Mavodelpar Clinical Development Program in Adult Patients with Primary Mitochondrial Myopathies: Results from a Phase 1b Study and Design of Ongoing Pivotal Study (STRIDE)

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on behalf of authors:

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*Dr Pitceathly is speaking in a capacity of a paid consultant on behalf of Reneo Pharma Ltd.

Author conflicts of interest

RDSP is a principal investigator on the Reneo Pharma Ltd Phase 2 STRIDE trial. He has received a research grant from Reneo Pharma Ltd and consultancy fees from Stealth BioTherapeutics, Reneo Pharma Ltd, and Abliva. He is also a paid speaker of Reneo Pharma Ltd.

RJS, AB, LA, JN, and **GSG** have no conflicts of interest to report.

GL is a statistical consultant to Reneo Pharma Ltd.

NR, LP, MD, and AD are employees of Reneo Pharmaceuticals, Inc. or Reneo Pharma Ltd.

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AK is a principal investigator on the Reneo Pharma Ltd Phase 2 STRIDE trial. She received research grant and clinical trial support from Stealth BT, Sanofi Genzyme, Astellas, Cyclerion, PTC Therapeutics, Idorsia and Takeda; is the chair-elect on the scientific and medical advisory board of the United Mitochondrial Disease Foundation; is a founder and board member of the mitochondrial care network; Past President of the Mitochondrial Medicine Society and current board member; and is an investigator in the North American Mitochondrial Disease Consortium.

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Background

Primary mitochondrial myopathies (PMM) are:[1,2]

- Rare genetic disorders
- Defects in oxidative phosphorylation (OXPHOS) and other pathways within the mitochondria, affecting predominantly skeletal muscles[2,3]
- Known to present with symptoms including myopathy, muscle weakness, fatigue and exercise intolerance
- An area of significant unmet need:
  - There are currently no approved therapies for PMM
  - Standard treatment focuses on symptom and dietary management

Peroxisome proliferator activated receptor delta (PPARδ) is:

- Highly expressed in muscle and adipose tissue[4]
- Abundant in skeletal muscle and preferentially expressed in oxidative muscle fibers[4]

- PPARδ-specific agonists may improve the cellular energy deficit by increasing fatty acid oxidization, OXPHOS activity and mitochondrial biogenesis

OXPHOS, oxidative phosphorylation; PMM, primary mitochondrial myopathies; PPARδ, peroxisome proliferator activated receptor delta.

1. de Barcelos IP, et al. Curr Opin Neurol. 2019;32(5):715–721. 2. Mancuso M, et al. Neuromuscul Disord. 2017;27(12):1126–1137. 3. Parikh S, et al. Genet Med. 2015;17(9):689-701.
4. Wang YX, et al. PLoS Biol. 2004;2(10):e294.

Background: Mavodelpar (REN001)

Selective PPARδ agonist[1]

Gene transcription regulation:[1]
- **Glucose homeostasis**
- **Fatty acid metabolism**

