Mavodelpar clinical development program in adult patients with primary mitochondrial myopathies (PMM): Design of the ongoing pivotal study (STRIDE) based on results from Phase 1b PMM study in adult patients

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INTRODUCTION

- Primary mitochondrial myopathies (PMM) are rare genetic disorders resulting in defects of oxidative phosphorylation, affecting predominantly skeletal muscles and resulting in muscle weakness, fatigue and exercise intolerance[1,2]
- PMM represent an area of significant unmet need as there is currently no approved pharmacological treatment for patients, and standard treatment focuses on symptom and dietary management[1,2]
- Mavodelpar (REN001) is a selective peroxisome proliferator-activated receptor delta (PPARδ) agonist that regulates the transcription of genes involved in the mitochondrial metabolism of fatty acids and glucose homeostasis. PPARδ is highly expressed in muscle and adipose tissue; it is the most abundant PPAR isoform in skeletal muscle and is preferentially expressed in oxidative fibers[3]
- PPARδ-specific agonists may improve the cellular energy deficit in patients with PMM by increasing fatty acid oxidization and oxidative phosphorylation (OXPHOS) activity
- The safety and efficacy findings from an open-label, Phase 1b study in adults with PMM informed the design of the pivotal study, REN001-201 (NCT04535609), which is a fully enrolled, ongoing, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of mavodelpar (100 mg once daily [QD]) in adults with PMM due to mitochondrial DNA (mtDNA) defects[4]

OPEN-LABEL PHASE 1B STUDY METHODS

- Eligible patients were male or female, aged 16 years or older with genetically-confirmed PMM caused by mtDNA defects
- Study candidates were excluded if they had documented evidence of ongoing rhabdomyolysis, history of cancer or liver disease, sensitivity to PPAR agonists, or hospitalization within the 3 months prior to screening
- This study was conducted in two parts:
  - Part A: Patients received mavodelpar 100 mg orally, QD for 12 weeks
  - Part B: Patients were provided with the option to extend dosing for an additional 36 weeks
- The study was conducted in two study centers in the United Kingdom (London and Newcastle upon Tyne). Modifications to limit the risk of Covid-19 infection, such as home visits, were implemented
- The primary endpoint was safety
- Secondary exploratory efficacy assessments included:
  - Distance (meters) walked in the 12-minute walk test (12MWT)
  - 30-second sit-to-stand test (30STS)
  - Peak exercise test (measuring peak oxygen consumption)
  - Patient-reported outcomes including Brief Pain Inventory (BPI), Modified Fatigue Impact Scale (MFIS) and 36-Item Short Form Survey (SF-36)

OPEN-LABEL PHASE 1B STUDY RESULTS

- Overall, 23 patients were enrolled (**Table 1**), 17 completed 12 weeks of treatment, and 6 withdrew during Part A (5 withdrew due to the Covid-19 pandemic and 1 withdrew consent). Thirteen of the patients who completed Part A were dosed in Part B. The study was terminated due to the Covid-19 pandemic before any patients completed Part B. The maximum duration of treatment (Part A + Part B) was 39.9 weeks

Table 1. Demographic characteristics

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 defects, n (%) m.3243A>G mutation Other	 11 (47.8) 12 (52.2)

Safety

- In Part A, the most frequently reported treatment-emergent adverse events (TEAEs) were constipation and headache (n=4 each, 17.4%) (**Table 2**)
- There were no severe TEAEs or deaths reported during either Part A (**Table 2**) or Part B
- One serious TEAE of hematoma post baseline muscle biopsy was reported in one patient in Part A (**Table 2**)
- In Part B, a total of 9/13 (69.2%) of patients reported TEAEs (n=29). The most frequently reported TEAEs (n=2 each, 15.4%) that had an onset in Part B were diarrhea and migraine

OPEN-LABEL PHASE 1B STUDY RESULTS (CONTINUED)

Table 2. Reported TEAEs in 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)

*Muscle biopsy hematoma

Exploratory Efficacy

- Improvements from baseline were observed in the 12MWT, 30STS and peak exercise test at Week 12 (n=17; **Figures 1, 2 and 3**)

