A prospective, multicenter, non-interventional study to investigate the disease characteristics of adult patients with long-chain fatty acid oxidation disorders: The FORWARD study

Melanie Gillingham[1], Daniela Karall[2], David Cassiman[3], Pavel Ješina[4], John Vissing[5], Pascal Laforêt[6], Robert Kirschner[7], Olimpia Musumeci[8], Alessandro Padovani[9], Joanna Jagłowska[10], María-Luz Couce[11], Montserrat Morales Conejo[12], Mark Roberts[13], John Phillips[14], Gary Layton[15], Jane Elgar[16], Lynn Purkins[16], Madhu Davies[16], Alejandro Dorenbaum[17], Jerry Vockley[18]

[1]Oregon Health & Science University (OHSU), OR, USA. [2]Medical University of Innsbruck, Innsbruck, Austria. [3]Leuven University Hospitals, Leuven, Belgium. [4]General University Hospital, Prague, Czech Republic. [5]Rigshospitalet, Copenhagen, Denmark. [6]Neurology Department, Raymond-Poincaré Hospital, APHP, FHU Phenix, NEIDF Neuromuscular Center, Garches, France. [7]Ferenc Flór Hospital, Kistarcsa, Hungary. [8]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy. [9]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. [10]The University Clinical Centre, Gdansk, Poland. [11]Santiago Clinic Hospital CHUS, Santiago de Compostela, Spain. [12]MetabERN, University Hospital "12 de Octubre", Madrid, Spain. [13]Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Manchester, UK. [14]Vanderbilt University Medical Center, Nashville, TN, USA. [15]Paramstat Ltd., UK. [16]Reneo Pharma Ltd., UK. [17]Reneo Pharmaceuticals Inc., USA. [18]University of Pittsburgh, PA, USA.

Introduction and Objectives

- The known population with long-chain fatty acid oxidation disorders (LC-FAOD) is expanding due to screening and diagnostic advances[1,2]
- There is a need to better characterize the disease manifestations of LC-FAOD in adult patients[1,2]
- In this study, we examined the natural history of LC-FAOD in adult patients and explored possible endpoints for future clinical trials

Patients and Methods[3]

- Patients (≥18 years, from 15 centers worldwide):
  - Confirmed diagnosis of CPT2, VLCAD, TFP or LCHAD deficiencies
  - On stable management for at least 30 days prior to baseline
- Data collected at baseline and Month 4 (14–18 weeks) after the baseline visit:
  - Disease characteristics and symptoms
  - Endurance measured by the 12-minute walk test (12MWT)
  - Blood and urine samples
  - Short Form Health Survey (SF-12)

Results

- 58 patients were enrolled, 52% diagnosed with CPT2
- Gender split was relatively even (56.9% males) **(Table 1)**
- 8 of 16 (50%) patients in the LCHAD subgroup reported neuropathy and related symptoms **(Table 1)**
- 48 of 58 (82.8%) patients reported a history of FAOD events of special interest **(Table 2)**

Table 1. Demographics and baseline characteristics

	Overall (N=58)	CPT2 (N=30)	LCHAD (N=16)	VLCAD (N=12)
Male, n (%)	33 (56.9)	16 (53.3)	11 (68.75)	6 (50.0)
Female, n (%)	25 (43.1)	14 (46.7)	5 (31.25)	6 (50.0)
Mean (SE) age at FAOD diagnosis, years	18.1 (2.0)	25.3 (2.5)	1.8 (1.4)	22.1 (3.9)
Mean (SE) age at informed consent, years	33.9 (1.8)	39.2 (2.7)	22.7 (0.9)	35.3 (2.4)
Musculoskeletal and connective tissue disorders, n (%)	12 (20.7)	6 (20.0)	3 (18.8)	3 (25.0)
Nervous system disorders, n (%)	8 (13.8)	5 (16.7)	3 (18.8)	0
Gastrointestinal disorders, n (%)	6 (10.3)	0	5 (31.3)	1 (8.3)
Psychiatric disorders, n (%)	6 (10.3)	3 (10.0)	3 (18.8)	0
Cardiac disorders, n (%)	2 (3.4)	0	2 (12.5)	0
Renal/urinary disorders, n (%)	1 (1.7)	1 (3.3)	0	0
Neuropathy, n (%)	8 (13.8)	0	8 (50.0)	0
Weakness, n (%)	6 (75.0)	0	6 (75.0)	0
Muscle wasting, n (%)	4 (50.0)	0	4 (50.0)	0
Foot drop, n (%)	5 (62.5)	0	5 (62.5)	0
Cramps, n (%)	4 (50.0)	0	4 (50.0)	0
Fasciculations, n (%)	4 (50.0)	0	4 (50.0)	0
Weak hand grip, n (%)	1 (12.5)	0	1 (12.5)	0

Table 2. History of FAOD events of special interest

	Overall (N=58)	CPT2 (N=30)	LCHAD (N=16)	VLCAD (N=12)
Total events of special interest prior to informed consent, n (%)	48 (82.8)	25 (83.3)	13 (81.3)	10 (83.3)
Rhabdomyolysis, n (%)	46 (79.3)	23 (76.7)	13 (81.3)	10 (83.3)
Myoglobinuria, n (%)	10 (17.2)	6 (20.0)	1 (6.3)	3 (25.0)
Hypoglycemia, n (%)	3 (5.2)	0	2 (12.5)	1 (8.3)
Cardiomyopathy, n (%)	1 (1.7)	0	1 (6.3)	0
Hospitalization, n (%)	36 (62.1)	16 (53.3)	12 (75.0)	8 (66.7)
Emergency Room visit, n (%)	4 (6.9)	1 (3.3)	2 (12.5)	1 (8.3)

