

Inclusion Criteria

- Age 18 years or older.
- A confirmed PMD diagnosis caused by a known pathogenic gene mutation or deletion of the mitochondrial genome (category 6 of the International Classification of Inborn Metabolic Disorders [ICIMD])¹² according to American College of Medical Genetics (ACMG)/Association of Molecular Pathology (AMP) criteria¹, with multisystemic disease expressions, including:
 - m.3243A>G associated MELAS-MIDD spectrum disorders,
 - single large scale mtDNA deletion associated KSS-CPEO spectrum disorders,
 - other multisystemic mtDNA-related disease (including MERRF).
- Presence of chronic mitochondrial fatigue:
 - History of mitochondrial fatigue for at least 3 months prior to the Screening Visit AND
 - Presence of at least moderate level of fatigue, assessed by PROMIS® Fatigue PMD Short form raw score ≥ 27 at Screening and Baseline
 - Presence of mitochondrial myopathy defined as:
 - Myopathy (proximal muscle weakness), NMDAS Section III Clinical Assessment, item 5 score ≥ 1 , which reads: "minimal reduction in hip flexion and/or shoulder abduction only (e.g. MRC 4+/5)". For the inclusion only hip flexion, but not shoulder abduction, should be taken into account. AND / OR
 - Exercise Tolerance: NMDAS Section I, item 9 score ≥ 1 , which reads: "unlimited on flat - symptomatic on inclines or stairs".
- Patients must be able to perform at least 2 repetitions and the maximal capacity must not exceed 17 repetitions in males or 16 repetitions in females in a 30s STS test at screening.
- Clinically stable, apart from symptoms associated with the diagnosis of mitochondrial disease, at Screening and Baseline, as determined by medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations at Screening, as assessed by the investigator.
- The patient is willing and able to attend study appointments within the specified time windows.
- Willingness and ability to complete electronic PROs.
- Willingness to maintain a stable diet during the Screening and study periods.
- Patients who take any mitochondrial disease-focused vitamins or supplemental therapies, including coenzyme Q10 (CoQ10), niacin/nicotinamide (vitamin B3), and L-arginine, has been on a stable dose regimen of these for 3 months prior to randomisation and intends to stay on a stable dose for the duration of the study period.
- Willingness to suspend treatment with idebenone during the study.
- Female patient is not pregnant and at least one of the following conditions apply:
 - Not a woman of childbearing potential (WOCBP)
 - WOCBP must agree not to try and become pregnant and use a highly effective method of contraception from the time of informed consent through at least 36 days (~5 half-lives of KL1333 plus 30 days) after the last dose of investigational medicinal product (IMP) administration.
 - Male patients with female partner(s) of childbearing potential must agree to use a male condom in addition to using highly effective contraception throughout the treatment period and for 96 days after the last dose of IMP administration. The requirement to use a male condom also applies to male patients with a pregnant or breastfeeding partner.



Inclusion Criteria cont.

- Female patients must agree not to breastfeed starting at Screening and throughout the study period and for 36 days after the last dose of IMP administration.
- Female patients must agree to not donate ova throughout the study period and for 36 days after the last dose of IMP administration, and male patients must agree to not donate sperm throughout the study period and for 96 days after the last dose of IMP administration.