A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of UX007 in Subjects with Glucose Transporter Type 1 Deficiency Syndrome

Protocol Number:	**UX007G-CL201**
Original Protocol:	**07 Aug 2013**
Amendment 1:	**04 Oct 2013**
Amendment 2:	**20 May 2014**
Amendment 3:	**09 Dec 2014**
Amendment 4:	**30 Nov 2015**

Investigational Product:	UX007 (triheptanoin)
Indication:	Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)
IND Number:	118855
EudraCT Number:	2013-003771-35
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA, USA 94949
Sponsor's Responsible Medical Officer:	Melanie Brandabur, MD Medical Director Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA USA 94949 PPD
Coordinating Investigator:	Pasquale Striano, MD

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-CL201 Amendment 1

04 October 2013

The Original Protocol version of Protocol UX007G-CL201 (dated 07 August 2013) has been modified by Amendment 1 to incorporate a number of changes based on additional information acquired since the beginning of the study, feedback from clinical investigators involved in the study, and review by the United States Food and Drug Administration (US FDA). The major changes to the protocol are summarized below; additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. Sponsor's Responsible Medical Officer and associated contact information have been updated to: Emil Kakkis, MD PhD, Chief Executive Officer, Ultragenyx.

2. Study Sites. The number of study sites has increased from 8 to 10 sites globally.

3. Number of Subjects Planned. If the interim analysis criteria have been met, the additional enrollment has been changed to 30-90 subjects, for a total of 80-140 subjects.

4. Study Procedures and Assessments. The following modifications have been made to the Schedule of Events (Table 2.1) and Study Procedures and Assessments (Section 7.5):
   - The visit to the site previously indicated at Week 2 will now be conducted by telephone. The Week 4 visit (originally a telephone visit) will now be conducted at the clinic and include clinical assessments of secondary efficacy variables (i.e. CANTAB, 6MWT, and GMFM-88).
   - In lieu of the Borg Scale referenced in the ATS guideline, the Borg Rating of Perceived Exertion (RPE) will be used to assess PED occurring during the test.
   - The 24-hour EEG has been changed to an overnight EEG.
   - At Week 26, a Population PK assessment has been added which requires a total of 3 blood samples (pre-dose for all subjects and 2 additional specimens 30-180 minutes post-dose).
   - Table 2.1 has been modified to list efficacy assessments in order of administration and reflect the range allowed to collect the sample for the Erythrocyte Glucose Uptake Assay (i.e. once during Week 26, 39, or 52 Visits).

- The requirement to complete a 3-day diet diary following dose adjustment was removed.

Rationale: During the 8-week placebo-controlled Treatment Period, visits to the clinic will now be conducted at 4-week intervals. A telephone assessment of seizure incidence and safety/tolerability will take place at the end of the 2-week dose titration period. At Week 4, all subjects will be stable at the maximum dose of study drug, providing for additional assessment of safety and efficacy during the placebo-controlled phase of the study.

Changes in the conduct of the 6MWT and associated PED assessment provide clarification of proper study procedures.

The duration of EEG monitoring has been shortened to minimize discomfort and inconvenience to the subject. A minimum of 12 hours EEG monitoring is believed to provide sufficient data to assess the frequency of EEG seizures and interictal epileptiform discharges.

The changes to PK and Bioassays are consistent with the study objectives and provide for a population PK assessment (as requested by the FDA) in addition to peak PK and metabolites. Modifying the range of visits for the Erythrocyte Glucose Uptake Assay provides greater flexibility and opportunity to obtain the sample in conjunction with other blood draws, thereby minimizing additional procedures for the subject.

A 3-day diet diary is used solely for the purposes of establishing caloric intake, and not necessary following dose adjustment during the Titration Period.

5. Primary Efficacy Hypothesis. The primary efficacy hypothesis as stated in Section 5.5 has been modified as follows:

"*The primary efficacy hypothesis for the study is that UX007 is ~~superior to~~* ***more effective than*** *placebo for the ~~treatment~~* ***reduction*** *of seizures in patients with Glut1 DS…"*

Rationale: The revised language provides a more accurate description of the statistical methodology planned for the study.

6. Study Objectives, Efficacy Measures and Endpoints. There is no change to the primary efficacy measure; the primary objective language has been modified as follows:

"*Evaluate the efficacy of UX007 compared to placebo between Weeks 2 and 8 of treatment as measured by the ~~median percent~~ reduction from baseline in frequency of generalized or partial-onset seizures*"

Secondary and exploratory objectives and associated efficacy measures/endpoints of the study have been modified as outlined below:

Modifications to Study Objectives, Efficacy Assessments and Endpoints

Objective/Efficacy Measure Related To:	Original Protocol Designation	Amended Protocol Designation	Description of Change
Seizure response rate/frequency & EEG abnormalities	Secondary	Secondary	Seizure response rate is now defined as the percentage of subjects with ≥50% reduction from baseline in generalized or partial-onset seizures. Frequency of EEG abnormalities is now a separate objective.
6MWT	Secondary	Secondary	Modified objective to specify distance walked and combine with PED
GMFM-88	Secondary	Secondary	No change
CNS	Secondary	Exploratory	Moved
CANTAB	Secondary	Secondary	Generalized objective to "cognitive function"
CGI-S/CGI-I	Secondary	Exploratory	Moved
Time to event assessment of seizures	Exploratory	Secondary analysis of primary endpoint	To be defined in the SAP
Within cohort analysis	Exploratory	N/A	Deleted
PED	Exploratory	Secondary	Moved and combined with 6MWT as above
Gait analysis	Exploratory	Exploratory	Modified to include base of support Removed requirement for GAITRite walkway
Beery-VMI, RCPM	Exploratory	Optional Exploratory	Site-specific assessments only
PPVT, SF-10, PEDI-CAT, PK	Exploratory	Exploratory	No change
EEG: degree of background slowing	Exploratory	N/A	Deleted
Long-term safety, persistence of effect, suicidal ideation/behavior	Exploratory	Removed from objectives	Not a specific study objective; conducted as safety analyses

Rationale: Upon further consideration of pre-specified endpoints and the potential implications for statistical analysis and interpretation of the data, the primary objective language has been modified, and a number of secondary endpoints have now been designated as exploratory endpoints. The secondary endpoints are focused on independent domains of disease: 1) motor dysfunction, 2) cognitive dysfunction, and 3) absence and unrecognized seizure activity by EEG count. We will also assess the fraction of patients achieving a clinically large response of 50% reduction in seizures. The secondary objectives and associated efficacy endpoints will now focus on the following:

- Seizure response rate, defined as the percentage of subjects with at least 50% reduction from baseline in generalized or partial-onset seizures
- Change from baseline in frequency of seizure activity as measured by electroencephalography (EEG) abnormalities
- Change from baseline in cognitive function using the Cambridge Neuropsychological Test Automated Battery (CANTAB)
- Change from baseline in distance walked as measured by 6MWT
- Time to onset of paroxysmal exertional dyskinesia (PED) as measured during 6MWT.
- Change from baseline in gross motor function using the Gross Motor Function Measure-88 (GMFM-88)

7. Inclusion Criteria. The inclusion criteria have been modified as follows:

   1) *"~~Confirmed diagnosis of Glut1 DS~~* ***Diagnosis of Glut1 DS confirmed by SLC2A1 mutation****"*

   7) "*Not on, or not **fully** compliant with a prescribed diet plan (e.g. ketogenic diet) comprised of at least 50% total daily caloric intake from fat during previous 60 days (confirmed by 3-day diet diary at Screening), or at any time during the course of the trial*"

   Rationale. The change to inclusion criterion #1 specifies all subjects must have the diagnosis of Glut1 DS confirmed by genetic analysis of *SLC2A1* mutations, thereby providing added assurance that the study population is consistent with the proposed indication. The mutation analysis must be completed prior to study entry; Ultragenyx will not collect additional blood samples for *SLC2A1* mutation analysis as previously indicated in Section 7.5.4.1 Medical History. The change to inclusion criterion #7 provides a degree of guidance to the investigator in assessing a potential subject's level of compliance with a prescribed diet plan.

8. Treatment Administration.

   A recommended dose titration schedule has been inserted (Table 7.4.1). In addition, dose administration guidelines have been modified as follows:

   *"Treatment will be **mixed with food and** administered PO ~~with food~~ or by gastronomy tube at least four times per day (breakfast, lunch, dinner, and before bed). The dose should be divided into smaller more frequent doses with food as needed. The dose **should always** be mixed with small amounts of food ~~or drink~~ as indicated in the administration guideline, **and never administered as the oil directly**."*

   Rationale: The original protocol specified initiation of dosing using a 2-week fixed titration schedule until the subject has reached a target of 35% of total daily calories by the end of the period. The table provides recommended guidelines for the titration, while providing for some degree of discretion by the investigator for individual subject needs.

   By removing the provision to administer study drug by mixing with drink, and assuring the oil is never directly administered will provide more consistent dosing across the study population and reduce the potential risk of GI-associated adverse reactions.

9. Drug Concentration Measurements. As described in Section 7.5.3, a population PK assessment will replace the planned PK sampling for peak UX007 and metabolites at Week 26. Samples will be obtained pre- and post-dose as specified in the Schedule of Events. The assessment will take place irrespective of the study adaptation decision.

   Rationale: The additional population PK assessment will further characterize the PK properties of UX007 at steady-state, including trough levels, following 6 months of continuous treatment.

10. Pregnancy Testing. A provision to perform a serum pregnancy test if pregnancy test by urine is not feasible has been added to the protocol (Section 7.5.4.6).

    Rationale: The addition of the serum pregnancy test option provides flexibility for the site and the subject, as both methods will provide an accurate assessment of pregnancy status.

11. Suicidal Ideation and Behavior Assessments. The Ask Suicide Screening Questions (ASQ) has been replaced by the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to assess suicidal ideation and behavior in this study. The timing and age range for the assessment remain as specified in the original protocol.

Rationale: The Columbia algorithm has been used to classify suicidal adverse events in an antidepressant safety analysis by the US FDA. The US FDA has recommended the use of the C-CASA as a standardized suicidal rating system for anticonvulsant trials and other centrally acting agents and nonpsychotropic drugs.

12. Statistical Methods. Populations for data analyses have been defined (Section 7.6.2). The description of the primary efficacy endpoint analysis has been generalized to state an appropriate rank-based analysis will be applied, instead of pre-specifying the 2-sided Wilcoxon Rank Sum test (Section 7.6.3). The secondary efficacy analyses will compare the secondary efficacy variables scores after treatment to before treatment between the treated and placebo groups (Section 7.6.4). An alpha-spending function will be used to adjust the type-I error significance level for the interim and final analysis (Section 7.6.6). The sample size assumptions for the maximum of 140 subjects have been provided in Section 7.6.8.

    Rationale: While full-details of planned statistical analyses will be presented in a formal Statistical Analysis Plan, the revised information provides transparency as pre-specified changes from the original protocol.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007G-CL201 Amendment 2

20 May 2014

The amended version of Protocol UX007G-CL201 (Amendment 1, dated 04 October 2013) has been modified by Amendment 2 to incorporate a number of changes based on additional information acquired since the beginning of the study, feedback from clinical investigators involved in the study, and review by Health Authorities. The major changes to the protocol are summarized below; additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. Sponsor's Responsible Medical Officer and associated Medical Monitor contact information (Section 8.5.6) have been updated to:

   Javier San Martin, MD, Vice President, Clinical Development, Ultragenyx.

2. Number of Subjects Planned. Section 7.8.6 has been revised to reflect statistical assumptions for the interim analysis used to determine enrollment and sample size re-estimation. An interim analysis will now be conducted after approximately 16 subjects have completed the double-blind Treatment Period. If the interim analysis criteria have been met, the total number of subjects has been changed from 80 - 140 to now be 40-100 subjects. If the interim analysis criteria are not met, the study will continue as a Phase 2 study until ~40 subjects have been enrolled. The previous protocol stated subjects may be replaced after receiving study drug and prior to Week 8. This has been amended such that subjects who withdraw or are removed from the study prior to randomization may be replaced on a case-by-case basis, at the discretion of Ultragenyx (Section 7.3.3).

   Rationale: As described in Section 7.6.10, for the study to be adequately powered as a pivotal study, a sample of approximately 40 completed subjects was estimated to be adequate to detect a 50% between-group difference in seizure rate per 4 weeks with power of 80% and population standard deviation of 55% using Wilcoxon's rank sum test.

3. Primary Efficacy Hypothesis. Section 5.5 has been modified as follows to clarify specific seizure types to be investigated as part of the primary efficacy hypothesis.

UX007 is more effective than placebo for the reduction of seizures in patients with Glut1 DS, as measured by the reduction from baseline in frequency of generalized or partial- onset seizures, ***including: 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 seizures,*** *between Weeks 2 and 8 of treatment*.

4. Study Objectives. The following objectives have been modified or added to Section 6 to align study objectives with modifications to study design and endpoints:

   Modified Primary Objectives:

   - *Evaluate the efficacy of UX007 compared to placebo, between Weeks 2 and 8 of treatment, as measured by the reduction from* ***the Baseline Period*** ~~*in*~~ *frequency of generalized or partial-onset seizures*

   Modified Secondary, Exploratory, and Optional Exploratory Objectives:

   The periods during which the efficacy of UX007 compared to placebo will be evaluated have been modified from "change from baseline" to specify either change from Randomization or the Baseline Period

   Additional Secondary Objectives:

   - *Evaluate long term efficacy as measured by changes from baseline in frequency of generalized or partial-onset seizures over time through week 52*
   - *Evaluate the optimal dose to control seizures and impact on other clinical manifestations during the Dose Exploration Period*

   Additional Exploratory Objective:

   - *Evaluate the efficacy of UX007 compared to placebo, between Weeks 2 and 8 of treatment, as measured by the reduction from the Baseline Period frequency of absence seizures*

5. Overall Study Design and Plan. Section 7.1 has been modified to include a Dose Exploration Period which will be conducted in a subset of approximately 40 subjects. The remaining subjects enrolled will continue with the optimal dose achieved during the previous 26 weeks. The study schematic (Figure 7.1.1) has been modified to reflect the design change. Specific rationale for the selection of 20 and 40% dose levels is provided in Section 7.4.4.1. The Dose Exploration Period is described as follows:

Following the Week 26 visit, approximately the first 40 subjects will participate in a 10-week Dose Exploration Period to assess the impact of UX007 dose level on seizure control, other clinical manifestations such as movement disorders and cognitive deficits, and tolerability. For subjects participating in the Dose Exploration Period, the dose will be titrated over 1 week down to 20% of total daily caloric intake. After 4 weeks at the 20% dose level, the subject will be evaluated for safety and efficacy measures of seizure control, motor and cognitive function.

If there are breakthrough seizures during the down titration period, as defined by an increase in frequency of 1 seizure in a 4 week period [except absence], relative to the previous 4 week period on a stable UX007 dose, or in the opinion of the investigator there has been a worsening of symptoms prior to completion of the 4 week period, the subject may begin the up-titration phase early.

