An Open-label Extension Study to Assess the Long-term Safety and Efficacy of UX007 in Subjects with Glucose Transporter Type 1 Deficiency Syndrome

Protocol Number:	**UX007G-CL202**
Original Protocol:	**26 February 2015**
Amendment 1:	**02 June 2016**
Amendment 2:	**28 July 2016**
Amendment 3:	**20 September 2017**

Investigational Product: UX007 (triheptanoin)

Indication: Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

IND Number: 118855

EudraCT Number: 2015-000389-69

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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

UX007G-CL202 Amendment 1

02 June 2016

The original Protocol UX007G-CL202 has been modified by Amendment 1 to incorporate a number of changes based on additional information acquired since the beginning of the study, and from feedback provided by clinical investigators involved in the study. The major changes impacting study design, conduct, and analyses are summarized below; additional minor changes have also been made for consistency, clarity, and updated information but are not included in this summary.

1. The number of study sites was changed from "approximately 12" to "up to 16". The number of subjects planned was approximated at 40 subjects from the UX007-CL201 study and additional subjects who participated in qualified ISTs.

   Rationale: The change clarifies the sample size and provides a more accurate estimate of the number of investigational sites.

2. Edited Inclusion Criterion #2 to state that all subjects at least 1 year of age at time of informed consent are eligible for participation in this study.

   Rationale: This change was made for clarification.

3. Inclusion Criterion #3 was modified to remove the 3 month window following completion of the feeder study.

   Rationale: The change allows more flexibility to the participant.

4. Inclusion Criterion #6 (and corresponding information in Section 7.5.4.5) regarding pregnancy testing and contraception was split into 2 separate inclusion criteria 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.

Rationale: The change provides clarification of study requirements.

5. Exclusion Criterion #1 was removed thereby eliminating specification of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels.

   Rationale: To date, elevated liver enzymes have not been observed in UX007G studies. Therefore, it is not considered a likely safety concern that rises to the need for an exclusion criterion. Laboratory samples for serum chemistry will be taken at every clinic visit to monitor for any significant laboratory changes in study subjects.

6. Removed Exclusion Criterion # 2 thereby removing specific requirements regarding percent of daily fat intake.

   Rationale: Change was made to allow individual investigators to directly manage subject diet as appropriate.

7. Exclusion Criterion #8 was modified to remove diabetes mellitus as an exclusionary condition.

   Rationale: The change provides additional flexibility for the Investigator. The presence of diabetes in the subject population treated with UX007 is not likely be a safety concern.

8. The first secondary objective was changed to 'Evaluate the long-term effect of UX007 efficacy on seizures associated with Glut1 DS'. This change affects multiple sections of the protocol related to statistical evaluations and analyses.

   Rationale: This change was made for clarification and to be more in line with the objectives of the feeder study, UX007G-CL201.

9. The Stopping Rules (Section 7.3.3.1) were modified to correct notification procedures should unexpected and study drug-related SAEs occur, or if the study is restarted.

   Rationale: The change reflects current sponsor procedures and aligns with Regulatory requirements.

10. Section 7.4.1 was modified to specify UX007 **should** be mixed with food; the requirement to never administer directly as the oil was removed. In addition, the language around dose level was modified to recognize and allow the subject to remain on current dose, which may be **different** (i.e. lower or higher) than 35% of total daily caloric intake.

Rationale: The change provides more dosing flexibility and more realistic expectations for continued dosing long-term extension treatment.

11. Section 7.4.4.1 was modified to state "*The planned duration of treatment in this study is 3 years, or until one of the following occurs: the* ***subject*** *withdraws consent* ***or*** ~~*, the patient*~~ *is discontinued from the study at the discretion of the Investigator or Ultragenyx; the study is terminated, or until* ~~*UX007 becomes commercially available*~~ ***commercial availability of study drug in a subject's region, whichever occurs first***.". Due to this change, specific references to a "3-year Treatment Extension" were changed to "Treatment Extension Period" throughout the protocol.

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

12. Updated Section 7.4.6.1 to remove valproate, MCT oil, KetoCal or other KD supplements, or other prescribed diet plan as prohibited medications; pancreatic lipase inhibitors was added to the list of prohibited medications. Prohibited medications are now specified in Exclusion Criteria #4 and 5. Prescribed diet plans are allowed provided details are captured in the diet diary or concomitant medications as appropriate (Section 7.4.6.2)

    Rationale: After a review of the literature on valproate, triheptanoin, and Glut1 DS, it did not appear that the addition of triheptanoin to valproate posed significant risk to those patients, due to the low concentrations of VPA in brain tissue; therefore, the Sponsor is allowing subjects stable on valproate into the study (Adkison et al. 1995).The removal of dietary or dietary supplement restrictions provides additional flexibility for the investigator in managing the patient during this long-term extension study. Pancreatic lipase inhibitors were included in the list of prohibited medications because in vitro studies have shown that pancreatic lipases hydrolyze triheptanoin into free fatty acids and glycerol; therefore inhibitors of pancreatic lipases (e.g., orlistat) should be avoided while taking UX007.

13. The frequency of overnight EEG assessments (Section 7.5.2.1.2 and Table 2.1) was increased. Interictal epileptiform discharges will not be examined as an efficacy variable.

    Rationale: Feeder study UX007G-CL201 was previously amended to include subjects who primarily experience absence seizures. Overnight EEG is an objective measure of seizures and diaries may not adequately capture the frequency of these events. Therefore, additional overnight EEG assessments will be conducted to capture these events and therefore increase the quality of data pertaining to maintenance of effect in these patients. However, the frequency of interictal epileptiform discharges is unlikely to yield informative data in this pre-treated study population and has been removed as an efficacy variable.

14. Efficacy assessments including Cambridge Neuropsychological Test Automated Battery (CANTAB; Section 7.5.2.2.1), Six Minute Walk Test and associated

paroxysmal exertional dyskinesia (6MWT/PED; Section 7.5.2.3), the Clinical Global Impression Scales (CGI; Section 7.5.2.4.1), and the Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT; Section 7.5.2.4.3) were removed from the study. Study objectives and endpoints (Section 6) were updated to reflect this change. The Short Form Health Surveys (SF-10 and SF-12v2) will not be performed if no pre-treatment baseline data is available from feeder study.

Rationale: Long-term efficacy data using the CANTAB, 6MWT, CGI, and PEDI-CAT assessments will be available from the feeder study, UX007-CL201; continuing to assess in this open-label, single-arm extension is unlikely to yield informative data. Assessing SF-10/SF-12v2 is unlikely to provide useful information if no pre-treatment baseline data are available from the feeder study. Removal of these assessments will reduce the burden to patients and investigational sites participating in the study.

15. Beta-ketopentanoic acid (BKP) will no longer be assayed (Section 7.5.3 Drug Concentration Measurements).

    Rationale: Assay methodology is not available to reliably evaluate this UX007 metabolite.

16. Physical examination of the genitourinary system is no longer specified (Section 7.5.4.3)

    Rationale: The genitourinary system is not directly impacted by study drug or indication.

17. Section 7.5.4.9 was modified to remove the requirement for a 3-day diet diary prior to the Baseline Visit. Daily caloric intake and UX007 dose will be determined by interview with the dietitian at the Baseline Visit.

    Rationale: Participants may enter the study at the Baseline Visit (following completion of a feeder study); signing of informed consent and initiation of treatment may occur on the same day and completion of a 3-day diet diary would not be possible.

18. The following changes were made to Section 7.6 (Statistical Methods):

    - Separate safety analysis and intent-to-treat populations were replaced with one analysis set to include all subjects who receive at least one dose of UX007 during the study.

    - The reduction in frequency of seizures was removed as an efficacy analysis and replaced with a list of efficacy measures to be assessed.

    Rationale: This is a single arm study and the analyses will include all subjects enrolled who receive at least one dose of UX007.

19. A coordinating investigator will be named for this multicenter study (Section 8.2 Investigators and Study Administrative Structure).

20. 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.

    Rationale: This administrative change has been made to reflect upcoming changes to EU clinical trial regulations and current regulations by other health authorities.

21. Updated Section 8.5.4 (Adverse Event Reporting)

    Rationale: Updated to match the sponsor's current safety reporting procedures.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007G-CL202 Amendment 2

28 July 2016

Protocol UX007G-CL202 Amendment 1 has been modified by Amendment 2 to incorporate the following three changes.

1. The list of examples of highly effective contraception methods was updated in Section 7.5.4.5.

   Rationale: This change was requested by Regulatory Authorities to better clarify examples of highly effective contraception methods.

2. A Safety Follow-up Phone Call was added to the schedule of events and relevant sections of the protocol (e.g., Sections 7.4.4.1 and 7.5.1).

   Rationale: This change was requested by Regulatory Authorities to standardize how adverse event information is collected 30 days following the last dose of UX007.

3. The synopsis (Study Duration) and Sections 7.1 and 7.5.1 were updated to clarify that the end of study is the last subject's Safety Follow-up Phone Call.

   Rationale: This change was requested by Regulatory Authorities to clarify the end of study.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007G-CL202 Amendment 3

20 September 2017

Protocol UX007G-CL202 Amendment 2 has been modified by Amendment 3 to incorporate the following changes.

1. Phone calls were added 3 months between study site visits during Years 2 and 3 (as described in Table 2.1).
   Rationale: Phone calls at Visits 6, 8, 10, and 12 were added to provide additional safety reporting, including adverse events and concomitant medication updates, and to inquire about study drug consumption and remaining supply; in lieu of the phone call, subjects may visit the clinic at the study site's discretion.
2. Optional study site visits were added 3 months between study site visits during Years 2 and 3 (as described in Table 2.1).
   Rationale: Optional study site visits were added for Visits 6, 8, 10, and 12 to allow subjects to attain study drug as needed at the request of the Investigator.
2. Additional language has been added throughout the protocol and within the Study Schema (Figure 2.1 and Figure 7.1.1) to specify that, at the discretion of the Sponsor, additional subjects who participated in other clinical studies, ISTs, or expanded access/compassionate use treatment programs may be eligible for inclusion in UX007G-CL202.
   Rationale: This addition is a clarification to include subjects already eligible for enrollment according to Inclusion Criterion #3 to ensure consistency throughout the study protocol.
4. The window of time to draw blood for UX007 metabolites has been expanded from 90 min (+/- 5 min) to 90 min (+/- 10 min) following consumption of food and study drug, as specified within Footnote 6 in the Schedule of Events (Table 2.1).
   Rationale: This change was made to reduce site burden and is not expected to affect the UX007 metabolite measurements.

2 SYNOPSIS

TITLE OF STUDY:

An Open-label Extension Study to Assess the Long-term Safety and Efficacy of UX007 in Subjects with Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

PROTOCOL NUMBER:

UX007G-CL202

STUDY SITES:

Up to 16 sites globally

PHASE OF DEVELOPMENT:

Phase 2

RATIONALE:

Glut1 DS is a rare, severely debilitating disease characterized by seizures, developmental delay, and movement disorder. Glut1 DS is caused by a mutation in the *SLC2A1* gene encoding the Glut1 protein responsible for transporting glucose across the blood-brain barrier. Because glucose is the primary source of energy for the brain, this disorder results in a chronic state of energy deficiency in the brain. Current therapy consists of ketogenic diet (KD) and antiepileptic drugs (AEDs) for the treatment of seizures. Because of the difficulties in maintaining the KD, some patients are not able to fully comply with or tolerate the diet; these patients need an alternative therapy for Glut1 DS.

