**INTRODUCTION**

- Primary mitochondrial myopathies (PMM) are a group of genetic disorders associated with impairment of mitochondrial function, and are characterized by respiratory chain dysfunction and debilitating skeletal muscle weakness.

- Patients with PMM experience muscle weakness and atrophy, fatigue, and exercise intolerance, which adversely affects physical functioning, activities of daily living, and quality-of-life (QoL).

- Elamipretide is an acyl-carnitine lipopeptide that readily penetrates cell membranes and selectively localizes to the inner mitochondrial membrane where it associates with cardiolipin to restore mitochondrial cardiolipin architecture and improve ATP generation.

- The clinical development program includes the MMPOWER-1 and MMPOWER-2 trials, in which treatment with elamipretide demonstrated improvements in endpoints for patients with genetically confirmed PMM.

- The primary objective of the open-label extension of MMPOWER-2 (MMPOWER-2 OLE) is to assess the safety and tolerability of a single daily subcutaneous injection of elamipretide for up to 260 weeks.

**METHODS**

**Study Design**

- **MMPOWER-2 Study**
  - MMPOWER-2 was a 4-week multicentre, randomized, double-blind, placebo-controlled crossover trial in patients with genetically confirmed PMM.
  - All patients who completed MMPOWER-2 were automatically enrolled into the MMPOWER-2 OLE study.
  - **Elamipretide treatment** (n=27)
    - Week 0: Placebo injection (n=12) and oral placebo (n=15).
    - Week 4: Elamipretide injection (n=12) and oral placebo (n=15).
    - Week 12: Placebo injection (n=15) and oral placebo (n=12).
    - Week 26: Elamipretide injection (n=15) and oral placebo (n=12).
    - The MMPOWER-2 study was terminated on May 30, 2014.

- **MMPOWER-2 OLE Study**
  - All patients who completed MMPOWER-2 were automatically enrolled into the MMPOWER-2 OLE study.
  - **Elamipretide treatment** (n=15)
    - Week 0: Elamipretide injection (n=8) and oral elamipretide (n=7).
    - Week 4: Elamipretide injection (n=8) and oral elamipretide (n=7).
    - Week 12: Elamipretide injection (n=7) and oral elamipretide (n=8).
    - Week 26: Elamipretide injection (n=8) and oral elamipretide (n=7).
    - The MMPOWER-2 OLE study was terminated on May 30, 2014.

- **Study modifications**
  - **Enrollment (N = 30)**
    - **Key inclusion criteria for OLE**
      - Neuro-QoL Fatigue questionnaire
      - PMSSA Total Fatigue score (n=27)
    - **Key exclusion criteria for OLE**
      - Any serious disease that may interfere with neuro-QoL fatigue measurements.

- **Trends over time for efficacy endpoints**
  - **Summary of Patient Characteristics**
    - Table 1.

- **Quality-of-Life and Functional Assessments**
  - **Neuro-QoL Fatigue questionnaire**
    - Neuro-QoL Fatigue Short Form (n=27)
  - **PMSSA Total Fatigue score**
    - Figure 2
  - **Distance walked**
    - Figure 3

- **Primary outcomes**
  - **Safety and Tolerability**
    - **Injection site reactions**
      - Injection site reactions were the most commonly reported AE with elamipretide, the rates of which were consistent with those observed in previous clinical trials.

**RESULTS**

**Patients**

- **Trends over time for efficacy endpoints**
  - **Summary of Patient Characteristics**
    - Table 1.

**Safety and Tolerability**

- The safety profile of elamipretide in this trial was consistent with the results obtained from previous trials with PMM.

- **Overall**, elamipretide therapy was well tolerated, with most adverse events reported to be of mild severity.

- Five SAEs were reported in three subjects.

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