After 4 weeks at the 20% dose level, the UX007 dose will then be titrated up over 1 week to 40% of total daily caloric intake and maintained at that level for 4 weeks. If a subject cannot tolerate titrating up to the 40% dose level, the dose should be titrated to the maximum tolerated dose as determined by the Investigator. After 4 weeks at the 40% (or maximum tolerated) dose level, the subject will be evaluated for safety, and efficacy measures of seizure control, motor and cognitive function.

At the end of the Dose Exploration Period, the subject will continue in the open-label Extension period, and maintained on the UX007 dose (as determined by the Investigator) that provided the maximum improvement in clinical status with acceptable tolerability, and continued on this dose for the duration of the study. If marked improvements in clinical status were not observed at a higher dose level and/or tolerability was unacceptable, the subject will return to the UX007 dose level where maximal benefit was achieved as defined by seizure control and improvements in motor and/or cognitive symptoms. As determined by the Investigator, this may be the pre-titration UX007 dose from Week 26 or the 20% dose given during the down titration phase.

<u>*Rationale*</u> (also provided in Section 7.2)*:* A dose exploration evaluation in approximately 40 subjects has been added to the protocol to determine whether the proposed dose is the optimal and necessary dose for UX007 to control seizures and impact other clinical manifestations. The demonstration of a withdrawal effect (with an exit clause that would allow the subject to more quickly move to the up titration phase if there is a marked change in clinical status during the down titration phase), and a return to control afterward would demonstrate both that a higher dose was necessary and that UX007 had a sustained effect.

6. <u>Inclusion Criteria</u>: Section 7.3.1 has been modified as follows:

   2) *Males and females, aged ~~3 – 17~~* ***1 – 35*** *years (inclusive) at the time of informed consent*

3) *Average of at least ~~5~~ **4** observable seizures (generalized [except absence] or partial-onset [simple partial motor, complex partial, or secondarily generalized] seizures) ~~per month~~ **in 4 weeks** over the last ~~6 months~~ **24 weeks**, by subject or caregiver report*

4) *At least 4 observable seizures (generalized [except absence] or partial-onset [simple partial motor, complex partial, or secondarily generalized] seizures) ~~per month~~ **in 4 weeks** during the Baseline Period, with no 3-week seizure-free period during the Baseline Period*

7) *Not on, or not fully compliant with a prescribed diet plan (e.g. ketogenic diet) comprised of at least **60%** ~~50%~~ total daily caloric intake from fat during previous ~~60~~ **14** days (confirmed by 3-day diet diary at Screening)~~, or at any time during the course of the trial)~~*

12) *Females ~~who have reached menarche~~ **of childbearing potential** must have a negative pregnancy test at Screening, be willing to use acceptable method of contraception and have additional pregnancy tests during the study. **Females considered not of childbearing potential include those who have not reached menarche, had total hysterectomy, have been in menopause for at least two years, or have had tubal ligation at least one year prior to Screening**.*

Rationale: The United States Food and Drug Administration (FDA) has recommended expanding recruitment to include patients younger than 3 years. Clinical experience with triheptanoin and nonclinical data with UX007 support dosing of children as young as 6 months of age. A GLP 3-month interim toxicology study in juvenile Yucatan Mini-Pigs which ran concurrently as part of the 9 month chronic toxicity study to allow dosing in younger age groups, has been completed; interim results have been inserted in Section 5.2.2.

The patient population was further expanded to also include adult subjects up to 35 years of age. The trial investigators have noted there are adult Glut1 DS patients who continue to have a similar phenotype of breakthrough seizures into their thirties, significant movement disorders (estimated at 90% by De Vivo), and have a more difficult time maintaining the ketogenic diet. The expanded age range of the population will strengthen the ability to evaluate a possible impact on seizures and movement disorders.

Modifications to inclusion criteria #3 and 4 provide alignment with study endpoints used to capture seizure frequency.

Based on feedback from investigators and experts in the field, inclusion criterion #7 was modified to increase the percent of calories from fat to 60% in a prescribed diet. The change aligns with standard practices. In addition, these investigators and experts in the field noted the potential for carryover effects from ketogenic or other high-fat prescribed diets are minimal, and a 7-14 day washout period would be more than adequate for patients who wish to discontinue or are non-compliant with current diet plans. Therefore, the duration required to demonstrate non-compliance (or no treatment) with a prescribed diet plan has been reduced to 14 days to minimize the time a potential subject would be without adequate dietary control of their condition, and thereby minimize burden and possible risk to the individual. In addition, guidance was added to Section 7.5.4.11 that subjects should be below 25% dietary fat (not including the oil) on the day of randomization and throughout the trial. The rationale is that if patients are on a diet with >25% dietary fat, then they could possibly become ketotic with the addition of placebo oil at 35% of caloric intake.

Modifications to inclusion criterion #12 provide alignment with the expanded age range for eligible patients.

7. Investigational Product. To ensure adequate blinding of the investigational product during the double-blind Treatment Period, 1000 mL UX007 and placebo will be provided in 1 L round amber-colored glass bottles. During the open-label Extension Period of the study, UX007 will be dispensed in 1 L round, translucent high-density polyethylene (HDPE) bottles (Section 7.4.1). A provision to allow mixing of UX007 (or placebo) with formula has been included given the revised age range of the study population.

8. Prohibited Medications. Barbituates and prescribed high-fat diets (e.g. ketogenic diet) have been added to the list of medications prohibited throughout the study (Section 7.4.6.1).

   Rationale: Barbituates may inhibit the Glut1 transporter, thereby confounding efficacy and interpretation of study results. As required for study inclusion, the subject must not be on, or compliant with a prescribed high-fat diet plan, and should not participate in such a plan throughout the course of the study.

9. Study Procedures and Assessments. The following modifications have been made to the Schedule of Events (Table 2.1) and Study Procedures and Assessments (Section 7.5):

   - Subjects participating in the Dose Exploration Period will return for 2 additional visits to assess efficacy, pharmacokinetic/metabolites, and safety following 1 week titration and 4-weeks treatment at each dose level (i.e. Weeks 31 and 36, within a 3 day visit window).
   - The visit previously scheduled at Week 39 has been changed to Week 44.
   - Peabody Picture Vocabulary Test will be administered at select sites only.

Rationale: Several components of efficacy and safety will be measured before and after each titration during the Dose Exploration Period to assess change in efficacy, safety and tolerability. These will include change in seizure frequency, cognition (i.e. CANTAB, PPVT), motor function (i.e. 6MWT, GMFM-88), EEG abnormalities (Week 31 only), levels of triheptanoin metabolites, AE rate, and changes in assessments of how the subject is doing (i.e. PEDI-CAT, CGI). Given the 2 additional visit requirements at Weeks 31 and 36, the Week 39 visit was moved out to Week 44.

10. Efficacy Measures. The following changes have been made to Section 7.5:

    - The description of the primary efficacy measure (Section 7.5.2.1) has been modified to clarify seizure types defined and recorded in the study diary.
    - The Borg Rating of Perceived Exertion (RPE) has been removed as an assessment during the 6-minute walk test (6MWT).
    - The severity of paroxysmal exertional dyskinesia (PED) will be assessed by the physical therapist, not the subject as previously indicated.
    - The frequency of absence (and other) seizures as captured in the study diary has been defined as an exploratory measure (Section 7.5.2.2).
    - The Short-Form 12 (SF-12) Health Survey for adults will be administered to adult subjects as an exploratory measure.

    Rationale: The listing of specific seizure types provides alignment with the study diary. Following review of the study protocol, the US FDA requested the daily diary be used in addition to electroencephalography to document absence and myoclonic seizures.

    The Borg RPE scale was removed as it is not possible to capture perceived exertion in the middle of the 6MWT. In addition the scale is difficult for children to comprehend and many subjects have cognitive impairment. The physical therapist is trained to assess the severity of PED events, as such PED severity will not be assessed by the subject.

    Since the age range of the population has expanded to include young children and adults, age-appropriate modifications have been made to the secondary and exploratory efficacy measures. The SF-12 was included to assess functional health and well-being in adult subjects (as a parallel assessment to the SF-10 in children).

11. Drug Concentration Measurements. Based on feedback received from the FDA, Section 7.5.3 has been modified to specify the trough (pre-dose) population PK sample will be obtained within 15 minutes of dosing. Additional PK samples will also be obtained should potentially related serious adverse events occur, if feasible.

12. Pregnancy Testing. The language in Section 7.5.4.6 has been modified to specify unknown risks and detail acceptable methods of contraception, including abstinence, for females and males of childbearing potential.
13. Suicidal Ideation & Behavior Assessments. Section 7.5.4.7 has been corrected to describe the Columbia-Suicide Severity Rating Scale (C-SSRS) as the instrument used to prospectively assess suicidal ideation and behavior.
14. Statistical Analysis & Determination of Sample Size. Section 7.6 has been updated to mention the handling of missing, unused, or spurious data, and include the aforementioned clarifications, additional endpoints, interim analyses, and determination of sample size. The analysis populations have been further defined. The FDA also requested a secondary analysis for the potential of tachyphylaxis (i.e., long term efficacy).

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007G-CL201 Amendment 3

09 Dec 2014

The amended version of Protocol UX007G-CL201 (Amendment 2, dated 20 May 2014) has been modified by Amendment 3 to incorporate a number of changes based on additional information acquired since the beginning of the study, from feedback provided by clinical investigators involved in the study, and review by Health Authorities. The major changes to the protocol are summarized below; additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. Sponsor's Responsible Medical Officer and associated Medical Monitor contact information (Section 8.5.6) have been updated to:

   Sunil Agarwal, MD, Chief Medical Officer.

2. The adaptive study design component of the protocol was eliminated. This change was carried throughout the protocol and the title of the study was updated to reflect this change.

   Rationale: An interim analysis to adapt this study design is no longer planned. The plan is to look at the totality of the data from this Phase 2 study to determine what additional studies will be needed to better characterize the safety and efficacy of UX007 in patients with Glut1 DS.

3. Inclusion criteria 3 and 4 were updated to include subjects with treatment-resistant absence seizures. This change was also updated in multiple sections of the protocol; the term absence seizure includes both typical and/or atypical absence seizures.

   Rationale: The inclusion criteria are being updated to also include subjects that have only absence seizures (based on medical history and Screening EEG). This change is secondary to recently published data by Pascual et al., which demonstrated clinical activity of triheptanoin in patients with Glut1 DS with absence seizures. In this study patients receiving triheptanoin demonstrated a reduction in their rate of absence seizures and improvements in their neuropsychological performance (Pascual et al. 2014).

4. Inclusion criterion #3 was updated to allow for fewer observable seizures in 4 weeks over the last 24 weeks; originally set at 4, this amendment reduces the observable seizures to 2.

   Rationale: This will allow potentially for the inclusion of more subjects into the study without compromising the ability to detect a signal with UX007, assuming UX007 meaningfully reduces seizure activity.

5. Inclusion criterion #9 was removed; subjects no longer are required to be naïve to UX007.

   Rationale: Taking into account the short-lived pharmacokinetic and pharmacodynamics profile of UX007, there should be no residual effect of UX007 if subjects have not been exposed in the past 30 days prior to screening. Additionally, taking into account the Screening period, the time off of drug would be even longer than 30 days.

6. Inclusion criterion #6 was updated to clarify that "up to" 3 concomitant AEDs are allowed for inclusion into the study.

   Rationale: This change was made for clarification.

7. The primary and secondary objectives of the study were updated (refer to the synopsis and Section 6). Similarly, the criteria for evaluation (synopsis and Section 7.5) and the primary and secondary endpoints (Section 7.6) were updated to reflect the changes to the objectives to include a more robust evaluation of triheptanoin in patients with absence seizures.

   Rationale: This change was made for clarification since we are now including patients who can qualify based on absence seizures only. This change was made secondary to the recent publication by Pascual et al. as referenced earlier.

8. The randomization was changed from 1:1 to 3:1 (UX007: placebo).

   Rationale: This change was based on discussions with caregivers of patients with Glut1 DS. The caregivers have stated that in a disease for which seizures are a primary manifestation, a 50% chance of receiving placebo has not been acceptable to the majority of potential patients and their families. Also, appreciating that this is a Phase 2 study and the fact that this change to the randomization schema will also enable the collection of additional safety data on subjects who receive UX007 during the study, the sponsor believes this change is clinically appropriate.

9. An EEG assessment was added at the Screening Visit.

   Rationale: The decision to add an EEG assessment at the Screening Visit is to confirm the diagnosis of absence seizures for patients who potentially qualify for the study based on a history of absence seizures. EEG is well recognized as the most reliable method to capture absence seizures, whereas for other seizure types a patient history is considered clinically acceptable.

10. Study drug accountability in Section 8.3 was clarified to indicate that study drug will be properly packaged for transport by the subject or for shipment by the clinical site.

    Rationale: This text was clarified to ensure a clear process for chain of custody of study drug.

11. Selection of Study Population in Section 7.3 was updated to clarify that enrollment may include subjects from neighboring countries within the European Union, Canada, and South America.

    Rationale: There are limited investigative sites participating in this study and because Glut1 DS is a rare disease, there may be subjects from neighboring countries who may be considered for study participation.

12. Exclusion criterion #5 was changed to read "pregnant and/or breastfeeding an infant at Screening" from "breastfeeding an infant at Screening."

    Rationale: This change was made for clarification that both pregnant and breastfeeding subjects will be excluded from participation in the study.

13. Section 7.3.3 (Removal of Subjects from Therapy or Assessment) was updated to clarify the conditions under which subjects either **will be** removed or **may be** removed from study participation.

    Rationale: It was important to clarify that subjects will be removed when an unacceptable AE occurs or if an illness occurs that (in the judgment of the investigator or Ultragenyx) might invalidate the study or place the subject at risk. Alternatively, subjects may be removed if requested (by subject, investigator, or Ultragenyx) for administrative/other reasons or if the subject has a protocol deviation or exhibits unreliable behavior.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX007G-CL201 Amendment 4

30 Nov 2015

The amended version of Protocol UX007G-CL201 (Amendment 3, dated 09 December 2014) has been modified by Amendment 4 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 and other experts in the field. The major changes to the protocol are summarized below; additional minor changes have also been made for consistency and clarity but are not included in this summary.

1. Sponsor's Responsible Medical Officer and associated Medical Monitor contact information (Section 8.5.5) have been updated to Melanie Brandabur, MD, Medical Director. In addition, the safety contact information in Section 8.5.5 has been updated.
2. Edited Inclusion Criterion #2 to state that all subjects at least 1 year of age are eligible for participation in this study. There is no longer an age limit of 35 years in the study. This change affected the synopsis and Section 7.3.1 of the protocol.

   Rationale: This change was made to allow inclusion of subjects regardless of age.

3. Edited Inclusion Criterion #7 by removing specific instructions regarding percent of daily fat intake.

   Rationale: This change was made for clarity.

4. Updated Exclusion Criterion #1 to allow for subjects to have serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels exceeding 3X (previously 2X) the upper limit of normal at Screening.

   Rationale: This change was made to be more consistent with agency guidelines for industry regarding drug-induced liver injury. USDHHS FDA, CDER, CBER, 2009.

5. Updated Section 7.4.6.1 of the protocol to remove valproate as a prohibited medication and include pancreatic lipase inhibitors in the list of excluded medications. A list of these medications was added to Exclusion Criterion 6.

