"An open-label study to evaluate the safety and tolerability of 12 weeks treatment with oral REN001 in patients with primary mitochondrial myopathy (PMM), with an optional extension of treatment"

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Objective: To evaluate the safety and tolerability of REN001, a selective peroxisome proliferator-activated receptor delta (PPARδ) agonist in adults with primary mitochondrial myopathy (PMM) caused by mitochondrial gene defects. Prespecified exploratory efficacy endpoints were assessed.

Methods: This was an open label, 2-centre, single-arm study in 23 patients with genetically confirmed PMM who received 100 mg/day REN001 for 12-weeks (Part A), with the option of continuing dosing for an additional 36-weeks (Part B).

Results:
The mean (SD) age of participants was 54 (7.8) years (range: 43-69) with 65% (n = 15) female and 48% harboring the m.3243A>G mutation. At baseline, the mean distance walked in 12 minutes was 603 metres (m), normative value ≥1,200 m. Baseline Patient Reported Outcome Measures (PROMs) were outside of normative values, indicative of the high impact of fatigue and pain on patient's daily life activities. [Modified Fatigue Impact Scale (MFIS), 46.5; Brief Pain Inventory (BPI), 2.54; Short-Form-36 (SF-36) Energy/Fatigue, 29.7 compared with normative values of 11, 0 and 60-70, respectively].

Disposition: Of 23 participants enrolled into Part A, 17 completed (5 were withdrawn due to the Covid-19 pandemic and 1 discontinued due to logistical reasons). Thirteen of the 17 participants who completed Part A enrolled into the Part B extension, with 11 withdrawn due to Covid-19 after a mean exposure of 27.7 weeks (range 20-40). Two subjects discontinued and 4 declined enrolment for reasons unrelated to dosing.

Safety: Treatment emergent adverse events were mild/moderate; no deaths, serious AEs (SAEs) related to treatment, or AEs leading to participant discontinuation were reported. There were no clinically significant changes in vital signs, electrocardiograms, or urinalysis during the trial.

Exploratory efficacy: Following 12 weeks treatment, patients achieved an average increase of 104 meters in distance walked during the 12Minute Walk Test (compared to baseline. Fifteen of 17 subjects (88%) had an increase in distance walked, with 13 of 17 (76%) increasing by a clinically significant 60 meters or more. Means of the submaximal exercise test (time to exhaustion) and PROMs: fatigue (MFIS), pain severity (BPI), and Energy & Fatigue energy (SF-36) also significant improved from baseline to week 12 ($p<0.05$).

Conclusion:
REN001 100 mg once daily (QD) was well tolerated with no drug-related SAEs in patients with PMM. Positive impacts on endurance were supported by changes in PROMs. The observed safety profile and the early exploratory efficacy data support further development of REN001 drug in this indication.

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