An Open-label Long-Term Safety and Efficacy Extension Study in Subjects with Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD) Previously Enrolled in UX007 or Triheptanoin Studies

Protocol Number: UX007-CL202
Original Protocol: 14 July 2014
Amendment 1: 16 April 2015
Amendment 2: 21 December 2015
Amendment 3: 12 April 2016
Amendment 4: 16 September 2016
Amendment 5: 02 October 2017
Amendment 6: 01 October 2019

Investigational Product:	UX007 (triheptanoin)
Indication:	Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD)
IND Number:	117053
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA, USA 94949
Sponsor's Responsible Medical Officer:	[redacted] Senior Medical Director, Clinical Sciences Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA USA 94949 [redacted]

This study is to be performed in compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007-CL202 Amendment 1

16 April 2015

The Protocol UX007-CL202 (dated 14 July 2014) has been modified by Amendment 1 to incorporate a number of changes based on additional information acquired since the beginning of the study. The major changes to the protocol impacting the conduct of the study are summarized below. Additional changes have also been made to provide supportive information and rationale for the proposed changes (along with minor edits for consistency and clarity) but are not detailed in this summary.

1. Sponsor's Responsible Medical Officer and associated Medical Monitor contact information (title page and Section 10) have been updated to:

   [redacted]

2. A study schematic was added to the synopsis and the body of the protocol.

   Rationale: A study schematic will assist the reader in visualizing the course of the study.

3. Inclusion Criterion 2 (synopsis and Section 7.3.1) was updated to allow inclusion of patients who have failed conventional therapy and who have documented severe unmet need. Similar changes were made to Sections 7.1, 7.3, and 7.6.5

   Rationale: This change was made to allow inclusion of patients with severe unmet need not previously eligible for this study.

4. Inclusion Criterion 7 (synopsis and Section 7.3.1) was updated to provide additional detail as to the acceptable methods of contraception required for inclusion into this study. A similar change was made in Section 7.5.4.6.

   Rationale: This change was made to clarify the contraception language.

5. Added Exclusion Criterion Number 2 indicating that patients qualifying for any other clinical trial designed to progressively evaluate the safety and efficacy of triheptanoin in LC-FAOD are not eligible for this study.

   Rationale: This change was made for clarification.

6. Exclusion criterion Number 4 in the synopsis and Section 7.3.2 was updated to exclude breastfeeding mothers from participation in this study.

   Rationale: This change was made for clarification and to ensure that breastfeeding mothers are not enrolled into the study.

7. Stopping Rules in Section 7.3.3.1 were updated to state that Regulatory Authorities, as well as Institutional Review Boards (IRBs) and Ethics Committees (ECs), will be informed should unexpected and possibly, probably, or definitely drug-related SAEs occur and/or if the study is paused or stopped. Language was also added stating that, if paused or stopped, the trial will only be restarted following approval by Regulatory Authorities.

   Rationale: This change was made to clearly convey that Regulatory Authorities will be contacted if any of the above occurs during the course of this study.

8. The Peabody Developmental Motor Scales (PDMS) and the Clinical Global Impression (CGI) scales were removed as efficacy variables in the study.

   Rationale: The PDMS was removed because gross motor function does not appear to be a problem for younger FAOD patients. The CGI scales were removed because pre-treatment assessments for comparison are not available for this pool of patients. Removal of these assessments will also alleviate patient burden.

9. A visit window of ±1 week was added to the phone visits in the schedule of events.

   Rationale: This change was made to reduce site and patient burden.

10. The definitions for AE relatedness were updated in Section 8.5.3.

    Rationale: This change was made to standardize the definitions across protocols.

11. Text was added to Section 8.5.1 noting that hospitalizations planned prior to study enrollment (e.g. for elective surgeries) are not considered SAEs. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

    Rationale: This change was made for clarification.

12. Sections 8.5.1, 8.5.4, 8.5.5, and 8.5.6 were updated to define the sponsor's responsibilities with regard to reporting SAEs/SUSARs.

    Rationale: These changes were made in accordance with European Directive 2001/20/EC.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007-CL202 Amendment 2

21 Dec 2015

The Protocol UX007-CL202 (dated 16 April 2015) has been modified by Amendment 2 to incorporate a number of changes based on additional information acquired since Amendment 1. The major changes to the protocol impacting the conduct of the study are summarized below. Additional changes have also been made to provide supportive information and rationale for the proposed changes (along with minor edits for consistency and clarity) but are not detailed in this summary.

1. Updated the medical director contact from [redacted], MD to [redacted], DO. This change affected Sections 8.5.7, 10, and the cover page.

2. Changed the term "Screening" to "Baseline" in Exclusion Criterion Number 4. Similar changes were made to Sections 7.5.4.9 and 8.1.1.

   Rationale: This change was made to clarify an earlier oversight.

3. Deleted the sentence: "For subjects completing the UX007-CL201 study, the last evaluable ECHO will serve as Baseline for this study" in Footnote 7 of Table 2.1 and in Section 7.5.2.4.

   Rationale: Since the last echocardiogram (ECHO) in the UX007-CL201 study is performed at week 24, nearly a year will have transpired and subjects will be due for a repeat ECHO (UX007-CL202 requires an ECHO be performed annually).

4. Additional detail was added to Table 2.1 (Footnote 6) regarding the performance of the 12MWT.

   Rationale: This change was made for clarity and patient convenience.

5. Added pancreatic lipase inhibitors and removed oral salicylates from the list of prohibited medications.

   Rationale: Pancreatic lipase inhibitors were added as prohibited medications because in vitro studies have shown that pancreatic lipases hydrolyze triheptanoin; therefore inhibitors of pancreatic lipases (e.g. orlistat) should be avoided while taking UX007. Salicylates are not routinely prescribed in children because of concern

for potential association with Reye's syndrome; however, they may be used at the physician's discretion. They may also be recommended as low dose daily treatment for adult subjects with risk for cardiovascular disease or those at risk for colon cancer.

6. Updated text in Sections 7.5.4 (Safety Measures & General Assessments) and 7.5.4.8 (Adverse Events).

   Rationale: This change was made for clarification.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007-CL202 Amendment 3

12 April 2016

The Protocol UX007-CL202 (Version 2 dated 21 December 2015) has been modified by Amendment 3 to incorporate a change based on Regulatory feedback. The change to the protocol impacting the conduct of the study is summarized below.

1. The protocol was updated to clarify the total duration of the study. Specifically, the phrase "whichever occurs first" was included indicating that patients will be treated with "UX007 for up to 3 years or until market approval, whichever occurs first." This change affects the synopsis (Rationale, Study Design and Methodology, and Duration of Treatment), Section 5, Section 5.4, Section 7.1, and Section 7.4.4.

   Rationale: This change was made per guidance from Regulatory Authorities and for clarification.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007-CL202 Amendment 4

16 September 2016

The Protocol UX007-CL202 (Version 3 dated 12 April 2016) has been modified by Amendment 4 to incorporate changes based on information obtained since the previous amendment. The changes to the protocol impacting the conduct of the study are summarized below. Additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. The length of study participation was increased to 5 years (60 months; end of treatment visit). This change affected multiple sections of the protocol including the schedule of events (Table 2.1) and Section 7.1 (Overall Study Design and Plan).

   Rationale: This change was made to ensure subjects are eligible to continue receiving study medication under the auspices of this clinical trial for 5 years or until market approval, whichever occurs first.

2. The following statement was added to Sections 7.1 (Overall Study Design and Plan) and 7.4.4 (Selection of Doses and Study Duration): Subjects who switch from medium chain triglycerides (MCTs) to UX007 may transition at the same dose and then titrate, as appropriate.

   Rationale: This change was made to ensure a safe transition for those subjects formerly on MCT therapy.

3. Inclusion Criterion #2 (Section 7.3.1, and corresponding information throughout) was updated to specifically include treatment-naïve (i.e., naïve to both UX007 and food-grade triheptanoin) patients.

   Rationale: Text was updated to provide clarification. This is not a change to the study eligibility.

4. Inclusion Criterion #6 (Section 7.3.1, and corresponding information in Section 7.5.4.6 [Pregnancy Testing]) regarding pregnancy testing and contraception was updated as follows:

   - Females of childbearing potential must have a negative urine pregnancy test at Baseline and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have not experienced menarche, are post-menopausal (defined as having no menses for

at least 12 months without an alternative medical cause), or are permanently sterile due to total hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

- Participants of child-bearing potential or fertile males with partners of child-bearing potential who are sexually active must consent to use a highly-effective method of contraception as determined by the investigator from the period following the signing of the informed consent through 30 days after last dose of study drug.
- Examples of highly effective contraception methods were added to Section 7.5.4.6.

Rationale: The change provides clarification of study requirements.

5. The 12-Minute Walk Test (12MWT) efficacy assessment was removed from the protocol (e.g., from Section 7.5.2 [Clinical Efficacy Measures] and the schedule of events [Table 2.1]).

   Rationale: Continuing to use the 12MWT assessment in this open-label, single-arm extension is unlikely to yield informative data. Removal of this assessment will reduce the burden to subjects and investigational sites participating in the study.

6. The Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT efficacy assessment was removed from the protocol (e.g., Section 7.5.2 [Clinical Efficacy Measures] and the schedule of events [Table 2.1]).

   Rationale: Continuing to use the PEDI-CAT assessment in this open-label, single-arm extension is unlikely to yield informative data. Removal of these assessments will reduce the burden to subjects and investigational sites participating in the study.

7. A Safety Follow-up Phone Call was added to the schedule of events (Table 2.1) and relevant sections of the protocol (e.g., Sections 7.4.4 [Selection of Doses and Study Duration] and 7.5.1 [Schedule of Events]).

   Rationale: This change was made to align language with other Ultragenyx protocols based on requests from Regulatory Authorities to standardize how adverse event information is collected 30 days following the last dose of study drug.

8. Text was added to clarify that the end of study is the last subject's Safety Follow-up Phone Call. This change affected multiple sections of the protocol including Sections 7.1 (Overall Study Design and Plan) and 7.5.1 (Schedule of Events), and the schedule of events (Table 2.1).

   Rationale: This change was made to align language with other Ultragenyx protocols based on requests from Regulatory Authorities to clarify the end of study.

9. The statement in Section 7.4.5.1 (Prohibited Medications) was edited to be clearer: MCT oil and metabolic formulas containing significant contributions from MCT oil, including coconut oil, must not be used after the first dose of study medication.

   Rationale: This change was made for clarity.

10. Section 7.5.2.3 (LC-FAOD Major Events) was updated to state that if events occur that represent a substantive change in the nature or an increase in frequency from a subject's prior medical history, the event should be reported as an adverse event (AE).

    Rationale: This change was made to ensure that major LC-FAOD events are captured as AEs.

11. Subject-reported fatigue, exercise tolerance, muscle pain, and activity level efficacy recording was removed from the protocol (e.g., from Section 7.5.2 [Clinical Efficacy Measures] and the schedule of events [Table 2.1]).

    Rationale: Continuing to record subject-reported symptoms of muscle weakness and fatigue in this open-label, single-arm extension is unlikely to yield informative data. Removal of this assessment will reduce the burden to subjects participating in the study. Note: New or worsened events of fatigue and muscle pain will still be collected as adverse events as described under Section 8.5 (Reporting and Follow-up of Adverse Events).

12. Section 7.5.4.2 (Growth and Weight Evaluations) was updated to state that height, weight, and head circumference (if applicable) data will be used to evaluate subject growth using published normative data, when available.

    Rationale: This change was made to clarify how the growth and weight evaluations will be assessed.

13. Section 8.4.3 (Record Retention) has been updated to state that all study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law and to clarify the responsibilities of the Investigator, Institution, and Ultragenyx with regard to record retention.

    Rationale: This administrative change to mandate retention of records for at least 25 years has been made to reflect upcoming changes to EU clinical trial regulations and current regulations by other health authorities. Record retention responsibility text was updated to clarify that it is not the explicit responsibility of Ultragenyx to assist with records retention.

14. Updated language in Section 8.5.4 (Adverse Event Reporting).

    Rationale: This change was made so the language would be aligned with the most current Ultragenyx protocol template.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007-CL202 Amendment 5

02 October 2017

The Protocol UX007-CL202 (Amendment 4 dated 16 September 2016) has been modified by Amendment 5 to provide pharmacokinetic assessments and modify dosing allowances. Primary and secondary endpoints have also been specified. The changes to the protocol impacting the conduct of the study are summarized below. Additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. Pharmacokinetic (PK) measurements were added to evaluate UX007 and UX007 metabolites in a subset of subjects at select sites (minimum of 12 subjects) in Section 7.5.4, the Schedule of Events in Table 2.1, and Section 7.6.4. PK analysis was also added as a study objective in Section 6.

   Rationale: A PK sub-study was added to characterize the steady-state PK of UX007 and UX007 metabolites in subjects with LC-FAOD.

2. Section 7.1 was modified to include dosing greater than the target range of 25-35% at the Investigator's discretion.

   Rationale: Dosing greater than the upper level of the target range has been included to allow subjects who enroll with a baseline UX007/triheptanoin dose greater than 35% to maintain that dose on UX007-CL202. Investigators may also dose individual subjects above target range at their discretion; it is recommended that doses above 35% are discussed with the Medical Monitor prior to administration. Anecdotal evidence from subjects on UX007-CL201 receiving MCT doses above 35% at Baseline and from subjects transitioning into UX007-CL202 with UX007/triheptanoin doses above 35% from Investigator-Sponsored Trials or Compassionate Use support that higher oil doses are safe and tolerable.

3. Section 7.5.5.4 was modified to specify that the genitourinary component of the physical exam will be performed as age-appropriate at the Investigator's discretion.

   Rationale: This modification was added to clarify that the genitourinary examination scope should be performed at the Investigator's discretion based on clinical judgement and/or safety need.

4. Primary, secondary, and exploratory endpoints were added within the synopsis and Section 7.6.2. Additional information on endpoint analysis was provided within Section 7.6.3.