   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).

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.

6. Updated Section 8.5.1 (Definition of Adverse Events) with the following text: "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."

   Rationale: Updated for clarification of the SAE definition.

7. Updated Section 8.5.4 (Adverse Event Reporting to Ultragenyx)

   Rationale: Updated to match the current Ultragenyx template.

8. Primary objective changed to 'Evaluate the efficacy of UX007 compared to placebo as measured by the reduction from randomization to week 8 in frequency of seizures'. This change affects multiple sections of the protocol related to statistical evaluations and analyses.

   Rationale: To correctly reflect that the primary endpoint is to measure change in seizure frequency for all seizure types, including absence seizures, as was the intent with the previous amendment.

9. The text "at select sites" is now used consistently for the Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT) and Gross Motor Function Measure-88 (GMFM-88) assessments in the schedule of events and body of protocol.

   Rationale: This change was made for clarification.

10. The EEG at Screening for patients with absence seizures only is required for ~3 hours, not overnight.

    Rationale: This change was made for patient convenience.

11. The Erythrocyte Glucose Uptake Assay has been removed from the protocol. This change affects the schedule of events (Table 2.1) and Section 7.5.3.

    Rationale: This change was made to reduce patient burden.

12. Plasma level sample collection range for the population PK study at Week 26 was changed from 30 – 180 minutes to 60 and 180 minutes.

    Rationale: In consultation with a PK expert/advisor, sampling timepoints have been defined as 60 and 180 minutes post-dose.

2 SYNOPSIS

TITLE OF STUDY:
A randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of UX007 in subjects with glucose transporter type 1 deficiency syndrome

PROTOCOL NUMBER:
UX007G-CL201

STUDY SITES:
Approximately 15 sites globally

PHASE OF DEVELOPMENT:
Phase 2

RATIONALE:
Glucose Transporter Type 1 Deficiency Syndrome (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 treatment 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 represent the subgroup of Glut1 DS patients who are most in need of an alternative therapy to the KD. Given the significant unmet medical need in Glut1 DS patients not on KD, UX007 will be studied in this subgroup.

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.

The seizures due to Glut1 DS are most prominent in the pediatric population and are typically refractory to AEDs. For these reasons, the proposed Phase 2 study is designed to assess the safety and efficacy of UX007 in reducing the frequency of seizures in the pediatric population (and older patients who are still having seizures) that are not able to comply with or tolerate the KD. The study will also evaluate the pharmacokinetics (PK) of energy-containing metabolites and correlate these to the potential treatment effects.

OBJECTIVES:
The primary objectives of the study are to:

- Evaluate the efficacy of UX007 compared to placebo as measured by the reduction from

randomization to week 8 in frequency of seizures. Observable generalized and partial-onset seizures measured for 6 weeks by diary and absence seizures measured overnight by electroencephalography (EEG).

- Evaluate the safety of UX007 via adverse event (AE) rates, laboratory values, and electrocardiogram (ECG)

The secondary objectives of the study are to:

- Evaluate the efficacy of UX007 compared to placebo, as measured by:
  - Seizure response rate, defined as the percentage of subjects with at least 50% reduction from randomization to week 8 in frequency of seizures
  - Change from randomization to Week 8 in cognitive function using the Cambridge Neuropsychological Test Automated Battery (CANTAB)
  - Change from randomization to Week 8 in distance walked as measured by 6MWT
  - Time to onset of paroxysmal exertional dyskinesia (PED) as measured during 6MWT from randomization to Week 8
  - Change from randomization to Week 8 in gross motor function using the Gross Motor Function Measure-88 (GMFM-88)
- Evaluate long-term efficacy as measured by changes from randomization in frequency of seizures over time through Week 52
- Evaluate the optimal dose to control seizures and impact on other clinical manifestations during the Dose Exploration Period

Exploratory objectives are to:

- Evaluate the effects of UX007, from randomization through Weeks 8 and 52 on:
  - Neurological function using the Columbia Neurological Score (CNS)
  - Physician global impression of change in clinical status using the Clinical Global Impression - Severity scale (CGI-S) and Clinical Global Impression - Improvement scale (CGI-I)
  - Receptive vocabulary using the Peabody Picture Vocabulary Test (PPVT)
  - Subject or caregiver-reported quality of life using Short Form-10™ (SF-10) Health Survey for Children or SF-12 for adults
  - Functional disability by caregiver report using the Pediatric Evaluation of Disability

Inventory – Computer Adaptive Test (PEDI-CAT)

- Gait, using gait analysis by computerized mat
- PK properties of UX007 and its metabolites

Exploratory objectives are to evaluate the effects of UX007, from randomization through Weeks 8 and 52 on (to be administered at select sites):

- Visual motor integration using the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery-VMI)
- Spatial understanding and abstract reasoning using the Raven's Coloured Progressive Matrices (RCPM)

PRIMARY EFFICACY HYPOTHESIS:

UX007 is more effective than placebo for the reduction of seizures in patients with Glut1 DS, as measured by the reduction from randomization in frequency of generalized or partial-onset seizures, including: Generalized Tonic-Clonic, Generalized Tonic, Generalized Clonic, Generalized Atonic, Partial/Focal with Secondary Generalization, Myoclonic, Myoclonic Atonic, Myoclonic Tonic, Complex Partial/Focal, Absence, and Simple Partial/Focal Motor seizures.

STUDY DESIGN AND METHODOLOGY:

UX007G-CL201 is a randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of UX007 in Glut1 DS. The study will enroll approximately 40 pediatric, adolescent, and adult subjects who are currently not on, or not compliant with a KD or other high fat diet. Enrolled subjects are otherwise able to maintain standard of care treatment with up to 3 AEDs throughout the duration of the study.

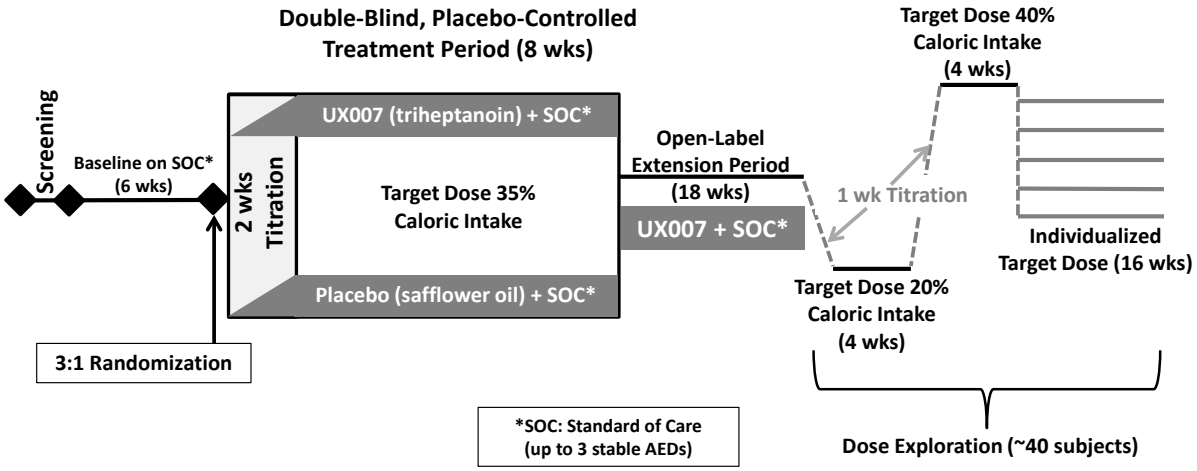
Beginning with the Screening visit, subjects will record seizure frequency during the 6-week Baseline Period. If the subject does not meet the seizure count criteria, the subject will be considered a screen failure and will not be randomized. At the end of the Baseline Period, eligible subjects will be randomized in a 3:1 ratio to either UX007 or placebo. Dosing will be initiated using a 2-week titration schedule until the subject has reached 35% of total daily calories from study drug (~1-4 g/kg/day depending on age). If a subject has not reached the target of 35% of total daily calories by the end of the 2-week titration period, dose titration should continue until the maximum tolerated dose is reached.

After the initial 8-week double-blind Treatment Period, the open-label Extension Period will begin, wherein all subjects will be treated with UX007 through Week 52 of the study. A population-PK analysis at Week 26 will provide data on metabolite levels with all subjects on UX007. Following the Week 26 visit, all 40 subjects will participate in a 10-week Dose Exploration Period to assess the impact of UX007 dose level on seizure control, other clinical manifestations such as movement disorders and cognitive deficits, and tolerability. At the end of the Dose Exploration Period, the

subject will continue in the open-label Extension period, maintained on the UX007 dose (as determined by the Investigator) that provided the maximum improvement in clinical status with acceptable tolerability, and continued on this dose for the duration of the study. Long term safety and maintenance of effect of UX007 will be assessed during the Extension Period.

Figure 2.1 provides a schematic of the study design. Subjects who complete treatment through Week 52 may have the option to continue UX007 treatment, if warranted, in a separate open-label extension study.

Figure 2.1: UX007G-CL201 Study Schema



NUMBER OF SUBJECTS PLANNED:

The study will enroll approximately 40 pediatric, adolescent, and adult subjects who are currently not on, or not compliant with a KD or other high fat diet. Subjects who withdraw or are removed from the study prior to randomization may be replaced on a case-by-case basis, at the discretion of Ultragenyx.

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 confirmed by *SLC2A1* mutation

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

3) Average of at least 2 observable seizures (generalized or partial-onset [simple partial motor, complex partial, absence, or secondarily generalized seizures) in 4 weeks over the last 24 weeks, by subject or caregiver report

4) At least 2 observable seizures (generalized or partial-onset [simple partial motor, complex partial, or secondarily generalized seizures) in 4 weeks during the Baseline Period, with no 3-week seizure-free period during the Baseline Period OR absence seizures documented on

Screening EEG

5) Continuing to have seizures despite a prior or current use of at least 1 AED

6) Allowed to be on up to 3 concomitant AEDs that must have been stable in dose at least 2 weeks prior to the beginning of screening and anticipated to remain stable in dose through the end of the 8-week, placebo-controlled Treatment Period

7) Not on, or not fully compliant with a prescribed diet plan (e.g. KD)

8) Plasma level of beta-hydroxybutyrate (BHB) ≤ 1 mmol/L (non-fasting) at Screening

9) Provide written or verbal assent (if possible) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures

10) Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, comply with accurate completion of the seizures diary, and likely to complete the 8-week, placebo-controlled, Treatment Period

11) Females of childbearing potential must have a negative pregnancy test at Screening, be willing to use an acceptable method of contraception, and have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have not reached menarche, had total hysterectomy, have been in menopause for at least two years, or have had tubal ligation at least one year prior to Screening.

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

1) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels exceeding 3X the upper limit of normal at Screening

2) Any known hypersensitivity to triheptanoin or safflower oil that, in the judgment of the investigator, places the subject at increased risk for adverse effects

3) Prior use of triheptanoin within 30 days prior to Screening

4) History of, or current suicidal ideation, behavior and/or attempts

5) Pregnant and/or breastfeeding an infant at Screening

6) Participants unwilling or unable to discontinue use of a prohibited medication (Section 7.4.6.1 [MCT oil, barbiturates, pancreatic lipase inhibitors, KetoCal or other KD supplements, and/or KD]) or other substance that may confound study objectives

7) Use of any investigational product (drug or supplement, including medium chain

triglyceride [MCT] oil) within 30 days prior to Screening, or at any time during the study

8) Has a condition of such severity and acuity, in the opinion of the investigator, that it warrants immediate surgical intervention or other treatment

9) 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 introduces additional safety concerns (e.g., diabetes mellitus, other concurrent neurological or psychiatric disorders)

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION:

UX007 (triheptanoin) is a colorless to yellow oil. During the 8 week double blind period of the study 1000 mL UX007 will be provided in 1 L round amber colored glass bottles. During the open label Extension Period of the study, UX007 will be dispensed in 1 L round, translucent high-density polyethylene (HDPE).

UX007 is titrated over 2 weeks to a dose of 35% of total daily caloric intake. During the Dose Exploration Period, the dose will be titrated down over 1 week to 20% of total daily caloric intake. If there are breakthrough seizures during the down titration period, as defined by an increase in frequency of 1 seizure in a 4 week period, relative to the previous 4 week period on a stable UX007 dose, or in the opinion of the investigator there has been a worsening of symptoms prior to completion of the 4 week period, the subject may begin the up-titration phase early. The UX007 dose will then be titrated up over 1 week to 40% of total daily caloric intake and maintained at that level for 4 weeks. If a subject cannot tolerate titrating up to the 40% dose level, the dose should be titrated to the maximum tolerated dose as determined by the Investigator.

At the end of the Dose Exploration Period, the subject will 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. If marked improvements in clinical status were not observed at a higher dose level and/or tolerability was unacceptable, the subject will return to the UX007 dose where maximal benefit was achieved as defined by seizures control and improvements in motor and/or cognitive symptoms.

UX007 is a liquid, intended for oral (PO) administration. UX007 will 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. The dose should always be mixed with small amounts of food as indicated in the administration guidelines and never administered as the oil directly.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

Placebo will consist of safflower oil matching the appearance of UX007. Dose level and mode of administration will be identical to that of UX007 during the double-blind Treatment Period.

DURATION OF TREATMENT:

The planned duration of treatment in this study is 52 weeks, consisting of an 8-week placebo-controlled, double-blind Treatment Period, followed by a 44-week open-label Extension Period. Within the open-label Extension Period, up to 40 subjects will participate in a 10-week Dose Exploration Period, beginning after the Week 26 visit. All subjects who have completed the 8-week Treatment Period will be eligible for the Extension Period, during which all subjects will receive UX007; no placebo will be administered during the Extension Period.

CRITERIA FOR EVALUATION:

Efficacy:

Primary Efficacy Variable:

- Seizure frequency reduction: Percent reduction from randomization to week 8 in frequency of seizures. Observable generalized and partial-onset seizures measured for 6 weeks by diary and absence seizures measured overnight by electroencephalography (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, and Simple Partial/Focal Motor and Absence.