UX007 (triheptanoin) is a triglyceride of medium, odd-carbon chain (C7) fatty acids. The rationale for UX007 in Glut1 DS is that: (1) triheptanoin is metabolized to heptanoate and C4 and C5 ketone bodies, providing an alternative energy source to the brain, (2) triheptanoin provides anaplerotic substrates to resupply intermediates of the tricarboxylic acid (TCA) cycle, and (3) triheptanoin can support gluconeogenesis in the brain.

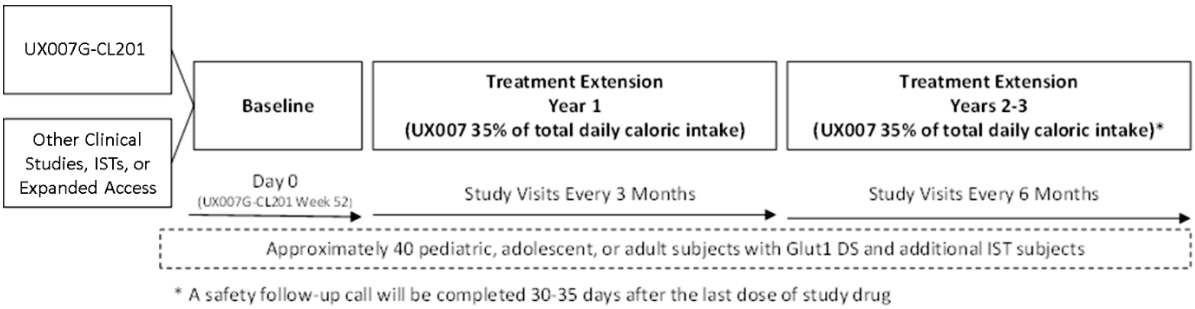
A Phase 2 study (UX007G-CL201) is ongoing to assess the safety and efficacy of UX007 in reducing the frequency of seizures in Glut1 DS patients. Investigator-sponsored trials (ISTs) and other treatment programs are also evaluating UX007/triheptanoin as a treatment for Glut1 DS. This open-label long-term safety and efficacy study will provide an opportunity for Glut1 DS patients to be treated with UX007 for up to 3 years, or until one of the following occurs: the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, the study is terminated, or until commercial availability of study drug in a subject's region, whichever occurs first. The study is designed to obtain long-term safety information and evaluate maintenance of efficacy in a pediatric and adult Glut1 DS population.

STUDY DESIGN AND METHODOLOGY:

UX007G-CL202 is an open-label, single-arm, multicenter extension study to assess the long-term safety and efficacy of UX007 in Glut1 DS. The study will enroll approximately 40 pediatric, adolescent, and adult Glut1 DS subjects who have completed the UX007G-CL201 study and, at the discretion of the Sponsor, additional subjects who participated in other clinical studies, ISTs, or expanded

access/compassionate use treatment programs. Figure 2.1 provides a schematic of the overall study design.

Figure 2.1: UX007G-CL202 Study Schema



For continuing UX007G-CL201 subjects, the Week 52 visit of that study may be conducted in conjunction with the Baseline Visit for this study to avoid duplication of assessments. Following the Baseline Visit, subjects will return to the study site at 3-month intervals from Baseline during Year 1 of the Treatment Extension, and 6-month intervals from Baseline during Years 2 and 3. Phone calls will take place 3-months between scheduled study site visits during Years 2 and 3 to collect adverse events and concomitant medications updates and to inquire about study drug consumption and remaining supply; in lieu of the phone call, subjects may visit the clinic at the study site's discretion. Additionally, optional study site visits may occur 3-months between scheduled study site visits during Years 2 and 3 to allow subjects to attain study drug as needed at the request of the Investigator. 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. Subjects will record seizure occurrence in a diary throughout the study; diet diaries will also be completed by the subject for the 3 days preceding each scheduled visit after the Baseline Visit. Overnight electroencephalograms (EEG) will be conducted in all subjects to monitor absence seizures. Safety assessments and a clinical neurological evaluation will further enable the characterization of long-term safety and maintenance of effect. Metabolites of UX007 in the blood will also be assayed.

UX007 dosing will be targeted at 35% of total daily caloric intake throughout the study. Subjects receiving a different dose of UX007 at study entry may continue treatment at the current established dose. If a subject has been off UX007 treatment for > 1 month, the dose may be titrated at the discretion of the investigator. Enrolled subjects are able to maintain standard of care treatment with up to 3 AEDs throughout the duration of the study.

OBJECTIVES:

The primary objective of the study is to:

- Evaluate the long-term safety of UX007 in Glut1 DS subjects

The secondary objectives of the study are to:

- Evaluate the long-term effect of UX007 efficacy on seizures associated with Glut1 DS
- Evaluate the long-term effect of UX007 on health-related quality of life related to Glut1 DS

ENDPOINTS:

The primary endpoint of the study is:

- Frequency of adverse events (AE) and serious adverse events (SAE) assessed as related to study drug over the Treatment Extension Period

General secondary endpoints of the study are:

- Frequency of seizures over the Treatment Extension Period
- Measures of neurological function over the Treatment Extension Period
- Health-related quality of life over the Treatment Extension Period

NUMBER OF SUBJECTS PLANNED:
The study will enroll approximately 40 pediatric, adolescent, and adult subjects who have completed the UX007G-CL201 study and, at the discretion of the Sponsor, additional subjects who participated in other clinical studies, ISTs, or expanded access/compassionate use treatment programs.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

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

1) Diagnosis of Glut1 DS as indicated by cerebrospinal fluid glucose concentration, erythrocyte 3-O-methyl-D-glucose uptake assay, or molecular genetic testing obtained from medical records.
2) Males and females, aged at least 1 year at the time of informed consent
3) Completion of UX007G-CL201 study (NCT01993186). Glut1 DS patients who received UX007/triheptanoin treatment as part of other clinical studies, ISTs, or expanded access/compassionate use treatment programs may be eligible at the discretion of the sponsor.
4) Provide written informed consent or verbal assent (if possible) with written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures
5) Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, and comply with accurate completion of the seizure diary
6) 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.

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) Any known hypersensitivity to triheptanoin that, in the judgment of the investigator, places the subject at increased risk for adverse effects
2) History of, or current suicidal ideation, behavior and/or attempts
3) Pregnant and/or breastfeeding an infant
4) Unwilling or unable to discontinue use of a prohibited medication (i.e. barbiturates, pancreatic lipase inhibitors) or other substance that may confound study objectives. Use of up to 3 concomitant AEDs is allowed, provided dose has been stable at least 14 days prior to Baseline.
5) Use of any investigational product, drug or supplement (other than UX007) within 30 days prior to Baseline, or at any time during the study
6) Has a condition of such severity and acuity, in the opinion of the investigator, that it warrants immediate surgical intervention or other treatment
7) Has a concurrent disease or condition, or laboratory abnormality that, in the view of the investigator, places the subject at high risk of poor treatment compliance or of not completing the study, or would interfere with study participation or introduce additional safety concerns (e.g. other concurrent neurological or psychiatric disorders)

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION:

UX007 (triheptanoin) is a liquid, intended for oral (PO) administration. UX007 is a colorless to yellow oil supplied in 1 L round, translucent high-density polyethylene (HDPE) or 1 L round amber-colored glass bottles.

UX007 dosing will be targeted and/or maintained at 35% of total daily caloric intake. If a subject has been receiving a different dose of UX007, the subject may be maintained on the UX007 dose that provided the maximum improvement in clinical status with acceptable tolerability, and continued on this dose for the duration of the study. A subject may have been off UX007 treatment prior to enrollment; in these cases, the UX007 dose may be titrated at the discretion of the investigator.

UX007 should be mixed with food (or formula, as appropriate) and administered PO or by gastronomy tube at least four times per day (breakfast, lunch, dinner, and before bed). The dose may be divided into smaller more frequent doses with food as needed.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

The study is a single-arm, open-label study. All subjects will be on active treatment; no reference therapy or placebo will be administered.

DURATION OF TREATMENT:

The planned duration of treatment in this study is 3 years, or until one of the following occurs: the patient withdraws consent, the patient is discontinued from the study at the discretion of the Investigator or Ultragenyx, the study is terminated, or until commercial availability of study drug in a subject's region, whichever occurs first. 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.

CRITERIA FOR EVALUATION:

Safety Assessments

Adverse Events and Serious Adverse Events: Incidence, frequency, severity, and relatedness of AEs and SAEs, including clinically significant changes in the following safety variables:

- Vital signs and weight
- Physical examination
- Clinical laboratory evaluations
- Pregnancy testing
- Suicidal ideation and behavior assessments
- Concomitant medications

Efficacy Assessments*

Seizures

- Seizure Diary: Observable seizures recorded via patient-reported diary. Observable seizures include: Generalized Tonic-Clonic, Generalized Tonic, Generalized Clonic, Generalized Atonic, Partial/Focal with Secondary Generalization, Myoclonic, Myoclonic Atonic, Myoclonic Tonic, Complex Partial/Focal, and Simple Partial/Focal Motor. Observable absence seizures will also be recorded, although the primary method of assessing them will be by EEG
- Electroencephalogram: Seizures detected by EEG, including absence.

Neurological Function and Development

- Columbia Neurological Score: Neurological findings in 12 domains quantitated to produce a total score ranging from 0-76

Health-related Quality of Life

- Short-Form Health Surveys (SF-10 for Children OR SF-12v2): Quality of life as measured by subject or caregiverreported- physical and mental health status

* The Investigator may use clinical judgment in deciding whether to administer certain assessments to subjects based on age, development, and cognitive ability, as appropriate. The SF-10/SF-12v2 will not be performed if no pre-treatment baseline is available from feeder study (e.g. subjects entering from other clinical studies, ISTs, or expanded access/compassionate use treatment programs or subjects from UX007G-CL201 who were too young or compromised at pre-treatment Baseline).

UX007 Metabolites:

- Plasma levels of UX007 metabolites

STATISTICAL METHODS:

General Principles:

The statistical analyses will be reported using summary tables, figures, and data listings. All analyses and tabulations will be performed using SAS®. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories. For time-to-event data, the Kaplan-Meier estimates will be computed and plotted. Graphical data displays may also be used to summarize the data. All raw data obtained from the CRFs as well as any derived data will be included in data listings. For certain data collected over time, the Generalized Estimating Equation (GEE) may be used as the marginal model approach.

Tests of treatment effects will be conducted at a one-sided alpha level of 0.05 and/or one-sided 95% confidence interval where possible. Each secondary endpoint will be tested independently at one-sided alpha=0.05. No adjustments for multiple comparisons will be performed. The statistical method employed for the analysis of each assessment and detailed procedures for handling missing, unused, or spurious data, will be defined in the statistical analysis plan. Analyses may be performed at any time during the study at the discretion of the Sponsor. Unblinding is not required during analysis since the study is open-label.

Safety Analysis:

The primary safety analysis will evaluate the incidence and frequency of AEs and SAEs, including clinically significant changes in safety parameters. The incidence and frequency of AEs will be summarized by System Organ Class and Preferred Term, relationship to study drug, and severity. No statistical significance will be assessed.

