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UX007 for the treatment of long chain-fatty acid oxidation disorders: Safety and efficacy in children and adults following 24 weeks of treatment

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ABSTRACT

Background: Long-chain fatty acid oxidation disorders (LC-FAOD) lead to accumulation of high concentrations of potentially toxic fatty acid intermediates. Newborn screening and early intervention have reduced mortality, but most patients continue to experience frequent hospitalizations and significant morbidity despite treatment. The deficient energy state can cause serious liver, muscle, and heart disease, and may be associated with an increased risk of sudden death. Triheptanoin is a medium odd-chain fatty acid. Anaplerotic metabolites of triheptanoin have the potential to replace deficient tricarboxylic acid (TCA) cycle intermediates, resulting in net glucose production as a novel energy source for the treatment of LC-FAOD.

Study design: A single-arm, open-label, multicenter Phase 2 safety and efficacy study evaluated patients with severe LC-FAOD evidenced by ongoing related musculoskeletal, cardiac, and/or hepatic events despite treatment. After a four-week run-in on current regimen, investigational triheptanoin (UX007) was titrated to a target dose of 25–35% of total daily caloric intake. Patients were evaluated on several age/condition-eligible endpoints, including submaximal exercise tests to assess muscle function/endurance (12-minute walk test; 12MWT) and exercise tolerance (cycle ergometry), and health related quality of life (HR-QoL). Results through 24 weeks of treatment are presented; total study duration is 78 weeks.

Results: Twenty-nine patients (0.8 to 58 years) were enrolled; most qualified based on severe musculoskeletal disease. Twenty-five patients (86%) completed the 24-week treatment period. At Week 18, eligible patients ($n = 8$) demonstrated a 28% increase (LS mean $= +181.9$ meters; $p = 0.087$) from baseline (673.4 meters) in 12MWT distance. At Week 24, eligible patients ($n = 7$) showed a 60% increase in watts generated (LS mean $= +409.3$ W; $p = 0.149$) over baseline (744.6 W) for the exercise tolerance test. Improvements in exercise tests were supported by significant improvements from baseline in the adult ($n = 5$) self-reported SF-12v2 physical component summary score (LS mean $= +8.9$; $p < 0.001$). No difference from baseline was seen in pediatric parent-reported ($n = 5$) scores (SF-10) at Week 24. Eighteen patients (62%) had treatment-related adverse events, predominantly gastrointestinal (55%), mild-to-moderate in severity, similar to that seen with prior treatment with medium chain triglyceride (MCT) oil. One patient experienced a treatment-related serious adverse event of gastroenteritis. One patient discontinued from study due to diarrhea of moderate severity; the majority of patients (25/29; 86%) elected to continue treatment in the extension period.

Conclusions: In patients with severe LC-FAOD, UX007 interim study results demonstrated improved exercise endurance and tolerance, and were associated with positive changes in self-reported HR-QoL.

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1. Introduction

Long-chain fatty acid oxidation disorders (LC-FAOD) represent a group of rare inborn errors of metabolism. These autosomal recessive genetic disorders are caused by defects in nuclear genes encoding mitochondrial enzymes involved in the conversion of dietary long-chain fatty acids into energy during times of fasting and physiologic stress. The four most common enzyme deficiencies are carnitine palmitoyl transferase 2 (CPT-II), very long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and mitochondrial trifunctional protein (TFP). Carnitine palmitoyl transferase 1 (CPT-I) and carnitine-acylcarnitine translocase (CACT) are less common. As a result of the defect, partial or incomplete oxidation of fatty acids leads to accumulation of high concentrations of potentially toxic fatty acid intermediates and a deficient energy state in multiple organ systems.

Clinical presentations of LC-FAOD include involvement of the liver, skeletal muscle, and/or heart. The pattern and severity of organ involvement is only partially predictable based on the specific mutation [1–5]. Skeletal muscle involvement may lead to hypotonia, weakness, muscle pain, and exercise intolerance, with acute episodes of severe rhabdomyolysis requiring hospitalization. Patients with heart involvement typically present with cardiomyopathy and arrhythmias [1,6–9]. Patients with liver involvement often present with hypoglycemia, steatohepatitis, hepatomegaly, liver dysfunction and potentially liver failure in untreated patients [10,11].

The most severely affected patients present from soon after birth through the first year of life with hypoglycemia, cardiomyopathy, and/or sudden death likely due to arrhythmia or hypoglycemia. A clinical survey of 187 cases over 30 years at one center reported mortality rates of 67%, 60%, and 63% for patients with CPT-II, VLCAD, and LCHAD, respectively, when diagnosed symptomatically and treated [11]. Newborn screening and early treatment have reduced mortality, but carefully followed cohorts indicate major medical events continue to occur despite earlier diagnosis and management [2,12–14].

Current management of LC-FAOD includes avoidance of fasting combined with the use of low fat/high carbohydrate diets, carnitine supplementation in some cases, and medium chain triglyceride (MCT) supplementation [12,13]. MCT oil is composed of medium even-chain fatty acids that can be metabolized by a separate set of medium-chain fatty acid oxidation enzymes distinct from those affected in LC-FAOD, and should bypass the LC-FAOD block. However many patients still experience frequent hospitalizations and significant morbidity despite treatment, presumed to be due to depletion of odd chain carbon substrates of the tricarboxylic acid (TCA) cycle [14,15].