Secondary Efficacy Variables*:

- Seizure response rate: Percentage of subjects with at least 50% reduction from randomization to week 8 in frequency of seizures
- Observable seizures via diary: Observable seizure frequency reduction and observable seizure response rate as measured by diary
- Absence seizures via EEG: Absence seizure frequency reduction and absence seizure response rate as measured by EEG
- Cambridge Neuropsychological Test Automated Battery: Neuropsychological function measured using a standardized, computerized battery of tests designed to assess visual memory, working memory, new learning and reaction time
- Six Minute Walk Test: Walking ability measured by the total distance walked (meters) in a 6-minute period. The percent of predicted normal distance walked will be determined.
- Paroxysmal Exertional Dyskinesia: Time to onset of PED as observed during the 6MWT
- Gross Motor Function Measure-88: Gross motor function evaluated using a standardized observational measure of abilities in the following 5 domains: lying/rolling, sitting, crawling/kneeling, standing, and walking/running/jumping (at select sites)

Exploratory Efficacy Variables*:

- Columbia Neurological Score: Neurological findings in 12 domains quantitated to produce a total score ranging from 0-76
- Clinical Global Impression - Severity scale and Clinical Global Impression - Improvement scale: The global impression of disease severity at baseline (CGI-S) and the degree of change in clinical status (CGI-I) as assessed by a physician
- Peabody Picture Vocabulary Test: Receptive vocabulary measured using picture tests administered by a clinician (at select sites)
- Short-Form Health Surveys (SF-10 for Children OR SF-12): Quality of life as measured by subject or caregiver-reported physical and mental health status
- Pediatric Evaluation of Disability Inventory – Computer Adaptive Test: Functional disability as measured by caregiver-reported ability to perform activities of daily living in the following functional domains: Daily Activities, Mobility, Social/Cognitive and Responsibility (at select sites)
- Gait analysis: Stride length, cadence, velocity, base of support and percentage of cycle time spent in double support performed and evaluated by a physical therapist during the 6MWT (at select sites)
- Beery-Buktenica Developmental Test of Visual Motor Integration: Visual-motor integration measured using a design copy test administered by a clinician (at select sites)
- Raven's Coloured Progressive Matrices: Spatial understanding and abstract reasoning using picture tests administered by a clinician (at select sites)

* The Investigator may use clinical judgment in deciding whether to administer certain assessments to subjects based on age, development, and cognitive ability, as appropriate.

Pharmacokinetics of UX007 and Metabolites:

- Plasma peak levels of UX007 and metabolites at specific times during the Treatment and Extension Periods
- Population PK study at Week 26: Plasma levels at trough (pre-dose [within 15 minutes]) and at 60 and 180 minutes after administration of UX007

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

- Vital signs and weight
- Physical examination and ECG findings
- Clinical laboratory evaluations

- Pregnancy testing/pregnancy of partner
- Suicidal ideation and behavior assessments
- Concomitant medications

Data Monitoring Committee
An independent DMC with appropriate expertise in the conduct of clinical trials in children will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial.

STATISTICAL METHODS:

A full description of the statistical evaluations will be provided in the Statistical Analysis Plan (SAP).

Sample size estimate:

For the study to be adequately powered, a sample of approximately 40 completed subjects was estimated to be adequate to detect a 50% between-group difference in seizure rate per 4 weeks with power of approximately 80% and population standard deviation of 55% using two-sample t test at one-sided alpha level of 0.05.

Primary Efficacy Analysis:

The primary efficacy evaluation is the percent reduction from randomization to week 8 in frequency, normalized to a 4 week rate, of seizures The primary efficacy comparison will be made using an appropriate analysis as defined in the SAP.

Secondary Efficacy Analyses

The secondary efficacy analyses will compare the secondary efficacy variables scores after treatment to before treatment between the treated and placebo groups. The specific tests and analyses will be defined in the SAP.

Included in these analyses will be a predefined per protocol analysis of those subjects that achieve at least 30% of calorie intake or higher as the tolerated dose level, in addition to receiving at least 80% of expected doses, to assess whether a subpopulation of the highest dose subjects have a larger difference in efficacy.

Adverse Events Analysis:

The original terms used in the CRFs by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during treatment (i.e., treatment-emergent AE) 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 using the safety population. Special attention will be given to those subjects who died, discontinued treatment due to an AE, or experienced a SAE.

Table 2.1: Schedule of Events

VISIT NUMBER*	1	2	3 (Phone)	4	5	6	7	DE 1#	DE 2#	8	9
VISIT NAME	Screening	Randomization	End of Titration	Treatment Period		Extension Period					
WEEK [1]	-6	0	2	4	8	14	26	31	36	44	52/ ET
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Medical History [2]	X										
EFFICACY MEASURES											
Seizure incidence (diary review) [3]	X	X	X	X	X	X	X	X	X	X	X
Computerized Neuropsychological Test - Cambridge Neuropsychological Test Automated Battery (CANTAB) [4]	X	X		X	X		X	X	X		X
Peabody Picture Vocabulary Test (PPVT) [4]	X				X		X	X	X		X
Short Form-10 (SF-10) or SF-12 Health Survey (age-appropriate instrument)		X			X		X				X
Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT)[4]		X			X		X	X	X		X
6-minute Walk Test (6MWT)[5] PED Observation Gait Analysis [select sites]	X	X		X	X		X	X	X		X
Gross Motor Function Measure-88 (GMFM-88)[4, 5]		X		X	X		X	X	X		X
Columbia Neurological Score (CNS)		X			X		X				X
Clinical Global Impression: Improvement (CGI-I) & Severity (CGI-S)[6]		X			X		X	X	X		X
Overnight Electroencephalogram (EEG)[7]	X	X			X		X	X			
Beery-Buktenica Developmental Test of Visual Motor Integration (Beery-VMI) [4]	X				X		X				X

VISIT NUMBER*	1	2	3 (Phone)	4	5	6	7	DE 1#	DE 2#	8	9
VISIT NAME	Screening	Randomization	End of Titration	Treatment Period		Extension Period					
WEEK [1]	-6	0	2	4	8	14	26	31	36	44	52/ ET
Raven's Coloured Progressive Matrices (RCPM)[4]	X				X		X				X
PHARMACOKINETICS/BIOASSAYS											
Peak Plasma UX007 and Metabolites[8]	X[7]	X			X			X	X		X
Population PK assessment[8]							X				
SAFETY ASSESSMENTS											
Vital Signs & Weight[9]	X	X		X	X	X	X	X	X	X	X
Electrocardiogram (ECG)[10]	X				X						X
Physical Examination[11]	X				X		X				X
Clinical Laboratory Tests[12]	X	X			X		X	X	X		X
Urine Pregnancy Test (if applicable)	X	X			X		X				X
Suicidal Ideation & Behavior Assessment	X	X		X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Interim Monitoring Calls[13]	X	X	X	X	X	X	X			X	X
TREATMENT & DIETARY ASSESSMENTS											
Dispense Study Drug[14]		X		X	X	X	X[14]			X	
Treatment Compliance & Accountability[15]			X	X	X	X	X	X	X	X	X
Dietitian Consultation & Diet Diary[16]	X	X [16]	X	X	X	X	X	X	X	X	X

*The Study Reference Manual will outline and describe a recommended schedule of the assessments during the 1-day and 2-day visits.

DE = Dose Exploration Period. Visits DE-1 (Week 31) and DE-2 (Week 36) (± 3 days) apply only to subjects who participate in the Dose Exploration Period.

[1] Assessments at Week 2 will be completed via telephone call; no visit to the study site will be required. Subjects will return to the clinic at Week 4 and at the end of the double-blind Treatment Period for Week 8 (± 3 days). Visits during the Extension period will occur at 6-13 week intervals (± 2 weeks).

[2] Medical history includes subject demographics and Glut1 DS diagnosis confirmed by *SLC2A1* mutation analysis.

[3] The seizure diary should be completed each study day, even on study days without seizures. Site personnel should help ensure that participants (parents/caregivers) are not leaving any blank pages in the seizure diaries.

[4] All neuropsychological tests and assessments should be performed after the consumption of food and, as indicated, study drug. PPVT, Beery-VMI, RCPM, PEDI-CAT, and GMFM-88 will be administered at select sites only.

[5] The 6MWT will include assessments of PED; a subset of sites may also perform gait analysis using a computerized portable walkway. Portions of the 6MWT, gait analysis and the GMFM-88 tests may be videotaped to monitor administration technique and assess qualitative changes in function. Subject identity will be protected by blurring out the facial area in the video.

[6] CGI-S will be assessed at Baseline (Week 0); CGI-I will be assessed at Weeks 8, 26, 31, 36 and 52 (or Early Termination).

[7] Confirmatory EEG at Screening for patients with absence seizures only is required for ~3 hours. For Week 0 EEG, begin EEG PRIOR TO Randomization date (requires 2-day visit); Week 8, 26, and 31 visits require a 2-day overnight visit to complete EEG. Monitoring periods of less than 12 hours in duration for Week 8, 26, and 31 visits will be considered a protocol violation.

[8] At the Screening and Randomization Visits, a non-fasting blood sample will be drawn to assess non-fasting BHB. At subsequent post-randomization visits, blood samples for UX007 and metabolites will be drawn approximately 90 min following consumption of food and study drug. At Week 26, 3 blood samples will be drawn: pre-dose (within 15 min), and 2 additional timepoints at 60 and 180 min following consumption of food and study drug.

[9] 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.

[10] Perform ECG prior to, or at least 15 min after administration of any motor function tests (if indicated at visit) so that the ECG is performed at resting heart rate.

[11] Physical examinations to include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems.

[12] Clinical laboratory tests include standard serum chemistry, hematology, and urinalysis. Fasting is not required.

[13] The study coordinator will telephone the subject/caregiver between each Extension Period visit to assess AE, discuss any problems or difficulties with treatment, assess protocol compliance, and inquire about study drug consumption and remaining supply. Additional telephone contacts may be made as needed. A follow-up call is recommended within 4 weeks following early termination or study completion.

[14] Following Randomization, study drug will be titrated over a 2-week period to achieve up to 35% of total daily calories from study drug. Subjects in the Dose Exploration Period will titrate study drug as outlined in the Administration Guideline in the Study Reference Manual. The manual randomization process will be followed at Randomization and Week 4 visits only.

[15] Instruct subjects to return all empty and opened study drug bottles to the next visit.

[16] Subjects and/or caregivers are required to maintain record of daily diet in the study diary for at least 3 days prior to each visit (except Screening). The diet diary will be reviewed with the dietitian or study staff upon each visit. The dietitian may telephone subjects and/or caregivers, as needed, to provide dietary advice and support. The 3-day diet history is recorded during the Screening (Baseline) Period and will be used to qualify subjects for the study. A 3-day diet diary is not required at the time of the Screening Visit, only a dietitian consultation. The 3-day diet history recorded prior to randomization will be reviewed by the site dietitian to establish daily caloric intake

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Abbreviations

6MWT	Six Minute Walk Test
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
APBD	adult polyglucosan body disease
AST	aspartate aminotransferase
Beery-VMI	Beery-Buktenica Developmental Test of Visual Motor Integration
BHB	beta-hydroxybutyrate
BHP	beta-hydroxypentanoic acid
BKP	beta-ketopentanoic acid
BUN	blood urea nitrogen
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Improvement scale
CGI-S	Clinical Global Impression – Severity scale
CNS	Columbia Neurological Score
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	electrocardiogram
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
GMFM-88	Gross Motor Function Measure-88
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
ISG	Independent Statistical Group
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
MOT	Motor Screening Test
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
PAL	Paired Associates Learning Test
PCS	Physical health component score
PED	paroxysmal exertional dyskinesia
PEDI-CAT	Pediatric Evaluation of Disability Inventory- Computer Adaptive Test
PHS-10	physical summary score
PK	pharmacokinetic
PO	oral, by mouth, *per os*
PPVT	Peabody Picture Vocabulary Test
PSS-10	psychosocial summary score
PT	Preferred Term
RBC	red blood cell
RCPM	Raven's Coloured Progressive Matrices
RPE	Rating of Perceived Exertion
RTI	Reaction Time
SAE	serious adverse event

SAP	Statistical Analysis Plan
SF-10	Short Form 10 Health Survey for Children
SF-12	Medical Outcomes Study 12-item Short-Form Health Survey for Adults
SOC	System Organ Class
SSP	Spatial Span
SWM	Spatial Working Memory
TCA	tricarboxylic acid
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 disorder (Pearson et al. 2013). 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 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. These patients represent the subgroup of Glut1 DS patients who are most in need of an alternative therapy to ketogenic diet.

UX007 (triheptanoin) is a triglyceride of medium, odd-carbon chain (C7) fatty acid. 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 (Deng et al. 2009), (Kinman et al. 2006), (Marin-Valencia et al. 2013).

The seizures due to Glut1 DS are typically refractory to antiepileptic drugs (AEDs) and are most prominent in the pediatric population. In addition, a subset of Glut1 DS patients is either not on, or unable to comply with or tolerate the KD. For these reasons, the proposed Phase 2 study is designed to assess the safety and efficacy of UX007 in reducing the frequency of seizures in this pediatric, adolescent, and adult population.

5.1 Overview of Glucose Transporter Type 1 Deficiency Syndrome

Glut1 DS is a rare, severely debilitating disease characterized by seizures, developmental delay, and movement disorder (Pearson et al. 2013). It is caused by a mutation in solute carrier family 2, member 1 gene (*SLC2A1*), 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.

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). The majority of reported patients (~90 %) have a *de novo* heterozygous mutation in *SLC2A1*. About 10 % of affected individuals have an affected parent (autosomal

dominant inheritance pattern). Autosomal recessive transmission has also been described in rare cases.

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. There are currently no approved treatments specific to Glut1 DS. Seizures are 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

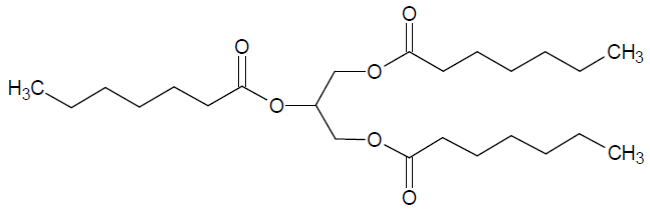
A brief overview of existing information on UX007 (triheptanoin) is provided below; a comprehensive review of the data is contained in the Investigator's Brochure (IB) provided by Ultragenyx Pharmaceutical Inc. (Ultragenyx), which should be reviewed prior to initiating the study.

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:

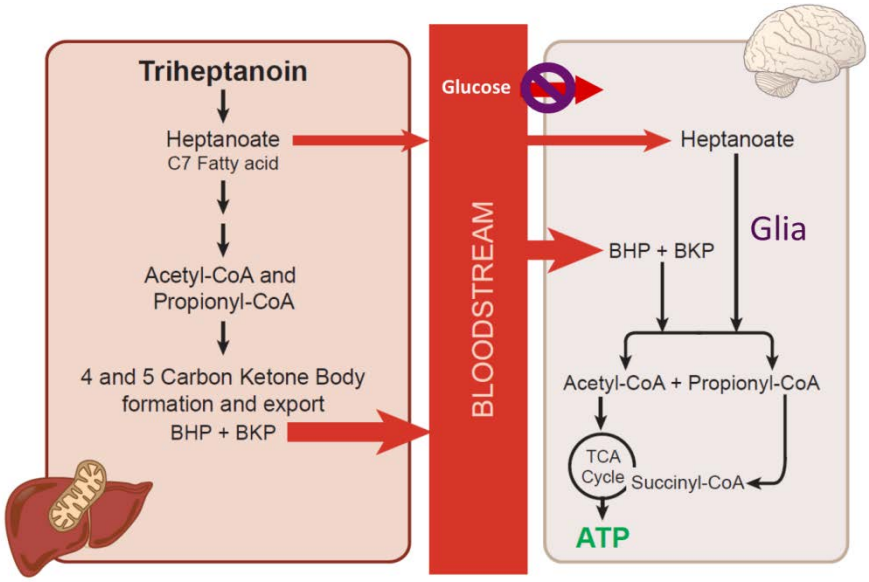


UX007 (triheptanoin) is a liquid, intended for oral (PO) administration. One thousand grams (1025 ± 25 g) of neat triheptanoin drug substance is filled into 1 Litre (L), high density polyethylene (HDPE) or round, amber-colored glass bottles. UX007 is manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations.

