STATISTICAL ANALYSIS PLAN

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
Protocol:	UX007-CL202-Amendment 6
Investigational Product:	UX007
Phase:	2
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA USA 94949
Author:	[redacted] Manager, Biostatistics
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Version Number:	2.0

STATISTICAL ANALYSIS PLAN AMENDMENT
SUMMARY OF CHANGES AND RATIONALE

21 December 2020

The Statistical Analysis Plan Version 1.0 dated 07 February 2019, for the UX007-CL202 study has been modified and the major statistical analysis plan changes are summarized below. These changes described in this amendment do not impact the primary method of analysis of the clinical endpoints.

a. A data listing of completed and missing visits will be provided for Echocardiogram, SF-10 and SF-12v2/SF-10 by pre- and post- UX007 treatment period (Section 8.5).

   Rationale: These listings will provide information on the amount of missing data for ECHO, SF-10, and SF-12v2 endpoints by treatment group.

b. Sensitivity analyses will be performed by removing identified outliers in pre- and post-UX007 treatment periods for:
   a. Triheptanoin-naive Cohort (Section 8.5.4.2)
      i. annualized event rate of MCEs and MCE hospitalizations
      ii. annualized duration of event rate of MCEs and MCE hospitalizations
   b. CL201 Rollover Cohort (Section 8.5.5.2)
      i. annualized event rate of MCEs and MCE hospitalizations
      ii. annualized duration of event rate of MCEs and MCE hospitalizations

   Rationale: Sensitivity analyses removing outliers will be performed to confirm the robustness of the primary MCE analysis findings.

c. Sensitivity analysis will be performed by using an alternative definition of MCEs in pre- and post-UX007 treatment periods in Triheptanoin-naïve (Section 8.5.4.3) and CL201-Rollover cohorts (Section 8.5.5.3) combined and separately for:
   a. Rhabdomyolysis MCEs alternatively defined as a patient having CK value >=1000
   b. Hypoglycemia MCEs alternatively defined as a patient having glycemia < 3.89 mmol

   c. *Rationale:* Sensitivity analyses with an alternative definition of Rhabdomyolysis and Hypoglycemia using clinical thresholds will be performed to confirm the robustness of the primary MCE analysis findings. The clinical assessment for an upper threshold of detecting hypoglycemia of glycemia <70 mg/dL (3.89 mmol) is recommended by the American Diabetes Association as a level for intervention required in diabetic patients. The clinical assessment for a lower threshold for Rhabdomyolysis, CK value >=1000, was chosen to be 5 times the upper limit of normal.

d. The data listing of prescribed dosing will be updated to include the total daily prescribed dose in mg/kg/day (Section 8.4.1).

Rationale: The data listing will be updated to include the dose adjusted for body weight.

e. Profile figures for individual subjects will be generated to display dietary parameters along with the occurrence of MCEs on the same plot, over the combined pre- and post- UX007 treatment period. Prescribed %DCI of the macronutrient intakes (UX007, MCT, other fat, carbohydrates, and protein) and total caloric intake (TCI) will be displayed over time (Section 8.4.1).

Rationale: Profile figures will create a visual display demonstrating the consistency of dietary intake as well as allowing for comparisons of MCEs occurrences with subject's dietary profiles over time.

f. Data listings of 3-day average subject diet diary parameters which includes fat, carbohydrates, and protein measured in g/kg/day and %DCI will be provided for the CL201-Rollover and the Naïve Cohort (Section 8.4.1).

Rationale: To provide for diet diary parameters adjusted for subject body weight.

g. The duration of treatment will be summarized for pediatric subjects (<18 years). (Section 8.4.1).

Rationale: Exposure in the pediatric population will be used to aid interpretation in any future analyses performed for the pediatric population.

h. Modification of the overall summary of adverse events table will be made by replacing the row for Grade 3/4 treatment-emergent adverse events (TEAEs) with a row for Grade 3 TEAEs and a row for Grade 4 TEAEs. (Section 8.7.1)

Rationale: More granularity for TEAEs of Grades 3 and 4 will be provided.

i. Summary safety tables and listings will be provided (Section 8.7.1) showing:
    a. TEAEs leading to dose reduction
    b. TEAEs leading to treatment interruption

Rationale: These tables and data listings will be prepared to facilitate an investigation of which TEAEs lead to dose reductions and which TEAEs lead to treatment interruptions.

j. Summary safety tables of gastrointestinal adverse drug reactions (GI ADRs) will be provided in order to characterize the severity, outcome, and time course of the GI

ADR. Additionally, Kaplan-Meier curves for time to first GI ADR will be provided by cohort. (Section 8.7.1.1)

Rationale: These summaries will provide information for an in-depth analysis of ADRs during Study UX007-CL202.

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate transaminase
BHB	beta-hydroxypentanoate
BHP	beta-hydroxybutyrate
CDC	Centers for Disease Control and Prevention
CK	creatinine kinase
CTCAE	common terminology criteria for adverse events
ECHO	echocardiogram
ICF	informed consent form
LC-FAOD	long-chain fatty acid oxidation disorders
LLN	lower limit of normal
MCE	major clinical event
MCS	mental health component summary score
MedDRA	Medical Dictionary for Regulatory Activity
OHSU	Oregon Health & Science University
PCS	physical health component summary score
PDMS-2	Peabody Developmental Motor Scales 2nd edition
PEDI-CAT	Pediatric Evaluation of Disability Inventory Computer Adaptive Test
PK	pharmacokinetics
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SDTM	study data tabulation model
SF	shortening fraction
SF-10	Medical Outcome Study 10-items Short Form for Children
SF-12	Medical Outcome Study 10-items Short Form
SI	*Le Système International d'Unités* (International System of Units)
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the UX007-CL202 original protocol and all amendments through Protocol Amendment 6 dated 01 October, 2019. This is the original version of SAP for this study. Changes from these guidelines must be substantiated by sound statistical reasoning and documented in the clinical study report (CSR).

Should there be a difference between the SAP and the protocol with respect to data analysis, the SAP will take precedence over the protocol.

2 STUDY OBJECTIVE(S)

2.1 Primary Objective(s)

The primary objective of the study is to:

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

2.2 Secondary Objective(s)

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

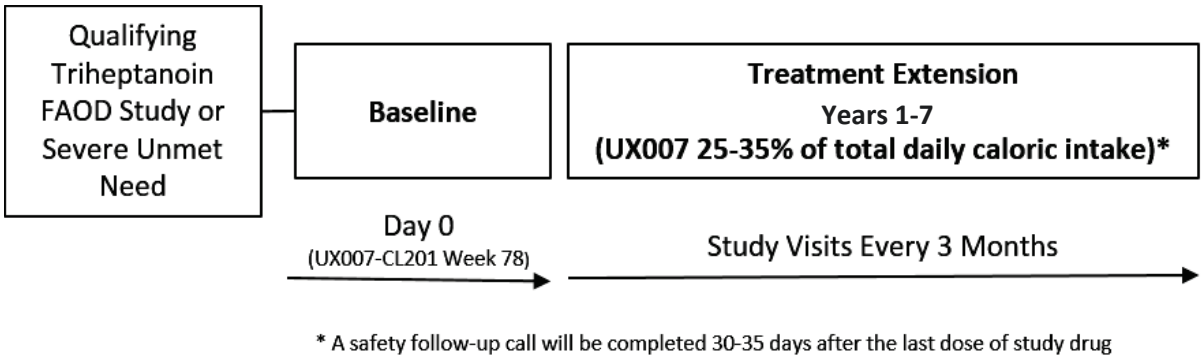
3 STUDY DESIGN

The study is an interventional, open-label, long-term safety and efficacy extension study of UX007 treatment in approximately 100 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 severe unmet need.

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. There will be periodic phone calls at specified intervals (± 1 week) for additional safety monitoring. The subjects will be followed to evaluate the long-term safety and continued effects of UX007 for approximately 7 years or until market approval, whichever occurs first. A Safety Followup- Phone Call will be conducted 30-35 days after last dose of study drug. The last subject's Safety Follow-up Phone Call is the End-of-study Time Point.

The following figure provides a schematic of the study design.

Figure 3.1: UX007-CL202 Study Schema



Biologic and clinical assessments will be conducted throughout the 84 month Treatment Period. Clinical efficacy measures, biomarkers and LC-FAOD laboratory measures, PK measurements, and safety measures will be collected per the schedule of assessment in Appendix 11.5. The occurrence of major LC-FAOD clinical events will be captured at each visit (clinic or phone) through early termination visit. Dosing compliance and diet will be regularly monitored along with a standard panel of safety assessments.