1.1. Rationale for UX007 in the treatment of LC-FAOD

UX007 is an investigational drug comprised of a highly purified, synthetic medium odd-chain (C7) triglyceride called triheptanoin. UX007 is initially catabolized to heptanoate, which can traverse the mitochondrial membrane without the carnitine carrier. Free heptanoate is then metabolized by the medium chain fatty acid oxidation enzymes, bypassing the deficient long chain ones. Metabolic end products include acetyl- and propionyl-CoA, and 4- and 5-carbon ketone bodies; all five metabolites can contribute to energy metabolism in the liver or elsewhere in the body. Propionyl-CoA is an anaplerotic molecule that replaces the deficient odd chain TCA cycle intermediates through conversion to succinyl-CoA [16], resulting in glycogen sparing and restoration of reducing equivalents for oxidative phosphorylation and ATP supplies for gluconeogenesis [15]. Thus, the anaplerotic properties of triheptanoin are hypothesized to be critical for restoring the energy deficiency state in LC-FAOD.

Studies of patients with LC-FAOD suggest triheptanoin can reduce hypoglycemia and rhabdomyolysis events, as well as improve cardiac function for patients in heart failure [10,14,17,18]. A follow-up study of patients treated under compassionate use suggests triheptanoin can also help reduce length of stay in hospital and the frequency of major medical events [2].

The potential for triheptanoin to provide both ketones and anaplerotic substrates for the TCA cycle, supported by clinical evidence of benefit, provides a strong rationale to investigate treatment of pediatric and adult patients with LC-FAODs in prospective, interventional clinical trials. An open-label Phase 2 study (UX007-CL201; ClinicalTrials.gov identifier NCT01886378) was conducted in pediatric and adult patients severely affected with LC-FAOD despite current therapy. The primary objective of the study was to evaluate the impact of UX007 on acute clinical pathophysiology associated with LC-FAOD following 24 weeks of treatment. Results from the primary analysis are reported; total study duration is 78 weeks.

2. Materials and methods

2.1. Patients

Patients were enrolled over 10.5 months from 10 investigative centers in the United States and United Kingdom. Written informed consent was obtained from the patient or the parent/legally authorized guardian prior to any study related procedures or study drug administration. The study was conducted in compliance with the Declaration of Helsinki, relevant Institutional Review Board practices, and the International Conference on Harmonisation Good Clinical Practice guidelines.

Patients at least 6 months of age with a confirmed diagnosis of CPT-II deficiency, VLCAD deficiency, LCHAD deficiency, or TFP deficiency were eligible if currently managed on a stable treatment regimen for 60 days prior to enrollment. This provision assured any changes observed during the 4 week run-in evaluation period were not confounded by recent changes in the treatment regimen. Only patients with significant clinical manifestations of LC-FAOD despite therapy were included, as evidenced by chronic elevated creatine kinase (CK) levels with major clinical events, episodic elevated CK with reported muscle dysfunction; highly elevated CK without symptoms; frequent severe major medical episodes with hypoglycemia, or evidence of cardiomyopathy requiring ongoing medical management. Patients with CACT and CPT-I were excluded due to the severity of the condition, which would likely limit full participation in study requirements, and the rarity of these diagnoses. Patients with conditions for which triheptanoin treatment is contraindicated (i.e. medium-chain acyl-CoA dehydrogenase [MCAD] deficiencies; short- or medium-chain FAOD, ketone body metabolism defects, propionic acidemia or methylmalonic acidemia) were also excluded. Additional provisions excluded patients based on prior adverse reactions to UX007/triheptanoin, confounding comorbidities, or prior clinical study participation within 30 days prior to the study.

2.2. Study design

UX007-CL201 was designed as a prospective, interventional, open-label, single-arm Phase 2 study. Eligible patients were enrolled and their available history of major clinical events during the prior 18–24 months was tabulated. Patients continued current therapy (including use of MCT oil) for 4 weeks to establish a stable baseline, particularly for relevant indicators of skeletal myopathy, hepatic and cardiac disease, and other physiologic measures of energy metabolism. Following completion of a 4-week run in period, patients discontinued MCT oil (if applicable) and began treatment with UX007.

The concept for evaluation was to study the effects of UX007 on energy physiology through biologic and clinical assessments within the 24-week treatment period. Patients had the option to continue treatment in a 54-week extension period (total of 78 weeks treatment) which was primarily designed to capture major medical events associated with LC-FAOD.

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UX007 is a pharmaceutical-grade investigational product in development by Ultragenyx Pharmaceutical, Inc. (Novato, CA USA). UX007 is supplied as a clear and colorless to light yellow oil intended for oral administration. Patients (or their caregiver) completed a representative 3 day diet diary prior to the run-in, baseline, and Week 12 visits. A clinical dietitian at the investigative site used Microdiet (Downlee Systems Ltd.), DietPlan6 (Forestfield Software Ltd.), or other approved nutrition analysis software to establish average daily caloric intake.UX007 was dose titrated to an individualized effective dose with a goal of 25–35% of total caloric intake, while ensuring tolerability. UX007 was administered at least 4 times daily orally with food or drink (or mixed with formula, as appropriate), or by gastrostomy tube as indicated. A treatment regimen log provided the prescribed dose volume and frequency of UX007 and was updated based on diet diaries as necessary.

