



# Results from a 78-week, single-arm, open-label Phase 2 study to evaluate UX007 in pediatric and adult patients with severe long-chain fatty acid oxidation disorders (LC-FAOD)

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## Abstract

Long-chain fatty acid oxidation disorders (LC-FAOD) are rare disorders characterized by acute crises of energy metabolism and severe energy deficiency that may present with cardiomyopathy, hypoglycemia, and/or rhabdomyolysis, which can lead to frequent hospitalizations and early death. An open-label Phase 2 study evaluated the efficacy of UX007, an investigational odd-carbon medium-chain triglyceride, in 29 subjects with severe LC-FAOD. UX007 was administered over 78 weeks at a target dose of 25–35% total daily caloric intake (mean 27.5%). The frequency and duration of major clinical events (hospitalizations, emergency room visits, and emergency home interventions due to rhabdomyolysis, hypoglycemia, and cardiomyopathy) occurring during 78 weeks of UX007 treatment was compared with the frequency and duration of events captured retrospectively from medical records for 78 weeks before UX007 initiation. The mean annualized event rates decreased from 1.69 to 0.88 events/year following UX007 initiation ( $p = 0.021$ ; 48.1% reduction). The mean annualized duration rate decreased from 5.96 to 2.96 days/year ( $p = 0.028$ ; 50.3% reduction). Hospitalizations due to rhabdomyolysis, the most common event, decreased from 1.03 to 0.63 events/year ( $p = 0.104$ ; 38.7% reduction). Initiation of UX007 eliminated hypoglycemia events leading to hospitalization (from 11 pre-UX007 hospitalizations, 0.30 events/year vs. 0;  $p = 0.067$ ) and intensive care unit (ICU) care (from 2 pre-UX007 ICU admissions, 0.05 events/year vs. 0;  $p = 0.161$ ) and reduced cardiomyopathy events (3 events vs. 1 event; 0.07 to 0.02 events/year; 69.7% decrease). The majority of treatment-related adverse events (AEs) were mild to moderate gastrointestinal symptoms, including diarrhea, vomiting, and abdominal or gastrointestinal pain, which can be managed with smaller, frequent doses mixed with food.

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## Introduction

Long-chain fatty acid oxidation disorders (LC-FAOD) are rare and life-threatening autosomal recessive disorders caused by defects in the metabolic pathway that convert fatty acids into energy. The clinical manifestations of the resultant energy deficiency may include rhabdomyolysis, liver dysfunction, severe hypoglycemia, and cardiomyopathy, leading to significant morbidity and mortality (Roe and Brunengraber 2015). Premature mortality as high as 60–90% has been reported in some LC-FAOD when diagnosed symptomatically (in non-newborn screened populations) and managed with currently available treatments (Baruteau et al. 2013).

No medications have been approved for the specific treatment of LC-FAOD. Current methods of disease management include avoidance of fasting, maintenance of a low-fat diet, and ingestion of medium-chain triglycerides (MCTs) to bypass the degradation defect in long-chain fatty acids. The use of carnitine supplementation is controversial (Spiekerkoetter et al. 2009a, b). In spite of these measures, many patients still experience major clinical events, and mortality rates remain high (Baruteau et al. 2013; Spiekerkoetter et al. 2009a, b), revealing an unmet medical need for improved LC-FAOD therapies.