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 after study drug administration will be presented for each clinical laboratory measurement.

Changes in findings from physical examinations will be tabulated and listed for each subject by examination category. If there are examination findings that change in more than one subject, these will be tabulated in a separate table and expressed as the number of subjects with the change out of the total.

Descriptive statistics of temperature, pulse, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized. The percentage of subjects with values beyond clinically important limits will be summarized.

Efficacy Analysis:

The efficacy analyses are primarily focused on seizures and alternative domains of Glut1 DS disease to assess the breadth of treatment effect of UX007. The analyses of secondary endpoints will evaluate maintenance of effect for each efficacy variable throughout the Treatment Extension Period.

Table 2.1: Schedule of Events*

VISIT NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13	SAFETY FOLLOW UP [14]
VISIT TYPE	Clinic	Clinic	Clinic	Clinic	Clinic	PC	Clinic	PC	Clinic	PC	Clinic	PC	Clinic	PC
MONTH [1]	0	3	6	9	12	15	18	21	24	27	30	33	36/ET	
Informed Consent [2]	X													
Inclusion/Exclusion Criteria	X													
Medical History [3]	X													
Seizure incidence (diary review)		X	X	X	X		X		X		X		X	
Overnight EEG [4]	X	X	X	X	X		X		X				X	
Columbia Neurological Score	X		X		X				X				X	
SF-10 or SF-12v2 (age-appropriate instrument) [5]	X		X		X		X		X		X		X	
UX007 Metabolites[6]	X		X		X		X		X		X		X	
Vital Signs & Weight [7]	X	X	X	X	X		X		X		X		X	
Physical Examination [8]	X		X		X		X		X		X		X	
Clinical Laboratory Tests [9]	X	X	X	X	X		X		X		X		X	
Urine Pregnancy Test (if applicable)	X	X	X	X	X		X		X		X		X	
Suicidal Ideation & Behavior Assessment [10]	X	X	X	X	X		X		X		X		X	

VISIT NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13	SAFETY FOLLOW UP [14]
VISIT TYPE	Clinic	Clinic	Clinic	Clinic	Clinic	PC	Clinic	PC	Clinic	PC	Clinic	PC	Clinic	PC
MONTH [1]	0	3	6	9	12	15	18	21	24	27	30	33	36/ET	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietitian Consultation & Diet Diary [11]	X	X	X	X	X		X		X		X		X	
Dispense Study Drug [12]	X	X	X	X	X	X[12]	X	X[12]	X	X[12]	X	X[12]		
Treatment Compliance & Accountability [13]		X	X	X	X	X[13]	X	X[13]	X	X[13]	X	X[13]	X	

*Refer to the Study Reference Manual for a recommended schedule of the assessments during the 1-day and 2-day visits. The Investigator may use clinical judgment in deciding whether to administer certain assessments to subjects based on age, development, and cognitive ability, as appropriate. The SF-10/SF-12v2 will not be performed if no pre-treatment baseline is available from feeder study (e.g. subjects entering from other clinical studies, ISTs, or expanded access/compassionate use treatment programs or subjects from UX007G-CL201 who were too young or compromised at pre-treatment Baseline).

[1] The Baseline Visit may occur in conjunction with the last scheduled visit from study UX007G-CL201 to avoid duplication of assessments. If the time elapsed between the last UX007G-CL201 study visit and the Baseline Visit for this study is > 1 month, the full panel of Baseline Visit assessments must be completed. Subjects will return to the clinic at 3-month intervals from Baseline during Treatment Extension Year 1 (± 1 week), and 6-month intervals from Baseline during Years 2 and 3 (± 2 weeks). Phone calls will take place 3-months between scheduled study site visits during Years 2 and 3 (Visits 6, 8, 10, and 12) to collect adverse events and concomitant medications updates and to inquire about study drug consumption and remaining supply; in lieu of the phone call, subjects may visit the clinic at the study site's discretion. Additionally, optional study site visits may occur 3-months between scheduled study site visits during Years 2 and 3 to allow subjects to attain study drug as needed at the request of the Investigator.

[2] Minors who reach legal age during the course of the study must provide written informed consent when eligible.

[3] Medical history includes subject demographics, triheptanoin treatment history, and Glut1 DS diagnosis, and will be collected only for subjects not previously enrolled in UX007G-CL201.

[4] A 2-day visit is required to complete the overnight EEG.

[5] If a subject is under 5 years of age at informed consent, the SF-10 will not be administered during the Extension study. If a subject turns 18 years of age during the study, the SF-12v2 will be administered beginning at the next study visit.

[6] Blood samples for UX007 metabolites will be drawn approximately 90 min (+/- 10 min) following consumption of food and study drug.
[7] Vital sign measurements consist of seated systolic/diastolic blood pressure (millimeters of mercury), heart rate (beats per minute), respiration rate (breaths per minute), and temperature in degrees Celsius (°C). Vitals to be obtained at the beginning of each visit before any additional assessments are completed.
[8] Physical examinations include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, musculoskeletal, and neurologic systems.
[9] Clinical laboratory tests include standard serum chemistry, hematology, and urinalysis. Fasting is not required.
[10] The Columbia Suicide Severity Rating Scale (C-SSRS) baseline questionnaire will be administered on the initial visit; the Since Last Visit questionnaire will be administered at all subsequent visits.
[11] At the Baseline visit, an interview with the study dietitian will establish daily caloric intake and UX007 dose. Subjects and/or caregivers are required to maintain a record of the subject's daily diet in a diary for the 3 days prior to each subsequent visit. The diet diary will be reviewed by study personnel at each visit to the clinic. The dietitian may telephone subjects and/or caregivers, as needed, to provide dietary advice and support.
[12] A subject may have been off UX007 treatment prior to enrollment; in these cases, UX007 may be titrated per discretion of the investigator. Study drug may be dispensed at Visits 6, 8, 10, and 12 to subjects who make optional study site visits to attain study drug as needed at the request of the Investigator.
[13] Refer to Pharmacy Manual for instructions on return of empty and opened study drug bottles. Phone calls at Visits 6, 8, 10, and 12 will inquire about study drug consumption and remaining supply; in lieu of a phone call, subjects may also visit the study site at the study site's discretion.
[14] Safety Follow-up Phone Call to 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 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. Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
APBD	adult polyglucosan body disease
AST	aspartate aminotransferase
BHB	beta-hydroxybutyrate
BHP	beta-hydroxypentanoic acid
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CNS	Columbia Neurological Score
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
EC	Ethics Committee
EDC	electronic data capture
EEG	electroencephalogram
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAOD	fatty acid oxidation disorders
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
GLP	Good Laboratory Practice
Glut1	glucose transporter type 1
Glut1 DS	glucose transporter type 1 deficiency syndrome
GMP	Good Manufacturing Practice
GSD II	glycogen storage disease type II
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IST	Investigator-sponsored Trial

ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
KD	ketogenic diet
LC-FAOD	long-chain fatty acid oxidation disorders
L	Litre
MCS	Mental health component score
MCT	medium chain triglyceride
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
PC	phone call
PCS	Physical health component score
PHS-10	physical summary score
PK	pharmacokinetic
PO	oral, by mouth, *per os*
PSS-10	psychosocial summary score
PT	Preferred Term
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SF-10	Short Form 10 Health Survey for Children
SF-12v2	Medical Outcomes Study 12-item Short-Form Health Survey for Adults (version 2)
SOC	System Organ Class
TCA	tricarboxylic acid
TK	toxicokinetic
US	United States
UX007	Investigational Product/study drug, triheptanoin
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

Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS) is a rare, severely debilitating disease characterized by seizures, developmental delay, and movement disorders (Pearson et al. 2013). Current treatment consists of a ketogenic diet (KD) to provide an alternative energy source to glucose (Pong et al. 2012), (Pearson et al. 2013) and antiepileptic drugs (AEDs). Because of the difficulties in maintaining a KD, some patients are not able to comply with or tolerate the diet. Furthermore, the seizures due to Glut1 DS are often refractory to AEDs and are most prominent in the pediatric population. These patients represent the subgroup of Glut1 DS patients who are most in need of an alternative therapy.

UX007 (triheptanoin) is a triglyceride of medium, odd-carbon chain (C7) fatty acid. The rationale for UX007 in Glut1 DS is that triheptanoin metabolites may provide an alternative energy source and support gluconeogenesis for the brain, and/or provide anaplerotic substrates to resupply tricarboxylic acid (TCA) cycle intermediates (Deng et al. 2009), (Kinman et al. 2006), (Marin-Valencia et al. 2013).

A Phase 2 study (UX007G-CL201) is ongoing to assess the safety and efficacy of UX007 in reducing the frequency of seizures in Glut1 DS patients. Investigator-sponsored trials (ISTs) or treatment programs are also evaluating UX007/triheptanoin as a treatment for Glut1 DS. This open-label long-term safety and efficacy study will provide an opportunity for Glut1 DS patients to be treated with UX007 for up to 3 years, or until one of the following occurs: the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, the study is terminated, or until commercial availability of study drug in a subject's region, whichever occurs first. The study is designed to obtain long-term safety information and evaluate maintenance of efficacy in a pediatric and adult Glut1 DS population.

5.1 Overview of Glucose Transporter Type 1 Deficiency Syndrome

Glut1 DS is a rare disease with an estimated birth incidence of 1:90,000 (Coman et al. 2006). This birth incidence translates to an estimated prevalence of ~ 8,500 in the US and Europe. Glut1 DS is caused by a mutation in the solute carrier family 2, member 1(*SLC2A1)* gene, which encodes Glut1. This protein transports glucose from blood into the brain. Because glucose is the primary source of energy for the brain, this disorder results in a chronic state of energy deficiency in the brain. Most commonly Glut1 DS is inherited in an autosomal dominant manner; approximately ~90 % of individuals with autosomal dominant Glut1 DS have a *de novo* heterozygous mutation in *SLC2A1*, and about 10% have a clinically-affected parent (Wang et al. 1993-2015). Autosomal recessive transmission has also been described in rare cases.

Glut1 DS is a severely debilitating disease characterized by seizures, developmental delay, and movement disorder (Pearson et al. 2013). Neurological symptoms in Glut1 DS fall into 3 domains: (1) epilepsy, (2) cognitive/behavioral disturbances, and (3) movement disorders. The classic phenotype is a developmental encephalopathy encompassing all 3 domains.

Seizures are present in approximately 90% of Glut1 DS patients and usually present in early infancy.

The laboratory hallmark of Glut1 DS is a low cerebrospinal fluid glucose concentration (<60 mg/dL or 3.3 mmol/L in all cases reported to date; <40 mg/dL or 2.2 mmol/L in the majority of cases). Decreased 3-O-methyl-D-glucose uptake in erythrocytes is observed and is abnormally low in almost all suspected cases of Glut1 DS (Wang et al. 1993-2015). Molecular genetic testing may also be used to detect pathogenic *SLC2A1* variants, however some reports estimate approximately 20% to 30% do not carry mutations in *SLC2A1* (Klepper et al. 2007), (Klepper 2008), (Verrotti et al. 2012).