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.

3.1 Study Population

The study is designed to obtain long-term safety information and evaluate maintenance of efficacy in a diverse LC-FAOD population.

The study will be conducted in approximately 100 subjects who have participated in clinical studies or compassionate use programs with UX007/triheptanoin, or who have failed conventional therapy and have documented severe 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). Refer to the protocol for detailed inclusion and exclusion criteria.

Subjects in this study are to meet one or more of the following requirements:

- Participated in the UX007-CL201 study (ClinicalTrials.gov Identifier: NCT01886378)
- Previously enrolled in another UX007/triheptanoin study.
    - Study Sponsors/Collaborators include: Oregon Health & Science University (referenced as OHSU)
    - University of Pittsburgh (referenced as CompUse; ClinicalTrials.gov Identifiers: NCT01379625 and NCT01461304).
    - Participated in the UX007-CL001 study
    - Received UX007/triheptanoin treatment as part of other clinical studies; investigator sponsored trials (IST); expanded access/compassionate use treatment programs; eIND.
- 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 severe unmet need, may also be eligible at the discretion of the sponsor.

3.2 Dosage and Administration

The UX007 investigational product, triheptanoin, will be administered orally 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. 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; it is recommended that doses above 35% are discussed with the Medical Monitor prior to administration.

3.3 Study Duration

Subject participation duration in this extension study will be up to 7 years (84 months) or until market approval, 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. A safety follow-up phone call will be conducted 30-35 days after last dose of study drug. The last subject's safety follow-up phone call is the end-of-study time point.

3.4 Blinding and Randomization Methods

Since this is a single-arm open label study, hence randomization and blinding are not applicable.

3.5 Stratification Factors

There is no randomization and thus no stratification factors.

3.6 Sample Size Considerations

Approximately 100 subjects with a history of participation in a UX007/triheptanoin clinical study, or who have failed conventional therapy and have documented severe 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 selected sites.

3.7 Interim Analysis

No formal interim analysis is planned for this study. Additional administrative analysis might be done at sponsor's discretion to support regulatory submission or product planning.

3.8 Data Monitoring Committee

There is no formal data monitoring committee planned for this study. Conduct of the study and safety of the subjects will be monitored by Ultragenyx on a regular basis.

3.9 Discussion of Study Design, Including Choice of Control Group

For subjects who previously participated in the UX007-CL201 study or were treatment naïve, historical major clinical events data will be collected for the 18-24 months prior to beginning UX007 (or from birth for subjects less than 18 months of age), enabling those subjects to represent an internal control for assessment of efficacy.

4 STUDY ENDPOINTS AND COVARIATES

All data are collected according to the schedule of assessments (Appendix 11.5). This section details the definition of each study endpoint. Table 11.1.1 in Appendix 11.1 provides a summary of efficacy endpoints and the statistical method for each efficacy endpoint.

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

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

The primary efficacy endpoint is also referred as annualized major clinical event (MCE) rate. Section 5.1 defines what constitute an MCE and Section 5.11 presents the mathematical formula for deriving an annualized event rate.

4.2 Secondary Efficacy Endpoints

- Cardiomyopathy and cardiac function endpoints as measured by Echocardiogram (ECHO):
  - Ventricle size
  - Ejection fraction (EF)
  - Shortening fraction (SF)
- Annualized duration rate of all MCEs, where duration is defined as the total duration in number of days of MCEs
- Number and duration of each type of MCE (i.e., rhabdomyolysis, cardiomyopathy, and hypoglycemic events):
  - 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

4.3 Exploratory Endpoints

Exploratory endpoints include the following:

- Functional disability and cognitive development endpoints based on the Medical Outcomes Study 10-Item Short Form for Children (SF-10) or the Medical Outcomes Study 12-Item Short Form (SF-12) (instrument selection based on age):
  - 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 as measured by:
  - Serum creatinine 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)

Additional endpoints were collected during earlier versions of the protocol and were later removed from the protocol amendments. These endpoints are listed below.

- Peabody Developmental Motor Scales 2nd edition (PDMS-2) for children under age 6 and children over age 6 that are unable to perform a valid and consistent cycle ergometry test or 12MWT (removed from Amendment 1)
- 12 Minute Walk Test (12MWT) (removed from Amendment 4)
- The Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT) for all subjects under the age of 18 (or for subjects 18- 20 years as clinically indicated) at the time of informed consent (removed from Amendment 4)

- Subject diary (removed from Amendment 4)

Data available for the above additional endpoints will be included in listings as collected.

4.4 Safety Endpoints

Safety events will be collected as adverse events (AE) or serious adverse events (SAE).

Primary safety endpoints are incidence and severity of treatment emergent AEs

The other safety endpoints in this study are:

- Vital signs
- Incidence of laboratory abnormalities
- Concomitant medications

4.5 Pharmacokinetics Endpoints

PK endpoints for this study include:

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

4.6 Potential Covariate(s)

No covariates are planned for use in the analysis of primary and secondary efficacy endpoints.

5 DEFINITIONS

5.1 Pharmacokinetic Objectives

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

5.2 MCE

Major clinical events (MCE) 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.

5.3 Study Day 1

For all subjects, study day 1 is defined as the day of the first UX007 dose during Study UX007-CL202. For subjects who previously participated in study UX007-CL201, study day 1 coincides with the last UX007-CL201 visit.

Study Day 1 will be used to calculate the study days for all listings.

5.4 UX007 Treatment Day 1

UX007 treatment day 1 is defined as the day of the first UX007 dose. For subjects who rolled over from UX007-CL201, UX007 treatment day 1 is the day of the first UX007 dose during the UX007-CL201 study. For subjects who were UX007/trihep naïve, UX007 treatment day 1 coincides with study day 1.

UX007 treatment day 1 will be used to calculate days on UX007 for subjects who rolled over from UX007-CL201 and for naïve subjects in select statistical analyses.

5.5 Study Days

Study days of an event/assessment is defined as the date of the event/assessment minus the date of Study Day 1. If the result is a positive number or zero, add one day.

All derivations of duration are initially done based on days and converted to weeks, months and years if needed using 7, 30.4375 and 365.25, respectively, as denominator, if not otherwise specified.

5.6 Subject Cohorts for Presentation

All CL202 subjects will be classified into one of the three non-overlapping cohorts in analysis presentations:

- UX007/trihep naïve subjects. This cohort consists of subjects who had no prior exposure to UX007/trihep before enrolling into CL202. However if a subject participated in a prior UX007/trihep study but was off UX007/trihep for more than two years before enrolling into this study, then this subject will be treated as a naïve subject and historical major clinical events will be collected.

- UX007-CL201 rollover subjects. This cohort consists of subjects who rolled over from UX007-CL201 to UX007-CL202 study.

- Other. This cohort includes subjects unassigned to the above two cohorts, i.e., subjects from Vockley Comp sites, OHSU site, eIND program and etc.

A subject may have participated in more than one prior UX007/trihep studies/programs, and the cohort that the subject will be assigned to is determined based on the following priority order: UX007-CL201 rollover subjects and Other.

5.7 Baseline

Baseline is defined as the last valid assessment prior to or on study day 1. This baseline definition will be used for all safety assessments.

5.8 UX007 Treatment Baseline

For UX007-CL201 rollover subjects, a second baseline is defined as the last valid assessment prior to or on UX007-CL201 from which they were enrolled. This baseline is referenced as UX007 treatment baseline in analysis presentations, if applicable.

5.9 Visits

The nominal visits according to schedule of assessment will be used for by-visit summaries. Assessments are assigned to visits using the visit labels in SDTM. In general, all summary tables by visit include all scheduled assessments as per Schedule of Events (Appendix 11.5).

5.10 Study Periods

A study period defines the period of time over which efficacy and safety parameters are reported in this study. There will be three types of study period used in statistical analysis.

5.10.1 Study Period 1 (Main Study Period)

Study period 1, or the main study period, starts from study day 1 till the last visit day in CL202. The last visit date is the last date among the early termination visit date, the study completion visit date, the safety follow up visit date, or the last visit date as of a clinical cutoff date, if applicable. Study period 1 will be used for all efficacy on FAS and safety analyses unless otherwise specified.

5.10.2 Study Period 2

Study period 2 has the same ending date as Study period 1 but starts from UX007 treatment day 1. Study period 2 will be used in select analyses for UX007-CL201 rollover subjects.