UX007 is a purified, pharmaceutical-grade form of triheptanoin, a synthetic medium odd-carbon chain (C7) triglyceride. Upon ingestion, UX007 is rapidly metabolized to heptanoate, which can diffuse across the mitochondrial membrane and bypass the long-chain transport and oxidation enzymes that are deficient in LC-FAOD. Heptanoate is metabolized to propionyl-CoA and acetyl-CoA, both essential precursors for the tricarboxylic acid (TCA) cycle. The 3-carbon propionyl-CoA is metabolized to succinyl-CoA, which resupplies the TCA cycle intermediates that may be secondarily deficient in patients, providing the potential to restore efficient generation of adenosine triphosphate (ATP) (Roe and Mochel 2006). The resupply of TCA intermediates can also provide intermediates transported out of the mitochondria to fuel gluconeogenesis (Marin-Valencia et al. 2013) and may increase liver glycogen stores (Gu et al. 2010). Because the production of propionyl-CoA is specific to odd-carbon fatty acids, the anaplerotic and gluconeogenic properties of UX007 may provide advantages over MCTs. Several retrospective or compassionate use studies of triheptanoin in patients with LC-FAOD have suggested benefit with reduced episodes of hypoglycemia or rhabdomyolysis and improved cardiac function in the face of acute cardiomyopathy (Roe and Brunengraber 2015; Roe and Mochel 2006; Roe et al. 2002, 2008; Vockley et al. 2015, 2016). A prospective, double-blind, short-term comparison of even-carbon C8 oil and triheptanoin (approximately 16% of daily caloric intake) showed an improvement in cardiac left ventricular mass and ejection fraction in patients with LC-FAOD treated with triheptanoin compared to C8 (Gillingham et al. 2017).

We report here a single-arm, open-label Phase 2 study evaluating the safety and efficacy of UX007 administered for 78 weeks to 29 pediatric and adult patients with severe LC-FAOD. The key objectives of the study were to evaluate the impact of UX007 on acute clinical pathophysiology [including muscle function, exercise tolerance, and health-related quality of life (HRQoL)] following 24 weeks of UX007 treatment (as previously reported by Vockley et al. 2017) and the impact of UX007 on major clinical events associated with LC-FAOD over 78 weeks of treatment, as documented in this report. Major clinical events were inclusive of hospitalizations, emergency room visits, and emergency interventions (i.e., any unscheduled administration of therapeutics at home or in the clinic) due to rhabdomyolysis, cardiomyopathy, and hypoglycemia. Efficacy and safety results from 78 weeks of treatment are reported, with emphasis on the effect of UX007 on major clinical events.

## Methods

### Study design

The study (NCT01886378) enrolled eligible subjects at least 6 months of age with severe LC-FAOD as evidenced by any of the following significant clinical manifestations, despite management: chronic elevated creatine kinase (CK) with major clinical events, episodic elevated CK with reported muscle dysfunction, highly elevated CK but asymptomatic, frequent severe major medical episodes, severe susceptibility to hypoglycemia, and/or evidence of functional cardiomyopathy (Vockley et al. 2017). A 4-week run-in period provided baseline data on current disease management. After the run-in period, subjects discontinued any MCT use (if applicable) and began treatment with UX007 (Ultragenyx Pharmaceutical Inc., Novato, CA), titrated to a target dose of 25–35% of total daily caloric intake, combined with a low-fat diet and other ongoing treatments, such as carnitine supplementation, if used. A schematic of the study design is shown in Supplemental Fig. 1. Subjects provided a 3-day diet diary of all foods and/or liquids consumed at run-in and baseline visits before initiating UX007 and at weeks 12, 24, 48, and 78 of UX007 treatment; at each of these visits, diet information was entered into metabolic software [MetabolicPro (USA) and Microdiet (UK)] that analyzed each individual's metabolic needs to calculate the UX007 dosage. UX007 was administered orally at least 4 times a day (mixed with food or formula at breakfast, lunch, dinner, and before bed). A validated electronic data capture system was used for entry of the data into electronic case report forms (CRFs); all data entered into the CRFs were verifiable and cross-checked with source documents for consistency. A Data Monitoring Committee acted in an advisory capacity to monitor subject safety on a routine basis throughout the trial.

## Major clinical events

Major clinical events in the 78 weeks prior to UX007 initiation were captured retrospectively directly from medical records, source verified, and compared with the 78 weeks following UX007 initiation. All major clinical events were categorized in the same manner, both prior to and following UX007 initiation. The principal investigator at each site determined whether individual events qualified as major clinical events associated with LC-FAOD. Major clinical events that occurred during the same time period and/or hospitalization were counted separately. The event type, the number of emergency room (ER), hospital, or intensive care unit (ICU) days, and the type and number of days of treatment and intervention were recorded.