There are currently no approved treatments specific to Glut1 DS. Seizures are typically refractory to conventional AED treatment (Pong et al. 2012). Reports suggest a KD is effective for the seizures of Glut1 DS by generating ketone bodies that provide an alternative energy source to glucose (Pong et al. 2012), (Pearson et al. 2013). However, KD is difficult to tolerate and some patients are not compliant with or are otherwise not on the diet. There exists a significant unmet medical need in the subset of patients who are not on KD, and the proposed clinical development plan targets this specific subset of patients.

5.2 Brief Overview of UX007 Development

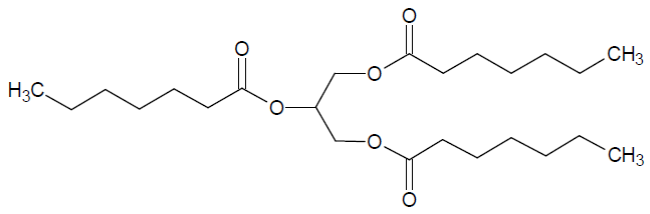
A brief overview of existing information on UX007 (triheptanoin) is provided below; a comprehensive review of the data is contained in the Investigator's Brochure (IB) provided by Ultragenyx Pharmaceutical Inc. (Ultragenyx), which should be reviewed prior to initiating the study.

5.2.1 Brief Description of the Investigational Product

Triheptanoin is a triglyceride composed of three heptanoate (C7 fatty acid) esters. 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:



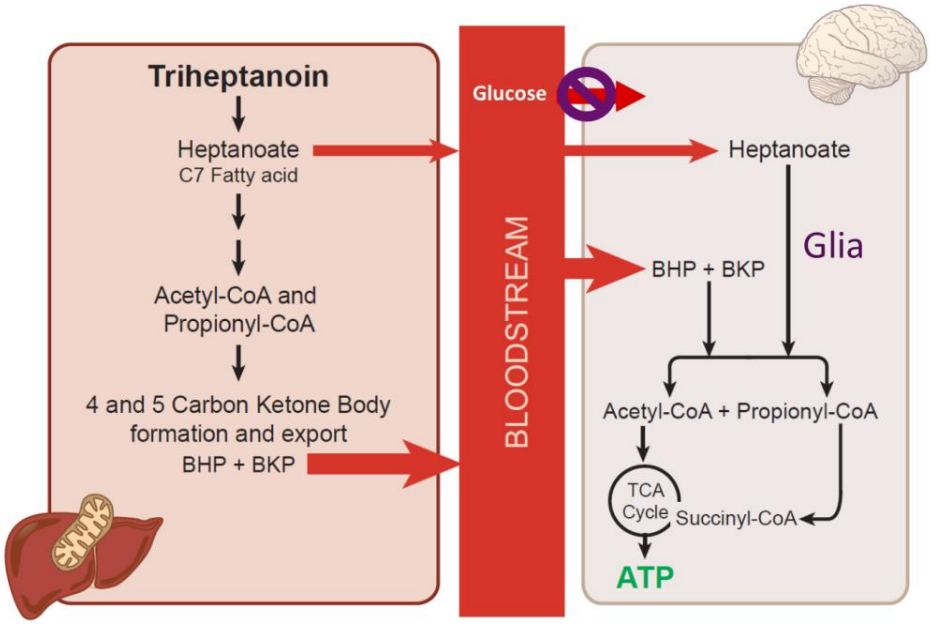
UX007 (triheptanoin) is a liquid, intended for oral (PO) administration. One thousand grams (1025 ± 25 g) of neat triheptanoin drug substance is filled into 1 Litre (L), high density

polyethylene (HDPE) or round, amber-colored glass bottles. UX007 is manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations.

5.2.1.1 Mechanism of Action in Glut1 DS

UX007 (triheptanoin) is metabolized to heptanoate, which in turn is further metabolized to 4- and 5-carbon ketone bodies. These metabolites bypass the Glut1 transporter to cross the blood-brain-barrier via the monocarboxylate transporter or potentially by mass action diffusion for heptanoate, and provide an alternative energy source to the brain (Figure 5.2.1.1.1). Once in the brain, the metabolites may be further metabolized by both glia and neurons to generate effective compounds to deliver energy. These metabolites also have the ability to provide propionyl-CoA in order to resupply intermediates of the TCA cycle (i.e. anaplerosis) within the brain as well as support gluconeogenesis and glycogen production.

Figure 5.2.1.1.1: Proposed mechanism of UX007 action in Glut1 DS



5.2.2 Nonclinical Studies

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. Furthermore, triheptanoin has been found to be effective in 4 animal models of epilepsy, similar to that of other AEDs (Borges et al. 2012), (Willis et al. 2010), (Thomas et al. 2012), (Kim et al. 2013). Studies of potential clinical significance and relevance to this protocol are summarized below; additional details are provided in the IB.

Triheptanoin is metabolized rapidly in the gut to form glycerol and heptanoate that is further metabolized in the liver to C4- and C5-ketone bodies (Kinman et al. 2006), (Deng et al. 2009). In the mouse model of Glut1 DS, triheptanoin administration led to the delivery of heptanoate to the brain which was metabolized into glucose and neurotransmitter intermediates, consistent with an important role of the odd-chain length C7 structure in restoring central nervous system metabolism (Marin-Valencia et al. 2013).

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.

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 also 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 GLP 9 month chronic toxicity study in juvenile mini-pigs was performed with UX007. The study demonstrated that there is no evidence of accumulation of triheptanoin or metabolites in plasma after daily PO dosing as high as 50% of the animal's daily caloric intake. UX007 was well-tolerated at up to 50% of the daily caloric intake and did not result in any evidence of systemic toxicity; therefore, the dose of 50% caloric replacement was considered the NOAEL for UX007 following 9-months of treatment.

The standard battery of genotoxicity tests did not result in any evidence of genotoxic, clastogenic or mutagenic effects.

5.2.3 Previous Clinical Studies

Approximately 200 subjects with various diseases have been treated with triheptanoin for periods of up to 15 years. Of these subjects, approximately 50 were pediatric patients as young as neonates; a significant portion of pediatric patients had treatment duration of over 5 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 patients with fatty-acid oxidation disorders (FAOD) as part of a compassionate use program (Roe et al. 2002), (Roe et al. 2006), (Roe et al. 2008), (Barone et al. 2012). Ultragenyx is currently developing UX007 as a substrate replacement therapy for long-chain FAOD (LC-FAOD).

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) (Roe et al. 2010), glycogen storage disease

type II (GSD-II; Pompe disease) (Roe et al. 2006) and congestive heart failure (IND 65827). Triheptanoin treatment has been generally safe and well tolerated in subjects with these disorders.

Triheptanoin was studied in 14 Glut1 DS subjects (including 11 pediatric subjects) in a clinical trial sponsored by Dr. Juan Pascual at the University of Texas, Southwestern. The results of this open-label study suggest clinical activity with triheptanoin in reducing the frequency of absence seizures (Pascual et al. 2014). No patient experienced serious or unexpected adverse events (AE). One patient (7%) discontinued triheptanoin therapy after 3 weeks owing to gastric discomfort. One other patient (7%) experienced significant (10%) weight gain at 2 months that did not lead to discontinuation. This patient did not follow recommended dietary and nutritional advice to decrease extra sources of fat and simple sugars. Two patients (14%) experienced diarrhea and/or digestive discomfort within days of treatment initiation; symptoms resolved by reducing the triheptanoin dose by one-half and gradually increasing the amount to the target levels over several days.

The Phase 2 randomized, double-blind, placebo-controlled study to assess the safety and efficacy of UX007 in pediatric, adolescent, and adult Glut1 DS patients (UX007G-CL201) is the primary feeder trial for subjects participating in this study, although subjects may also enroll from investigator-sponsored studies. Ultragenyx also plans to conduct additional studies in patients with movement disorders associated with Glut1DS. The IB provides current information on the status of UX007 clinical development along with additional information on UX007 effects in humans and associated Reference Safety Information.

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 Glut1 DS. UX007 is being developed to address the needs of Glut1 DS patients who continue to have disease crises despite the best available treatment. For Glut1 DS patients, the current standard of care, KD and AEDs, is not sufficient to prevent all seizure events. The KD is difficult to tolerate and some patients are not compliant with or are otherwise not on the diet; seizure are often refractory to AEDs. There exists a significant unmet medical need in these patients.

Triheptanoin has been used clinically for periods of up to 15 years in approximately 200 subjects in human studies of a variety of different diseases, including Glut1 DS (Roe et al. 2002), (Roe et al. 2006), (Mochel et al. 2010). Of these subjects, 11 were Glut1 DS pediatric subjects and approximately 50 were pediatric subjects with other diseases. A significant portion of pediatric subjects received over 5 years of treatment duration with triheptanoin. These data support the safety of triheptanoin when administered at approximately 35% of daily caloric intake in pediatric patients as young as neonates.

Nonclinical studies evaluating triheptanoin and its metabolites in mice and rats have been published and further support the safety of triheptanoin in the Glut1 DS population. Data from the animal pharmacokinetic (PK), TK, and toxicity studies indicate that triheptanoin is well absorbed after oral dosing and is well-tolerated without overt toxicities at

doses as high as 1.14 g/kg in mice and 50% daily caloric intake in juvenile minipigs for 9 months, with no signs of hepatic or renal injury.

Data from nonclinical and clinical studies to date suggest triheptanoin does not pose any serious 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 (MCT oil). The most commonly reported adverse effects are gastrointestinal distress and excessive weight gain at high doses. Both of these issues appear to resolve when triheptanoin is consumed in small doses mixed with foods throughout the day and when total caloric intake is appropriately managed. Overall the risk-benefit ratio of UX007 is sufficient to support clinical development for the treatment of seizures associated with Glut1 DS.

5.4 Study Rationale

Glut1 DS is a rare, severely debilitating disease characterized by seizures, developmental delay, and movement disorder. Glut1 DS is caused by a mutation in SLC2A1 encoding the Glut1 protein responsible for transporting glucose across the blood brain barrier. Because glucose is the primary source of energy for the brain, this disorder results in a chronic state of energy deficiency in the brain. Current therapy consists of KD, and AEDs for the treatment of seizures. Because of the difficulties in maintaining the KD, some patients are not able to fully comply with or tolerate the diet; these patients need an alternative therapy for Glut1 DS.

UX007 (triheptanoin) is a triglyceride of medium, odd-carbon chain (C7) fatty acids. The rationale for UX007 in Glut1 DS is that:

1) triheptanoin is metabolized to heptanoate and C4 and C5 ketone bodies, providing an alternative energy source to the brain,
2) triheptanoin provides anaplerotic substrates to resupply intermediates of the TCA cycle, and
3) triheptanoin can support gluconeogenesis in the brain.

A Phase 2 study (UX007G-CL201) is ongoing to assess the safety and efficacy of UX007 in reducing the frequency of seizures in Glut1 DS patients. ISTs and other treatment programs are also evaluating UX007/triheptanoin as a treatment for Glut1 DS. This open-label long-term safety and efficacy study will provide an opportunity for Glut1 DS patients to be treated with UX007 for up to 3 years, or until one of the following occurs: the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, the study is terminated, or until commercial availability of study drug in a subject's region, whichever occurs first, under a single standardized protocol for maintenance therapy and consistent safety monitoring. The study is designed to obtain long-term safety information and evaluate maintenance of efficacy in a pediatric and adult Glut1 DS population.