5.2.1.1 Mechanism of Action in Glut1 DS

UX007 is highly purified triheptanoin, a triglyceride of 3 fatty acids with 7 carbons each. 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

Studies of potential clinical significance and relevance to this protocol are summarized below.

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).

Nonclinical studies in rats have demonstrated that triheptanoin is hydrolyzed to heptanoate and glycerol, which are efficiently absorbed by the liver (Kinman et al. 2006). Studies have demonstrated that triheptanoin is metabolized rapidly in the gut to form a series of energy containing metabolites, including heptanoate, C4- and C5-ketone bodies (Kinman et al. 2006), (Deng et al. 2009). 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 CNS 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 (IND-59303)

A 9 month oral toxicity study in rats was performed with an experimental oil containing 64% triheptanoin to determine the effects of a diet containing triheptanoin on animal growth, lipid digestibility, clinical chemistry, and toxicity in liver, kidney, and small intestine (Ataide et al. 2009). After 9 months of consumption of a standard diet containing doses up to 1.14 g triheptanoin per kg of body weight per day, no toxic effects attributed to triheptanoin were found in rats. Liver, kidney and small intestine were collected for histological analysis. Significantly, from the limited histopathology data available, there were no target organs of toxicity identified in this study. Microscopic examination of the liver demonstrated that all diet groups showed macrovesicular hepatic steatosis, but this finding was not considered a hepatotoxic effect since the control group also contained the lesion. This is likely to be due to the high fat in the diet. The severity of hepatic steatosis was determined to be less in the rats fed 30% and 50% experimental oil compared to the control group fed the soybean oil-based diet. 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. No major systemic toxicities were observed in either general toxicity study.

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). 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 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).

Ultragenyx is currently developing UX007 as a substrate replacement therapy for long-chain FAOD (LC-FAOD). A prospective open-label Phase 2 study to assess safety and clinical effects of UX007 in subjects with LC-FAOD (UX007-CL201) is currently underway.

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 was developed to address the needs of Glut1 DS patients who continue to have disease crises despite the best available treatment. The current standard of care, KD and AEDs, for these patients 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. There exists a significant unmet medical need in the subset of pediatric patients who are not on, or not compliant with a KD; the proposed Phase 2 study targets this specific subset of patients.

Triheptanoin has been used clinically for over 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, approximately 50 were pediatric subjects with some as young as neonates; a significant portion of pediatric subjects received over 5 years of treatment duration with triheptanoin (Table 7.4.4.1). 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) and toxicity studies indicates that triheptanoin is well absorbed after oral dosing and is well-tolerated without overt toxicities at doses as high as 1.14 g/kg in mice 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 subjects consume triheptanoin 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 (Pearson et al. 2013). It is caused by a mutation in *SLC2A1*, which encodes for 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. Current treatment consists of KD and AEDs. KD generates 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.

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. These metabolites provide an alternative energy source to the brain.

2. Triheptanoin has the ability to provide succinyl-CoA via propionyl-CoA to resupply intermediates of the TCA cycle (i.e., anaplerosis).

3. Triheptanoin can support gluconeogenesis in the brain.

Because of the difficulties in maintaining a KD, some patients are not able to fully comply with or tolerate the diet. These patients represent the subgroup of Glut1 DS patients who are most in need of an alternative therapy to KD. Given the significant unmet medical need in Glut1 DS patients not on KD, UX007 will be studied in this subgroup. The seizures due to

Glut1 DS are most prominent in the pediatric population and are typically refractory to AEDs (Pearson et al. 2013). For these reasons, the proposed Phase 2 study is designed to assess the safety and efficacy of UX007 in reducing the frequency of seizures in the pediatric, adolescent, and adult population. The study will also evaluate the PK of energy-containing metabolites and correlate the achieved concentrations of different metabolites to the potential treatment effects.

5.5 Primary Efficacy Hypothesis

UX007 is more effective than placebo for the reduction of seizures in patients with Glut1 DS, as measured by the reduction from randomization in frequency of seizures, including: Generalized Tonic-Clonic, Generalized Tonic, Generalized Clonic, Generalized Atonic, Partial/Focal with Secondary Generalization, Myoclonic, Myoclonic Atonic, Myoclonic Tonic, Complex Partial/Focal, Absence, and Simple Partial/Focal Motor seizures.

6 STUDY OBJECTIVES

The primary objectives of the study are to:

- Evaluate the efficacy of UX007 compared to placebo as measured by the reduction from randomization to week 8 in frequency of seizures. Observable generalized and partial-onset seizures measured for 6 weeks by diary and absence seizures measured overnight by electroencephalography (EEG).

- Evaluate the safety of UX007 via adverse event (AE) rates, laboratory values, and electrocardiogram (ECG)

The secondary objectives of the study are to:

- Evaluate the efficacy of UX007 compared to placebo, as measured by:

  - Seizure response rate, defined as the percentage of subjects with at least 50% reduction from randomization to week 8 in frequency of seizures

  - Change from randomization to Week 8 in cognitive function using the Cambridge Neuropsychological Test Automated Battery (CANTAB)

  - Change from randomization to Week 8 in distance walked as measured by 6MWT

  - Time to onset of paroxysmal exertional dyskinesia (PED) as measured during 6MWT from randomization to Week 8

  - Change from randomization to Week 8 in gross motor function using the Gross Motor Function Measure-88 (GMFM-88)

- Evaluate long-term efficacy as measured by changes from randomization in frequency of seizures over time through week 52

- Evaluate the optimal dose to control seizures and impact on other clinical manifestations during the Dose Exploration Period

Exploratory objectives are to:

- Evaluate the effects of UX007, from randomization through Weeks 8 and 52 on:

  - Neurological function using the Columbia Neurological Score (CNS)

  - Physician global impression of change in clinical status using the Clinical Global Impression - Severity scale (CGI-S) and Clinical Global Impression - Improvement scale (CGI-I)

- Receptive vocabulary using the Peabody Picture Vocabulary Test (PPVT)
- Subject or caregiver-reported quality of life using Short Form-10™ (SF-10) Health Survey for Children or SF-12 for adults
- Functional disability by caregiver report using the Pediatric Evaluation of Disability Inventory – Computer Adaptive Test (PEDI-CAT)
- Gait, using gait analysis by computerized mat
- PK properties of UX007 and its metabolites

Exploratory objectives are to evaluate the effects of UX007, from randomization through Weeks 8 and 52 on (to be administered at select sites):

- Visual motor integration using the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery-VMI)
- Spatial understanding and abstract reasoning using the Raven's Coloured Progressive Matrices (RCPM)

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

UX007G-CL201 is a randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of UX007 in Glut1 DS. The study will enroll approximately 40 pediatric, adolescent, and adult subjects who are currently not on, or not fully compliant with a ketogenic or other prescribed high-fat diet. Enrolled subjects are otherwise able to maintain standard of care treatment with up to 3 AEDs throughout the duration of the study.

Beginning with the Screening visit, subjects will record seizure frequency during the 6-week Baseline Period. At the end of the Baseline Period, eligible subjects will be randomized in a 3:1 ratio to either UX007 or placebo. Dosing will be initiated using a 2-week titration schedule until the subject has reached 35% of total daily calories from study drug (~1-4 g/kg/day depending on age) (Section 7.4). If a subject has not reached the target of 35% of total daily calories by the end of the 2-week titration period, dose titration should continue until the maximum tolerated dose is reached.

After an 8-week double-blind Treatment Period, the open-label Extension Period will begin, wherein all subjects will be treated with UX007 through Week 52 of the study.
A population-PK analysis at Week 26 will provide data on metabolite levels with all subjects on UX007.

Following the Week 26 visit, all 40 subjects will participate in a 10-week Dose Exploration Period to assess the impact of UX007 dose level on seizure control, other clinical manifestations such as movement disorders and cognitive deficits, and tolerability. For subjects participating in the Dose Exploration Period, the dose will be titrated over 1 week down to 20% of total daily caloric intake. After 4 weeks at the 20% dose level, the subject will be evaluated for safety and efficacy measures of seizure control, motor and cognitive function.

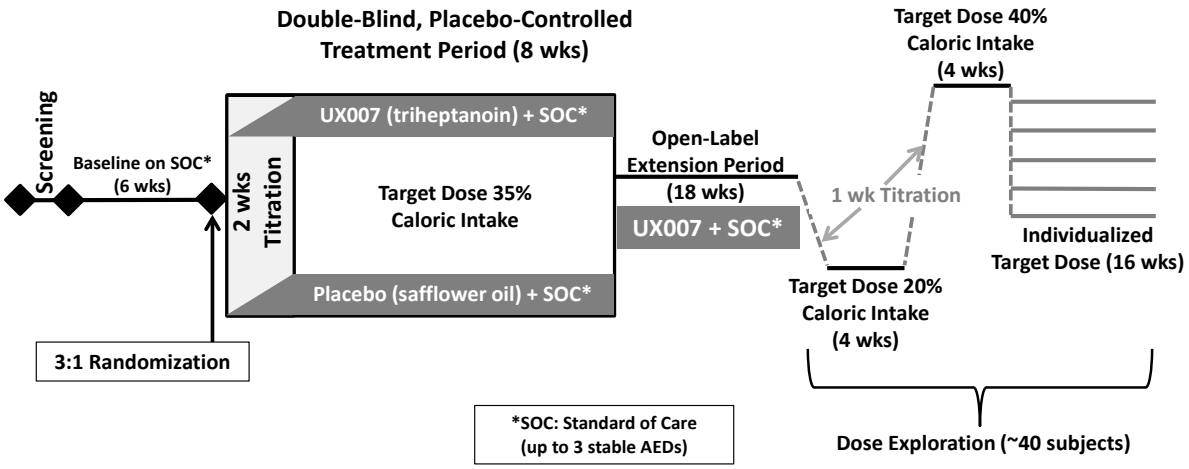
If there are breakthrough seizures during the down titration period, as defined by an increase in frequency of 1 seizure in a 4 week period, relative to the previous 4-week period on a stable UX007 dose, or in the opinion of the investigator there has been a worsening of symptoms prior to completion of the 4-week period, the subject may begin the up-titration phase early.

After 4 weeks at the 20% dose level, the UX007 dose will then be titrated up over 1 week to 40% of total daily caloric intake and maintained at that level for 4 weeks. If a subject cannot tolerate titrating up to the 40% dose level, the dose should be titrated to the maximum tolerated dose as determined by the Investigator. After 4 weeks at the 40% (or maximum tolerated) dose level, the subject will be evaluated for safety, and efficacy measures of seizure control, motor and cognitive function.

At the end of the Dose Exploration Period, the subject will continue in the open-label Extension period, and maintained on the UX007 dose (as determined by the Investigator) that provided the maximum improvement in clinical status with acceptable tolerability, and continued on this dose for the duration of the study. If marked improvements in clinical status were not observed at a higher dose level and/or tolerability was unacceptable, the subject will return to the UX007 dose level where maximal benefit was achieved as defined by seizure control and improvements in motor and/or cognitive symptoms. As determined by the Investigator, this may be the pre-titration UX007 dose from Week 26 or the 20% dose given during the down titration phase.

Forty subjects will participate in the Dose Exploration Period; the remaining subjects enrolled will continue with the optimal dose achieved during the previous 26 weeks. Long term safety and maintenance of effect of UX007 will be assessed during the Extension Period. Subjects who complete treatment through Week 52 may have the option to continue UX007 treatment, if warranted, in a separate open-label extension study. Figure 7.1.1 provides a schematic of the study design.

Figure 7.1.1: UX007G-CL201 Study Schema



7.2 Discussion of Study Design, Including Choice of Control Group

The study is a randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of UX007 in Glut1 DS. Beginning with the Screening visit, subjects will record their seizure frequency during the 6-week Baseline Period. At the end of the Baseline Period, eligible subjects will be randomized to either UX007 or placebo (3:1 ratio) and begin a 2-week titration schedule to increase dosing until they have reached 35% of total daily calories (~1-4 g/kg/day depending on age). The dose will then be maintained for an additional 6 weeks (total 8-week Treatment Period).

The duration of the Baseline Period and the Treatment Period were designed to: 1) minimize the likelihood of changes to concomitant AED regimens, 2) minimize subject discontinuations due to lack of efficacy since subjects completing the Baseline Period and/or randomized to placebo will not benefit from study drug, and 3) be of sufficient length to allow for accurate determination of the seizure frequencies during those periods.

Ultragenyx has discussed the baseline and treatment period durations with 8 physician experts PPD The unanimous advice is that the baseline and treatment periods must be kept to a minimum because the study will enroll a predominantly young pediatric patient population, the majority of whom will likely be under the age of 12 years. This young pediatric population is especially vulnerable to the effects of seizures. The proposed baseline and treatment durations total 14 weeks, and in their opinion is deemed the maximum acceptable duration to them, their patients, and their Institutional Review Boards (IRBs).

Another factor considered in deciding on the duration of the Treatment Period is extent of efficacy over the long term. After the initial 8-week double-blind Treatment Period, the open-label Extension Period will begin, wherein all subjects will be treated with UX007 through Week 52 of the study. Extending the placebo-controlled treatment period is not warranted in this population. Long term safety and maintenance of effect of UX007 will be assessed during this Extension Period. Seizure counts will continue during the Extension Period such that the seizure frequency will be determined over a one-year period, and if warranted, in an additional extension study.

A dose exploration in 40 subjects has been added to the protocol to determine whether the proposed dose is the optimal and necessary dose for UX007 to control seizures and impact other clinical manifestations. The demonstration of a withdrawal effect (with an exit clause that would allow the subject to more quickly move to the up titration phase if there is a significant loss of efficacy during the down titration phase), and a return to control afterward would demonstrate both that a higher dose was necessary and that UX007 had a sustained effect.

7.3 Selection of Study Population

The study will be conducted in pediatric (at least 1 year of age at time of consent), adolescent, and adult subjects with a confirmed diagnosis of Glut1 DS who are currently not on, or not compliant with a prescribed KD or other high fat diet. Enrollment may include subjects from neighboring countries within the European Union, Canada, and South America. Appropriate local or country requirements will be followed.

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), and 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.

The goal of the study is to assess whether UX007 is more effective than placebo for the reduction of seizures in patients with Glut1 DS. Therefore, specific criteria were included to define a study population experiencing a quantifiable number of events despite current treatment. The inclusion criteria are structured to enroll subjects currently experiencing observable seizures despite a prior or current use of at least 1 AED, with an average frequency of at least 2 seizures in 4 weeks over the last 24 weeks. To confirm seizure activity and establish an accurate baseline frequency for treatment comparison, only subjects with at least 2 observable seizures per 4 weeks during the Baseline Period will be randomized.

Glut1 DS patients currently on or fully compliant with a KD or other prescribed high-fat diet of at least 60% calories from fat will be excluded from the study population. 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 to KD. Thus, a significant unmet medical need exists in this subgroup that justifies the study of UX007 in subjects not on KD.