2.3. Assessments

Following the 4-week run-in, patients completed the baseline visit (Week 0) and returned to the investigational center at 4–6 week intervals (±1 week) during the 24-week treatment period. Assessments were included to evaluate clinical effects on the three main organ systems impacted by LC-FAOD and were administered based on age, health status, and ability. Skeletal myopathy was assessed by measures of exercise tolerance (sub-maximal exercise test using cycle ergometry), endurance and motor function/development (12-minute walk test [12MWT] and Peabody Developmental Motor Scales [PDMS-2]), health-related quality of life (HR-QoL; Medical Outcomes Study 10-Item Short Form [SF-10] or Medical Outcomes Study 12-Item Short Form version 2 [SF-12v2], and the Pediatric Evaluation of Disability Inventory Computer Adaptive Test [PEDI-CAT]).

The effects of treatment on major clinical events associated with LC-FAOD were also captured during the initial treatment period. A series of additional assessments were included in the study to monitor skeletal, hepatic, and cardiac disease; disease progression, pharmacokinetics, and long-term safety; results from these variables were not part of the pre-specified Week 24 data cut and will be part of the final analysis at Week 78.

Treatment emergent adverse events (TEAEs) were captured throughout the study and evaluated for duration, severity, and relatedness to study drug. Safety measures included routine monitoring through vital signs, physical examinations, and clinical laboratory tests (serum chemistry, hematology, and urinalysis); concomitant medications were tracked, and pregnancy testing was conducted as applicable. Patients were also contacted by telephone at specified intervals for additional safety monitoring. A Data Monitoring Committee with appropriate expertise in the conduct of clinical trials in children and adults acted in an advisory capacity to monitor subject safety on a routine basis throughout the trial.

2.3.1. 12-Minute walk test

The 12MWT is a variation of the 6MWT used to assess self-paced endurance through walking [19,20]. Patients at least 6 years old during the study or those who mastered all PDMS-2 skills were administered the 12MWT, if feasible. The 12MWT was administered during the run-in period (baseline value) and Weeks 8 and 18 (or early termination). Patients were fed a standardized macronutrient meal including either MCT oil (at the run-in visit, if applicable) or UX007 (all visits post-baseline), approximately 2 h prior to test administration.

The 12MWT was administered by a trained clinician based on American Thoracic Society guidelines [21] for the 6MWT. Patients were observed throughout the duration of the 12MWT; the test was not performed if there were safety concerns. Heart rate and blood pressure were checked both before and after the test. The test could be discontinued at any time at the discretion of the administering clinician if there were concerns about the induction of rhabdomyolysis or the occurrence of any other major safety event, including the onset of dizziness, chest pain, muscle pain, and respiratory distress. The efficacy assessment following the 12MWT evaluated distance walked and also included measures of perceived exertion (pre- and post-12MWT) using the OMNI scale [22,23], and perceived muscle pain (pre- and post-12MWT) using a visual analog scale (subjects aged ≥18 years) or Faces Pain Scale-revised (subjects 6–12 years) [24].

2.3.2. Cycle ergometry

A sub-maximal aerobic cycle ergometry exercise trial was performed in patients aged ≥6 years who were capable at the screening visit (baseline value) and Weeks 4, 12, and 24 (or early termination). A manual combined with formal training were used to standardize the administration of the test. The exercise trial included expired gas analysis for assessment of oxygen consumption with special reference to the measurement of respiratory gas exchange ratio (RER). Patients were fitted with a reusable non-rebreathing mask or equivalent to ensure standardized assessment of expired air during each trial. Patients were fed a standardized macronutrient meal including either MCT oil (at screening, if applicable) or UX007 (all visits post-baseline), approximately 2 h prior to test administration. At select visits, a catheter was inserted into the antecubital vein (or other accessible vein) for access to sample lactate, acylcarnitine, and CK levels during the testing period; patients returned to the clinic the following day (within 24 h) for a post-testing sample.

Prior to the testing, patients were prepped and fitted with electrodes on the chest to allow for continuous ECG monitoring. During the trial, patients were asked to pedal continuously for up to 10 min until approximately 60% of their age-predicted maximum heart rate (APMHR) was achieved (calculated as 220 (beats per minute) − age (years)). Once the 60% target was reached, the patient was asked to pedal continuously and maintain 60% APMHR for 40 min. After 40 min, patients continued to pedal at a progressively decreasing workload for recovery period up to 5 min. Oxygen consumption (O_2, CO_2 and ventilation [Ve]), RER, blood pressure, and perceived pain and exertion were monitored during the test. Workload was adjusted based on perception of exertion and RER to ensure maintenance of aerobic effort.

Patients were observed throughout the duration of the cycle ergometry; the test was not performed if there were safety concerns, and could be discontinued at any time at the discretion of the clinician administering the test if there were concerns about the induction of rhabdomyolysis or the occurrence of any other major safety event, including the onset of dizziness, chest pain, muscle pain and respiratory distress.

Cycle ergometry efficacy variables included workload (measured in watts produced at a fixed heart rate); RER, a measure of energy supply; and duration of cycling.

