

# Exclusion Criteria

- Primary mitochondrial disease with predominant neurodegenerative phenotypes, such as, but not limited to, Leigh syndrome, Leber hereditary optic neuropathy (LHON) and Neuropathy ataxia-retinitis pigmentosa syndrome (NARP).
- Primary mitochondrial disease nuclear DNA mutations or mutations causing mtDNA destabilisation. Genetic mtDNA variants of uncertain significance, likely pathogenic, or pathogenic mutations with degrees of heteroplasmy below what can be considered to definitely cause PMD.
- General fatigue or muscle weakness due to causes other than mitochondrial disease, in the opinion of the investigator.
- Significant cardiovascular disease (e.g., sustained or symptomatic arrhythmia; dilated heart chambers or reduced function; Mobitz II atrioventricular block or greater) OR abnormal ECG that is clinically significant, as determined by the investigator. Any QTcF > 450 msec for male patients and > 470 msec for female patients is exclusionary. In the case of an exclusionary QTcF, the ECG can be repeated twice and the average of 3 QTcF intervals should be used to determine the QTcF eligibility.
- Recent history of unstable disease, inadequately controlled neurological manifestations or not recovered from stroke-like episodes including but not limited to:
  - stroke-like episodes within the last 6 months
  - more than 1 seizure/month within the last 6 months
  - hospitalised for Status Epilepticus within the last 6 months
  - more than 4 days of migraine episodes/month within the last 6 months
- History of inflammatory bowel disease, gastric erosions, peptic ulcer disease, or gastrointestinal bleeding episodes. Gastroesophageal reflux disease diagnosed by objective endoscopic or radiographic means, and clinically symptomatic at any point over the last 6 months.
- The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at the Screening Visit, that are of potential risk to the patient's safety, or the patient has, at the Screening Visit:
  - estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation <30 mL/min/1.73 m<sup>2</sup>
  - a serum total bilirubin value > 1.5 times the upper limit of the reference range unless elevation is related to Gilbert's syndrome and the investigator can rule out any underlying liver dysfunction based on other tests, the patient has a Child-Pugh score ≤6, and after discussing the case with the medical monitor
  - a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value > 2 times the upper limit of the reference range. Values between 2 and 3 times the upper limit of the reference range may be allowed if concomitant to elevation in creatine kinase as long as the investigator can rule out any underlying liver dysfunction based on other tests, the patient has a Child-Pugh score ≤6, and after discussing the case with the medical monitor
- The patient has, in the investigator's opinion, severe ataxia, neuropathy, balance problems or other medical condition that would interfere the evaluation of the 30s STS test.
- Untreated or undertreated sleep apnoea, in the opinion of the investigator.
- Use of idebenone within 14 days prior to the first dose.
- Patients have a history of unstable or severe pulmonary, immunological, oncological, hepatic disease, renal disease, or another medically significant illness other than PMD or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.
- The patient is, in the investigator's opinion, unlikely to comply with the protocol e.g. due to cognitive impairment or is unsuitable for any reason.
- The patient has an immediate family member (defined as family members residing at the same address) who participates in the study.
- Female patients with a positive pregnancy result at Screening or at Baseline.



# Exclusion Criteria

- A patient cannot participate if they received an investigational drug 30 days or 5 half-lives prior to the Screening Visit (whichever is longer), or plans to use an investigational drug (other than the study intervention) during the study
- Hypersensitivity to the active substance or to any of the excipients or placebo.