Summary:
Evaluation of the effect of Triheptanoin on fatty acid oxidation and exercise tolerance in patients with debrancher deficiency, glycogenin-1 deficiency and phosphofructokinase deficiency at rest and during exercise. A randomized, double-blind, placebo-controlled, cross-over study.

EudraCT#2017-004153-17

The study was prematurely ended due to recruitment difficulties. Three participants with phosphofructokinase deficiency were studied.

Synopsis:

Name of sponsor: Prof. John Vissing, Copenhagen Neuromuscular Center, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen, Denmark.
Name of Finished Product: UX007
Name of Active Ingredient: Triheptanoin
Title of Study: Evaluation of the effect of Triheptanoin on fatty acid oxidation and exercise tolerance in patients with debrancher deficiency, glycogenin-1 deficiency and phosphofructokinase deficiency at rest and during exercise. A randomized, double-blind, placebo-controlled, cross-over study.
Investigators: Daniel Emil Raaschou-Pedersen; Karen Lindhardt Madsen; Nicoline Løkken; Jesper Helbo Storgaard; Ros Quinlivan; Pascal Laforêt; Allan Lund; Gerrit Van Hall; John Vissing; Mette Ørngreen.
Study center: Copenhagen Neuromuscular Center, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen, Denmark.
Publication: https://doi.org/10.1016/j.nmd.2022.01.012.
Studied period:
Start: 01. May 2018
End: 28. August 2019, ended prematurely.

Phase of development: phase II

Objectives: To investigate the effect of Triheptanoin on fatty acid oxidation and exercise tolerance in patients with debrancher deficiency, glycogenin-1 deficiency and phosphofructokinase deficiency at rest and during exercise.

Methodology: Primary outcome measures were assessed during constant load exercise (and included (a) heart rate (HR) and (b) fatty acid oxidation measured via stable isotope technique and indirect calorimetry. Constant load exercise test on a cycle ergometer: 30 min at an intensity that matched 65% of the participant's VO_2max followed by an increasing load every minute until maximal exercise. Stable isotope technique: Two hours prior to exercise, a single priming dose of Na13HCO3 (0.0735mg × kg-1) and 6,6-2H2-glucose (2.44 mg × kg-1) dissolved in saline was delivered intravenously, followed by a constant-rate infusion of U-13C16-palmitate (0.02 µmol × kg-1 × min-1) and 6,6-2H2-glucose (0.7 µmol × kg-1 × min-1). Infusions were delivered by a Gemini PC2 pump (IMED, San Diego, California). The infusion rates were doubled at the onset of exercise. Breath

samples were collected in a non-diffusible 15-liter Douglas bag (Hans Rudolph, Kansas, United States) and transferred to a vacutainer (BD, New Jersey, United States). Isotope enrichments of the used tracers, C7-ketones, and 13CO2 were determined by gas chromatography-combustion-isotope ratio mass spectrometry (Finnigan MAT, Bremen, Germany) at Clinical Metabolomics Core Facility, Rigshospitalet, Copenhagen.

Number of patients:

Planned: 24 participants divided in groups of 8 based on diagnosis.
Analysed: 3 participants with phosphofructokinase deficiency.

Diagnosis and main criteria for inclusion: Inclusion criteria included (a) a genetically and/or biochemically verified diagnosis of PFKD, and (b) age ≥15 years. Women of fertile age had to be on contraceptive treatment.

Test product, dose and mode of administration, batch number: Triheptanoin is an odorless and tasteless liquid. Treatments were delivered by Ultragenyx Pharmaceutical Inc. (Novato, CA) and came in 1L round, amber-colored glass bottles (USP, Ph. Eur. Grade). During the first 7 days of treatment, participants were treated with an increasing dose of 0.3, 0.5 and 0.7 $g \times kg^{-1} \times day^{-1}$ followed by 7 days on full dose ($1 g \times kg^{-1} \times day^{-1}$). Dosages were divided and ingested with 3-4 meals daily.

Duration of treatment: 14 days.

Reference therapy, dose and mode of administration, batch number: Placebo treatment was safflower liquid with similar characteristics to triheptanoin without odd-chained heptanoate. Treatments were delivered by Ultragenyx Pharmaceutical Inc. (Novato, CA) and came in 1L round, amber-colored glass bottles (USP, Ph. Eur. Grade). During the first 7 days of treatment, participants were treated with an increasing dose of 0.3, 0.5 and 0.7 $g \times kg^{-1} \times day^{-1}$ followed by 7 days on full dose ($1 g \times kg^{-1} \times day^{-1}$). Dosages were divided and ingested with 3-4 meals daily.

Criteria for evaluation: Completion of all exercise test and at least 5 consecutive days of full dose treatment before test day evaluation.

Statistical methods: We calculated a sample size of 8 participants to detect a minimal relevant difference in the primary outcome measure, heart rate, during submaximal exercise of ≥5 bpm between active and placebo treatments. A power calculation was (n=((Z_(1-α/2)+Z_(1-β))/(μ / σ))^2) performed with regards to the primary endpoint heart rate during constant load cycling. This gave 80% power and two-sided 95% confidence intervals around assumed mean value for heart rate. A standard deviation (SD) of 5 ± bpm for heart rate was assumed based on a previous study in patients with McArdle disease [13]. Because of recruitment challenges we ended up including only three participants. Results are presented as means ± SE and statistical analyses were not performed due to the small sample size.

Summary – conclusions:

Efficacy results:

Summary of primary outcomes: Triheptanoin did not improve the primary outcome measure heart rate (BPM) during submaximal exercise 86 BPM ± 8 SE compared to placebo 89 BPM ± 11 (n=3). In fact, two out of three participants had increased heart rate during exercise with triheptanoin treatment. Palmitate oxidation was increased during submaximal exercise in one patient. Palmitate oxidation did not increase in the two other patients during triheptanoin treatment.

Summary of secondary outcomes: Palmitate production (rate of appearance) and palmitate utilization (rate of disappearance) increased during exercise and increased to a greater extent with triheptanoin treatment compared to placebo both after submaximal exercise and after maximal exercise in all three patients (1.04 ± 0.96 vs. 2.20 ± 2.59 and 1.20 ± 1.06 vs. 2.06 ± 2.38 µmol × kg-1 × min-1). Consistently, plasma palmitate and total free fatty acids concentrations increased during exercise and increased to a greater extent with triheptanoin during submaximal exercise in all three patients (ΔPalmitate concentration 85 ± 40 vs. 146 ± 92 and 255 ± 209 vs. 419 ± 454 µmol × L-1). Exercise duration was longer with placebo vs triheptanoin (35:03 ± 03:19 vs. 35:40 ± 02:09). However, mean perceived exertion during submaximal exercise was comparable between treatments.

Safety results:

During the trial period, no serious adverse events were reported. One participant had a bacterial dental infection. The infection occurred during triheptanoin treatment, was treated with antibiotics, and was not considered as treatment-related by the investigators. Rhabdomyolysis or myoglobinuria did not occur in relation to exercise tests or at any other time during study period. One of three participants reported periods of nausea and diarrhea on the placebo treatment.

Conclusion:

This study suggests that triheptanoin treatment has no effect on heart rate or exercise performance despite increased palmitate production and utilization in patients with PFKD.

Date of the report:
14. March 2022