2.3.3. Health-related quality of life instruments

The SF-10 [25] and SF-12v2 Healthy Survey [26] were administered at the baseline visit and at Weeks 12 and 24 (or early termination); responses were based on a 4-week recall period. The instrument was dependent on the age at informed consent; SF-10 was used for patients aged 5 through 17 years and SF-12v2 for patients ≥18 years.

2.4. Statistical methods

The planned sample size was approximately 30 patients. Patients were evaluated on several age/condition-eligible endpoints; thus, the small sample size for each endpoint was not powered for hypothesis testing for statistically significant changes from baseline.

For each patient, overall mean daily dose consumed was derived using the following calculation: Sum of (the caloric intake * duration) / Sum of duration in the UX007 treatment regimen log.

The observed effects within the 24-week treatment period were compared to baseline values obtained during the screening or baseline evaluations scheduled prior to initiating UX007 or during the 4 week

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run-in period. The endpoints were summarized descriptively. When the sample size and number of observations allowed, change from baseline over time was analyzed using a generalized estimation equation (GEE) model which included time as the categorical variable and adjusted for baseline measurement. The covariance structure used for the GEE model was compound symmetry which specified constant variance for the assessments and constant covariance between the assessments over time.

Definitions, analysis populations, data handling, derived efficacy variables and analyses were pre-specified in a statistical analysis plan. Data manipulation, tabulation of descriptive statistics, graphical representations and estimation of model parameters were performed primarily using SAS (release 9.4 or higher) for Windows (SAS Institute Inc., Cary, NC).

The energy expenditure index (EEI) was derived using heart rate (beats/min) measurements obtained before and after the 12MWT and calculated using the following formula: $EEI = (HR_{post} - HR_{pre}) / V_{overall}$; where $V_{overall}$ represents the total distance during the 12MWT, and the result is valued in beats/meter.

The RER was calculated as V_{CO2} / V_{O2}. To evaluate the impact 24 weeks of treatment with UX007 on exercise intolerance, the time-adjusted area under the curve (AUC) for RER during cycle ergometry was derived.

The SF-10 and SF-12v2 instruments were scored using T-score based scoring software (QualityMetric, Inc., Lincoln, RI). Component scores related to physical functioning and mental/psychosocial HR-QoL were derived for each instrument per standard scoring practices (QualityMetric Health Outcomes™ Scoring Software 5.0).

3. Results

3.1. Study population

Of the 30 patients screened, one did not have the protocol-defined disease severity and was deemed ineligible. The study population (Table 1; N = 29) spanned a wide age range from 10 months to 58 years old. Most participants were children or adolescents (72.4%). Gender was relatively balanced (58.6% male). LC-FAOD genotypes included: twelve (41%) with VLCAD, ten (35%) with LCHAD, four (14%) with CPT-II and three (10%) with TFP deficiencies.

The majority of patients enrolled presented with ongoing severe musculoskeletal disease (86%) and elevated CK levels compared to a limited number with hepatic or cardiac disease. Clinical pathophysiology was consistent with reported disease history; most patients had prior or ongoing rhabdomyolysis, muscle pain, exercise intolerance, and muscle weakness. Relative to normative data for age and gender, the overall mean baseline 6MWT distance (observed during the first half of the 12MWT) was 54% of predicted (n = 8).

Most patients entered the study with normal cardiac function (supported by echocardiogram) and no prior cardiac involvement. Those with a history of clinical involvement showed minimal dysfunction at baseline by echocardiogram. The majority of patients entered the study with normal findings on hepatic ultrasound.

Prior to initiating treatment with UX007, 27 of the 29 patients were on MCT oil therapy and remained on this regimen during the 4-week run-in period. The overall mean dose of UX007 through 24 weeks was 30% of daily caloric intake. In pediatric patients (n = 23) the mean daily dose tended to decrease with age (34% in patients <1 year of age to 27% in patients 6–18 years of age); adults (n = 6) averaged 31% of daily caloric intake. The majority (72%) of patients were compliant with the treatment regimen (defined as overall completion of ≥80%, where percent of daily caloric intake was at least 25% UX007).

Patients performed only the assessments that were appropriate and valid for their age at study entry. Of the 25 patients who completed the 24-week treatment period, the majority (17 patients; 68%) were either too young to complete the exercise testing (14/17) or unable to complete the testing due to other physical constraints (3/17). These subjects will contribute to the major medical event rate analysis in the second stage of the study.

Table 1
Baseline characteristics of study population.