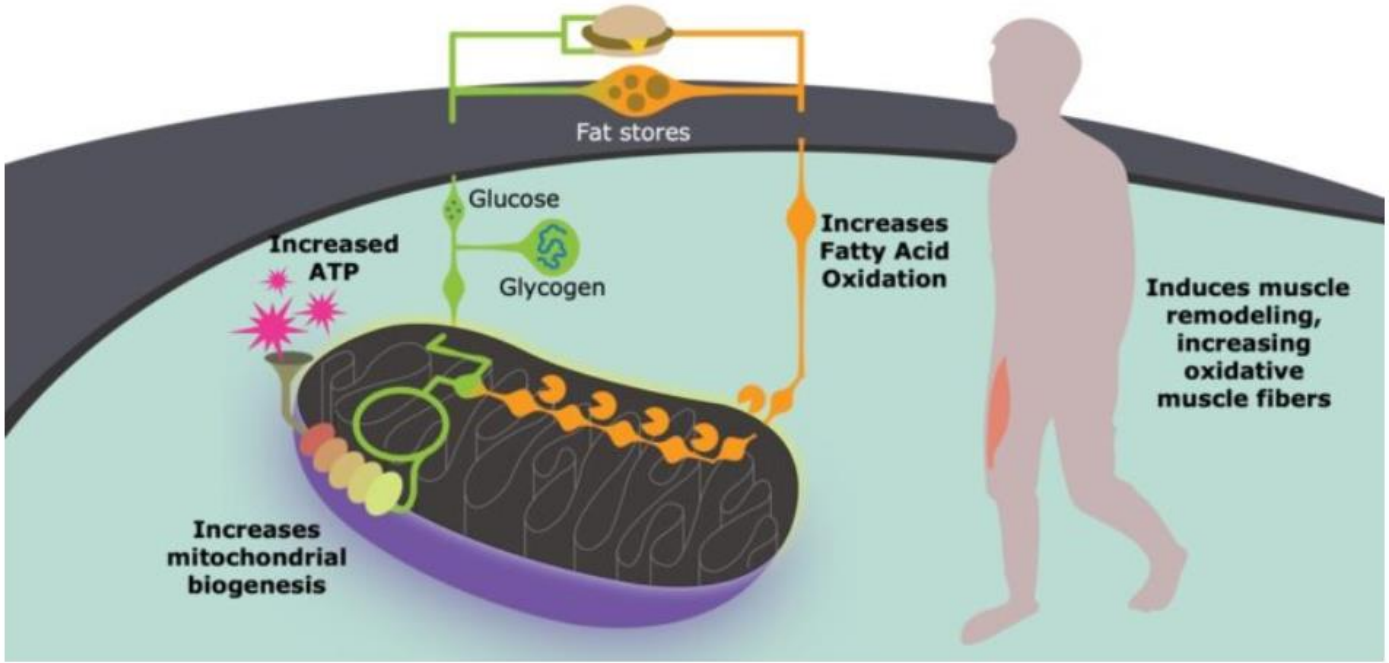


Image source: Reneo Pharmaceuticals, Inc. Available at: https://reneopharma.com/programs

Mavodelpar is an investigational drug not yet approved by any regulatory agency for prescription to patients and is not available outside Reneo Pharma Ltd's research program

PPARδ, peroxisome proliferator-activated receptor delta.

1. Davies M, Dorenbaum A, Wang S and Mittendorfer B. J Clin Trials. 2022;12(2) No: 1000495.

Open-label Phase 1b study: Methods

Participants

- Male or female
- ≥16 years
- Genetically-confirmed PMM caused by mtDNA variants
- Evidence of myopathy

Excluded if:

- Documented evidence of ongoing rhabdomyolysis
- History of cancer or liver disease
- Sensitivity to PPAR agonists
- Hospitalization within the 3 months prior to screening

Design

Two parts:

- Part A: mavodelpar 100 mg orally, QD for 12 weeks
- Part B: option to extend dosing for an additional 36 weeks

Two UK study centers:

- London and Newcastle upon Tyne

Modifications to limit the risk of COVID-19 infection

- Home visits

Endpoints

Primary:

- Safety

Exploratory endpoints:

- 12MWT (distance walked)
- 30STS
- Peak exercise test (peak oxygen consumption)
- Newcastle Mitochondrial Disease Adult Scale
- Patient-reported outcomes:
  - BPI short-form
  - MFIS
  - SF-36

12MWT, 12-minute walk test; 30STS, 30-second sit-to-stand test; BPI, Brief Pain Inventory; MFIS, Modified Fatigue Impact Scale; mtDNA, mitochondrial DNA; PMM, primary mitochondrial myopathies; QD, once daily; SF-36, 36-Item Short Form Survey.