## Exercise tolerance and health-related quality of life

Assessments to evaluate exercise tolerance and HRQoL have been described previously (Vockley et al. 2017). Primary analysis for the 12-minute walking test (12MWT) was performed at week 18, with final analysis at week 60 compared to baseline. Primary analysis for the cycle ergometry assessment was performed at week 24, with final analysis at Week 78 to assure that the subjects were not overexerted by performing both exercise assessments at the same visit. The HRQoL in pediatric and adult subjects was evaluated through week 78 using the caregiver-reported SF-10 and patient-reported SF-12v2 assessments, respectively.

## Statistical analysis

The annualized event rate and annualized duration rate were calculated for rhabdomyolysis, hypoglycemia, and cardiomyopathy events as recorded in the major clinical event CRF. The annualized event rate was defined as

Annualized Event Rate

$$= \frac{\text{Total number of clinical events of interest}}{\text{Duration of data collection period in days}/365.25}$$

The annualized duration rate was defined as

Annualized Duration Rate

$$= \frac{\text{Total duration of clinical events of interest}}{\text{Duration of data collection period in days}/365.25}$$

The pretreatment and UX007 treatment annualized event rates and annualized duration rates were compared at week 78 using paired *t*-tests. For all exercise and quality of life assessments, changes from baseline were analyzed

using the generalized estimation equation, as described by Vockley et al. (2017).

