An open-label study to evaluate the safety and tolerability of 12 weeks of treatment with oral REN001 in subjects with long-chain fatty acid oxidation disorders (LC-FAOD)

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Introduction

- LC-FAOD is an area of significant unmet medical need with management largely consisting of dietary and lifestyle adjustment[1]
- Available treatment for LC-FAOD improves symptoms but does not eliminate them[2]
- This open-label, Phase 1b, multi-center study (NCT03833128)[3] investigated the use of REN001, an oral PPAR delta (PPARδ) agonist, in the treatment of LC-FAOD
- PPARδ increases transcription of genes involved in fatty acid oxidation (FAO), resulting in increased production of cellular energy

Methods and Study Design

- Eligible participants were male or female and aged 18 years or older. They had a confirmed LC-FAOD diagnosis of CPT2, VLCAD, LCHAD, or TFP, and a history of at least one of the following: elevated creatine phosphokinase, hypoglycemia, rhabdomyolysis and/or cardiomyopathy
- Participants received 50 mg/day (n=3) or 100 mg/day (n=21) of REN001 orally for 12 weeks
- Seven home or study center visits were carried out, as shown in **Figure 1**
- Primary and secondary endpoints are summarized in **Table 1**

Results

Baseline characteristics

- Of the 24 patients, 8 had CPT2, 5 LCHAD, 9 VLCAD and 2 TFP deficiency **(Table 2)**
- The median age was 23 years, and gender was relatively evenly divided (54.2% were male) **(Table 2)**

Safety

- Reported TEAEs were primarily mild or moderate **(Table 3)**, and 3 patients with TEAEs discontinued the study drug
- There were 78 TEAEs reported. Musculoskeletal and connective tissue disorders were the most common TEAEs reported by patients **(Table 4)**, including rhabdomyolysis and myalgia, each reported by 4 (16.7%) patients

Clinical outcome and QoL measures

- The mean distance in 12MWT increased over 12 weeks in the overall population, indicating improved function. The greatest increase was observed in the CPT2 and LCHAD subgroups (51.9 meters and 73.7 meters, respectively) **(Figure 2)**
- Mean changes in MFIS total and SF-36 energy/fatigue domain scores from baseline to Week 12 were inconsistent across the subgroups **(Figures 3 and 4)**. Lower MFIS scores indicate less symptoms and higher SF-36 scores indicate a more favorable health status
- Patients in the LCHAD subgroup demonstrated the greatest increase in 12MWT, increase in SF-36, and decrease in MFIS

Figure 1. Study design

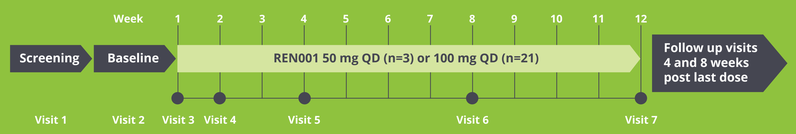


Table 1. Endpoints

Primary endpoint (Safety)	Number and severity of adverse events (AE)
Exploratory endpoints	Change from baseline to Week 12 • 12-minute walk test (12MWT) • 36-Item Short Form Health Survey (SF-36) score • Modified Fatigue Impact Scale (MFIS) score

Table 2. Baseline characteristics

	Overall patients (N=24)
CPT2, n (%)	8 (33.3)
LCHAD, n (%)	5 (20.8)
VLCAD, n (%)	9 (37.5)
TFP, n (%)	2 (8.3)
Minimum age, years	18
Maximum age, years	74
Median age, years	23
Male, n (%)	13 (54.2)
Female, n (%)	11 (45.8)

Table 3. Reported TEAEs

	Overall patients (N=24)
Total number of subjects reporting TEAEs, n (%)	18 (75)
Total number of TEAEs	78
TEAEs related to study drug	33
Subjects reporting mild TEAEs, n (%)	6 (25)
Subjects reporting moderate TEAEs, n (%)	9 (37.5)
Subjects reporting severe TEAEs, n (%)	3 (12.5)
Patients with TEAEs who discontinued treatment, n (%)	3 (12.5)

Table 4. Most commonly reported TEAEs by system organ class

System organ class	Overall patients (N=24)
Musculoskeletal and connective tissue disorders, n (%)	9 (37.5)
Gastrointestinal disorders, n (%)	8 (33.3)
Nervous system disorders, n (%)	6 (25)
General disorders and administration site conditions, n (%)	5 (20.8)