6 STUDY OBJECTIVES

The primary objective of the study is to:

- Evaluate the long-term safety of UX007 in Glut1 DS subjects

The secondary objectives of the study are to:

- Evaluate the long-term effect of UX007 efficacy on seizures associated with Glut1 DS
- Evaluate the long-term effect of UX007 on health-related quality of life related to Glut1 DS

6.1 Study Endpoints

6.1.1 Primary Endpoint

The primary endpoint of the study is the frequency of AEs and SAEs assessed as related to study drug over the Treatment Extension Period.

6.1.2 Secondary Endpoints

General secondary endpoints of the study are:

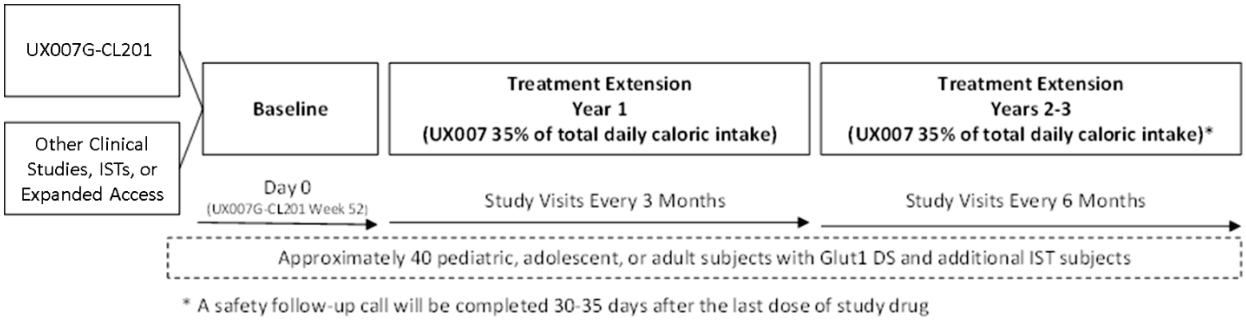
- Frequency of seizures over the Treatment Extension Period
- Measures of neurological function over the Treatment Extension Period
- Health-related quality of life over the Treatment Extension Period

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

UX007G-CL202 is an open-label, single-arm, multicenter extension study to assess the long-term safety and efficacy of UX007 in Glut1 DS. The study will enroll up to 40 pediatric, adolescent, and adult Glut1 DS subjects who have completed the UX007G-CL201 study and, at the discretion of the Sponsor, additional subjects from participated in other clinical studies, ISTs, or expanded access/compassionate use treatment programs. Figure 7.1.1 provides a schematic of the study design.

Figure 7.1.1: UX007G-CL202 Study Schema



For continuing UX007G-CL201 subjects, the Week 52 visit of that study may be conducted in conjunction with the Baseline visit for this study to avoid duplication of assessments. Following the Baseline visit, subjects will return to the study site at 3-month intervals from Baseline during Year 1 of the Treatment Extension, and 6-month intervals from Baseline during Years 2 and 3. Phone calls will take place 3-months between scheduled study site visits during Years 2 and 3 to collect adverse events and concomitant medications updates and to inquire about study drug consumption and remaining supply; in lieu of the phone call, subjects may also visit the clinic at the study site's discretion. Additionally, optional study site visits may occur 3-months between scheduled study site visits during Years 2 and 3 to allow subjects to attain study drug as needed at the request of the Investigator. 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. Subjects will record seizure occurrence in a diary throughout the study; diet diaries will also be completed by the subject for the 3 days preceding each scheduled visit after Baseline. Overnight electroencephalograms (EEG) will be conducted in all subjects to monitor absence seizures. Safety assessments and a clinical neurological evaluation will further enable the characterization of long-term safety and maintenance of effect. Metabolites of UX007 in the blood will also be assayed.

UX007 dosing will be targeted at 35% of total daily caloric intake throughout the study. Subjects receiving a different dose of UX007 at study entry may continue treatment at the

current established dose. If a subject has been off UX007 treatment for > 1 month, the dose may be titrated at the discretion of the investigator. Enrolled subjects are able to maintain standard of care treatment with up to 3 AEDs throughout the duration of the study.

7.2 Discussion of Study Design, Including Choice of Control Group

UX007G-CL202 is designed as an open-label, multicenter extension study. The goal of the study is to evaluate the long-term safety of UX007 treatment in Glut1 DS patients while providing continuing treatment for clinical trial participants in an associated Phase 2 study and, at the discretion of the Sponsor, additional subjects who participated in other clinical studies, ISTs, or expanded access/compassionate use treatment programs. The study will also explore maintenance of UX007 effects on clinical features associated with Glut1 DS.

Sample size is limited to subjects who have completed the Phase 2 safety and efficacy study, UX007G-CL201, or, at the discretion of the Sponsor, additional subjects who participated in other clinical studies, ISTs, or expanded access/compassionate use treatment programs. The study is intended to provide the maximum amount of information regarding UX007 long-term safety and efficacy in a diverse Glut1 DS population. Since all subjects will continue to receive the same investigational product, randomization and blinding are unnecessary; study drug will be provided open-label.

Historical data obtained from prior clinical study participation and/or medical records may be used as a comparator for the Treatment Extension Period, enabling those subjects to represent an internal control for assessment of safety and 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.

Given the chronic nature of Glut1 DS, subjects will be eligible to continue maintenance UX007 treatment for up to 3 years, or until one of the following occurs: the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, the study is terminated, or until commercial availability of study drug in a subject's 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 Glut1 DS patients under a single study protocol.

7.3 Selection of Study Population

The study will be conducted in pediatric, adolescent, and adult Glut1 DS patients (aged at least 1 year at the time of informed consent) who have successfully completed the associated Phase 2 study (UX007G-CL201) or, at the discretion of the Sponsor, additional subjects who participated in other clinical studies, ISTs, or expanded access/compassionate use treatment programs. Enrollment may include subjects from neighboring countries where clinical sites are located. Appropriate local or country requirements will be followed. All subjects in this study will have prior treatment exposure to UX007/triheptanoin.

Children with Glut1 DS have been included in the study population since they have the greatest medical need and an increased number of clinical events. The manifestation of seizures in Glut1 DS occurs predominantly in the pediatric age range, especially under the age of 12 (Pong et al. 2012); adult patients may also continue to have a similar phenotype of breakthrough seizures into their thirties, significant movement disorders (estimated at 90%; De Vivo personal communication), and have a more difficult time maintaining the KD. The expanded age range of the population will strengthen the ability to evaluate a possible impact on seizures and movement disorders. In addition, the seizures are typically refractory to AEDs (Pearson et al. 2013), (Pong et al. 2012) and thus represent a significant unmet medical need that justifies the study of UX007 for the treatment of Glut1 DS.

Reports suggest that KD is effective for the treatment of the seizures of Glut1 DS, although controlled trials have not been performed (Pong et al. 2012), (Pearson et al. 2013). Nevertheless, KD is prescribed in most Glut1 DS patients. There exists a subset of patients who are not on KD because it is difficult to tolerate and some patients are not compliant with or are otherwise not on the diet. In addition, some subjects continue to experience breakthrough seizures while on KD. Because the seizures of Glut1 DS are typically refractory to AEDs, the subset of patients who are not on KD represents those most in need of an alternative therapy.

Additional exclusion criteria were incorporated to protect the study population from possible contraindicated treatments or unnecessary safety risks. *In vitro* studies have shown that pancreatic lipases hydrolyze triheptanoin into free fatty acids and glycerol; therefore inhibitors of pancreatic lipases (e.g. orlistat) should be avoided while taking UX007.

Many Glut1 DS patients are severely impacted by their disorder from early infancy. Triheptanoin has been administered previously to newborns, infants, children, and adults. The previous clinical experience and nonclinical data 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 with children enrolled, and efforts will be focused on minimizing risk, fear, pain and distress 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) Diagnosis of Glut1 DS by cerebrospinal fluid glucose concentration, erythrocyte 3-O-methyl-D-glucose uptake assay, or *SLC2A1* molecular genetic testing. Information will be obtained from medical records.

2) Males and females, aged at least 1 year at the time of informed consent

3) Completion of UX007G-CL201 study (NCT01993186). Glut1 DS patients who received UX007/triheptanoin treatment as part of other clinical studies, ISTs, or

expanded access/compassionate use treatment programs may be eligible at the discretion of the sponsor.

4) Provide written informed consent or verbal assent (if possible) with written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures
5) Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, and comply with accurate completion of the seizures diary
6) 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.
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) Any known hypersensitivity to triheptanoin that, in the judgment of the investigator, places the subject at increased risk for adverse effects
2) History of, or current suicidal ideation, behavior and/or attempts
3) Pregnant and/or breastfeeding an infant
4) Unwilling or unable to discontinue use of a prohibited medication (barbiturates, pancreatic lipase inhibitors) or other substance that may confound study objectives. Use of up to 3 concomitant AEDs is allowed, provided dose has been stable at least 14 days prior to Baseline.
5) Use of any investigational product, drug or supplement (other than UX007) within 30 days prior to Baseline, or at any time during the study
6) Has a condition of such severity and acuity, in the opinion of the investigator, that it warrants immediate surgical intervention or other treatment
7) Has a concurrent disease or condition, or laboratory abnormality that, in the view of the investigator, places the subject at high risk of poor treatment compliance or of not completing the study, or would interfere with study participation or introduce additional safety concerns (e.g. other concurrent neurological or psychiatric disorders).

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 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 AE
- An illness that, in the judgment of the investigator or Ultragenyx, might place the subject at risk or invalidate the study
- Pregnancy of subject
- 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.

7.3.3.1 Stopping Rules

Individual subjects who experience any unexpected and possibly, probably, or definitely drug-related SAEs (Section 8.5.3) that represent a change in the nature or an increase in frequency of the serious event from their prior medical history or known Glut1 DS-related medical issues will be assessed as to whether the subject will continue on the study.

The Institutional Review Board (IRB)/Ethics Committee (EC) will be informed should unexpected and possibly, probably, or definitely study 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 the IRBs/ECs, will be informed should unexpected and possibly, probably, or definitely study 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

At the Baseline Visit and each subsequent visit through Month 30, each subject will be dispensed an adequate supply of study drug to comprise up to 35% total daily caloric intake. Due to the extended time between scheduled clinic visits, additional supplies of study drug may be shipped to directly the subject or a designated pharmacy for logistical purposes.

7.4.1 Investigational Product

UX007 (triheptanoin) is a liquid, intended for PO administration. UX007 is a colorless to yellow oil supplied in 1 L round, translucent high-density polyethylene (HDPE) or 1 L round amber-colored glass bottles. UX007 is manufactured, packaged, and labeled according to GMP regulations.

UX007 dosing will be targeted and/or maintained at 35% of total daily caloric intake. If a subject has been receiving a different dose of UX007 at study entry, the subject may be maintained on the UX007 dose that provided the maximum improvement in clinical status with acceptable tolerability, and continued on this dose for the duration of the study.
A subject may have been off UX007 treatment prior to enrollment; in these cases, the UX007 dose may be titrated at the discretion of the investigator.