## Results

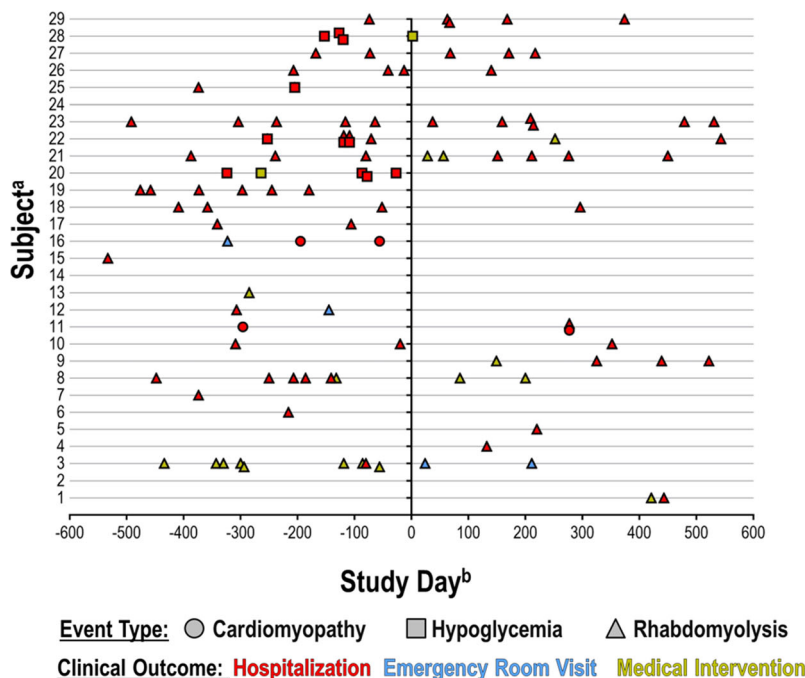
### Study population

The study population ( $N=29$ ) was as described previously (Vockley et al. 2017). Briefly, the mean age was 12.06 years (range: 0.87–58.78 years), with a slight preponderance of males (17 males, 12 females) (Supplemental Table 1). The subject medical histories reflected common LC-FAOD manifestations, including rhabdomyolysis (89.7%), muscle pain (75.9%), exercise intolerance (72.4%), hypoglycemia (62.1%), and muscle weakness (55.2%) (Vockley et al. 2017). The majority of subjects in the study (27/29, 93%) received MCTs as part of their disease management prior to UX007 initiation; at run-in and baseline visits, MCT consumption for subjects managed with MCTs averaged 18.6% and 18.7% of daily calories, respectively (medians: 19.9% and 20.5%, respectively). Most subjects (22/29, 76%) also received carnitine supplementation, and all (100%) were noted to be on a high-carbohydrate, low-fat diet. The daily caloric intake fluctuated but generally increased over the course of the study, possibly due to increasing caloric demands of growing children or increased fat intake due to UX007 (Supplemental Table 2). The overall mean dose of UX007 through 78 weeks of treatment was 27.5% of daily calories (target dose: 25–35%). Most subjects (25/29, 86.2%) recorded an overall UX007 completion greater than or equal to 80% of the target dose (defined as at least 25% of daily caloric intake). Twenty-four of the 29 subjects (82.8%) completed the study and 25 (86.2%) enrolled in a separate long-term extension study.

### Major clinical events

Treatment with UX007 significantly reduced both the frequency and duration of major clinical events. In total, 70 major clinical events occurred in the 78-week period prior to UX007 treatment and 39 events occurred following UX007 initiation through week 78, a 44.3% reduction (Fig. 1). The annualized event rates decreased from a mean pretreatment rate of 1.69 major clinical events/year to 0.88 events/year following UX007 initiation (a 48.1% reduction in the mean annualized event rates;  $p=0.021$ , Fig. 2), with a median annualized event rate decreasing from 1.33 events/year pre-UX007 to 0.66 events/year after UX007 initiation, a 50.6% reduction (Table 1). Additionally, the mean annualized duration rate decreased from 5.96 days/year to 2.96 days/year ( $p=0.028$ ; 50.3% reduction), with

**Fig. 1** Major clinical events (rhabdomyolysis, cardiomyopathy, and hypoglycemia) for all subjects. The subjects are presented on the Y-axis in order of age, with individual events shown on the X-axis. The vertical line represents the day of UX007 initiation, with pre-UX007 time (78 weeks) on the left and UX007 time (78 weeks) on the right



<sup>a</sup>Subjects are listed in order of age, with subject 29 as the youngest subject and subject 1 as the oldest subject.  
<sup>b</sup>Study Day 1 is the date of UX007 initiation.

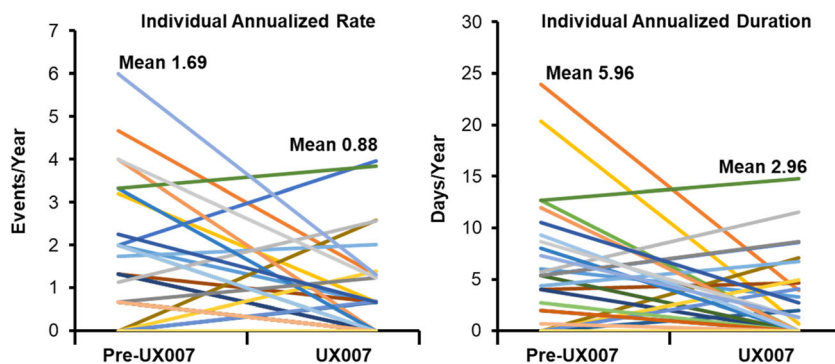
median values showing a 77% reduction from 5.33 days/year pretreatment to 1.24 days/year after UX007 initiation (Fig. 2).

Hospitalizations comprised the majority of the clinical events, both before and after UX007 initiation (81% and 74%, respectively). In the 78-week period prior to UX007 initiation, most subjects (21/29, 72.4%) were hospitalized at least once and spent an average of 5.7 days/year in the hospital for clinical manifestations due to LC-FAOD. Both the annualized hospitalization event rate and the annualized hospitalization duration rate were significantly reduced following UX007 initiation. Hospitalizations decreased from a pre-UX007 mean of 1.39 events/year to 0.65 events/year in the UX007 period ( $p = 0.016$ , a 53.1% reduction in mean events, Table 1), and the median hospitalization rates decreased from 1.39 events/year to 0.00 events/year following UX007 introduction. The

mean annualized hospital duration decreased from 5.66 days/year to 2.74 following UX007 initiation ( $p = 0.032$ , 51.5% decrease, Table 1), while a complete reduction in median annualized duration rates was observed following UX007 treatment, from 5.66 days/year pretreatment to 0.00 days/year.