Open-label Phase 1b study: Demographics and patient disposition

Demographics	Overall patients (N=23)
Mean (SD) age, years	54.5 (7.8)
Minimum age, years	43
Maximum age, years	69
Female, n (%)	15 (65.2)
Race, n (%)	
White	22 (95.7)
mtDNA variants, n (%)	
m.3243A>G variants	11 (47.8)
Other mtDNA variants	12 (52.2)

Withdrawal from study, n (%)	Overall patients (N=23)
Part A (n=17)	
COVID-19 pandemic	5 (21.7)
Consent withdrawn	1 (4.3)
Part B (n=13)	
COVID-19 pandemic	11 (47.8)
Physician decision	2 (8.7)

n=13 patients started Part B. This part of the study was terminated early due to the COVID-19 pandemic

Open-label Phase 1b study: Results
Safety

Part A	Patients (N=23)
Total number of patients reporting TEAEs, n (%)	20 (87.0)
Total number of TEAEs	85
Total number of patients reporting TEAEs considered related to study drug, n (%)	13 (56.5)
TEAEs related to study drug	55
Total number of serious TEAEs	1*
Patients reporting moderate TEAEs, n (%)	11 (47.8)
Patients who discontinued treatment due to TEAEs, n	0
Total number of patients with TEAEs leading to death	0
Most frequently reported TEAEs (≥7 patients) by system organ class	
Gastrointestinal disorders, n (%)	9 (39.1)
Musculoskeletal and connective tissue disorders, n (%)	7 (30.4)
Nervous system disorders, n (%)	7 (30.4)
Skin and subcutaneous tissue disorders, n (%)	7 (30.4)
Most frequently reported TEAEs (≥4 patients) by preferred term	
Constipation, n (%)	4 (17.4)
Headache, n (%)	4 (17.4)

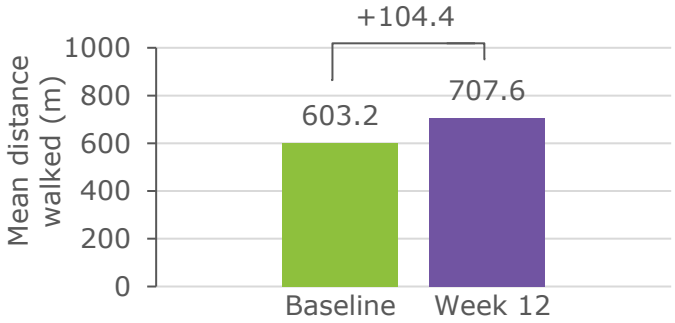
- No severe TEAEs or deaths reported in Part A or Part B
- In Part B, 9/13 (69.2%) patients reported TEAEs (n=29), before the study completed early

*Muscle biopsy hematoma

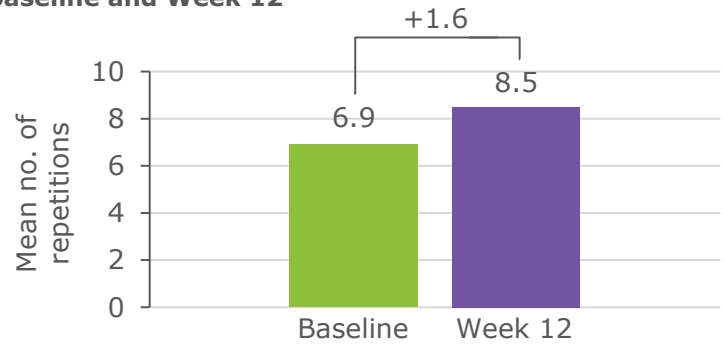
TEAE, treatment-emergent adverse event.