	N = 29
Age (years)	
Mean (SD)	12.06 (13.2)
Median	5.26
Min, Max	0.87, 58.78
Age group, n (%)	
0–1 year	2 (6.9%)
>1–6 years	13 (44.8%)
>6–18 years	8 (27.6%)
>18 years	6 (20.7%)
Gender, n (%)	
Male	17 (58.6%)
Female	12 (41.4%)
LC-FAOD subtype, n (%)	
VLCAD	12 (41.4%)
LCHAD	10 (34.5%)
CPT-II	4 (13.8%)
TFP	3 (10.3%)
Qualifying severe clinical manifestation[a], n (%)	
Skeletal myopathy	25 (86.2%)
Hepatic disease	3 (10.3%)
Cardiac disease[b]	2 (6.9%)
MCT treatment at study entry, n (%)	27 (93.1%)
Elevated CK[c], n (%)	21 (72.4%)
Disease history, n (%)	
Rhabdomyolysis	26 (89.7%)
Muscle pain	22 (75.9%)
Exercise intolerance	21 (72.4%)
Hypoglycemia	18 (62.1%)
Muscle Weakness	16 (55.2%)
Cardiomyopathy[b]	13 (44.8%)
Feeding difficulties, poor weight gain	9 (31.0%)
Abnormal gait	6 (20.7%)
Respiratory distress	6 (20.7%)
Altered mental status/coma	5 (17.2%)
Hepatomegaly	5 (17.2%)
Hypotonia	5 (17.2%)
Retinopathy	5 (17.2%)
Hemolysis, elevated LFTs, low platelets, maternal HELLP syndrome	4 (13.8%)
Seizures	4 (13.8%)
Developmental delay	2 (6.9%)
Peripheral neuropathy	1 (3.4%)

[a] One patient qualified fulfilling 2 clinical manifestation criteria.
[b] Of the 13 patients with a disease history of cardiomyopathy, 2 qualified for the study based on severe cardiac disease.
[c] Defined as Non-acute CK with >1× ULN at baseline.

The subgroup of patients qualified to perform exercise tolerance assessments included 8 patients (5 with VLCAD; and 1 each with LCHAD, CPT-II, and TFP) who completed the 12MWT; this subgroup included 4 adults, 3 adolescents, and 1 pediatric patient. Of these 8 patients, 7 patients met the age and other eligibility requirements for the cycle ergometry trial; one 5 year old patient with LCHAD was ineligible.

3.2. Efficacy and safety outcomes

Since the overwhelming majority of patients entered the study with significant musculoskeletal pathophysiology, the results related to endurance and exercise tolerance are described in this report.

Eight qualified patients performed the 12MWT at baseline; the mean distance walked was 673.4 m. Improvements were observed as early as the Week 8 time point (Fig. 1A). Paired data at Week 18 (n = 8) demonstrated a mean (SD) change from baseline of 188 (322.3) meters (LS mean (SE) = 181.9 (106.2); p = 0.087) in 12MWT distance, representing a 28% increase (Fig. 1B). At baseline, the mean (SD) EEI during the 12MWT was 0.249 (0.197) beats/m (n = 12). At Week 18

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the observed mean (SD) EEI was 0.080 (0.258) beats/m (n = 8), representing a significant improvement (LS mean change from baseline = −0.178 beats/m; $p < 0.05$).

Seven patients performed cycle ergometry at all indicated time points. Patients showed improvements in workload; changes were observed beginning at Week 4 and appeared to plateau at Week 12 and were maintained throughout the treatment period (Fig. 2). At Week 24, the mean change from baseline in workload increased by 60%, representing a mean (SD) increase of +446.8 (924.6) watts (LS mean (SE) = 409.3 (283.7); $p = 0.149$) from baseline of 744.6 W.

Of the patients (n = 4) who completed the entire 40-minute cycle ergometry at baseline and Week 24, no patient exhibited reduced duration between baseline and Week 24. For the patients (n = 3) who were not able to complete all 40 min at baseline (mean 11.5 min), mean duration was extended by 11.1 min at Week 24, representing an increase of 97%. The mean (SD) time adjusted AUC of RER at baseline was 0.982 (0.054); no change in RER was observed at Week 24 (mean (SD) = 0.966 (0.063).

The maximum change in CK levels from before and after cycle ergometry decreased to a mean (±SD) of 687.83 IU/L (±1104.5) at Week 24, represented a mean change from baseline of [−104.12 IU/L (±790.7); n = 6]. The mean change in lactate levels of the first post-cycle ergometry measurement from pre-cycle ergometry was −0.30 mMol/L (±0.365) at Week 24, representing a −0.22 mMol/L change from baseline (n = 6). Changes in acyl carnitine levels during cycle ergometry were not significantly changed.

3.3. Health-related quality of life

Age-appropriate questionnaires were completed by the patient (SF-12v2) or reported from the parent perspective (SF-10) for children. During the run-in period (on prior treatment), significant impairments in HR-QoL related to physical functioning were reported for both adult and pediatric participants relative to normative data (Fig. 3). The mental component summary in adults and the psychosocial summary scores in pediatric patients were within normal ranges at baseline. In adult patients (n = 5) significant improvements in physical component score (LS mean = +8.9; $p < 0.001$) and in mental component summary score (LS mean = +9.7; $p < 0.05$) were observed after 24 weeks of treatment with UX007 (Fig. 3A).