Figure 1. 12MWT mean scores at baseline and Week 12

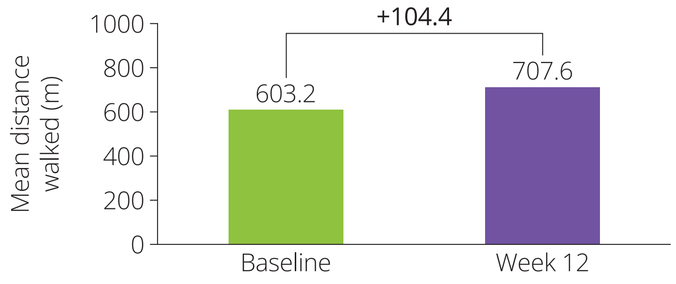


Figure 2. 30STS mean scores at baseline and Week 12

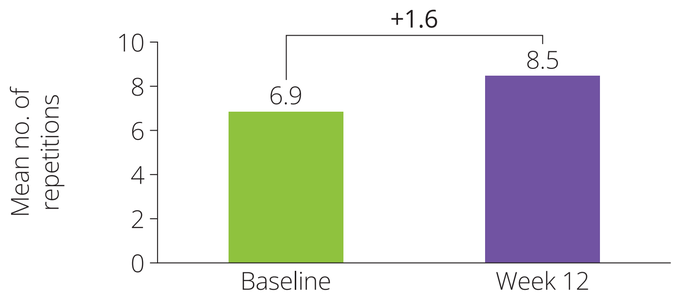
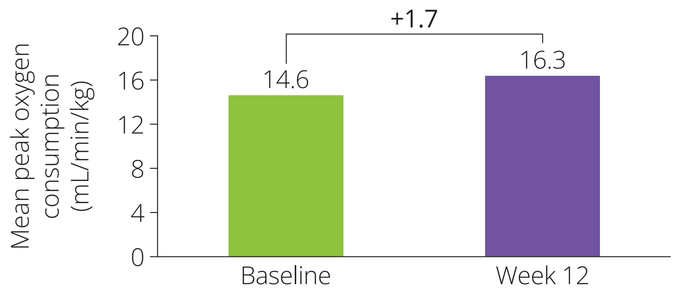
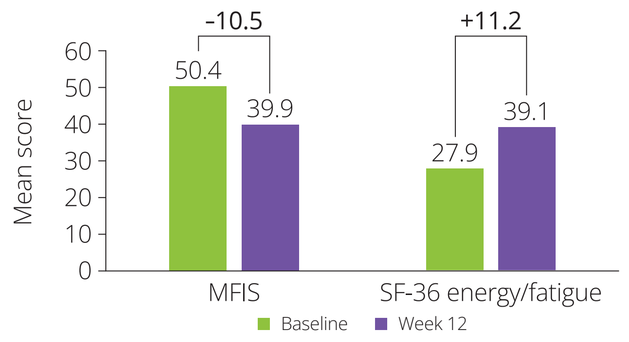


Figure 3. Peak exercise test mean scores at baseline and Week 12



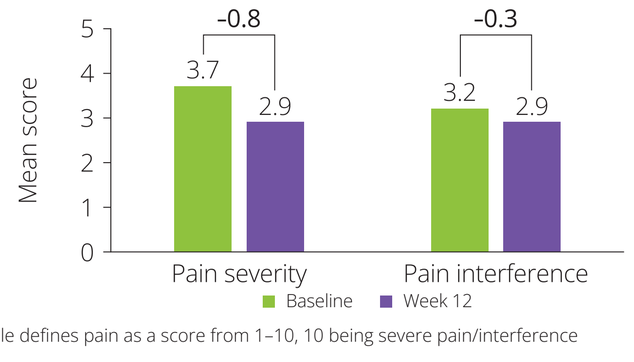
- Overall improvements in quality-of-life assessments were observed with positive changes from baseline in the SF-36 energy/fatigue score, fatigue as measured by MFIS mean total score and mean BPI (short form) severity and interference scores (**Figures 4 and 5**)