Rationale: To adhere to clinical trial disclosure requirements, primary and secondary endpoints were clarified based on the study objectives outlined in Section 6. Exploratory endpoints were identified to characterize the potential effect of UX007 treatment on functional disability and cognitive development, clinical biomarkers, and growth measurements, as outlined in Section 7.5.2.1, Section 7.5.3, and Section 7.5.5.2, respectively, as well as PK data for the UX007 metabolites as added to Section 7.5.4.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007-CL202 Amendment 6

01 October 2019

The Protocol UX007-CL202 (Amendment 5 dated 02 October 2017) has been modified by Amendment 6 to extend the study duration and potential subject enrollment.
Additional language was added to clarify the echocardiogram and lymphatic examination assessments. Modifications were also made to the exclusion criteria and to the study stopping rules. The changes to the protocol impacting the conduct of the study are summarized below. Additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. The study duration (Section 7.1 and throughout) has been extended from 5 years to up to 7 years or until commercial availability of UX007 in any region, whichever occurs first. The study duration has been extended to allow subjects to continue to receive study drug until UX007 is commercially available. An End of Study Visit was added in the case of commercial availability.
2. The planned number of subjects (Section 7.3, Section 7.6.6, and throughout) was increased from approximately 100 subjects to approximately 150 subjects as the study continues to enroll subjects from investigator sponsored trials (ISTs) and UX007-naive subjects.
3. Exclusion criterion #3 was modified in the synopsis and in Section 7.3.2 to allow exclusion of subjects who may be at increased risk of hypersensitivity adverse effects per the judgment of the Investigator.
4. Inclusion criterion #2 was modified in the synopsis and in Section 7.3.1 from “severe unmet need” to “clear unmet need” to more accurately reflect the clinical presentation of LC-FAOD in the study population.
5. Additional clarifying language was added to Section 7.5.2.2 and the Schedule of Events (Table 2.1) to allow for echocardiogram assessments performed as routine care within 30 days prior to the scheduled clinic visits.
6. Additional clarifying language regarding the lymphatic portion of the physical examination was added to Section 7.5.5.4 to ensure that the exam scope is age-appropriate and at the Investigator’s discretion based on clinical judgement.
7. Additional text was added to Section 7.3.3.1 to clarify the SAE severity (Grade 3 or higher) to be considered by the Investigator for the study stopping rules.

2 SYNOPSIS

TITLE OF STUDY: An Open-label Long-Term Safety and Efficacy Extension Study in Subjects with Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD) Previously Enrolled in UX007 or Triheptanoin Studies
PROTOCOL NUMBER: UX007-CL202
STUDY SITES: Approximately 10 sites globally
PHASE OF DEVELOPMENT: Phase 2
RATIONALE: Long-chain fatty acid oxidation disorders (LC-FAOD) are caused by defects in the metabolic pathway that converts fatty acids into energy, leading to deficiencies in energy metabolism. The metabolic deficiency can deplete energy sources, resulting in serious clinical manifestations including hypotonia, rhabdomyolysis, liver dysfunction andhypoglycemia, and cardiomyopathy. These LC-FAOD major events are not sufficiently controlled in many patients by current standard of care, usually consisting of avoidance of fasting, low-fat/high-carbohydrate diet, dietary medium chain triglycerides (MCT oil), and/or carnitine supplementation. MCT oil, an even chain fatty acid, can provide medium chain fatty acids that bypass the specific LC-FAOD pathway defects but may not restore energy metabolism fully. In addition to supplying medium chain fatty acids, UX007 (triheptanoin), a specialized medium odd-chain (C7) triglyceride, also replaces deficient mitochondrial tricarboxylic acid (TCA) cycle intermediates via the generation of 3-carbon intermediates, thereby improving energy metabolism. Triheptanoin has been studied in many types of LC-FAOD for approximately 20 years. Published reports describe profound clinical responses to triheptanoin, including improved physical capacity and a reduction of frequency and severity of major LC-FAOD events (rhabdomyolysis, hypoglycemia, liver function and hepatomegaly, and cardiomyopathy). Numerous LC-FAOD patients have participated, or are actively participating in multiple clinical studies or treatment programs with UX007/triheptanoin conducted by various sponsors and investigational sites. This open-label long-term safety and efficacy study will provide an opportunity for LC-FAOD patients to be treated with UX007 for up to 7 years or until commercial availability of UX007 in any region, whichever occurs first, under a single standardized protocol. The subjects may have participated in other studies or treatment programs with UX007/triheptanoin or be treatment naïve and have clear unmet need but would be consolidated into one program for long-term triheptanoin treatment and consistent safety monitoring. The study is designed to obtain long-term safety information and evaluate maintenance of efficacy in a diverse LC-FAOD population.

OBJECTIVES:

The primary objective of the study is to:

- Evaluate the long-term safety and efficacy of UX007 in LC-FAOD subjects

The secondary objectives of the study are to:

- Evaluate the effect of UX007 on energy metabolism in LC-FAOD
- Evaluate impact of UX007 on clinical events associated with LC-FAOD

The objective of the pharmacokinetic sub-study is to:

- Characterize the steady-state pharmacokinetics (PK) of UX007 and UX007 metabolites in subjects with LC-FAOD

ENDPOINTS:

Efficacy Endpoints

The primary efficacy endpoint:

- The annualized LC-FAOD major events rate inclusive of skeletal myopathy (rhabdomyolysis), hepatic (hypoglycemia) and cardiomyopathy events.

The secondary efficacy endpoints:

- Energy metabolism in LC-FAOD on the basis of the following endpoints:
  - Ventricle size
  - Ejection fraction (EF)
  - Shortening fraction (SF)
- Clinical events associated with LC-FAOD on the basis of the following endpoints
  - Annualized duration rate of all MCEs
  - Annualized event rate of rhabdomyolysis MCEs
  - Annualized duration rate of rhabdomyolysis MCEs
  - Annualized event rate of cardiomyopathy MCEs
  - Annualized duration rate of cardiomyopathy MCEs
  - Annualized event rate of hypoglycemic MCEs
  - Annualized duration rate of hypoglycemic MCEs

Exploratory endpoints include the following:

- Functional disability and cognitive development (instrument selection based on age) endpoints:
  - SF-10 physical health component summary (PCS) score
  - SF-10 mental health component summary (MCS) score
  - SF-12 physical health component summary (PCS) score
  - SF-12 mental health component summary (MCS) score
- Clinical biomarkers endpoints:
  - Serum creatine kinase
  - Fasting serum glucose
  - Alanine aminotransferase (ALT)
  - Aspartate transaminase (AST)
  - Gamma glutamyl transpeptidase (GGT)
- Growth measurement endpoints:

- Height
- Weight
- Head circumference, if applicable (subjects ≤ 36 months of age)

PK endpoints

- Plasma levels of UX007
- Plasma levels of UX007 metabolites, including heptanoate, beta-hydroxypentanoate (BHP), and beta-hydroxybutyrate (BHB)

Safety Endpoints

Safety events will be collected as adverse events (AE) or serious adverse events (SAE). The analyses of safety will include all subjects who receive at least one dose of study drug.

The safety endpoints in this study are:

- Incidence and severity of treatment emergent AEs (primary safety endpoint)
- Vital signs
- Incidence of laboratory abnormalities
- Concomitant medications

STUDY DESIGN AND METHODOLOGY:

The study is an interventional, open-label, long-term safety and efficacy extension study of UX007 treatment in approximately 150 LC-FAOD subjects who have participated in prior clinical studies or treatment programs with UX007/triheptanoin or are treatment naïve (i.e., naïve to both UX007 and food-grade triheptanoin), have failed conventional therapy, and have clear unmet need. UX007 dosing will be targeted at 25-35% of total caloric intake. If a subject has been receiving a lower dose of UX007/triheptanoin, the individual may continue treatment at the current dose. If however, the subject has symptomatic disease or clinical signs of exercise limitation while on UX007 doses below the target range, the Investigator should consider titrating the dose to 25-35% of total caloric intake. UX007 doses above 35% of total caloric intake may be considered as needed at the discretion of the Investigator on an individual basis; it is recommended that doses above 35% are discussed with the Medical Monitor prior to administration. If a subject has been off UX007/triheptanoin treatment for > 1 month or is treatment naïve, the dose will be titrated according to the Study Drug Administration Guidelines. Subjects who switch from MCT to UX007 may transition at the same dose and then titrate, as appropriate. The subjects will be followed to evaluate the long-term safety and continued effects of UX007 for up to 7 years or until commercial availability of UX007 in any region, whichever occurs first. A Safety Follow-up Phone Call will be conducted 30-35 days after last dose of study drug. The end of study is defined as the last day that protocol-specified assessments (including telephone contact) are conducted for the last subject in the study.

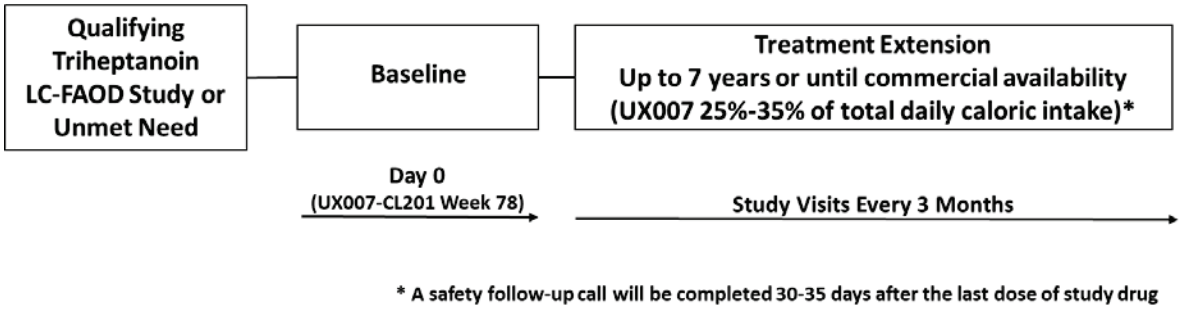
If UX007 becomes commercially available during the study, each subject will return for an End of Study Visit; this will be recorded as study completion rather than early termination. For subjects not immediately continuing UX007 through another mechanism (ie, commercial product, IST, or compassionate use), a Safety Follow-up Phone Call will be conducted 30-35 days after last dose of investigational study drug.

The continued effects of UX007 treatment on clinical and physiologic disease of the skeletal muscle, the liver and the heart will be assessed. Creatine kinase (CK) will be measured as a biomarker of skeletal myopathy. The metabolic effects on the liver and energy homeostasis will be assessed by

evaluating liver enzymes and serum glucose as biomarkers. Cardiac disease will be assessed by annual echocardiograms (ECHO).

The impact of UX007 treatment on major clinical events will also be assessed throughout the study. Major events are defined as musculoskeletal, hepatic, and cardiac events caused by LC-FAOD, or intercurrent illness complicated by LC-FAOD, resulting in any hospitalization, ER visit, or emergency intervention (any unscheduled administration of therapeutics at home or in the clinic). In subjects for which prior medical events data have already been collected during a prior UX007 protocol, the effect of UX007 treatment on major clinical events during this study will be compared with the subject's available historical information for the 18-24 months prior to beginning UX007 (or from birth for subjects less than 18 months of age). For subjects who are treatment naïve, available historical event data will be collected prior to UX007 administration. The event rate per year during UX007 treatment will be compared with the subject's available historical information for the 18-24 months prior to beginning UX007 (or from birth for subjects less than 18 months of age). Dosing compliance and diet will be regularly monitored along with a standard panel of safety assessments. Figure 2.1 provides a schematic of the study design.

Figure 2.1: UX007-CL202 Study Schema



PK sub-study:

A PK sub-study will evaluate the steady-state PK of UX007 and UX007 metabolites in a minimum of 12 subjects with LC-FAOD. Subjects enrolled in the sub-study will have serial PK samples collected.

NUMBER OF SUBJECTS PLANNED:
Approximately 150 subjects with LC-FAOD are planned to participate in this study.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

Individuals eligible to participate in this study must meet all of the following criteria:

1. Male or female, 6 months of age or older
2. Prior participation in a clinical study assessing UX007/triheptanoin treatment for LC-FAOD. Study Sponsors/Collaborators include: Oregon Health & Science University, University of Pittsburgh, and Ultragenyx Pharmaceutical (ClinicalTrials.gov Identifiers: NCT01379625, NCT01461304, and NCT01886378). Patients who received UX007/triheptanoin treatment as part of other clinical studies; investigator sponsored trials (IST); expanded access/compassionate use

treatment programs; or patients who are treatment naïve (i.e., naïve to both UX007 and food-grade triheptanoin), have failed conventional therapy and, in the opinion of the Investigator and Sponsor, have documented clear unmet need, may also be eligible at the discretion of the Sponsor.

3. Confirmed diagnosis of LC-FAOD including: carnitine palmitoyltransferase (CPT I or CPT II) deficiency, very long chain acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency, trifunctional protein (TFP) deficiency, or carnitine-acylcarnitine translocase (CACT) deficiency. Information on diagnosis will be obtained from medical records and should include confirmed diagnosis by results of acylcarnitine profiles, fatty acid oxidation probe studies in cultured fibroblasts, and/or mutation analysis.
4. Willing and able to complete all aspects of the study through the end of the study, including visits and tests, documentation of symptoms and diet, and administration of study medications. If a minor, have a caregiver(s) willing and able to assist in all applicable study requirements.
5. Provide written informed consent (subjects aged ≥ 18 years), or provide written assent (where appropriate) and have a legally authorized representative willing and able to provide written informed consent, after the nature of the study has been explained and prior to any research-related procedures.
6. Females of child-bearing potential must have a negative urine pregnancy test at Baseline and be willing to have additional pregnancy tests during the study. Females considered not of child-bearing potential include those who have not experienced menarche, are post-menopausal (defined as having no menses for at least 12 months without an alternative medical cause), or are permanently sterile due to total hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
7. Participants of child-bearing potential or fertile males with partners of child-bearing potential who are sexually active must consent to use a highly effective method of contraception as determined by the Investigator from the period following the signing of the informed consent through 30 days after last dose of study drug.

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, short- or medium-chain FAOD, ketone body metabolism defect, propionic acidemia or methylmalonic acidemia
2. Patient qualifies for any other clinical trial designed to progressively evaluate the safety and efficacy of triheptanoin in LC-FAOD
3. Any known hypersensitivity to triheptanoin that, in the judgment of the Investigator, places the subject at increased risk for adverse effects
4. Pregnant and/or breastfeeding an infant at Baseline or planning to become pregnant (self or partner) at any time during the study
5. Have any co-morbid conditions, including unstable major organ-system disease(s) that in the opinion of the Investigator, places the subject at increased risk of complications, interferes with study participation or compliance, or confounds study objectives or unwilling to discontinue prohibited medications.

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION:

UX007 is colorless to light yellow oil packaged in 1L round, translucent high-density polyethylene (HDPE) bottles. UX007 will be administered orally (PO) with food or by gastronomy tube; usually four times per day: breakfast, lunch, dinner, and before bed, at the target dose range of 25-35% of total calories. The dose may be divided into smaller more frequent doses with food as needed. The dose may be mixed with small amounts of food or drink (including formula) as indicated in the administration guideline. If a subject has been receiving a lower dose of triheptanoin, the individual may continue treatment at the current dose provided there is no evidence of symptomatic disease or clinical signs of exercise limitation. UX007 doses above 35% of total caloric intake may be considered as needed at the discretion of the Investigator on an individual basis; and it is recommended that doses above 35% are discussed with the Medical Monitor prior to administration. If a subject has been off UX007/triheptanoin treatment for > 1 month or is treatment naïve, the dose will be titrated according to the Study Drug Administration Guidelines. Subjects who switch from MCT to UX007 may transition at the same dose and then titrate, as appropriate.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

The study is designed as an open-label interventional trial. Therefore, no reference therapy or placebo will be administered.