While impairment in the physical health summary of the SF-10 parent-reported survey for pediatric patients (n = 5) was reported at baseline (mean (SD) = 13.9 (11.9)), there was no change at Week 24 (Fig. 3B). There was no change from baseline (n = 5; mean [SD] = 13.9 [11.9]) at Week 24 for the psychosocial summary score of the SF-10 parent-reported survey for pediatric patients (Fig. 3B). The PDMS-2, an assessment of gross motor skills in patients under six years old,

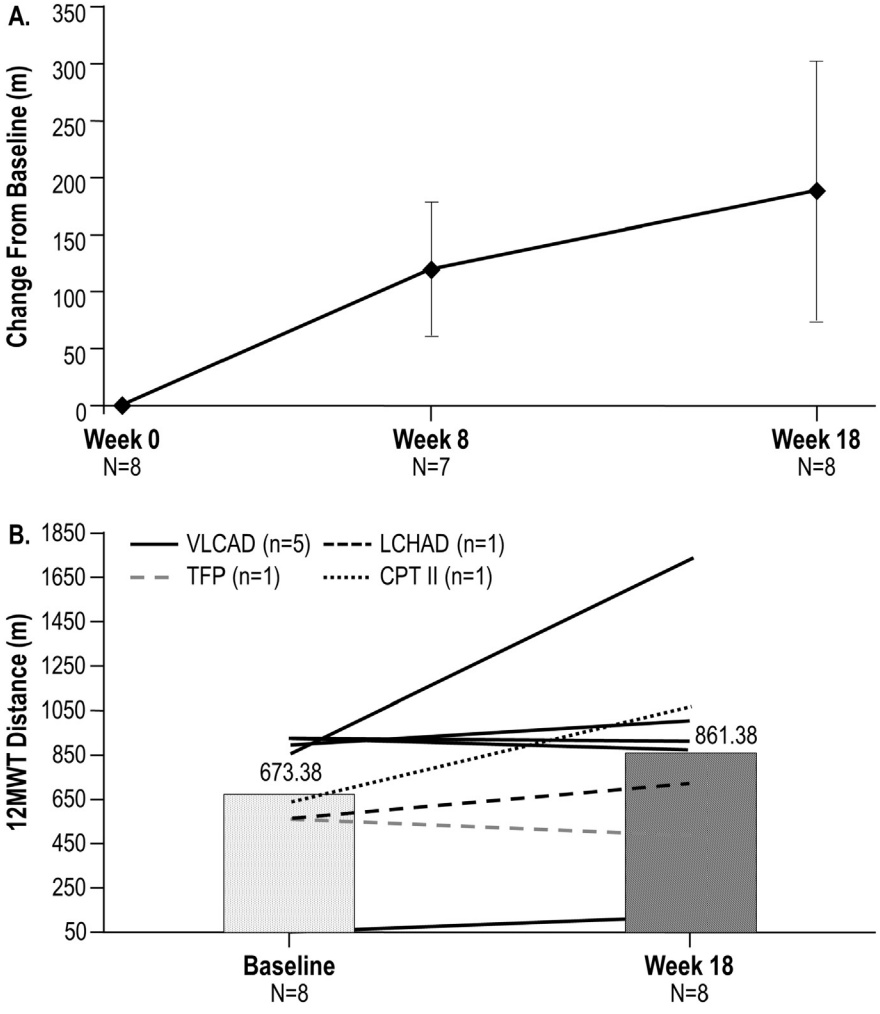

Fig. 1. 12MWT results. Mean (SE) change from baseline in distance walked during the 12MWT (A). Mean 12MWT distance (bars) and individual patient data (lines by LC-FAOD subtype) for patients completing 12MWT at baseline and Week 18 (B).

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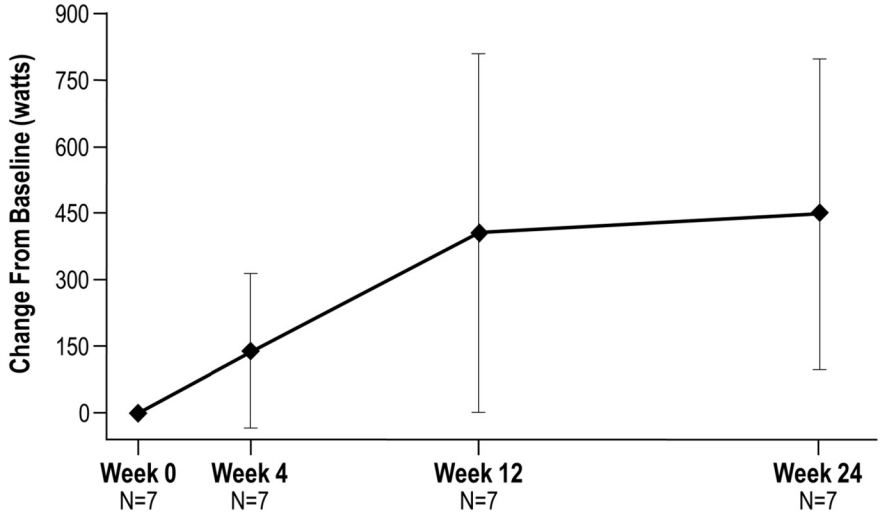

Fig. 2. Cycle ergometry results. Mean (SE) change from baseline in area under the curve for cycle ergometry workload (watts).

and the PEDI-CAT, a caregiver score of functional disability, also showed no impairment in the overall patient population at baseline and no change after 24 weeks of UX007 treatment (data not shown).