Additional exclusion criteria were incorporated to protect the study population from possible contraindicated treatments or unnecessary safety risks. Although triheptanoin is not known to adversely affect the liver, many of the commonly prescribed AEDs are. In order to minimize confounding factors on interpreting the safety of UX007, subjects with greater than 3 times the upper limit of normal of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) will be excluded from the study. 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 confirmed by *SLC2A1* mutation

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

3) Average of at least 2 observable seizures (generalized or partial-onset [simple partial motor, complex partial, absence, or secondarily generalized] seizures) in 4 weeks over the last 24 weeks, by subject or caregiver report

4) At least 2 observable seizures (generalized or partial-onset [simple partial motor, complex partial, or secondarily generalized] seizures) in 4 weeks during the baseline period, with no 3-week seizure-free period during the Baseline Period OR absence seizures documented on Screening EEG

5) Continuing to have seizures despite a prior or current use of at least 1 AED

6) Allowed to be on up to 3 concomitant AEDs that must have been stable in dose at least 2 weeks prior to the beginning of screening and anticipated to remain stable in dose through the end of the 8-week, placebo-controlled Treatment Period

7) Not on, or not fully compliant with a prescribed diet plan (e.g. KD)

8) Plasma level of beta-hydroxybutyrate (BHB) ≤ 1 mmol/L (non-fasting) at Screening

9) Provide written or verbal assent (if possible) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures

10) Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, comply with accurate completion of the seizures diary, and likely to complete the 8-week, placebo-controlled, Treatment Period

11) Females of childbearing potential must have a negative pregnancy test at Screening, be willing to use an acceptable method of contraception, and have additional

pregnancy tests during the study. Females considered not of childbearing potential include those who have not reached menarche, had total hysterectomy, have been in menopause for at least two years, or have had tubal ligation at least one year prior to Screening.

7.3.2 Exclusion Criteria

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

1) Serum ALT or AST levels exceeding 3X the upper limit of normal at Screening

2) Any known hypersensitivity to triheptanoin or safflower oil that, in the judgment of the investigator, places the subject at increased risk for adverse effects

3) Prior use of triheptanoin with 30 days prior to Screening

4) History of, or current suicidal ideation, behavior and/or attempts

5) Pregnant and/or breastfeeding an infant at Screening

6) Participants unwilling or unable to discontinue use of a prohibited medication (Section 7.4.6.1 [MCT oil, barbiturates, pancreatic lipase inhibitors, KetoCal or other KD supplements, and/or KD]) or other substance that may confound study objectives

7) Use of any investigational product (drug or supplement, including MCT oil) within 30 days prior to Screening, or at any time during the study

8) Has a condition of such severity and acuity, in the opinion of the investigator, that it warrants immediate surgical intervention or other treatment

9) 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 introduces additional safety concerns (e.g., diabetes mellitus, 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 will 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 invalidate the study or place the subject at risk

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

- 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.

Subjects who withdraw or are removed from the study prior to randomization may be replaced on a case-by-case basis, at the discretion of Ultragenyx.

7.3.3.1 Stopping Rules

A DMC will be constituted for Study UX007G-CL201 and will act in an advisory capacity to monitor the safety of UX007 on a routine basis throughout the trial (Section 7.6.8). The DMC may provide advice to Ultragenyx in any determination of whether study enrollment should be paused or if the study should be halted.

Individual subjects who experience any unexpected and possibly, probably, or definitely drug-related SAEs (Section 8.5.2) that represent a change in the nature or an increase in frequency of the serious event from their prior medical history will be assessed as to whether the subject will continue on 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

Subjects will be randomized to receive either investigational product (UX007) or reference therapy (matched placebo) and begin a 2-week dose titration period to achieve study drug treatment comprising up to 35% of total daily calories or to the maximum tolerated dose level (Table 7.4.1). If a subject has not reached the target of 35% of total daily calories by the end of the 2-week titration period, dose titration should continue until the maximum tolerated dose is reached.

Table 7.4.1: Dose Titration Recommendation

The table is an example for how to titrate subject to 35% of caloric intake or the maximum tolerated dose if it is < 35% within two weeks. Discretion and flexibility may be used by the Investigator for each subject.

Days of Dosing	Caloric Intake	If Tolerability Issues Arise:
Days 1-2	~10%	N/A
Days 3-5	~15%	N/A
Days 6-8	~20%	N/A
Days 9-11	~25%	Down-titrate to 20% for 3 more days, then continue to titrate up if possible
Days 12-14	~30%	Down-titrate to 25% for 3 more days, then continue to titrate up if possible
Day 15 - study duration	~35%*	Down-titrate to 30% for 3 more days, , then continue to titrate up if possible

**Some subjects may not be able to tolerate up to 35% of daily caloric intake, despite down titration and re-titrating up. For those subjects, their individual maximum tolerated dose, as determined by the Investigator, will be administered for the duration of the study.*

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

The dose should always be mixed with small amounts of food as indicated in the administration guideline and never administered as the oil directly.

Subjects will maintain treatment at the 35% total daily calorie dose level for a 6-week Treatment Period (Weeks 2-8). Following completion of the Week 8 study visit, all subjects will continue treatment with open-label UX007 at the 35% dose level for an additional 44 weeks (Weeks 8-52).

For subjects participating in the Dose Exploration Period, the dose will be titrated down over 1 week to 20% of total daily caloric intake. Provided there is no significant loss of efficacy during the down-titration phase, the subject will remain at the 20% dose level for 4 weeks. The dose will then be titrated up over 1 week to 40% of total daily caloric intake. Following 4 weeks at the 40% dose level, the subject will be maintained on the minimum dose of drug that provided the maximum achievable efficacy and tolerability, and continued on this dose for the duration of the study. Refer to the Dose Administration Guidelines in the Study Reference Manual for additional information on dosing and dose titration.

7.4.1 Investigational Product

UX007 (triheptanoin) is a colorless to yellow oil. UX007 is a liquid, intended for oral (PO) administration. One thousand grams (1025 ± 25 g) of neat triheptanoin drug substance is filled into 1 L bottles. During the 8 week double blind period of the study 1000 mL UX007 will be provided in 1 L round amber colored glass bottles. During the open label Extension Period of the study, UX007 will be dispensed in 1 L round, translucent HDPE bottles. UX007 is manufactured, packaged, and labeled according to GMP regulations.

7.4.2 Reference Therapy

Placebo will consist of safflower oil and will match the appearance of UX007. Dose level, titration, and mode of administration will be identical to that of UX007 during the double-blind Treatment Period.

7.4.3 Method of Assigning Subjects to Treatment Groups

Eligible subjects will be enrolled in the study and sequentially assigned an identification number. Subjects will be assigned to investigational product or placebo treatment groups based on a manual randomization process developed by the Sponsor. Patients with a broad spectrum of seizure types and frequency will be eligible for enrollment in the study. The frequency of seizures varies among individuals affected with Glut1 DS; some experience daily events, while others experience occasional seizures separated by days, weeks, or months (Pascual et al. 2004). Seizure frequency does not correlate with phenotypic severity (Wang et al. 2012). Randomization will seek to stratify subjects based on seizure frequency reported during the 6-week baseline period. At the end of the Baseline Period, eligible subjects will be randomized in a 3:1 ratio to either UX007 or placebo.

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 13 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 (Table 7.4.4.1), (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.

Table 7.4.4.1: Demographics and Treatment Duration in Clinical Trials

Age at Start of Treatment	Duration of Treatment					
	0-6 months	6 months - 1 year	1-2 years	2-5 years	>5 years	Total N (%)
0-1 month (Neonates)		1			2	3 (3.7%)
1 month-2 years (Children)		3	1	3	3	10 (12.2%)
2-12 years (Children)	5	2	4	4	18	33 (40.2%)
12-16 years (Adolescents)		1	2	2		5 (6.1%)
>16 years (Other)	11	5	11	2	2	31 (37.8%)
Total N (%)	16 (19.5%)	12 (14.6%)	18 (22.0%)	11 (13.4%)	25 (30.5%)	82 (100%)

Source: Summary of Clinical Trials of Triheptanoin Therapy for Metabolic Disorders Done at the Institute of Metabolic Disease from Dec. 28, 1999 to Aug. 7, 2009 at Baylor Research Institute, and Personal Communication, Dr. Vockley, U. Pittsburgh 2013.
N (%) is defined as the total from each column or row divided by the total number of study subjects (82).

The target dose of 35% of calories by UX007 will be administered PO with food (or formula, as appropriate) divided into at least 4 doses per day, as tolerated (breakfast, lunch, dinner, and before bed). The dose may be divided into smaller more frequent doses with food as needed. The daily dose 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 poorly tolerated due to gastrointestinal disturbance, such as diarrhea; lower doses would likely provide suboptimal

efficacy. The planned Dose Exploration Period is intended to evaluate the effect of UX007 dose level on safety and efficacy.

7.4.4.1 Dose Exploration Period

Based on the historical use of triheptanoin, it is expected that sufficient energy substrate replacement will be obtained with dosing of 35% of calories (roughly equivalent to 2-4 grams per kg for small children and 1-2 grams per kg for teenagers and adults). The Dose Exploration Period will also explore doses above and below the anticipated clinical dose of 35% in a subset of approximately 40 subjects and assess for maintenance of effect. In addition to seizures, efficacy in other parameters should be considered before making the assessment of dose adequacy in Glut1 DS, and may necessitate individualized dosing. Therefore it is important to integrate the response in seizures frequency, developmental testing and motor dysfunction to establish the impact of dose level and to test a series of doses in the same individuals to allow for proper individualization of dose. This is also best done after a period of stable treatment to assure that a steady state has been reached in energy metabolism. This proposed design has been successfully used in a prior development program for sapropterin dihydrochloride for the treatment of phenylketonuria (Lee et al. 2008).

The Dose Exploration Period will look at forced dose titration establishment of efficacy as an approach to verify the benefit of the proposed dose range across all domains of disease. At the same time it should verify that there is maintenance of treatment effect after all patients have been on active treatment for at least 18 weeks, by titrating patients downward to observe for recurrence of symptoms.

The lower dose of 20% was chosen for the down titration phase based on anecdotal reports of a significant loss of efficacy when triheptanoin is dosed below 25%. The upper dose of 40% was chosen based on anecdotal reports that tolerability becomes an issue above 25% in some patients and above 35% in most patients. If there are breakthrough seizures during the down titration period, as defined by an increase in frequency of 1 seizure in a 4 week period, relative to the previous 4 week period on a stable UX007 dose, or in the opinion of the investigator there has been a worsening of symptoms prior to completion of the 4 week period, the subject may begin the up-titration phase early. The demonstration of a withdrawal effect and a return to control afterward would demonstrate both that a higher dose was necessary and that UX007 had a sustained effect.

7.4.4.2 Study Duration

Subject participation will be up to 58 weeks in duration, including screening, the Baseline Period, titration/Treatment Period, and Extension Period. Following completion of the double-blind Treatment Period (8 weeks), subjects may continue open-label UX007 treatment for an additional 44 weeks within the Extension Period, if indicated by the investigator. The total treatment duration of up to one year enables a long-term assessment

of the safety and efficacy of UX007 in subjects with Glut1 DS. Beyond this period, subjects may be eligible for an extension study, if warranted, through a separate protocol.

7.4.5 Blinding

The titration and Treatment Period (Weeks 0-8) will be conducted as a randomized, double-blind, placebo-controlled study. Double-blind conditions will be established so that neither the sponsor, subject or site personnel involved in study conduct will know the identity of a subject's treatment. Following completion of the double-blind period, all eligible subjects will receive open-label UX007 for a 44-week Extension Period (Weeks 8-52) to assess long-term safety and duration of effect.

Study parameters to achieve and maintain the double-blind status of the study include:

- Sequential assignment of subject numbers
- A randomization schedule developed by an independent third-party vendor so that Ultragenyx and site personnel receive no knowledge of treatment assignment during the study
- Management of subject treatment assignment via manual randomization
- Labeling of study drug with the study number and a unique kit number
- Packaging and delivery of study drug supplies to sites in a manner that maintains blinding of site personnel
- Matched appearance of investigational product and placebo

The investigator and site personnel will remain blinded to the randomization code during the study. Treatment assignment for an individual subject should be unblinded by the Investigator only in an emergency, and only if when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. Treatment should be provided in accordance with the medical condition and with regard to the information provided in the IB. The Investigator should contact the medical monitor or project manager before unblinding, when possible, but priority should be given to treatment of the subject.

The Investigator must record the date and reason for revealing the blinded treatment assignment for that subject on the CRF. Treatment assignment may be unblinded by the sponsor to satisfy expedited reporting requirements of regulatory authorities. If a subject's treatment assignment is unblinded prior to completion of the study, the subject will be discontinued from the double-blind portion of the study (but may still be eligible to complete the open-label Extension Period).

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 within the last 30 days prior to screening, or are unwilling to discontinue use of a substance that may confound study objectives. The following medications are prohibited throughout the study:

- MCT oil
- KetoCal or other KD supplements
- Barbiturates
- Pancreatic lipase inhibitors (e.g., Orlistat) due to possible inhibition of metabolism of triheptanoin
- A prescribed diet plan (e.g. KD) comprised of at least 60% total daily caloric intake from fat

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 Screening visit will be reviewed and recorded. Some medications, such as AEDs, must not be changed or discontinued, and must be kept at the same dose for the Baseline and double-blind Treatment Periods.

7.4.7 Treatment Compliance

At the Randomization visit and each subsequent visit through Week 36, each subject will be dispensed an adequate supply of study drug to comprise 35% total daily caloric intake (or appropriate dose level if participating in the Dose Exploration Period). Subjects and/or caregivers will record consumption of study drug in a study diary. The diary will also be used to maintain a daily diet record for the 3 days prior to each visit. 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 to the site at the next visit for administration during the day(s) of the visit. Site personnel will maintain a record of all medication dispensed to each subject. The remaining volume of unused medication returned to the site upon early termination or study completion will be estimated for study drug accountability.

7.5 Study Procedures and Assessments

7.5.1 Schedule of Events

Following the signing of informed consent at the Screening visit, each subject will complete a 6-week Baseline Period to establish a clinical baseline and confirm eligibility. The Randomization visit (Week 0 ± 3 days) will be 2 days in duration to complete all assessments and the overnight EEG (prior to randomization). Subjects will be randomized to treatment after inclusion/exclusion criteria have been confirmed. Assessments at Week 2 will be completed during a telephone call, including the dietitian consultation; no visit to the study site will be required. Subjects will return to the clinic at Week 4 (± 3 days) and at the end of the double-blind Treatment Period for a 2-day study visit (Week 8 ± 3 days).
If deemed feasible by the investigator, subjects will continue on open-label UX007 treatment and return for study visits at 6-13 week intervals (± 2 weeks) to assess long-term safety and efficacy during the Extension Period. Subjects participating in the Dose Exploration Period will return for additional visits following 1 week titration and 4-weeks treatment at each dose level (i.e. Weeks 31 and 36 ± 3 days). The study coordinator will telephone the subject/caregiver as needed throughout the study for additional monitoring. 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.

The parameters to be assessed in Study UX007G-CL201, along with timing of assessments, are provided in the Schedule of Events (Table 2.1). Where caregiver assessments are required, the same individual should complete the assessment for consistency of reporting, when possible. Refer to the Study Reference Manual for additional details on specific assessments.