DURATION OF TREATMENT:

Subjects may receive UX007 treatment for up to 7 years (84 months) during the study or until commercial availability of UX007 in any region, whichever occurs first. The end of study is defined as the last day that protocol-specified assessments (including telephone contact) are conducted for the last subject in the study.

CRITERIA FOR EVALUATION:

The concept for evaluation is to study the long-term safety and continued effects of UX007 on energy metabolism and clinical events associated with LC-FAOD. Biologic and clinical assessments will be conducted throughout the 84 month Treatment Extension Period. The occurrence of major LC-FAOD clinical events will be captured and compared to available data prior to initiation of UX007 treatment. Dosing compliance and diet will be regularly monitored along with a standard panel of safety assessments.

Clinical Efficacy Variables:

Functional disability and cognitive development (instrument selection based on age):

- Medical Outcomes Study 10-Item Short Form (SF-10) OR Medical Outcomes Study 12-Item Short Form (SF-12)

- Cardiomyopathy and cardiac function measured by ECHO; includes ventricle size, ejection fraction and shortening fraction
- LC-FAOD major events inclusive of skeletal myopathy (rhabdomyolysis), hepatic (hypoglycemia) and cardiac disease (cardiomyopathy) events. Defined as any visit to the ER/acute care, hospitalization, emergency intervention (i.e. any unscheduled administration of therapeutics at home or in the clinic), or any similar event whether caused primarily by LC-FAOD or by an intercurrent illness complicated by LC-FAOD. The event type, levels of relevant laboratory

parameters (including CK, glucose, and BNP/troponin), the number of days hospitalized and in ICU, and the type and number of days of treatment and intervention will be recorded.

Biomarkers & LC-FAOD Laboratory Measures:

- Biomarkers of clinical manifestations:
  - Skeletal myopathy: CK
  - Hepatic disease: fasting serum glucose and liver enzymes (ALT, AST, GGT)
- Laboratory measures of LC-FAOD disease activity, including total and free plasma carnitine, plasma acylcarnitines, and urine organic acids

Pharmacokinetics of UX007 and Metabolites

- Plasma levels of UX007
- Plasma levels of UX007 metabolites, including heptanoate, beta-hydroxypentanoate (BHP), and beta-hydroxybutyrate (BHB)

Safety & General Assessments:

Safety events will be collected as adverse events (AE) or serious adverse events (SAE). Study assessments to evaluate safety include:

- Clinical laboratory tests
- Vital signs
- Physical examination
- Concomitant medications
- Growth rate, height and weight: The amount and rate of growth in pediatric and adolescent subjects will be measured using standard methods and compared to baseline height and weight, and head circumference, if applicable (subjects ≤ 36 months of age), and to normal growth rates and published LC-FAOD growth rates, if available.

STATISTICAL METHODS:

A full description of the planned analyses will be provided in a Statistical Analysis Plan.

The primary efficacy endpoint, ie annualized MCE event rate, will be calculated using all MCE events collected post-UX007 treatment through the end of study. The primary analysis of the annualized MCE rate is descriptive statistics using mean, standard deviation (SD), median, quartiles, minimum, and maximum values. Two-sided 95% confidence interval will also be provided when appropriate. Annualized event rates for MCE by event type (ie, rhabdomyolysis, cardiomyopathy and hypoglycemic events) will be calculated and summarized in a similar fashion as with the primary efficacy endpoint.

In addition, for subjects who have historical event rate data collected, comparisons of pre- and post-UX007 treatment annualized event rates for overall MCE events will be conducted. In addition, intra-patient comparisons of pre- and post-UX007 treatment for MCE events by event type might be considered if sample size permits.

Summary statistics will be produced for all exploratory endpoints using all available assessments. For continuous variables, the number of observations and the mean, standard deviation (SD), median, quartiles, minimum, and maximum values were tabulated by endpoint. For categorical variables, the counts and proportions of each value were tabulated. Two-sided 95% confidence interval will also be provided when appropriate. Efficacy data collected for age-specific assessments (e.g. SF-10/12) will be summarized for subjects in that age group only. Other age-specific summaries may be provided for measures collected across all age groups.

PK Analyses

Summary statistics of plasma concentration will be provided for UX007 and metabolites. PK parameters such as area under the plasma concentration-time curve (AUC), time to maximum plasma concentration (Tmax), maximum plasma concentration (Cmax), and trough plasma concentration (Ctrough) will be estimated for participating subjects.

Safety Analyses

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of AEs will be summarized by System Organ Class (SOC), Preferred Term (PT), severity, and relationship to UX007 treatment, if possible. A by-subject listing will be provided for those subjects who experience a SAE, including death, or experience an AE associated with early withdrawal from the study or study drug treatment.

Clinical laboratory data will be summarized by the type of laboratory test. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e. outside reference ranges) and/or clinically significant abnormalities will be presented for each measurement.

Table 2.1: Schedule of Events

	Baseline[1]		Treatment Extension[2] Year 1				Treatment Extension[2] Years 2-7			Early-Term/End of Study[3]	Safety Follow-up (30-35 days)[13]
MONTH	**0**	**0.5**	**3**	**6**	**9**	**12**	**15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81**	**18, 30, 42, 54, 66, 78**	**24, 36, 48, 60, 72, 84**		
TYPE	**Clinic**	**Phone**	**Phone**	**Clinic**	**Phone**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**
Informed Consent[1]	X										
Medical & Triheptanoin Treatment History[4]	X										
Growth[5]	X			X		X		X	X	X	
SF10/12	X			X		X		X	X	X	
Echocardiogram (ECHO)[6]	X					X			X	X	
LC-FAOD Major Events Assessment[7]	X	X	X	X	X	X	X	X	X	X	
LC-FAOD Biomarkers & Laboratory Measures[8]	X			X		X		X	X	X	
Vital Signs[9]	X			X		X		X	X	X	
Physical Examination	X			X		X		X	X	X	
Clinical Laboratory Tests[10]	X			X		X		X	X	X	
Urine Pregnancy Test	X			X		X		X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X

	Baseline[1]		Treatment Extension[2] Year 1				Treatment Extension[2] Years 2-7			Early-Term/End of Study[3]	Safety Follow-up (30-35 days)[13]
MONTH	**0**	**0.5**	**3**	**6**	**9**	**12**	**15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81**	**18, 30, 42, 54, 66, 78**	**24, 36, 48, 60, 72, 84**		
TYPE	**Clinic**	**Phone**	**Phone**	**Clinic**	**Phone**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**
Dietary Assessment and Diet diary[11]				X		X		X	X	X	
UX007 Treatment & Compliance[12]	X	X	X	X	X	X	X	X	X[12]	X[12]	
Plasma UX007 and Metabolites[14]				X[14]		X[14]		X[14]	X[14]		
Standardized Meal[14]				X[14]		X[14]		X[14]	X[14]		

1 The Baseline visit may occur in conjunction with the last scheduled visit from study UX007-CL201. Assessments conducted at the last UX007-CL201 visit will be used for Baseline data to avoid duplication. Minor subjects who turn 18, should provide consent at their next visit.

2 Clinic Visits will occur at 6 month intervals (± 2 weeks). The window for phone visits is ± 1 week.

3 Early Termination Visit should take place within 4 weeks of treatment discontinuation, if possible. The End of Study Visit will take place following commercial availability of UX007 in any region; if the End of Study Visit occurs within 2 weeks of a previous clinic visit, only the following assessments will occur: growth, vital signs, physical examination, urine pregnancy testing, AEs, concomitant medications, and UX007 compliance.

4 Medical history including major medical illness, diagnoses and surgeries will be collected for all subjects not previously enrolled in UX007-CL201. LC-FAOD maintenance treatment history, including triheptanoin treatment history, and relevant concomitant medications will be recorded (start date, stop date, dose, dose regimen). Any available sibling history of LC-FAOD will be noted.

5 Growth measurements include height and weight for all subjects, as well as head circumference for subjects aged ≤ 36 months.

6 ECHO will be performed at Baseline and annually thereafter at indicated clinic visits (or if performed as routine care within 30 days prior to the Baseline or indicated clinic visits) or Early Termination if not performed within 6 months prior to termination. Additional tests may be performed during Treatment Extension Period if any abnormalities are detected or if medically indicated.

7 Major LC-FAOD events include skeletal myopathy (rhabdomyolysis), hepatic (hypoglycemia) and cardiac disease (cardiomyopathy) events, and are defined as any visit to the ER/acute care, hospitalization, emergency intervention (ie any unscheduled administration of therapeutics at home or in the clinic), or any similar event whether caused primarily by LC-FAOD or by an intercurrent illness complicated by LC-FAOD. The event type, levels of relevant laboratory parameters (including CK, glucose, and BNP/troponin), the number of days hospitalized and days in ICU, and the type and number of days of treatment and intervention will be recorded.

[8] Biomarkers of clinical manifestations include skeletal myopathy (CK) and hepatic disease (fasting serum glucose and liver enzymes [ALT, AST, GGT]). Laboratory measures of LC-FAOD disease activity include total and free plasma carnitine, plasma acylcarnitines, and urine organic acids.

[9] Vital sign measurements consist of seated systolic/diastolic BP measured in millimeters of mercury (mm Hg), HR (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Obtain at the beginning of each visit before any additional assessments are completed.

[10] Clinical Laboratory Tests include standard serum chemistry, hematology, and urinalysis. These panels may overlap with LC-FAOD-specific biomarkers (including glucose and liver enzymes) which are called out separately in the table.

[11] Subjects and/or caregivers are required to maintain record of daily diet in a diary for 3 days prior to each clinic visit after consenting to participate in the trial. The daily diet should be representative of typical consumption for the subject. The diet diary will be reviewed with the site staff upon each indicated visit.

[12] Treatment with UX007 will begin after any necessary washout period for prohibited medications. UX007 dosing will be targeted at 25-35% of total caloric intake. If a subject has been receiving a lower dose, the individual may be titrated to a UX007 dose up to 25-35% of total caloric intake, while ensuring tolerability. However, a subject may remain at a lower dose if higher doses are not tolerated or at a higher dose at the discretion of the Investigator. UX007 will not be dispensed at the Month 84 (end-of-treatment visit), End of Study, Early Termination visits (as applicable).

[13] Safety Follow-up Phone Call to be conducted 30-35 days after last dose of investigational study drug. Following commercial availability of UX007, a Safety Follow-up Phone Call will be conducted 30-35 days after last dose of investigational study drug for subjects not immediately continuing UX007 through another mechanism (ie, commercial product, IST, or compassionate use). The site personnel will initiate this safety follow-up telephone call to collect information on any ongoing or new AEs, serious adverse events (SAEs), and concomitant medications, as appropriate. Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved.

[14] PK measurements will occur at select sites in a subset of subjects at two consecutively scheduled clinic visits (eg Month 18 and Month 24), excluding the Baseline Visit. Participating subjects (minimum of 12 subjects) will be fed a standardized meal containing one of their divided daily doses of UX007. Blood for plasma UX007 and metabolites will be collected pre-dose (within 15 minutes prior to start of meal) and at 30, 90, 120, and 240 minutes [± 5 minutes] after finishing the meal. For each sample collection, the meal start/stop times, calories consumed, UX007 dosing, and sampling times will be recorded.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

AE	adverse event
ALT	alanine aminotransferase
APBD	adult polyglucosan body disease
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BNP	B-type natriuretic peptide
BP	blood pressure
BUN	blood urea nitrogen
CACT	carnitine-acylcarnitine translocase
CFR	Code of Federal Regulations
CK	creatine kinase
CPT	carnitine palmitoyltransferase
CRF	Case Report Form
ECHO	echocardiogram
EC	Ethics Committee
EDC	electronic data capture
EF	ejection fraction
ER	emergency department/room
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAOD	fatty acid oxidation disorders
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
GMP	Good Manufacturing Practice
GSD II	glycogen storage disease type II
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	intensive care unit
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IUD	intrauterine device

IUS	intrauterine system
LC-FAOD	long-chain fatty acid oxidation disorders
LCHAD	L-3-hydroxy-Acyl-CoA dehydrogenase
LDH	lactate dehydrogenase
MADD	multiple acyl-CoA dehydrogenase deficiency
MCAD	medium-chain acyl-CoA dehydrogenase deficiency
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCS	Mental Component Summary
MCT	medium chain triglyceride
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NADH	nicotinamide adenine dinucleotide hydrogen (reduced form)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
PCS	Physical Component Summary
PK	pharmacokinetic
PO	oral, by mouth
PT	Preferred Term
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SF	shortening fraction
SF-10	Medical Outcomes Study 10-Item Short Form for Children
SF-12	Medical Outcomes Study 12-Item Short Form
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TCA	tricarboxylic acid
TFP	trifunctional protein
US	United States
UX007	Investigational Product/study drug, triheptanoin
VLCAD	very long chain acyl-CoA dehydrogenase
WBC	white blood cell

Definition of Terms

Investigational Product is defined as, "A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice).

The terms "Investigational Product" and "study drug" may be used interchangeably in the protocol.

5 INTRODUCTION

Long-chain fatty acid oxidation disorders (LC-FAOD) are caused by enzyme deficiencies in the metabolic pathway that converts fatty acid into energy, leading to inadequate energy metabolism. LC-FAOD can result in serious and potentially life-threatening clinical manifestations, including rhabdomyolysis, hypotonia/weakness, hypoglycemia, and cardiomyopathy. The clinical manifestations are usually managed through the avoidance of fasting, a low-fat/high-carbohydrate diet, supplementation with medium chain triglycerides (MCT oil) and/or carnitine supplementation. Despite treatment, many patients still suffer significant morbidity and mortality. The mortality rate can be above 50% for subjects diagnosed symptomatically and treated with the standard of care (Baruteau et al. 2012).

Triheptanoin (UX007), a highly purified medium-odd-chain triglyceride consisting of 3 fatty acids with 7 carbons each, is intended as a substrate replacement therapy in patients with LC-FAOD and potentially other metabolic disorders to restore deficient intermediates in the mitochondria required for energy metabolism. Triheptanoin has been studied in many types of LC-FAOD and various other disorders. Some patients have been treated with triheptanoin for approximately 20 years with evidence of clinical benefit and no significant safety issues reported. Published reports suggest that LC-FAOD patients failing current therapy can exhibit profound positive clinical responses to triheptanoin (Roe et al. 2002); (Barone 2012); (Vockley et al. 2015); (Vockley et al. 2016); (Vockley et al. 2017); (Vockley et al. 2018).