Because LC-FAOD clinical manifestations can change with age, ad hoc analyses evaluated the effects of UX007 on major clinical events by age (< 3, ≥ 3 to < 6, ≥ 6 to < 18, and ≥ 18 years old). For all age subgroups, the mean annualized event rate decreased following UX007 initiation compared with the pre-UX007 period (Supplemental Table 3). The annualized duration rate also decreased across age groups during UX007 treatment, though this difference was most noticeable in the young children (below age 6 years), who experienced generally higher annualized duration rates compared to older children (at least 6 years old) and adults.

**Fig. 2** Individualized subject annualized event and duration rates. The colored lines represent individual subject responses. All 29 subjects are depicted



**Table 1** Frequency and duration of major clinical events, 78 weeks before and during UX007 treatment

N = 29 subjects	Annualized event rate (no. of events/year)				Annualized duration rate (no. of days/year)			
	Pre	UX007	<i>p</i> -Value	% change	Pre	UX007	<i>p</i> -Value	% change
<b>All events</b>								
Mean	1.690	0.877	0.0208	– 48.1	5.961	2.964	0.0284	– 50.3
Median	1.333	0.659	–	– 50.6	5.332	1.244	–	– 76.7
Q1, Q3	0.667, 2.2250	0.000, 1.3111	–	–	0.667, 8.665	0.000, 4.666	–	–
<b>All hospitalization events</b>								
Mean	1.391	0.652	0.0160	– 53.1	5.662	2.739	0.0316	– 51.6
Median	1.145	0.000	–	– 100.0	4.328	0.000	–	– 100.0
Q1, Q3	0.000, 2.000	0.000, 0.678	–	–	0.000, 7.998	0.000, 4.128	–	–
<b>Rhabdomyolysis events</b>								
Mean	1.303	0.833	0.1189	– 36.1	3.949	2.792	0.2043	– 29.3
Median	0.667	0.619	–	– 7.2	2.666	1.276	–	– 52.1
Q1, Q3	0.000, 2.000	0.000, 1.3111	–	–	0.000, 5.999	0.000, 4.333	–	–
<b>Rhabdomyolysis hospitalization events</b>								
Mean	1.027	0.630	0.1044	– 38.7	3.674	2.589	0.2232	– 29.5
Median	0.667	0.000	–	– 100.0	2.000	0.000	–	– 100.0
Q1, Q3	0.000, 1.731	0.000, 0.668	–	–	0.000, 5.724	0.000, 4.158	–	–
<b>Hypoglycemia events</b>								
Mean	0.318	0.023	0.0677	– 92.8	1.414	0.023	0.0852	– 98.4
Median	0.000	0.000	–	–	0.000	0.000	–	–
Q1, Q3	0.000, 0.000	0.000, 0.000	–	–	0.000, 0.000	0.000, 0.000	–	–
<b>Hypoglycemia hospitalization events</b>								
Mean	0.295	0.000	0.0666	– 100	1.391	0.000	0.0852	– 100
Median	0.000	0.000	–	–	0.000	0.000	–	–
Q1, Q3	0.000, 0.000	0.000, 0.000	–	–	0.000, 0.000	0.000, 0.000	–	–
<b>Cardiomyopathy events</b>								
Mean	0.069	0.021	0.3090	– 69.6	0.598	0.149	0.2882	– 75.1
Median	0.000	0.000	–	–	0.000	0.000	–	–
Q1, Q3	0.000, 0.000	0.000, 0.000	–	–	0.000, 0.000	0.000, 0.000	–	–

The annualized event rate (events/year) and annualized duration rate (days/year) were calculated for the 78 weeks pre- and post-UX007 initiation. *p*-Values were calculated using a two-tailed Student's *t*-test and the percent change of the means or medians is also shown

