Natural History of Disease Progression in Patients with Primary Mitochondrial Myopathy

Goldstein A., on behalf of the RePOWER and MMPOWER-3 Investigators

Children's Hospital of Philadelphia, Philadelphia, PA, U.S.A.

INTRODUCTION

- Primary mitochondrial myopathies (PMMs) are a group of genetic disorders that negatively impact the efficient generation of adenosine triphosphate (ATP) by the mitochondrial respiratory chain
- PMM largely manifests as fatigue, exercise intolerance, and muscle weakness, which adversely affects physical function and quality-of-life (QoL); however, characterization of natural disease progression in this patient population is limited
- An analysis of claims data using the ICD-9 codes for primary mitochondrial disease places the overall incidence in the United States at approximately 36,000 adults (≥16 years of age)

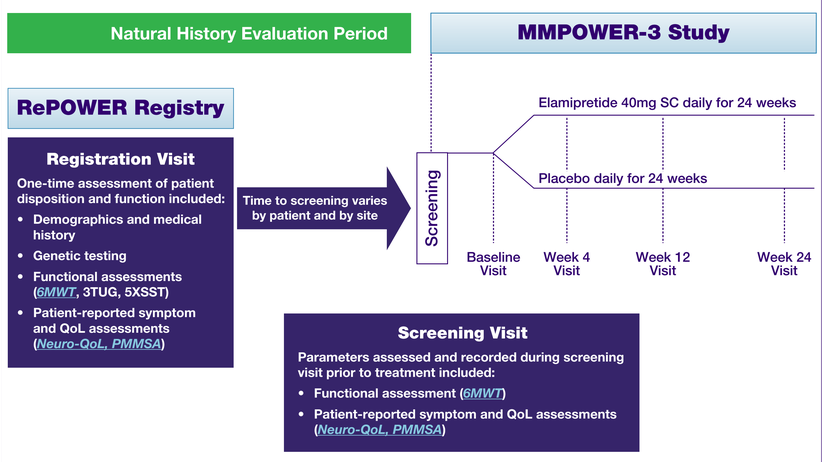
OBJECTIVE

- Subject data from the non-interventional period between registration in the RePOWER registry and the screening visit for the MMPOWER-3 clinical development program were analyzed to augment the understanding of the natural progression of PMM

METHODS

- RePOWER was a global, prospective, non-interventional registry that enrolled ambulatory subjects aged 16-80 years with signs and/or symptoms of PMM and sought to obtain demographic, genetic/phenotypic, and functional assessments
- RePOWER also served to identify potential participants for MMPOWER-3, a 24-week, double-blind, randomized, placebo-controlled study designed to investigate the efficacy and safety of elamipretide in patients with PMM
- In the RePOWER registry and MMPOWER-3 study, eligible patients completed a single screening visit in which all demographic, genetic, and clinical assessments were performed (**Figure 1**)

Figure 1. Baseline Assessments and Patient Flow: RePOWER Registry to MMPOWER-3 Study



Patients

- Patients included in RePOWER registry and screened for entry into MMPOWER-3 were aged ≥16 and ≤80 years, with a clinical presentation of PMM (i.e., patient-reported symptoms indicative of a mitochondrial respiratory chain disorder or physical examination findings of myopathy)
  - Patients were also required to be ambulatory and able to attempt the 6-Minute Walk Test (6MWT)
- For inclusion into the RePOWER registry, patients could not have:
  - Myopathic signs and/or symptoms due to a neuropathic process or gait problem that would interfere with the 6MWT
  - Prior exposure to elamipretide
  - Clinically significant cardiac disease and/or respiratory disease
  - A score of "not at all" for tiredness and muscle weakness symptoms on the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)
- In order to provide for ample patient numbers for analysis, patient groupings were obtained by bracketing elapsed time from RePOWER registration; groupings were set as:
  - Baseline: registration in RePOWER
  - 6-Month: elapsed time from the beginning of month 5 through the end of month 6 (RePOWER registration to screening for MMPOWER-3)
  - 12-Month: elapsed time from the beginning of month 5 through the end of month 6 (RePOWER registration to screening for MMPOWER-3). These patients are mutually exclusive of the patients in the 6-month group