A retrospective medical record review study (UX007-CL001) has been conducted to formally assess the clinical outcome of triheptanoin treatment in 20 of 24 LC-FAOD patients who have been participating in an ongoing compassionate use program (IND-106011) for up to 13 years. The data suggest triheptanoin is effective in reducing serious and potentially life-threatening energy crises as indicated by a 69% decrease in the number of hospitalization days during major medical events (Vockley et al. 2015). The results imply the possibility to reduce major medical events, and provide the basis for further evaluation of UX007 in prospective clinical studies to verify this effect on the clinical manifestations and major events of LC-FAOD disease.

A completed Phase 2 clinical trial (UX007-CL201) evaluated the safety and effectiveness of UX007 in LC-FAOD patients who continued to suffer the effects of LC-FAOD disease despite current therapy. Following completion of a 24-week Treatment Period and 54-week Extension Period, subjects from UX007-CL201 were eligible to continue treatment in this extension study (UX007-CL202). Numerous LC-FAOD patients have also participated, or are actively participating in multiple clinical studies or compassionate use treatment programs with UX007/triheptanoin conducted by various sponsors and investigational sites. This open-label long-term safety extension study will provide an opportunity for these patients and treatment-naïve patients (i.e., naïve to both UX007 and food-grade triheptanoin) with clear unmet need to be treated with UX007 for up to 7 years or until commercial availability of UX007 in any region, whichever occurs first, under a single standardized protocol. The study is designed to obtain long-term safety information and evaluate maintenance of efficacy in a diverse LC-FAOD population.

5.1 Overview of Long-chain Fatty Acid Oxidation Disorders

Inherited autosomal recessive defects in the mitochondrial long-chain fatty acid oxidation pathways are collectively referred to as LC-FAOD. LC-FAOD are caused by defects in the mitochondrial β-oxidation pathways that convert fatty acids into energy, leading to deficiencies in energy metabolism. As a result, partial or incomplete oxidation of fatty acids leads to accumulation of high concentrations of fatty acids or other metabolic intermediates and an energy deficient state in most organs. The clinical manifestations of the various LC-FAOD frequently overlap and include rhabdomyolysis, hypoglycemia, hepatomegaly, cardiomyopathy, hypotonia and developmental delay, as well as sudden infant death (reviewed in Roe et al. 2002).

Clinical surveys suggest patients with LC-FAOD as a group have an overall premature mortality rate from birth of about 50% or higher when diagnosed symptomatically and treated (Baruteau et al. 2012). Mortality may now have been reduced by newborn screening and early presymptomatic treatment, including diligent prevention of fasting combined with the use of low fat/high carbohydrate diets, carnitine supplementation in some cases, and MCT oil supplementation (Spiekerkoetter et al. 2009). MCT oil has medium even-chain fatty acids that can be metabolized by the separate set of medium-chain fatty acid oxidation enzymes that are distinct from those affected in LC-FAOD and should therefore bypass the LC-FAOD block.

Despite improved mortality rates achieved with newborn screening, Spiekerkoetter and colleagues noted that patients on the best available treatment, including MCT oil with compliance of ≥ 80%, still had significant problems (Spiekerkoetter et al. 2009). Lindner and colleagues studied the outcome of expanded newborn screening on major decompensation events in different classes of disease diagnosed in South-West Germany (Lindner et al. 2011). The 16 patients (6 very long chain acyl-CoA dehydrogenase [VLCAD], 5 L-3-hydroxy-Acyl-CoA dehydrogenase [LCHAD], 2 carnitine-acylcarnitine translocase [CACT] deficiency, 3 multiple acyl-CoA dehydrogenase [MADD]) in the group had a 25% rate of major decompenstion after only 2 years of follow-up.

5.2 Brief Overview of UX007 (Triheptanoin) Development

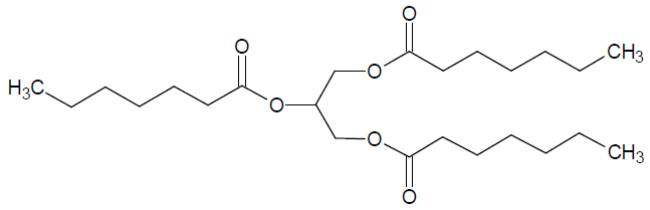
A brief overview of existing information on UX007 (triheptanoin) is provided below; a comprehensive review of the data is contained in the Investigator's Brochure (IB) provided by Ultragenyx Pharmaceutical Inc. (Ultragenyx), which should be reviewed prior to initiating the study.

5.2.1 Brief Description of the Investigational Product

UX007 is a liquid, intended for oral (PO) administration. UX007 is highly purified triheptanoin, a triglyceride of 3 fatty acids with 7 carbons each. UX007 is manufactured by chemical synthesis from glycerol and heptanoic acid. The molecular formula and structure are as follows:

Molecular Formula: $C_{24}H_{44}O_6$

Structure:

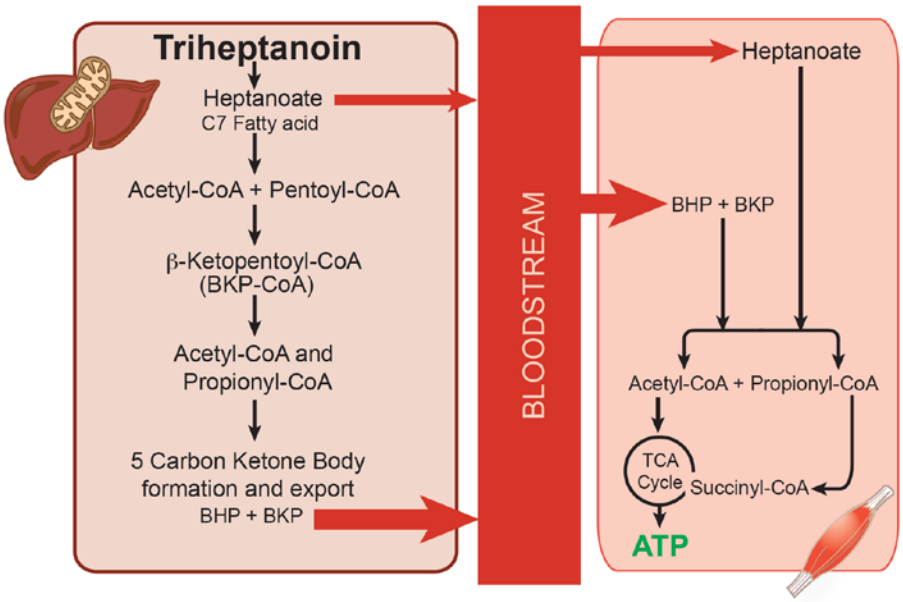


Triheptanoin is metabolized to heptanoate, which in turn is further metabolized to 4- and 5- carbon ketone bodies and the 3-carbon propionyl CoA (derived from the 5-carbon ketones). Therefore, UX007 is designed as a pro-drug that is metabolized to heptanoate to provide substrate replacement as an odd-carbon medium-chain fatty acid for both fatty acid metabolism and anaplerosis (replacement of tricarboxylic acid [TCA] cycle intermediates) required for generation of energy.

5.2.1.1 Mechanism of Action

The mechanism of action of UX007 in restoring energy metabolism is dependent on its medium chain length as well as its odd-carbon properties. UX007 can be metabolized by LC-FAOD patients into free heptanoate which can traverse the mitochondrial membrane without the carnitine carrier. The free heptanoate from UX007 is then metabolized by a different set of medium chain fatty acid oxidation enzymes, bypassing the long chain oxidation enzymes that are deficient in LC-FAOD. The heptanoate is converted to both propionyl-CoA and acetyl-CoA required for energy metabolism (Figure 5.2.1.1.1).
The restoration of energy metabolism is accomplished by two modalities: 1) the acetyl-CoA is condensed into citrate, the first step of the energy generating TCA cycle, and 2) the 3-carbon unit in propionyl-CoA resupplies the TCA cycle intermediates that may be secondarily deficient in these patients. The production of propionyl-CoA is specific to odd-carbon fatty acids and is responsible for the anaplerotic properties of UX007, which are believed to be critical for restoring the energy deficiency state in LC-FAOD.

Figure 5.2.1.1.1: Mechanism of Action



Propionyl-CoA is a particularly efficient compound for restoring depleted TCA cycle intermediates due to the low succinyl-CoA concentration which can differ by 2-3 orders of magnitude compared to other compounds in TCA cycle intermediate pools. Propionyl-CoA is an anaplerotic substrate for all tissues, and is also gluconeogenic in the liver, kidney cortex, and brain (Kinman et al. 2006); (Gu et al. 2010); (Marin-Valencia et al. 2013). Production of anaplerotic propionyl-CoA stimulates acetyl-CoA oxidation, NADH production, and ATP regeneration, which should result in improved cardiac and skeletal muscle function. Although it is clear that even-carbon medium-chain triglycerides such as MCT oil can help LC-FAOD patients by bypassing defects, the additional effect of anaplerosis, and subsequent gluconeogenesis, is believed to be responsible for the further benefits observed in triheptanoin clinical programs.

In addition to restoration of energy metabolism, UX007 reduces the production of toxic fatty acid intermediates by providing an external source of energy which is preferentially utilized over endogenous long-chain fatty acids, thus suppressing lipolysis. UX007 provides an efficient source of energy from fatty acids for muscles, potentially preserving glucose and glycogen stores during periods of fasting. This leads to a potentially more stable energy state whereby fasting and exercise episodes can be better tolerated due to both increased energy stores and also leads to better utilization of fats and ketone bodies as energy sources.

5.2.2 Nonclinical Studies

Studies of potential clinical significance and relevance to this protocol are summarized below. Additional details are provided in the UX007 IB.

Nonclinical studies evaluating triheptanoin and its metabolites in mice and rats have been published and further support the safety of UX007. These studies provide data on the absorption, and metabolism of triheptanoin when administered intravenously and PO at doses up to 40% the recommended caloric intake. Triheptanoin is metabolized rapidly in the gut to form a series of energy containing metabolites, including heptanoate, C4- and C5-ketone bodies (Kinman et al. 2006), (Deng et al. 2009).

Nonclinical studies in rats have demonstrated that triheptanoin is hydrolyzed to heptanoate and glycerol, which are efficiently absorbed by the liver (Kinman et al. 2006). A study in mice infused with intravenous ^{13}C-heptanoate at 50% the caloric requirement demonstrated increased plasma ^{13}C-enriched glucose levels over baseline plasma glucose levels, confirming that heptanoate is a substrate for gluconeogenesis in the liver (Marin-Valencia et al. 2013). Gu et al. also showed that triheptanoin infusion can generate glucose and also increase glycogen stores in liver (Gu et al. 2010).

The acute oral toxicity of triheptanoin was performed in rats at four dose levels ranging from 0.5 ml/kg (n= 2) to 5 ml/kg (n=5M/5F). There were no deaths or signs of toxicity at any time throughout the duration of the study and up to 7 days post dose (IND-59303).

A 9 month oral toxicity study in rats was performed with an experimental oil containing 64% triheptanoin to determine the effects of a diet containing triheptanoin on animal growth, lipid digestibility, clinical chemistry, and toxicity in liver, kidney, and small intestine (Ataide et al. 2009). After 9 months of consumption of a standard diet containing doses up to 1.14 g triheptanoin per kg of body weight per day, no toxic effects attributed to triheptanoin were found in rats. There was no significant difference in the clinical chemistries that would indicate hepatic damage or adverse effect on renal function compared to control animals fed a standard diet supplemented with soybean oil as the lipid source.

A Good Laboratory Practice (GLP) 9-month chronic toxicology study in juvenile Yucatan Mini-Pigs has been completed. UX007 was well tolerated for 9-months with no evidence of toxicity in mini-pigs receiving up to 50% of their daily caloric intake from UX007. Systemic exposure to UX007 was evident from the dose-related increase in its primary metabolites (heptanoic acid and C5 ketone bodies). No accumulation was seen after 9 months of treatment. No gross or microscopic lesions were noted due to UX007 administration at any of the dose levels. Based on the lack of toxicity in these animals after 9 months of treatment, the no observed adverse effect level (NOAEL) for systemic toxicity following oral administration of UX007 to juvenile Yucatan minipigs was 50% of daily caloric intake.

5.2.3 Previous Clinical Studies

Over 500 subjects with various diseases have been treated with triheptanoin for up to approximately 20 years. The clinical experience supports the safety of triheptanoin when administered at approximately 35% of daily caloric intake in pediatric patients as young as neonates.

Triheptanoin has been studied for over a decade in a large cohort of LC-FAOD patients (Roe et al. 2002), (Roe et al. 2006), (Roe et al. 2008), (Barone 2012). Patients with other disorders have also been treated with triheptanoin, including those with pyruvate carboxylase deficiency (Mochel et al. 2005), Huntington's disease (Mochel et al. 2010), adult polyglucosan body disease (APBD, a form of glycogen storage disorder due to brancher enzyme deficiency; (Roe et al. 2010), and Pompe disease (also known as glycogen storage disease type II [GSD-II] or acid maltase deficiency; (Roe et al. 2006). Ultragenyx also evaluated UX007 as treatment for Glut1 deficiency syndrome (Glut1 DS). The use of UX007 in the Glut1 DS indication is no longer under clinical development as the clinical studies did not meet their primary efficacy endpoints.

Roe and colleagues described triheptanoin treatment of 3 subjects with VLCAD (Roe et al. 2002). Despite 2 - 5 years on standard of care including MCT oil as fat supplement, all subjects had numerous clinical problems. Within hours of initiating triheptanoin treatment, improvements in muscle pain and function were seen in all subjects. Within 1 week, both subjects with hepatomegaly had normal liver size. The subject with cardiomyopathy had a shortening fraction (SF) of 19% prior to treatment which improved to 30% after 1 month on triheptanoin therapy.

A cumulative summary of triheptanoin treatment was reported for 48 LC-FAOD patients by Roe and Mochel (Roe et al. 2006). Following initiation of triheptanoin, a large decrease in hepatomegaly/hypoglycemia in nearly all patients was observed. Substantial decreases in rhabdomyolysis event frequency, and a decrease in cardiac disease were also reported.

Roe and colleagues described the impact of triheptanoin treatment in 7 patients with carnitine palmitoyltransferase type II (CPT II) deficiency (Roe et al. 2008). During the 18 month assessment period, there were no rhabdomyolysis events or hospitalizations, and all patients returned to normal physical activity within 2 months following initiation of triheptanoin. The treatment was well tolerated when triheptanoin was consumed over a 20-30 minute period (Roe et al. 2008).