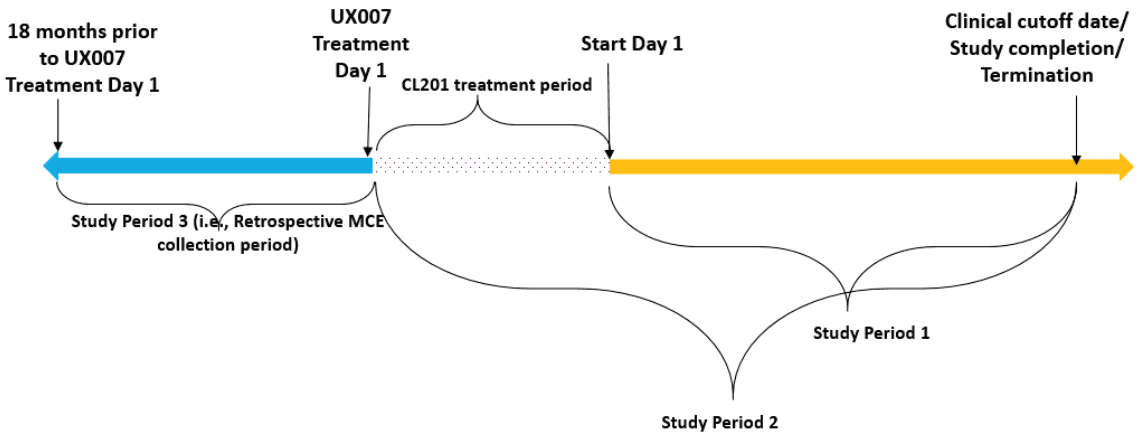
5.10.3 Study Period 3

Study period 3 starts from the 18 months (548 days) preceding UX007 treatment day 1 and ends 1 day prior to UX007 treatment Day 1. Study Period 3 is referred as the retrospective period for MCE data collection.

Study period 3 will be used for UX007-CL201 rollover subjects and UX007/trihep naïve subjects only in select analyses.

The following figure illustrates the definitions of the three study periods.

Figure 5.10.3.1: Diagram of Study Periods in CL202



Study Period 1 is defined for all enrolled subjects in CL202; Study Period 2 is defined for CL201 rollover subjects only; Study Period 3 is defined for CL201 rollover subjects and UX007/trihep naïve subjects. CL201 treatment period exists for CL201 subjects only;

5.11 Annualized Event Rate

The numbers of MCE will be annualized for each subject using the following formula:

$$\text{Annualized Event Rate} = \frac{\text{Number of events}}{\text{Duration of data collection period in days}/365.25}$$

The number of MCEs will be derived as the total number of events as recorded in the major clinical event CRF that occurred during the specific data collection period. Whenever an annualized rate is calculated over study period 1, the number of days is calculated from study day 1 till the data cutoff date or the early termination/study completion visit date for subjects who have early terminated/completed the study.

Annualized event rates will be calculated for MCEs overall and for each event type (ie., rhabdomyolysis, hypoglycemia, and cardiomyopathy respectively).

5.12 Annualized Duration Rate

The total duration in number of days of MCEs will be calculated and annualized for each subject using the following formula:

$$\text{Annualized Duration Rate} = \frac{\text{Total duration (days) of events}}{\text{Duration of data collection period in days}/365.25}$$

The number of days during the data collection period is determined in the same way as for annualized event rate.

Annualized duration rates will be calculated for MCEs overall and for each event type (ie., rhabdomyolysis, hypoglycemia, and cardiomyopathy respectively).

5.13 Age at Enrollment

Unless otherwise specified, the age will be derived based on the informed consent date in CL202: Age = (Inform Consent Date (ICF) – Birth Date +1)/365.25. The age will be rounded down to the nearest years and kept to one (1) decimal place. When date of birth is missing, the age recorded on CRF will be used.

5.14 Age at First Dose of UX007/trihep

The age at first dose of UX007/trihep will be derived for subjects with known date of first dose of UX007/trihep.

5.15 Total Duration of UX007 Exposure

For each subject, the total duration of UX007 exposure is defined as sum of duration in the UX007 treatment regimen log. For each analysis, the total duration will be calculated up to last visit date as of the specified clinical cutoff date or the early termination/study completion date, whichever is earlier.

5.16 % of Daily Caloric Intake Provided by Prescribed UX007 Dose

For each subject, an overall average percent of daily caloric intake provided by prescribed UX007 dose will be derived using the UX007 treatment log based on the following rules:

- Percent of daily caloric intake provided by prescribed UX007 dose will be as entered in that entry of the UX007 treatment regimen log for the duration between the start and stop dates when a single log entry has no duplicates with same start and stop date.

- For multiple log entries with same start date and same stop date, the total percent of daily caloric intake is the sum of percent of daily caloric intake of those log entries for that duration.

- Duration is defined as stop date – start date + 1 for each entry in the UX007 treatment log. If a treatment log has a stop date after the specified clinical cutoff date, the duration will be calculated as clinical cutoff date – start date + 1 for each entry in the UX007 treatment log .

Overall average percent of daily caloric intake = Sum of (percent of daily caloric intake * duration) / Sum of duration in the UX007 treatment regimen log.

5.17 Overall Average Prescribed UX007 Dose

For each subject, an overall average prescribed UX007 daily dose in mL will be derived using the UX007 treatment log according to the following rules:

- Daily dose will be the field "Total Daily Prescribed Dose" in that entry of the UX007 treatment regimen log for the duration between the start and stop dates when the one log entry has no duplicates with same start and stop date.

- For multiple log entries with same start date and same stop date, the daily dose is the sum of the field "Total Daily Prescribed Dose" of those log entries for that duration.

- Duration is defined as stop date – start date + 1 for each entry in the UX007 treatment log. If a treatment log has a stop date after the specified clinical cutoff date, the duration will be calculated as clinical cutoff date – start date + 1 for each entry in the UX007 treatment log.

Overall average prescribed daily UX007 dose = Sum of (the daily dose * duration) / Sum of duration in the UX007 treatment regimen log

5.18 Overall UX007 dosing completion percentage

For each patient, an overall UX007 dosing completion percentage will be derived using the dosing compliance diary.

- Percent of prescribed UX007 taken will be as entered in that entry of the dosing compliance diary for the duration between the start and stop dates when a single log entry has no duplicates with same start and stop date.

- Duration is defined as stop date – start date + 1 for each entry in the dosing compliance diary. If a dosing compliance diary has a stop date after the specified clinical cutoff date, the duration will be calculated as clinical cutoff date – start date + 1.

Overall UX007 dosing completion percentage = Sum of (percent of prescribed UX007 taken * duration) / Sum of duration of each dosing compliance diary.

5.19 SF-12 PCS and MCS

The SF-12 Health Survey version 2 is assessed for adults 18 years of age and older. Eight domain scores (Physical Functioning, Role Limitations due to Physical Health, Bodily Pain, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotions Problems, and Mental Health) are calculated from raw scores. Additionally two summary component scores are calculated from domain scores (Physical Component Summary Scale [PCS] and the Mental Component Summary Scale [MCS]).

Raw scores range from 0 to 100 with higher scores indicating better health. Domain scores are calculated from raw scores such that domain scores have a mean of 50 and SD of 10. The PCS and MCS summary component scores also have mean of 10 and SD of 10 to allow comparisons with domain scores.

Scoring the SF-12 version 2 is accomplished using T-score Based scoring software from QualityMetric Inc. (Lincoln, RI). T-score Based scoring is standardized across the SF family of adult tools using the means and standard deviations from the 2009 U.S. general population. The T-score Based scores in the U.S. general population have a mean of 50 and a standard deviation of 10. The Medical Outcomes Study (MOS) tools utilize 2009 t-scores.

The main advantage of T-score Based scoring of the adult SF tools is easier interpretation. By using the T-score Based scoring method, your data are scored in relation to U.S. general population t-scores. Therefore, all scores obtained that are below 50 can be interpreted as below the U.S. general population t-score and scores above 50 can be interpreted as above the U.S. general population t-score. Because the standard deviation for each scale is 10, it is easier to see exactly how far above or below the mean a score is in standard deviation units (10 points = 1 standard deviation unit).

5.20 SF-10 PCS and MCS

The SF-10 Health Survey is assessed for children 5 to 17 years of age. Two summary measures (the Physical Summary Score and the Psychosocial Summary Score) are calculated from raw scores to have a mean of 50 and SD of 10.

The T-score based scoring (described in Section 5.19) is also used to score the SF-10 Health Survey for Children summary scales. The scale scores have been centered so that a score of 50 corresponds to the average score in a comprehensive 2006 sample (a combination of general population and supplemental disability and chronic condition samples). Although scale scores are standardized to a mean of 50 and a standard deviation of 10 in the combined U.S. general population and clinical samples, age-specific t-scoreative data should always be used for comparison purposes when results for individual children are being considered or when aggregate data are limited to a specific age range for which t-scoreative data are available.