Study Assessments

- Parameters assessed and recorded at the baseline visit for the RePOWER registry and MMPOWER-3 studies included demographics, functional assessments, patient-reported outcomes, and QoL assessments
  - **6MWT** (a performance-based test of exercise capacity that measures the distance in meters an individual is able to walk over a total duration of 6 minutes) was a functional assessment included in both the RePOWER registry and MMPOWER-3 study
  - **Neuro-QoL Fatigue Short Form Questionnaire (Neuro-QoL)** (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) was included in both the RePOWER registry and MMPOWER-3 study
  - **PMMSA** (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; PMMSA Total Fatigue score, a pre-specified fatigue subscale, assessed tiredness and muscle weakness at rest and during activities) was included in both the RePOWER registry and MMPOWER-3 study

Analysis Approach

- Disease progression was determined by comparing the data from the non-interventional time that elapsed between RePOWER registration and time of screening for MMPOWER-3
- Only subjects included in the RePOWER registry who were screened for MMPOWER-3 participation were included in the analysis
- Evaluations performed at both clinic visits, the 6MWT, Total Fatigue on the PMMSA, and the Neuro-QoL Fatigue Short Form, serve as the basis of the analysis of natural disease progression

RESULTS

Patients

- The analysis included 269 patients who underwent the non-interventional natural history evaluation period between RePOWER registry and MMPOWER-3 screening
- Baseline demographic values are provided for patient subsets and are based on the variability of available values (**Table 1**)

Table 1. Patient Demographics

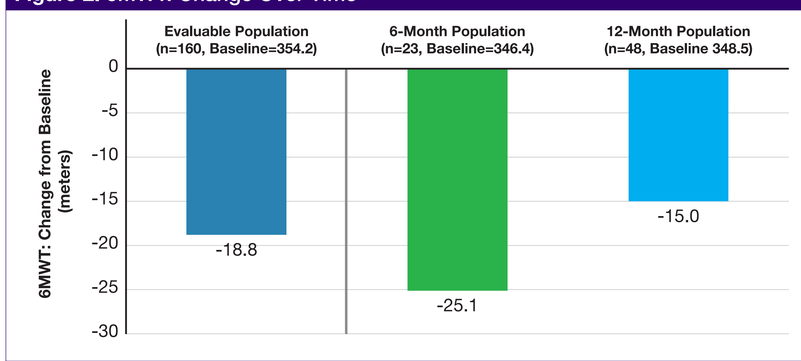
Demographic Variable	Subjects*
Overall patient population (N)	269
Average Age (n)	42.2 yrs (192)
Sex, n (%)	
Female	166 (62)
Male	103 (38)
Race, n (%)	
White	252 (94)
Asian	11 (4)
Other	5 (2)
Ethnicity, n (%)	
Non-Hispanic/Non-Latino	241 (90)
Hispanic/Latino	22 (8)
Other	6 (2)
Confirmed PMM Genetic Defects (n)	242
mtDNA defect	185 (116 women; 69 men)
nDNA defect	57 (35 women; 22 men)

*Variable n-values reflect available data.

6-Minute Walk Test

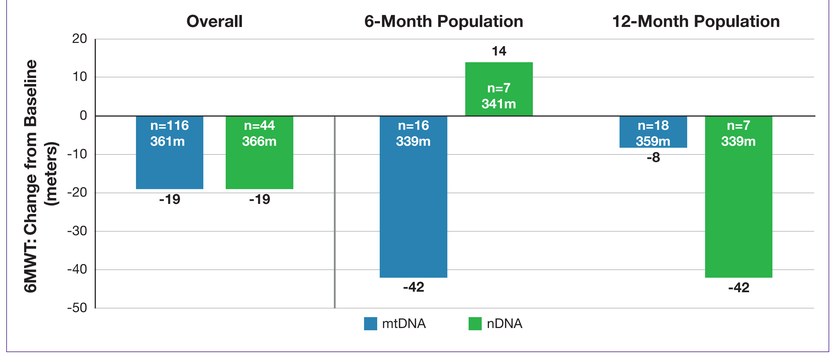
- Mean 6MWT was 354 meters at baseline (range: 60-597 meters) for all patients analyzed (n=160), and distance walked decreased throughout the non-interventional observation period (**Figure 2**)

Figure 2. 6MWT: Change Over Time



- Patients with an mtDNA or nDNA genetic defect had a similar overall change from baseline of -19 meters (**Figure 3**)