In total, 61 LC-FAOD patients have been treated with triheptanoin by Dr. Charles Roe and colleagues in a study sponsored by the Baylor Research Institute (IND-59303). A subset of subjects continued triheptanoin treatment for up to 10 years as part of a compassionate use program. These patients were transferred to the University of Pittsburgh Medical Center, under Dr. Jerry Vockley and their treatment continued (IND-106011). Some of these patients have been reported to exhibit profound clinical responses to triheptanoin including reduction of frequency and severity of rhabdomyolysis events, reduction or elimination of

hypoglycemia events, improved physical capacity, and resolution of cardiomyopathy (Roe et al. 2002); (Barone 2012). Anecdotal evidence suggests triheptanoin treatment is well tolerated and does not result in excess weight gain with proper management of caloric intake (Barone 2012).

A retrospective medical record review study (UX007-CL001) was conducted for LC-FAOD subjects who have been treated with triheptanoin for 0.6 – 13 years under the aforementioned treatment program (Vockley et al. 2013). The study evaluated the impact of triheptanoin treatment on the rate and extent of hospitalizations in 20 of 24 patients who consented to be part of the study. A total of 120 individual charts were evaluated, which covered 241 years of patient data and included a total of 319 hospitalizations. The study compared the major medical event rate before and after initiation of triheptanoin treatment including the total number of hospitalizations and hospital days per year due to all causes, muscle rupture, hypoglycemia, or cardiomyopathy. Results demonstrated significant decreases in the number of hospitalization days during major medical events (69%; $p < 0.05$), and the mean number of hypoglycemia events per year (96%; $p<0.01$) after initiation of triheptanoin treatment (Vockley et al. 2015).

In the Phase 2 study, UX007-CL201, the frequency and duration of major clinical events including rhabdomyolysis, hypoglycemia, and cardiomyopathy were consistently reduced during 78 weeks of UX007 treatment compared with the 78-week pre-UX007 period (Vockley et al. 2018), supported by the consistent results from the retrospective study CL001. In addition to total events, a clinically meaningful reduction in events leading to hospitalizations was observed, indicating an effect of UX007 on the most serious manifestations of LC-FAOD. Walking distance improved for the 12 Minute Walk Test (12MWT) in UX007-CL201, indicating that subjects maintained pace and exhibited increased stamina throughout the entire distance walked, consistent with an improvement in energy metabolism. In addition, both workload and duration improved during cycle ergometry testing following 24 weeks of UX007 treatment, with an observed 60% mean increase in workload over Baseline, suggesting the potential for improved exercise capacity following treatment with triheptanoin (Vockley et al. 2017).

5.3 Summary of Overall Risks and Potential Benefits

UX007 is intended as a substrate replacement therapy to restore the full process of energy metabolism in patients with LC-FAOD. Triheptanoin was developed to address the needs of LC-FAOD patients who continued to have disease crises despite the best available treatment. The current standard of care for these patients is not sufficient to prevent all LC-FAOD manifestations, and is still associated with a high mortality rate (Baruteau et al. 2012).

Over 500patients with various disorders, including LC-FAOD patients ranging from neonates to adults, have been treated with triheptanoin for up to approximately 20 years with evidence of clinical benefit and no significant safety issues reported. Published reports indicate that triheptanoin has improved a wide range of LC-FAOD symptoms in the subjects studied and some LC-FAOD patients failing current therapy can exhibit profound positive clinical

responses to triheptanoin, including a reduction of frequency and severity of rhabdomyolysis events, reduction or elimination of hypoglycemia events, improvements in liver function and hepatomegaly, improved physical capacity, and resolution of cardiomyopathy.

Nonclinical studies evaluating triheptanoin and its metabolites in mice and rats have been published and further support the safety of triheptanoin in the LC-FAOD population. Data from pharmacokinetic and toxicity studies indicates that triheptanoin is well absorbed after oral dosing and is well-tolerated without overt toxicities at doses as high as 1.14 g/kg for 9 months. There were no signs of hepatic or renal injury.

Data from nonclinical and clinical studies to date suggest triheptanoin does not pose any significant safety risks that can be identified at this time. Triheptanoin has been well tolerated in humans with no significant safety issues and toxicology or adverse pharmacology findings were not observed in triheptanoin-treated animals. Studies in animals and humans suggest triheptanoin consumed orally has side effects that are similar to those of orally consumed medium chain triglycerides.

In clinical trials with UX007, the most common treatment-related treatment-emergent adverse events (TEAEs) were gastrointestinal (GI) in nature. Of these most frequently reported TEAEs were diarrhea and abdominal pain, which were mild or moderate in severity, and mostly occurred during up-titration of the initial dose of triheptanoin, and lasted a median duration of 3 days. Where it was deemed clinically necessary in the judgment of the Investigator, treatment-related GI events may be managed with UX007 dose reductions. The adverse drug reactions for triheptanoin in subjects with LC-FAOD are diarrhea, abdominal pain (including preferred terms of abdominal pain, abdominal pain upper, abdominal discomfort, abdominal distention, and gastrointestinal pain), vomiting and nausea.

Overall the risk-benefit ratio of triheptanoin/UX007 appears to be favorable based on the safety record to date and the benefit observed in published observational studies, compassionate use programs, and Ultragenyx clinical trials.

5.4 Study Rationale

LC-FAOD are caused by defects in the metabolic pathway that converts fatty acids into energy, leading to deficiencies in energy metabolism. The metabolic deficiency can deplete energy sources, resulting in serious clinical manifestations including hypotonia, rhabdomyolysis, liver dysfunction and hypoglycemia, and cardiomyopathy. These LC-FAOD major events are not sufficiently controlled in many patients by current standard of care, usually consisting of avoidance of fasting, low-fat/high-carbohydrate diet, dietary medium chain triglycerides (MCT oil), and/or carnitine supplementation. MCT oil, an even chain fatty acid, can provide medium chain fatty acids that bypass the specific LC-FAOD pathway defects but may not restore energy metabolism fully. In addition to supplying medium chain fatty acids, UX007 (triheptanoin), a specialized medium odd-chain (C7) triglyceride, also replaces deficient mitochondrial TCA cycle intermediates via the generation of 3-carbon intermediates, thereby improving energy metabolism.

At the time of protocol development, triheptanoin had been studied in many types of LC-FAOD for more than 13 years. Published reports describe profound clinical responses to triheptanoin, including improved physical capacity and a reduction of frequency and severity of major LC-FAOD events (rhabdomyolysis, hypoglycemia, liver function and hepatomegaly, and cardiomyopathy). Numerous LC-FAOD patients have participated, or are actively participating in multiple clinical studies or treatment programs with UX007/triheptanoin conducted by various sponsors and investigational sites.

This open-label long-term safety and efficacy extension study will provide an opportunity for LC-FAOD patients to be treated with UX007 for up to 7 years or until commercial availability of UX007 in any region, whichever occurs first, under a single standardized protocol. The subjects may have participated in other studies or treatment programs with UX007/triheptanoin or be treatment naïve and have clear unmet need but would be consolidated into one program for long-term maintenance and consistent safety monitoring. The study is designed to obtain long-term safety and efficacy information and evaluate maintenance of efficacy in a diverse LC-FAOD population.

6 STUDY OBJECTIVES

The primary objective of the study is to:

- Evaluate the long-term safety and efficacy of UX007 in LC-FAOD subjects

The secondary objectives of the study are to:

- Evaluate the effect of UX007 on energy metabolism in LC-FAOD
- Evaluate impact of UX007 on clinical events associated with LC-FAOD

The objective of the pharmacokinetic sub-study is to:

- Characterize the steady-state pharmacokinetics (PK) of UX007 and UX007 metabolites in subjects with LC-FAOD.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

The study is an interventional, open-label, long-term safety and efficacy extension study of UX007 or triheptanoin treatment in approximately 150 LC-FAOD subjects who have participated in prior clinical studies or treatment programs with UX007/triheptanoin, or who have failed conventional therapy and have documented clear unmet need (in the opinion of the Investigator and Sponsor). UX007 dosing will be targeted at 25-35% of total caloric intake. If a subject has been receiving a lower dose of UX007/triheptanoin, the individual may continue treatment at the current dose. If however, the subject has symptomatic disease or clinical signs of exercise limitation while on UX007 doses below the target range, the Investigator should consider titrating the dose to 25-35% of total caloric intake. UX007 doses above 35% of total caloric intake may be considered as needed at the discretion of the Investigator on an individual basis; it is recommended that doses above 35% are discussed with the Medical Monitor prior to administration. If a subject has been off UX007/triheptanoin treatment for > 1 month or is treatment naïve, the dose will be titrated following Dose Administration Guidelines. Subjects who switch from MCT to UX007 may transition at the same dose and then titrate, as appropriate.

The subjects will be followed to evaluate the long-term safety and continued effects of UX007 for up to 7 years or until commercial availability of UX007 in any region, whichever occurs first. A Safety Follow-up Phone Call will be conducted 30-35 days after last dose of study drug. The end of study is defined as the last day that protocol-specified assessments (including telephone contact) are conducted for the last subject in the study.

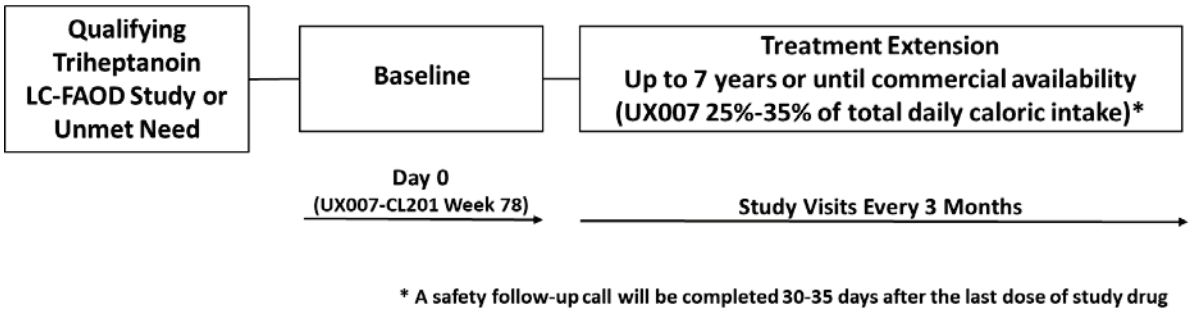
If UX007 becomes commercially available during the study, each subject will return for an End of Study Clinic Visit; this will be recorded as study completion rather than an early termination. For subjects not immediately continuing UX007 through another mechanism (ie, commercial product, IST, or compassionate use), a Safety Follow-up Phone Call will be conducted 30-35 days after last dose of investigational study drug.

The continued effects of UX007 treatment on clinical and physiologic disease of the skeletal muscle, the liver and the heart will be assessed. Creatine kinase (CK) will be measured as a biomarker of skeletal myopathy. The metabolic effects on the liver and energy homeostasis will be assessed by evaluating liver enzymes and serum glucose as biomarkers. Cardiac disease will be assessed by annual echocardiograms (ECHO).

The impact of UX007 treatment on major clinical events will also be assessed throughout the study. Major events are defined as musculoskeletal, hepatic, and cardiac events caused by LC-FAOD, or intercurrent illness complicated by LC-FAOD, resulting in any hospitalization, ER visit, or emergency intervention (any unscheduled administration of therapeutics at home or in the clinic). In subjects for which prior medical events data have already been collected during a prior UX007 protocol the effect of UX007 treatment on major clinical events during this study will be compared with the subject's available historical information for the

18-24 months prior to beginning UX007 (or from birth for subjects less than 18 months of age). For subjects who are treatment naïve, available historical event data will be collected prior to UX007 administration. The event rate per year during UX007 treatment will be compared with the subject's available historical information for the 18-24 months prior to beginning UX007 (or from birth for subjects less than 18 months of age). Dosing compliance and diet will be regularly monitored along with a standard panel of safety assessments. Figure 7.1.1 provides a schematic of the study design.

Figure 7.1.1: UX007-CL202 Study Schema



A PK sub-study will evaluate the steady-state PK of UX007 and UX007 metabolites in a minimum of 12 patients with LC-FAOD. Subjects enrolled in the sub-study will have serial PK samples collected.

7.2 Discussion of Study Design, Including Choice of Control Group

The primary objective of this open-label Phase 2 extension study is to evaluate the long-term safety and efficacy of UX007 in patients with LC-FAOD. The study will also explore long-term effects of UX007 on energy metabolism and clinical events associated with LC-FAOD. Evaluations of biomarkers will also be performed to provide supportive evidence and potentially confirm surrogate endpoints of efficacy. LC-FAOD laboratory measures may potentially provide supportive evidence of effects on energy metabolism and safety.

The sample size is intended to provide the maximum amount of information regarding UX007 long-term safety and efficacy in a diverse LC-FAOD population. Since all subjects will receive the same investigational product, randomization and blinding are unnecessary; study drug will be provided open-label.

Any historical data obtained from medical records will be used as a comparator for the Treatment Extension Period, enabling those subjects to represent an internal control for assessment of efficacy. While the lack of a parallel control group may introduce difficulties in discerning natural disease progression from treatment effectiveness, a placebo -controlled study of this duration is difficult to conduct and possibly not ethical given the need for ongoing disease management, and the potential for acute, life-threatening crises in untreated patients.

Given the acute-on-chronic nature of LC-FAOD, subjects will be eligible to continue maintenance UX007 treatment for up to 7 years (84 months) or until commercial availability of UX007 in any region, whichever occurs first. The treatment duration is intended to provide additional long-term safety information and provide sufficient insight on sustained clinical effects in LC-FAOD patients under a single study protocol.

7.3 Selection of Study Population

The study will be conducted in approximately 150 subjects who have participated in clinical studies or compassionate use programs with UX007/triheptanoin, or who have failed conventional therapy and have documented clear unmet need (in the opinion of the Investigator and Sponsor). Most subjects in this study will have prior treatment exposure to UX007/triheptanoin, although it is possible to enroll treatment-naïve individuals if prior study participation involved assignment to a control treatment arm.

The inclusion criteria are structured to enroll subjects with various types of LC-FAOD (CPT-I, CPT-II, VLCAD, LCHAD, TFP, or CACT deficiencies).

Many LC-FAOD patients are seriously impacted by their disorder from birth. Triheptanoin has been administered previously to LC-FAOD patients, including newborns, infants, children, and adults. The experience reported in clinical studies and compassionate use programs suggests a favorable risk/benefit profile for the target study population. The Sponsor has taken all reasonable measures to ensure the protection and safety of this population. Appropriate pediatric expertise will be available at all trial sites, and efforts will be focused on minimizing risk, fear, pain and distress for this population during conduct of the study.