## Hypoglycemia events

Twelve hypoglycemia events occurred in four subjects during the pre-UX007 treatment period, compared with only one event in one subject following the initiation of UX007. After UX007 treatment, the mean annualized hypoglycemia event rate decreased from the pretreatment rate of 0.32 events/year to 0.02 events/year ( $p = 0.068$ ; 92.8% reduction, Table 1). The mean hypoglycemia event duration improved from 1.41 days/year to 0.02 days/year ( $p = 0.085$ ; 98.4% reduction). Although hypoglycemia incidence is known to decrease with age, UX007 treatment had a consistent effect among all four subjects with hypoglycemia events in the pretreatment period (aged 11 months to 4.8 years at enrollment). The majority of the pretreatment hypoglycemia events led to hospitalization (11/12, 91.7%), with two events (16.7%) resulting in ICU

admission; the single hypoglycemia event occurring during UX007 treatment did not result in hospitalization and occurred early during the UX007 treatment period (Fig. 1).

## Cardiomyopathy events

Cardiomyopathy is one of the most severe LC-FAOD complications and a major cause of mortality. Three cardiomyopathy events occurred in two subjects in the pretreatment period and one event occurred in one subject in the UX007 treatment period. This translated to a mean event rate due to the cardiomyopathy of 0.07 events/year pretreatment and 0.02 events/year during UX007 treatment (69.6% reduction). The average annualized duration decreased from 0.60 days/year to 0.15 following UX007 initiation (75.1%

reduction, Table 1). Due to their serious nature, all cardiomyopathy events led to ICU admission.

### Rhabdomyolysis events

Rhabdomyolysis events were the most common of the three major clinical events evaluated during the study (with 55 events in 19 subjects and 37 events in 15 subjects during the pre-UX007 and UX007 periods, respectively). Following UX007 initiation, the mean rhabdomyolysis event rate decreased from 1.30 days/year to 0.83 days/year ( $p = 0.119$ ; 36.1% reduction, Table 1) and the mean duration decreased from 3.95 days/year before UX007 to 2.79 days/year during UX007 treatment (29.3% reduction;  $p = 0.204$ ). The majority of rhabdomyolysis-related events consisted of hospitalizations (78.2% and 75.7% in the pre-UX007 and UX007 periods, respectively). Similar results were observed in the reduction of both the annualized rhabdomyolysis hospitalization event rate ( $p = 0.104$ ; 38.7% reduction) and the annualized hospitalization duration rate ( $p = 0.223$ ; 29.5% reduction) following UX007 initiation (Table 1). There was no clinically meaningful difference when comparing the mean (standard deviation, SD) peak CK levels collected during rhabdomyolysis events during the pre-UX007 and UX007 periods [28,419 (39,126) U/L pretreatment and 28,637 (45,917) U/L after UX007 initiation].

### Health-related quality of life

The HRQoL in adult and pediatric subjects was evaluated using the patient-reported SF-12v2 and caregiver-reported SF-10 assessments, respectively. At baseline, significant impairments in HRQoL related to physical functioning were reported for both adult and pediatric participants relative to normative data. In adult subjects ( $n = 5$ ), significant improvements were reported in the physical health composite scores of the SF-12v2 after 24 weeks of UX007 treatment (Vockley et al. 2017). Improvements were maintained through 78 weeks of UX007 treatment [least squares (LS) mean (standard error, SE) change: +3.6 (1.7),  $p = 0.035$ ], including the domain for role limitations due to physical health [LS mean (SE) change: + 5.9 (3.0),  $p = 0.049$ ]. No baseline impairment or change was observed in the SF-12v2 mental health composite scores, though significant improvement was reported in the vitality domain [LS mean (SE) change: +7.9 (8.2),  $p = 0.017$ ] at week 78.

Caregivers of pediatric subjects reported baseline SF-10 physical summary scores that were reflective of substantial impairments, more than two standard deviations below normal [ $n = 7$ , mean (SD): 22.6 (19.2)]. There was no change from baseline at week 24 (Vockley et al. 2017); however, the physical health summary scores increased significantly at week 78 [ $n = 3$ , LS mean (SE) change: +17.3 (1.4)]. No

baseline impairment or change was reported in the psychosocial summary of the SF-10 for pediatric subjects.

