MMPOWER-3 Study Design: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial of Elamipretide in Primary Mitochondrial Myopathy

Authors: Aiudi A, DiMatteo M, Carr J

Stealth BioTherapeutics, Newton, MA

INTRODUCTION

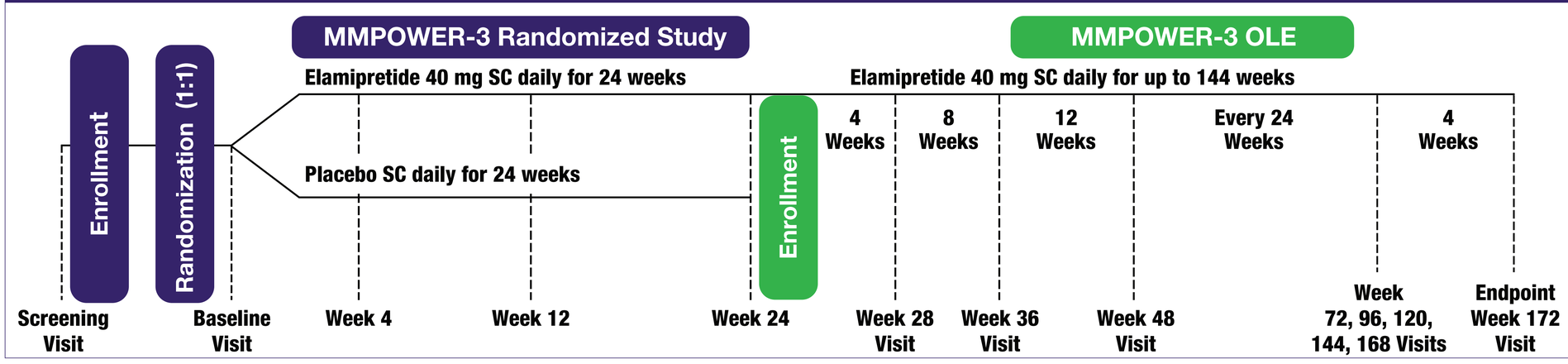
- Primary Mitochondrial Myopathy (PMM) can be caused by various genetic disorders that negatively impact the mitochondrial respiratory chain, adversely affecting physical function, exercise capacity, and quality of life (QoL)
- Currently, there are no approved treatments for patients with PMM
  - Available standard of care revolves largely around the use of supplements and nutritional agents that address symptoms only
- Elamipretide is a first-in-class agent being developed for the treatment of patients with PMM
- Elamipretide penetrates cell membranes, localizing to the inner mitochondrial membrane where it associates with cardiolipin, thereby improving ATP production and exercise capacity
- The clinical development program for elamipretide includes the MMPOWER-1, MMPOWER-2 and MMPOWER-2 OLE trials, in which treatment with elamipretide demonstrated treatment effects for patients with genetically confirmed PMM

OBJECTIVE

- MMPOWER-3 is an on-going, pivotal, Phase 3 clinical trial designed to evaluate the efficacy and safety of elamipretide 40 mg subcutaneously (SC) once daily as a treatment for patients with PMM
- MMPOWER-3 open-label extension (OLE) is designed to assess the long-term safety and tolerability of elamipretide in patients with PMM

STUDY DESIGN

Figure 1. MMPOWER-3 Study Design



- MMPOWER-3 is a 24-week, randomized, double-blind, placebo-controlled clinical trial for patients with genetically-confirmed PMM
- Patients were randomized in a 1:1 ratio to receive either 24 weeks of daily SC dose of 40 mg elamipretide or placebo
- All subjects completing the MMPOWER-3 randomized study may be eligible to enter into MMPOWER-3 OLE and receive treatment with 40 mg SC elamipretide for up to 144 weeks to assess the long-term safety and tolerability of elamipretide

Treatment Period

- Treatment will begin on the day of the baseline visit
  - Assessments will be conducted at weeks 4, 12, and 24 during randomized treatment
- Those patients who complete the week 24 visit may elect to continue into the MMPOWER-3 OLE 144-week treatment period
  - Treatment period for the OLE will begin on the day of the week 24 visit
  - Subjects will continue elamipretide or be switched from placebo to treatment with elamipretide
  - Subjects will return to the clinical site for week 28, 36, and 48 visits with additional visits occurring every 24 weeks up to the week-168 visit

Subjects

- MMPOWER-3 was designed to enroll 202 patients with PMM
- Patients had to meet all of the inclusion criteria and none of the exclusion criteria at the baseline visit to be eligible for enrollment (**Table 1**)