7.3.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1. Male or female, 6 months of age or older
2. Prior participation in a clinical study assessing UX007/triheptanoin treatment for LC-FAOD. Study Sponsors/Collaborators include: Oregon Health & Science University, University of Pittsburgh, and Ultragenyx Pharmaceutical (ClinicalTrials.gov Identifiers: NCT01379625, NCT01461304, and NCT01886378). Patients who received UX007/triheptanoin treatment as part of other clinical studies; investigator sponsored trials (IST); expanded access/compassionate use treatment programs; or patients who are treatment naïve (i.e., naïve to both UX007 and food-grade triheptanoin), have failed conventional therapy and, in the opinion of the Investigator and Sponsor, have documented clear unmet need, may also be eligible at the discretion of the Sponsor.
3. Confirmed diagnosis of LC-FAOD including: carnitine palmitoyltransferase (CPT I or CPT II) deficiency, very long chain acyl-CoA dehydrogenase (VLCAD) deficiency, long chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency, trifunctional protein (TFP) deficiency, or carnitine-acylcarnitine translocase (CACT) deficiency. Information

on diagnosis will be obtained from medical records and should include confirmed diagnosis by results of acylcarnitine profiles, fatty acid oxidation probe studies in cultured fibroblasts, and/or mutation analysis.

4. Willing and able to complete all aspects of the study through the end of the study, including visits and tests, documentation of symptoms and diet, and administration of study medications. If a minor, have a caregiver(s) willing and able to assist in all applicable study requirements.
5. Provide written informed consent (subjects aged ≥ 18 years), or provide written assent (where appropriate) and have a legally authorized representative willing and able to provide written informed consent, after the nature of the study has been explained and prior to any research-related procedures.
6. Females of child-bearing potential must have a negative urine pregnancy test at Baseline and be willing to have additional pregnancy tests during the study. Females considered not of child-bearing potential include those who have not experienced menarche, are post-menopausal (defined as having no menses for at least 12 months without an alternative medical cause), or are permanently sterile due to total hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
7. Participants of child-bearing potential or fertile males with partners of child-bearing potential who are sexually active must consent to use a highly effective method of contraception as determined by the Investigator from the period following the signing of the informed consent through 30 days after last dose of study drug.

7.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Diagnosis of MCAD deficiency, short- or medium-chain FAOD, ketone body metabolism defect, propionic acidemia or methylmalonic acidemia
2. Patient qualifies for any other clinical trial designed to progressively evaluate the safety and efficacy of triheptanoin in LC-FAOD
3. Any known hypersensitivity to triheptanoin that, in the judgment of the Investigator, places the subject at increased risk for adverse effects
4. Pregnant and/or breastfeeding an infant at Baseline or planning to become pregnant (self or partner) at any time during the study
5. Have any co-morbid conditions, including unstable major organ-system disease(s) that in the opinion of the Investigator, places the subject at increased risk of complications, interferes with study participation or compliance, or confounds study objectives, or unwilling to discontinue prohibited medications.

7.3.3 Removal of Subjects from Therapy or Assessment

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The Principal Investigator and Ultragenyx also have the right to remove subjects from the study. Ultragenyx must be notified of all subject withdrawals as soon as possible. Ultragenyx also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual subject or Investigator due to poor enrollment or noncompliance, as applicable.

Subjects may be removed from the study for the following reasons:

- Occurrence of an unacceptable adverse event (AE)
- An illness that, in the judgment of the Principal Investigator or Ultragenyx, might place the subject at risk or invalidate the study
- At the request of the subject, Investigator, or Ultragenyx, for administrative or other reasons
- Protocol deviation or unreliable behavior

If the reason for removal of a subject from the study is an AE, the AE and any related test or procedure results will be recorded in the source documents and transcribed onto the Case Report Form (CRF). Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve. If such abnormalities do not return to normal within 30 days after the last dose given, their etiology should be identified and Ultragenyx should be notified. All unscheduled tests must be reported to Ultragenyx immediately.

If a subject discontinues from the study prematurely, every reasonable effort should be made to perform the Early Termination Visit procedures within four weeks of discontinuation. A Safety Follow-up Phone Call will be conducted 30-35 days after last dose of investigational study drug, even if the Early Termination Visit does not occur.

7.3.3.1 Stopping Rules

Individual subjects who experience a Grade 3 or higher SAE that is unexpected and possibly, probably, or definitely related to UX007 (Section 8.5.3) that represents a change in the nature or an increase in frequency of the serious event from their prior medical history will be assessed, by the Investigator, as to whether the subject will continue on the study.

Commonly occurring LC-FAOD medical events include rhabdomyolysis, cardiomyopathy, hypoglycemia, and other events as described in the IB. If a subject experiences a major LC-FAOD medical event, which represents a change in the nature or an increase in frequency of the serious event from their prior medical history, the Investigator should determine whether the subject should be discontinued from the study. In these cases, the

subject visit schedule may need to be modified or assessments withheld to allow the subject to continue as deemed appropriate by the Investigator.

Regulatory Authorities, as well as the IRBs/ECs, will be informed should unexpected and possibly, probably, or definitely drug-related SAEs occur, a full evaluation of the event will be performed in order to make a decision regarding what actions to take, including whether to recommend stopping the study. Regulatory Authorities, as well as IRBs/ECs, will be informed if the study is paused or stopped. If the Sponsor deems it appropriate to restart the trial following an internal safety review, this will be done only following approval by Regulatory Authorities.

7.4 Treatments

7.4.1 Reference Therapy

The study design is open-label; all subjects will receive investigational product. No placebo or reference therapy will be administered in this study.

7.4.2 Investigational Product

Subjects will begin or continue treatment with daily open-label UX007 while maintaining their other dietary restrictions.

The UX007 investigational product, triheptanoin, will be administered orally (PO) with food or by gastronomy tube (usually four times per day: breakfast, lunch, dinner, and before bed), at the target dose range of 25-35% of total calories. The dose may be divided into smaller more frequent doses with food as needed. The dose may be mixed with small amounts of food or drink (including formula) as indicated in the Study Drug Administration Guidelines.

If a subject has been receiving a lower dose of triheptanoin, the individual may continue treatment at the current dose provided there is no evidence of symptomatic disease or clinical signs of exercise limitation. If a subject has been off UX007/triheptanoin treatment for > 1 month or is treatment naïve, the dose will be titrated following the Study Drug Administration Guidelines. UX007 doses above 35% of total caloric intake may be considered as needed at the discretion of the Investigator on an individual basis; it is recommended that doses above 35% are discussed with the Medical Monitor prior to administration.

7.4.3 Identity of Investigational Product

UX007 is a colorless to light yellow oil packaged in 1L round, translucent high-density polyethylene (HDPE) bottles. UX007 should be stored at room temperature. The study drug was manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations.

7.4.4 Selection of Doses and Study Duration

The UX007 dose and regimen is selected based on the extensive information derived from over 13 years of clinical experience in LC-FAOD at the time of protocol development. These data show an age-dependent dose related to the relatively higher energy requirements for young children versus older children versus adults. The target dose is 25-35% of total calories by UX007, as tolerated, which is equivalent to approximately 2-4 g/kg in young children, decreasing to 1-2 g/kg for older children and adolescents, and 1 g/kg for adults. Since this treatment is a substrate replacement therapy and not an enzyme inhibitor or other type of drug class, dosing is individualized based on tolerability, metabolism, and energy needs. The following information provides support for the UX007 dose and regimen:

- Clinical doses used in the compassionate use program and previous clinical studies (IND-59303); (Roe et al. 2006)
- Barone and colleagues reported safety and efficacy of triheptanoin administered at 1-2 g/kg/day to 22 LC-FAOD patients (aged 1.5 – 58 years) (Barone 2012).
- Roe and colleagues reported safety and efficacy of triheptanoin administered at a dose level between 2.6 - 4.0 g/kg/day to 3 VLCAD patients (aged 2-8 years) (Roe et al. 2002)
- Consultations with physicians and dietitians experienced in the administration of triheptanoin to LC-FAOD patients in clinical practice resulted in consensus on a dose of triheptanoin titrated to comprise 25 – 35% of daily caloric intake [redacted]: personal communication).

Based on these data, the target dose range for UX007 will be an estimated 25-35% of daily caloric intake.

- If a subject has been receiving a lower dose of UX007/triheptanoin, the individual may continue treatment at the current dose. If however, the subject has symptomatic disease or clinical signs of exercise limitation while on UX007 doses below the target range, the Investigator should consider titrating the dose to 25-35% of total caloric intake.

- If a subject has been receiving a dose of UX007/triheptanoin greater than 35% total caloric intake, the individual may continue treatment at the current dose at the Investigator's discretion. Investigators may also dose individual subjects above target range as needed at their discretion; it is recommended that doses above 35% are discussed with the Medical Monitor prior to administration.

- If a subject has been off UX007/triheptanoin treatment for > 1 month or is treatment naïve, the dose will be titrated following Study Drug Administration Guidelines. Subjects who switch from MCT to UX007 may transition at the same dose and then titrate as appropriate.

- Daily caloric intake will be established based on the most recent dietary analysis in the medical record, and collected periodically during the study.
    - For patients over 1 year old, if the most recent dietary analysis available is not within 6 months prior to study initiation, a Baseline diet diary will be completed after the initial visit and discussed with the dietitian within a month.
    - For patients under 1 year old, if the most recent dietary analysis available is not within 3 months prior to study initiation, a Baseline diet diary will be completed after the initial visit and discussed with the dietitian within a month. The dose may be recalculated by the study nutritionist as necessary for normal weight gain/growth based on the study diet diary analysis.

Subject participation duration in this extension study will be up to 7 years (84 months) or until commercial availability of UX007 in any region, whichever occurs first. The total UX007 treatment duration per subject will vary depending on prior exposure from participation in clinical studies and compassionate use programs. The 7-year study duration will provide a continued treatment option and enable a long-term assessment of the safety and efficacy of UX007 in subjects with LC-FAOD under a single study protocol. The end of study is defined as the last day that protocol-specified assessments (including telephone contact) are conducted for the last subject in the study.

7.4.5 Prior and Concomitant Therapy

7.4.5.1 Prohibited Medications

Subjects may not be enrolled if they are unwilling to discontinue use of a substance that may confound study objectives. The following medications are prohibited during the study and must be discontinued at minimum 1 week prior to the first dose:

- Valproate products (e.g. Depacon, Depakote, Depakene, Stavzor, and their generics)
- Pancreatic lipase inhibitors (e.g., Orlistat) due to possible inhibition of metabolism of triheptanoin

The following medications are prohibited during the study and must be discontinued prior to the first dose:

- MCT oil and metabolic formulas containing significant contributions from MCT oil, including coconut oil, must not be used after the first dose of study medication

7.4.5.2 Permitted Medications

Other than the medications specifically prohibited in this protocol, subjects may receive concomitant medications as required. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to the Baseline visit will be reviewed and recorded.

7.4.6 Treatment Compliance

At the Baseline visit and each subsequent visit through Month 81, each subject will be dispensed an adequate supply of study drug to comprise 25-35% total daily caloric intake (or prescribed dose). Additional study drug will be shipped to the subject between clinic visits. UX007 will not be dispensed at the Month 84 (end-of-treatment visit), End of Study, or Early Termination visits (as applicable). The subject will maintain a weekly diary to record adherence to prescribed treatment. The diary will be reviewed upon each indicated visit and an estimate of overall treatment compliance will be made by the site staff. Subjects will be instructed to return all used (empty study drug containers) study drug to the site at the next visit. Site personnel will maintain a record of all medication dispensed to each subject and returned to the site.

7.5 Study Procedures and Assessments

The concept for evaluation is to study the long-term safety and continued effects of UX007 on energy metabolism and clinical events associated with LC-FAOD. Biologic and clinical assessments will be conducted throughout the 84 month Treatment Extension Period. The occurrence of major LC-FAOD clinical events will be captured and compared to available data prior to initiation of UX007 treatment. Dosing compliance and diet will be regularly monitored along with a standard panel of safety assessments.

7.5.1 Schedule of Events

The Baseline visit may occur in conjunction with the last scheduled visit from study UX007-CL201. Assessments conducted at the last UX007-CL201 visit will be used for Baseline data to avoid duplication. Following the signing of informed consent at the Baseline visit, subjects will complete required assessments and return for clinic visits at 6 month intervals (± 2 weeks) to assess long-term safety and efficacy. The study coordinator will telephone the subject/caregiver at specified intervals (± 1 week) for additional safety monitoring.

A Safety Follow-up Phone Call will be conducted 30-35 days after last dose of study drug. The site personnel will initiate this safety follow-up telephone call to collect information on any ongoing or new AEs, SAEs, and concomitant medications. Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved. The end of study is defined as the last day that protocol-specified assessments (including telephone contact) are conducted for the last subject in the study.

For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination Visit procedures within four weeks of discontinuation. A Safety Follow-up Phone Call will be conducted 30-35 days after last dose of investigational study drug, even if the Early Termination Visit does not occur.

If UX007 becomes commercially available during the study, each subject will return for an End of Study Clinic Visit; this will be recorded as study completion rather than an early termination. For subjects not immediately continuing UX007 through another mechanism (ie, commercial product, IST, or compassionate use), a Safety Follow-up Phone Call will be conducted 30-35 days after last dose of investigational study drug.

The parameters to be assessed in Study UX007-CL202, along with timing of assessments, are provided in the Schedule of Events (Table 2.1). Where caregiver assessments are required, the same individual should complete the assessment for consistency or reporting when possible. Refer to the Study Reference Manual for additional details on specific assessments.

7.5.2 Clinical Efficacy Measures

7.5.2.1 Functional Disability and Cognitive Development

Functional disability often limits daily activities of living and health-related quality of life in patients with LC-FAOD. Individuals with LC-FAOD may also have delayed cognitive development. Functional disability and cognitive development will be assessed at clinic visits as specified in Table 2.1. Parameters will be evaluated using the following age appropriate validated health assessment questionnaires:

- The Medical Outcomes Study 10-Item Short Form (SF-10) is a 10-item caregiver completed questionnaire designed to assess generic health-related quality of life in healthy and ill pediatric populations (Saris-Baglama et al. 2006). The 10 items were adapted from the Child Health Questionnaire and utilize a 4-week recall period. Responses are used to generate 2 component summary scores: physical component summary (PCS) and mental component summary (MCS). Higher global scores are associated with better quality of life. The SF-10 will be administered to caregivers of subjects aged 6 through 17 years. The SF-10 will be administered -at the Baseline visit and at 6 month intervals thereafter (or Early Termination).