5.21 Exposure-adjusted Adverse Event Incidence Rate

The exposure-adjusted adverse event incidence rate is defined as the total number of occurrences of an AE summed across all subjects in the group divided by the total observation time for AEs for subjects in that group. The observation time for each subject is the duration from study day 1 (i.e., first dose of UX007) till the end of study period 1 or the date of clinical cutoff, whichever occurs earlier. The total observation time for AEs is the sum of observation times for all subjects in that group.

5.22 Outlier

An outlier value is defined as a value that lies outside the interval (Q1 – 1.5*IQR, Q3 +1.5*IQR), where Q1 and Q3 are Quartiles 1 and 3, respectively, and IQR is the interquartile range, ie, Q1-Q3 of the underlying distribution during the pre- or post-UX007 treatment period.

6 ANALYSIS POPULATIONS

6.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all subjects enrolled and had at least one post-baseline efficacy assessment. The full analysis set will be used for efficacy analyses.

6.2 Safety Analysis Set

The safety analysis set consists of all subjects who were enrolled and treated with at least 1 dose of UX007 while on CL202.

6.3 Full Analysis Set-SF-10

The full analysis set – SF-10 is the subset of subjects in the full analysis set whose age at enrollment was ≥ 6 to <18 years old and who had at least one SF-10 test performed while on study CL202.

6.4 Full Analysis Set-SF-12

The primary analysis set – SF-12 is the subset of subjects in the full analysis set whose age at enrollment was ≥ 18 years old and who had at least one SF-12 test performed while on study CL202.

6.5 PK Sub-study Set

The PK sub-study set consists of subjects who participated in PK assessments at selected sites.

7 DATA SCREENING AND ACCEPTANCE

7.1 General Principles

Data will be reviewed periodically. Any questionable data will be reported to the clinical data manager promptly for query and resolution.

7.2 Handling of Missing and Incomplete Data

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through the data quality review plan for this study. Missing and incomplete data will be identified for investigation, and possible resolution be done by Data Management prior to the final study database lock or interim snapshot.

Unless specified otherwise, only the observed data (not imputed data) will be presented in listings.

7.2.1 Missing Medical History Related Dates

To impute a missing date related to medical history, for example, diagnosis date, the following rules will be applied:

- If only day is missing, impute 1.
- If month is missing, impute January 1st.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is earlier than the birth date, then the birth date will be used.

7.2.2 Missing Birth Dates

To impute missing birth date, the following rules will be applied:

- If day is missing, impute 15.
- If month is missing, impute June.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is later than any study visit date/observed adverse event start date/ observed concomitant medication start date, then earliest available visit date/adverse event start date/ concomitant medication start date will be used without changing observed information.

7.2.3 Missing Date Imputation for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date.

Missing Start Dates

- If the day is unknown, then:
  - If the month and year match the first dose of investigational product start date month and year in this study, then impute the day of the first dose date.
  - Otherwise, assign the first day of the month.
- If the month is unknown, then:
  - If the year matches the year of the first dose of investigational product date in this study, then impute the month and day of the first dose date in this study.
  - Otherwise, assign 'January'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the imputed date is earlier than birth date, then birth date will be used. If the imputed start date is later than the end date, then the start date will be set as the same date as the end date.

Missing Stop Dates (not applicable to ongoing)

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign 'December.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value, and the event will be considered ongoing. If the AE has been recorded as resolved/recovered, all efforts should be made to obtain the date from the Investigator.
- If the resulting end date is after the date of study completion / discontinuation/ data cutoff, set the imputed end date as close to the date of study completion / discontinuation/ data cutoff as possible without overwritten existing information.

If the year is missing for the start date and the stop date (observed or imputed) is on or after the first dose or event is ongoing, the start date will be imputed as the first dose date.

7.2.4 Missing Data for Efficacy Endpoints

For efficacy endpoints based on the duration of study period, the date of the study exit needs to be available. In case it is missing, the study period will end at the date of last assessment.

When a change from baseline is assessed, missing data will not be imputed and only subjects with a baseline and at least one post-baseline measurement will be included in the analysis.

7.2.5 Missing Causal Relationship to Investigational Product for Adverse Event

If the causal relationship to the investigational product is missing for an AE that started on or after the date of the first dose of UX007, a causality of "definitely related" will be assigned. The imputed values for causal relationship to investigational product will be used for the incidence summary, but be reported as collected and shown as missing in the data listings.

7.2.6 Visit Window

In general, all summary tables by visit include all scheduled assessments per schedule of assessments. Assessments scheduled at a planned study visit but are collected during an unscheduled visit or early termination visit will be mapped into the closest study visit based on the study day of the unscheduled visit or early termination visit, and the schedule of assessment in the protocol.

The mapped unscheduled visit will not be used unless the scheduled visit is missing. If a subject early terminated the study, the early termination visit will be mapped to the closest scheduled visit.

In case of multiple unscheduled assessments fall into the same scheduled visit, the earlier one is taken.

7.3 Testing/Validation Plan

Data will be reviewed by cross functional team periodically and issues will be addressed by clinical data management.

7.4 Software

SAS® software version 9.4 or higher will be used to perform statistical analyses unless otherwise specified.

8 STATISTICAL METHODS OF ANALYSES

8.1 General Principles

This statistical analyses are mostly descriptive analyses with statistical tests performed for select. All statistical tests will be two-sided and tested at statistical significant level of 0.05. The statistical analyses will be reported using summary tables, figures, and data listings. Continuous variables will be summarized by number of subjects and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. All raw data obtained from the CRFs will be included in data listings

8.1.1 Repeated Measure Model: General Estimating Equations

When the sample size and number of observations are allowed, change from baseline endpoints over time will be analyzed using a generalized estimation equation (GEE) model that includes time as the categorical variable and adjusted for the baseline measurement. The covariance structure that will be used for the GEE model is compound symmetry which specifies constant variance for the assessments and constant covariance between the assessments over time. In general, the p-value will be presented for testing the statistical significance of the change from the baseline to assessments at Months 6, 12, 24, 60, 72, and 84, if applicable, respectively. For an analysis of change from baseline to assessment at a particular month, only measurements up to that month will be included in the model. For the analysis of change from baseline to assessments at Month 84, all measurements collected up to and including Month 84 will be included in the model.

If the number of observations are insufficient for analyses using a GEE model, a descriptive summary will be provided, and analyses using observations at a single time point, such as paired t-test or other nonparametric methodologies, may be considered.

8.2 Subject Accountability

All subjects enrolled (with ICF signed) for the study will be used for reporting of disposition. Subject disposition summaries will include the number and percentage of subjects who consist of each analysis population, such as the FAS, safety, etc. The number and percentage of subjects who received study drug treatment, completed the study or discontinued the study (with reasons) will be summarized.

8.3 Protocol Deviations

Protocol deviations, both major and minor, will be listed. Major protocol deviations will also be summarized.

8.4 Investigational Product Administration

8.4.1 UX007 Dosing,Exposure, and Diet

UX007 dosing and exposure parameters will be summarized based on UX007 treatment regimen log. Descriptive summary statistics will be produced for the following parameters.

- Total duration of UX007 exposure
- Overall average prescribed UX007 dose
- % of daily caloric intake provided by prescribed UX007 dose
- Total daily prescribed dose in mg/kg/day

In addition, % of daily caloric intake provided by daily UX007 intake will be derived using the 3-day average based on the 3-day diet diary. Daily caloric intake (total calories per kg), daily protein intake (% of total caloric intake), daily carbohydrate intake (% of total caloric intake), daily total fat intake (% of total caloric intake), and daily UX007 intake (% of total caloric intake) will be summarized by visit using descriptive statistics.

Profile figures for individual subjects will be generated to display dietary parameters along with the occurrence of MCEs on the same plot, over the combined pre- and post- UX007 treatment period. Prescribed %DCI of the macronutrient intakes (UX007, MCT, other fat, carbohydrates, and protein) and total caloric intake (TCI) will be displayed over time

Data listings will be generated displaying the 3-day average subject diet diary parameters which includes fat, carbohydrates, and protein measured in g/kg/day and %DCI will be provided for the CL201-Rollover and the Naïve Cohort separately.

8.4.2 Treatment Compliance

Summary statistics will be produced for the following UX007 treatment compliance parameters based on dosing compliance diary.