Open-label Phase 1b study: Results
Exploratory efficacy outcomes

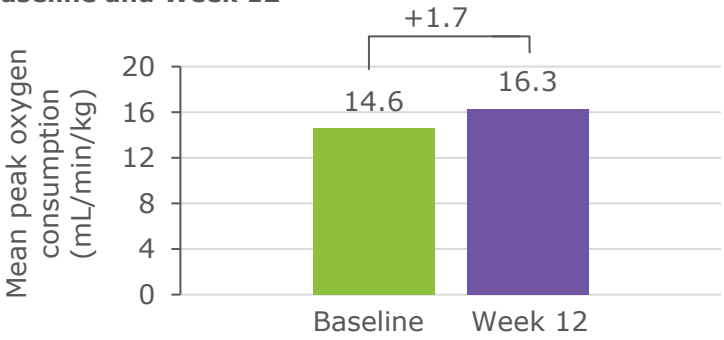
12MWT mean score improved between baseline and Week 12



30STS mean scores improved between baseline and Week 12



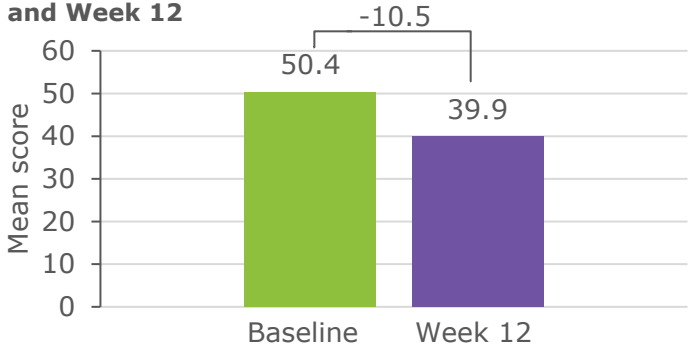
Peak exercise test (peak oxygen consumption) mean score improved between baseline and Week 12



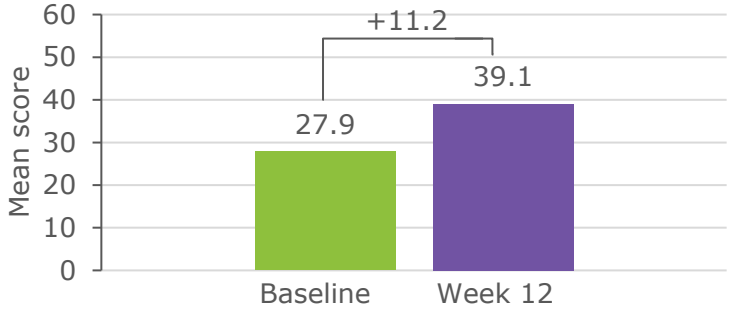
12MWT, 12-minute walk test; 30STS, 30-second sit-to-stand test.

Open-label Phase 1b study: Results
Quality of life outcomes

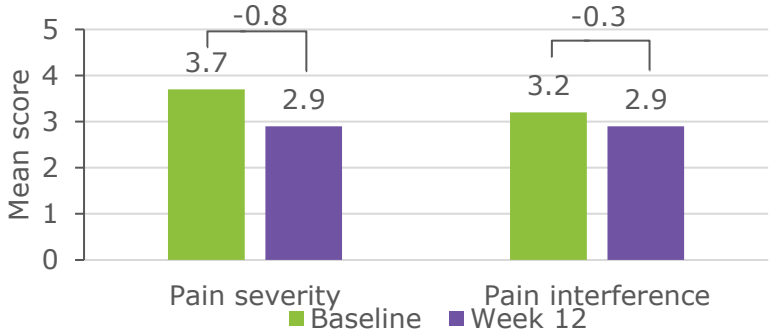
MFIS* total score improved between baseline and Week 12



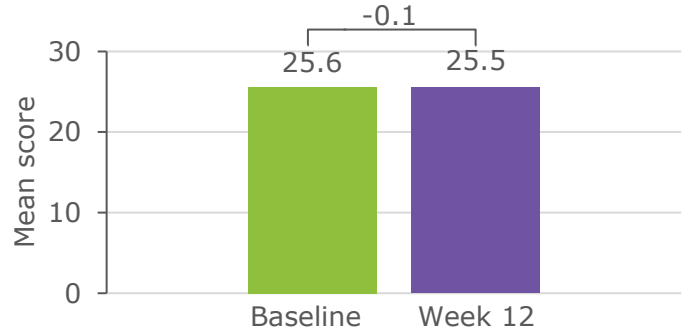
SF-36† energy/fatigue score improved between baseline and Week 12