- The Medical Outcomes Study 12-Item Short Form (SF-12) is a 12-item interview and self-administered questionnaire designed to assess generic health-related quality of life in healthy and ill adult populations (Ware et al. 1996). The 12 items in the SF-12 are a subset of the items in the SF-36 and measure physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health. Responses are used to generate 2 component summary scores: physical health (PCS) and mental health (MCS). Higher global scores are associated with better quality of life. The standard version of the instrument with a 4-week recall period will be used in this study.
  The SF-12 will be administered to subjects 18 years of age and older. The SF-12 will be administered at the Baseline visit and at 6-month intervals thereafter (or Early Termination).

7.5.2.2 Cardiomyopathy and Cardiac Function

ECHO will be performed at the Baseline Visit and annually thereafter at clinic visits indicated in Table 2.1 (or if performed as routine care within 30 days prior to the Baseline or indicated clinic visits) or Early Termination if not performed within 6 months prior to termination. Additional tests may be performed if any abnormalities are detected or if medically indicated.

ECHO efficacy variables include ventricle size, ejection fraction (EF), and shortening fraction (SF), as described within the Study Reference Manual.

7.5.2.3 LC-FAOD Major Events

Major LC-FAOD events include skeletal myopathy (rhabdomyolysis), hepatic (hypoglycemia) and cardiac disease (cardiomyopathy) events, and are defined as any visit to the ER/acute care, hospitalization, emergency intervention (i.e. any unscheduled administration of therapeutics at home or in the clinic), or any similar event whether caused primarily by LC-FAOD or by an intercurrent illness complicated by LC-FAOD. The event type, levels of relevant laboratory parameters (including CK, glucose, and BNP/troponin), the number of days hospitalized and in ICU, and the type and number of days of treatment and intervention will be recorded.

By definition, events requiring inpatient hospitalization or that cause persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, are classified as a serious adverse event (SAE) or serious suspected adverse reaction, and will be reported as described in Section 8.5. If the event represents a substantive change in the nature or an increase in frequency from a subject's prior medical history, the event should be reported as an adverse event (AE) and the Investigator should evaluate whether the subject should be discontinued from the study.

In these cases, the subject visit schedules may need to be modified or assessments withheld to allow the subject to continue as deemed appropriate by the Investigator. Information on the incidence of major rhabdomyolysis events will be collected at each visit.

7.5.3 Biomarkers & LC-FAOD Laboratory Measures

A panel of biomarkers will be assessed as clinical indicators of skeletal myopathy and hepatic disease. CK is a useful marker in the investigation of skeletal muscle disease. The presence of CK suggests that muscle cells somewhere in the patient are sufficiently energy deficient to over-contract and rupture, providing an ongoing chronic or non-acute total CK release. Chronic elevations of CK have been reported to indicate patients at risk for major rhabdomyolysis events, although no quantitative relationship has been established yet.

Assessing glucose levels is central to the management of hypoglycemia associated with LC-FAOD. Samples for fasting serum glucose (as tolerated) will be collected on arrival to the clinic; the length of fast, the date and time of the last dose of study medication, and time of collection will be recorded on the CRF. Relevant liver enzymes, including alanine aminotransferase (ALT), aspartate transaminase (AST), and gamma glutamyl transpeptidase (GGT) will be evaluated as indicators of liver injury related to LC-FAOD.

Biomarkers and relevant indicators of LC-FAOD are summarized in Table 7.5.3.1.
Blood samples will be collected at each clinic visit to assess relevant biomarkers and laboratory measures of LC-FAOD. For each sample collection, the duration of fasting and time elapsed since last study drug administration will be recorded on the CRF.
Where possible, assessment of certain parameters (i.e. glucose, ALT, AST, GGT) will be performed as part of the routine clinical laboratory test panel to avoid unnecessary duplication of testing (see Section 7.5.5.5). Refer to the Study Reference Manual for additional details.

Table 7.5.3.1: Biomarkers and LC-FAOD-related Laboratory Measures

Biomarkers of UX007 Effects	LC-FAOD Laboratory Measures
Skeletal myopathy biomarkers: serum creatine kinase (CK)	Total and free plasma carnitine
Hepatic disease biomarkers: serum glucose, serum liver enzymes (ALT, AST, GGT)	Plasma acylcarnitines Urine organic acids

7.5.4 Pharmacokinetics of UX007 and Metabolites

PK measurements will occur at select sites in a subset of subjects (minimum of 12 subjects) at their next two consecutively scheduled clinic visits (eg Month 18 and Month 24) excluding the Baseline Visit. Participating subjects will be fed a standardized meal containing one of their divided daily doses of UX007. Blood for plasma UX007 and metabolites will be collected pre-dose (within 15 minutes prior to start of meal) and at 30, 90, 120, and 240 minutes after finishing the meal [± 5 minutes]. For each sample collection, the meal start/stop times, calories consumed, UX007 dosing, and sampling time will be recorded. Plasma UX007 and the following UX007 metabolites will be assessed:

- Beta-hydroxypentanoate (BHP)
- Beta-hydroxybutyrate (BHB)
- Heptanoate

7.5.5 Safety Measures & General Assessments

General assessments include medical history, concomitant medications, demographics, and growth. Safety will be evaluated by the incidence, frequency, severity and relatedness of AEs and SAEs, including clinically significant changes from baseline to scheduled timepoints in vital signs, weight, physical examination, and clinical laboratory evaluations. Pregnancy testing (or pregnancy of partner, if needed) will also be conducted as appropriate. Refer to the Study Reference Manual for additional details.

7.5.5.1 Medical History and Triheptanoin Treatment History

Medical history will be obtained for all subjects not previously enrolled in UX007-CL201. General medical information includes subject demographics (date of birth, ethnicity, and sex) and a history of major medical illnesses, diagnoses, and surgeries. The review will also include an assessment of major medical conditions associated with LC-FAOD, including clinical or subclinical rhabdomyolysis, cardiomyopathy, hypoglycemia, and hypotonia/exercise intolerance. Any available sibling history of LC-FAOD will be noted including relationship and outcome.

LC-FAOD maintenance treatment history, including triheptanoin treatment history, and relevant concomitant medications will be recorded (start date, stop date, dose, dose regimen). Other LC-FAOD treatments include MCT oil (including coconut oil), carnitine supplements, other standard of care treatments, and all other relevant concomitant medications (e.g. diuretics, inotropes, seizure medications, supplements, etc.). Medications include prescription, over-the-counter, herbal and nutritional supplements. Any relevant concomitant therapy, including physical/occupational therapy will be recorded.

7.5.5.2 Growth and Weight Evaluations

At each clinic visit, measurements of height and weight will be collected for each subject using a stadiometer and a scale. Head circumference will be obtained for subjects ≤ 36 months of age. Height, weight, and head circumference (if applicable) data will be used to evaluate each subject's growth using published normative data, when available.

7.5.5.3 Vital Signs

Vital signs will include seated systolic and diastolic blood pressure (BP) measured in millimeters of mercury (mm Hg), heart rate (HR) in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). Vital sign measurements will be performed at every clinic visit before any additional assessments are completed.

7.5.5.4 Physical Examination

Complete physical examinations will be performed at the Baseline visit and at 6-month intervals (or Early Termination). Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. The lymphatic exam scope should be as per age-appropriate standard of care, at the Investigator's discretion based on the clinical judgement and/or safety need. If a PI determines there is no clinical indication for a lymphatic exam, it is not necessary to perform. The genitourinary exam scope should be non-invasive and as per age-appropriate standard of care, at the Investigator's discretion based on the clinical judgement and/or safety need. If the PI determines there is no clinical indication for a genitourinary exam, it is not necessary to perform.

7.5.5.5 Clinical Laboratory Tests

The clinical laboratory evaluations to be performed in this study are listed in Table 7.5.5.5.1 Clinical laboratory testing will be performed at each visit. Blood samples obtained as part of scheduled visits will be obtained following ≥ 4 hours fasting, where possible.

Table 7.5.5.5.1: Clinical Laboratory Assessments

Chemistry	Hematology	Urinalysis
Alanine aminotransferase (ALT) [1]	Hematocrit	Appearance
Alkaline phosphatase	Hemoglobin	Color
Aspartate aminotransferase (AST) [1]	MCH concentration (MCHC)	pH
Bilirubin (total)	Mean corpuscular hemoglobin (MCH)	Specific gravity
Blood urea nitrogen (BUN)	Mean corpuscular volume (MCV)	Ketones
Chloride	Platelet count	Protein
Cholesterol (total)	Red blood cell (RBC) count	Glucose
Serum creatinine	Reticulocyte count	Bilirubin
Gamma-glutamyl transpeptidase (GGT)[1]	WBC differential	Nitrite
Serum glucose, fasting [1]	Neutrophil count (absolute and %)	Urobilinogen
Lactate dehydrogenase (LDH)	Lymphocyte count (absolute and %)	Blood
Potassium	Monocyte count (absolute and %)	Creatinine
Protein (albumin and total)	Eosinophil count (absolute and %)	
Sodium	Basophil count (absolute and %)	Pregnancy test (if applicable)
	White blood cell (WBC) count	
		***Special Assessment**
		Serum pregnancy test (if a positive urine pregnancy test)

[1] Analyte is also a biomarker of clinical efficacy

Subjects who experience a SAE possibly or probably related to study drug or other AE of concern may, at the discretion of the Investigator (and/or Medical Monitor), have additional blood samples taken for safety laboratory tests.

7.5.5.6 Pregnancy Testing

Female subjects of childbearing potential will have urine pregnancy tests as described in the Schedule of Events (Table 2.1). Females considered not of childbearing potential include those who have not experienced menarche, are post-menopausal (defined as having no menses for at least 12 months without an alternative medical cause); or are permanently sterile due to total hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

Female subjects with a positive pregnancy test at Baseline will not be enrolled in the study. Pregnancy in subject or partner must be reported (Section 8.5.4.3); pregnant subjects will be discontinued from the study. Additional pregnancy tests may be performed at any time in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result, or can be performed if pregnancy test by urine is not feasible.

Experience with UX007 (triheptanoin) in pregnant women is limited. The study drug may involve risks to a pregnant female or unborn baby which are currently unknown.
Sexually active fertile males or females of child-bearing potential must use highly effective contraception during heterosexual intercourse throughout the study period and for 30 days after stopping the study drug. Examples of highly effective methods (CTFG 2014) include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (i.e., refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, when this is in line with the preferred and usual lifestyle of the subject)

7.5.5.7 Adverse Events

All AEs will be recorded from the time the subject signs the informed consent through 30 days following the last administration of study drug. Assessments of AEs will occur at each study visit (phone and clinic). At each visit subjects will be asked about any new or ongoing AEs since the previous visit. The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.5.

Clinically significant changes from Baseline in physical examination findings, vital signs, weight, and clinical laboratory parameters will be recorded as AEs or SAEs, if appropriate.

7.5.5.8 Concomitant Medications

Concomitant medications will be reviewed and recorded in the subject's CRF at each study visit (phone and clinic). Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Baseline will be reviewed and recorded. At each subsequent visit, change in medications since the previous visit will be recorded. A discussion of concomitant medications is provided in Section 7.4.5.

7.5.5.9 Dietary Assessment

The initial 3-day diet history recorded will be reviewed by the site in order to establish daily caloric intake. Subjects and/or caregivers will maintain a record of the subject's daily diet using a diary for 3 days prior to each clinic visit. The daily diet should be representative of typical consumption for the subject. The diet diary will be reviewed with the site staff upon each indicated visit.

7.5.6 Appropriateness of Measures

The efficacy parameters to be evaluated in this study focus on the key disease areas impacted by LC-FAOD, including skeletal myopathy, hepatic disease, and cardiac disease. The clinical assessments in the study employ standard measures used in other diseases and conditions that impair muscle, liver, and heart function.

Where possible, additional validated, age-appropriate, patient-reported outcomes were included to assess functional disability, cognitive development and health-related quality of life (i.e. SF-10/12). ECHO is a routine, non-invasive procedure inflicting minimal pain/distress for the subject, while providing relevant indicators of cardiac disease.

Additional relevant biomarkers of LC-FAOD disease status will be assessed using blood samples. Where possible, timing of assessments has been coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary duplication of testing.

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs, serum chemistry, concomitant medications, and other routine clinical and laboratory procedures.

7.6 Statistical Methods and Determination of Sample Size

Because the completeness of the data affects the integrity and accuracy of the final study analysis, every effort will be made to ensure complete, accurate and timely data collection, and to avoid missing data. The detailed method for analyses along with procedures for accounting for missing, unused, and spurious data will be presented in the Statistical Analysis Plan (SAP); the information below is intended as a guide to planned analyses.

7.6.1 Analysis Populations

All subjects with any post-dose efficacy assessment will be included in the efficacy analysis; the evaluable set only includes subjects who complete at least 80% of treatment doses and assessments. A complete treatment dose is defined as at least 25% of caloric intake from UX007.

Subjects with historical medical events collected will be analyzed separately for changes in the rates of medical events and hospitalization days. Individual genetic disease types will be analyzed together in separate subset populations. Subsets based on dominant clinical phenotype may also be analyzed. Subsets may also be defined based on prior study participation assessing UX007 treatment. Other analysis subset populations will be defined in the SAP.

7.6.2 Endpoints

The primary efficacy endpoint:

- The annualized LC-FAOD major events rate inclusive of skeletal myopathy (rhabdomyolysis), hepatic (hypoglycemia) and cardiomyopathy events.

The secondary efficacy endpoints:

- Energy metabolism in LC-FAOD on the basis of the following endpoints:
    - Ventricle size
    - Ejection fraction (EF)
    - Shortening fraction (SF)
- Clinical events associated with LC-FAOD on the basis of the following endpoints
    - Annualized duration rate of all MCEs
    - Annualized event rate of rhabdomyolysis MCEs
    - Annualized duration rate of rhabdomyolysis MCEs
    - Annualized event rate of cardiomyopathy MCEs
    - Annualized duration rate of cardiomyopathy MCEs
    - Annualized event rate of hypoglycemic MCEs
    - Annualized duration rate of hypoglycemic MCEs

Exploratory endpoints include the following:

- Functional disability and cognitive development (instrument selection based on age) endpoints:
    - SF-10 physical health component summary (PCS) score

  - SF-10 mental health component summary (MCS) score
  - SF-12 physical health component summary (PCS) score
  - SF-12 mental health component summary (MCS) score

- Clinical biomarkers endpoints:
  - Serum creatine kinase
  - Fasting serum glucose
  - Alanine aminotransferase (ALT)
  - Aspartate transaminase (AST)
  - Gamma glutamyl transpeptidase (GGT)

- Growth measurements:
  - Height
  - Weight
  - Head circumference, if applicable (subjects ≤ 36 months of age)

PK endpoints:

  - Plasma levels of UX007
  - Plasma levels of UX007 metabolites, including heptanoate, beta-hydroxypentanoate (BHP), and beta-hydroxybutyrate (BHB)

Safety endpoints:

Safety events will be collected as adverse events (AE) or serious adverse events (SAE). The analyses of safety will include all subjects who receive at least one dose of study drug.