7.5.2 Efficacy Measures

The concept for evaluation is to study the effects of UX007 treatment on seizures, movement disorders, and neurological development in Glut1 DS subjects through clinical assessments within the double-blind Treatment Period and the open-label Extension Period.

The primary efficacy endpoint is the reduction from Randomization in seizure frequency. This endpoint is the most commonly used primary 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. Secondary efficacy endpoints related to the effects of UX007 on seizures will help further understand the effects of UX007 on seizure activity from different methodologies. The long term effects will be examined using the same endpoints.

The effect of UX007 treatment on Glut1 DS will be assessed by evaluating additional critical variables of disease impacting motor and neurological function, along with relevant biomarkers and metabolites. Secondary and exploratory efficacy endpoints related to the

effects of UX007 on parameters other than seizures will help to define whether UX007 has effects on the developmental delay and motor abnormalities due to Glut1 DS.

The effects on Glut1 DS clinical features will be studied over the Treatment and Extension Periods of the study (52 weeks total). While changes in seizure frequency can occur within 6 weeks, a longer treatment period is needed to observe maintenance of effect and long-term safety.

7.5.2.1 Primary Efficacy Variable

Seizure Frequency Reduction: Percent reduction from randomization to week 8 in frequency of seizures. Observable generalized and partial-onset seizures measured for 6 weeks by diary and absence seizures measured overnight by electroencephalography (EEG).

Seizures are a hallmark of Glut1 DS in approximately 90% of affected individuals (Wang et al. 2012). 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.

The frequency of different seizure types will be recorded. 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 for the primary efficacy measure 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

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 at the Week 0, 8, 26, and 31 visits. Confirmatory EEG at Screening for patients with absence seizures only is required for ~3 hours. For Week 0 EEG, begin EEG PRIOR TO Randomization date. Monitoring periods of less than 12 hours in duration for Week 0, 8, 26, and 31 visits will be considered a protocol violation. Key measures will include: (1) frequency of EEG seizures, including absence; and (2) frequency of interictal epileptiform discharges.

7.5.2.2 Secondary Efficacy Variables

The secondary clinical efficacy variables in this study will evaluate additional measures of seizure frequency and response, movement disorders, and neurological function using the evaluations detailed below. Portions of physical therapy assessments may be videotaped to monitor assessment administration and assess for qualitative changes in function (e.g. gait). Subject identity will be protected by blurring the facial area in the video(s). The Investigator may use clinical judgment in deciding whether to administer certain assessments to subjects based on age, development, and cognitive ability, as appropriate.

Refer to the Study Reference Manual for additional details on secondary clinical efficacy measures.

Seizure Response Rate: The seizure response rate is defined as the percentage of subjects with at least a 50% reduction from randomization to week 8 in seizures

Observable seizures via diary: Observable seizure frequency reduction and observable seizure response rate as measured by diary

Absence seizures via EEG: Absence seizure frequency reduction and absence seizure response rate as measured by EEG

Cambridge Neuropsychological Test Automated Battery: Cognitive impairment is common in Glut1 DS patients and can range from learning disabilities to severe intellectual disability (Wang et al. 2012). Neuropsychological function will be measured using CANTAB tests, which have been applied to many age groups, including evaluation in children as young as 4 years of age (Luciana et al. 2002). A standardized, computerized battery of the following 5 nonverbal tests: 1) Motor Screening Test (MOT), 2) Paired Associates Learning Test (PAL), 3) Reaction Time (RTI), 4) Spatial Span (SSP) and 5) Spatial Working Memory (SWM) will be administered. Completion time is approximately 20 minutes. The MOT will be used as a screening tool to identify visual, motor and comprehension difficulties that could impact the reliability of the test. The remaining 4 tests will not be administered to subjects who are not able to complete the MOT. The PAL is a

visual memory test that assesses episodic memory and new learning and is most sensitive to changes in medial temporal lobe function. The RTI is an attention test that measures movement and speed of response to a visual target. The SSP is a test of executive function, working memory and planning test that evaluates working memory capacity and is most sensitive to changes in frontal lobe function. The SWM is also a test of working memory that evaluates the ability to retain visual information and manipulate it in working memory using heuristic strategy. The CANTAB tests will be administered by a trained clinician in a standardized order to minimize variability. CANTAB tests will be administered to age-appropriate subjects during the Screening visit (Week -6), Randomization visit (Week 0), and Weeks 4, 8, 26 and 52 (or Early Termination). CANTAB test will also be performed on subjects participating in the Dose Exploration Period at Weeks 31 and 36.CANTAB tests should be performed within 90 minutes of food consumption and, as indicated, study drug administration.

Six Minute Walk Test: Glut1 DS patients often develop complex movement disorders and gait disturbances characterized by ataxia, dystonia, and chorea (Pons et al. 2010). As some subjects may be too young, cognitively impaired, or physically impaired to reliably perform the test, a practice administration will be performed at the Screening visit to determine feasibility. The 6MWT will not be performed at subsequent study visits if the subject is unable to reliably or safely perform the test at Screening. The 6MWT will be administered to appropriate subjects during the Randomization visit (Week 0), and Weeks 4, 8, 26 and 52 (or Early Termination). The 6MWT will also be conducted at Weeks 31 and 36 for subjects participating in the Dose Exploration Period.

The 6MWT will be administered by a physical therapist in accordance with American Thoracic Society (ATS) guidelines (ATS 2002). Subjects will be observed by trained study staff throughout the duration of the 6MWT, and the test will be terminated if there are any concerns as to whether the subjects can reliably and safely complete the test. Pre-existing gait or balance disturbances, or PED induced by the testing may have the potential to compromise safety.

Subjects will be instructed to walk the length of a pre-measured 20-30 meter course in a hallway for 6 consecutive minutes. Instructions and encouragement will be given according to the script provided in the ATS guidelines. The total distance walked (meters) in a six minute period will be recorded. The percent of predicted normal distance walked will also be determined based on published normative data. PED occurring during the 6MWT will be assessed as an exploratory variable; a subset of sites may also perform gait analysis (Section 7.5.2.3).

Time of Onset of Paroxysmal Exertional Dyskinesia: PED is characterized by transient abnormal, involuntary movements primarily affecting the legs and feet, and typically precipitated by prolonged exertion. PED and co-occurring epilepsy have been associated with Glut1 deficiency (Suls et al. 2008). The presence, time of onset (i.e. time elapsed from

start of 6MWT), and severity of PED events during the 6MWT will be recorded on the CRF. Severity will be assessed as mild, moderate, or severe.

Gross Motor Function Measure: The GMFM-88 was initially designed and validated to evaluate change in gross motor function in children with disabilities (Russell et al. 1989). The original validation sample included children 5 months to 16 years of age. Gross motor function in Glut1 DS subjects will be evaluated using this standardized observational measure of abilities that includes the following 5 domains: lying/rolling, sitting, crawling/kneeling, standing, and walking/running/jumping. Completion time is typically 30-45 minutes. The assessment will be administered at select sites by a trained physical therapist at the Randomization visit and Weeks 4, 8, 26, and 52 (or Early Termination) visits. GMFM-88 will also be conducted at Weeks 31 and 36 for subjects participating in the Dose Exploration Period.

7.5.2.3 Exploratory Efficacy Measures

The Investigator may use clinical judgment in deciding whether to administer certain assessments to subjects based on age, development, and cognitive ability, as appropriate.

Columbia Neurological Score: The classic phenotype of Glut1 DS is also characterized by delayed neurologic development, acquired microcephaly, and complex movement disorders (Pascual et al. 2004). 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 Randomization visit and at Weeks 8, 26, and 52 (or Early Termination).

Clinical Global Impression-Severity scale and Clinical Global Impression-Improvement scale: The CGI-S and CGI-I scales evaluate global impression of disease severity (CGI-S) at baseline and the degree of change in clinical status (CGI-I) at subsequent study visits as assessed by a physician. Both assessments utilize 7-point scales to rate the degree of severity and improvement, respectively (Guy 1976). The CGI-S will be administered during the Randomization visit (Week 0). The CGI-I will be administered at Weeks 8, 26 and 52 (or Early Termination). The CGI-I will also be assessed at Weeks 31 and 36 for subjects participating in the Dose Exploration Period

Neuropsychological Assessments:

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. Therefore, a panel of neuropsychological assessments will be administered (some at select sites only) to provide additional characterization of the cognitive and behavioral features in the Glut1 DS population. All neuropsychological tests and assessments should be performed within 90 minutes of food consumption and, as indicated, study drug administration.

Peabody Picture Vocabulary Test: Individuals with Glut1 DS commonly have receptive language deficits that affect their vocabulary and ability to communicate. The PPVT is a test of receptive vocabulary achievement and verbal ability that is normed for children as young as 2 years of age (Dunn et al. 2007). Administration time is typically 20-30 minutes. The PPVT will be administered at select sites to subjects 2 years of age and older by a trained clinician during the Screening visit (Week -6), and Weeks 8, 26 and 52 (or Early Termination). The PPVT will also be conducted at Weeks 31 and 36 for subjects participating in the Dose Exploration Period.

Beery-Buktenica Developmental Test of Visual Motor Integration: Individuals with Glut1 DS have verbal and motor deficits that limit the ability to complete tasks that require visual and motor coordination. The Beery-VMI measures the extent to which individuals can integrate their visual and motor abilities (Beery et al. 2004). The test is normed for children 2-18 years of age. Administration time is typically 10-15 minutes. The Beery-VMI will be administered to subjects at select sites by a trained clinician during the Screening visit (Week -6), and Weeks 8, 26 and 52 (or Early Termination).

Raven's Coloured Progressive Matrices: Spatial reasoning deficits are a key feature of the cognitive deficits observed in individuals with Glut1 DS. The RCPM is a test of spatial understanding and abstract reasoning developed for individuals 5 years of age and older (Raven et al. 1998). Administration time is typically 15-30 minutes. At select sites, the RCPM will be administered to all subjects, at the clinical judgment of the test administrator, during the Screening visit (Week -6), and Weeks 8, 26 and 52 (or Early Termination).

Short Form Health Surveys: 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. 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 or SF-12 will be administered during the Randomization visit (Week 0), and Weeks 8, 26 and 52 (or Early Termination).

The SF-10 Health Survey for Children 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. Every attempt will be made to ensure that the responder completing the first administration completes subsequent administrations to minimize variability. Completion time is approximately 10 minutes.

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

Pediatric Evaluation of Disability Inventory-Computer Adaptive Test: The constellation of clinical signs and symptoms of Glut1 DS can impact a patient's ability to independently perform activities of daily living. The PEDI-CAT is a measure of functional capabilities and performance designed for use in children and youth from birth to 20 years of age with a variety of physical conditions (Haley et al. 2011). The PEDI-CAT measures abilities in the three functional domains of Daily Activities, Mobility and Social/Cognitive. The PEDI-CAT also includes a Responsibility domain to measure the extent to which a child takes responsibility for the managing multi-step activities of daily living. The PEDI-CAT will be completed for all subjects, as deemed appropriate. Caregivers will be asked to complete the questionnaire for subjects less than 14 years of age at the time of informed consent. Subjects who are 14 years of age or older at the time of informed consent may be asked to complete the questionnaire by self-report. The PEDI-CAT will be administered at select sites during the Randomization visit (Week 0), and Weeks 8, 26 and 52 (or Early Termination). The PEDI-CAT will also be assessed at Weeks 31 and 36 for subjects participating in the Dose Exploration Period.

Gait Analysis: Most Glut1 DS patients present with a spectrum of movement disorders. A study characterizing the spectrum of movement disorders in Glut1 DS observed gait disturbances in 89% of Glut1 DS subjects (Pons et al. 2010). A computerized walkway mat is an electronic walkway providing objective spatial and temporal measurements of gait, with demonstrated test-retest reliability (van Uden et al. 2004). Gait parameters include stride length, velocity, cadence, base of support, and percentage of cycle time spent in double support. The computerized mat will be placed between meters 11 and 15 on the 20-30 meter walking course used for the 6MWT. At select sites, the computerized mat may be used to assess gait during the 6MWT as the subject walks across the mat. Gait assessments will be performed and evaluated by a physical therapist at select sites during the Screening visit,

Randomization visit (Week 0), and Weeks 4, 8, 26 and 52 (or Early Termination). Gait will also be assessed at Weeks 31 and 36 for subjects participating in the Dose Exploration Period.

7.5.3 Drug Concentration Measurements and Bioassays

To assess the peak PK of UX007 and UX007 metabolites, blood samples will be collected approximately 90 minutes following consumption of food and study drug at Weeks 8 and 52 (or Early Termination), and at Weeks 31 and 36 for subjects participating in the Dose Exploration Period. For each sample collection, the time elapsed since last study drug administration will be recorded on the CRF. The following analytes will be assessed:

- Plasma peak levels of UX007
- Plasma levels of UX007 metabolites: C4 ketone (BHB), C5 ketones (beta-hydroxypentanoate [BHP] and beta-ketopentanoate [BKP]), and heptanoate

At the Screening and Randomization (Week 0) study visits, the blood samples will be collected in the non-fasting state in order to assess a non-fasting BHB.

All subjects are on study drug at Week 26, at which time a population PK study will be conducted. Samples for trough (pre-dose [within 15 minutes]) UX007 and metabolites (same as above) will be obtained from all subjects, and 2 additional time points will be drawn for each subject at 60 and 180 minutes following consumption of food and study drug.

If feasible, additional PK samples will be collected whenever a potentially related SAE occurs.

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 serious adverse events (SAEs), including clinically significant changes from baseline to scheduled time points in vital signs, weight, physical examination and ECG findings, clinical laboratory evaluations, pregnancy testing (or pregnancy of partner), suicidal ideation and behavior assessments, and concomitant medications. Refer to the Study Reference Manual for additional details.

7.5.4.1 Medical History

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 laboratory diagnosis. Diagnosis must be confirmed by *SLC2A1*

mutation analysis. Any available family history of Glut1 DS will be noted including diagnosis, disease course, treatment and outcome.

Glut1 DS maintenance 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.

7.5.4.3 Electrocardiogram

At the Screening visit and Weeks 8 and 52 (or Early Termination), a standard 12-lead ECG will be performed prior to or at least 15 minutes after administration of any motor function tests (where indicated) so that the ECG is performed at a resting heart rate. The Screening ECG should be within normal limits or have abnormalities that clearly reflect a stable condition that would not pose a risk to an individual participating in this trial. Abnormal findings and clinically significant changes from baseline will be recorded as AE.

7.5.4.4 Physical Examination

Complete physical examinations will be performed at Screening and the Week 8, 26 and 52 study visits (or Early Termination Visit). Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. Clinically significant changes from Baseline will be recorded as AEs.

7.5.4.5 Clinical Laboratory Tests

The clinical laboratory evaluations to be performed in this study are listed in Table 7.5.4.5.1. Clinical laboratory testing will be performed at the Screening, Randomization (Week 0), and Week 8, 26, 31, 36, and 52 study visits (or Early Termination visit). Blood and urine samples will be collected; fasting is not required. At the Screening and Randomization (Week 0) study visits, the blood samples should be collected in the non-fasting state in order to collect a non-fasting BHB. Refer to the Study Reference Manual for additional details.

