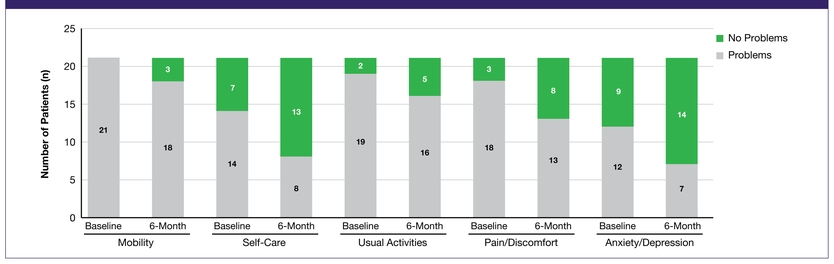
- Patients continued to improve on all EQ-5D Individual Domain scores during the additional 6 months of elamipretide treatment (n=21)

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



- Patients shift from reporting any level of "problem" to reporting "no problem" on the EQ-5D Problem to No Problem Transition scores during the additional 6 months of elamipretide treatment (n=21)

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



Safety and Tolerability

- Safety and tolerability information reported is for the current subanalysis cohort of patients (n=21) plus the patients not included in this subanalysis (n=7) for 12 months of the OLE (N=28) in this ongoing study
- 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.

CONCLUSIONS

- Elamipretide demonstrated a favorable effect over the duration of the additional 6-month period in the current OLE study subanalysis
- Treatment with elamipretide resulted in improvements in all patient-reported outcome and QoL assessments in this subset of patients who met the elamipretide-naïve 6MWT range
- The safety profile of elamipretide in this trial was consistent with the results obtained from previous trials in patients with PMM
- 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

Disclosures*

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). **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. **Jerry Vockley:** received research grant, reimbursement for travel, and consulting payments from Stealth BT. **Bruce Cohen:** received research grant, reimbursement for travel, and consulting payments from Stealth BT; received research grants from Reata pharmaceuticals, BioElectron Technology (Edison Pharma), and Horizon Pharma (Raptor Pharma); received travel support from Reata; is a consultant with MitoBridge and Wellstat Pharma; and serves on the UMDF Board of Trustees and is an investigator for the NAMDC. **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.

*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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