The safety endpoints in this study are:

- Incidence and severity of treatment emergent AEs (primary safety endpoint)
- Vital signs
- Incidence of laboratory abnormalities
- Concomitant medications

7.6.3 Efficacy Analyses

The primary efficacy endpoint, ie, annualized MCE event rate, will be calculated using all MCE events collected post-UX007 treatment through the end of study. The primary analysis of the annualized MCE rate is descriptive statistics using mean, standard deviation (SD), median, quartiles, minimum, and maximum values. Two-sided 95% confidence interval will also be provided when appropriate. Annualized event rates for MCE by event type (ie, rhabdomyolysis, cardiomyopathy and hypoglycemic events) will be calculated and summarized in a similar fashion as with the primary efficacy endpoint.

In addition, for subjects who have historical event rate data collected, comparisons of pre- and post-UX007 treatment annualized event rates for overall MCE events will be conducted. In addition, intra-patient comparisons of pre- and post-UX007 treatment for MCE events by event type might be considered if sample size permits.

Summary statistics will be produced for all exploratory endpoints using all available assessments. For continuous variables, the number of observations and the mean, standard deviation (SD), median, quartiles, minimum, and maximum values were tabulated by endpoint. For categorical variables, the counts and proportions of each value were tabulated. Two-sided 95% confidence interval will also be provided when appropriate. Efficacy data collected for age-specific assessments (e.g. SF-10/12) will be summarized for subjects in that age group only. Other age-specific summaries may be provided for measures collected across all age groups.

7.6.4 Pharmacokinetic (PK) Analyses:

Summary statistics of plasma concentration will be provided for UX007 and metabolites. PK parameters such as area under the plasma concentration-time curve (AUC), time to maximum plasma concentration (Tmax), maximum plasma concentration (Cmax), and trough plasma concentration (Ctrough) will be estimated for participating subjects.

7.6.5 Safety Analyses

For the safety analysis, the incidence and frequency of treatment-emergent AEs and SAEs will be evaluated. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of AEs will be summarized by System Organ Class (SOC), Preferred Term (PT), relationship to study drug, and severity.
A by-subject listing will be provided for those subjects who experience a SAE, including death, or experience an AE associated with early withdrawal from the study or study drug treatment.

Clinical laboratory data will be summarized by the type of laboratory test. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e., outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement.

7.6.6 Determination of Sample Size

Approximately 150 subjects with a history of participation in a UX007/triheptanoin clinical study, or who have failed conventional therapy and have documented clear unmet need (in the opinion of the Investigator and Sponsor) may be enrolled for this study. The sample size is intended to provide the maximum amount of information regarding UX007 long-term safety, along with indicators of sustained efficacy and durability of response.

A minimum of 12 subjects will participate in the PK sub-study at select sites.

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board or Ethics Committee

The IRB/EC must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, and the associated informed consent forms (ICFs) must be submitted to the IRB/EC for review and must be approved before enrollment of any subject into the study. Study drug may not be shipped to the Investigator until Ultragenyx or its designee has received a copy of the letter or certificate of approval from the IRB/EC for the protocol and any protocol amendments, as applicable.

All subject recruitment and/or advertising information must be submitted to the IRB/EC and Ultragenyx or its designee for review and approval prior to implementation. IRB/EC approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to protect subject safety. In such cases, the chair of the IRB/EC should be notified immediately and the amendment forwarded to the IRB/EC for review and approval.

8.1.2 Ethical Conduct of Study

This protocol is written in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The Investigator will make every effort to assure the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, and local ethical and regulatory requirements. Should a conflict arise, the Investigator will follow whichever law or guideline affords the greater protection to the individual subject.
The Investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in this protocol and the IB, prior to the initiation of the study.

8.1.3 Subject Information and Consent

Appropriate forms for documenting written informed consent will be provided by the Investigator and reviewed and approved by Ultragenyx or its designee before submission to the IRB/EC. Ultragenyx or its designee must receive a copy of the IRB/EC's approval of the ICF before the shipment of study drug to the study site.

It is the Investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent will be obtained after the methods, objectives, requirements, and potential risks of the study have been fully explained to each potential subject. The Investigator must explain to each subject that the subject is completely free to refuse to enter the study or to withdraw

from it at any time. Subjects under the age of 18 years (or 16 years, depending on the region) will provide written assent (if required), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent for such subjects. Subjects who are minors should provide consent as soon as they turn 18.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements. Subjects will be given a copy of the signed ICF and will be provided any new information during the course of the study that might affect their continued participation in the study. The Investigator or a qualified designee will be available to answer each subject's questions throughout the study, and all of the subject's questions must be answered to the subject's satisfaction. If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised ICF.

Receipt of written informed consent will be documented in each potential subject's CRF. The signed ICF will remain in each subject's study file and must be available to the study monitor(s) at all times.

8.2 Investigators and Study Administrative Structure

Each Investigator must provide Ultragenyx and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all sub-investigators listed on Form FDA 1572.

Ultragenyx and/or its designee will be responsible for managing and monitoring the clinical trial to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's trained designated representative (the monitor) will conduct regular visits to the clinical site, to perform source document verification. The monitor will verify the Investigator's ongoing qualifications, inspect clinical site facilities, and inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements.

8.3 Investigational Product Accountability

While at the clinical site, study drug must be stored in a secure limited access location at controlled temperature as described in the IB and according to product packaging. The storage facility must be available for inspection by the study monitor at any time during the study. Subjects will be given instructions on the proper storage of study drug when initially dispensed and reminded of storage requirements at all subsequent visits.

A drug accountability record must be maintained for all study drug received, dispensed, returned, and/or lost during the study. This record must be kept current and made available to the study monitor for inspection. Following the close-out of the study, all unused study drug

must be returned to Ultragenyx and/or its designee unless other instructions have been provided for final disposition of the study drug.

8.4 Data Handling and Record Keeping

8.4.1 Case Report Forms and Source Documents

The Investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. A validated electronic data capture (EDC) system will be used for entry of the data into electronic CRFs. Data must be recorded on CRFs approved by Ultragenyx or its designee. All information recorded on CRFs for this study must be consistent with the subject's source documentation.

Initial data entry and any changes to the electronic CRF data will be made only by Ultragenyx-authorized users, and data entries and changes will be captured in an electronic audit trail. An explanation of any data change should be recorded in the CRF. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by Ultragenyx or its designee. The Investigator must allow direct access to all source documents.

8.4.2 Data Quality Assurance

Monitoring and auditing procedures developed by Ultragenyx and/or its designee will be implemented to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's designated representative (the monitor) will contact the Investigator and conduct regular visits to the study site. The monitor will be expected and allowed to verify the Investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents including progress notes, laboratory test reports and other subject records. Instances of missing or uninterpretable data will be resolved in coordination with the Investigator.

The monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and/or mail. The Investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and any and all issues identified by the monitor.

The Investigator understands that regulatory authorities, the IRB/EC, and/or Ultragenyx or its designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least two years after the last approval of a marketing application or for at least two years after clinical development of the study drug for the indication being studied has been discontinued. The Investigator is required to guaranty access to these documents and to cooperate with and support such audits and inspections.

8.4.3 Record Retention

All study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 25 years. Ultragenyx must be notified should the Investigator/institution be unable to continue maintenance of subject files for the full 25 years. All study records must be stored in a secure and safe facility.

8.5 Reporting and Follow-up of Adverse Events

8.5.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of expedited safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Life-threatening adverse event or life-threatening suspected adverse reaction is an adverse event or suspected adverse reaction that, in the view of either the Investigator or Sponsor, places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

A serious adverse event (SAE) or serious suspected adverse reaction is an adverse event or suspected adverse reaction that at any dose, in the view of either the Investigator or Sponsor, results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or disability (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect

Note that hospitalizations planned prior to study enrollment (e.g. for elective surgeries) are not considered SAEs. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

8.5.2 Severity of Adverse Events

Wherever possible, the severity of all AEs will be graded using the NCI CTCAE Version 4.0. The majority of AEs can be graded using this system.

If an AE cannot be graded using the CTCAE criteria, it should be graded as mild, moderate, severe, life-threatening, or death using the following definitions.

- ***Mild (Grade 1)***: Awareness of signs or symptoms, but easily tolerated and are of a minor irritant type, causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- ***Moderate (Grade 2)***: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- ***Severe (Grade 3)***: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.
- ***Life-threatening (Grade 4)***: Events that place the participant at immediate risk of death or are disabling.
- ***Death (Grade 5)***: Events that result in death.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5.3 Relationship of Adverse Events to Study Drug

The Investigator will assess the potential relationship of the AE to study drug using the following descriptions.

Categories of attributions for "Unrelated" events:

- ***Unrelated:*** This category applies to an AE that ***is clearly not related*** to the investigational agent/procedure.
- ***Unlikely Related:*** This category applies to an AE that ***is doubtfully related*** to the investigational agent/procedure.

Categories of attributions for "Related" events:

- ***Possibly Related:*** This category applies to an AE that ***may be related*** to the investigational agent/procedure.
- ***Probably Related:*** This category applies to an AE that ***is likely related*** to the investigational agent/procedure.
- ***Definitely Related:*** This category applies to an AE that ***is clearly related*** to the investigational agent/procedure.

For the purposes of reporting to regulatory agencies, AEs deemed as Definitely, Probably or Possibly Related will be considered Related and those deemed Unrelated or Unlikely Related will be considered Unrelated.

8.5.4 Adverse Event Reporting

8.5.4.1 General

All AEs (i.e. any new or worsening in severity or frequency of a preexisting condition) with onset after the subject signs consent for study participation must be promptly documented on the CRF. The Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring documentation of the event is adequate. Details of the AE must include severity, relationship to study drug, duration, and outcome.

All AEs will be collected from the time the subject signs informed consent through 30 days following the last dose of study drug. In addition, the Investigator should report any AE that occurs after this time period that is believed to have a reasonable possibility of being associated with study drug.

AEs ongoing at 30 days following the last dose of study drug should have a comment in the source document by the Investigator whether the event has recovered, recovered with sequelae, or stabilized.

8.5.4.2 Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

Ultragenyx or its designee must be notified of any SAE that occurs at any time during the reporting period within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. SAEs will be reported by completing and submitting SAE report forms to Ultragenyx or its designee.

Follow-up SAE information must be submitted in a timely manner as additional information becomes available. All SAEs regardless of relationship to study drug must be followed to resolution or stabilization if improvement is not expected.

All deaths, regardless of causality, occurring from the signing of the informed consent until 30 days following the last dose of study drug are to be reported as SAEs to Ultragenyx or its designee within 24 hours of knowledge.

8.5.4.3 Pregnancy in Subject or Partner, and Requirements for Immediate Reporting

Ultragenyx or its designee must be notified of the occurrence of any pregnancy in a subject or subject's partner that occurs during the reporting period within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. Pregnancies will be reported by completing and submitting Pregnancy Notification forms to Ultragenyx or designee. Reported pregnancy of a subject or a subject's partner, while participating in the study, will be monitored for the full duration and/or followed until the outcome of the pregnancy is known. In the event of a pregnancy in the partner of a subject, the Investigator should make every effort to obtain the female partner's consent for release of protected health information.

Ultragenyx or its designee must be notified of the outcome of the pregnancy within 24 hours of the Investigator, designee, or site personnel's knowledge of the outcome.
Pregnancy outcomes will be reported by completing and submitting Pregnancy Outcome forms to Ultragenyx or designee.

8.5.5 Communication Plan

8.5.5.1 Serious Adverse Drug Reaction Reporting

Ultragenyx or its designee will submit suspected unexpected serious adverse reactions (SUSAR) to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), Ethics Committees, and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7-calendar days of first knowledge of the event and follow-up information submitted within an additional eight (8) days. All other SUSARs will be submitted within 15-calendar days of first knowledge of the event.

The Investigator will notify the IRBs/ECs of SAEs and urgent safety matters, in accordance with IRB/EC requirements and local laws and regulations. A copy of this notification must be provided to Ultragenyx or its designee.

8.5.5.2 Urgent Safety Matters and Non-SUSAR Reporting

Principal Investigators are required to report any urgent safety matters to Ultragenyx or its designee within 24 hours. Ultragenyx or its designee will inform the Regulatory Authorities, ECs, and Investigators of any events (e.g. change to the safety profile of UX007, major safety findings) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical trials, as required, in accordance with applicable laws and regulations. The reporting period for urgent safety issues is the period from the signing of the ICF through 30 days following the last dose of study drug.

The Investigator will notify the IRBs/ECs of urgent safety matters, in accordance with IRB/EC requirements and local laws and regulations. A copy of this notification must be provided to Ultragenyx or its designee.

Non-SUSARs will be maintained in the Ultragenyx safety database and provided in annual and/or periodic reports as per local laws and regulations. Ultragenyx or its designee will prepare and submit annual safety reports and/or other aggregate periodic summary reports to Regulatory Authorities and ECs, as per local laws and regulations.

8.5.5.3 Pregnancy Reporting

Reported pregnancy of a subject or a subject's partner, while participating in the study, will be monitored for the full duration and/or followed until the outcome of the pregnancy is known. Any pregnancy-associated SAEs must be reported as per the SUSAR reporting process indicated in Section 8.5.5.1.

8.5.6 Safety Contact Information

Drug Safety	Medical Monitor
PrimeVigilance Fax: [redacted] e-mail: [redacted]	[redacted] Telephone: [redacted] Mobile: [redacted] e-mail: [redacted]

8.6 Financing and Insurance

Financing and insurance for this clinical trial will be addressed in clinical trial agreements with the study site.

8.7 Publication Policy

Any publication or presentation by the Investigator and/or the Institution based on data or results resulting from the Ultragenyx study shall only be done in strict accordance with the Publication section in the Clinical Trial Agreement executed between Ultragenyx and the Institution and/or the Investigator.

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10 SIGNATURE PAGE

Protocol Title: An Open-label Long-Term Safety and Efficacy Extension Study in Subjects with Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD) Previously Enrolled in UX007 or Triheptanoin Studies

Protocol Number: UX007-CL202 (Amendment 6)

I have read Protocol UX007-CL202 (Amendment 6). I agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

_____

Investigator Signature Date

Printed Name: _____

Accepted for the Sponsor:

As the Sponsor representative, I confirm that Ultragenyx will comply with all Sponsor obligations as detailed in all applicable regulations and guidelines. I will ensure the Investigator is informed of all relevant information that becomes available during the conduct of this study.

[redacted]

[redacted]

Date