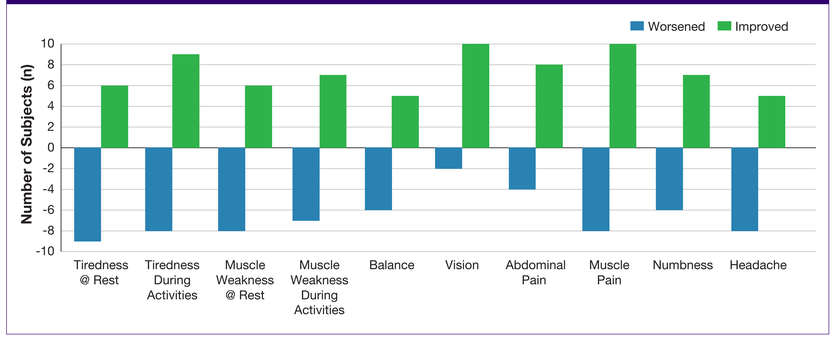
Figure 3. 6MWT: Change Over Time by Genetic Category



PMMSA Questionnaire

- The evaluable population of patients analyzed (n=27) demonstrated variable impact over time in each domain of the assessment (**Figure 4**)

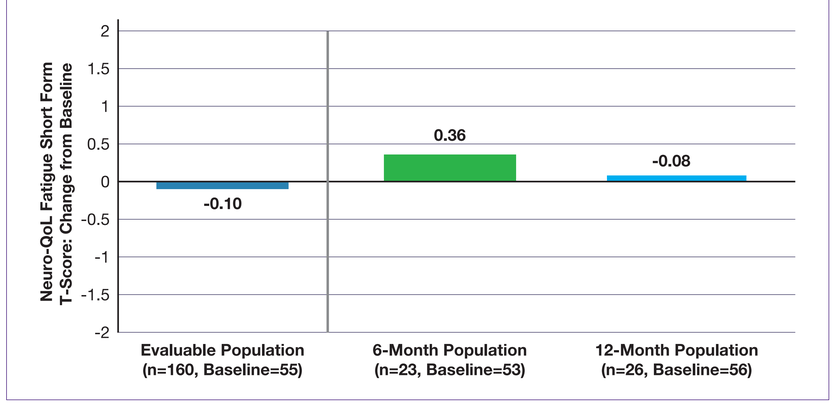
Figure 4. PMMSA Domain "Shift Analysis"



Neuro-QoL Fatigue Short Form

- Mean Neuro-QoL was 55 at baseline (range: 38.2-74.1) for all patients analyzed (n=160), with the average patient response being variable over the observation period. (**Figure 5**)

Figure 5. Neuro-QoL Fatigue Short Form T-Score: Change from Baseline



CONCLUSIONS

- The RePOWER registration population of patients with confirmed PMM demonstrated a significant level of disease burden at time of registration
- Disease progression was observed in the functional parameter of distance walked on the 6MWT for patients screened at 6 months and at 12 months for entry into the MMPOWER3-study
- Patient-reported symptom and QoL assessments proved to be challenging to interpret due to variability in available data and relatively small patient numbers
- These results demonstrate a need for additional research and characterization of the natural history of disease for patients with confirmed PMM

Funding Sources: Trial funded by Stealth BioTherapeutics, Newton, MA

Acknowledgements: On Behalf of the RePOWER & MMPOWER Investigators. **Australia:** Wools C, Sue C (RePOWER only); **Canada:** Lehman A, Tarnopolsky M; **Denmark:** Vissing J; **Germany:** Kornblum B, Klopstock T; **Hungary:** Molnar MJ; **Italy:** Bertini E, Mancuso M, Lamperti C, Servidei A; Toscano A, Carelli V; **UK:** Pitceathy R, Gorman G; **US:** Cohen BH, Haas R, Karaa A, Goldstein A, Koenig MK, Enns G, Van Hove J, Parikh S, Longo N, Hirano M, Falk M, Phan H, Scaglia F, Saneto R, Vockley J

Medical writing assistance was provided by James A. Shiffer, RPh, Write On Time Medical Communications, LLC

To view this poster on the Stealth BioTherapeutics website, snap a photo of this QR code with your smart phone (QR reader required).

Stealth BIOTHERAPEUTICS