BPI‡ mean severity and interference scores improved between baseline and Week 12



NMDAS§ mean score was similar at baseline and Week 12



BPI, Brief Pain Inventory; MFIS, Modified Fatigue Impact Scale; NMDAS, Newcastle Mitochondrial Disease Adult Scale; SF-36, 36-Item Short Form Survey.
*MFIS evaluates how fatigued a patient is and comprises a 0–84 scale, where 84 indicates greater impact of disease on daily function (i.e., worse health).
†SF-36: each scale is scored as a number 0–100 with a higher score indicating a better state of health. ‡BPI scale defines pain as a score from 1–10, 10 being severe pain/interference.
§NMDAS score ranges from 0–140 with a higher score indicating poorer health.

Open-label Phase 1b study: Conclusions

- Following 12 weeks of dosing in an open-label Phase 1b study, mavodelpar was considered well tolerated in adults with PMM

- Improvements were observed at Week 12 in:
  - Endurance/exercise tolerance (12MWT)
  - Aerobic capacity (peak exercise test)
  - Fatigue and pain (MFIS, SF-36 and BPI)

- This study has informed the design of the STRIDE pivotal study (REN001-201)

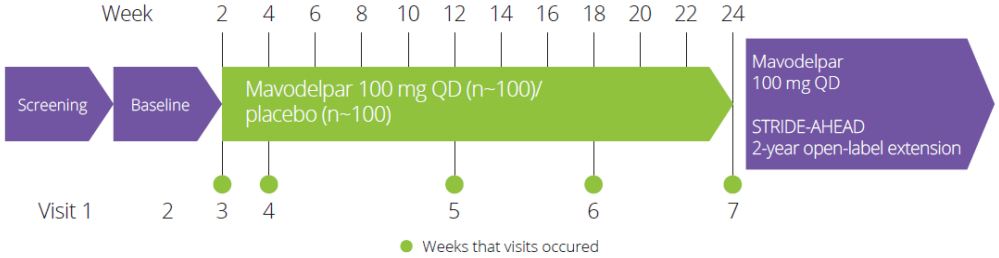
12MWT, 12-minute walk test; BPI, Brief Pain Inventory; MFIS, Modified Fatigue Impact Scale; PMM, primary mitochondrial myopathies; SF-36, 36-Item Short Form Survey.

1. Mancuso M, et al. Neuromuscul Disord. 2017;27(12):1126–1137. 2. de Barcelos IP, et al. Curr Opin Neurol. 2019;32(5):715–721.

The STRIDE Phase 2b pivotal study: Design

STRIDE study (NCT04535609)[1]

- Randomized (1:1), double-blind, placebo-controlled 24-week Phase 2b pivotal trial
- Efficacy and safety of oral mavodelpar (100 mg QD) in adults with PMM; enrollment completed (n=213)
- 41 sites, internationally
- Modifications to limit COVID-19 infection risk (home visits)
- Endpoints:
  - Primary: baseline to Week 24 change in the 12MWT
  - Secondary/exploratory: PROMIS® Fatigue score, 30STS, MFIS Physical sub-scale score, PGIC score (muscle symptoms), and other patient-reported outcomes
- Top-line results expected Q4 2023



12MWT, 12-minute walk test; 30STS, 30-second sit-to-stand test; MFIS, Modified Fatigue Impact Scale; PGIC, Patient Global Impression of Change, PROMIS, Patient Reported Outcome Measurement Information System; QD, once daily.

1. STRIDE study; NCT04535609. Available at: https://clinicaltrials.gov/ct2/show/NCT04535609 (Accessed July 2023).

Thank you

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