### Exercise tolerance

As previously reported, UX007 treatment resulted in an improvement in the distance walked in the 12MWT at week 18, from a baseline mean of 673.4 (296.3) m to 861.4 (467.5) m at week 18, a 28% increase. Improvements were sustained through week 60, with a mean increase of + 199.8 (372.7) m at week 60, a 29.7% increase, suggesting a stabilized subject response [ $n = 8$ ; LS mean (SE) change: +193.1 (120.5),  $p = 0.109$ ].

Deficits in walking ability were evaluated using percent of predicted distance—factoring in subject age, height, and sex—in the first 6 min of the 12MWT. At week 18, the mean percent of predicted distance improved from a baseline mean of 54.1% (21.6%) to 66.4% (28.6%) [ $n = 8$ ; LS mean (SE) change: +12.4 (7.4),  $p = 0.085$ ]. This improvement was sustained through week 60, where the mean percent predicted value increased + 16.1% (29.9%) from baseline at week 60 [ $n = 8$ ; LS mean (SE) change: + 16.1 (9.7),  $p = 0.098$ ].

After 24 weeks of UX007 treatment, improvements were observed in cycle ergometry performance in both workload and duration ( $n = 7$ ) (Vockley et al. 2017). Four subjects completed the cycle ergometry testing at week 78, although UX007 treatment was interrupted for one of these four subjects in the months prior to the week 78 assessment due to unrelated illness. No improvement in workload or duration was observed for subjects who performed the assessment at week 78, though the small sample size limits the interpretation of the data. Out of the four subjects who participated in the week 78 cycle ergometry, only two subjects previously completed the entire 40 min cycle duration at baseline. For the two additional subjects who did not complete the baseline assessment, there was no change in the duration measured for one subject, while the other demonstrated slightly improved duration from 8 min at baseline to 10 min at week 78.

### Safety profile

Over 78 weeks, all 29 subjects (100%) experienced at least one adverse event (AE) during the study. The most frequently reported AEs are shown in Table 2. Mild to moderate gastrointestinal symptoms, including diarrhea, vomiting, and abdominal pain, were managed with smaller, more frequent doses mixed with food. Other commonly reported AEs were typical for a pediatric population (including gastroenteritis or viral gastroenteritis, upper respiratory tract infection, and pyrexia) or common manifestations of LC-FAOD (including rhabdomyolysis and myalgia). UX007 treatment was not associated with excessive weight gain; after 78 weeks of treatment, grown subjects, on average, did not gain weight

**Table 2** Adverse events occurring in > 20% of patients

System organ class	Preferred term	Safety analysis set (N = 29)
Gastrointestinal disorders	Diarrhea	16 (55.2%)
	Vomiting	14 (48.3%)
	Abdominal pain	8 (27.6%)
Infections and infestations	Upper respiratory tract infection	12 (41.4%)
	Gastroenteritis viral	10 (34.5%)
	Gastroenteritis	6 (20.7%)
Musculoskeletal and connective tissue disorders	Rhabdomyolysis	14 (48.3%)
General disorders	Pyrexia	9 (31.0%)
Nervous system disorders	Headache	9 (31.0%)

compared to baseline. Growth curves in children demonstrate maintained growth in height and weight consistent with the pretreatment percentiles (data not shown).

Nineteen subjects (65.5%) experienced serious adverse events (SAEs) while on UX007. The most common SAEs included rhabdomyolysis, gastroenteritis, and viral gastroenteritis. All SAEs were considered unrelated to treatment except for one event of moderate gastroenteritis in an 11-month-old female that required hospitalization and was considered possibly related to the study drug. The event resolved within 8 days and dosing was maintained throughout. One subject discontinued the study due to an AE of diarrhea. Three subjects discontinued UX007 treatment due to AEs (one each of myalgia, gastroesophageal reflux disease, and pain and vomiting). No deaths were reported in this study. Twenty-five subjects are currently continuing UX007 treatment in a separate ongoing extension study to evaluate the efficacy and safety of long-term UX007 treatment up to 5 years.