- Overall UX007 dosing completion percentage as defined in Section 5.17.
- Number and percentage of subjects with overall UX007 dosing completion percentage $\geq$ 80%

8.4.3 Demographic and Baseline Characteristics

Summary statistics will be presented for the Full Analysis Set and by subgroup for the following (but not restricted) parameters

- Gender

- Ethnicity
- Race
- Gestational age at birth
- Age at enrollment (ICF date)
- Age at LC-FAOD diagnosis
- Age at first dose of UX007 (in CL202)
- Age at first dose of UX007 (only for CL201 rollover subjects and UX007/trihep naïve subjects)
- Height at baseline
- Weight at baseline
- BMI at baseline

As only limited demographics data (i.e., date of birth and sex) and LC-FAOD diagnosis and LC-FAOD medical history are entered into the clinical database for subjects who previously participated in the UX007-CL001 or UX007-CL201 study, the UX007-CL001 and UX007-CL201 databases will be integrated with UX007-CL202 database to obtain complete data on demographics , LC-FAOD diagnosis, and LC-FAOD medical history.

8.4.4 Prior and Concomitant Medication

Prior medication is defined as any medication started before the date of the first dose of UX007 in CL202.

Concomitant medication is defined as any medication taken during the study that starts on or after the date of the first dose of UX007 in CL202. A medication started before the date of the first dose of UX007 and also taken after the date of first dose of UX007 during CL202 will be counted both as a prior and concomitant medication.

Concomitant medications will be coded using the latest World Health Organization (WHO) Drug Dictionary.

If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject will be counted only once (i.e., subject incidence) for the coded drug name or therapeutic class.

8.5 Efficacy Analysis

An overview of efficacy analyses is provided below.

The efficacy analyses will be based on FAS unless otherwise specified. The analysis of SF-10 and SF-12V2 will be based on the FAS-SF-10 and FAS-SF-12, respectively. Safety analyses will be based on the safety analysis set. All analyses will be presented by subject cohort unless other specified.

The primary efficacy analysis of the annualized MCE rate will be summarized using descriptive statistics with mean, standard deviation (SD), median, quartiles, minimum, and maximum values.

Secondary efficacy analysis on cardiac function endpoints based on ECHO and annualized event/duration rates for MCE by event type will be performed in a similar fashion as with the primary efficacy endpoint.

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 will be tabulated. For categorical variables, the counts and percentages of will be tabulated. Two-sided 95% confidence interval will also be provided.

For UX007/trihep naïve subjects, efficacy will be assessed by comparing pre- and post-UX007 MCE rates for MCE related endpoints and by testing change from baseline for non-MCE efficacy endpoints; See section 8.5.4 for details.

For UX007-CL201 rollover subjects, an integrated analysis by combining data collected from UX007-CL201 and UX007-CL202 to assess the long-term effects of UX007 on key efficacy parameters; See section 8.5.5 for details.

8.5.1 Analysis of Primary Efficacy Endpoint

The primary efficacy parameter is the annualized MCE event rate inclusive of skeletal myopathy (rhabdomyolysis), hepatic (hypoglycemia) and cardiomyopathy events. Study period 1, or the main study period, will be used for the primary efficacy analysis. Annualized MCE event rate will be calculated for the entire study period 1 and by 18-month interval. The descriptive statistics will be provided using the methodology specified in Section 8.1.

The numbers of MCE events will also be summarized by precipitating factors (infectious disease, exercise, other, and unknown) and by type of intervention (emergency intervention, hospitalization, and ER visit).

8.5.2 Analysis of Secondary Efficacy Endpoints

Summary statistics will be presented for ECHO variables (ventricle size, EF, and SF) and corresponding changes from the study baseline by visit.

All annualized event/duration rate endpoints will be summarized in a similar fashion as for the primary efficacy endpoint.

A data listing of missing visits will be provided for ECHO endpoint by treatment.

8.5.3 Analysis of Exploratory Endpoint(s)

8.5.3.1 SF-10/12

For SF-10 and SF-12, analyses include summary statistics of baseline and change from the study baseline over time for each individual domain and the summary scores. The full analysis set-SF-10 will be used for statistical analyses of SF-10. The full analysis set-SF-12 will be used for statistical analyses of SF-12.

Individual subject listings will be provided for all SF-10/12 tests performed for all subjects in FAS.

A data listing of missing visits will be provided for SF-10 and SF-12v2.

8.5.3.2 Clinical biomarkers endpoints

Biomarker results and corresponding changes from baseline will be summarized descriptively by visit.

8.5.3.3 Growth measurements

Height, weight, and head circumference measurements and the corresponding changes and percent changes from baseline will be summarized descriptively by visit and by age group with summary statistics.

Z-score will be calculated for growth measurements including standing height (or sitting height if applicable) and weight for the male ≤18 years, or for the female ≤15 years. Z-scores and percentiles will be calculated using (CDC/NCHS) Clinical Growth Charts (Kuczmarski et al. 2000). The plot of height over age with reference to CDC growth chart for each subject will be provided. Data used to produce the United States Growth Charts smoothed percentile curves will be downloaded from the official CDC/NCHS web site: http://www.cdc.gov/growthcharts/percentile_data_files.htm

The data files from the CDC/NCHS that are used for this analysis are summarized below. These files represent the different growth curves for children. LMS refers to the parameters in the CDC Growth Charts Percentile Data Files used to construct the growth curves; these are: the power in the Box-Cox transformation (L); the median (M); and the generalized coefficient of variation (S).

The data files used are:

- Length-for-age charts, birth to 36 months, LMS parameters and selected smoothed recumbent length percentiles in centimeters, by sex and age (LENAGEINF).

- Stature-for-age charts, 2 to 20 years, LMS parameters and selected smoothed stature percentiles in centimeters, by gender and age (STATAGE).

Calculation of Z-scores for length/stature values above and below the median will be performed. Using the CDC/NCHS Clinical Growth Charts, the height-for-age Z score will be calculated using the following equation:

$$Z = \{(X/M)^L - 1\} / (L \times S),$$

where X is the physical measurement (stature in cm) and the LMS parameters are obtained from the appropriate CDC/NCHS Clinical Growth Chart corresponding to the age in months of the child. The percentile corresponding to the Z score is then the corresponding percentile from the standard normal distribution.

For male subjects >18 years and female subjects >15 years, the height and weight will be summarized in centimeter and kilogram respectively.

Weight will be evaluated by z score and percentile using the same method as height based on Centers for Disease Control/National Center for Health Statistics (CDC/NCHS) Clinical Growth Charts (Kuczmarski et al. 2000). The data files used for weight Z-score and percentile are:

- Weight-for-age charts, birth to 36 months, LMS parameters and selected smoothed weight percentiles in kilograms, by sex and age (WTAGEINF).

- Weight-for-age charts, 2 to 20 years, LMS parameters and selected smoothed weight percentiles in kilograms, by sex and age (WTAGE).

8.5.4 Triheptanoin-Naïve Cohort: Statistical Comparisons in Efficacy Endpoints

For UX007/trihep naïve subjects, additional analyses will be conducted to assess the effects of UX007 by comparing post-UX007 assessments with baseline assessment via statistical tests.

8.5.4.1 Pre- and Post-UX007 Comparisons in MCE in Triheptanoin-Naïve Cohort

All MCE related endpoints (i.e., annualized event/duration rates of MCE overall and by event type) will be analyzed by comparing pre- and post-UX007 treatment period. The pre-UX007 treatment period for UX007/trihep naïve subjects corresponds to the retrospective MCE collection period, i.e., study period 3.

The 18 months pre-UX007 treatment period will be compared to the 18 months post-UX007 treatment period using the paired t-test. The Wilcoxon signed rank test will be performed as a nonparametric alternative to the paired t-test when the normality assumption is questionable. For subjects who had longer than 18 months of follow up on study as of the data cutoff date, MCEs that occurred between UX007 initiation and 18 months post UX007 initiation will be

included for calculating number of MCEs and total durations in days of MCEs will be calculated accordingly. For subjects who terminated the study prior to reaching 18 months on study, MCEs that occurred between UX007 initiation and the termination visit will be included for calculating number of MCEs and total durations in days of MCEs will be calculated accordingly. For historical annualized event rate and annualized duration rate observed during study period 3, the data collection period is 18 months (548 days) preceding the date of UX007 initiation. For subject's age less than 18 months at UX007 initiation, the data collection period will be between the birthdate and the date prior to UX007 initiation.