UX007 should be mixed with food (or formula, as appropriate) and administered PO or by gastronomy tube at least four times per day (breakfast, lunch, dinner, and before bed).
The dose may be divided into smaller more frequent doses with food as needed.

7.4.2 Reference Therapy

The study is a single-arm, open-label study. All subjects will be on active treatment; no reference therapy or placebo will be administered.

7.4.3 Method of Assigning Subjects to Treatment Groups

Subjects continuing treatment following completion of the UX007-CL201 study will retain the same identification number. Eligible subjects entering from other studies will be enrolled in the study and sequentially assigned an identification number. All subjects will receive active treatment (UX007); there is only one treatment group in the study.

7.4.4 Selection of Doses and Study Duration

The UX007 dose and regimen for this study was selected based on the extensive clinical information derived from over 15 years of clinical experience in a variety of diseases. Approximately 200 subjects have received triheptanoin treatment, 51 of which involved pediatric patients as young as neonates, with 23 of these 51 with over 5 years of treatment duration (Roe et al. 2002), (Roe et al. 2006), (Mochel et al. 2010).

The data support the safety of triheptanoin when administered at approximately 35% of daily caloric intake in pediatric patients as young as neonates. Previous clinical data also suggest an age-dependent dose that relates to the relatively higher energy requirements for young children versus older children versus adults.

The target dose of 35% of calories by UX007 is consistent with prior clinical use in other diseases and is equivalent to approximately 2-4 g/kg in infants and young children, decreasing to 1-2 g/kg for older children and adolescents. Triheptanoin treatment has been generally safe and well tolerated at the aforementioned dose levels. Higher doses are generally poorly tolerated due to gastrointestinal disturbance, such as diarrhea; lower doses would likely provide suboptimal efficacy.

7.4.4.1 Study Duration

The planned duration of treatment in this study is 3 years, or until one of the following occurs: the subject withdraws consent, the subject is discontinued from the study at the discretion of the Investigator or Ultragenyx, the study is terminated, or until commercial availability of study drug in a subject's region, whichever occurs first. The length of the study is intended to define whether UX007 is safe for long-term use and provide sufficient insight on sustained clinical effects. 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.

7.4.5 Blinding

The study drug will be administered open-label; no study participants will be blinded to study treatment.

7.4.6 Prior and Concomitant Therapy

7.4.6.1 Prohibited Medications

Subjects may not be enrolled if they have used any investigational product (other than UX007) within the last 30 days prior to the Baseline Visit, or are unwilling to discontinue use of a substance that may confound study objectives. The following medications are prohibited throughout the study:

- Barbiturates

- Pancreatic lipase inhibitors (e.g. Orlistat) due to possible inhibition of metabolism of triheptanoin

7.4.6.2 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 Baseline visit will be reviewed and recorded. Prescribed diet plans (as managed by the investigator) are allowed provided details of diet are captured in the diet diary or concomitant medications as appropriate. Up to 3 AEDs are permitted, provided the dose has been stable for 14 days prior to study entry.

7.4.7 Treatment Compliance

Subjects and/or caregivers will record consumption of study drug in a study diary. The diary will be reviewed by a dietitian or site personnel upon each visit. Subjects will be instructed to return all used (empty study drug containers) and open/partially used study drug. Study personnel will maintain a record of all medication dispensed to each subject. Refer to the Pharmacy Manual for additional information on study drug accountability.

7.5 Study Procedures and Assessments

The parameters to be assessed, along with timing of assessments, are provided in the Schedule of Events (Table 2.1). Refer to the Study Reference Manual for additional details on specific assessments and the suggested order of administration. Whenever possible, study site staff (including trained clinicians, physical therapists, and the Investigator or site designee) performing the assessments should be consistent from visit to visit throughout the study.

The concept for evaluation is to study the long-term safety and continued effects of UX007 treatment on clinical manifestations associated with Glut1 DS. Safety and clinical efficacy assessments will be conducted throughout the Treatment Extension Period to enable primary and secondary endpoint analysis and achieve study objectives. Dosing compliance and will also be regularly monitored.

7.5.1 Visit Schedule

The Baseline Visit may occur in conjunction with the last scheduled visit from study UX007G-CL201. Assessments conducted at the last UX007G-CL201 visit will be used for Baseline data to avoid duplication. If the time elapsed between the last UX007G-CL201 study visit and the Baseline Visit for this study is > 1 month, the full panel of Baseline Visit assessments must be completed. Informed consent must be obtained prior to any Baseline procedures specific to the UX007G-CL202 study. Subjects will be provided UX007 treatment continuation only after all inclusion/exclusion criteria have been confirmed.

The Baseline Visit will be 2 days in duration to complete all assessments and the overnight EEG.

Subjects will return to the clinic at 3-month intervals from Baseline (± 1 week) during Year 1, and at 6-month intervals from Baseline (± 2 weeks) during Years 2 and 3 of the Treatment Extension Period to assess long-term safety and efficacy. Phone calls will take place 3-months between scheduled study site visits during Years 2 and 3 to collect adverse events and concomitant medications updates and to inquire about study drug consumption and remaining supply; in lieu of the phone call, subjects may visit the clinic at the study site's discretion. Additionally, optional study site visits may occur 3-months between scheduled study site visits during Years 2 and 3 to allow subjects to attain study drug as needed at the request of the Investigator. 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. 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. Minors who reach legal age during the course of the study must provide written informed consent when eligible. For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination visit procedures within 4 weeks of discontinuation.

7.5.2 Efficacy Measures

The concept for evaluation is to study maintained effects of UX007 treatment on seizures, neurological examination, and movement disorders in Glut1 DS subjects through clinical assessments conducted throughout the Treatment Extension Period. Patient-reported outcomes to evaluate health-related quality of life will also be administered. The Investigator may use clinical judgment in deciding whether to administer certain assessments to subjects based on age, development, and cognitive ability, as appropriate. The SF-10/SF-12v2 will not be performed if no pre-treatment baseline is available from feeder study (e.g. subjects entering from other clinical studies, ISTs, or expanded access/compassionate use treatment programs or subjects from UX007G-CL201 who were too young or compromised at pre-treatment Baseline).

The primary objective of the study is to assess long-term safety; all efficacy endpoints are therefore considered secondary (Section 6.1). The efficacy measures and assessments are described below; planned analysis of efficacy endpoints is described in Section 7.6.4. Refer to the Study Reference Manual for additional details on efficacy measures.

7.5.2.1 Seizure Monitoring

7.5.2.1.1 Seizure Diary

Seizures are a hallmark of Glut1 DS in approximately 90% of affected individuals (Wang et al. 1993-2015). The frequency of seizures varies among individuals; some experience daily events while others may have seizures separated by days, weeks, or even months.

The number of observable seizures will be recorded by the subject or caregiver via diary throughout the study. Seizure types will be defined and standardized according to the ILAE Commission on Classification and Terminology (Berg et al. 2010). Indicated seizure types are consistent with those observed in a large Glut1 DS cohort study designed to define epilepsy phenotypes in this population (Pong et al. 2012).

Observable seizures are defined as:

- Generalized Tonic-Clonic, Generalized Tonic, Generalized Clonic, Generalized Atonic
- Partial/Focal with Secondary Generalization
- Myoclonic, Myoclonic (Astatic) Atonic, Myoclonic Tonic
- Complex Partial/Focal
- Simple Partial/Focal Motor
- Absence (although the primary method of assessing will be by EEG)

7.5.2.1.2 Electroencephalography

Case-report studies in limited groups of Glut1 DS patients suggest a normal interictal background is the most common finding on both routine and prolonged EEG recordings. Both absence and myoclonic seizures have been observed in pediatric Glut1 DS patients during overnight continuous monitoring (Leary et al. 2003). Several studies have examined electrophysiologic characteristics in Glut1 DS patients on KDs (Kessler et al. 2011).

Abnormalities on EEG (including absence seizures) will be recorded with an overnight EEG conducted as indicated in Table 2.1. Indicated visits require a 2-day period to complete the overnight monitoring. The frequency of seizures, including absence is the key measure.

7.5.2.2 Neurological Function

The classic phenotype of Glut1 DS is also characterized by delayed neurologic development, acquired microcephaly, and complex movement disorders (Pascual et al. 2004).
The majority of Glut1 DS patients experience some degree of developmental delay and cognitive impairment. The broad spectrum of neuropsychological features in Glut1 DS includes effects on general intellectual function (ranging from mild learning disability to severe intellectual impairment), language development, adaptive behavior, behavior and sustained attention. Clinical efficacy measures in this study also include measures of neurological function.

7.5.2.2.1 Columbia Neurological Score

The CNS is a quantitative tool developed to summarize neurological exam findings (Kaufmann et al. 2004). The tool focuses on physical findings, capturing the following domains: 1) height, weight, and head circumference; 2) general medical examination; 3) general neurologic examination; 4) cranial nerves; 5) stance and gait; 6) involuntary

movements; 7) sensation; 8) cerebellar function; 9) muscle bulk, tone, and strength; 10) myotatic reflexes; 11) Babinski signs; and 12) other findings. The CNS total score ranges from 0 to 76; higher scores are associated with higher neurological function. The CNS will be administered at the Baseline Visit and at Months 6, 12, 24, and 36 (or Early Termination).

7.5.2.3 Health-related Quality of Life

Individuals with Glut1 DS are affected by a broad spectrum of clinical symptoms, including seizures, cognitive and speech impairment and movement disorders which may impact physical and mental health status. The following efficacy measures will evaluate patient-reported quality of life.

7.5.2.3.1 Short Form Health Surveys

Short-Form (SF) health surveys capture practical, reliable, and valid information about functional health and well-being from the patient's perspective. Depending on the age of the subject, the SF-10 Health Survey for Children (SF-10) or Medical Outcomes Study 12-Item Short Form version 2 (SF-12v2) will be administered during at the Baseline Visit and at 6-month intervals thereafter (or Early Termination). SF-10/SF-12v2 will not be performed if no pre-treatment baseline is available from feeder study (e.g. other clinical studies, ISTs, or expanded access/compassionate use treatment programs or subjects from UX007G-CL201 who were too young or compromised at pre-treatment Baseline).

The SF-10 is a 10-item caregiver-completed questionnaire for pediatric subjects designed to assess physical and psychosocial health-related quality of life in healthy and ill individuals (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 summary score (PHS-10) and psychosocial summary score (PSS-10). Higher global scores are associated with better quality of life. The SF-10 will be administered to caregivers of subjects aged 5 to 17 years at the time of informed consent for this study. If a subject is under 5 years of age at informed consent, the SF-10 will not be administered during the Extension study. The responder completing the first administration should complete subsequent administrations to minimize variability.

The SF-12v2 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-12v2 are a subset of the items in the SF-36v2 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-12v2 will be administered to subjects 18 years of age and older at the time of informed consent for this study. If a subject turns 18 years of age during the study, the SF-12v2 will be administered beginning at the next study visit.