Figure 2. 12MWT mean scores at baseline versus Week 12 by total and subgroups?*†

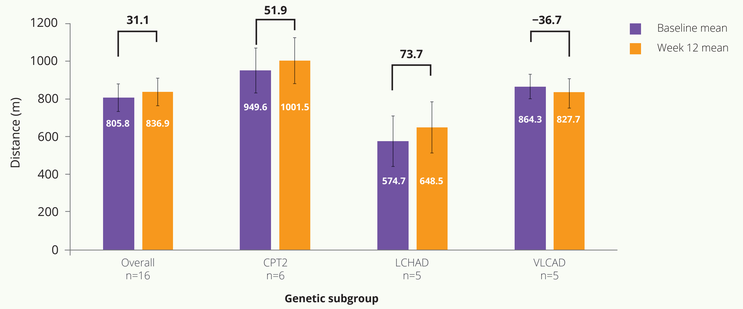


Figure 3. MFIS total mean scores at baseline versus Week 12 by total and subgroups*†

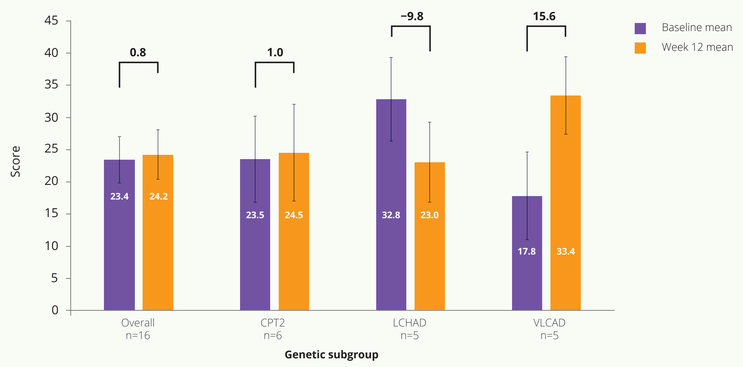
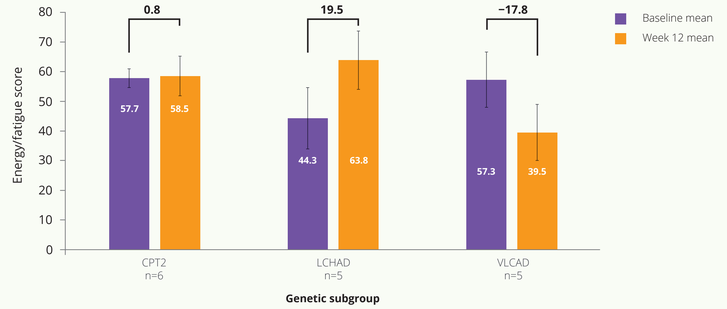


Figure 4. SF-36 energy/fatigue mean scores at baseline and Week 12 by subgroups*†



Conclusions

- 12-weeks of treatment with REN001 was generally well tolerated, with reported TEAEs being primarily mild to moderate
- The reported TEAEs were overall consistent with the disease state
- Patients with LCHAD exhibited the greatest improvement in endurance, with an accompanying reduction in fatigue
- Data from this study support further evaluation of REN001 in patients with LC-FAOD

References

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Abbreviations

12MWT, 12-Minute Walk Test; AE, adverse event; CPT2, carnitine palmitoyltransferase II deficiency; FAO, fatty acid oxidation; FAOD-MSI, Fatty Acid Oxidation Disorder – Muscular Symptoms Inventory; LC-FAOD, long-chain fatty acid oxidation disorder; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; MFIS, Modified Fatigue Impact Scale; PPARδ, peroxisome proliferator-activated receptor delta; QD, every day; QoL, quality of life; SE, standard error; SF-36, 36-Item Short Form Health Survey; TEAE, treatment-emergent adverse event; TFP, trifunctional protein; VLCAD, very long-chain acyl-CoA dehydrogenase deficiency.

*TFP genotype has not been summarized as only 2 subjects had this genotype.
†SE bars included.

Disclosures

JV, MMc and MG received research funding from Reneo Pharma Ltd. to participate as investigators in this study. AK is a site PI for Reneo Pharma Ltd. study at Children's Colorado. PL received fees from Sanofi-Genzyme, AMICUS therapeutics, Spark Therapeutics, Roche, Biogen, and grants from Sanofi-Genzyme and AMICUS. NL: Advisory board and clinical trials for Reneo Pharma Ltd. GO, LP and MD are employees of Reneo Pharma Ltd. AD is an employee of Reneo Pharmaceuticals Inc. MMo has no disclosures.

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