8.5.4.2 Sensitivity Analyses for Triheptanoin-Naïve Cohort

8.5.4.2.1 Negative Binomial Regression in Triheptanoin-naïve

The comparison between pre- and post-UX007 MCE rates will also be performed using a negative binomial regression model, which accounts for different follow-up times, with the time that each subject stays in the study (study period 1) included as an offset in the model. This analytic model estimates the ratio of event rate of the post-UX007 treatment period over that of the pre-UX007 treatment period. The model can be performed using SAS GENMOD procedure where the REPEATED statement is used to account for the within patient comparison. Two-sided 95% confidence interval will be provided for the rate ratio along with the p-value.

8.5.4.2.2 Removing Outliers in Triheptanoin-naïve

Sensitivity analysis will be performed by removing identified outliers in pre- and post-UX007 treatment periods for:

- Annualized event rate of MCEs and MCE hospitalizations
- Annualized duration of event rate of MCEs and MCE hospitalizations

See definition of outlier in section 5.21.

8.5.4.2.3 Alternative Clinical Definitions of MCEs in Triheptanoin-naïve Cohorts

Sensitivity analysis will be performed by using an alternative definition of MCEs in pre- and post-UX007 treatment periodsfor:

- Rhabdomyolysis MCEs alternatively defined as a patient having CK value >=1000 (5 times the upper limit of normal)
- Hypoglycemia MCEs alternatively defined as a patient having glycemia < 3.89 mmol (recommended by the American Diabetes Association as a level for intervention required in diabetic patients)

8.5.4.3 Analyses of Non-MCE Endpoints in Triheptanoin-naïve Cohort

When the sample size and number of observations are allowed, statistical tests will be performed on the following non-MCE endpoints to assess the statistical significance of change from the baseline to assessments at Months 6, 12, 24, 60, 72, and 84 if applicable, respectively. Two-sided 95% confidence interval and p-value will be presented at these visits.

- Echo variables: EF, ventricle size, and SF: the paired t-test will be used to assess the statistical significance of change from baseline variables. The Wilcoxon signed rank test will be performed if the normality assumption is questionable.
- Clinical biomarkers: the paired t-test will be used to assess the statistical significance of change from baseline variables. The Wilcoxon signed rank test will be performed if the normality assumption is questionable.
- SF-10 PHS and PSS: the GEE model as described in Section 8.1.1 will be used to analyze change from baseline scores.
- SF-12v2 PCS & MCS: the GEE model as described in Section 8.1.1 will be used to analyze change from baseline scores.

Statistical testing of the above endpoints will only be performed at the final analysis when the sample size permits. Summary statistics will be provided by visit at a snapshot analysis due to the anticipated limited number of subjects and number of observations at the time of a snapshot. Two-sided 95% confidence intervals will be presented for change from baseline values at all visits.

8.5.5 CL201-Rollover Cohort: Integrated Analyses for efficacy endpoints

For UX007-CL201 rollover subjects, the long-term effects of UX007 will be assessed through both MCE related endpoints and non-MCE related efficacy parameters using data collected during study period 2, i.e., by integrating data collected from UX007-CL201 and UX007-CL202.

8.5.5.1 Pre- and Post-UX007 MCEs in CL201-Rollover Cohort

Annualized event and duration rates of MCE and by MCE type will be calculated for the three time periods: study period 3 (i.e., 18 months pre-UX007 treatment period), the 18 month CL201 treatment period, and study period 1 (CL202 UX007 treatment period). Within study period 1, annualized event/duration rates will be calculated by 18-month time interval. Summary statistics will be provided for calculated annualized event/duration rates. In addition, annualized event/duration rates will be plotted as box plots over time to show the time trend.

Annualized event rates (AER) and Annualized Event Duration rates (AED) will be analyzed by comparing pre- and post-UX007 treatment period. The pre-UX007 treatment period for UX007-CL201 Rollover subjects corresponds to study period 3.

For subjects who had longer than 18 months of follow up on study (CL202) as of the data cutoff date, MCEs that occurred between UX007 initiation and 18 months post UX007 initiation will be included for calculating number of MCEs and total durations in days of MCEs will be calculated accordingly. For subjects who terminated the study prior to reaching 18 months on study, MCEs that occurred between UX007 initiation and the termination visit will be included for calculating number of MCEs and total durations in days of MCEs will be calculated accordingly. For historical annualized event rate and annualized duration rate observed during study period 3, the data collection period is 18 months (548 days) preceding the date of UX007 initiation. For subject's age less than 18 months at UX007 initiation, the data collection period will be between the birthdate and the date prior to UX007 initiation.

Patient level plots to show all MCEs over time and time-points of start of retrospective period relative to the UX007 initiation and early discontinuation in a subject if applicable will be presented.

8.5.5.2 Sensitivity Analyses for CL201-Rollover Cohort

8.5.5.2.1 Negative Binomial Regression in CL201-Rollover Cohort

The comparison between pre- and post-UX007 MCE rates will also be performed using a negative binomial regression model, which accounts for different follow-up times, with the time that each subject stays in the study included as an offset in the model. This analytic model estimates the ratio of event rate of the post-UX007 treatment period over that of the pre-UX007 treatment period. The model can be performed using SAS GENMOD procedure where the REPEATED statement is used to account for the within patient comparison. Two-sided 95% confidence interval will be provided for the rate ratio along with the p-value.

8.5.5.2.2 Alternative Clinical Definitions of MCEs in CL201-Rollover Cohorts

Sensitivity analysis will be performed by using an alternative definition of MCEs in pre- and post-UX007 treatment periods for:

- Rhabdomyolysis MCEs alternatively defined as a patient having CK value >=1000 (5 times the upper limit of normal)

- Hypoglycemia MCEs alternatively defined as a patient having glycemia < 3.89 mmol (recommended by the American Diabetes Association as a level for intervention required in diabetic patients)

8.5.5.3 Analyses of Non-MCE endpoints in CL201-Rollover Cohorts

The following efficacy endpoints will be analyzed for this analysis:

- ECHO variables: Ventricle size, EF, and SF
- Growth measurements

In these analyses, baseline will be shifted to the UX007 treatment baseline. Scheduled visits in UX007-CL201 will be converted to months and then aligned with UX007-CL202 visits. For example, Week 24 visit in UX007-CL201 is mapped to Month 5.5 visit. Assessments taken during the UX007-CL202 baseline visit or the last scheduled visit from study UX007-CL201 are mapped to Month 18 visit. For other visits in UX007-CL202, 18 months will be added to the visit number. For example, Month 6 visit in UX007-CL202 is mapped to Month 24 visit.

Summary statistics will be presented for ECHO variables (ventricle size, EF, and SF) and corresponding changes from UX007 treatment baseline by visit.

The same analysis methodology as described in Section 8.5.3.3 will be adopted for these integrated analyses of growth measurements.

8.6 Pharmacokinetics Analysis

PK data will be summarized based upon PK sub-study set.

Plasma levels of UX007 metabolites will be summarized using descriptive statistics. 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 using standard non-compartmental analysis for participating subjects when there are sufficient data points. Descriptive statistics will be provided for PK parameters for UX007 metabolites.

8.7 Safety Analysis

The safety analysis will be performed using the safety analysis set. The safety parameters will include adverse events (AEs) and clinical laboratory, vital sign, and electrocardiographic (ECG) parameters and other safety parameters.

8.7.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA version 23.1). The severity of an AE will be based on Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. If an AE cannot be graded based on CTCAE, the investigator will assign a severity based on 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = Death.

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it occurred on or after the first dose of UX007 and was not present prior to the first dose or worsening in severity or frequency of a preexisting condition. AEs that started in UX007-CL201 and continued into UX007-CL202 will not be considered UX007-CL202 TEAE since the start date is prior to UX007-CL202 first dose.

The following subject incidence of AEs will be summarized:

- Summary of TEAEs
- TEAEs by SOC and PT (preferred term)
- Related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- Grade 3 or 4 TEAEs by SOC and PT
- Deaths by SOC and PT
- TEAEs leading to discontinuation of study treatment by SOC and PT
- TEAEs by PT
- TEAEs leading to dose reduction by SOC and PT
- TEAEs leading to treatment interruption by SOC and PT
- TEAEs by PT
- TEAEs in the GI SOC
- Related TEAEs in the GI SOC
- GI ADRs
- GI ADRs leading to treatment discontinuation

Hepatobiliary TEAEs (see Appendix 11.4)For those AEs that occurred more than once during the study, the maximum severity or highest grade causality will be used to summarize the subject incidence. Exposure-adjusted adverse event incidence rates will also be presented at the preferred term level.

The number and percent of subjects experiencing one or more TEAE by SOC and PT in order of descending frequency may be summarized by age, gender and subtype of FAOD

history depending on the sample size. The planned age categories are '0-1 year', '>1-6 years', '>6-18 years' and '>18 years' and some may be combined if their number of subjects is small.