## Discussion

Patients with LC-FAOD suffer from severe energy deficiency and life-threatening acute episodes of metabolic decompensation, leading to premature mortality or frequent hospitalizations and a substantial impact on daily function throughout their lives. Even with careful management, including avoidance of fasting and dietary supplementation with MCTs, patients continue to suffer from cardiomyopathy, hypoglycemia, liver disease, rhabdomyolysis, exercise intolerance, and muscle weakness. Prior to enrollment into this Phase 2 study, subjects had severe disease, as manifested by a history of major clinical events, including hospitalizations or severe skeletal myopathy, hepatic, or cardiac disease.

UX007 is the first investigational drug in development to treat LC-FAOD. Unlike current LC-FAOD management, including MCTs, the odd-chain UX007 restores TCA cycle intermediates and supports glucose reserves through gluconeogenesis and, potentially, increased glycogen accumulation.

LC-FAOD often causes muscle weakness and pain that limits gross motor function or motor development. Due to its role in improving oxidative phosphorylation as well as gluconeogenesis, UX007 is believed to provide an efficient alternative source of energy for long-chain fatty acids in muscle, so that fasting and aerobic exercise can be better tolerated. The improvement in 12MWT that was observed at week 18 was sustained through week 60, with a 29% increase in the distance walked compared to baseline, suggesting an improvement in exercise tolerance that will need to be confirmed in larger controlled studies. With muscle weakness and frequent hospitalizations, functional disability often limits daily activities and HRQoL in patients with LC-FAOD. Following 78 weeks of UX007 treatment, HRQoL physical scores in both adult and pediatric subjects improved above baseline, indicating reduced limitations due to health problems.

Major clinical event rates were reduced following the initiation of UX007 treatment compared with the pretreatment period when subjects received currently available LC-FAOD management. Both the mean annualized event rate and the mean annualized duration rate of major clinical events were reduced by approximately half with UX007 treatment (48.1 and 50.3%, respectively). The current study is limited by the uncontrolled, open-label study design and relatively small sample size, as well as the variability of the study population in terms of age and disease presentation/severity. However, while not defined by specified criteria in the study protocol, the key evaluation of major clinical events, including hospitalizations, is largely objective and unlikely to change in a blinded study. Additionally, the reduction in the frequency and duration of major clinical events is consistent with a previous retrospective medical record review of 20 severe LC-FAOD patients administered food-grade triheptanoin for up to 13 years (Vockley et al. 2015). Both the retrospective record review and the results presented here support that UX007 or triheptanoin treatment results in a consistent response pattern in the type of major event reductions, including reduced hospitalizations due to rhabdomyolysis, fewer cardiomyopathy events, and near-elimination of hypoglycemic events.

This Phase 2 study was conducted in subjects who continued to exhibit severe clinical manifestations or a history of major clinical events related to LC-FAOD despite being well managed prior to UX007 initiation. The reduction in major clinical events in this patient population demonstrates improvement over previous disease management, including MCTs.

## Conclusion

In this Phase 2 study in subjects with severe long-chain fatty acid oxidation disorders (LC-FAOD), UX007 treatment for 78 weeks reduced the rate of major clinical events compared with the pretreatment period, maintained improvements in walking exercise tolerance, and increased health-related quality of life (HRQoL). As the majority of subjects were on medium-chain triglycerides (MCTs) prior to UX007, the significant reduction in major clinical events suggests that UX007 may offer an improvement over existing disease management.

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## Compliance with ethical standards

**Conflict of Interest** J. Vockley, B. Burton, G. T. Berry, N. Longo, J. Phillips, A. Sanchez-Valle, P. Tanpaiboon, S. Grunewald, E. Murphy, A. Bowden, W. Chen, C.-Y. Chen, J. Cataldo, D. Marsden, and E. Kakkis declare that they have no conflict of interest.

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