7.5.3 Drug Concentration Measurements and Bioassays

To assess the UX007 metabolites, blood samples will be collected approximately 90 minutes following consumption of food and study drug at the Baseline Visit and at 6-month intervals throughout the Treatment Extension Period (or Early Termination). For each sample collection, the time elapsed since last study drug administration will be recorded on the CRF. The following UX007 metabolites will be assessed:

- C4 ketone: beta-hydroxybutyrate (BHB)
- C5 ketones: beta-hydroxypentanoate (BHP)
- Heptanoate

7.5.4 Safety Measures & General Assessments

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

7.5.4.1 Medical History and Triheptanoin Treatment History

Medical history will be obtained at the Baseline Visit for all subjects not previously enrolled in UX007G-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 phenotypic characteristics associated with Glut1 DS, including seizures, cognitive impairment, movement disorders, and microcephaly. The specific history of Glut1 DS will be recorded, along with date of onset, clinical presentation, and date and method of confirmed diagnosis. Any available family history of Glut1 DS will be noted including diagnosis, disease course, treatment and outcome.

Glut1 DS maintenance treatment history, including UX007 (triheptanoin) treatment history, and relevant concomitant medications will be recorded (start date, stop date, dose, dose regimen). Treatments include prescribed diets, other standard of care treatments, and all other relevant concomitant medications (e.g. seizure medications, L-carnitine, vitamin supplements, etc.). Medications include prescription, over-the-counter, herbal and nutritional supplements. Any relevant concomitant therapy, including physical/occupational therapy will be recorded.

7.5.4.2 Vital Signs and Weight

Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in millimeters of mercury (mm Hg), heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). Vital signs measurements will be

performed at every clinic visit before any additional assessments are completed. At each visit, weight (in kilograms) will be obtained using a scale. Clinically significant changes will be recorded as AEs.

7.5.4.3 Physical Examination

Complete physical examinations will be performed at the Baseline Visit and at 6-month intervals for the duration of the study (or Early Termination Visit). Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, musculoskeletal, and neurologic systems. Clinically significant changes will be recorded as AEs.

7.5.4.4 Clinical Laboratory Tests

The clinical laboratory evaluations to be performed in this study include routine serum chemistry, hematology, and urinalysis; specific analytes are listed in Table 7.5.4.4.1. Clinical laboratory testing will be performed at each scheduled study clinic visit (or Early Termination visit). Blood and urine samples will be collected; fasting is not required. Refer to the Study Reference Manual for additional details.

Table 7.5.4.4.1: Clinical Laboratory Assessments

Chemistry	Hematology	Urinalysis
Alanine aminotransferase (ALT)	Hematocrit	Appearance
Alkaline phosphatase	Hemoglobin	Color
Aspartate aminotransferase (AST)	Platelet count	pH
Bilirubin (total)	Red blood cell (RBC) count	Specific gravity
Blood urea nitrogen (BUN)	White blood cell (WBC) count	Ketones
Calcium		Protein
Chloride		Glucose
Serum creatinine		
Gamma-glutamyl transpeptidase (GGT)		Pregnancy test (if applicable)
Serum glucose		
Potassium		
Protein (albumin and total)		
Sodium		

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

7.5.4.5 Pregnancy Testing

Female subjects of childbearing potential will have urine pregnancy tests at each scheduled study visit (or Early Termination). 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 the Baseline visit will not be enrolled in the study. Pregnancy in subject or partner must be reported (Section 8.5.5.1); 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 childbearing potential must use highly effective contraception as determined by the investigator during heterosexual intercourse throughout the study period and for 30 days after stopping the study drug. Examples of some 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)

7.5.4.6 Suicidal Ideation and Behavior Assessments

Assessment of suicidal ideation and behavior is a regular part of development programs involving AEDs and other neurologic drugs with central nervous system activity (FDA Draft Guidance 2012). The Columbia Suicide Severity Rating Scale (C-SSRS) is a standardized suicidal rating instrument used to assess the suicidal ideation and behavior in an at-risk population (Posner et al. 2011). To prospectively assess suicidal ideation and behavior, the C-SSRS will be administered by a clinician. Depending on the cognitive state of the subject, some questions within the C-SSRS may be deemed by the investigator to be inappropriate to ask the subject and can be omitted. Suicidal ideation and behavior will be

assessed in subjects ≥ 10 years of age at each visit. The Baseline questionnaire will be administered on the initial visit; the Since Last Visit questionnaire will be administered at all subsequent visits. The responses to the questionnaire will be reviewed by site personnel during the study visit; if emergent suicidal ideation or behavior is indicated, the investigator should promptly evaluate the subject to ensure proper management and protection of subject safety. Determination of whether the subject should continue on study will be made by the investigator based on the severity of symptoms and follow-up needed, and the Sponsor will be informed.

7.5.4.7 Concomitant Medications

Concomitant medications will be reviewed and recorded in the subject's CRF at each study visit or phone call, beginning at the Baseline Visit. 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 or phone call, change in medications since the previous visit will be recorded. A discussion of concomitant medications is provided in Section 7.4.6.

7.5.4.8 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. The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.5. At each visit or phone call, subjects will be asked about any new or ongoing AEs since the previous visit. Assessments of AEs will occur at each study visit.

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

7.5.4.9 Dietitian Consultation and Diet Assessment

At the Baseline visit, an interview with the study dietitian will establish daily caloric intake and UX007 dose. Subjects and/or caregivers are required to maintain a record of the subject's daily diet in a diary for the 3 days prior to each subsequent visit. The diet diary will be reviewed by study personnel at each visit to the clinic. The dietitian may telephone subjects and/or caregivers, as needed, to provide dietary advice and support. Refer to the Study Reference Manual for details on the dietary assessment.

7.5.5 Appropriateness of Measures

The efficacy parameters to be evaluated in this study encompass the characteristic phenotype observed in Glut1 DS affected individuals, including seizures, delayed neurologic development, and complex movement disorders. The clinical assessments in the study employ standard measures used in other diseases and conditions that impact the central nervous and skeletal muscle systems.

Seizure frequency is the most commonly used endpoint in AED trials for refractory epilepsy and would be able to similarly determine the clinically relevant effects of UX007 on the seizure due to Glut1 DS. Diaries will be used by subjects and/or caregivers to capture seizure events, thereby minimizing recall bias at site visits. EEG is a routine, non-invasive procedure inflicting minimal pain/distress for the subject, while providing relevant indicators of absence seizure events. The incorporation of overnight EEGs may introduce a level of inconvenience for the subject, however a higher proportion of abnormalities in pediatric Glut1 DS patients were observed in 24-h EEG data compared with routine EEGs (Leary et al. 2003). The CNS was included as a measure of neurological involvement.

Since the study will be conducted in a pediatric, adolescent, and adult population, ageappropriate- efficacy measures and patient-reported outcomes were included to assess health-related quality of life (SF-10/SF-12v2).

UX007 metabolites will be assessed using blood samples. The panel has been included to provide additional metabolite data on peak levels at steady-state. Where possible, timing of assessments has been coordinated with standard safety laboratory tests to minimize risk and discomfort and avoid unnecessary sampling.

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 and weight, serum chemistry, concomitant medications, and other routine clinical and laboratory procedures. Suicidal ideation and behavior will be assessed as an additional safety measure given the central nervous system involvement with Glut1 DS and the likelihood for most if not all subjects to be prescribed at least 1 AED as concomitant treatment.

7.6 Statistical Methods and Determination of Sample Size

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

The statistical analyses will be reported using summary tables, figures, and data listings. Statistical tests will be one-sided at the alpha =0.05 significance level. All analyses and tabulations will be performed using SAS®. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories.
For time-to-event data, the Kaplan-Meier estimates will be computed and plotted. Graphical data displays may also be used to summarize the data. All raw data obtained from the CRFs as well as any derived data will be included in data listings. For certain data collected over time, the Generalized Estimating Equation (GEE) may be used as the marginal model approach.

Tests of treatment effects will be conducted at a one-sided alpha level of 0.05 and/or one-sided 95% confidence interval where possible. Each secondary endpoint will be tested independently at one-sided alpha=0.05. No adjustments for multiple comparisons will be performed.

Specific details of primary and secondary endpoints as defined in Section 6.1, and associated analyses will be provided in the SAP.

7.6.1 Subject Information

Summaries and listings will be provided for all subjects who received at least 1 dose of study drug and provided at least 1 safety or efficacy evaluation. Subject disposition summaries will include the number of enrolled subjects, the number of subjects receiving study medication, the number of subjects completing the study, and the reasons for discontinuation. Demographic variables include age, sex, and race.

7.6.2 Analysis Population

The analysis set will include all subjects who receive at least one dose of UX007 during the study.

7.6.3 Safety Analyses

The primary safety analysis will evaluate the incidence and frequency of AEs and SAEs, including clinically significant changes in safety parameters throughout the Treatment Extension Period. The incidence and frequency of AEs will be summarized by System Organ Class and Preferred Term, relationship to study drug, and severity. No formal hypothesis testing will be performed.

Safety will be evaluated by the incidence, frequency and severity of AEs and SAEs, including clinically significant changes from baseline to scheduled time points in:

- Vital signs and weight
- Physical examination
- Clinical laboratory evaluations
- Pregnancy testing
- Suicidal ideation and behavior assessments
- Concomitant medications

The analyses of safety will be performed on the safety analysis population.

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. All reported AEs with onset

during treatment (i.e. treatment-emergent AEs) will be included in the analysis. For each AE, the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized by treatment group. The numbers (frequency) and incidence rates of AEs and SAEs will be summarized during exposure to UX007 throughout the study. Special attention will be given to those subjects who died, discontinued treatment due to an AE, or experienced a SAE (e.g. summaries, listings, and narrative preparation, as appropriate).

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 after study drug administration will be presented for each clinical laboratory measurement.

Changes in findings from physical examinations will be tabulated and listed for each subject by examination category. If there are examination findings that change in more than one subject, these will be tabulated in a separate table and expressed as the number of subjects with the change out of the total.

Descriptive statistics of temperature, pulse, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized. The percentage of subjects with values beyond clinically important limits will be summarized.

The SAP will provide additional details on the planned safety analyses.

7.6.4 Efficacy Analysis

The efficacy analyses are focused on alternative domains of Glut1 DS disease to assess the long-term effect of UX007 throughout the Treatment Extension Period.

The following efficacy measures will be assessed:

- Seizures: Observable generalized and partial-onset seizures measured by diary, and absence seizures measured by overnight EEG. Seizure types include: Generalized Tonic-Clonic, Generalized Tonic, Generalized Clonic, Generalized Atonic, Partial/Focal with Secondary Generalization, Myoclonic, Myoclonic Atonic, Myoclonic Tonic, Complex Partial/Focal, Simple Partial/Focal Motor, and Absence seizures
- Neurological function using the CNS
- Subject or caregiver-reported quality of life using SF-10 for children or SF-12v2 for adults

The specific tests and analyses will be defined in the SAP.

7.6.5 Pharmacokinetic and Bioassay Analyses

Descriptive statistics, including mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum will be calculated for each plasma UX007 metabolite (BHB, BHP, and heptanoate) at each sampling time point to evaluate peak

levels. Data will be listed for all subjects with available plasma concentrations. All concentrations below the lowest quantifiable concentration of the assay or missing data will be labeled as such in the concentration data listings. Concentrations below the lowest quantifiable concentration of the assay will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report. Results for each plasma UX007 metabolite will be provided. Additional details of the UX007 metabolite analyses will be provided in the SAP.

7.6.6 Subgroup Analysis

Details on any planned subgroup analysis will be provided in the SAP.