Table 7.5.4.5.1: 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)	Beta-hydroxybutyrate (BHB) (at Screening)	Pregnancy test (if applicable)
Serum glucose		
Potassium		
Protein (albumin and total)		
Sodium		

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

7.5.4.6 Pregnancy Testing

Female subjects of childbearing potential will have urine pregnancy tests at the Screening and Randomization visits and at Weeks 8, 26, and 52 (or Early Termination). Females considered not of childbearing potential include those who have not reached menarche, had total hysterectomy, or have been in menopause for at least one year prior to Screening.

Female subjects with a positive pregnancy test at the Screening visit will not be enrolled in the study; female subjects who become pregnant during the study will be removed 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 males or females of childbearing potential must use two forms of highly effective methods of contraception during heterosexual intercourse throughout the study period and for 30 days after stopping the study drug. Examples of highly effective methods include:

- Established use of hormonal contraceptives, such as the birth control pill, injection or implant
- Barrier method, such as a condom with spermicide, or cervical cap

- Intrauterine device (IUD) or intrauterine system (IUS), a small device with hormones that goes inside the uterus
- Male sterilization, also called vasectomy
- True abstinence which means not having sex because subject chooses not to (when this is in line with the preferred and usual lifestyle of the subject)

7.5.4.6.1 Pregnancy in Subject or Partner

Pregnancies in subjects or partners must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. The investigator must make every effort to follow the pregnancy of either subject or partner through resolution of the pregnancy (delivery or termination) and report the resolution to Ultragenyx or its designee. 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. Refer to the Study Reference Manual for details on the reporting procedures to follow in the event of pregnancy.

7.5.4.7 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 pediatric 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.

7.5.4.8 Concomitant Medications

Concomitant medications will be reviewed and recorded in the subject's CRF at each study visit, beginning at the Screening visit. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Screening will be reviewed and recorded. At each subsequent visit, change in medications since the previous visit will be recorded. A discussion of concomitant medications is provided in Section 7.4.6.

7.5.4.9 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 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 from Baseline in physical examination findings, vital signs, clinical laboratory parameters, suicidal ideation and behavior, and ECGs will be recorded as AEs or SAEs, if appropriate. If feasible, additional PK samples will be collected whenever a potentially related SAE occurs.

7.5.4.10 Interim Monitoring Calls

For additional safety monitoring, the study coordinator will telephone the subject/caregiver between each Extension Period study visit through Week 52. Additional telephone contacts may be made during the Baseline and Treatment Periods as needed. A follow-up call is recommended within 4 weeks following early termination or study completion. The calls will be used to assess AE, discuss any problems or difficulties with treatment, and assess protocol compliance. Study staff will ask about potential adverse effects of study drug including presence of gastrointestinal upset, steatorrhea or frequent loose stools, and weight gain. Staff will inquire about study drug consumption and remaining supply.

7.5.4.11 Dietitian Consultation and Diet Assessment

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 visit. The initial 3-day diet history obtained during screening will be used to confirm the subject is not currently on a KD or other high-fat diet, and thereby satisfies requisite inclusion/exclusion criteria. The 3-day diet history recorded prior to randomization will be reviewed by the site dietitian to establish daily caloric intake 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. A dietitian consultation will also take place during the Week 2 telephone assessment. 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. EEG and ECG are routine, non-invasive procedures inflicting minimal pain/distress for the subject, while providing relevant indicators of seizure

events and cardiac safety, respectively. 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).

Performance measures such as the 6MWT and GMFM-88 have been successfully used in clinical development programs. The 6MWT and GMFM-88 were incorporated into the study design as a performance measure of muscle function to evaluate movement disorders characteristic in Glut1 DS patients. The CNS and CANTAB were included as measures of neurological involvement and cognitive function.

Diaries will be used by subjects and/or caregivers to capture seizure events on a daily basis, thereby minimizing recall bias at site visits. Where possible, additional validated, age-appropriate patient-reported outcomes were included to assess health-related quality of life and activities of daily living (SF-10/SF-12 and PEDI-CAT).

Additional measurements of UX007 and known triheptanoin metabolites will be assessed using blood samples. The panel has been included in this Phase 2 study to provide information on relevant PK parameters following a single-dose and 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, ECGs, 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.

Since the study will be conducted in a pediatric, adolescent, and adult population, age-appropriate efficacy measures and additional safety measures including interim telephone calls and a DMC have been incorporated into the study design.

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. The information below is intended as a guide to planned analyses. Planned analyses will occur at the end of the double-blind Treatment Period, and at the end of the study (Extension Period).

The statistical analyses will be reported using summary tables, figures, and data listings. Statistical tests will be at one-sided alpha level of 0.05. 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. All raw data obtained from the CRFs as well as any derived data will be included in data listings.

Each secondary endpoint will be tested independently. No adjustments for multiple comparisons on secondary and exploratory analyses will be performed. The statistical method employed for the analysis of each assessment will be defined in more detail 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 randomized 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 Populations

The efficacy analysis set will include all randomized subjects who received at least one dose of investigational product. Subjects will be analyzed as randomized.

The safety analysis set will include all subjects who receive at least one dose of investigational product, and subjects will be included in the treatment corresponding to the study treatment actually received for the safety analysis.

7.6.3 Primary Efficacy Analysis

The primary efficacy analysis will be based on the efficacy analysis set. The UX007 treatment group will be compared with placebo. The primary efficacy evaluation is the percent reduction from randomization to week 8 in frequency, normalized to a 4 week rate, of seizures Observable generalized and partial-onset seizures measured for 6 weeks by diary and absence seizures measured overnight by electroencephalography (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. Summaries using descriptive statistics: n, mean, SE, median, minimum and maximum will be provided. The primary efficacy comparison will be made using an appropriate analysis as defined in the SAP.

7.6.4 Secondary Efficacy Analyses

The secondary efficacy analyses are primarily focused on alternative domains of Glut1 DS disease to assess the breadth of treatment effect of UX007. The secondary analyses will compare the secondary efficacy variables scores after treatment to before treatment between the treated and placebo groups. The specific tests and analyses will be defined in the SAP.

Included in these analyses will be a predefined per protocol analysis of those subjects that achieve at least 30% of calorie intake or higher as the tolerated dose level and have received at least 80% of the expected doses, to assess whether a subpopulation of the highest dose subjects have a larger difference in efficacy.

In general, each of the efficacy variables assessed at Week 52 (or Week 26 for EEG only) will be compared to the value obtained during the Baseline Period or Randomization (i.e., Screening visit if not performed at the Baseline visit) utilizing the same statistical test as conducted at the Week 8 analysis, but adjusted for the difference that the analyses for the Week 52 data will only utilize a within-cohort comparison and not a between-cohort comparison.

Secondary endpoints evaluating the efficacy of UX007 compared to placebo will include:

- Seizure response rate, defined as the percentage of subjects with at least 50% reduction from randomization to week 8 in frequency of seizures
- Observable seizure frequency reduction and observable seizure response rate as measured by diary
- Absence seizure frequency reduction and absence seizure response rate as measured by EEG
- Change from randomization to Week 8 in cognitive function using the CANTAB
- Change from randomization to Week 8 in distance walked as measured by 6MWT
- Time to onset of PED as measured during 6MWT from randomization to Week 8
- Change from randomization to Week 8 in gross motor function using the GMFM-88
- Long term efficacy as measured by changes from randomization in frequency of generalized or partial-onset seizures over time through week 52
- Optimal dose to control seizures and impact on other clinical manifestations during the Dose Exploration Period

7.6.5 Exploratory Efficacy Analyses

Exploratory endpoints, evaluating the efficacy of UX007 compared to placebo, will include:

- The effects of UX007, from randomization through Weeks 8 and 52 on:
    - Neurological function using the CNS
    - Physician global impression of change in clinical status using the CGI-S and CGI-I
    - Receptive vocabulary using the PPVT
    - Subject or caregiver-reported quality of life using SF-10 Health Survey for Children or SF-12 for adults
    - Functional disability by caregiver report using the PEDI-CAT
    - Gait, using gait analysis by computerized mat
    - PK properties of UX007 and its metabolites

Optional exploratory endpoints evaluating the efficacy of UX007, from randomization through Weeks 8 and 52, will include:

- Visual motor integration using the Beery-VMI
- Spatial understanding and abstract reasoning using the RCPM

7.6.6 Pharmacokinetic Analyses

Descriptive statistics, including mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum will be calculated for the plasma UX007 concentrations and its metabolites (including plasma BHB, BHP, BKP, and heptanoate) at each sampling time point for 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. Individual plasma UX007 concentrations and its metabolites (including plasma BHB, BHP, BKP, and heptanoate) will be provided. Additional details of the peak PK and population PK analyses will be provided in the SAP.

7.6.7 Safety Analyses

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 and ECG findings
- Clinical laboratory evaluations
- Pregnancy testing/pregnancy of partner
- Suicidal ideation and behavior assessments
- Concomitant medications

The analyses of safety will include all subjects in the safety analysis set. Safety data will be periodically reviewed by the DMC.

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 including the continuation period. 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 may be provided, as appropriate).

Clinical laboratory data will be summarized by the type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any markedly abnormal laboratory results will be provided. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e., outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement.

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.

7.6.8 Data Monitoring Committee

A DMC with appropriate expertise in the conduct of clinical trials in children will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial.

The DMC will also monitor individual subject tolerability and implement individual subject stopping criteria based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. The DMC will be consulted for the management of individual subjects who experience unacceptable tolerability issues (such as significant gastrointestinal distress).

The DMC may:

- Review the study protocol and informed consent documents, and plans for data monitoring
- Evaluate the progress of the trial, study data quality, timeliness, subject recruitment, accrual and retention, subjects' risk versus potential benefit, and other factors that could affect the study outcome
- Consider relevant information that may have an impact on the safety of the participants or the ethics of the study
- Make other recommendations to Ultragenyx concerning continuation, termination or other modifications of the study based on their observations of the study

7.6.9 Determination of Sample Size

The proposed Phase 2 study will have a sample size that would likely detect a 50% reduction from randomization in seizure frequency compared to placebo. Such a treatment effect would be greater than or equal to that demonstrated by many of the approved AEDs for refractory epilepsy, such as lamotrigine, oxcarbazepine and levetiracetam (Glauser et al. 2000), (Glauser et al. 2006), (Trevathan et al. 2006). A theoretical treatment effect of this magnitude, in light of the benign safety profile of UX007 shown to date, is considered to be clinically meaningful by physician experts. From the perspective of accurately determining seizure frequency, the proposed durations are deemed sufficient and are accounted for in the standard deviation (55%) used in the power calculation.

For the study to be adequately powered, a sample of approximately 40 completed subjects was estimated to be adequate to detect a 50% between-group difference in seizure rate per 4 weeks with power of approximately 80% and population standard deviation of 55% using two-sample t test at one-sided alpha level of 0.05.

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.

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

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

8.2 Investigators and Study Administrative Structure

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

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

8.3 Investigational Product Accountability

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

will be properly packaged for transport by the subject or for shipment by the clinical site. 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 two years after the last approval of a marketing application in the US or an ICH region and until: 1) there are no pending or contemplated marketing applications in the US or an ICH region, or 2) at least two years have elapsed since the formal discontinuation of clinical development of the investigational product under study. The investigator/institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. 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 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an Ultragenyx agreement. Ultragenyx must be notified and will assist with retention should the investigator/institution be unable to continue maintenance of subject files for the full 15 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 AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE.

Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

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

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that at any dose, in the view of either the investigator or Ultragenyx, results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or 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. 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 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 "Not Related" events:

- ***Definitely Not Related:*** This category applies to an AE that ***is clearly not related*** to the investigational agent/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the exposure to study drug and/or a causal relationship is considered biologically implausible.

- ***Probably Not Related:*** This category applied to an AE that ***is doubtfully related*** to the investigational agent/procedure. That is, an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), known consequences of the disease under investigation or the relationship in time suggest that a causal relationship is unlikely.

Categories of attributions for "Related" events:

- ***Possibly Related:*** This category applies to an AE that ***may be related*** to the investigational agent/procedure. That is the AE follows a reasonable temporal sequence from administration of the study drug and that follows a known or expected response

pattern to the suspected study drug, but that could readily have been produced by a number of other factors.

- ***Probably Related:*** This category applies to an AE that ***is likely related*** to the investigational agent/procedure. That is, the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known or suspected pattern of response, and is strongly associated with study drug exposure. An alternative explanation is less likely, e.g., concomitant drugs(s), concomitant medication(s).

- ***Definitely Related:*** This category applies to an AE that ***is clearly related*** to the investigational agent/procedure. That is, the AE is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s), known consequences of the disease under investigation or the relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

For the purposes of reporting to regulatory agencies, AEs deemed as Definitely, Probably or Possibly Related will be considered Related and those deemed Definitely Not or Probably Not Related will be considered Unrelated.

8.5.4 Adverse Event Reporting to Ultragenyx

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 AE eCRF via the EDC system. The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring documentation of the event is adequate. Details of the AE must include severity, relationship to study drug, duration, and outcome.

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

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

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

Any SAE that occurs at any time during the study, including a clinically significantly abnormal laboratory test result that is considered serious, must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. These requirements apply equally to all subjects, regardless of the study phase or the at-risk subject's treatment assignment or dosage. The reporting requirement for SAEs is from the time of signing of the ICF through 30 days following the last study drug administration.

SAEs will be reported by completing and submitting SAE report forms to Ultragenyx or its designee. Initial SAE reports must be followed by detailed descriptions. These should include copies of hospital case records and other documents when requested. 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.

A death occurring during the study, during the per-protocol follow-up period, or within 30 days after stopping treatment with the study drug must be reported to Ultragenyx or its designee within 24 hours of knowledge of the death whether or not it is considered treatment-related.

The investigator also must notify the IRB/EC of the occurrence of the SAE, in writing, as soon as is practicable and in accordance with IRB/EC requirements and local law. A copy of this notification must be provided to Ultragenyx or its designee.

8.5.4.3 Urgent Safety Reporting

The regulations governing clinical studies state that the sponsor and investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee (EC) is notified at the same time." 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. Investigators are required to report any urgent safety measures to Ultragenyx within 24 hours.

8.5.4.4 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.

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, Ethics Committees, 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/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.

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 Ethics Committees, as per local laws and regulations.

8.5.4.5 Pregnancy in Subject or Partner

Pregnancies in subjects or partners must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. The reporting period for pregnancies is the period from the signing of the ICF through 30 days following the last dose of study drug.
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. Refer to the Study Reference Manual for details on the reporting procedures to follow in the event of pregnancy. Pregnancy-associated SAEs will be processed and submitted, as necessary, as per the SUSAR reporting process (Section 8.5.4.4).

8.5.5 Safety Contact Information

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

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10 SIGNATURE PAGE

Protocol Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess the Safety and Efficacy of UX007 in Subjects with Glucose Transporter Type 1 Deficiency Syndrome

Protocol Number: UX007G-CL201 Amendment 4

I have read Protocol UX007G-CL201 (Amendment 4). 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.

PPD

Melanie Brandabur, MD Date
Medical Director
Ultragenyx Pharmaceutical Inc.