In the overall summary of adverse events table, there will be separate summaries for Grade3 and Grade 4 TEAEs.

Detailed subject listings for all AEs, serious TEAEs, AEs leading to the discontinuation of study, AEs leading to the discontinuation of treatment, and death TEAEs leading to dose reduction, and TEAEs leading to treatment interruption will also be generated.

8.7.1.1 Gastrointestinal Adverse Drug Reactions

Summaries of gastrointestinal adverse drug reactions (GI ADRs) will be prepared to within each cohort. GI ADRs include the following PTs: Diarrhea, Abdominal pain, Abdominal pain upper, Gastrointestinal pain, Abdominal discomfort, Abdominal distension, Vomiting, and Nausea.

Summaries to characterize the severity and outcome of GI ADRs will include the following:

1) incidence of subjects with at least one GI ADR,
2) incidence of GI ADRs leading to treatment discontinuation,
3) a frequency distribution of the number of GI ADRs per subject,
4) descriptive statistics (n, mean, standard deviation, standard error, median and first and 3rd quartiles) for the number of GI ADRs per subject,
5) the frequency GI ADRs by severity and seriousness grade
6) a frequency distribution of the outcome of the GI ADRs that were
    a) Recovered/Resolved
    b) Resolving/Recovering
    c) Recovered/Resolved with Sequelae
    d) Death
    e) Not Resolved

Characterization of the time course of GI ADRs will be provided for:

1) Time to first GI ADR with
2) Frequency of GI ADRs by time categories
3) Number of Subjects with GI ADR by time categories
4) descriptive statistics by time categories for any GI ADR

The frequency distributions will the following categories: <= 8 Weeks, > 8 Weeks to <= 24 Weeks, > 24 Weeks to <= 48 Weeks, > 48 Weeks to <= 78 Weeks, > 78 Weeks to <= 102 Weeks, > 102 Weeks to <= 126 Weeks, > 126 Weeks to <= 150 Weeks, > 198 Weeks to <= 222 Weeks, etc.

The duration of a treatment-emergent GI ADR that was resolved is defined as AE end date minus AE start date plus 1 day. The duration of a treatment-emergent GI ADR for GI events

that are ongoing is defined as data cutoff date minus AE start date plus 1 day. The duration of treatment-emergent GI ADRs will be categorized as follows: 1 Day, 2 to <= 3 Days, 4 to <= 7 Days, 8 to <= 14 Days, 15 to <= 28 Days, and > 28 Days. Descriptive statistics will be also be provided.

Kaplan-Meier curves will be provided by cohort for time to first treatment-emergent GI ADR which is defined as AE start date minus the first UX007 dose date in UX007-CL202 plus 1 day. For the Kaplan-Meier curves, subjects will be censored at the end of study date or the data cutoff date, whichever is earlier. Time to first GI ADR in a subject is determined by the first GI ADR with non-missing start date of the subject. For the Rollover cohort, only UX007-CL202 data will be used and time plotted will be in weeks since the start of UX007-CL202.

8.7.2 Clinical Laboratory Parameters

8.7.2.1 Biomarkers & LC-FAOD Laboratory Measures

Biomarkers and relevant indicators of LC-FAOD are summarized in Table 8.7.1.
Blood samples will be collected at each clinic visit to assess relevant biomarkers and laboratory measures of LC-FAOD.

Table 8.7.1: 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

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each scheduled visit will be presented for the following laboratory parameters:

- Total and free plasma carnitine
- Plasma acylcarnitines
- Urine organic acids

Shift tables pairing each subject's baseline severity grade with the subject's highest post-baseline severity grade will be presented for the following parameters:

- Fasting serum glucose
- Triglycerides

- Creatine kinase (CK)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma glutamyl transpeptidase (GGT)

8.7.2.2 Clinical Laboratory Tests

Clinical laboratory values (in SI units) at each visit will be presented for the following laboratory parameters as listed in the following table:

Table 8.7.2: 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 %)	
	White blood cell (WBC) count	

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.

All valid assessments will be converted into SI units. In calculating change from baseline at each scheduled visit, only subjects with non-missing values at both baseline and the individual scheduled visit are included. All available data (i.e., scheduled and unscheduled assessments) are, however, used in identifying abnormalities in shift tables. Severity for the selected clinical laboratory parameters will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. CTCAE severity grades for selected laboratory parameters are listed in Appendix 11.

Hy's Law criteria will be applied against test results. Subjects with serum total bilirubin >2 x ULN and ALT or AST >3 x ULN will be identified and further reviewed to confirm there is no other reason to explain the lab increases before confirming Hy's law status. Results will be presented in shift tables. For Hy's Law, shift tables will be produced:

- Hy's Law negative at baseline, remaining Hy's Law negative throughout the study
- Hy's Law negative at baseline, becoming Hy's Law positive at any point during the study
- Hy's Law positive at baseline and Hy's Law negative throughout the study
- Hy's Law positive at baseline and Hy's Law positive at any point during the study

A data listing of all subjects who are Hy's Law positive will be produced.

Potential liver / muscle damage will be assessed based on clinical laboratory test results (and to differentiate it from possible muscle degradation) based on AST, ALT, GGT and CK test results shown below. All results will be listed, and subjects identified with potential toxicity stemming from liver, muscle or both will be flagged.

Table 8.7.3: Screen for Liver/Muscle Damage

AST and ALT	GGT ≤1.5 x ULN		GGT >1.5 x ULN	
	CK ≤ULN	CK >ULN	CK ≤ULN	CK >ULN
Both ≤1.5 x ULN	No Toxicity Flag	No Toxicity Flag	No Toxicity Flag	No Toxicity Flag
Either >1.5 x ULN	Neither	Muscle	Liver	Both

8.7.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, and pulse rate) and changes from baseline values at each scheduled visit and at the end of study will be presented.

8.7.4 Cardiac Safety – Echocardiograms

LVEF (% and Z-score) over time from echocardiograms will be summarized descriptively. Shift table for LVEF will be provided comparing baseline and post-baseline changes. Echocardiogram results will be provided in subject listing.

CTCAE severity grades for decreased ejection fraction are:

- Grade 1: Not available
- Grade 2: LVEF 50-40% or 10-19% drop from baseline
- Grade 3: LVEF 39-20% or >20% drop from baseline
- Grade 4: LVEF < 20%

8.7.5 Physical Examination

A complete physical examination is performed at the Baseline visit and at 6-month intervals (or Early Termination). Clinically significant changes from baseline to scheduled timepoints in physical examination will be reported on the adverse event CRF and thus not presented separately.

8.7.6 Pregnancy Test

Pregnancy test for females with child-bearing potential will be conducted at the scheduled study visit and the results will be provided in a listing.

9 LIST OF PLANNED TABLES, LISTINGS, AND FIGURES

List of planned tables, listings, and figures will be provided in a separate document.

10 REFERENCES

Kuczmarski, R, Ogden, C, Grummer-Strawn, L, Flegal, K, Guo, S, Wei, R, Mei, Z, Curtin, L, Roche, A, and Johnson, C. 2000. "CDC growth charts: United States." *Adv Data* (314):1-27.

11 APPENDICES

11.1 Summary of Efficacy Endpoints and Analysis

Table 11.1.1: Summary Table of UX007-CL202 Efficacy Endpoints and Analysis

Test / Instrument	Efficacy Endpoint	Analysis Population (Age criteria if applicable)	Type of Efficacy Analysis	Study Period (Visits selected if not all)	Statistical approach
MCE	Annualized event rate of MCE	Full analysis set	Primary	Period 1	Descriptive statistics
MCE	Annualized event rate of MCE by event type	Full analysis set	Secondary	Period 1	Descriptive statistics
	Annualized duration of MCE, and by event type	Full analysis set	Secondary	Period 1	Descriptive statistics
MCE	Annualized event rate of MCE and by event type; Annualized event rate of MCE and by event type;	UX007/trihep naïve subjects	Additional Efficacy Analyses	Period 1 & 3	Descriptive statistics & Comparison between pre- and post-UX007 MCE rates via paired t-test, Wilcoxon signed rank test, and NB
MCE	Annualized event rate of MCE and by event type; Annualized event rate of MCE and by event type;	UX007-CL201 rollover subjects	Integrated Analyses	Period 2 & 3	Descriptive statistics
ECHO	Change from baseline of EF, ventricle size, and SF	Full analysis set	Secondary	Period 1	Descriptive statistics
		UX007/trihep naïve subjects	Additional Efficacy Analyses	Period 1 (all visits)	Descriptive statistics & Paired t-test
		UX007-CL201 rollover subjects	Integrated Analyses	Period 2 (all visits)	Descriptive statistics