Results – continued

12MWT (Figure 1):

- Compared with baseline, at Month 4 overall mean (SE) distance walked increased by 24.4 (10.0) meters
- VLCAD patients exhibited the highest mean (SE) increase from baseline; 37.9 (17.4) meters
- LCHAD patients exhibited the lowest mean (SE) change from baseline; 11.9 (26.7) meters, and the lowest mean distance walked compared with the other subgroups at both baseline and Month 4

SF-12 (Figure 2):

- Compared with baseline, at Month 4 overall mean (SE) score in the Physical Functioning component increased by 4.7 (2.9)
- All genetic subgroups exhibited an increase in the Physical Functioning score compared with baseline
- The LCHAD subgroup exhibited the highest mean (SE) change with an 8.3 (7.1) point increase
- The VLCAD subgroup exhibited the lowest mean (SE) change, with a 4.2 (8.6) point increase

Figure 1. 12MWT mean distance walked and mean change (meters) at baseline and Month 4

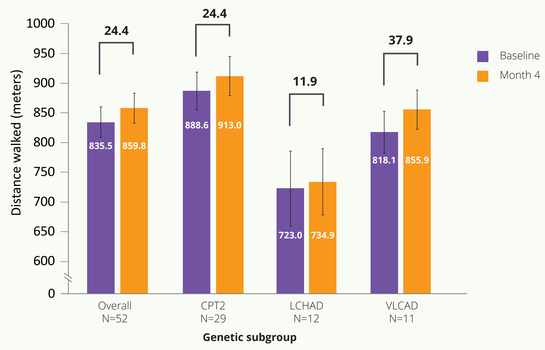
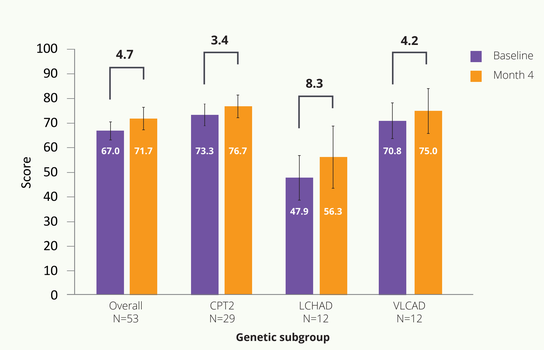


Figure 2. SF-12 Physical Functioning mean score at baseline and Month 4



Conclusions

- This study provides valuable information about disease characteristics, key safety events and the natural history of LC-FAOD in adults followed for 4 months
- The increases in distance walked from baseline in the 12MWT are consistent with a learning effect
- Healthy individuals are able to walk 636 meters in 6 minutes, whereas individuals with LC-FAOD could only walk 835.5 meters in double the time (12 minutes)[4]
- The LCHAD population's low mean SF-12 physical component score at baseline (47.9) suggests that this population has more meaningful physical limitations than other LC-FAOD populations[5]
- Both baseline values and changes from baseline observed at Month 4 in the 12MWT and SF-12 score support calculating performance of a placebo group in future interventional trials

References

1. Knottnerus SJG *et al. Rev Endocr Metab Disord.* 2018(1):93–106.
2. Baker JJ and Burton BK. *touchREV Endocrinol.* 2021(2):108–111. doi: 10.17925/EE.2021.17.2.108.
3. REN001-903 study; NCT04482049. https://clinicaltrials.gov/ct2/show/NCT04482049 (Accessed 12 August 2022).
4. Halliday SJ *et al. Respir Med.* 2020;165:105933.
5. Soh SE *et al. Health Qual Life Outcomes.* 2021;19(1):157.

Abbreviations

12MWT, 12-minute walk test; CPT2, carnitine palmitoyltransferase II deficiency; FAOD, fatty acid oxidation disorders; LC-FAOD, long-chain fatty acid oxidation disorders; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; SE, standard error; SF-12, 12-item Short Form Health Survey; TFP, trifunctional protein deficiency; VLCAD, very long-chain acyl-CoA dehydrogenase deficiency.

Acknowledgments

The study is sponsored by Reneo Pharma Ltd. Editorial support provided by Makara Health.

Disclosures

MG is a consultant for Reneo Pharma Ltd., Ultragenyx, Kriya Therapeutics and TLC. DK, JVi and JVo were supported with research funding by Reneo Pharma Ltd. to participate as investigators in this study. PJ, RK, OM, JJ, M-LC and MMC have no disclosures. PL has received fees from Sanofi-Genzyme, AMICUS therapeutics, Spark Therapeutics, Roche, Biogen, and grants from Sanofi-Genzyme and AMICUS. GL is a statistical consultant to Reneo Pharma Ltd. JE, LP and MD are all employees of Reneo Pharma Ltd. AD is an employee of Reneo Pharmaceuticals Inc.

INFORM Meeting, Freiburg, Germany, August 28–29, 2022