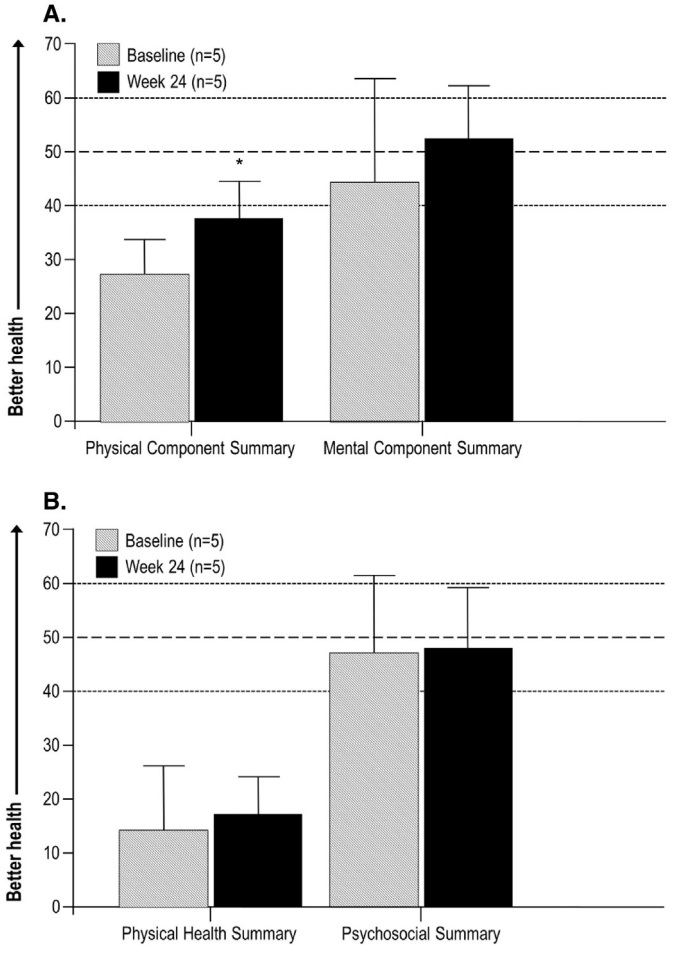

Fig. 3. Health-related quality of life. Mean (SD) adult self-reported HR-QoL assessed by SF-12v2 (A) and parent-reported HR-QoL for pediatric patients assessed by SF-10 (B). Dashed line indicates normed mean (50); dotted lines indicate one standard deviation from mean (±10); the asterisk denotes significant ($p < 0.0001$) change from baseline.

3.4. Tolerability and treatment continuation

TEAEs were reported by 28 of 29 patients (96.6%). The majority were mild to moderate (Grade 1 or 2) in severity. The most common TEAEs irrespective of relationship to UX007 include diarrhea, rhabdomyolysis, upper respiratory tract infection, vomiting, abdominal pain, gastroenteritis viral, headache, and pyrexia (Table 2). Sixteen patients (55.2%) experienced at least one serious TEAE requiring hospitalization, most commonly due to viral infection or rhabdomyolysis; most of these events occurred in pediatric patients and only one patient experienced a serious TEAE assessed by the investigator as related to UX007 treatment, although viral infection was suspected.

The majority of patients (16/29; 55.2%) experienced at least one TEAE impacting the gastrointestinal system which was considered related to UX007 treatment. The most common adverse effect associated with UX007 treatment was diarrhea (12 patients; 41.4%). Other TEAEs assessed as related to UX007 occurring in >5% of patients included abdominal or gastrointestinal pain, nausea and vomiting, abdominal distention, flatulence, gastroenteritis, and acne. Some gastrointestinal symptoms were managed by administering smaller doses of UX007 or mixing with food.

One event of moderate gastroenteritis was considered serious and required hospitalization; however the patient maintained UX007 dosing during the event and continued on the study. One patient

Table 2
Treatment emergent adverse events in >20% of patients.

		Safety analysis set N = 29
Patients with any TEAE		28 (96.6%)
System organ class	Preferred term	Safety analysis set N = 29
Infections and infestations	Upper respiratory tract infection	11 (37.9%)
	Gastroenteritis (viral)	7 (24.1%)
Gastrointestinal disorders	Diarrhea	15 (51.7%)
	Vomiting	11 (37.9%)
	Abdominal pain	7 (24.1%)
Musculoskeletal and connective tissue disorders	Rhabdomyolysis	12 (41.4%)
General disorders and administration site conditions	Pyrexia	6 (20.7%)
Nervous system disorders	Headache	6 (20.7%)

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experienced moderate diarrhea and abdominal pain 6 days after initiation of UX007 treatment and withdrew from the study; symptoms resolved within 2 days of discontinuation. Three patients withdrew from the study within the first 8 weeks of dosing for reasons not attributed to UX007 treatment. The majority of patients (25/29; 86.2%) completed the 24-week treatment period and elected to continue treatment in the extension period.

4. Discussion

LC-FAODs are caused by defects in the catabolic pathway that ultimately lead to a deficiency in mitochondrial energy production during times of physiologic stress and fasting. Anaplerosis refers to replenishment of TCA cycle intermediates, essential for efficient harvesting of energy from fatty acid oxidation. Unlike MCT oil, triheptanoin is an anaplerotic compound that restores TCA cycle substrate balance in patients with LC-FAODs due to its medium chain length, allowing it to bypass defects in the long-chain fatty acid oxidation pathway, and generation of propionyl-CoA. Propionyl-CoA is an anaplerotic molecule that is metabolized to succinate, providing both even and odd carbon substrates for the TCA cycle. Triheptanoin can also be gluconeogenic via the TCA cycle, which can also contribute to energy metabolism. Thus, triheptanoin is hypothesized to improve energy generation in LC-FAOD patients who manifest symptoms of energy deficit such as chronic muscle weakness, cardiomyopathy, and rhabdomyolysis [17,27].