Figure 4. MFIS* total score and SF-36** energy/fatigue score at baseline and Week 12



*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

Figure 5. BPI* mean severity and interference scores at baseline and Week 12

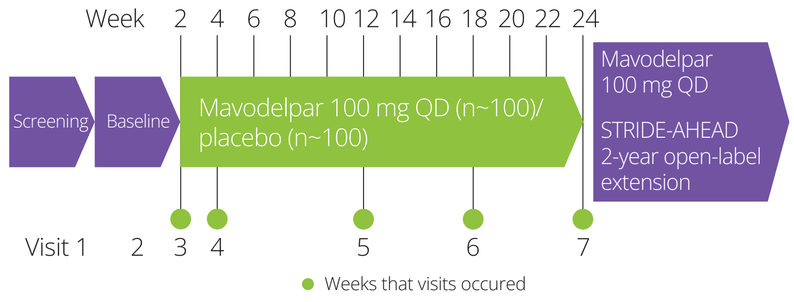


*BPI scale defines pain as a score from 1–10, 10 being severe pain/interference

PHASE 2B PIVOTAL STUDY DESIGN

- The ongoing STRIDE study (NCT04535609) is a randomized (1:1), double-blind, placebo-controlled, 24-week Phase 2b trial to evaluate the efficacy and safety of oral mavodelpar (100 mg QD) in adults with PMM caused by confirmed mtDNA defects[4] (**Figure 6**)
- The STRIDE study is fully enrolled (N=213) and is being conducted at 41 sites in Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, New Zealand, Norway, Spain, The Netherlands, the UK and the United States
- The STRIDE design incorporates modifications to limit the risk of Covid-19 infection, such as home visits
- The primary efficacy endpoint for STRIDE is change from baseline to Week 24 in the distance walked during the 12MWT
- Secondary/exploratory efficacy endpoints include Patient Reported Outcome Measurement Information System (PROMIS) Fatigue score, 30STS, MFIS Physical sub-scale score, Patient Global Impression of Change (PGIC) score (muscle symptoms), and other patient-reported outcomes

Figure 6. STRIDE study design



CONCLUSIONS

- Following 12 weeks of dosing in an open-label Phase 1b study, mavodelpar was considered well tolerated in adult patients with PMM
- Mavodelpar treatment improvements were observed at Week 12 compared to baseline in endurance/exercise tolerance in the 12MWT, aerobic capacity, fatigue and pain
- The Phase 1b study results support the ongoing development of mavodelpar and informed the design of the STRIDE pivotal study in PMM, a debilitating disease with high unmet need and no approved drug treatment options[1,2]
- Although the Phase 1b study was an open-label study, it offered important information that enabled the design of the pivotal trial (STRIDE) including selection of efficacy endpoints; top-line results from the pivotal STRIDE study are anticipated Q4 2023

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ABBREVIATIONS

12MWT, 12-minute walk test; 30STS, 30-second sit-to-stand test; BPI, Brief Pain Inventory; MFIS, Modified Fatigue Impact Scale; mtDNA, mitochondrial DNA; PGIC, Patient Global Impression of Change; PMM, primary mitochondrial myopathies; PPARδ, peroxisome proliferator-activated receptor delta; QD, once daily; SD, standard deviation; SF-36, 36-Item Short Form Survey; TEAEs, treatment-emergent adverse events.

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DISCLOSURES

R.D.S. Pitceathly, R.J. Stefanetti, J. Newman, A. Blain and **G.S. Gorman** have no conflicts of interest. **G. Layton** is a statistical consultant to Reneo Pharma Ltd. **N. Regan, L. Purkins** and **M. Davies** are employees of Reneo Pharma Ltd. **A. Dorenbaum** is an employee of Reneo Pharmaceuticals Inc. **M. Mancuso** received research funding, and received fees from Stealth BT, Shire, Sanofi Genzyme, Khondrion, Abliva, Reneo, Zogenix. **A. Karaa** 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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