Test / Instrument	Efficacy Endpoint	Analysis Population (Age criteria if applicable)	Type of Efficacy Analysis	Study Period (Visits selected if not all)	Statistical approach
SF-12	Change from baseline –PCS, MCS, and individual domain	FAS-SF-12 (age ≥18)	Exploratory	Period 1 (all visits)	Descriptive statistics
		UX007/trihep naïve subjects in FAS-SF-12	Additional Efficacy Analysis	Period 1 (all visits)	Descriptive statistics & GEE
SF-10	Change from baseline –PHS and PSS	FAS (age ≥6 - <18)	Exploratory	Period 1	Descriptive statistics
		UX007/trihep naïve subjects in FAS-SF-10	Additional Efficacy Analysis	Period 1 (all visits)	Descriptive statistics & GEE
Clinical Biomarker	Change from baseline in serum creatine kinase, fasting serum glucose, ALT, AST, GGT	Full analysis set	Exploratory	Period 1 (all visits)	Descriptive statistics
		UX007/trihep naïve subjects	Additional Efficacy Analysis	Period 1 (all visits)	Descriptive statistics & Paired t-test
Growth Measurements	Change from baseline –Height, Weight, and head circumference (subjects ≤36 months of age only)	Full analysis set	Exploratory	Period 1	Descriptive statistics
		UX007-CL201 rollover subjects	Integrated Analyses	Period 2 (baseline, all visits)	Descriptive statistics

Note that sensitivity analyses of MCE endpoints are not included above but are summarized in Sections 8.5.4.2 and 8.5.5.2 for the Naïve Cohort and the CL201 Rollover Cohort, respectively.

11.2 Reference Values/Severity Grades

Table 11.2.1: CTCAE Severity Grades for Selected Laboratory Parameters

Laboratory Parameter	CTCAE severity grades
Fasting serum glucose	Grade 1: <LLN – 55 mg/dL; <LLN – 3.0 mmol/L Grade 2: <55 – 40 mg/dL; <3.0 – 2.2 mmol/L Grade 3: <40 – 30 mg/dL; <2.2 – 1.7 mmol/L Grade 4: < 30 mg/dL; <1.7 mmol/L
Triglycerides	Grade 1: 150 – 300 mg/dL; 1.71 – 3.42 mmol/L Grade 2: > 300 – 500 mg/dL; > 3.42 – 5.7 mmol/L Grade 3: >500 – 1000 mg/dL; > 5.7 – 11.4 mmol/L Grade 4: >1000 mg/dL; > 11.4 mmol/L

CK	Grade 1: >ULN to 2.5 x ULN Grade 2: >2.5 x ULN to 5 x ULN Grade 3: >5 x ULN to 10 x ULN Grade 4: >10 x ULN
ALT, AST	Grade 1: >ULN to 3.0 x ULN Grade 2: >3.0 x ULN to 5.0 x ULN Grade 3: >5.0 x ULN to 20.0 x ULN Grade 4: >20.0 x ULN
GGT	Grade 1: >ULN to 2.5 x ULN Grade 2: >2.5 x ULN to 5.0 x ULN Grade 3: >5.0 x ULN to 20.0 x ULN Grade 4: >20.0 x ULN

11.3 MedDRA Search Strategy for GI TEAEs and Hepatobiliary TEAEs

Adverse Events of Special Interest for ISS for UX007 LC-FAOD	**MedDRA Search Strategy (version 23.1)**
Gastrointestinal Disorders	Gastrointestinal Disorders SOC (all Preferred Terms)
Hepatobiliary Disorders	See table below

MedDRA search strategies for all AESIs are based on MedDRA version 23.1.

Table 11.3.1: Hepatobiliary Disorders

Hepatobiliary Disorders	**System Organ Class**	**Preferred Term**
	Hepatobiliary Disorders	Bile duct stenosis
	Hepatobiliary Disorders	Bile duct obstruction
	Hepatobiliary Disorders	Bile duct stone
	Hepatobiliary Disorders	Obstructive pancreatitis
	Hepatobiliary Disorders	Pancreatitis acute
	Hepatobiliary Disorders	Pancreatitis chronic
	Hepatobiliary Disorders	Pancreatitis relapsing
	Hepatobiliary Disorders	Cholecystitis
	Hepatobiliary Disorders	Cholecystitis acute
	Hepatobiliary Disorders	Cholecystitis chronic

Hepatobiliary Disorders	System Organ Class	Preferred Term
	Hepatobiliary Disorders	Cholelithiasis
	Hepatobiliary Disorders	Cholelithiasis obstructive
	Hepatobiliary Disorders	Pseudocholelithiasis
	Hepatobiliary Disorders	Gallbladder enlargement
	Hepatobiliary Disorders	Gallbladder obstruction
	Hepatobiliary Disorders	Hepatic failure
	Hepatobiliary Disorders	Acute hepatic failure
	Hepatobiliary Disorders	Subacute hepatic failure
	Hepatobiliary Disorders	Acute on Chronic hepatic failure
	Hepatobiliary Disorders	Chronic hepatic failure
	Hepatobiliary Disorders	Drug-induced liver injury
	Hepatobiliary Disorders	Mixed liver injury
	Hepatobiliary Disorders	Cholestasis
	Hepatobiliary Disorders	Hepatitis cholestatic
	Hepatobiliary Disorders	Jaundice
	Hepatobiliary Disorders	Jaundice cholestatic
	Hepatobiliary Disorders	Icterus
	Hepatobiliary Disorders	Ocular icterus
	Hepatobiliary Disorders	Ascites
	Hepatobiliary Disorders	Biliary ascites
	Hepatobiliary Disorders	Hepatic congestion
	Hepatobiliary Disorders	Hepatomegaly
	Hepatobiliary Disorders	Hepatosplenomegaly
	Hepatobiliary Disorders	Hepatic liver injury
	Hepatobiliary Disorders	Hepatic steato-fibrosis
	Hepatobiliary Disorders	Hepatic steatosis
	Hepatobiliary Disorders	Hepatocellular injury
	Hepatobiliary Disorders	Liver injury
	Hepatobiliary Disorders	Non-alcoholic fatty liver
	Hepatobiliary Disorders	Non-alcoholic steatohepatitis
	Hepatobiliary Disorders	Steatohepatitis
	Investigations	Alanine aminotransferase abnormal
	Investigations	Alanine aminotransferase increased
	Investigations	Aspartate aminotransferase abnormal
	Investigations	Aspartate aminotransferase increased
	Investigations	Blood bilirubin abnormal
	Investigations	Blood bilirubin increased
	Investigations	Bilirubin conjugated abnormal
	Investigations	Bilirubin conjugated increased
	Investigations	Gamma-glutamyltransferase abnormal
	Investigations	Gamma-glutamyltransferase increased
	Investigations	Hepatic enzyme abnormal
	Investigations	Hepatic enzyme increased
	Investigations	Transaminases abnormal
	Investigations	Transaminases increased
	Investigations	Amylase abnormal

Hepatobiliary Disorders	System Organ Class	Preferred Term
	Investigations	Blood amylase abnormal
	Investigations	Amylase increased
	Investigations	Blood amylase increased
	Investigations	Lipase abnormal
	Investigations	Lipase increased
	Investigations	Alkaline phosphatase abnormal
	Investigations	Blood alkaline phosphatase increased

11.4 Visit Windows

The visit window assigned for scheduled clinic visits at 6 months interval and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 11.4.1: Visit Time Windows

Analysis Visit	Scheduled Visit Day	Window
Baseline	1	Days ≤ 1
Month 6	183	[169, 197]
Month 12	365	[351, 379]
Month 18	548	[534, 562]
Month 24	730	[716,744]
Month 30	913	[899, 927]
Month 36	1096	[1082, 1110]
Month 42	1278	[1264, 1292]
Month 48	1461	[1447,1475]
Month 54	1644	[1630, 1658]
Month 60	1826	[1812, 1840]
Month 66	2009	[1995, 2023]
Month 72	2192	[2178, 2206]
Month 84	2557	[2543, 2571]

11.5 Schedule of Events

Table 11.5.1: 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
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]		

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.

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

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.

Medical history including major medical illness, diagnoses and surgeries will be collected for all subjects not previously enrolled in UX007-CL201. LCFAOD 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.

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

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.

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.

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.

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.

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.

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.

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).

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 Followup 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.

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.