Table 1. Study Inclusion and Exclusion Criteria*

Inclusion Criteria

- Willing and able to provide consent form and adhere to trial requirements
- ≥16 and ≤ 80 years of age
- Diagnosed with PMM consisting of:
  - Molecular genetic abnormality consistent with PMM
  - Symptoms (i.e., exercise intolerance, fatigue, muscle weakness) or physical examination findings of myopathy that are the predominant symptoms of the subject's mitochondrial respiratory chain disorder

Exclusion Criteria

- Myopathic signs and/or symptoms due to a neuropathic process (i.e., cerebellar dysfunctions and peripheral neuropathies) or a gait problem that would interfere with the 6MWT, in the opinion of the Investigator
- Pregnant, planning to become pregnant, or lactating
- Walking < 100 meters or > 450 meters during the 6-Minute Walk Test (6MWT)
- Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2
- Severe vision impairment or seizure disorder that, in the opinion of the Investigator, may interfere with their ability to complete all trial requirements
- Active substance abuse during the past year

MMPOWER-3 OLE Continuation Criteria

- A subject must meet all of the following MMPOWER-3 OLE continuation criteria at the week 24 visit in MMPOWER-3 to be eligible for the OLE:
  - Continue to be able and willing to adhere to the trial requirements
  - Appropriate to continue in the OLE (i.e., subject was compliant in MMPOWER-3), in the opinion of the Investigator
  - Not had a serious adverse event (SAE)/serious adverse device effect (SADE) attributed to the study drug
  - Not permanently discontinued the study drug

*Summary of key criteria, full list available.

- Patient's medical history and other standard demographic characteristics will be recorded

Data Analysis

- Subject disposition will be tabulated by treatment group for the randomized portion of the study, with number (%) of subjects by exposure duration being assessed

Efficacy Measures

- MMPOWER-3 is designed to assess the safety and efficacy of elamipretide through multiple primary, secondary, and exploratory clinical study endpoints (**Table 2**)

Table 2. Clinical Study Endpoints in MMPOWER-3

Endpoint Classification	Study Endpoint(s)
Primary	Evaluate the effect of elamipretide 40 mg/d SC for 24 weeks on the: • 6-Minute Walk Test (6MWT) • Total Fatigue on the Primary Mitochondrial Myopathy Symptom Assessment© (PMMSA)
Secondary	Evaluate the effect of elamipretide 40 mg/d SC for 24 weeks on the: • Fatigue during activities on the PMMSA • Neuro-QoL Short Form Fatigue • Most bothersome symptom on the PMMSA • Neuro-QoL Fatigue activities of daily living (specific items from the Neuro-QoL Item Bank) • Safety and tolerability
Exploratory	Evaluate the effect of elamipretide 40 mg/d SC for 24 weeks on the: • Individual symptoms on the PMMSA • Alternate version of the PMMSA Total Fatigue Score • Individual items of the Neuro-QoL Fatigue • EQ-5D-5L • Patient Global Impression (PGI) Scales • Clinician Global Impression (CGI) Scales
Pharmacokinetic	To evaluate the PK of elamipretide

- 6-Minute Walk Test (6MWT)
  - Distance walked in meters
- Total Fatigue on the 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 Short Form (Neuro-QoL)
  - 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 Short Form 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, based on a 5-point scale: Never (1), Rarely (2), Sometimes (3), Often (4), Always (5)
- 5-level EQ-5D (EQ-5D-5L)
  - 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 five domains are scored using a 5-point scale
- Patient Global Impression (PGI) and Clinician Global Impression (CGI) Scales
  - Patients and clinicians provide an overall assessment of the severity of the patient's symptoms related to PMM on a 5-point scaled question scored 0 to 4 (0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Very Severe) and changes to their symptoms on a 7-point scale scored -3 to 3 (-3=very much worse, -2=moderately worse, -1=a little worse, 0=no change, 1=a little better, 2=moderately better, 3=very much better)

Safety Measures

- Safety and tolerability of elamipretide 40 mg/d SC for 24 weeks in the randomized study and long-term safety and tolerability for 144 weeks in the OLE portion of the study will be assessed through assessment of:
  - Adverse Events (AEs)
  - Vital Signs
  - Electrocardiograms (ECGs)
  - Clinical Laboratory Evaluations
  - Columbia-Suicide Severity Rating Scale (C-SSRS)

CONCLUSIONS

- MMPOWER-3 and MMPOWER-3 OLE are designed as part of the clinical development program for elamipretide, which includes previously conducted MMPOWER-1, MMPOWER-2, and MMPOWER-2 OLE studies with PMM
- MMPOWER-3 is an on-going clinical trial in patients with PMM
- MMPOWER-3 study will provide important information on how a novel therapeutic agent might impact cellular energetics, functional changes, and patient-reported outcomes (PROs) in patients with PMM

Disclosures*

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