In this study, the majority of patients had muscle weakness and pain that limited gross motor function as evidenced by a mean baseline 6MWT of 54% predicted for the overall study population. Performance measures such as the 6MWT and the 12MWT have been successfully used in other clinical development programs and were used here in order to challenge FAOD patients with a longer walking exercise period than the 6 min period. A relationship between a 12-minute endurance test and physical fitness was originally described by Cooper [19]. Subsequently, the 12MWT was validated as a measure to assess disability in chronic bronchitis patients [20]. In this study, improvements in the 12MWT were observed following 24 weeks of UX007 treatment. Paired with significant improvements in EEI, the ratio of heart rate per meter walked, the data suggest an increase in exercise efficiency during the walk test.

LC-FAOD patients frequently experience exercise intolerance due to muscle pain and leg cramps on exertion leading to limitation of activity. Cycle ergometry has been used in studies of other inherited metabolic myopathies [28] and was employed in this study to assess exercise tolerance. Cycle ergometry was of sufficient intensity and duration to reduce glycogen stores such that fatty acid oxidation becomes increasingly utilized by exercise muscle. In LC-FAOD subjects who performed the tests, improvements were observed in both measures of exercise tolerance, suggesting an increase in muscle performance at a steady level of cardiac exertion as measured by heart rate. The data on the 12MWT and cycle ergometry together support an improvement in muscle function, and exercise efficiency, endurance and tolerance in a small number of patients that need to be confirmed in a larger controlled study.

Functional disability often limits daily activities of living and health-related quality of life in patients with LC-FAOD. These parameters were evaluated using age-appropriate health assessment questionnaires. Significant improvements in adult patient-reported HR-QoL scores in physical functioning domains were observed in those patients, consistent with improvements in exercise tolerance and endurance.

Cycle ergometry and the 12MWT were not performed in the cohort of subjects <6 years of age. Since these children did not perform these measures of exercise tolerance and endurance, alternative assessments were incorporated to evaluate gross motor development using the PDMS-2 [29] and measure functional capabilities and performance using the PEDI-CAT [30] in children. At baseline, the PDMS-2 gross motor quotient of the study population was within the normal range for age equivalent, and there was minimal or no impairment evidenced by the PEDI-CAT. Additionally, no differences were observed in scores for pediatric patients using the age-appropriate SF-10 as completed by caregivers, compared to the SF12 which was completed by the subjects themselves. It is not clear whether delayed motor and/or cognitive development was not a prominent feature in this study population or whether interpretation was limited by sample size and study entry criteria.

Clinical presentations of LC-FAOD can be categorized by the organ system with greatest involvement (liver, skeletal muscle, or heart). Patients with hepatic dysfunction/hypoglycemia (n = 3) and cardiac disease (n = 2) comprised a limited proportion of the study population. The 24-week treatment period mainly evaluated the acute effects of UX007 on musculoskeletal aspects of the disease. While changes in exercise tolerance and endurance can occur within 6 months, a longer treatment period is needed to observe a sufficient number of major clinical events for comparison with the historical data, and therefore forms the primary basis for analysis following the second phase of the study. The majority of patients elected to remain on treatment and will continue to be followed for major clinical event rate measurement over 78 weeks.

These Phase 2 interim results are based on open-label uncontrolled treatment referenced to a baseline run-in period for each patient, which limits definitive conclusions about efficacy and safety. Efficacy outcomes were instead based on accumulated data across three clinically relevant disease areas: skeletal myopathy, hepatic disease and cardiac disease, to inform for the design of confirmatory studies. Additional limitations include the small subgroup of patients qualified to complete exercise tolerance and endurance testing. Although the study was not powered for a specific endpoint, statistically significant changes from baseline in some efficacy parameters (12MWT and SF-12v2 physical functioning scores) were observed.

The targeted dose range and regimen of UX007 were selected based on information derived from over 13 years of clinical experience with UX007/triheptanoin in infants, children, adolescents, and adults with LC-FAOD. These data generally show an age-dependent dose related to the relatively higher energy requirements for young children versus older children versus adults. In this study the mean dose administered was highest in the infant population (34%), but was relatively consistent across all age groups. Since this treatment is a substrate replacement therapy, dosing will likely need to be individualized based on tolerability, metabolism, and energy needs.

5. Conclusions

Pediatric and adult patients with LC-FAODs continue to suffer significant morbidity and mortality despite management with available treatment options, including MCT oil, a medium even-chain triglyceride. Treatment with UX007, a medium odd-chain fatty acid, may provide alternative substrate replacement due to its ketogenic, gluconeogenic, and anaplerotic properties. The presented interim data demonstrate a potential therapeutic effect of UX007 in the management of limited endurance and exercise intolerance associated with LC-FAODs supported by significant improvements in HR-QoL physical functioning outcomes. Continued treatment and further studies are warranted to confirm these initial promising findings.

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