7.6.7 Interim Analysis

No formal interim analysis is planned for this study. Analyses may be performed at any time during the study at the discretion of the Sponsor. There is no unblinding during these analyses since it is an open-label study.

7.6.8 Data Monitoring Committee

A data monitoring committee will not be constituted for this open-label treatment extension study.

7.6.9 Determination of Sample Size

Sample size is limited to subjects who have completed the Phase 2 safety and efficacy study, UX007G-CL201, or, at the discretion of the Sponsor, additional subjects who participated in other clinical studies, ISTs, or expanded access/compassionate use treatment programs. The current study design is open-label with all subjects receiving the same treatment; therefore the study is not powered to assess treatment comparisons. Instead, 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 in Glut1 DS patients.

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board or Ethics Committee

The IRB/Ethics Committee (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 screening 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 Food and Drug Administration (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 possible), and his/her legally authorized representative (parent or legal guardian) will provide written informed consent for such subjects. Minors who reach legal age during the course of the study must provide written informed consent when eligible.

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.

The date 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.

A Coordinating Investigator will be identified for multicenter trials. The Coordinating Investigator will be selected on the basis of active participation in the trial, thorough knowledge of the therapeutic area being studied, and the ability to interpret data. The Coordinating Investigator will read and sign the Clinical Study Report.

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. Study drug will be properly packaged for transport. Refer to the Pharmacy Manual for further details on packaging and shipping.

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 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 uninterruptable 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.

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.

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 applied 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.

8.5.5 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.

8.5.5.1 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.

8.5.6 Communication Plan

8.5.6.1 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/Research Ethics Boards (REB)/ECs of SAEs and urgent safety matters, in accordance with IRB/REB/EC requirements and local laws and regulations. A copy of this notification must be provided to Ultragenyx or its designee.

8.5.6.2 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/ REB/ECs of urgent safety matters, in accordance with IRB/REB/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.

8.5.6.3 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 8.5.6.1.

8.5.7 Safety Contact Information

Drug Safety	Medical Monitor
PPD Fax: PPD e-mail: PPD	Melanie Brandabur, MD Telephone: PPD Mobile: PPD e-mail: PPD

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.

9 REFERENCES

Ataide, TR, de Oliveira, SL, da Silva, FM, Vitorino, LGC, Tavares, MCN, and Sant'Ana, AEG. 2009. "Toxicological analysis of the chronic consumption of diheptanoin and triheptanoin in rats." *Int.J.Food Sci.Tech* 44:484-492.

Barone, A, DeWard, S, Payne, N, Goldstein, A, and Vockley, J. 2012. "Triheptanoin therapy for inherited disorders of fatty acid oxidation. Poster presentation. ." *Society for Inherited Metabolic Disorders Annual Meeting, Charlotte, NC, Mar 31 – Apr 3, 2012.*

Berg, AT, Berkovic, SF, Brodie, MJ, Buchhalter, J, Cross, JH, van Emde, BW, Engel, J, French, J, Glauser, TA, Mathern, GW, Moshe, SL, Nordli, D, Plouin, P, and Scheffer, IE. 2010. "Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009." *Epilepsia* 51 (4):676-685.

Borges, K, and Sonnewald, U. 2012. "Triheptanoin--a medium chain triglyceride with odd chain fatty acids: a new anaplerotic anticonvulsant treatment?" *Epilepsy Res.* 100 (3):239-244.

Coman, DJ, Sinclair, KG, Burke, CJ, Appleton, DB, Pelekanos, JT, O'Neil, CM, Wallace, GB, Bowling, FG, Wang, D, De Vivo, DC, and McGill, JJ. 2006. "Seizures, ataxia, developmental delay and the general paediatrician: glucose transporter 1 deficiency syndrome." *J.Paediatr.Child Health* 42 (5):263-267.

Deng, S, Zhang, GF, Kasumov, T, Roe, CR, and Brunengraber, H. 2009. "Interrelations between C4 ketogenesis, C5 ketogenesis, and anaplerosis in the perfused rat liver." *J.Biol.Chem.* 284 (41):27799-27807.

FDA. Draft Guidance 2012. *Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials (Draft)*, *Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf. Accessed 07 Jul 2013.*

IND 65827. "One Time Emergency Use of Anaplerotic Dietary Therapy (Triheptanoin) for Congestive Heart Failure & Cardiomyopathy under Charles Roe MD, Baylor Research Institute."

Kaufmann, P, Shungu, DC, Sano, MC, Jhung, S, Engelstad, K, Mitsis, E, Mao, X, Shanske, S, Hirano, M, Dimauro, S, and De Vivo, DC. 2004. "Cerebral lactic acidosis correlates with neurological impairment in MELAS." *Neurology* 62 (8):1297-1302.

Kessler, SK, Gallagher, PR, Shellhaas, RA, Clancy, RR, and Bergqvist, AG. 2011. "Early EEG improvement after ketogenic diet initiation." *Epilepsy Res* 94 (1-2):94-101.

Kim, TH, Borges, K, Petrou, S, and Reid, CA. 2013. "Triheptanoin reduces seizure susceptibility in a syndrome-specific mouse model of generalized epilepsy." *Epilepsy Res.* 103 (1):101-105.

Kinman, RP, Kasumov, T, Jobbins, KA, Thomas, KR, Adams, JE, Brunengraber, LN, Kutz, G, Brewer, WU, Roe, CR, and Brunengraber, H. 2006. "Parenteral and enteral metabolism of anaplerotic triheptanoin in normal rats." *Am.J.Physiol Endocrinol.Metab* 291 (4):E860-E866.

Klepper, J. 2008. "Glucose transporter deficiency syndrome (GLUT1DS) and the ketogenic diet." *Epilepsia* 49 Suppl 8:46-49.

Klepper, J, and Leiendecker, B. 2007. "GLUT1 deficiency syndrome--2007 update." *Dev Med Child Neurol* 49 (9):707-16.

Leary, LD, Wang, D, Nordli, DR, Jr., Engelstad, K, and De Vivo, DC. 2003. "Seizure characterization and electroencephalographic features in Glut-1 deficiency syndrome." *Epilepsia* 44 (5):701-707.

Marin-Valencia, I, Good, LB, Ma, Q, Malloy, CR, and Pascual, JM. 2013. "Heptanoate as a neural fuel: energetic and neurotransmitter precursors in normal and glucose transporter I-deficient (G1D) brain." *J Cereb.Blood Flow Metab* 33 (2):175-182.

Mochel, F, DeLonlay, P, Touati, G, Brunengraber, H, Kinman, RP, Rabier, D, Roe, CR, and Saudubray, JM. 2005. "Pyruvate carboxylase deficiency: clinical and biochemical response to anaplerotic diet therapy." *Mol.Genet.Metab* 84 (4):305-312.

Mochel, F, Duteil, S, Marelli, C, Jauffret, C, Barles, A, Holm, J, Sweetman, L, Benoist, JF, Rabier, D, Carlier, PG, and Durr, A. 2010. "Dietary anaplerotic therapy improves peripheral tissue energy metabolism in patients with Huntington's disease." *Eur.J.Hum.Genet.* 18 (9):1057-1060.

Pascual, JM, Liu, P, Mao, D, Kelly, DI, Hernandez, A, Sheng, M, Good, LB, Ma, Q, Marin-Valencia, I, Zhang, X, Park, JY, Hynan, LS, Stavinoha, P, Roe, CR, and Lu, H. 2014. "Triheptanoin for Glucose Transporter Type I Deficiency (G1D): Modulation of Human Ictogenesis, Cerebral Metabolic Rate, and Cognitive Indices by a Food Supplement." *JAMA Neurol*.

Pascual, JM, Wang, D, Lecumberri, B, Yang, H, Mao, X, Yang, R, and De Vivo, DC. 2004. "GLUT1 deficiency and other glucose transporter diseases." *Eur J Endocrinol* 150 (5):627-33.

Pearson, TS, Akman, C, Hinton, VJ, Engelstad, K, and De Vivo, DC. 2013. "Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS)." *Curr.Neurol.Neurosci.Rep.* 13 (4):342.

Pong, AW, Geary, BR, Engelstad, KM, Natarajan, A, Yang, H, and De Vivo, DC. 2012. "Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes." *Epilepsia* 53 (9):1503-1510.

Posner, K, Brown, GK, Stanley, B, Brent, DA, Yershova, KV, Oquendo, MA, Currier, GW, Melvin, GA, Greenhill, L, Shen, S, and Mann, JJ. 2011. "The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults." *Am J Psychiatry* 168 (12):1266-77.

Roe, CR, Bottiglieri, T, Wallace, M, Arning, E, and Martin, A. 2010. "Adult Polyglucosan Body Disease (APBD): Anaplerotic diet therapy (Triheptanoin) and demonstration of defective methylation pathways." *Mol.Genet.Metab* 101 (2-3):246-252.

Roe, CR, and Mochel, F. 2006. "Anaplerotic diet therapy in inherited metabolic disease: therapeutic potential." *J.Inherit.Metab Dis.* 29 (2-3):332-340.

Roe, CR, Sweetman, L, Roe, DS, David, F, and Brunengraber, H. 2002. "Treatment of cardiomyopathy and rhabdomyolysis in long-chain fat oxidation disorders using an anaplerotic odd-chain triglyceride." *J.Clin.Invest* 110 (2):259-269.

Roe, CR, Yang, BZ, Brunengraber, H, Roe, DS, Wallace, M, and Garritson, BK. 2008. "Carnitine palmitoyltransferase II deficiency: successful anaplerotic diet therapy." *Neurology* 71 (4):260-264.

Saris-Baglama, RN, DeRosa, MA, Raczek, AE, Bjorner, JB, and Ware, JE. 2006. "Development, validation, and norming of the SF-10 for Children Health Survey." *Quality of Life Research* 15 (S1):A-145.

Thomas, NK, Willis, S, Sweetman, L, and Borges, K. 2012. "Triheptanoin in acute mouse seizure models." *Epilepsy Res.* 99 (3):312-317.

Verrotti, A, D'Egidio, C, Agostinelli, S, and Gobbi, G. 2012. "Glut1 deficiency: when to suspect and how to diagnose?" *Eur J Paediatr Neurol* 16 (1):3-9.

Wang, D, Pascual, JM, and De Vivo, D. 1993-2015. "Glucose Transporter Type 1 Deficiency Syndrome." In *GeneReviews(R)*, edited by R. A. Pagon, M. P. Adam, H. H. Ardinger, T. D. Bird, C. R. Dolan, C. T. Fong, R. J. H. Smith and K. Stephens. Seattle (WA): University of Washington, Seattle.

Ware, J, Jr., Kosinski, M, and Keller, SD. 1996. "A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity." *Med Care* 34 (3):220-33.

Willis, S, Stoll, J, Sweetman, L, and Borges, K. 2010. "Anticonvulsant effects of a triheptanoin diet in two mouse chronic seizure models." *Neurobiol.Dis.* 40 (3):565-572.

10 SIGNATURE PAGE

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety and Efficacy of UX007 in Subjects with Glucose Transporter Type 1 Deficiency Syndrome

Protocol Number: UX007G-CL202 Amendment 3

I have read the amended Protocol UX007G-CL202. 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.

Melanie Brandabur, MD Date
Medical Director
Ultragenyx Pharmaceutical Inc.